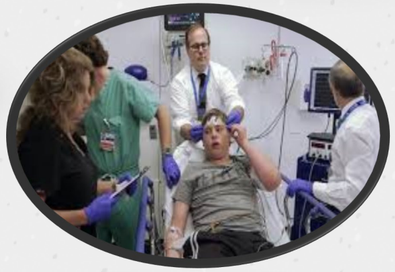
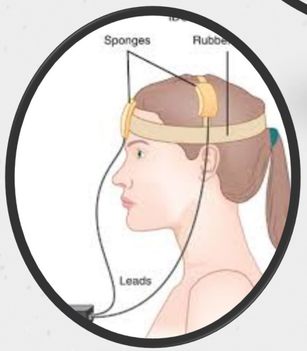
Management of Depression in Children & Adolescent

Elham Salari
Child & Adolescent Psychiatrist

What we'll look at today…





Child and Adolescent with MDD

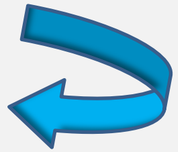
Psychotherapy

- Which type of psychotherapy
- How to deliver
- How long

Pharmacotherapy

- Which class of antidepressant/other drug
- Which dose
- Possible adverse effects & how to monitor and managed
- What duration

- Treatment-resistant Depression
- Treatment-Refractory Depression



Treatment Adolescents with Depression Study

- Major depression in adolescents:
- Prevalent,
- Of significant public health importance,
- Improvements in the treatment of adolescent depression should have both a strong public health impact
- An important economic impact.

- In this context and in accordance with parameters set forth in Request for Proposals (RFP) NIH-NIMH 98-DS-0008 titled “Effectiveness of Treatments for Adolescent Depression,” in 1999.

March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J; Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292(7):807-820.

Dr. March's life's work is dedicated to determining how best to treat young people with a range of serious mental illnesses.

Dr. March has been part of a group of people who have essentially built the current interventions evidence base over the last 20 years. He led and/or contributed to many large-scale, multiyear randomized clinical trials—such as MTA, POTS, CAMS and TADS— that constitute a body of hard evidence showing the impact of different treatments and treatment combinations upon young people.

John S. March, M.D., M.P.H.
Brain & Behavior Research Foundation

Treatment Adolescents with Depression Study

- TADS has made a major contribution to the knowledge base concerning the treatment of major depression in adolescents,
- with 45 articles published
- and another 30 plus articles either “in press” or “in preparation.”

Clinical Trial > JAMA. 2004 Aug 18;292(7):807-20. doi: 10.1001/jama.292.7.807.

Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial

John March [1], Susan Silva, Stephen Petrycki, John Curry, Karen Wells, John Fairbank, Barbara Burns, Marisa Domino, Steven McNulty, Benedetto Vitiello, Joanne Severe, Treatment for Adolescents With Depression Study (TADS) Team

Affiliations + expand

PMID: 15315995 DOI: 10.1001/jama.292.7.807

National Institute of Mental Health

National Institute of Mental Health

Journal of the American Academy of Child & Adolescent Psychiatry
Volume 42, Issue 5, May 2003, Pages 531-542

SPECIAL ARTICLE

Treatment for Adolescents With Depression Study (TADS): Rationale, Design, and Methods

THE TREATMENT FOR ADOLESCENTS WITH DEPRESSION STUDY TEAM

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Fluoxetine, Cognitive-Behavioral Therapy, and Their Combination for Adolescents With Depression

Treatment for Adolescents With Depression Study (TADS) Randomized Controlled Trial

The Treatment for Adolescents with Depression Study (TADS): Long-term effectiveness and safety outcomes

John S. March*, Susan Silva, Stephen Petrycki, John Curry, Karen Wells, John Fairbank, Barbara Burns, Marisa Domino, Steven McNulty, Benedetto Vitiello, Joanne Severe, Charles Casat, Jeanette Kolker, Karyn Riedal, Norah Feeny, Robert Findling, Sheridan Stull, Susan Baab, Elizabeth B. Weller, Michele Robins Show 30 others

*Corresponding author for this work

Psychiatry and Behavioral Sciences

cents With Depression Study (TADS): rationale, design, and methods. *J Am Acad Child Adolesc Psychiatry*. 2003;42(5):531-542.

urry JF, Wells KC. Striving for effectiveness in the treatment of ession: cognitive behavior therapy for multisite community intervention. *Cogn ehav Pract*. 2005;12(2):177-185.

Rogers GM, Reinecke MA, Curry JF. Case formulation in TADS CBT. *Cogn Behav Pract*. 2005;12(2):198-208.

Sweeney M, Robins M, Ruberu M, Jones J. African-American and Latino fa lies in TADS: recruitment and treatment considerations. *Cogn Behav Pract*. 20 12(2):221-229.

Treatment for Adolescents With Depression Study Team. The Treatment for Adolescents With Depression Study (TADS): demographic and clinical characteristics. *Psychiatry*. 2005;44(1):28-40.

March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J; Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination with depression: Treatment for Adolescents With Depression Study nized controlled trial. *JAMA*. 2004;292(7):807-820.

Journal of the American Academy of Child & Adolescent Psychiatry
Volume 45, Issue 12, December 2006, Pages 1404-1411

SPECIAL SECTION: TREATMENT FOR ADOLESCENTS WITH DEPRESSION STUDY-TADS

Remission and Residual Symptoms After Short-Term Treatment in the Treatment of Adolescents With Depression Study (TADS)

BETSY KENNARD Psy.D., SUSAN SILVA Ph.D., BENEDETTO VITIELLO M.D., JOHN CURRY Ph.D., CHRISTOPHER KRATOCHVIL M.D., ANNE SIMONS Ph.D., JENNIFER HUGHES B.A., NORAH FEENY Ph.D., ELIZABETH WELLER M.D., MICHAEL SWEENEY Ph.D., MARK REINECKE Ph.D., SANJEEV PATHAK M.D., GOLDA GINSBURG Ph.D., GRAHAM EMSLIE M.D., JOHN MARCH M.D. (THE TADS TEAM)

Journal of the American Academy of Child & Adolescent Psychiatry
Volume 45, Issue 12, December 2006, Pages 1427-1439

SPECIAL SECTION: TREATMENT FOR ADOLESCENTS WITH DEPRESSION STUDY-TADS

Predictors and Moderators of Acute Outcome in the Treatment for Adolescents With Depression Study (TADS)

NS Ph.D., SUSAN SILVA Ph.D., BENEDETTO EINECKE Ph.D., NORAH FEENY Ph.D., ELLER M.D., DAVID ROSENBERG M.D., INSBURG Ph.D., JOHN MARCH M.D. (THE

Reviews and Overviews

Clinical Messages From the Treatment for Adolescents With Depression Study (TADS)

Cognitive and Behavioral Practice
Volume 12, Issue 2, Spring 2005, Pages 209-220

Special Issue: Treatment For Adolescents With Depression

Parent involvement in CBT treatment of adolescent depression: Experiences in the treatment for adolescents with depression study (TADS)

Karen C. Wells, Anne Marie Albano

mons AD, Rohde P, Kennard BD, Robins M. Relapse and recurrence preve n in the Treatment for Adolescents With Depression Study. *Cogn Behav Prac* 005;12(2):240-251.

P, Feeny NC, Robins M. Characteristics and components of the TA ch. *Cogn Behav Pract*. 2005;12(2):186-197.

ratochvil CJ, Simons A, Vitiello B, Walkup J, Emslie G, Rosenberg D, M S. A multisite psychotherapy and medication trial for depressed adoles ackground and benefits. *Cogn Behav Pract*. 2005;12(2):159 oi:10.1016/S1077-7229(05)80021-5.

ennard BD, Ginsburg GS, Feeny NC, Sweeney M, Zagurski R. Implementat hallenges to TADS cognitive-behavioral therapy. *Cogn Behav Pract*. 20 2(2):230-239.

, Albano AM, Findling RL, Kratochvil C, Walkup J. Integrating c nitive behavioral therapy and pharmacotherapy in the treatment of adolesc depression. *Cogn Behav Pract*. 2005;12(2):252-262.

NIMH-funded effectiveness studies to evaluate “best practice” in the treatment of adolescents with depression

Psychotherapy

- More than 10 randomized controlled trials indicate that individual or group administered CBT is an effective treatment for depressed children and adolescents (Reinecke et al., 1998).
- In some studies, CBT has been associated with more rapid relief and proved more credible to parents than family or supportive psychotherapy (Brent et al., 1997).

Pharmacotherapy

- At the inception of TADS, the empirical literature on medication management of MDD in youth was far less persuasive than the literature favoring CBT.
- Apart from Emslie’s randomized controlled trial of fluoxetine (Emslie et al., 1997, 2000), which along with the lack of efficacy data for the tricyclic antidepressants (Birmaher et al., 1998) formed the empirical basis for the TADS pharmacotherapy condition,
- controlled data favoring medication management were largely lacking.

Treatment for Adolescents With Depression Study Team.. *J Am Acad Child Adolesc Psychiatry*. 2003;42(5):531-542.

NIMH-funded effectiveness studies to evaluate “best practice” in the treatment of adolescents with depression

Combined Psychotherapy & Pharmacotherapy

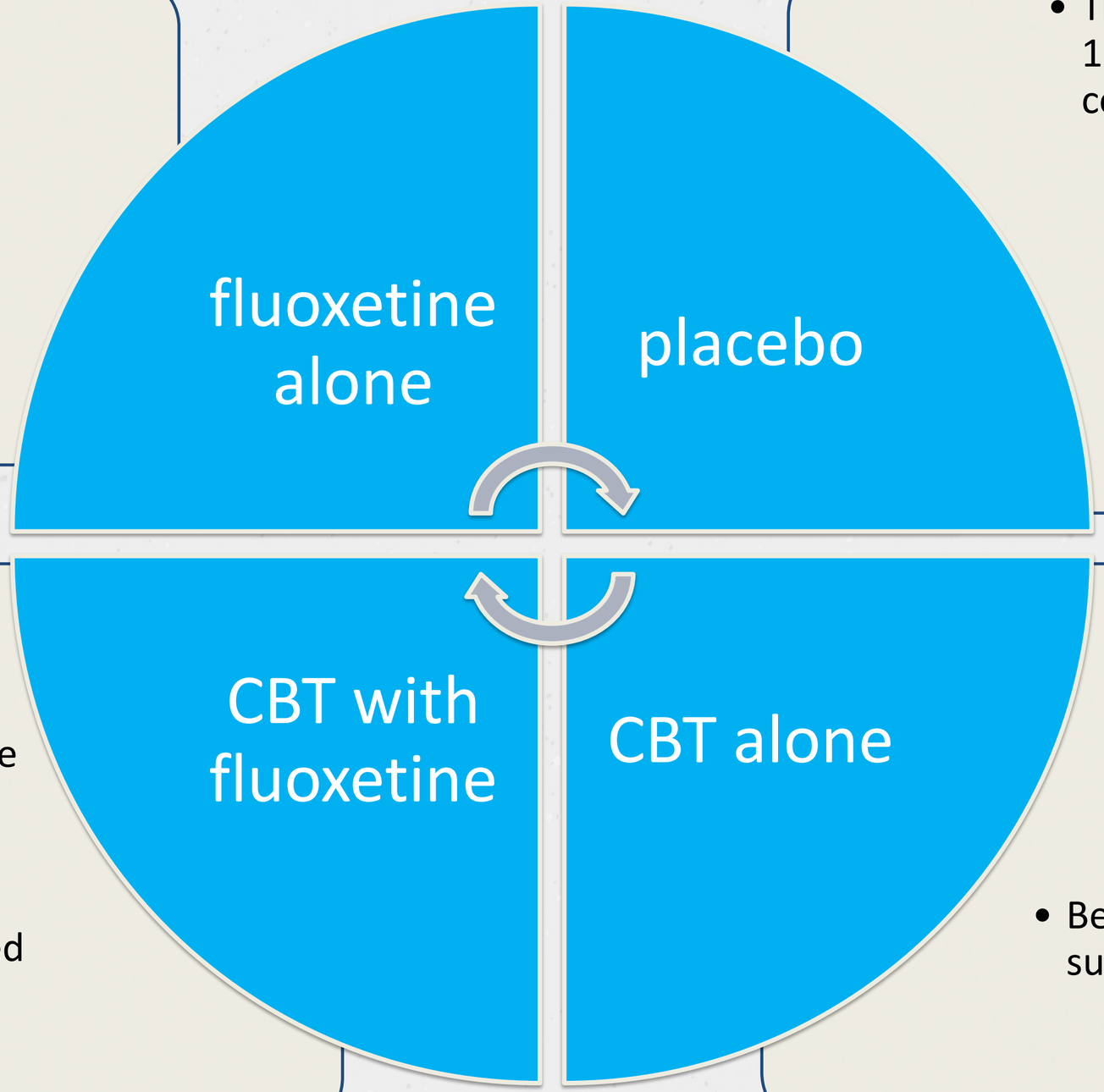
Placebo

- Given that response rates for both CBT and medication hover around 60% (e.g., 40% do not do well with either monotherapy) and that up to half of patients who respond relapse during the first year off treatment,
- expert clinicians often recommend combined treatment as the treatment of choice for MDD in the pediatric population

Treatment for Adolescents With Depression Study Team.. *J Am Acad Child Adolesc Psychiatry*. 2003;42(5):531-542.

- Randomized controlled trial of a volunteer sample of 439 patients between the ages of 12 to 17 years with a primary diagnosis of MDD.

- The trial was conducted at 13 US academic and community clinics.



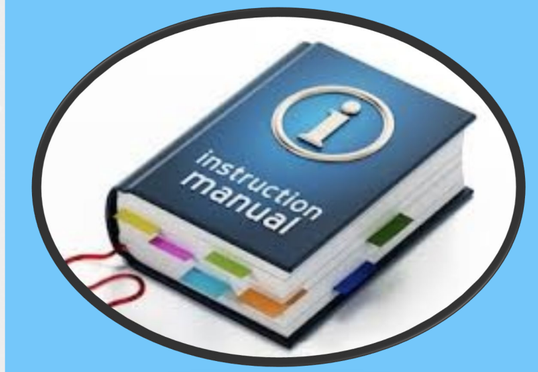
- Placebo and fluoxetine alone were administered double-blind;
- CBT alone and CBT with fluoxetine were administered unblinded.

- Between spring 2000 and summer 2003.

Treatment for Adolescents with Depression Study
Cognitive Behavior Therapy Manual

The required aspects of treatment (weeks 1–5) include psychoeducation about depression and its causes, goal-setting with the adolescent, mood-monitoring, increasing pleasant activities, social problem-solving, and cognitive restructuring.

Subsequently, modules chosen jointly by therapist and adolescent during weeks 6–12 address relevant social skills deficits of the individual teenager, such as problems in social engagement, communication, negotiation, compromise, or assertion.



https://tads.dcri.org/wp-content/uploads/2015/11/TADS_CBT.pdf

Stage 1

12 week stage I acute phase:

evaluate the short-term (0-12 weeks) effectiveness of

the 3 active treatments for adolescents with MDD

Stage 2

6-week stage II maintenance/consolidation Phase:

For partial respondersto FLX. advancing to 60 mg FLX as tolerated

For partial responders to CBT, weekly visits, which last 50 to 60 minutes (higher dose), are tailored to the patient's needs utilizing problem- specific individual or family modules

Stage 3

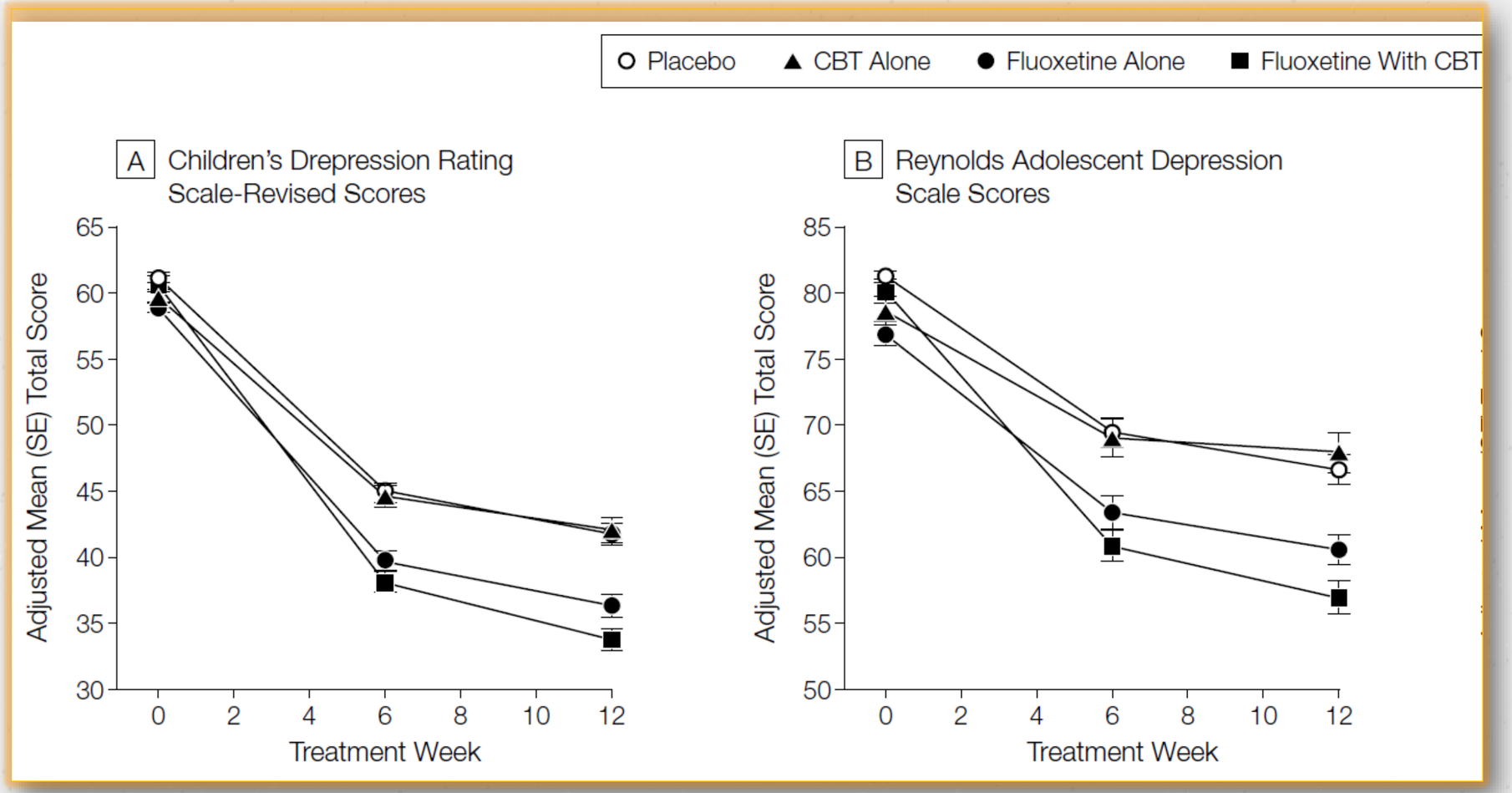
18 weeks of stage III maintenance:

Other than downward adjustment of the dose because of adverse events, no adjustments to the dosing regimen arrived at in stage II are permitted. Similarly, the stage III CBT every 6 weeks are intended as CBT booster sessions, with no provision for introducing new material.

→

Treatment for Adolescents With Depression Study Team.. *J Am Acad Child Adolesc Psychiatry*. 2003;42(5):531-542.

TADS Randomized Controlled Trial Results



March J et al. JAMA. 2004;292(7):807-820.

CBT Alone Arm of Study

- The 43% response rate for CBT alone in TADS is surprising given previous research showing that approximately 60% of depressed adolescents responded positively to CBT,
- Albeit CBT used in TADS was based on models previously shown to be efficacious.

- Regarding sample composition, patients receiving CBT alone appear to have had more severe and chronic depression and higher rates of comorbidity than participants in previous CBT trials and thus may have faired more poorly with treatment.

- CBT did show the specific effect of decreasing suicidality in both the CBT alone group and the CBT combined with fluoxetine group.

March J et al. JAMA. 2004;292(7):807-820

The Impact of Placebo Response Rates on Clinical Trial Outcome
A Systematic Review and Meta-Analysis of Antidepressants in Children and Adolescents with Major Depressive Disorder

- The results of meta-analysis showed that the overall placebo response rate was 48% (95% CI 44–52).
- The results showed that the lower the placebo response rate, the greater the efficacy difference between antidepressants and placebo.
- Previous metanalyses and many clinical trials indicate that antidepressants are minimally effective or equivalent to placebo

Yanfei Li et al, J Child Adolesc Psychopharmacol, 2019 Nov;29(9):712-720

Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents

- The within-placebo group analysis stratified by disorder yielded a large placebo response for studies of Depressive Disorders(g = 1.57; 95% CI, 1.36-1.78;P < .001), which was significantly larger (P < .001) than the placebo response in studies of Anxiety Disorders (g = 1.03; 95% CI, 0.84-1.21;P < .001).
- The moderate placebo response in the OCD group (g = 0.63; 95% CI, 0.47-0.79; P < .001) was significantly lower than in both the DD (P < .001) and AD (P = .002) groups.

Locher, C et al, JAMA, 2017 Oct 1;74(10):1011-1020

More Than Just a Sugar Pill
Why the placebo effect is

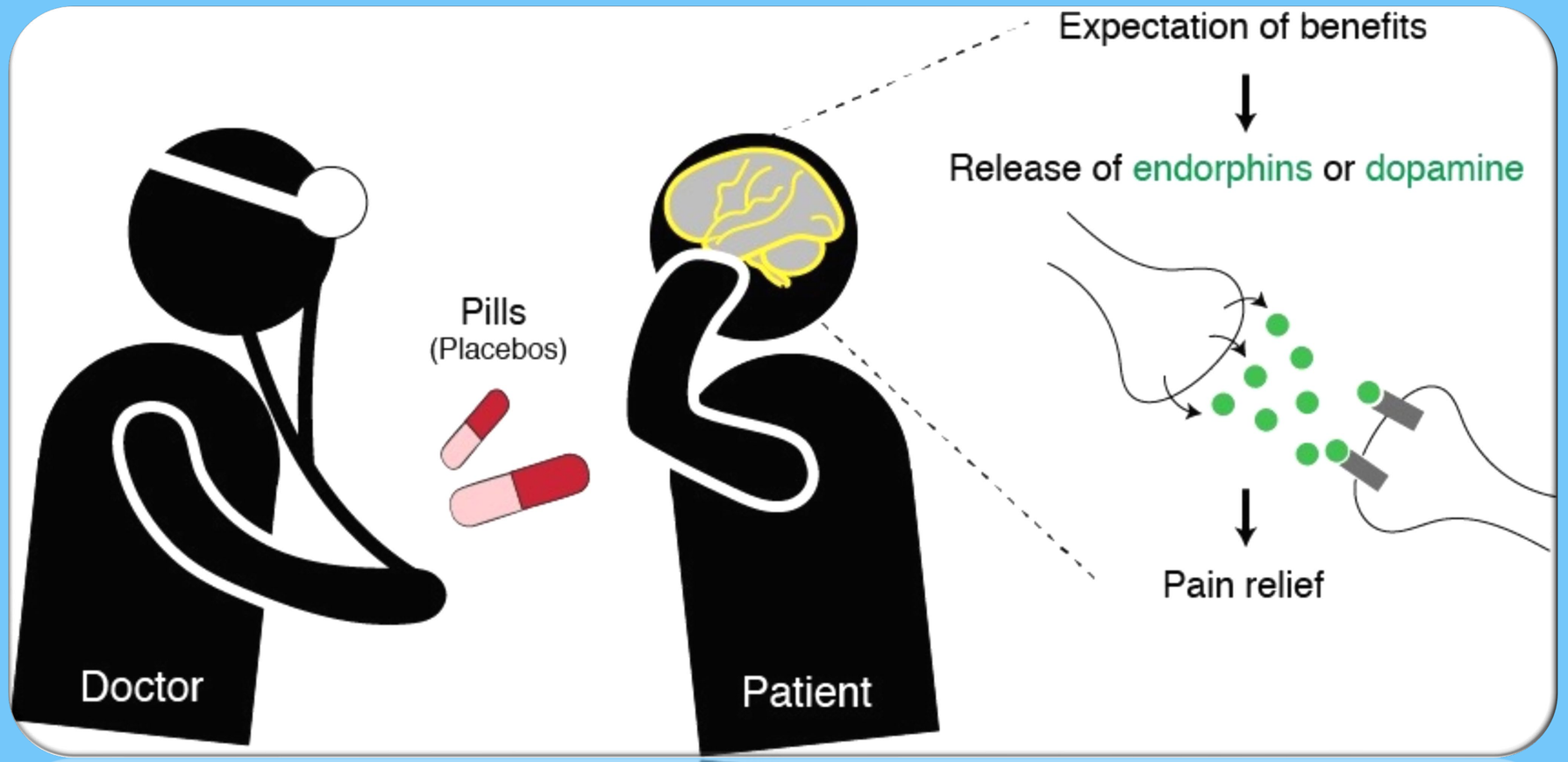
- One explanation might be that children and adolescents with major DD may be more demoralized than patients with AD and are therefore more sensitive to changes in hope and favorable meanings

- Depressed children and adolescents might benefit from innovative treatment modalities including clinician contact and other common factors, such as the patients' expectations of improvement, their desire for relief, and the.

- Factors such as contact with research staff, exposure to treatment rituals, the patients' expectations of improvement, and their desire for relief may lead to large placebo response rates in pediatric DD and may explain much of the variability in pediatric antidepressant trials.

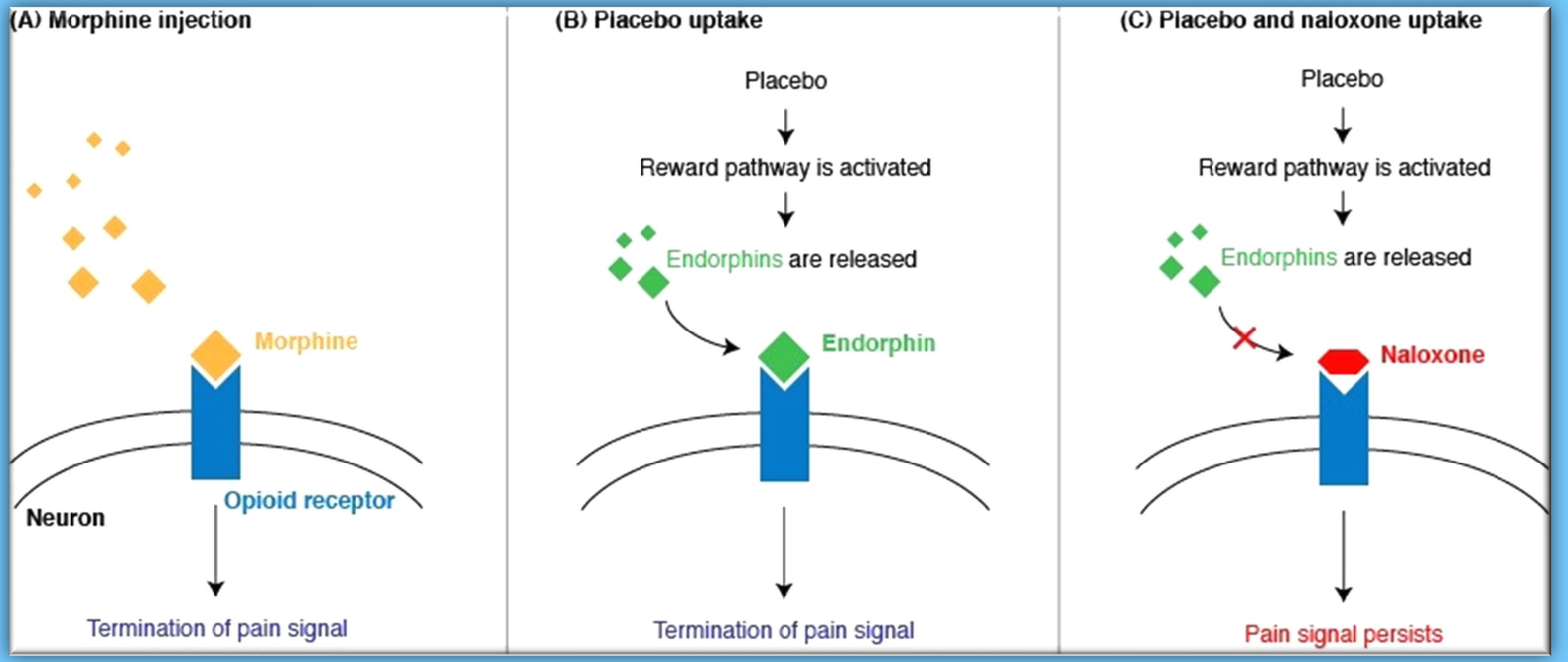
Locher, C et al, JAMA, 2017 Oct 1;74(10):1011-1020

More Than Just a Sugar Pill
Why the placebo effect is



More Than Just a Sugar Pill
Why the placebo effect is

- The positive expectation activates reward pathways in the brain, in turn stimulating the release of substances called endorphins, which are chemically similar to opiates like morphine.
- This effect can be partially negated by a chemical called naloxone, and partially prevents placebo responses.



More Than Just a Sugar Pill
Why the placebo effect is

- Specifically, genetic signatures that alter the opioid and dopamine signaling pathways are predictive of whether a patient is more or less likely to experience a strong placebo effect.
- Patients with opioid receptors that are less active are less likely to be placebo responders.

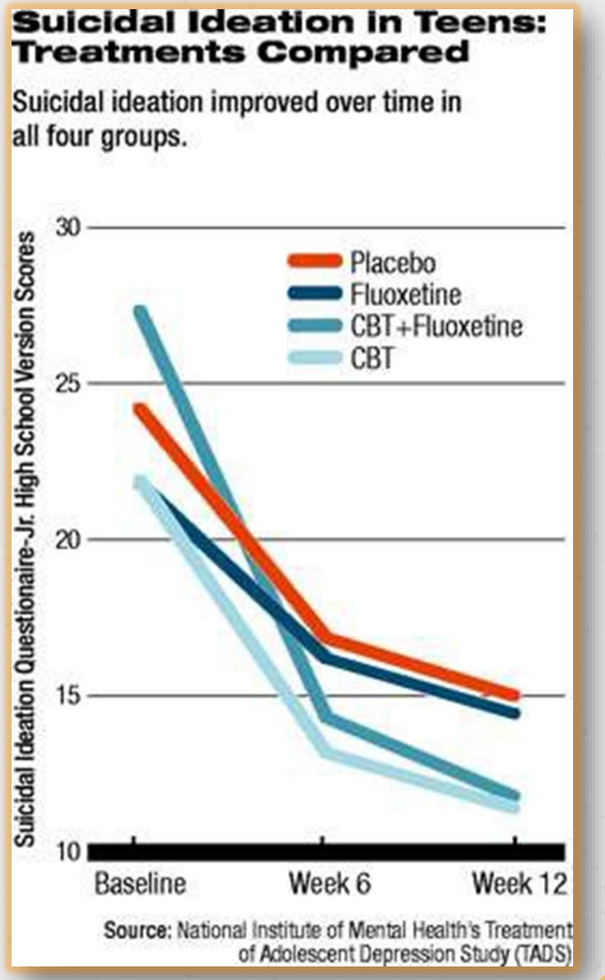
More Than Just a Sugar Pill
Why the placebo effect is

- Placebos also increase the release and uptake of dopamine, a neurotransmitter involved in reward-motivated behavior and decreased pain sensitivity.
- Specifically, in anticipation of benefit when a placebo is administered, dopamine receptors are activated in regions of the brain associated with reward.
- Patients with reduced dopamine metabolism, and therefore higher dopamine levels in the brain, are more likely to experience a strong placebo effect.
- Placebos cause measurable changes in neurobiological signaling pathways

TADS: Suicidal ideation in acute treatment

- Clinically significant suicidal thinking, which was present in 29% of the sample at baseline, improved significantly in all 4 treatment groups.
- Fluoxetine with CBT showed the greatest reduction (*P*=.02).
- CBT did show the specific effect of decreasing suicidality in both the CBT alone group and the CBT combined with fluoxetine group.

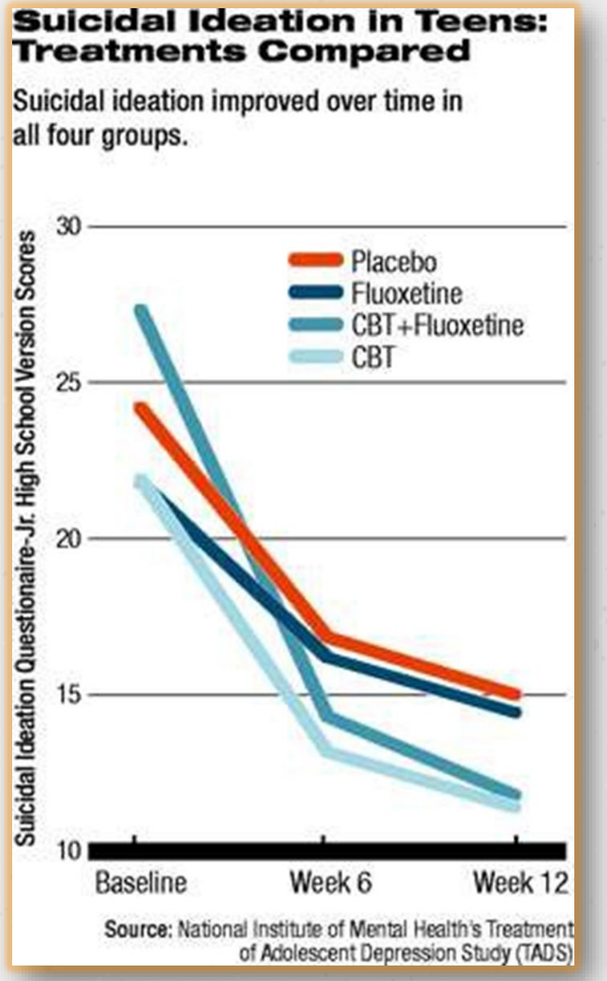
- Seven (1.6%) of 439 patients attempted suicide;
- there were no completed suicides.



March J et al. JAMA. 2004;292(7):807-820

TADS: Suicidal ideation in acute treatment

- When considered in light of the SIQ-Jr results, which showed no exacerbation of suicidal ideation in fluoxetine-treated compared with placebo-treated patients,
- The impact of treatment with fluoxetine on reduction of suicidal ideation was identical to that of placebo, suggesting that fluoxetine on average does not increase suicidal ideation.



March J et al. JAMA. 2004;292(7):807-820

FDA & Black Box Warning

- Suicidal thought and behavior, no complete suicide.
- Inconsistent across trials and across sites.
- Suicidality (not suicide) occurs in 4% of children on antidepressant compared with 2 % on placebo on the basis of **spontaneous report,**
- the prospectively collected **rating scales** from those studies did not demonstrate any differences in suicidality between active treatment and placebo.
- the majority of trials did not have pre-planned suicidality outcomes.
- the treatment groups had a significant drop-out rate.

Bridge et al, 2007; Hammad et al, 2006

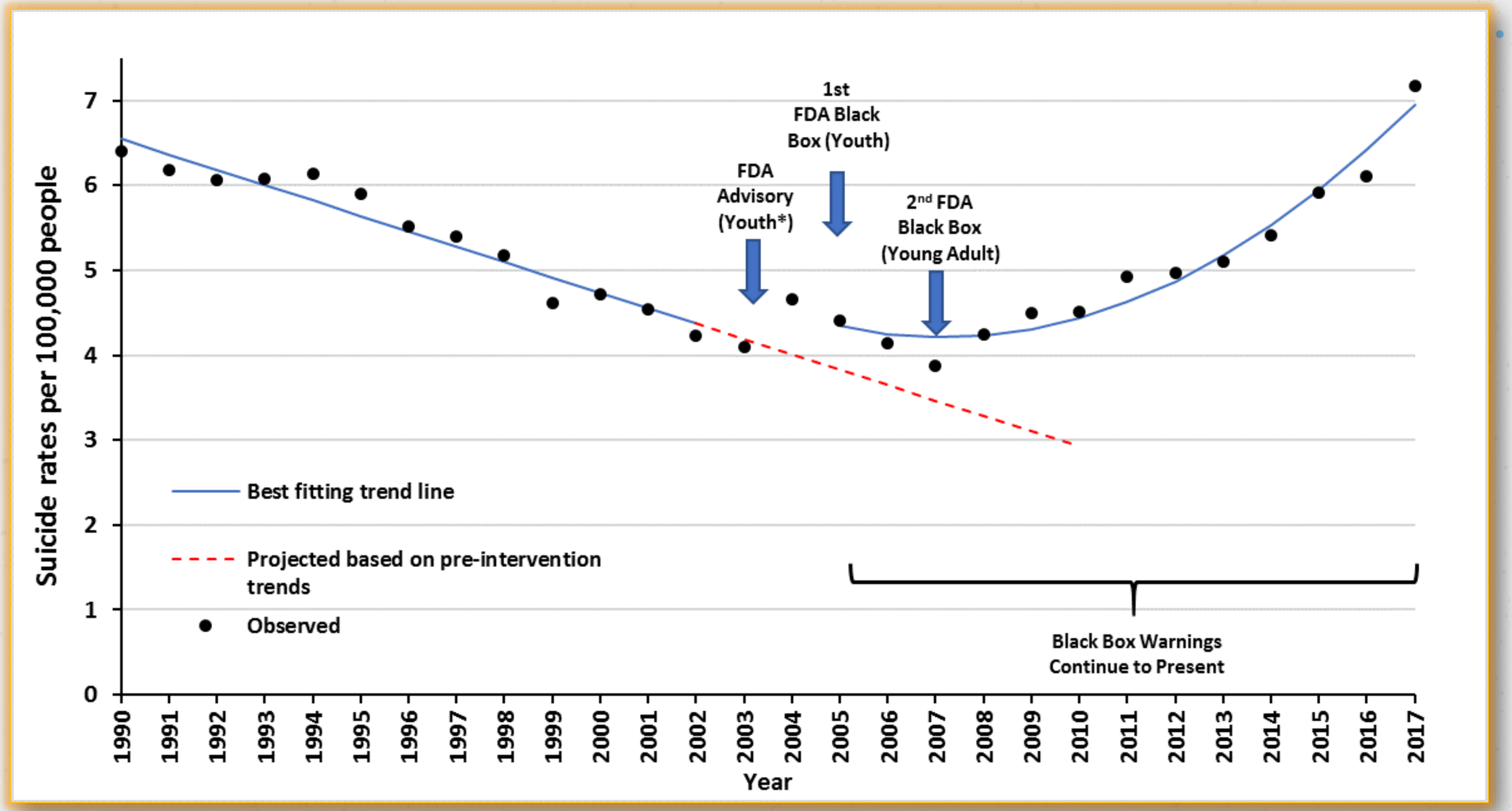
FDA & Black Box Warning

- SSRI prescriptions for youth decreased by 22% in both the US and the Netherland after the warning were issued in October 2004.
- In the US, the suicide rates increased by 14% between 2003 and 2004,
- In the Netherland, the suicide rates increased by 49% between 2003 and 2004.
- This was the largest year-to-year change in the suicide rate for this population ever since the CDC started collecting data.

Gibbons et al, 2007

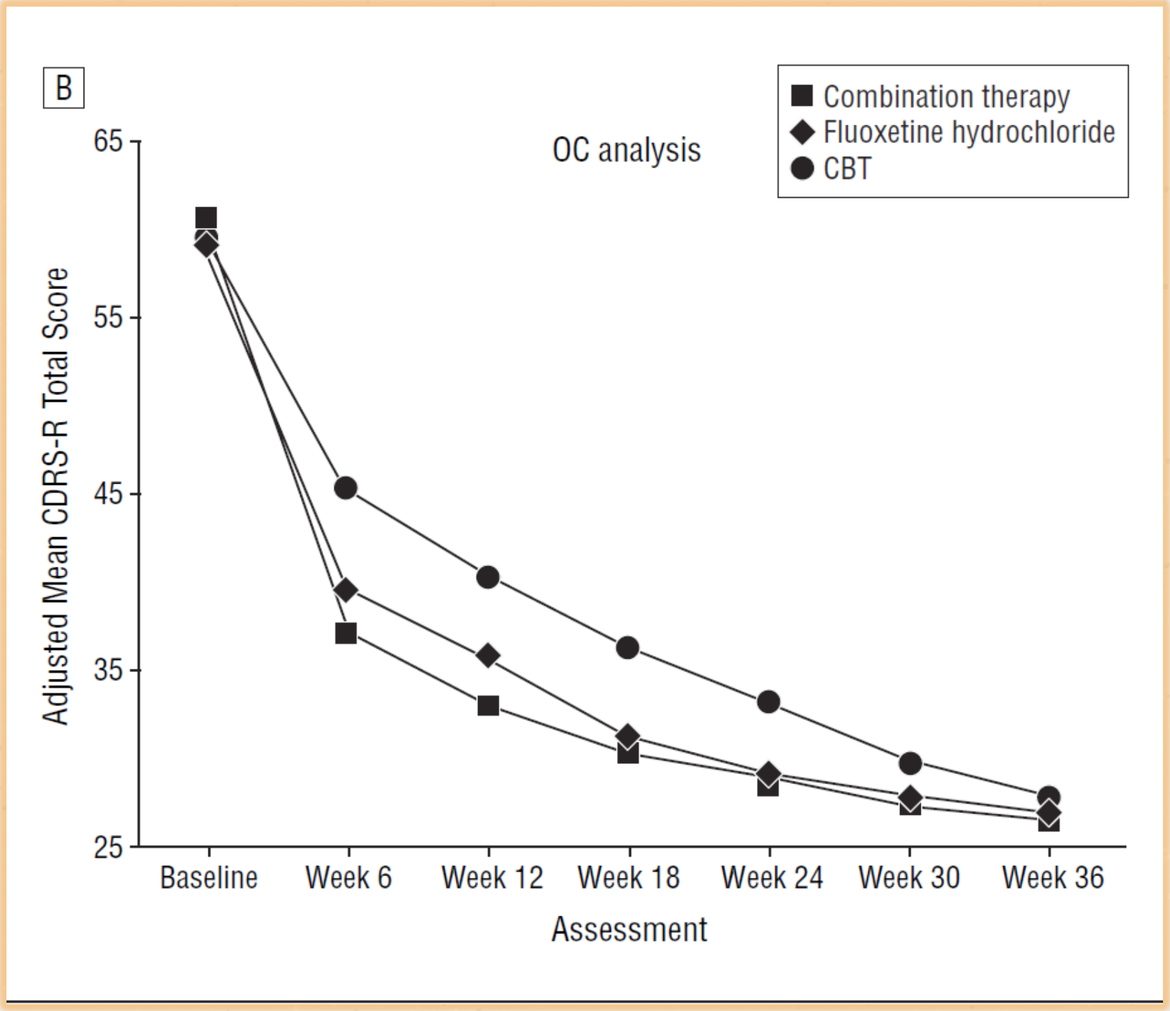
FDA & Black Box Warning

Christine Y. Lu, et al, *PRCP*, 2020
DOI: 10.1176/appi.prcp.20200012



The Treatment for Adolescents With Depression Study

Long-term Effectiveness and Safety Outcomes

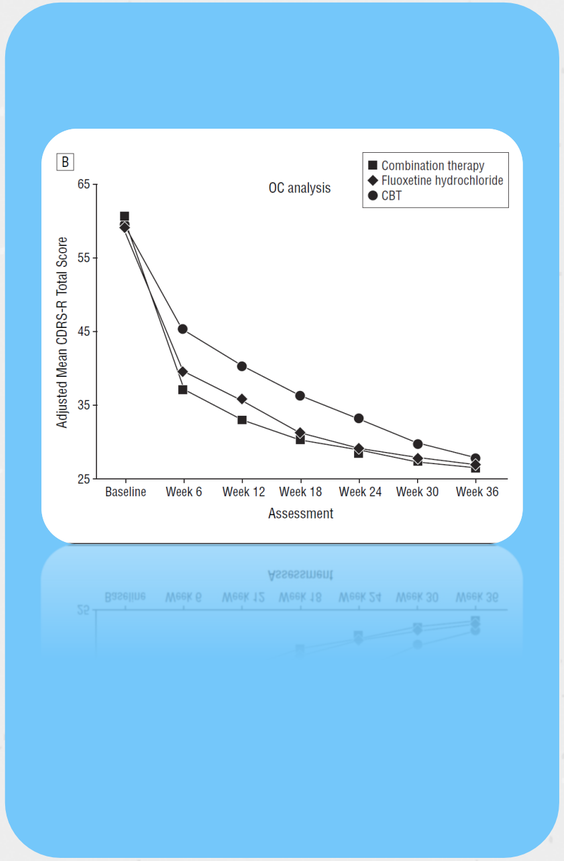


The TADS Team, Arch Gen Psychiatry. 2007;64(10):1132-1144

The Treatment for Adolescents With Depression Study

Long-term Effectiveness and Safety Outcomes

- Rates of response were 85% for combination therapy, 69% for fluoxetine therapy, and 65% for CBT at week 18;
- and 86% for combination therapy, 81% for fluoxetine therapy, and 81% for CBT at week 36.

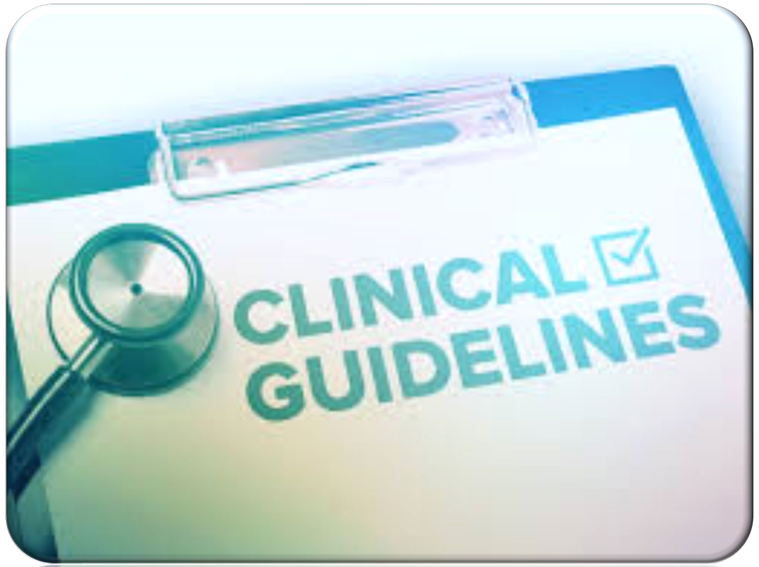


The TADS Team, Arch Gen Psychiatry. 2007;64(10):1132-1144

Developing Guidelines

Guidelines exist regarding first-line treatments once a pediatric MDD diagnosis is made, largely informed by four large pediatric depression clinical trials:

- Treatment of Adolescents with Depression Study [*TADS* (N = 439; March et al., 2004)],
- Treatment of Resistant Depression in Adolescents [*TORDIA* (N = 334; Brent et al., 2008)],
- Adolescent Depression Antidepressants and Psychotherapy Trial [*ADAPT* (N = 208; Goodyer et al., 2008)],
- Improving Mood with Psychoanalytic and Cognitive Therapies [*IMPACT* (N = 465; Goodyer et al., 2017)].



Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

The ADAPT trial

- To determine if, in the short term, depressed adolescents attending routine NHS Child and Adolescent Mental Health Services (CAMHS), and receiving ongoing active clinical care, who had not responded to a psychosocial brief initial intervention (BII) prior to randomisation treatment with selective serotonin reuptake inhibitors (SSRIs) plus cognitive behaviour therapy (CBT) compared with SSR alone, results in better healthcare outcomes.

- The duration of the trial was a 12-week treatment phase, followed by a 16-week maintenance phase

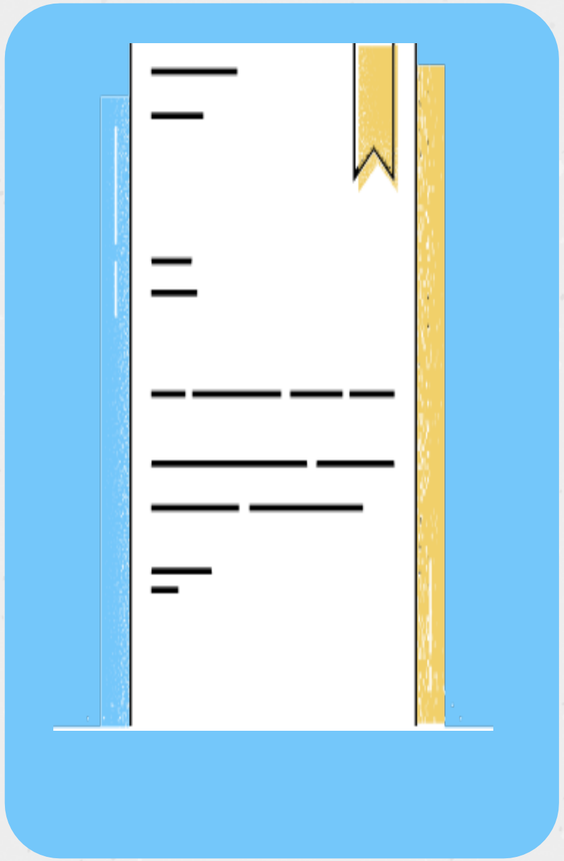
Goodyer I.M, Health Technol. Assess. 2008; Vol. 12: No. 14

The ADAPT trial

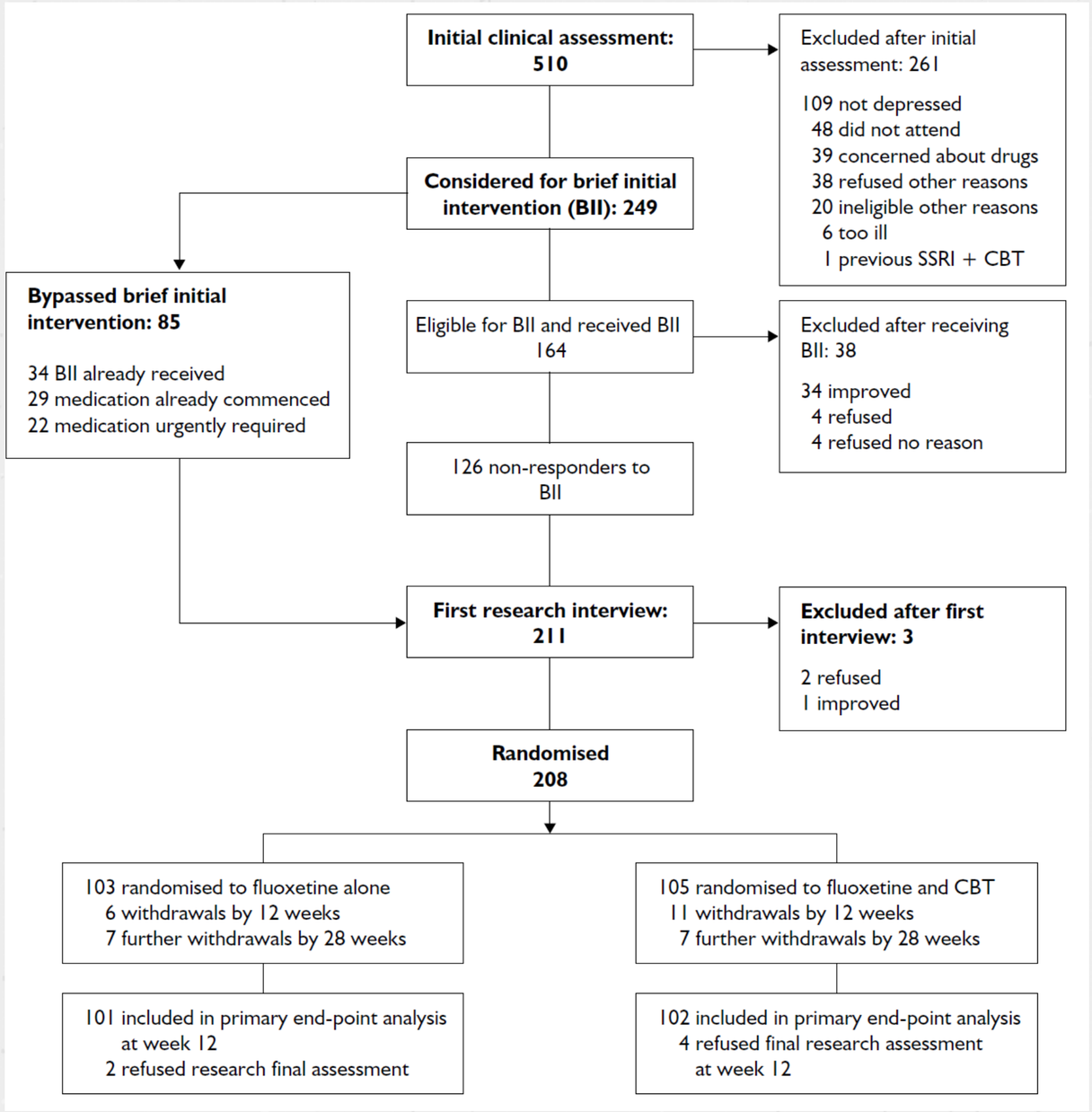
Brief psychosocial intervention (BII) consisting of

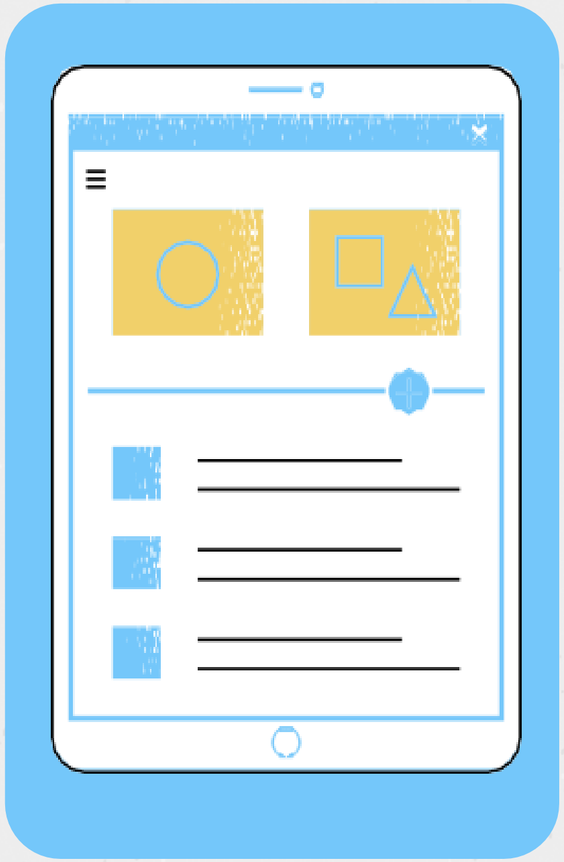
- (a) education about their condition;
- (b) advice on general well-being (mental and physical);
- (c) parent support;
- (d) help in problem solving adverse consequences arising from recent negative life events.

- This could be delivered relatively easily in specialist CAMHS settings



Goodyer I.M, Health Technol. Assess. 2008; Vol. 12: No. 14





Goodyer I.M, Health Technol. Assess. 2008; Vol. 12: No. 14

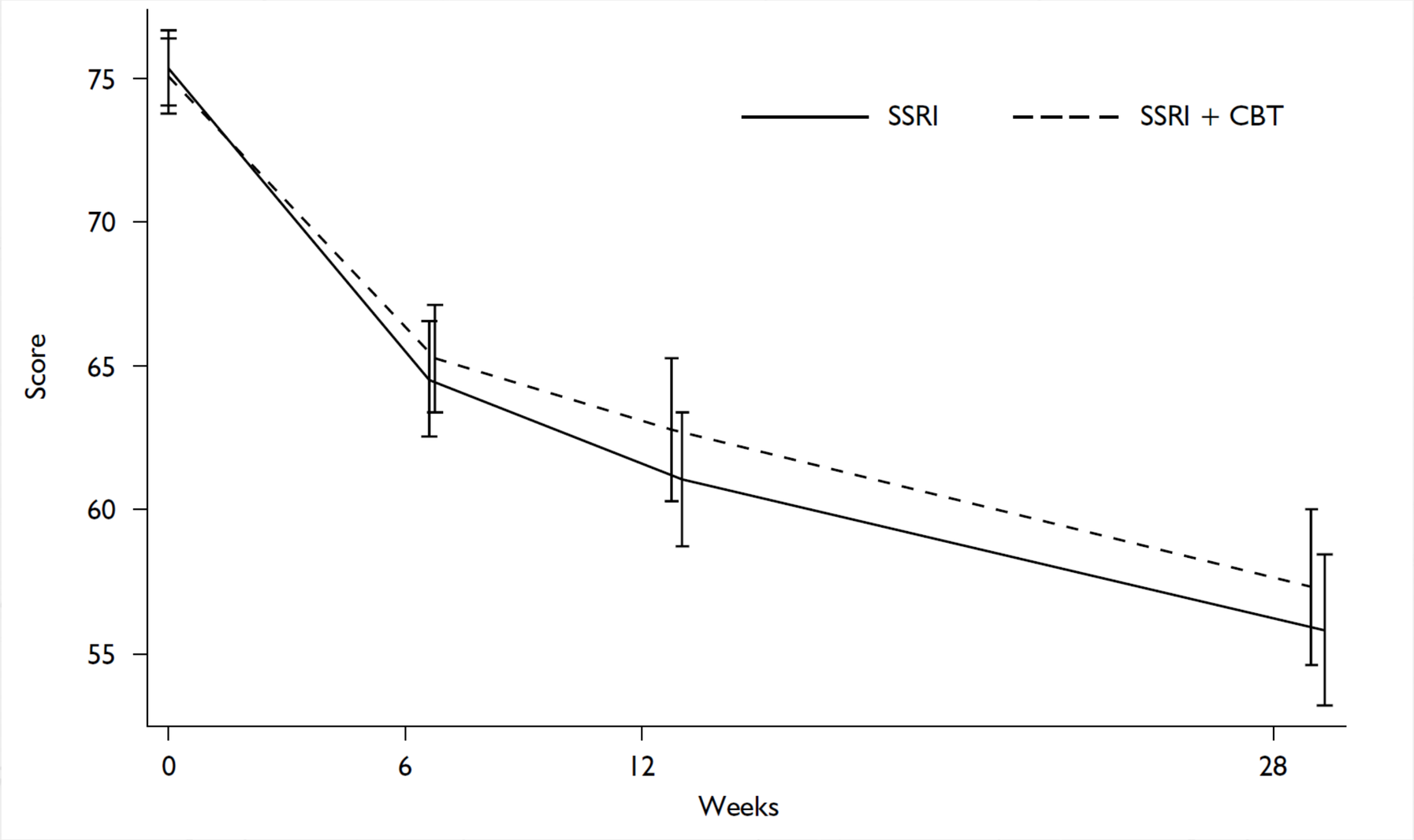
The ADAPT trial

- The sample studied closely reflects a typical CAMHS population, with a significant degree of severity, co-morbidity, suicidality and also psychosis.
- The participants were not recruited through advertisements, and therefore the results are particularly relevant to the type of patients seen in the NHS.
- In addition, this study is unique as it is a true effectiveness study of NHS treatment, a variety of CBT therapists with different levels of experience were used, as would occur in real-life practice,
- not an efficacy trial of gold-standard treatment with a highly selected patient group.

Goodyer I.M, Health Technol. Assess. 2008; Vol. 12: No. 14

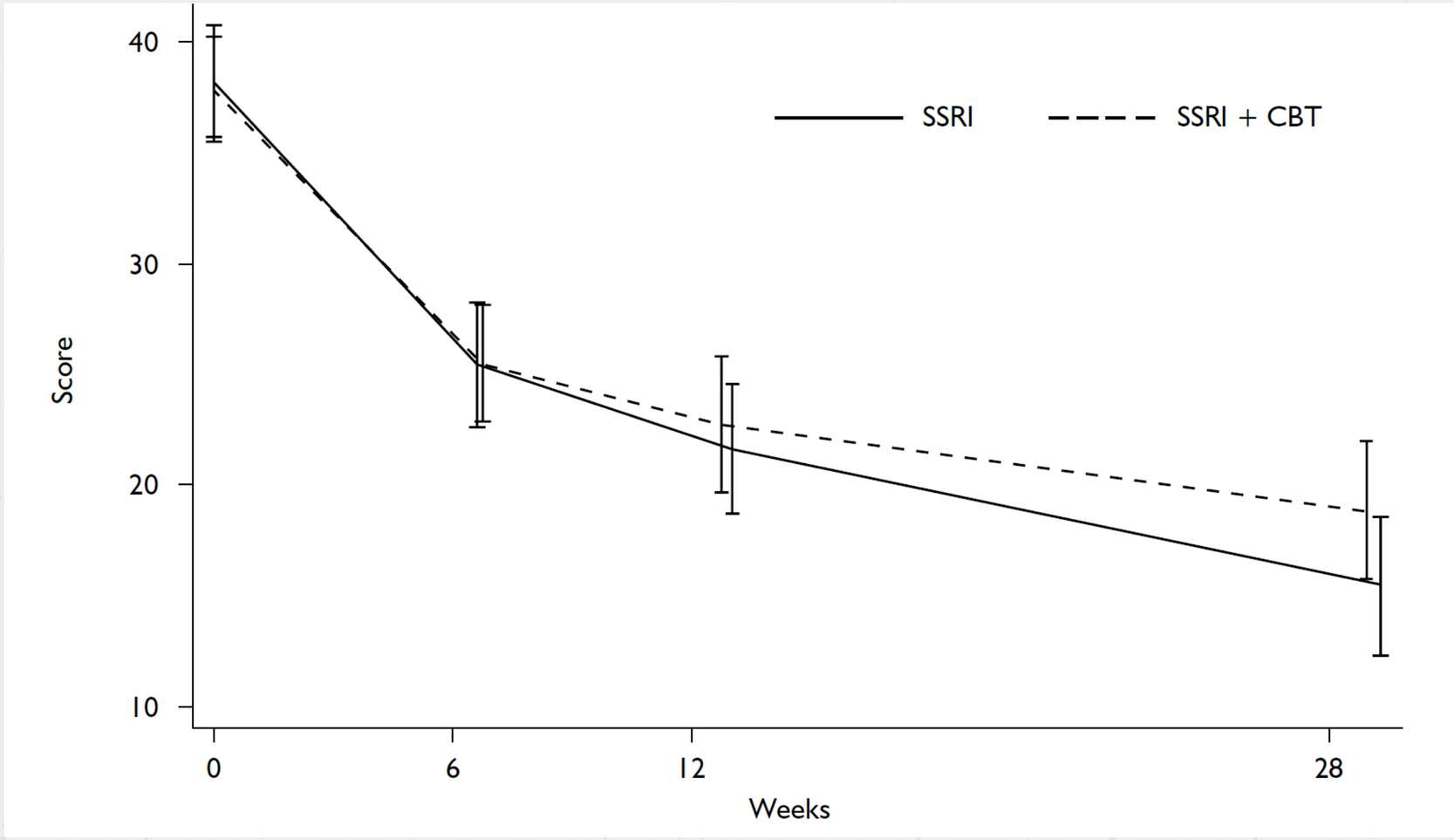
Clinician Rated Depression Scale

Mean outcome by treatment group for Children's Depression Rating Scale (CDRS)



Goodyer I.M, Health Technol. Assess. 2008; Vol. 12: No. 14

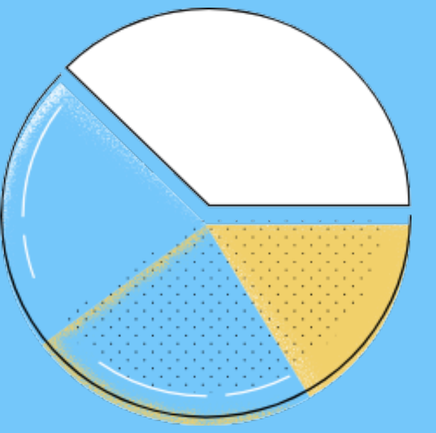
Self Report Depression Symptoms
Mean outcome by treatment group for Mood and Feelings Questionnaire (MFQ)



Goodyer I.M, Health Technol. Assess. 2008; Vol. 12: No. 14

The ADAPT trial

- These findings are differed from the Treatment for Adolescents with Depression Study (TADS), which showed combined treatment to be more effective than fluoxetine alone on some but not all of the outcome measures.
- This was only true, however, for cases of moderate, and not severe, depression in the TADS study .
- A recent reanalysis of TADS has also found that combined treatment does not offer any advantages over fluoxetine in the most impaired cases, consistent with our findings.



Goodyer I.M, Health Technol. Assess. 2008; Vol. 12: No. 14

The ADAPT trial

- Overall attendance in the SSRI + CBT arm did not reflect the amount of treatment that was available (19 sessions or more). By 28 weeks, the mean attendance in this arm was 11 sessions.

- The level of attendance in this study reflects the difficulties of engaging with such an impaired population and is probably greater than would normally be achieved in the NHS,
- in view of the fact that the research team endeavoured to retain participants as much as possible, over and above the efforts that would normally be made in a busy NHS clinic.

Goodyer I.M, Health Technol. Assess. 2008; Vol. 12: No. 14

The ADAPT trial

- In policy terms, the findings may be best applied to patients with unipolar depressions characterised by high (>6) levels of depressive symptoms, increased risk for suicidality, marked psychosocial impairment (CGAS < 50) and at least one co-morbid disorder likely to contain levels of worry, phobic or compulsive behaviours.

Goodyer I.M, Health Technol. Assess. 2008; Vol. 12: No. 14

Treatment-Resistant Depression

- Only about 60% of adolescents with depression will show an adequate clinical response to an initial treatment trial with a selective serotonin reuptake inhibitor (SSRI).
- Despite the high frequency of nonresponse and the serious consequences of persistent depression in this age group (12–18 years), there were no empirical studies to guide clinicians regarding the management adolescents with depression not responsive to an initial treatment with an SSRI.

Brent, D, *JAMA*. 2008 February 27; 299(8): 901–913

The TORDIA Randomized Controlled Trial

- To address the clinical management of this clinically important population, a 6-site, National Institute of Mental Health–funded study, the Treatment of SSRI Resistant Depression in Adolescents (TORDIA) trial was developed.

- This study focuses on nonresponse to SSRI medications rather than on nonresponse to psychotherapy, because SSRI medications have been the predominant method of treatment for adolescent depression for at least the past decade.

Brent, D, *JAMA*. 2008 February 27; 299(8): 901–913

The TORDIA Randomized Controlled Trial

334 adolescents aged 12 to 18 years, being in treatment with an SSRI regimen for at least 8 weeks, which were at a dosage of at least 40 mg per day of fluoxetine or its equivalent (e.g, 40 mg paroxetine, 40 mg citalopram, 20 mg escitalopram, or 150 mg sertraline) for 24 weeks with 1 year follow-up

Dosage schedule for SSRI: 10 mg per day for the first week and 20 mg per day for weeks 2 to 6, with an option to increase to 40 mg per day if insufficient clinical improvement

The venlafaxine dosages for weeks 1 to 4 were 37.5, 75, 112.5, and 150 mg, respectively, with an option to increase to 225 mg at week 6.

The protocol called for as many as 12 sessions (60–90 minutes each) of CBT during the first 12 weeks, 3 to 6 of which were to be family sessions, added to group one.

CBT drew upon the manuals that emphasize cognitive restructuring and behavior activation, emotion regulation, social skills, and problem solving for participants. also emphasize parent-child sessions to decrease criticism and to improve support, family communication, and problem solving, added to group two.

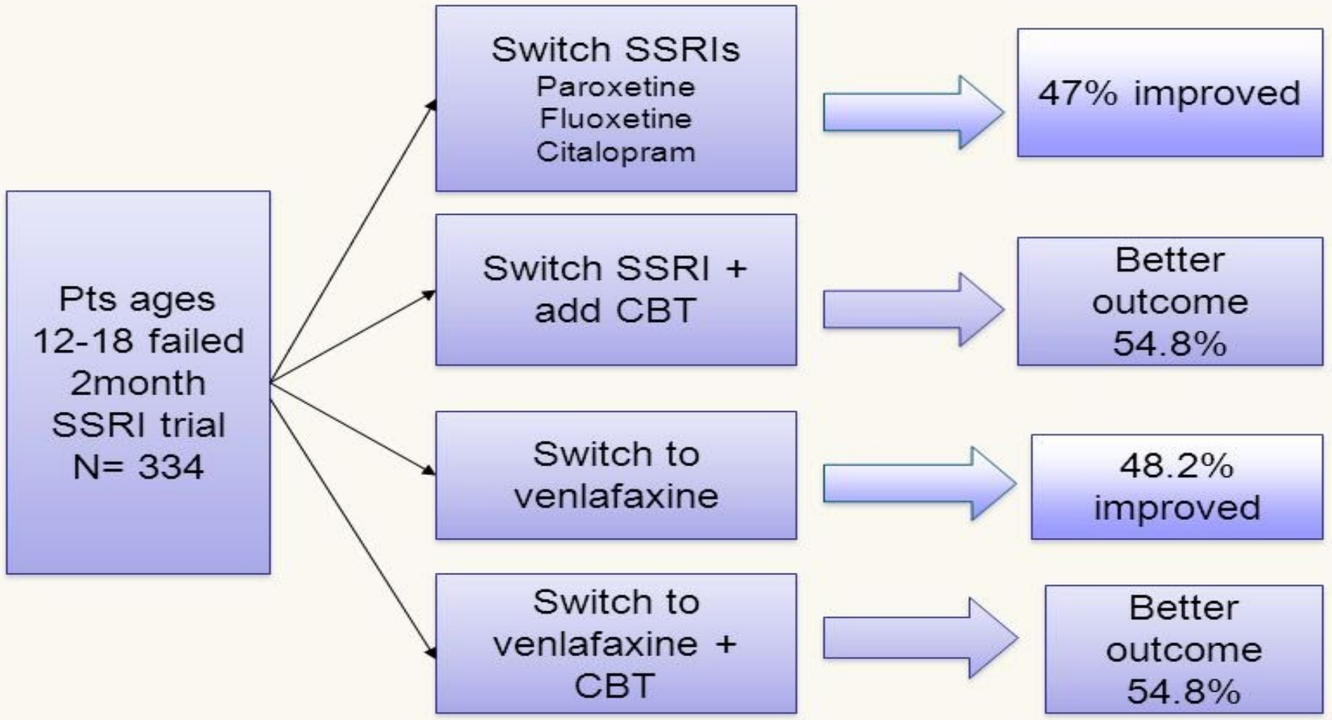
Brent, D, *JAMA*. 2008 February 27; 299(8): 901–913

Published in final edited form as:
JAMA. 2008 February 27; 299(8): 901–913.

Switching to Another SSRI or to Venlafaxine With or Without Cognitive Behavioral Therapy for Adolescents With SSRI-Resistant Depression:

The TORDIA Randomized Controlled Trial

Tordia study
JAMA 2008



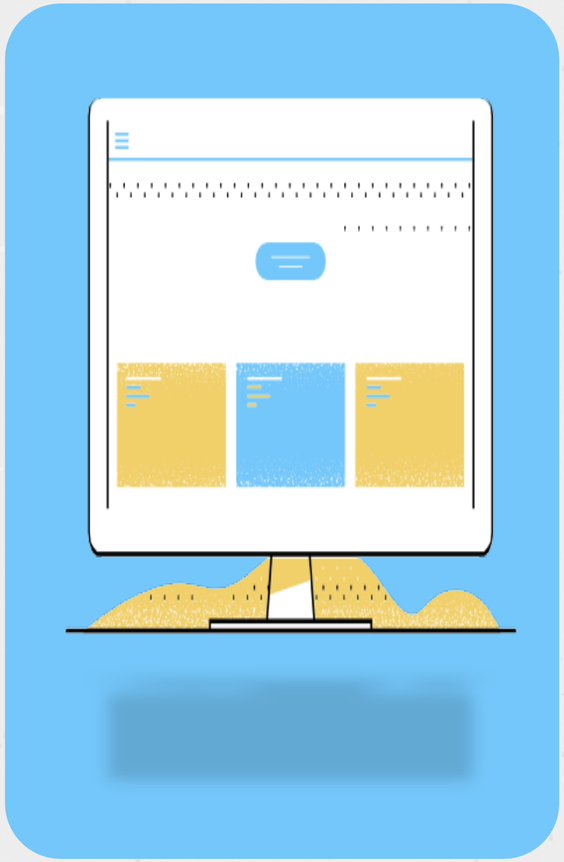
UNIVERSITY OF SOUTH FLORIDA

USF HEALTH

The TORDIA Randomized Controlled Trial

- There was no difference in response rate between venlafaxine (48.2%; 95% CI, 41%–56%) and a second SSRI (47.0%; 95% CI, 40%–55%; *P*=.83).
- Post hoc, there were no significant differences among the 3 SSRI medications with regard to clinical response (*P*=.25):
- Paroxetine, 19/50 [38.0%; 95% CI, 25%–52%];
- Fluoxetine, 41/84 [48.8%;95% CI, 38%–60%];
- Citalopram, 19/34 [55.9%; 95% CI, 39%–73%];

- There was a significant difference in CBT response by site (; *P* <.05),
- but no site differences with regard to response to SSRI (; *P*=.61) or to venlafaxine (; *P*=.21).



Brent, D, *JAMA*. 2008 February 27; 299(8): 901–913

Choice of a Second-Line Medication

- Contrary to our hypothesis, venlafaxine was not superior to the option of switching to another SSRI.

- There was a greater increase in diastolic blood pressure and pulse and more frequent occurrence of skin problems during venlafaxine than SSRI treatment, although these adverse effects were rarely of clinical impact.

Brent, D, *JAMA*. 2008 February 27; 299(8): 901–913

Cognitive–behavioural therapy and short-term psychoanalytic psychotherapy versus brief psychosocial intervention in adolescents with unipolar major depression (IMPACT): a multicentre, pragmatic, observer-blind, randomised controlled trial

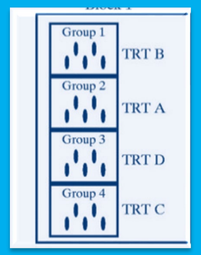
- Would specialist treatment of CBT be superior to short term psychoanalytic therapy (STPP) in achieving the objectives?
- Would CBT and/or STPP be superior to the reference treatment of brief psychosocial intervention (BPI)?

Goodyer I.M, Health Technol Assess. 2017 Mar;21(12):1-94

Study Design

MDD

N=470



Randomised to

One of 3

Treatment arms

BPI

12 sessions/20 weeks

N= 155

End of study = 132

CBT

20 sessions/20 weeks

N=154

End of study = 130

STPP

28 sessions /30 weeks

N=156

End of study = 119

Goodyer I.M, Health Technol Assess. 2017 Mar;21(12):1-94

Improving Mood With Psychoanalytic Psychotherapy And Cognitive Behaviour Therapy: THE IMPACT STUDY

- The BPI treatment manualised for this study,
- was delivered in this study as the standard control psychosocial intervention.
- BPI did not use cognitive or reflective analytic techniques.
- Therefore, there was no discussion of unconscious conflict and no deliberate effort to modify maladaptive models of attachment relationships.
- Emphasis was placed on the importance of psychoeducation about depression and action-oriented, goal-focused, interpersonal activities as therapeutic strategies.

Goodyer I.M, Health Technol Assess. 2017 Mar;21(12):1-94

THE IMPACT STUDY

- Specific advice on:
  - improving and maintaining mental and physical hygiene,
  - engaging in pleasurable activities,
  - engaging with and maintaining school work and peer relations,
  - and diminishing solitariness.

- Liaison with external agencies and personnel (e.g. teachers, social care workers and peer groups) were commonly undertaken.

Goodyer I.M, Health Technol Assess. 2017 Mar;21(12):1-94

Therapy Duration

- BPI : 12 sessions, (8 individual + 4 family/parent), over 20 weeks.
- STPP: 28 sessions (+ 7 parent sessions) over 28 weeks.
- CBT: Up to 20 sessions over 30 weeks (parent involvement if indicated).

Goodyer I.M, Health Technol Assess. 2017 Mar;21(12):1-94

THE IMPACT STUDY

- There was an average 49–52% reduction in depression symptoms by the end of the study.
- There were no superiority effects for the two specialist treatments (CBT + STPP) compared with BPI (treatment effect by final follow-up = –1.898, 95% CI –4.922 to 1.126; p = 0.219).
- At final assessment there was no significant difference in the mean depressive symptom score between treatment groups.

- *BPI offers an additional patient choice for psychological therapy.*

Goodyer I.M, Health Technol Assess. 2017 Mar;21(12):1-94

Practice Parameter for the Assessment and Treatment of Children and Adolescents With Depressive Disorders

2007

J . AM. ACAD. CHILD ADOLESC. PSYCHIATRY, 46:11, NOVEMBER 2007

2016

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 6. Special Populations: Youth, Women, and the Elderly

The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie
2016, Vol. 61(9) 588-603

DOI: 10.1177/0706743716659276
TheCJP.ca | LaRCP.ca
SAGE

Depression in children and young people: identification and management

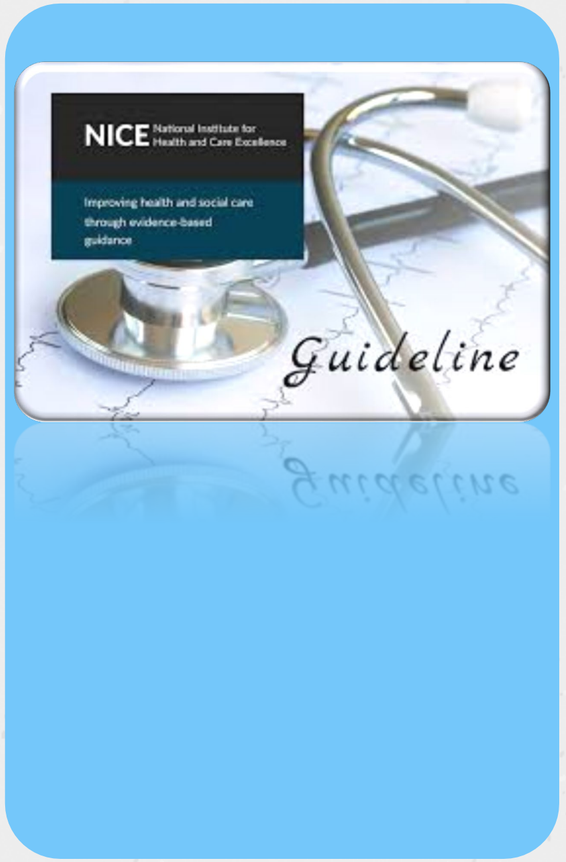
2019

NICE guideline
Published: 25 June 2019
www.nice.org.uk/guidance/ng134

Mild Depression

- For children and young people with diagnosed mild depression who do not want an intervention or who, in the opinion of the healthcare professional, may recover with no intervention, a further assessment should be arranged, normally within 2 weeks ('watchful waiting).

- Healthcare professionals should make contact with children and young people with depression who do not attend follow-up appointments.



www.nice.org.uk/guidance/ng134

Mild vs Moderate-To-Severe Depression

- The first approach for mild depression should be family education, supportive counseling, case management, and problem solving.

- For adolescents with moderate-to-severe depression, both guidelines also recommend an evidence-based psychotherapy [e.g., cognitive-behavioral therapy (CBT)], ***and/or*** fluoxetine, although the choice of sequential versus combined treatment is left to the practitioner to decide.

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

Moderate-To-Severe Depression

- CBT is the therapy with the most data in adolescent populations, studied alone or in combination with medication in three large trials: TADS, TORDIA, ADAPT.

- Despite being more thoroughly studied than other specialized psychotherapies, ***CBT*** and ***interpersonal psychotherapy*** for adolescents (IPT-A) have been demonstrated equally (Weersing, Jeffreys, Do, Schwartz, & Bolano, 2017) or near equally (Eckshtain et al., 2019) clinically effective,
- and the IMPACT trial demonstrated equal improvement in depressed adolescents with ***CBT, STPP***, and a ***brief psychosocial intervention*** at the end of the treatment and at a year later (Goodyer et al., 2017).

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

Moderate-To-Severe Depression

- There is no clear evidence to guide decisions regarding which type of psychotherapy might be most appropriate.
- NICE guidelines suggest heavily involving the patient and his or her family in choosing a psychotherapy, which includes providing psychoeducation regarding the different school of thoughts, and their conceptions of dysfunction and recovery.

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

Depression Unresponsive to Psychological Therapy

-]If moderate to severe depression in a child or young person is unresponsive to psychological therapy ***after 4 to 6 treatment sessions***, a multidisciplinary review should be carried out.

www.nice.org.uk/guidance/ng134

Depression Unresponsive to Psychological Therapy

- Following ***multidisciplinary review***, if the child or young person's depression is not responding to psychological therapy as a result of other coexisting factors such as the presence of comorbid conditions, persisting psychosocial risk factors such as family discord, or the presence of parental mental ill-health:

➢ alternative or perhaps additional psychological therapy for the parent or other family members,

➢ or alternative psychological therapy for the patient, should be considered.

➢ Following multidisciplinary review, offer fluoxetine if moderate to severe depression in a young person is unresponsive to a specific psychological therapy after 4 to 6 sessions.

www.nice.org.uk/guidance/ng134

Depression unresponsive to combined treatment

- If moderate to severe depression in a child or young person is unresponsive to combined treatment with a specific psychological therapy and fluoxetine after a further 6 sessions,
- or the patient and/or their parents or carers have declined the offer of fluoxetine:

the multidisciplinary team should make a ***full needs and risk assessment***.

- This should include a ***review of the diagnosis***,
- examination of the possibility of ***comorbid diagnoses***,
- reassessment of the ***possible individual, family and social causes*** of depression,
- consideration of whether there has been a ***fair trial*** of treatment,
- and assessment for further psychological therapy for the patient and/or additional help for the family.

www.nice.org.uk/guidance/ng134

Depression unresponsive to combined treatment

Following multidisciplinary review, the following should be considered:

- an alternative psychological therapy, which has not been tried previously (individual CBT, interpersonal therapy or shorter-term family therapy, of at least 3 months' duration) or
- systemic family therapy (at least 15 fortnightly sessions) or
- psychodynamic psychotherapy (approximately 30 weekly sessions)

www.nice.org.uk/guidance/ng134

Moderate-To-Severe Depression

- The NICE guidelines make an explicit recommendation to prescribe fluoxetine only in conjunction with psychotherapy.

- The NICE guideline recommendation to only prescribe medication in conjunction with current psychotherapy may be difficult to implement in health systems where pediatric depression is common and therapists scarce.

- The AACAP practice parameter is more lenient with fluoxetine alone as a reasonable strategy.

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

FDA-approved AD for Pediatric MDD

Only two antidepressants (fluoxetine and escitalopram) are FDA-approved for pediatric MDD.
Fluoxetine: MDD≥8yrs, OCD≥7yrs.
Escitalopram≥12yrs.

FDA-approved AD for Pediatric MDD

- The American Academy of Pediatrics adopted a policy statement on the use of off-label medications in children:
- They defined off-label use as “use of a drug that is not included in the package insert (FDA-approved labeling) [and] does not imply improper, illegal contraindicated or investigational use”.
- This statement also emphasizes that off-label use does not necessarily require prescribers to obtain informed consent if the decision to use the medication is supported by scientific or anecdotal evidence.

Allen HC et al, J Okla State Med Assoc. 2018 Oct; 111(8): 776–783

First-line pharmacological treatments for adult depression and evidence of their effects in pediatric populations

	Pediatric			
	Starting dose (mg/day)	Typical dose range (mg/day)	Level of evidence in MDD	FDA indications
Selective serotonin reuptake inhibitors				
Citalopram	10–20	20–40	C	–
Escitalopram	10	10–20	A	MDD (12+)
Fluoxetine	10–20	20–80	A	MDD (8+), OCD (7+)
Fluvoxamine	25–50	50–300	C	OCD (8+)
Paroxetine	10–20	20–60	C	–
Sertraline	25–50	100–200	A	OCD (6+)

Grade A evidence is based on meta-analysis of RCT data or 1 or more RCTs.
Grade B evidence is based on at least 1 controlled trial that was not randomized.
Grade C evidence is based on either data from nonexperimental studies or extrapolated from Grade A or Grade B evidence in a different population.
Grade D is based on expert opinion or clinical experience.

Only two medications are FDA-approved for treatment of major depression in pediatric populations (fluoxetine and escitalopram).
Sertraline has additional evidence of efficacy in multiple placebo-controlled trials in pediatric populations.

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

First-line pharmacological treatments for adult depression and evidence of their effects in pediatric populations

	Pediatric			
	Starting dose (mg/day)	Typical dose range (mg/day)	Level of evidence in MDD	FDA indications
Serotonin–norepinephrine reuptake inhibitors				
Venlafaxine	37.5	150–225	C	–
Duloxetine	30	40–60	C	GAD (7+)
Desvenlafaxine	25	25–100	C	–
Atypical antidepressants				
Bupropion	100	150–300	C	–
Mirtazapine	7.5–15	15–45	C	–
Vilazodone	5	10–20	C	–
Vortioxetine	5	10–20	C	–

Grade A evidence is based on meta-analysis of RCT data or 1 or more RCTs.
Grade B evidence is based on at least 1 controlled trial that was not randomized.
Grade C evidence is based on either data from nonexperimental studies or extrapolated from Grade A or Grade B evidence in a different population.
Grade D is based on expert opinion or clinical experience.

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

Continuation & Maintenance phase

- In the event that a patient's depression remits on a particular medication, the acute phase is followed by a ***continuation phase*** of 16 to 20 weeks with a goal of consolidating gains and preventing relapse.
- These phases are then followed by a ***maintenance phase*** of variable duration that depends on the child's history and the families' preferences and values, with generally more severe courses or protracted recoveries warranting a longer maintenance phase

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

Moderate-To-Severe Depression

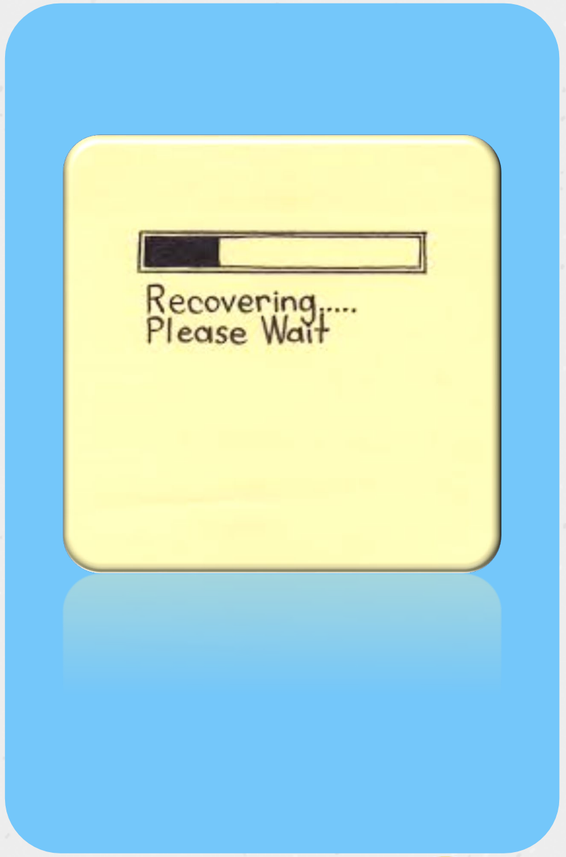
- Current NICE guidelines recommend utilizing fluoxetine as the first-line pharmacological treatment in this population.
- There is no strong evidence base to suggest that any particular SSRI agent is more effective than any other for pediatric depression.
- Meta-analyses comparing the efficacy of different SSRI agents in pediatric depression have typically failed to demonstrate a difference between individual medications within the SSRI class.

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

Moderate-To-Severe Depression

- AACAP Practice Parameter recommends that, ‘patients should be treated with ***adequate and tolerable doses*** for at least 4 weeks.
- Clinical response should be assessed at 4-week intervals,
- and if the child has tolerated the antidepressant, the dose may be increased up to ***the maximum recommended*** tolerated dose to gauge treatment response if a complete response has not been obtained.

- Furthermore, there is no evidence for efficacy of ***subtherapeutic*** dosing of SSRI in children in the acute phase of treatment or for relapse prevention.



Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

Maximum Dose Strategy

A previous trial that examined 29 children who had not responded adequately to 20 mg of fluoxetine at 9 weeks of treatment suggested that raising the dose of fluoxetine to 40–60 mg (response rate 71%) was more effective than maintaining the dose at 20 mg (response rate 36%; Heiligenstein et al., 2006).

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

Moderate-To-Severe Depression

- However, patients who are showing minimal or no response after 8 weeks of treatment are likely to need alternative treatments.
- Furthermore, by about 12 weeks of treatment, the goal should be remission of symptoms, and in youths who are not remitted by that time, alternative treatment options may be warranted.

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

Treatment-Resistant Depression

However, it is important to rule out reasons for continued depression such as:

- ***rapid drug metabolism***,
- ***nonadherence***,
- presence of ***undiagnosed medical or psychiatric comorbidity*** (e.g., insomnia, psychosis, cannabis abuse, bipolar disorder),
- or ***environment stressors***, such as family conflict, parental depression, peer victimization, or same-sex attraction.

Martin, A. et al, (2018), *Lewis's child and adolescent psychiatry: a comprehensive textbook*, Wolters Kluwer

Treatment-Resistant Depression

- After nonresponse to a second SSRI, one should consider switching to an antidepressant of a different class.
- If the patient has ***prominent anxiety***, then a selective norepinephrine/serotonin reuptake inhibitor is a logical next step.
- If a patient has ***low motivation and fatigue, or comorbid ADHD***, then bupropion might be a logical next step.

- After treatment nonresponse to three antidepressants, patients should be considered for ECT, with naturalistic studies indicating best outcomes in those with psychosis or mania, and less favorable outcomes in those with personality disorder.

Martin, A. et al, (2018), *Lewis's child and adolescent psychiatry: a comprehensive textbook*, Wolters Kluwer

Treatment-Resistant Depression

- Expert consensus recommends that if a patient shows ***partial response*** to an agent, then augmentation should be considered,
- While empirical studies in youth are lacking, adult studies support augmentation with ***lithium, bupropion, and antipsychotics*** among other agents

Martin, A. et al, (2018), *Lewis's child and adolescent psychiatry: a comprehensive textbook*, Wolters Kluwer

Augmentation strategies for treatment-resistant depression

Intervention	Response		Time to effect		Level of evidence for efficacy	
	Odds ratio	NNT	Duration of trials	Time to maximum effect	Adults	Pediatrics
Pharmacological augmentation strategies						
Antipsychotics	1.68	8	6–12 Weeks	6–8 Weeks	A	D
Lithium	1.56	10	1–6 weeks	4 Weeks	A	D
Thyroid hormone	1.84	7	12 weeks	6–8 weeks	B	D
Bupropion	1.29	18	6–12 weeks	4 Weeks	B	D
Buspirone	1.25	20	4–12 weeks	4 Weeks	B	D
Lamotrigine	1.12	41	8 weeks	8 weeks	C	D
Psychostimulants	1.37	14	1–4 weeks	2 weeks	A	D
Interventional treatments						
ECT	8.91	2	4 weeks	4 Weeks	A	D
rTMS	1.72	8	4–6 weeks	4 Weeks	A	D
Ketamine	8.97	2	2 Weeks	1 Day	A	D

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

Lithium & Atypical Antipsychotic Augmentation

- There are no randomized, placebo-controlled trials examining the efficacy of lithium as a monotherapy or augmentation strategy in pediatric depression

- There are no randomized, placebo-controlled studies examining the efficacy of antipsychotic augmentation for treatment-refractory pediatric depression.
- Although a secondary analysis of 6-month TORDIA outcomes suggested a potential benefit of earlier augmentation with an atypical antipsychotic or mood stabilizer, numbers were small (5 of 10 subjects improved with augmentation vs. 27 of 153 improved without; Emslie et al., 2010)
- and more pediatric evidence is sorely needed.

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

Advancement to the Less Evidence-Based Augmentation and Interventional strategies

Thus, there is no substitute for careful clinical formulation and judgment for each individual case,
and there may be instances when patients may rightly progress more quickly through this proposed staging schema.

- For example, patients with severe depressive symptoms
- or persistent suicidality,
- who have multiple risk factors for treatment resistance,

could reasonably be triaged for accelerated advancement to the less evidence-based augmentation and interventional strategies once past a full trial of an SSRI and evidence-based psychotherapy.

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

10 Proposed stages of treatment resistance in pediatric depression

Stage	Definition (substantial residual symptoms of depression despite …)
0	No previous treatment for depression
1	Previous counseling for depression of unclear modality or efficacy
2	Previous evidence-based psychotherapy for depression
3	1 prior pharmalogical trial of FDA approved antidepressant for depression (fluoxetine, escitalopram, sertraline) of adequate duration and at the ***minimally*** recommended dose
4	1 prior pharmalogical trial of FDA approved antidepressant for depression (fluoxetine, escitalopram, sertraline) of adequate duration and at the ***maximally*** tolerated dose *Treatment Resistant Depression* (see Box 1)
5	Two trials of adeqaute dose and duration with SSRI medications *Treatment Refractory Depression* (see Box 1)

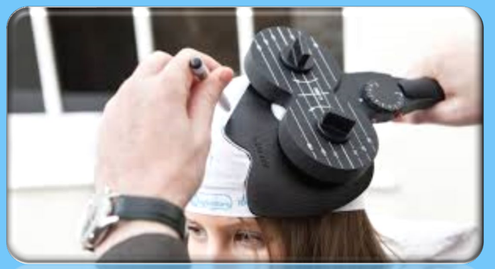
Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

10 Proposed stages of treatment resistance in pediatric depression

Stage	Definition (substantial residual symptoms of depression despite …)
6	≥2 trials of SSRI medications (adeqaute dose and duration) **AND** [≥ 1 trial with an alternative antidepressant (SNRI, bupropion, or mirtazapine) **OR** evidence-based augmentation strategy in adults (antipsychotics, lithium, bupropion, mirtazapine, stimulant)]
7	≥2 trials of SSRI medications (adeqaute dose and duration) **AND** ≥ 2 trials with an alternative antidepressant agents or augmentation strategies with evidence of efficacy in adults
8	≥2 trials of SSRI medications (adeqaute dose and duration) **AND** ≥ 1 trial with an alternative antidepressant agent (SNRI, bupropion or mirtazapine) **AND** ≥ 2 augmentation strategies with evidence of efficacy in adults
9	≥2 trials of SSRI medications (adeqaute dose and duration) **AND** ≥ 2 trials with an alternative antidepressant agents or augmentation strategies with evidence of efficacy in adults **AND** an interventional treatment (rtms or ketamine)
10	≥2 trials of SSRI medications (adeqaute dose and duration) **AND** ≥ 2 trials with an alternative antidepressant agents or augmentation strategies with evidence of efficacy in adults **AND** electroconvulsive therapy

Repetitive Transcranial Magnetic Stimulation

- rTMS is currently approved as a treatment for treatment-resistant depression in adults.
- Meta-analysis of adult studies suggests that at the end of an acute treatment series there was a small effect size of 0.33 (95% CI 0.17–0.50) compared with sham treatment (Ontario, 2016).
- Uncontrolled studies of rTMS in adolescent depression have suggested ***possible efficacy and safety*** of rTMS (Bloch et al., 2008; Croarkin et al., 2018; MacMaster et al., 2019),
- but there are no controlled trials.
- Sham-controlled trials of rTMS for pediatric depression are currently ongoing (NCT01804270).



Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

Electroconvulsive Therapy

- There are no published randomized controlled trials of ECT in adolescents or children with MDD or TRD.
- Meta-analysis of adult ECT trials suggests strong evidence of efficacy for ECT compared to sham treatments with an effect size of 0.90 (95% CI: 0.52–1.27) compared to sham treatments (Kho, van Vreeswijk, Simpson, & Zwinderman, 2003; Mutz et al., 2019).
- Given the lack of data on efficacy and safety of ECT in pediatric populations, ECT is generally considered in adolescent depression ***after at least 3-4 failed antidepressant trials and at least one substantial psychotherapy trial*** (Birmaher et al., 2007; Brent & Birmaher, 2006).

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

ketamine

Meta-analysis of single-dose, controlled crossover trial of intravenous ketamine (0.5 mg/kg over 40 min) in adults with treatment-refractory depression suggests that more than half of adults with MDD who are given a single ketamine infusion experience a greater than 50% reduction in depressive symptoms within 1 day (Newport et al., 2015).

Meta-analysis of controlled studies suggests an odds ratio of treatment response at 1 day following infusion of 9.87 (4.37–22.29) and ***an effect size*** of slightly over 1 [ES = 1.01 (95% CI: 0.69–1.34)] (Lee, Della Selva, Liu, & Himelhoch, 2015).

Although the benefits of ketamine typically dissipate within a week or two, further research has suggested that when ketamine is given twice a week for several weeks, it can induce a prolonged treatment response (Singh et al., 2016).

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32

ketamine

Initial case reports (Dwyer et al., 2017) and a small open-label trial (Cullen et al., 2018) have suggested ***possible efficacy*** in pediatric populations, although there are currently no published randomized, controlled trials evaluating efficacy in pediatric populations.
Trials examining the efficacy of ketamine (NCT02579928 and NCT03889756) and esketamine (an intranasally delivered formulation of the l-enantiomer of ketamine) (NCT03185819) in pediatric depression populations are currently ongoing.

Dwyer JB et al, J Child Psychol Psychiatry 2020;61:312–32