Mood Disorders in Children & Adolescents

Bennett L. Leventhal, MD
University of California San Francisco

22 October 2021

Disclosures

- Research Support
  - ✓NIH
- Speaker Bureaus
  - ✓None
- Consulting Relationships
  - ✓Janssen/J&J
  - ✓Ascent Autism
- Stock and Investments
  - ✓None
- Family Financial Interests
  - ✓None
- Honorarium
  - ✓None
- Travel
  - ✓None

Why didn’t clinicians think childhood depression existed?

1. "Depressive reactions" were “apparently rare in children, **at least in the form seen in adults**" Slater and Roth, 1967

2. Psychoanalytic theory: Depression doesn’t exist immature ego without the defenses to become melancholic

3. Developmental -Depression exists but appears different from depression in adults
   A. Masked Depression/Depressive equivalents: “depressive feelings in a growing child are displaced by behavioral problems” *and called “depressive equivalents”* (Toolan, 1962; Rie, 1966)
   B. Depressive symptoms are common in children and are relatively brief and not clinically significant; “the syndrome of childhood depression rests largely on surmise”. Lefkowitz and Burton, 1978.

4. Not all: Citryn and McNew (1972)

Important considerations for MDD in youth

- Developmental differences in symptom expression
- Parent vs. Child information
- Frequently comorbidity
  - (e.g., ADHD, anxiety, oppositional behavior disorder, SUD)

DSM-5 Depressive Disorders

- Disruptive Mood Dysregulation Disorder (DMDD)
- Major Depressive Disorder
- Persistent Depressive Disorder (Dysthymia)
- Premenstrual Dysphoric Disorder
- Substance/Medication Induced Depressive Disorder
- Depressive Disorder Due to Another Medical Condition
- Other Specified Depressive Disorder
  - Reccurent Brief Depressive Disorder (2-13 days)
  - Short Duration Depressive Episode (4-13 days)
  - Depressive Episode with Insufficient Symptoms
- Unspecified Depressive Disorder

DSM-5 Disruptive Mood Dysregulation Disorder

A. Severe recurrent temper outbursts
B. Temper outbursts inconsistent with developmental level
C. Temper outbursts occur, on average, three or more times/week
D. Mood between temper outbursts is persistently irritable
   - Most of the day, nearly every day
E. Criteria A-D present for 12 months or more
F. Criteria A & D present in 2 of 3 settings (home, school, with peers)
G. Diagnosis not before age 6 or after age 18
H. Never been a distinct period of more than 1 day when symptoms were not present (except if manic or hypomanic)

DSM-5 Major Depressive Disorder

A. 5 or more of the following in a 2-week period, representing a change in function with at least depressed mood and/or anhedonia
   1. Depressed mood most of the day, nearly every day
   2. Decreased interest or pleasure in almost all activity
   3. Significant weight loss
   4. Insomnia or hypersomnia
   5. Psychomotor agitation or retardation
   6. Fatigue or loss of energy
   7. Feelings of worthlessness or excessive guilt
   8. Diminished ability to think or concentrate; indecisiveness
   9. Recurrent thoughts of death; suicidal ideation; suicidal plan or attempt

B. Symptoms cause clinically significant stress or impairment

C. Episode not attributable to physiological effects of substances or another medical condition

D. Not better explained by another disorder

E. No manic or hypomanic episodes.

Persistent Depressive Disorder (Dysthymia)

A. Depressed mood for most of the day, more days than not, x2 years
B. Presence of two or more of the following
    1. Poor appetite or over-eating
    2. Insomnia or hypersomnia
    3. Low energy or fatigue
    4. Low self-esteem
    5. Poor concentration or difficulty making decisions
    6. Feelings of hopelessness
C. During 2-year period (1 for children & adolescent), never with out A & B criteria for more than 2 months at a time
D. Major depressive disorder may be continuously present for 2 years
E. No mania or hypomania
F. Mot explained by other psychiatric disorder
G. Not attributable effects of substance or other medical condition
H. Cause distress and impairment

Dysthymia in DSM-5: “Persistent Depressive Disorder”

- Merges 2 former concepts: chronic major depressive disorder and dysthymic disorder
- Depressed mood, more days than not, subjectively or observed for at least a year, never without dysthymic symptoms for more than 2 months
- Unique Dysthymia Specifiers
  - Pure dysthymic syndrome – No MDD in past 2 years
  - Persistent MDE – MDE full criteria chronically for past 2 years
  - Intermittent MDEs with current episode – “double depression”
  - Intermittent MDEs without current episode – “double depression”, but not currently in an MDE
  - Specify mild, moderate, severe

Premenstrual Dysphoric Disorder

A. During most menstrual cycles, at least 5 symptoms must be present
   - in the final week before the onset of menses
   - Improve within a few days after onset of menses
B. 1 or more of: Affective lability; Irritability or anger; Depressed mood (hopelessness, helplessness, self-deprecation); Anxiety or tension
C. 1 or more of the follow: Decreased interest; Difficulty concentrating; Lethargy/fatigue; Appetite change; Hyper/Hyposomnia; Feeling overwhelmed; Physical symptoms
D. Symptoms associated stress or impairment
E. Not exacerbation of another disorder
F. Criterion A confirmed by ratings
G. Not attributable to substances or other medical condition

Substance/Medication-Induced Depressive Disorder

A. Prominent, persistent disturbance of mood and anhedonia
B. Evidence that
    1. Symptoms develop during or after substance intoxication or exposure
    2. Involved substance can produce symptoms in A
C. Not better explained by depressive disorder
D. Does not occur during delirium
E. Causes distress & impairment

Depression Specific Diagnostic Instruments

- Diagnosis: Various semi-/structured interviews
  - I - Kiddie Schedule of Affective Disorders – Present and Lifetime (K-SADS-PL)
  - I - Children Depression Rating Scale (CDRS)
- Rating Scales - past week to two weeks
  - S - Patient Health Questionnaire (PHQ) 9:
  - S - Children's Depression Inventory (CDI)
  - S - Mood and Feelings Questionnaire (MFQ)
  - S - Center for Epidemiologic Studies-Depression (CES-D-A)

I=interview S=rating scale

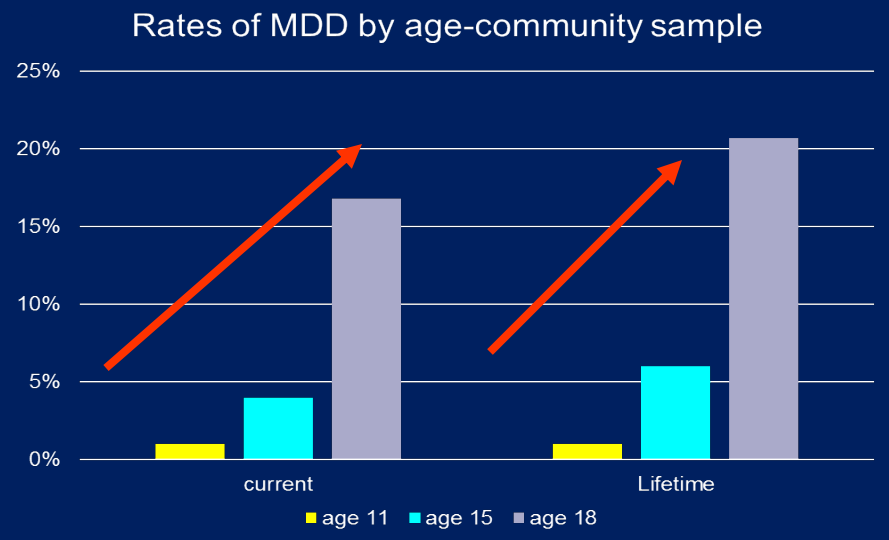
Natural History of Depressive Disorders: remission and relapse

- Episodes last at least 7-9 months
- 90% remit by 1.5-2 years
- 8-22% chronic from childhood
- 50-60% of child and adolescents with MDD have at least 1 recurrence; 10% had ≥4
  - 40% recur in 2 years; 70% in 5 years
- 60-70% Persists from adolescence to adulthood in of cases
- Conversion to bipolar (BP) depends on sample; several longitudinal studies put rates at 4%; others as high as 49%
  - 12-20% found in a number of studies; only 6% in adults
    - Associated with acute, severe depression
    - Psychomotor retardation and psychosis
    - Family history of manic-depression or MDD
    - Possible pharmacological mania
    - Possible ADHD with mood instability
- Adverse outcomes: suicide, drug and alcohol problems, social impairment, school drop-out, adult depression
- No consistent predictors of recovery or recurrence including age of onset and family history

Kovacs. *JAACAP.* 1996.

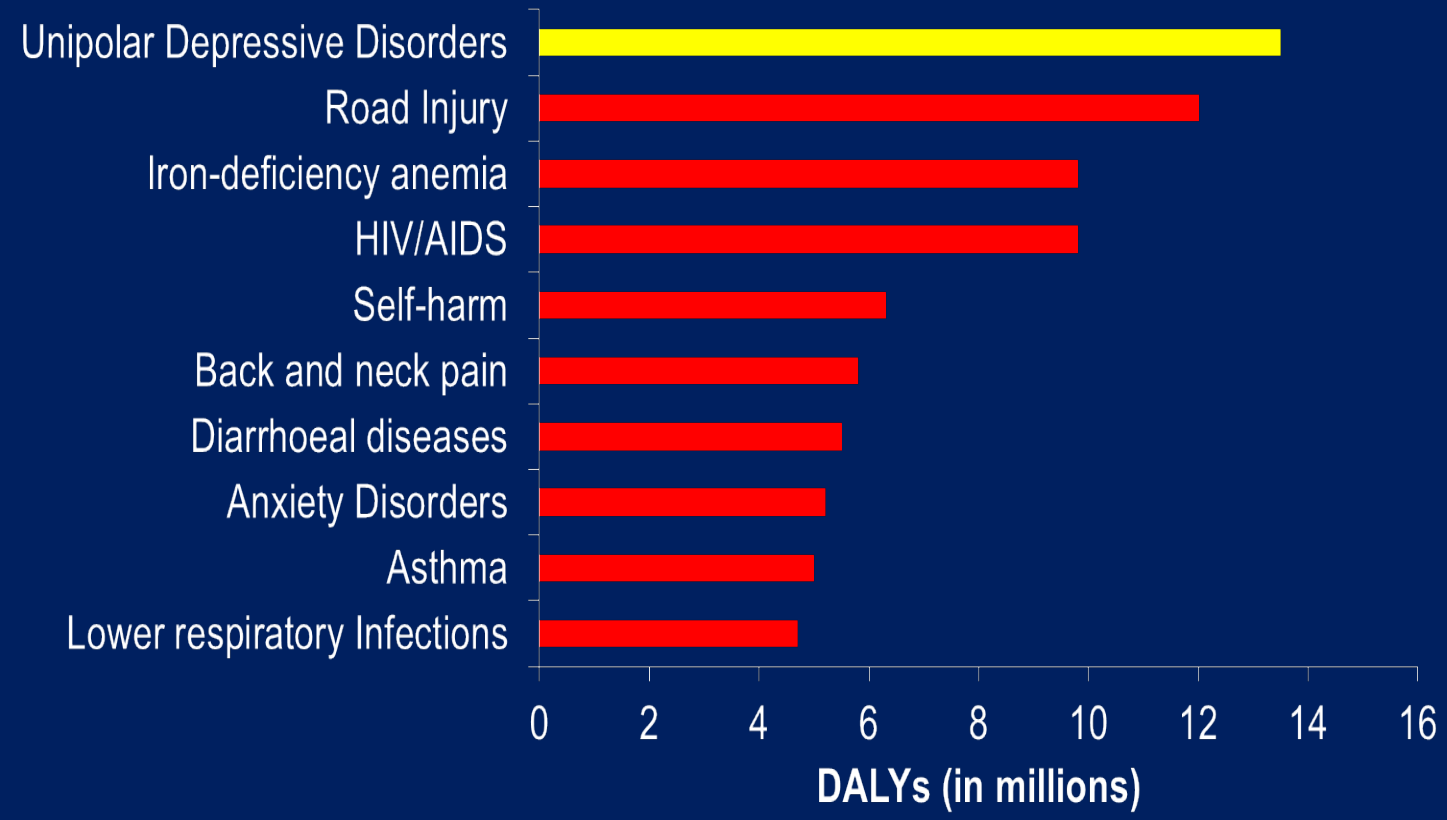
Epidemiology

Parent report		**Rate**		**Rate**
Past year	child	1.7%	teen	3.5%
Lifetime	child	2.3%	teen	7-12%
Teen report				Rate
Past year			teen	8-12%
Lifetime			teen	8-12%



Center for Disease Control's Morbidity and Mortality Weekly Report. May 17, 2013
Thapar, et al. *Lancet*. 2012.

Top Ten Causes of DALYs Lost Among Adolescents



DALYs – Disability-adjusted life years lost

World Health Organization 2016, Health for The World's Adolescents, www.who.int/adolescent/second-decade

What about comorbidity?

- 40-70% depression with comorbidity - always preceded the onset of depression.
- 20-50% have 2 or more comorbid disorders.
  - Anxiety disorders: 30-80% (but remember about a 1/3)
  - Disruptive behavior disorders: 10-80% (about 1/4).
  - Dysthymia 30-80% (remember about 1/3 have recurrent depression)
  - Substance abuse; It, too, frequently precedes depression (teens).
  - Medical comorbidities: esp. irritable bowel, migraine, asthma, diabetes, circulatory and endocrine problems
- Comorbidity predicts more severe, longer depressions; more suicidality and more substance abuse.

Angold, et al. JCPP, 1999
Kline-Simon, JAACAP, 2016.

What Comes First?

	Clinical sample Ezpeleta 2009	Community Nock NCSR-2007
Behavior Problems 1st	74%	72.2 % CD; 77.6% ODD
Mood disorder 1st	16.8%	19.1% CD 15.2% ODD
Simultaneous	12.8%	8.8% CD 7.1%ODD

Risk Factors and Implications: Biological

Family history of MDD	Increase index of suspicion; Treat parent
Parent Substance abuse	Treat parent
Family history of Bipolar	Watch for child bipolar; Treat parent
Female/puberty	Rates of MDD increase
Prior episode	Add relapse prevention
Subsyndromal depression	Life-style changes? Stress reduction

Rey, et al. IACAPAP e-Textbook of Child and Adolescent Mental Health; ch.1.
Thapar, et al. *Lancet.* 2012.

Risk Factors and Implications: Psychological

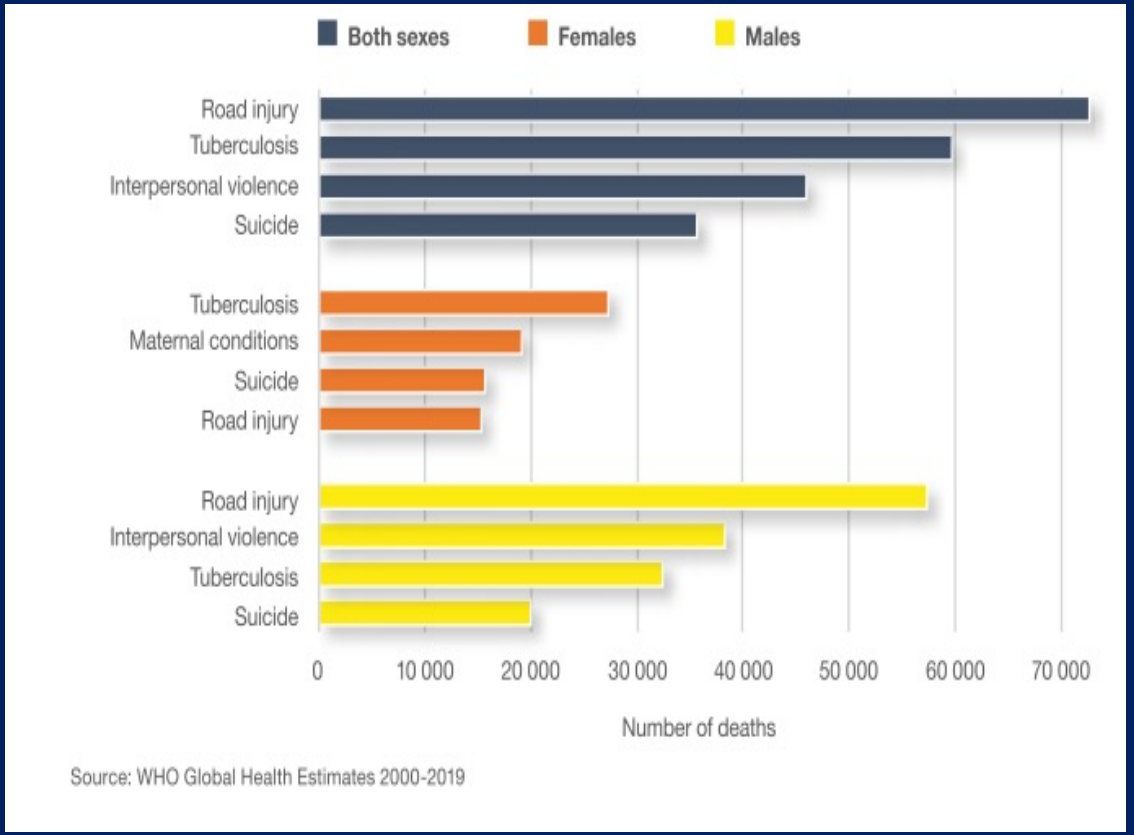
Comorbid disorder ADHD, anxiety esp.	Detect and treat comorbidity
Negative affect temperament	CBT
Negative cognitive style	
Trauma/Abuse	Remove; target of treatment
Negative parenting style	Parent education/treatment
Parent/child conflict	Parent education/family treatment
Bullying	School intervention; social skills

Rey, et al. IACAPAP e-Textbook of Child and Adolescent Mental Health; ch.1.
Thapar, et al. *Lancet.* 2012.

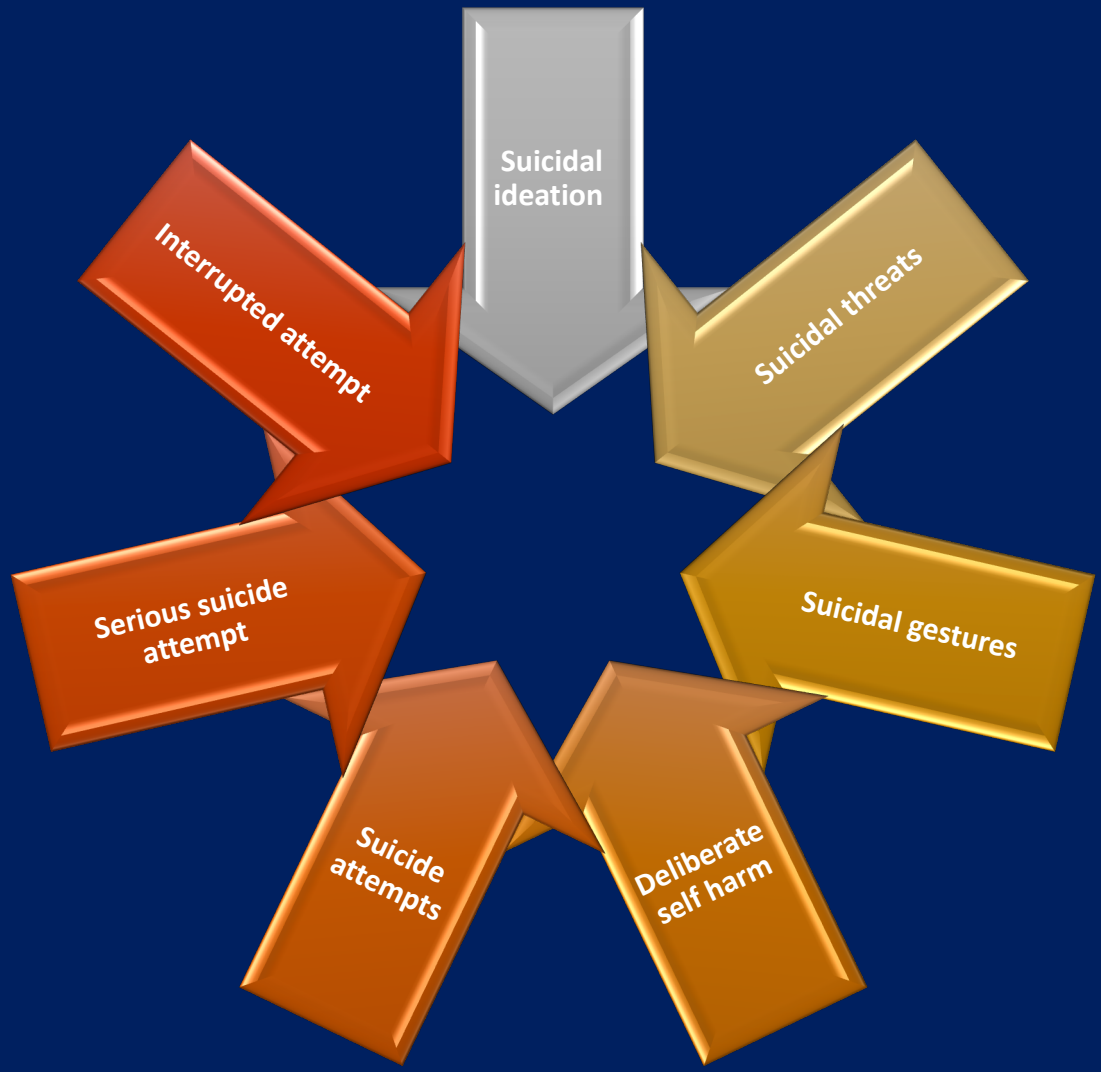
Protective Factors

- Positive parent–child relationship
- Parental supervision and monitoring
- Pro-social peer group
- Connection to school
- Higher intellectual quotient (IQ)
- Participation in sports and physical activity

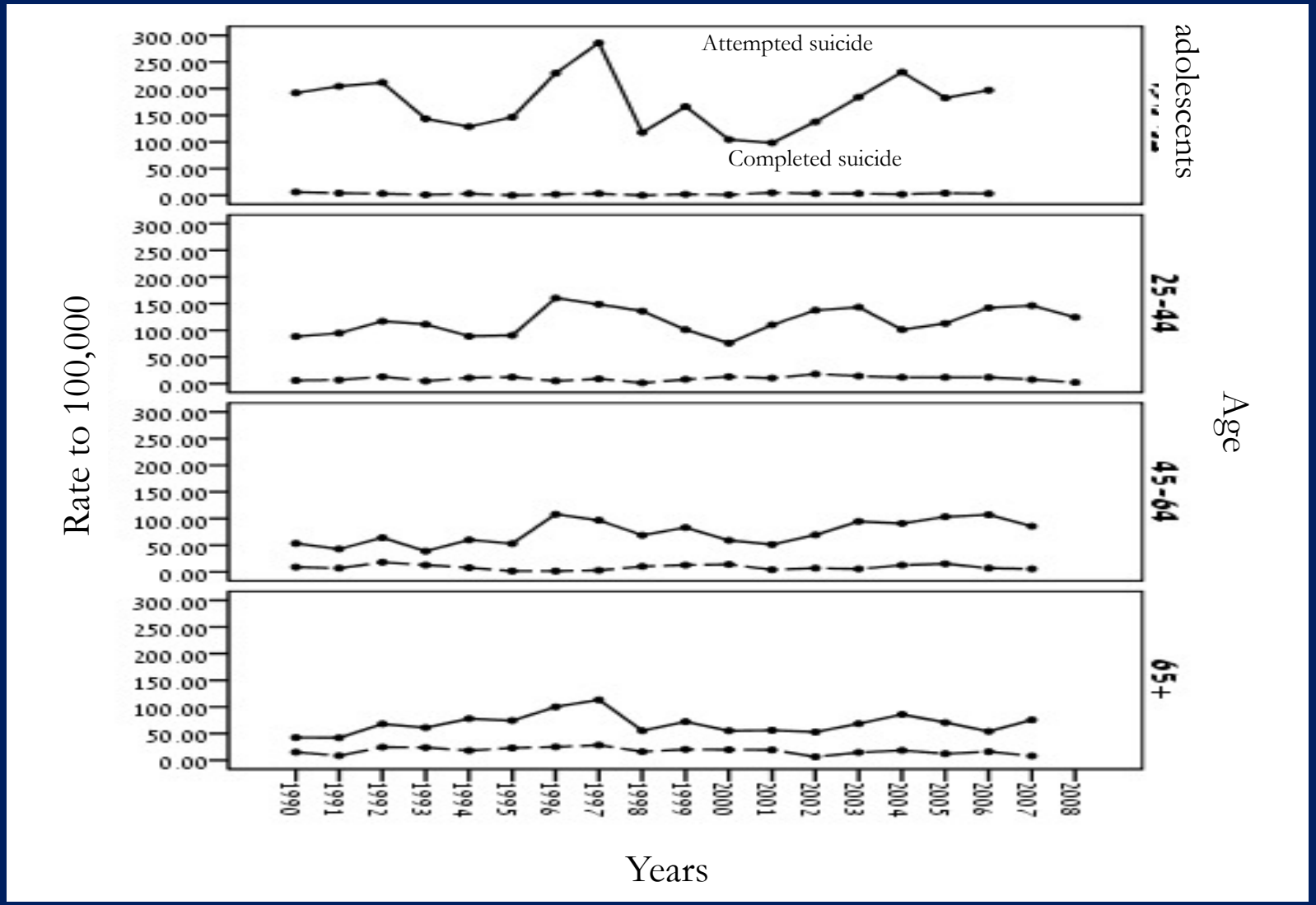
Global top four causes of death, ages 15–19 years, 2019



Suicide Spectrum



Completed vs. Attempted Suicide
Holon-Bat Yam (WHO-EURO)

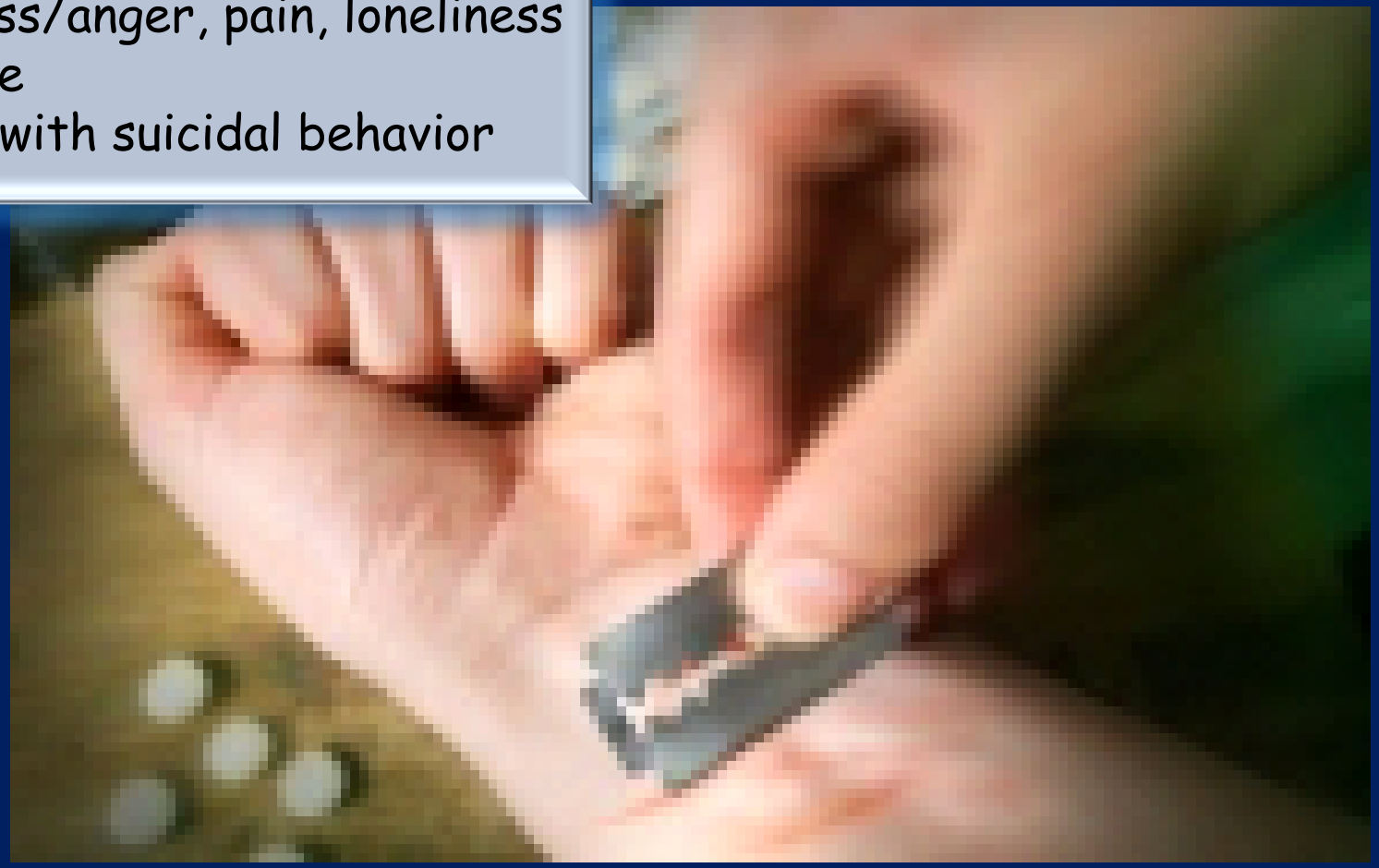


Three personality constellations Associated with Suicide Risk

- Narcissism , perfectionism and the inability to tolerate failure
- Impulsive and aggressive characteristics combined with over sensitivity
- Hopelessness often related to underlying depression

Non-Suicidal Self-Harm

Self-cutting, repetitive and stereotypical
To relieve distress/anger, pain, loneliness rather than to die
Often co-occurs with suicidal behavior



Psychopathology & Suicidality

- Over 80% of attempters and 90% of completers have at least one major psychiatric disorder
- Most commonly mood disorder
- High risk for bipolar disorder, particularly mixed state
- Substance abuse
- Borderline Personality Disorder
- Conduct disorder
- Comorbidity, chronicity, severity

Treatment

Phases of Treatment

- Acute (6-12 weeks)
- Continuation (to prevent ***relapses***) (6-12 months)
- Maintenance (to prevent ***recurrences***) (≥ 1 year)

Treatment Tools

- Psychoeducation
- Psychotherapy
- Pharmacotherapy
- Other Biological Therapies
- Other
  - Exercise
  - Diet
  - rTMS
  - Ketamine
  - ???

Psychoeducation

- Teach about:
  - Signs and symptoms
  - Course
  - Effects on the patients, family, peers, school
  - Treatment
  - Role of parents, siblings, teachers
  - Safety issues
- Benefits:
  - improve adherence
  - understand depression as an illness
  - reduce stigmatization
  - Sometimes, improves symptoms of depression, and
  - Helps family member to identify and seek treatment for their own depression

Psychosocial Interventions

- Psychodynamic Psychotherapies
- ***Cognitive Behavioral Therapy (CBT)***
- ***Interpersonal Psychotherapy (IPT)***
- Mindfulness
- Dialective Behavior Therapy (DBT)
- Supportive Psychotherapy
- Family Therapy
- Group Psychotherapy
- Computerized CBT
  - For example: Tablets (Kobak et al., 2015)
  - Smart, Positive, Active, Realistic, X-Factor Thoughts (SPARX) (Merry et al., BMJ, 2012)-

Acute Treatment with Psychotherapy

- Most studies utilize Cognitive Behavior Therapy (CBT) and to a lesser extent interpersonal psychotherapy (IPT)
- Alone or combine with pharmacotherapy
- Most studies have been done with adolescents
- Overall results:
  - **60% - 70% vs. Controls: 30% -50%**

Psychotherapy for Adolescent Depression

- **Cognitive Behavioral Therapy (CBT)**
  - monitor and modify negative cognitions, automatic thoughts, assumptions, and beliefs.[1]
- **Interpersonal Psychotherapy (IPT) for Adolescents**
  - IPT-A links onset and perpetuation of depression symptoms to problems with interpersonal relationships though acknowledges contributions of genetic, biological, and personality factors to causing episodes.[2]
  - IPT-A tries to improve the teens' communication and social problem-solving skills and increase their personal effectiveness and satisfaction with current relationships

[1]Weisz, et al. 2006.
[2]Mufson, et al. 1999.

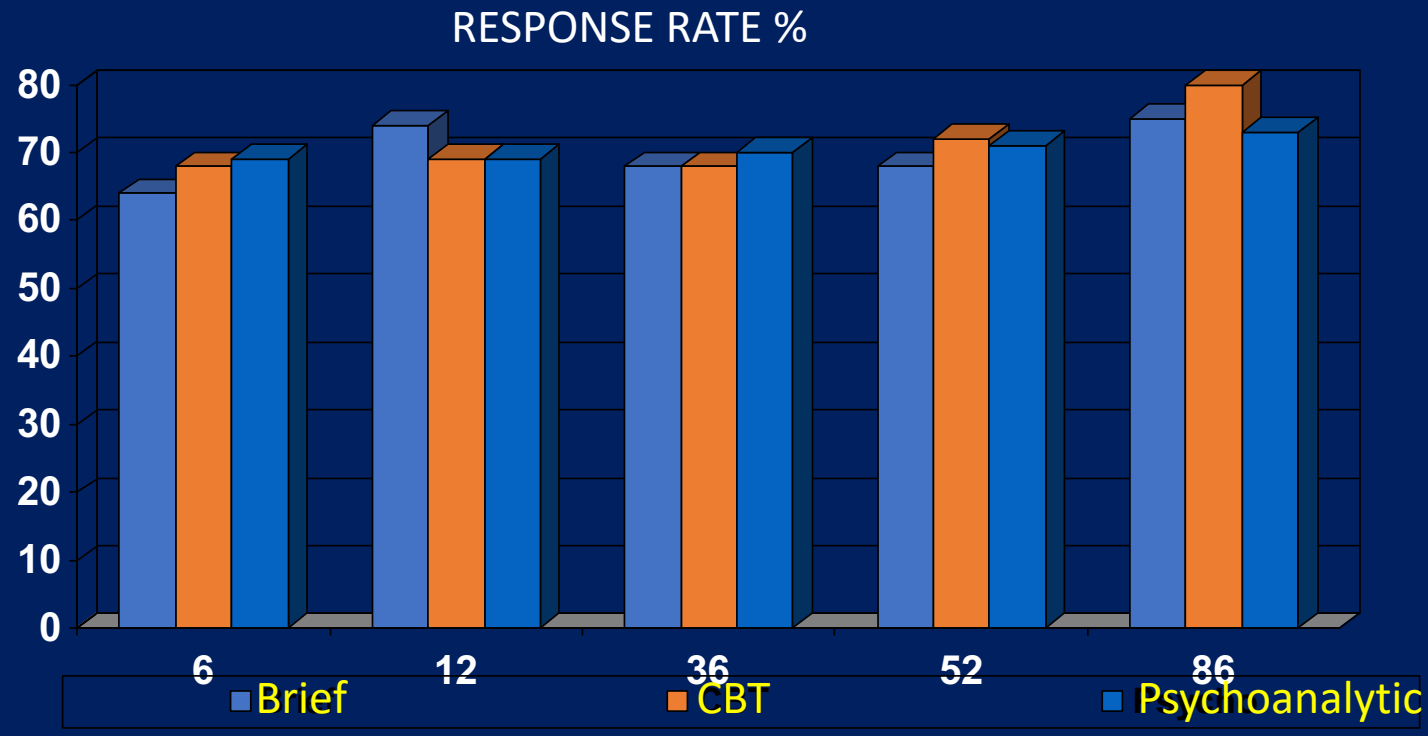
IMPACT Depression Treatment Study
15 National Health Service Child and Adolescent Clinics in England

- 3 manualized psychotherapeutic interventions in 470 youths 11-17 with unipolar MDD; 392 completed trial (84%)
- Comorbid: GAD=21%; Social phobia=13%; ODD=9.5%, CD=3%
- 3 therapies – all manualized, checked for fidelity:
  - BRIEF: psychoeducation, action-oriented, goal-focused, interpersonal activities as therapeutic strategies; 12 sessions/20 wks
  - CBT: identify behaviors and cognitions that maintain depression and amend them with therapists' collaboration; 20 sessions/30 wks
  - Psychoanalytic: close and detailed observation of relationship between youth and therapist to help promote self-understanding of feelings and difficulties; 28 sessions/30 wks
- Mood and Feelings Questionnaire, Revised Children's Manifest Anxiety Scale, Leyton Obsessional Inventory, Health of the Nation Outcome Scale, KSADS MDD

Goodyer et al., Lancet Psychiatry 2017

IMPACT
3 therapy interventions equally effective in MDD treatment

~ 20% taking SSRIs prior to therapy; ~ 40% had used SSRIs at any time
Over the course of the 86 week trial; no difference by therapy type



Goodyer et al., Lancet Psychiatry, 2017

Which Psychotherapies Work? A Systematic Review and Network Meta-Analysis

- Many RCTs:
  - IPT and CBT are significantly better than control conditions
    - At post-treatment and follow-up.
  - IPT and CBT were significantly more effective than play therapy at post-treatment;
  - IPT and CBT are more effective than problem-solving therapy at follow-up.
  - Psychodynamic Therapy and Play Therapy
    - No better than waitlist in reducing depression symptoms at post-treatment and follow-up.

Zhou, et al. *World Psychiatry.* 2015;14:207-222.

Other treatments

- **Family therapy:** Evidence-based psychosocial treatments for child and adolescent depression [2]
- **School-based therapy:** some efficacy for school-based prevention and early intervention programs for depression [3]
- **E-Therapy:** internet-based prevention and treatment programs for anxiety and depression in children and adolescents has promise [4]

2 David-Ferdon, Kaslow. *J Clin Child Adolesc Psychol.* 2008;37(1):62-104.
3 Calear, Christensen. *J Adolesc.* 2010;33(3):429-438.
4 Pennant, et al. *Behavior Research and Therapy*. 2015;67:1-18..

Large-Scale Controlled MDD Treatment Studies

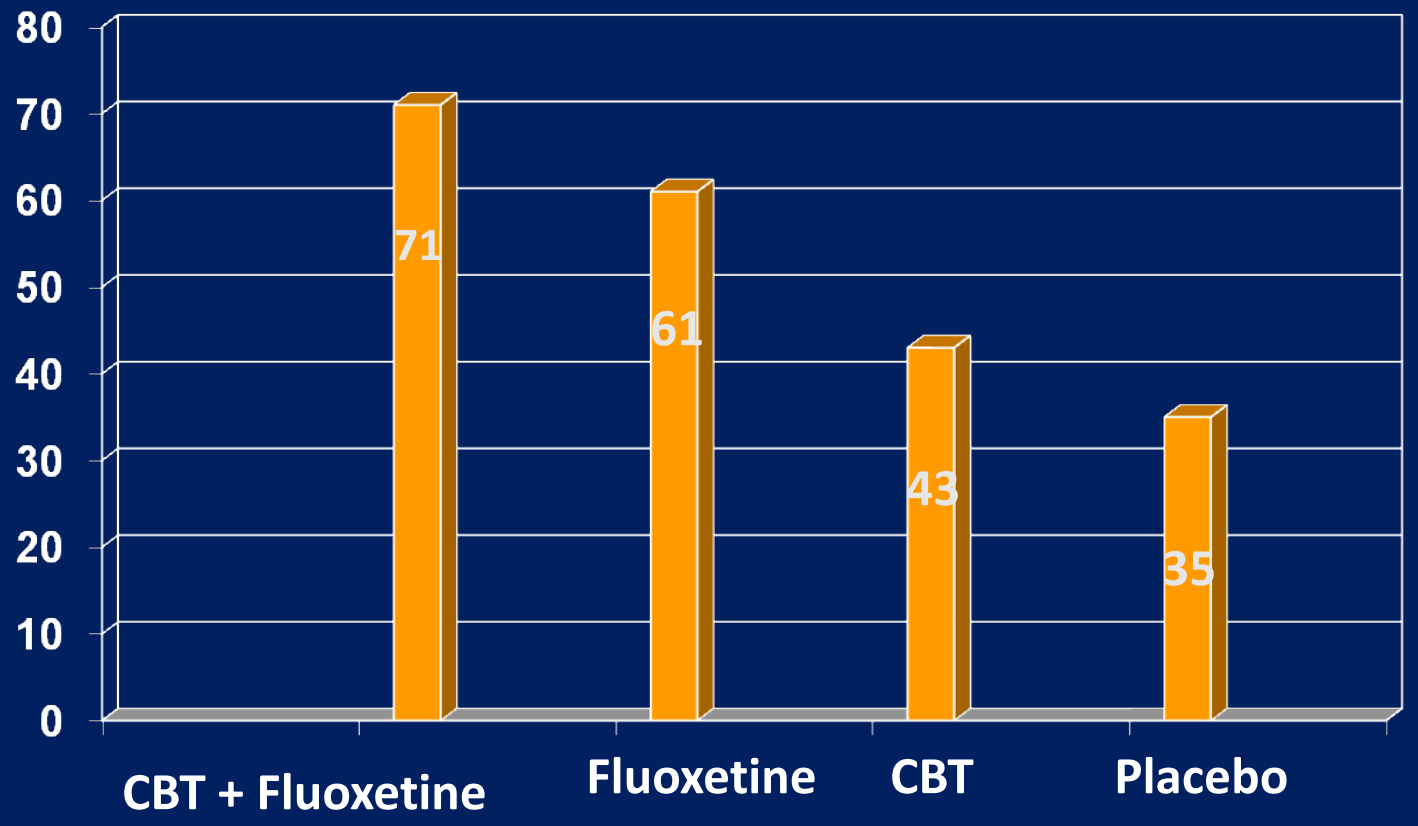
TADS: Treatment of Adolescent Depression

- Fluox +CBT>Fluox>CBT>PBO acutely (12 weeks)
- Medication effect by 4 weeks
- Open treatment phase: response ~80% by 36 weeks (mean duration of a depressive episode is about 36 weeks) – treatment arm didn't matter

- **ADAPT: Adolescent Depression Antidepressant Psychotherapy Trial** (28 weeks)
  - Brief CBT didn't add anything to fluoxetine
  - ~60% responded by 28 weeks; 80% by a year
  - British sample was sicker than TADS (47% vs. 27% suicidal; CGAS 41 vs. 50)

[1]March, et al. *JAMA.* 2004.
[2]Goodyer, et al. *BMJ.* 2007.

Treatment of Adolescent Depression Study (TADS)
Acute 12-week



>>>At week 36 no differences between CBT + FLX, FLX and CBT)

TEAM group, Arch Gen Psychiatry 2007; Kennard et al., AJP, 2009

SSRIs- Randomized Controlled Trials

Medication	Study	Dosage	Outcome	FDA approval
Citalopram	Wagner et al. 2004	20–40 mg/day	Citalopram > placebo	No
	von Knorring et al. 2006	10–40 mg/day	Did not separate from placebo	
Escitalopram	Wagner et al. 2006	10–20 mg/day	Did not separate from placebo escitalopram > placebo in adolescents	Yes; MDD ages 12–17 years
	Emslie et al. 2009	10–20 mg/day	Escitalopram > placebo	
Fluoxetine	Emslie et al. 1997	20 mg/day	Fluoxetine > placebo	Yes; MDD ages 8–18 years
	Emslie et al. 2002	20 mg/day	Fluoxetine > placebo	
	March et al. 2004	10–40 mg/day	Fluoxetine > placebo	

Birmaher B. Major Depression- -Clinical Manual of Child and Adolescents Psychopharmacology Edited by McVoy and Findling -American Psychiatric Publishing, 2nd edition , 2013

SSRIs Randomized Controlled Trials (Cont')

Medication	Study	Dose		FDA approval
Paroxetine	Keller et al. 2001	20–40 mg/day	Paroxetine > placebo	No
	Berard et al. 2006	20–40 mg/day	Did not separate from placebo	
	Emslie et al. 2006	10–50 mg/day	Did not separate from placebo	
Sertraline	Wagner et al. 2003[a]	50–200 mg/day	Sertraline > placebo	No
	Donnelly et al. 2006	50–200 mg/day	Did not separate from placebo in children; sertraline > placebo in adolescents	
Duloxetine	Emslie et. al 2014	30-60 mg/day	Did not separate from placebo in children; Also no separation between fluoxetine (20mg/day) and placebo	No No No
Duloxetine	Atkinson et al., 2014	30-120 mg/day	Did not separate from placebo in adolescents; Also no separation between fluoxetine (20-40mg /day) and placebo	
Venlafaxine *	Mandoki et al. 1997	Children: 37.5 mg/day Adolescents: 75 mg/day	Did not separate from placebo in children adolescents (Small sample- very low dosages)	
Desvenlafaxine	Clinicaltrials.gov	weight based dosing 35 mg/day w	Desvenlafaxine and fluoxetine not different from placebo	

[a] Data pooled from two controlled trials

• an unpublished study was also negative, but a reanalysis showed that was only positive for adolescents(cited by Bridge et al., 2009)

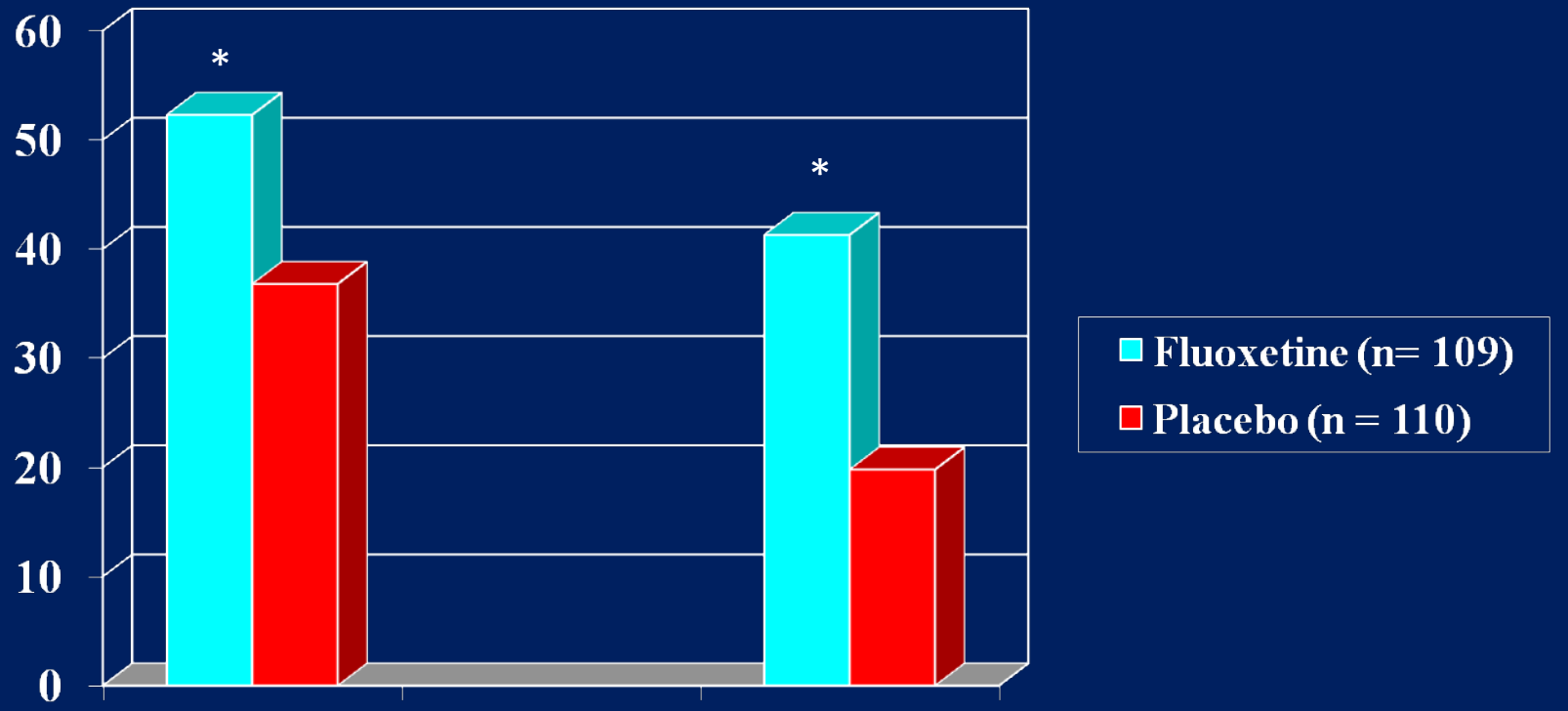
Acute Treatment of MDD
Selective Serotonin Reuptake Inhibitors (SSRIs)

Overall Response in Adolescents:
Antidepressants ~ 40% -70% vs. placebo ~30% to 60% (most studies: adolescents)

- The goal is to achieve **Remission**
  - Children's Depression Rating Scale-Revised-CDRS-R ≤ 28.
  - **Current remission rates reported between: 30% - 40%**

Bridge et al., JAMA, 2007

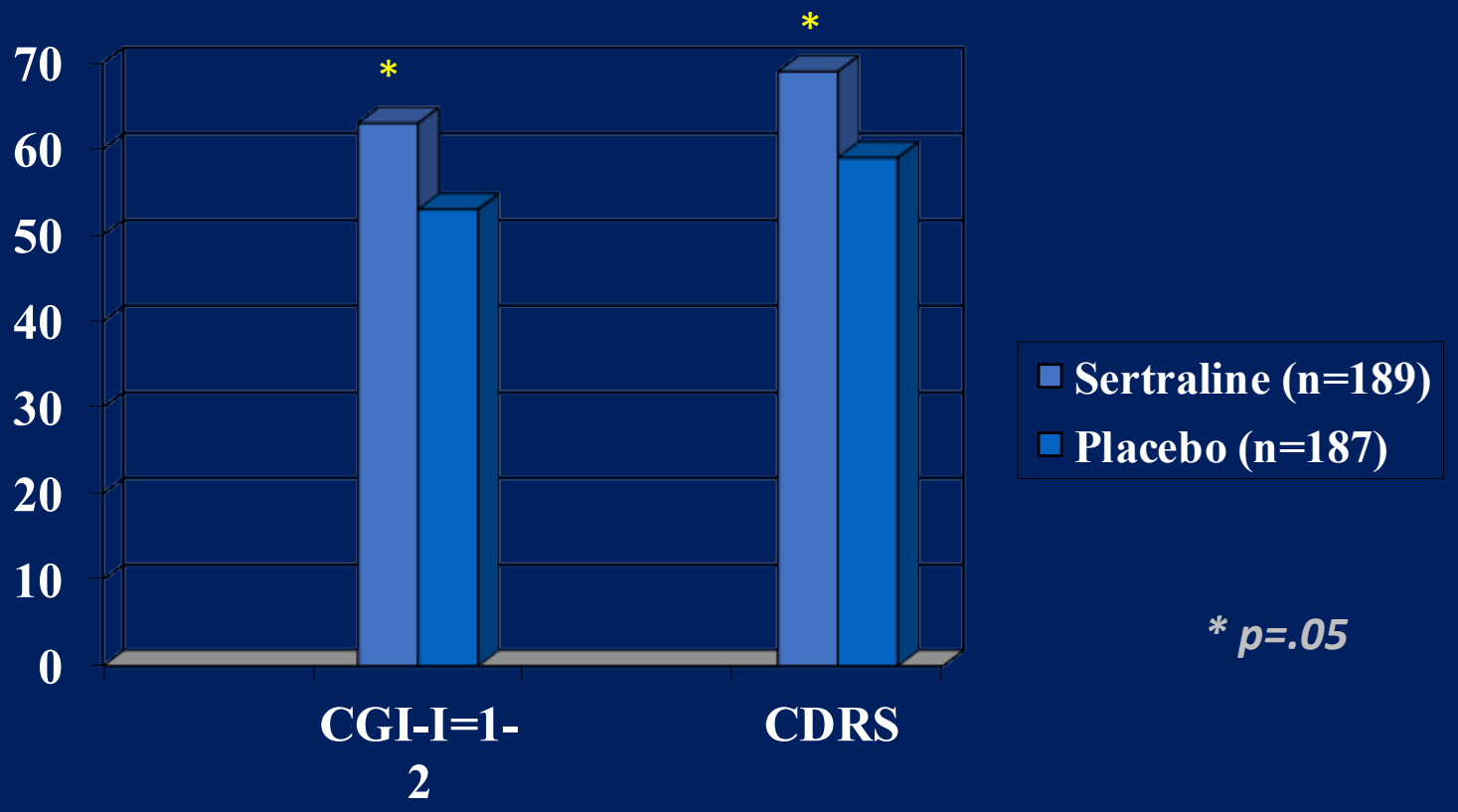
Fluoxetine (20 mg) vs. Placebo for Children and Adolescents- Study #2 (8 weeks) (Multicenter)



* $P_s < 0.05$

Emslie et al., 2002

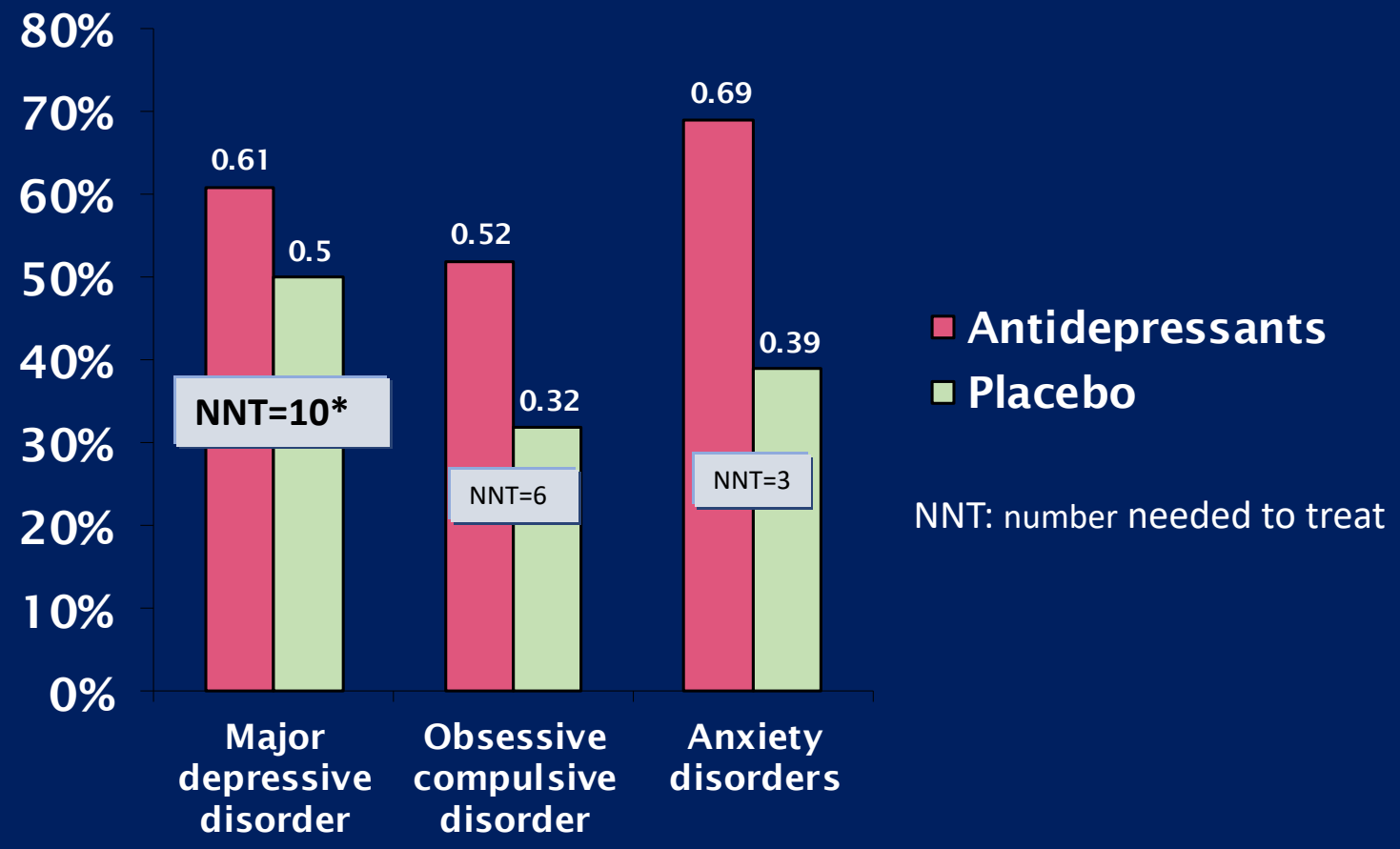
Sertraline (50-200 mg): Depressed Children & Adolescents (10 weeks) Multicenter



*At least 40% decrease in CDRS

Wagner et al., 2003

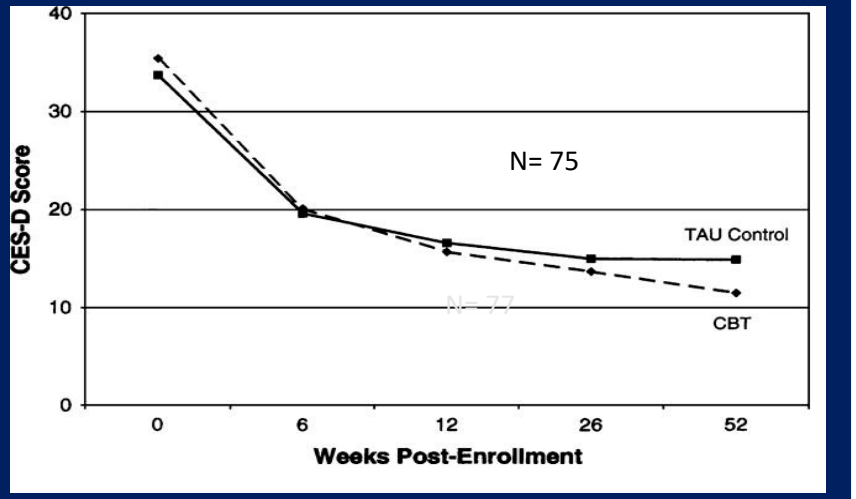
Summary of the acute effects of the SSRIs: MDD, anxiety and OCD



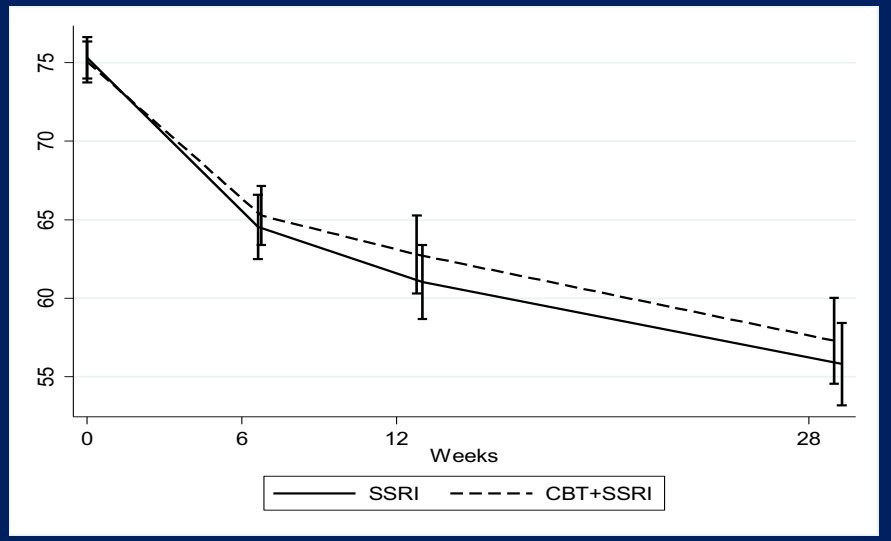
- *MDD NNT ONLY NIMH STUDIES: 3
- Negative vs. Failed Trials (Walkup 2017)

Bridge et al., *JAMA*, 2007

Other studies did not show symptomatic benefit of combined treatment vs. pharmacotherapy- (Meta-analyses: Dubicka et al., Br J of Psychiatry 2010:197:433)



TAU: treatment as usual
Clarke et al., JAACAP 44:888-898, 2005



Adolescent Depression Antidepressant and Psychotherapy Trial (ADAPT)
SSRI: fluoxetine
Goodyer, Harrington, et al., BJM 2008

However: SSRI's
increases remission
Prevent recurrences
Lowers suicidality
Improves psychosocial functioning, awareness, copying, social skills, and adherence

Dosing:
In Adults, Meta-Analysis → Higher Dose BETTER but Too High causes Drop Put

Compared to placebo

Imipramine equivalents	OR prescription response	NNT	OR for AEs	NNH dropout
Medium 200mg-250mg	2.72	4	3.16	10

Sertraline	240-300mg
Fluvoxamine	200 -250 mg
Fluoxetine	40-50 mg
Citalopram	[40mg]
Escitalopram	30-40 mg

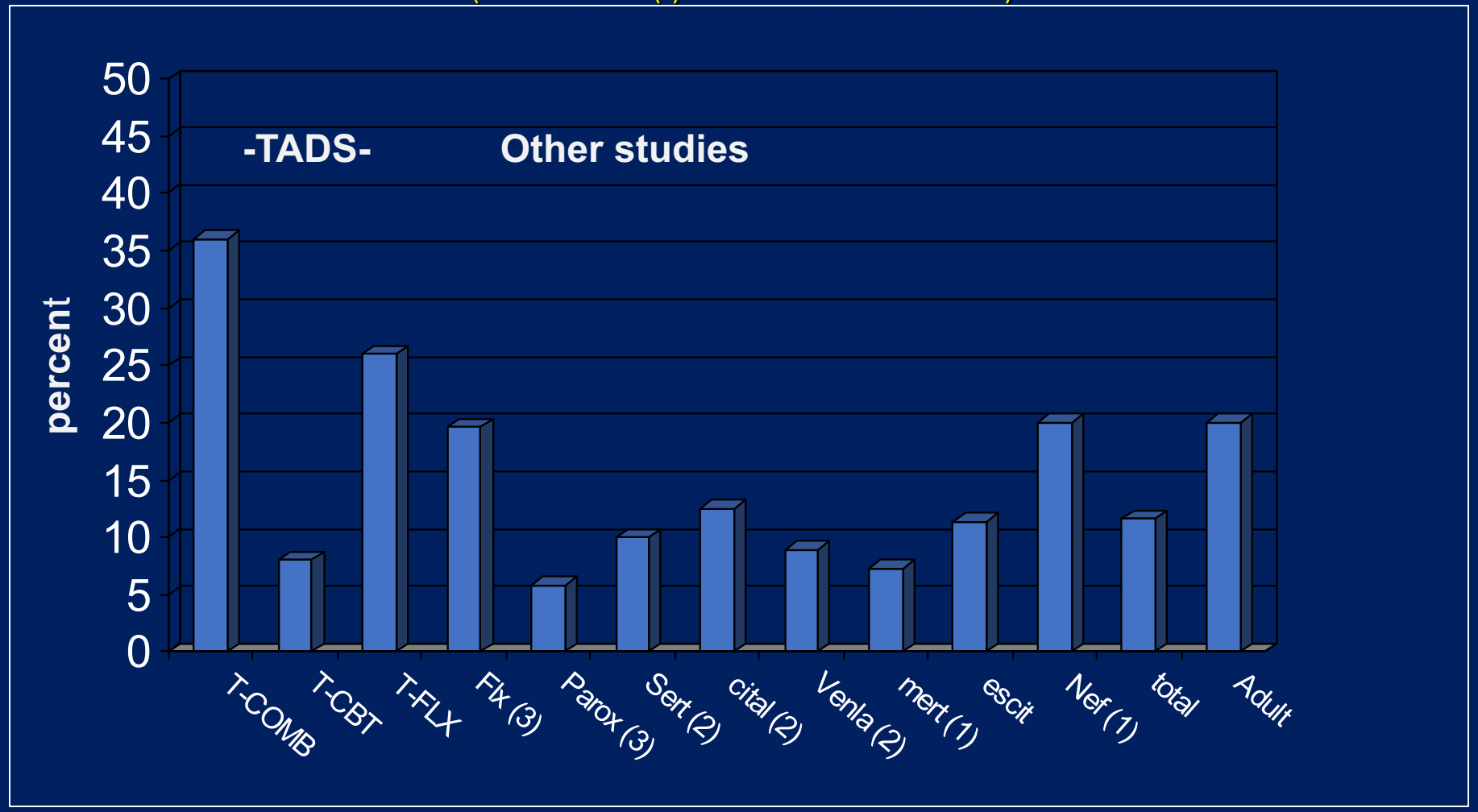
Jakubovski, et al. *Am J Psychiatry, 2016.*
Rector et al., Am J Psychiatry, 2016

Absolute Benefit Increase Attributable to Antidepressants

(using various response outcomes)

(difference between percent responded and placebo response)

(number in ( ) = number of studies)

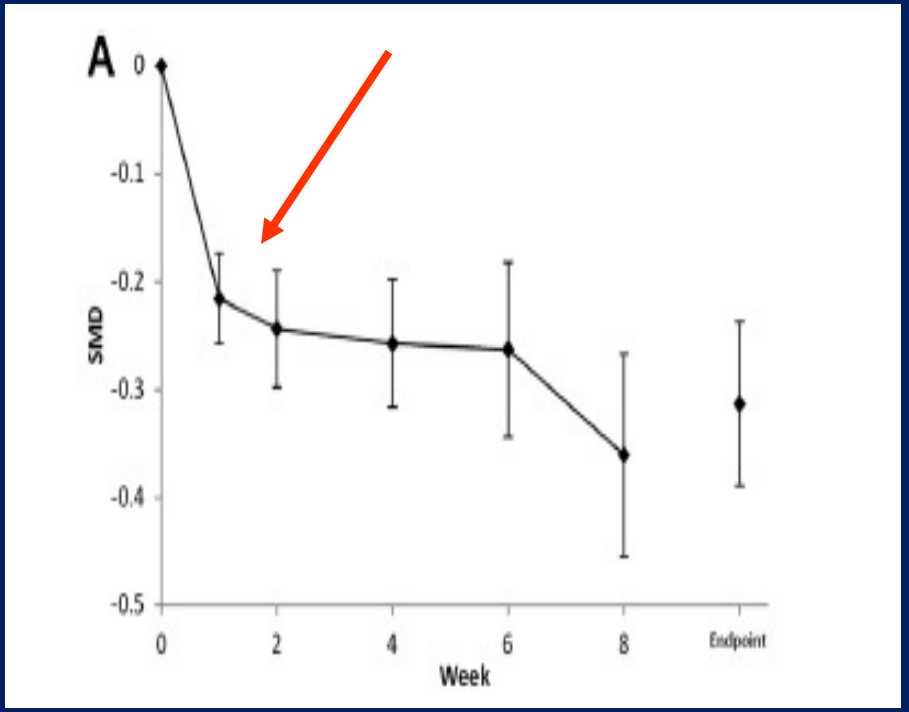


Bridge, Ann Med, 2005

When is SSRI Response First Evident?

- Meta analysis of 13 trials from 1997-2014
- **69% of improvement compared to placebo observed by week 2**
- Age, dose, SSRI type didn't matter
- More recent publications show higher placebo response

SSRI response on MDD ratings



Standardized mean differences between SSRI and placebo over time

Varigonda, et al. *JAACAP.* 2015.

SSRIs: Half-Lives

Drug	Half-Life	Developmental Effect
Fluoxetine	4-6 days	Higher levels in children than adults
Paroxetine	11 hours	But non-linear, may be “overdosing”
Sertraline	15.3-20.4 hours	Non-linear, lower than in adults
(Es)Citalopram	16.4-19.2 hours	Lower than in adults
Venlafaxine	9-13 hours	Lower than in adults
Nefazadone	3.9 vs. 7 hours	Lower than in adults

SSRI Side Effects

Common

- Gastrointestinal
- Sleep ↓↑
- Fatigue
- Nightmares
- Sexual ↓
- Weight ↓↑
- Sweating ↑
- 3%-8% agitation, hyper, silly, manic-like behaviors (vs. bipolar)
- Interactions with other medicines

RARE

- Easy Bruising
- Serotonin Syndrome
- Suicidal Ideation/Attempts

Activation in SSRIs

- Rates vary considerably (6% to 48%);
  - Depends on what you call activation
  - the more systematic the study, the lower the rates
  - Higher in children than adults
  - Higher in immature brains (ADHD, autism) than typically developing children
  - Might have diagnostic significance in kids at risk for bipolar disorder
  - The distinction between activation and true mania is that activation goes away when you stop the drug

Bridges. *Ann Med*. 2005.

SSRI-induced suicidality

Black Box Warning

- **Medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects**

Examples:

- all antidepressant medications warn they may result in increased risk of suicidal tendencies in children and adolescents.
- warfarin, due to the risk of bleeding to death
- fluoroquinolones, due to the risk of tendon ruptures

etc

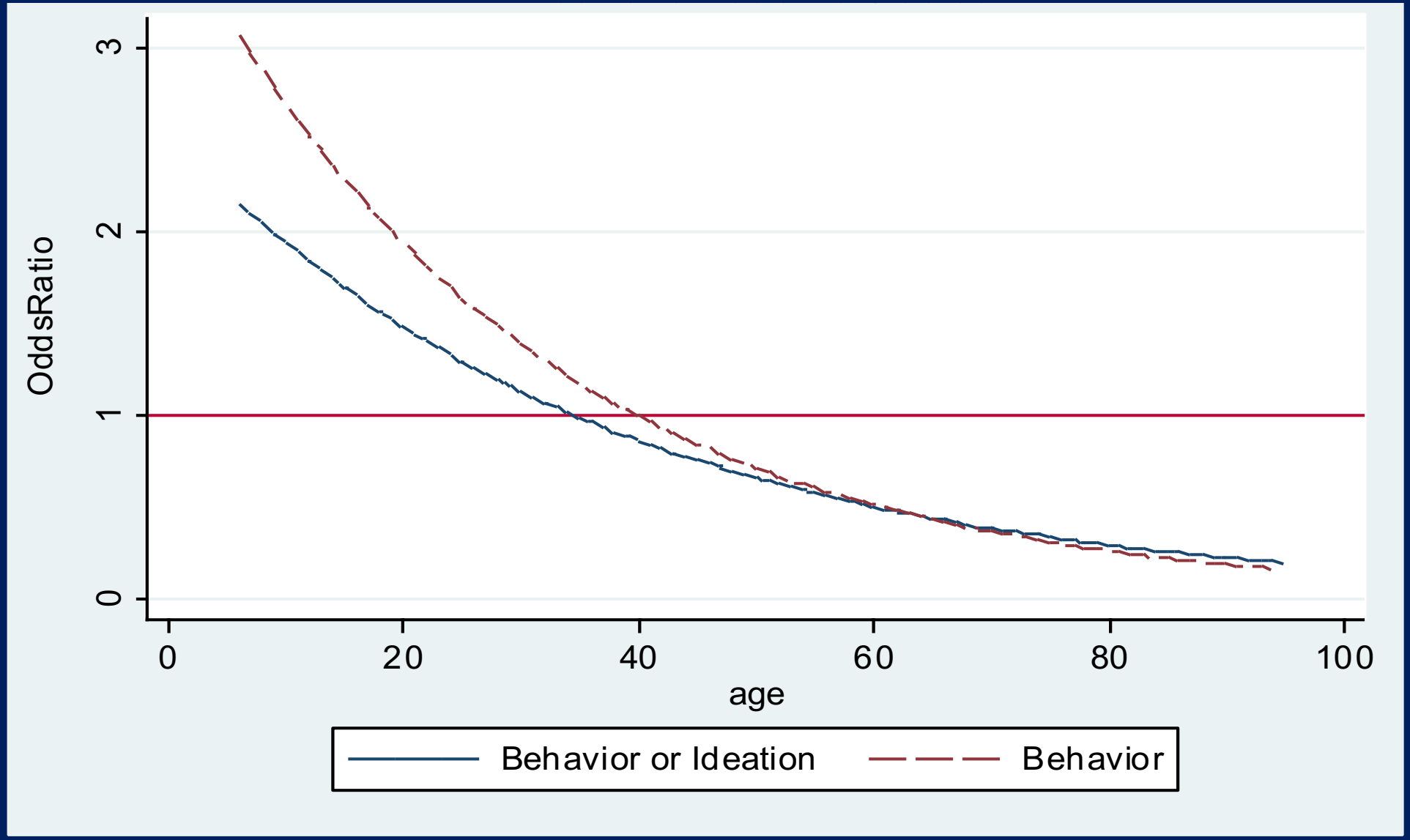
Impact of Black Box Warning on Clinical Practice

- Rates of diagnosis of depression in children made by general practitioners and pediatricians have decreased significantly[1]
- Significant decreases in overall prescription of antidepressants to children, adolescents, young adults, and middle-aged adult range[2]
- Rate of suicide in children has been steadily decreasing since the late 1980s, which may be related to the availability of new antidepressant medications[3]
- Largest increases in youth suicide rates (2004-2005) since black box warnings[2,3]
- Suicide rate has continued to decline steadily and consistently in people 60+ years of age since these warnings in antidepressant medications[3]

1. Libby AM, et al. *Am J Psychiatry*. 2007;164:884-891.
2. Gibbons RD, et al. *Am J Psychiatry*. 2007;164:1356-1363.
3. Bridge JA, et al. *JAMA*. 2009;300:1025-1026.

Medscape

Suicidality Risk With Drug Treatment by Age
Adult and Pediatric Studies



Debate about Suicide and the Use of SSRIs in Youth

From the “ spontaneous adverse events” analyses:

Estimated 1-3/100 on antidepressants

Onset/ or worsening of suicidality

Withdrawal Syndrome

- Result of abruptly stopping SSRI / SNRI
- No so much with fluoxetine
- Flu-like symptoms – malaise, GI distress, dizziness, anxiety, dysphoria
- Taper gradually, warn patient about possibility

Antidepressants with varying efficacy from DBPC Trials

- **Fluoxetine** (Prozac): 3 studies (including TADS); **(NNT-5)**
- **Duloxetine – failed trial**
- **Atomoxetine – failed trial**
- **Sertraline** (Zoloft): combined study **(NNT-10)**
- **Citalopram** (Celexa): positive, 1 negative, study
- **Paroxetine** (Paxil): 1 pretty positive, several negative
- **Venlafaxine/Desvenlafaxine** (Effexor/Pristiq): in teens not children or overall
- **Escitalopram** (Lexapro): in teens not children or overall, but with citalopram got approved
- **Bupropion** – open trials positive; never studied in RCTs and probably never will beBupropion: Open trials positive, never been studied with RCTs (not good for anxiety)
- **Atomoxetine**: Not effective
- **Nefazodone-Mirtazepine-Selegine**: Negative
- **Tricyclic antidepressants**: Not effective - In some cases may be helpful as augmenting agent. More side effects- may be lethal
- Omega-3 Fatty Acids: not likely to be effective

Cipriani et al., Network Meta-analysis, the Lancet, 2016

Newer Antidepressants (failed trials)

	CDRS change score				CGI-improvement %	
	Drug		Placebo		Drug	Placebo
Selegeline patch	**56.7**	**35.4**	**57.9**	**36.4**	58.6	59.3
Duloxetine 30mg Duloxetine 60mg	**59.8** **59.3**	35.2 35.4	**PI-58.2** **FI-57.9**	36.6 35.3		
Desvenlafaxine-L Desvenlafaxine-H	**58.5** **58.45**	34.8 34.08	**57.28**	34.38	56.2 62.3	55.9
Vilazodone-15mg Vilazodone-30mg	**57.8** **56.8**	33.8 32.5	**57.5**	34.0	56.3 62.2	54.1

Delbello MP et al, *J Child Adol Psychopharm.* 2014; 24:1-7;Atkinson SD et al. *JCAP*. 2018;28(1),55-65. Emslie GJ et al. *J Child and Adol Psychopharm*. 2014; Durgam, S. et al., *Pediatric Drugs*. 2018;20,353-363

Reasons for Modest Response Rate

- High placebo response rates; rates children > teens > adults
- Increasing placebo response with year of study. Walsh. 2003.
- Pharmacokinetics differ in young people so dosing may not have always been accurate.
- In MDD trials, decrease in the magnitude of antidepressant treatment effects as the number of study sites increased.
- In 9 of 15 MDD trials less efficacy with longer duration of illness.
- Some think that higher rate of child BP decreases response rate but lithium treatment in putatively bipolar depressed children had no effect.
- Duration of trials aren't long enough.
- Depression may be epiphenomenon of primary disorder
- Drugs just aren't effective enough.

Treatment Resistant Depression

Indicators of Poor Response

- Severe depression
- ↓ expectations to treatment benefits
- < 50% symptom improvement during the first 4-weeks of treatment
- ↓ Coping skills
- ↑ Comorbid disorders
- ↓ Adherence to treatment
- ↓ Socio-economical Status
- ↑ Family conflict and dysfunction
- ↑ Exposure to negative events (e.g., abuse)
- Parental depression

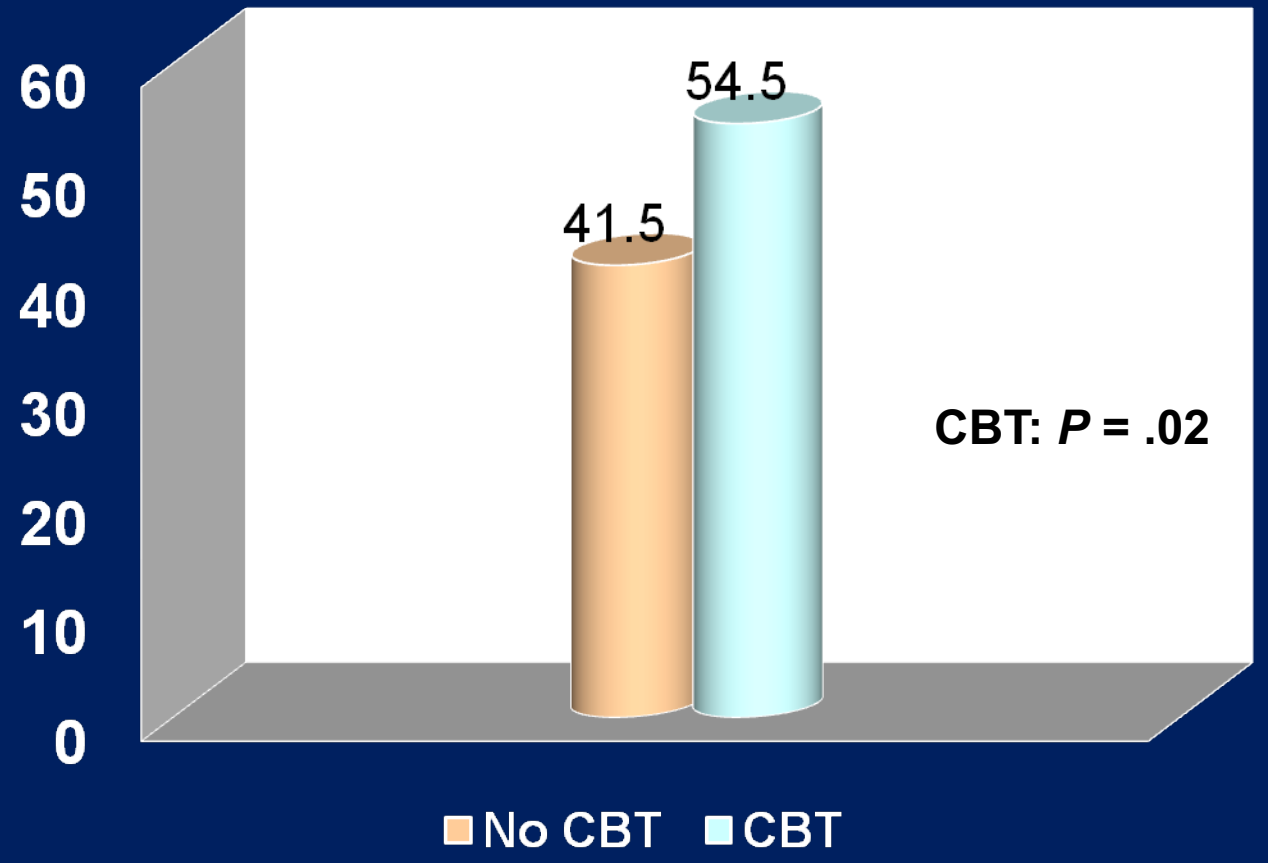
TORDIA: Treatment of Resistant Depression in Adolescence

- What if first SSRI doesn't work (8 weeks of treatment)?
  - **Increase the dose** (at least to 40mg fluox or 225mg of venlafaxine
  - **CBT** + drug (either one) worked better than either drug alone (54.8% vs. 40.5% response)
    - At least 9 CBT sessions; problem solving and social skills most helpful
  - No response difference in SSRI vs. SNRI
  - Although the efficacy of venlafaxine was similar to that of the SSRI's, its use was associated with more side effects
  - Higher plasma concentrations, associated with higher doses, appeared to be associated with better response

[1]Brent, et al. *JAMA*. 2008;299:901-913.
[2]Cheung. *JCAP.* 2008.
Sakolsky, et al. 2011.
Kennard et al., 2009

Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)

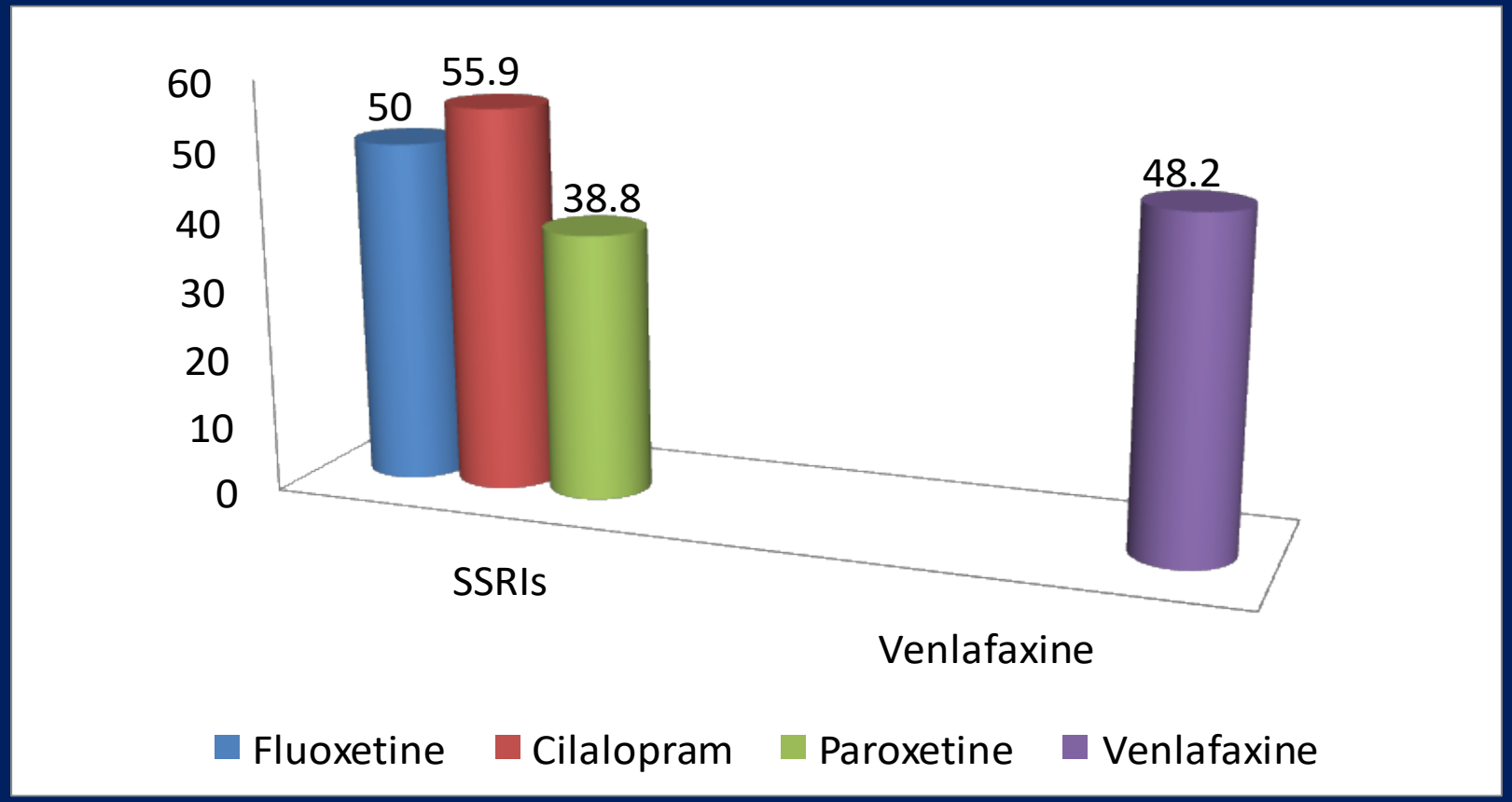
Antidepressants + CBT > Antidepressants without CBT
Long-term up to 60% remitted



Brent et al., JAMA, 2008; Vitiello JCP, 2011

Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)

40%-56% of adolescents who did not respond to one SSRI responded to a second antidepressant (no significant different among antidepressants)



Adequate clinical response: CGI-I $\leq$ 2 *and* an improvement in the CDRS-R $\geq$ 50%

Brent et al., JAMA, 2008

What about Inadequate Responders?

- Recheck the diagnosis
- Inadequate treatment (meds, therapy, dose, duration)
- Non-adherence
- Pharmacodynamic/pharmakokinetic factors
- Side effects
- Co-occurring psychiatric/med conditions stressors, abuse, conflicts, parental psychopathology, school issues
- Clarify what has not responded: depression, subsyndromal mania, ADHD, anxiety?
- Poor fit between patient and therapist

Dosages of antidepressants usually used for Treatment of youth with MDD

Medication group	Medication	Starting dosage (mg/day)*	Dosage range (mg/day)*
SSRIs	Citalopram	10	20–40[a]
	Escitalopram	10	10–40
	Fluoxetine	10	20–80
	Fluvoxamine	25	50–150
	Paroxetine	10	20–60
	Sertraline	25	50–300
SNRIs	Venlafaxine XR Duloxetine	37.5 20	75–375 60- 120
Others	Bupropion SR Bupropion XL	100 150	150–450 150–450

SNRI = serotonin-norepinephrine reuptake inhibitor; SR = sustained release; SSRI = selective serotonin reuptake inhibitor; XL = extended release; XR = extended release.

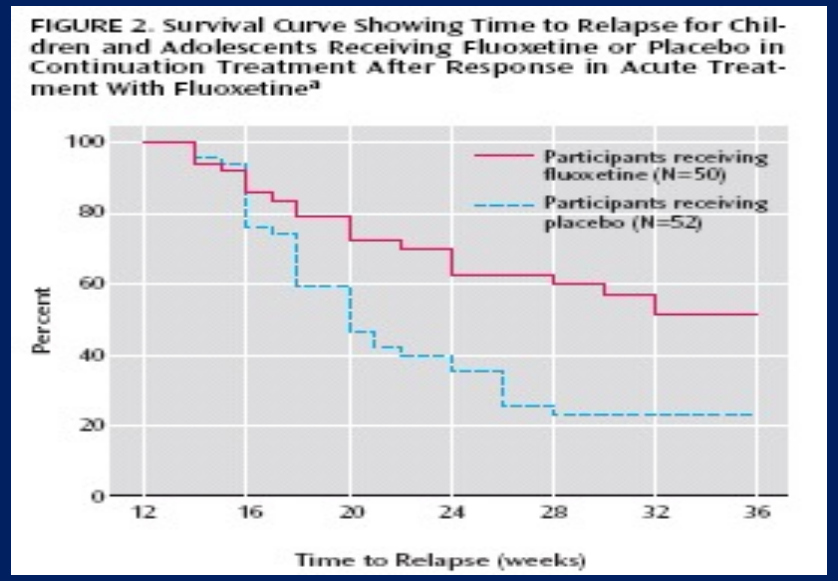
[A] Dose adjusted by U.S. Food and Drug Administration recently because of concerns about QT prolongation.

*In children consider using lower dosages

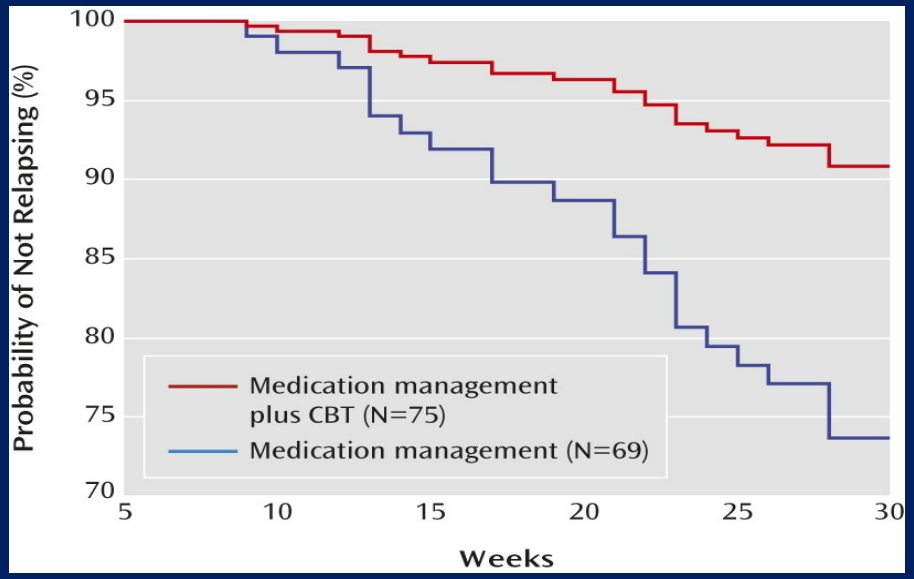
ONLY fluoxetine (ages 8-18) and Escitalopram (ages 12-17) have FDA approval

Continuation Treatment

Need for Continuation Treatment to Avoid Relapses



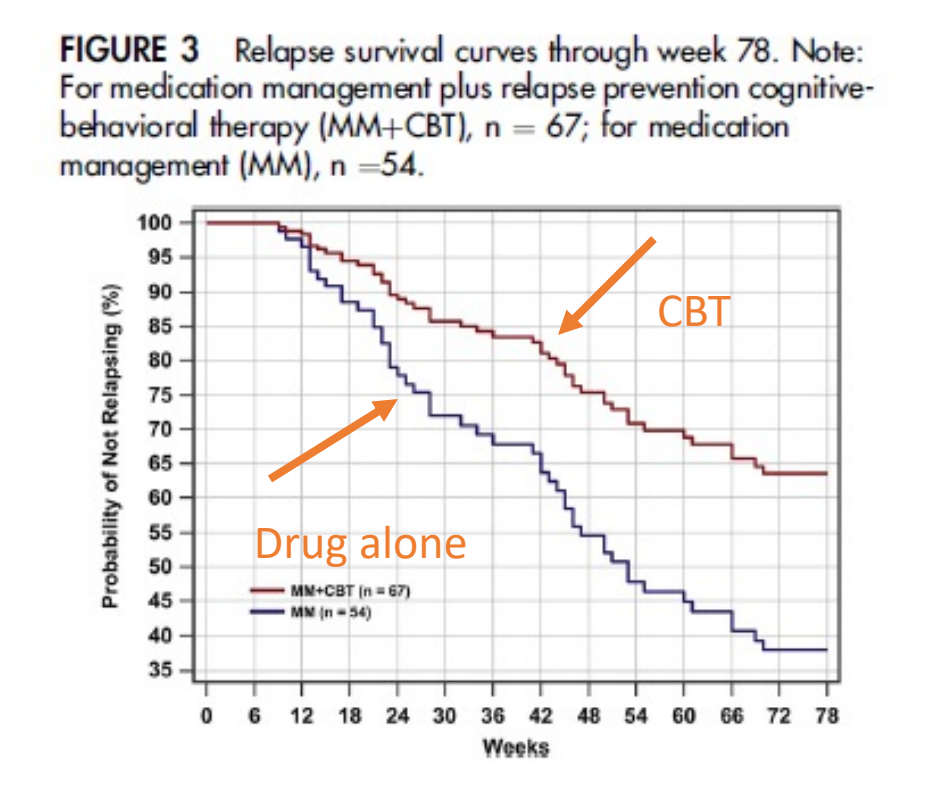
Emslie et al., AJP, 2008



Kennard et al., AJP,2014

CBT decreases relapse

- Fluoxetine treatment for 6 weeks; responders randomized to continued Fluox or Fluox + CBT
- Time to remission the same; lower relapse rate with combined Fluox + CBT



Estimate of relapse by 78 weeks

36% with Fluox + CBT
62% with Fluox only

Mean time to relapse:
Fluox + CBT 64.4 weeks
Fluox only 50.9 weeks

Emslie, et al. *JAACAP.* 2015.

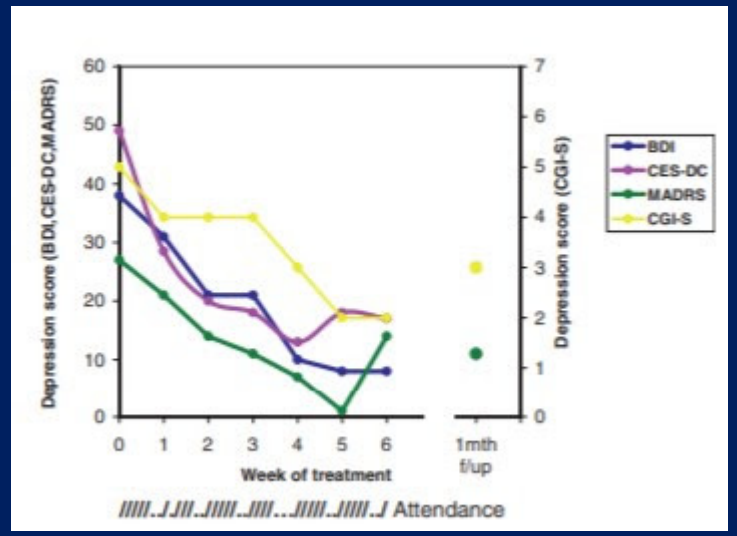
rTMS: Significant improvements observed adolescents with depression

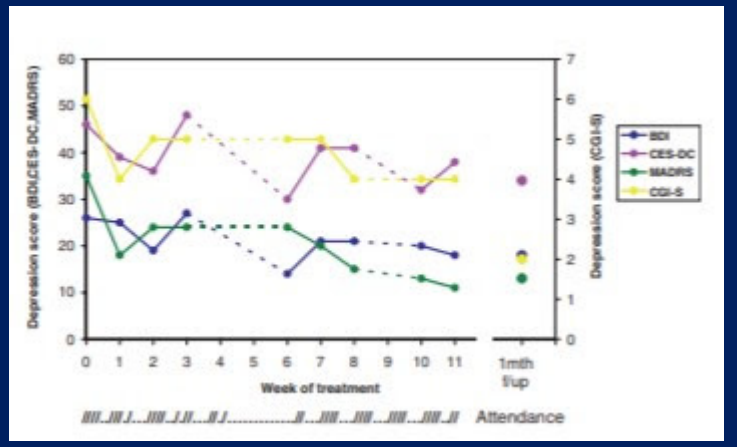
Table 1: Cognitive testing results over the treatment period: subjects 1 and 2

	Subject 1			Subject 2		
	Baseline	*Post TMS 20*	*End treatment*	*Baseline*	*Post TMS 20*	*End treatment*
RAVLT						
Total recall	71	66	66	56	59	60
Immediate recall	15	15	15	12	14	14
Delayed recall	12	15	14	11	13	14
Recognition	13	15	15	15	15	15
Learning slope	2	6	3	6	6	7
Retention	3	0	1	1	1	0
TMT						
A (second)	38	29	28	47	28	24
B (second)	53	61	36	71	44	65
Digit Span						
Forwards	7	10	9	8	6	9
Backwards	5	6	10	7	9	8
Total	12	16	19	15	15	17
Digit Symbol						
Total	67	74	71	74	73	79
COWAT						
Letter	30	39	35	44	39	48
Category	25	14	18	25	23	28

COWAT, Controlled Oral Word Association Test; RAVLT, Rey Auditory Verbal Learning Task; TMS, transcranial magnetic stimulation, TMT, Trail Making Test.

Cognitive test performances of subject 1 and 2 at 3 timepoints.





Results of subject 1 (above) and subject 2 (left) on BDI, CES-DC, CGI-S, and MADRS pre- and post- rTMS[4]

Ketamine in Adolescents

- Literature Lacking
- Systematic Review
  - Kim, et. al., (2021) Eur Child & Adol Psychiatry. 30:1485-1501
  - 4 identified papers
  - 3 did not meet criteria
  - Generally
    - Improve depressive symptoms
    - Decrease acute suicidality
    - Reduce mood lability
    - Not all patients responded
    - Duration of effect and long-term safety not established

Summary

- Depressive disorders are common in childhood and adolescence and have significant morbidity.
  - Don’t miss the diagnosis.
  - Ask for 2nd opinion when diagnosis is unclear.
- Benefit of most antidepressants in children and adolescents for depression (except for fluoxetine) is often modest.
- Be on the alert for potential side effects (including uncommon ones such as suicidal behavior and activation). Be open about risks and benefits with parents.
- For non-medical therapists, child psychiatry involvement should occur at the beginning even if medications aren’t used. Don’t wait until prolonged psychotherapy has failed.
- Involving educators is critical: accommodations, placement, education of teachers regarding depression in youth.
- We are a long way from understanding etiology.

Acute Treatment of MDD Recommendations

- For a patient with:
  - Mild depression (perhaps moderate depressions)
  - Mild psychosocial impairment
  - Brief depression

- Begin with education, support, and case management related to possible environmental stressors in the family and school

- If after 4-6 weeks of treatment these patients do not respond offer more specific types of treatment

Acute Treatment of MDD Recommendations

- *If the patient has any of the following conditions psychotherapy alone may not be sufficient*
  - Severe Depression / ↑melancholic symptoms
  - Chronic Depression
  - Psychosis
  - Seasonal MDD
  - Patient, family, and/or therapist factors (e.g., lack of motivation, no expertise)

If Antidepressants are going to be prescribed

- How to choose the antidepressant?
  - Evidence-base
  - Anticipated side effects
  - Drug interactions
    Half-life
  - Prior response (patient and family)
  - Comorbidity
- Monitor side effects
- Carefully monitor for
  - Agitation, mania–like symptoms
  - Possible emergent or worsening of existing suicidality
  - Other Side effects
  - Withdrawal symptoms
  - Drug interactions
  - Adherence to treatment

Depression in Children & Adolescents

- Common
- Recurrent
- Painful (for patient and family)
- Debilitating
- Dangerous
- Treatable

Depressive Disorders in Children & Adolescents

Bennett L. Leventhal, MD
University of California San Francisco

22 October 2021