The Treatment of Youth Depression

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The treatment of youth depression

• Youth depression
• Antidepressant medication
• Cognitive behavioural therapy
• Recent trials
• YoDA trials
Main causes of disease burden in 15- to 24-year-olds (worldwide)

Onset of depression

Burke et al. (1990), Arch. Gen. Psychiatry, 47, 511-518.
Recurrence

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Number of patients in Australia who had a prescription for an antidepressant drug during the 2009-10 financial year.
Based on data from 13 trials and 2910 participants

Response rate:
- to antidepressants 61%
- to placebo 50%

Effect size 0.25, NNT 10

Effect size of fluoxetine 0.46, NNT 6
Placebo response rates

Bridge et al. (2007), *JAMA*, 297, 1683-1696.
Suicidal ideation with SSRIs


Age-Specific Odds Ratios for Suicidal Ideation and Behavior

Safety concerns

• The Bridge et al. (2007) meta-analysis reported rates of suicidal behaviours of:
  – 3% in antidepressant-treated participants
  – 2% in those receiving placebo

Risk difference of 1% (95% CI, −0.1% to 2%)

NNH 112 (c.f. NNT 10)
Regulatory responses to safety concerns

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PROZAC or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PROZAC is approved for use in pediatric patients with MDD and Obsessive Compulsive Disorder (OCD) [see Warnings and Precautions (5.1) and Use in Specific Populations (8.4)]. When using PROZAC and olanzapine in combination, also refer to Boxed Warning section of the package insert for Symbyax.

- FDA ‘black box’ warning for antidepressants
  - initially for children & adolescents
  - later extended for young people up to 25 years
**NHMRC (beyondblue) guidelines**

"Prescription of the SSRI fluoxetine should be considered for acute, short-term reduction of depressive symptoms in adolescents with moderate to severe major depressive disorder where psychological therapy has not been effective, is not available or is refused, or if symptoms are severe."

**NICE guidelines (UK)**

"If there is no response to a specific psychological therapy within four to six sessions, then . . . consider combining psychological therapy with fluoxetine."
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Effectiveness of CBT for adolescent depression

**Fig. 1** Cumulative effect sizes of cognitive-behavioral therapy over time (random effects, acute treatment stage). Information steps defined by subsequent publications. Study: 1 Reynolds and Coats, 1986; 2 Kahn and Kehle, 1990; 3 Lewinsohn et al., 1990; 4 Vostanis et al., 1996a; 5 Wood et al., 1996; 6 Brent et al., 1997; 7 Clarke et al., 1999; 8 Rossello and Bernal, 1999; 9 Clarke et al., 2002; 10 Rohde et al., 2004; 11 Treatment for Adolescents With Depression Study (TADS) Team, 2004.

Effectiveness of CBT for adolescent depression

Effect size

Recruited via advertisement

Clinically referred

Weisz (2013), *JAMA Psychiatry*
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Treatment for Adolescents with Depression Study (TADS)

- Large NIMH-funded trial
- Enrolled 439 patients between 12 and 17 years of age
- Randomised to either:
  - CBT + fluoxetine
  - fluoxetine alone
  - CBT alone
  - pill placebo
TADS results

March et al. (2004), JAMA, 292, 807-820.
Fig. 1. Response rates in TADS (Treatment for Adolescents with Depression Study).\textsuperscript{[7,30]} Response was defined as a score of ‘much’ or ‘very much’ improved on the Clinical Global Impression-Improvement scale. At week 12, COMB and FLX were better than PBO and CBT (p<0.001). Treatment groups did not differ at week 36. Last available observation was carried forward. PBO treatment continued for 12 weeks. CBT = cognitive-behavioural therapy; COMB = combination (FLX plus CBT); FLX = fluoxetine; PBO = placebo.

March et al. (2004), JAMA, 292, 807-820.
• Conducted in UK CAMHS services
• Enrolled 208 patients between 11 and 17 years of age
• Randomised to:
  • SSRI + CBT
  • SSRI + standard clinical care
ADAPT results

Mean outcome by treatment group (95% confidence interval) for the Health of the Nation outcome scale (SSRI = selective serotonin reuptake inhibitor, CBT = cognitive behaviour therapy)

Goodyer et al. (2007), BMJ, 335, 142.
• NIH-funded RCT focused on second-step treatment

• Enrolled 334 patients, 12–18 years
  • lack of response to 2 months of treatment with an SSRI

• Four treatment options:
  • switch to a different SSRI (paroxetine, citalopram, or fluoxetine, 20-40 mg daily)
  • switch to a different SSRI plus CBT;
  • switch to venlafaxine
  • switch to venlafaxine plus CBT
TORDIA results

![Graph showing the results for SSRI, Venlafaxine, No CBT, and CBT treatments. The CBT group shows a significant result with a p-value < 0.01.](image-url)
Summary

- SSRIs have modest effects
  - fluoxetine is the most effective
- CBT has modest effects in clinically referred patients
  - it should be added where there has been no response to medication
- An essential question remains unanswered:

  Is CBT alone sufficient for first-line treatment of youth MDD?
  
or
  is combined treatment with medication and CBT the better approach?
Youth depression

- Epidemiology
- Clinical features
- Treatments
- Recent trials
- YoDA trials
Youth Depression Alleviation (YoDA)

• Two trials funded by NHMRC
  – YoDA-C: A randomised controlled trial of cognitive behavioural therapy with fluoxetine or placebo
    • aims to examine whether there is any advantage to adding medication to CBT in the treatment of youth depression
  – YoDA-A: Augmentation with anti-inflammatory agents
    • aims to examine whether the addition of an anti-inflammatory agent to treatment-as-usual is useful
• A 12-week RCT of participants with moderate-to-severe MDD, who will be allocated to CBT+PBO or CBT+FLX

• Participants recruited from OYH and headspace centres in Sunshine and Glenroy

• Assessments will be completed at baseline and weeks 4, 8 and 12
  – a follow-up assessment will be completed via phone at week 26

• All patients will receive CBT, which will be offered weekly for 12 weeks
Study hypotheses

• The primary hypothesis
  – participants will show greater improvement after 12 weeks of CBT+FLX compared to CBT+PBO
  – primary outcome measure is change in MADRS score

• Secondary hypotheses
  – the CBT+FLX group will show greater improvement compared to the CBT+PBO group on efficacy, functioning, quality of life, and safety measures at 12 weeks
  – differences between groups will not be sustained at 26 weeks
Inclusion & exclusion criteria

- Aged between 15 and 25 years inclusive
- Diagnosis of MDD and score on the MADRS ≥ 20, indicating at least moderate severity
- No history of psychosis or bipolar disorder (I and II)
- No treatment with an antidepressant medication for at least the previous 2 weeks
- No previous treatment with fluoxetine that was either ineffective or poorly tolerated
CBT for youth depression

• Trial manual recently developed in YMC
• ‘Modular’ structure, allowing flexible, formulation-driven approach
• Weekly sessions offered for 12 weeks
  – participants expected to attend each week
• Therapists at headspace have been recruited to work specifically on the trial
YoDA-A

• Treatment-as-usual for 12 weeks, augmented with either:
  • aspirin 100 mg daily
  • rosvuastatin 10 mg daily
  • placebo

• Same assessments, follow-ups and use of outcome measures as for YoDA-C

• Major difference in exclusion criteria is that patients already taking antidepressant medication can be included
YoDA referrals

- email — c.davey@unimelb.edu.au
- Refer to headspace Northern Melbourne
  - phone 1300 880 218
  - mental health care plan and a referral to a psychiatrist