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**Table DS1** Study characteristics at baseline[a]

| | Treatment for Adolescents with Depression Study (2004)[3] | Clarke *et al* (2005)[13] | Melvin *et al* (2006)[15] | Adolescent Depression Antidepressant and Psychotherapy Trial (2007)[14] | Treatment of SSRI-Resistant Depression in Adolescents (2008)[12] |
|---|---|---|---|---|---|
| Entry criteria | 12–17 years, out-patients, DSM–IV major depression, CDRS–R score 45 or more | 12–18 years, DSM–IV major depression | 12–18 years, DSM–IV major depression, dysthymic disorder or depressive disorder NOS | 11–17 years, DSM–IV major depression or probable major depression (4 symptoms plus psychosocial impairment); HoNOSCA score of 7 or more | 12–18 years, DSM–IV major depression, unresponsive to 2-month treatment with SSRI |
| Trial design | 4 arms: fluoxetine, combination (fluoxetine + CBT), CBT, placebo | 2 arms: CBT + SSRI + TAU *v.* SSRI + TAU | 3 arms: sertraline *v.* sertraline + CBT *v.* CBT | 2 arms: CBT + SSRI + TAU *v.* SSRI + TAU | 4 arms: SSRI *v.* venlafaxine *v.* SSRI + CBT *v.* venlafaxine + CBT |
| Participants, *n* (total *n* = 1206) | 439 | 152 | 73 | 208 | 334 |
| Recruitment method | Clinics, advertisements (56%), primary care physicians, mental health clinicians, schools and juvenile justice facilities | Searched health maintenance organisation's medical records for those aged 12–18 with a recent dispense of SSRI prescribed by a paediatric healthcare provider. Recruited by letter and telephone | Physicians or school counsellors to child and adolescent mental health services | Child and adolescent mental health services | Clinics and advertisement (20%) |
| Exclusion criteria | IQ < 80, on antidepressants, bipolar disorder, severe conduct disorder, current substance misuse or dependence, pervasive developmental disorder, thought disorder, concurrent treatment with psychotropic medication or psychotherapy, 2 failed SSRI trials, poor response to CBT, intolerance to fluoxetine, confounding medical condition, non-English speaking participant or parent, pregnancy or refusal to use birth control. Hospitalised for dangerousness to self or others within 3 months of consent or deemed to be 'high risk' because of a suicidal attempt within 6 months of consent or active suicidal ideation. Missed > 25% school days in past months | Extreme suicidal risk, schizophrenia, significant learning disability | Major physical illness or epilepsy, bipolar disorder, organic brain syndrome, learning disability, psychosis, primary diagnosis of substance misuse, active suicidality or illness that required acute hospital admission, pregnancy or breastfeeding, current psychotropic medication | Schizophrenia, bipolar disorder, immediate admission required, pregnancy or unreliable contraception use, learning disability (inability to understand questionnaires), sensitivity or allergy to SSRI, medication and medical contraindications, previous combined optimal treatment with an SSRI and CBT with no effect | 2 or more adequate trials of an SSRI, non-response to venlafaxine or to 7 sessions of CBT, receiving CBT or psychoactive medications, except prescribed stable doses of stimulants, hypnotics or anti-anxiety, bipolar disorder, psychosis, pervasive developmental disorder, eating disorder, substance misuse, hypertension, pregnancy, breastfeeding, unprotected sex |
| Age, years: mean (s.d.) | 14.6 (1.5) | 15.3 (1.6) | 15.3 (1.5) | 14.0 (1.5) | 15.9 (1.6) |
| Female, % | 54 | 79 | 65 | 74 | 70 |
| Ethnicity, % | 21 (Black or Hispanic) | 14 ('minority') | 90% born in Australia. No specific information | 97% White European | 19% Black and minority ethnic |
| Depression severity, mean (s.d.) | | | | | |
| CDRS–R | 60.1 (10.4) | | | 59.0 (10.0) | 58.8 (10.4) |
| RADS | 79.2 | | 84.2 (13.1) | | |
| HRSD | | 21.4 (6.3) | | | |
| CES–D | | 34.6 | | | |
| CBCL depression scale | | 12.8 | | | |
| MFQ | | | | 38.1 | |
| BDI | | | | | 20.5 |

*(continued)*

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|---|---|---|---|---|---|
| Impairment, CGAS: mean (s.d.) | 49.6 (7.5) | 49.7 (8.1) | NA | 41.0 (6.2) | 50.6 (7.7) |
| Comorbidity | 52% at least one comorbid disorder | NA | 69% at least one comorbid disorder, 22% between 2 and 4 comorbid diagnoses | 89% with comorbidity. Average number of comorbid diagnoses 3 | 52% at least one comorbid diagnosis |
| Suicidality | Active suicidality excluded. SIQ–Jr mean 16, 29% scored 31 or more; Kiddie–SADS–PL thoughts of death 29% | Excluded one participant because of 'extreme suicidal risk'. No specific assessment of suicidality reported, but states '74% reported significant levels of suicidal behaviour' | Active suicidality excluded. SIQ–Jr mean 29 | Participants with active suicidality and self-harm included. Kiddie–SADS–PL: thoughts of death 47%, 26% self-harming, 16% suicidal acts | SIQ–Jr mean 41, 59% scored 31 or higher |
| Attrition to 12 weeks and follow-up | 359 participants (82%) remained and 351 (80%) were assessed in their assigned treatment group at week 12. At 36-week follow-up, 178 of 327 participants allocated to active treatment remained in their allocated treatment arm (54.4%). Of these 327, 243 adolescents remained in the study (74.3%). | Follow-up completion rate at 12 weeks was 122 participants (80.2%); 114 (75%) were assessed at 52-week follow-up | 3 participants were dissatisfied with programme or did not pursue treatment at 12 weeks. 66 (90.4%) participants completed follow-up assessment at 9.5 months | Primary end-point data were available for 202 (97%) participants at 12 weeks and 193 (93%) at 28 weeks. There were 17 teatment withdrawals at 12 weeks (8%) and 14 by 28 weeks (7%). | 287 (85.9%) participants completed 12-week assessment. The total sample was included in the overall analysis. |

NOS, not otherwise specified; HoNOSCA, Health of the Nation Outcome Scales for Children and Adolescents; CBT, cognitive–behavioural therapy; SSRI, selective serotonin reuptake inhibitor; TAU, treatment as usual; CDRS–R, Children's Depression Rating Scale-Revised; RADS, Reynolds Adolescent Depression Scale; HRSD, Hamilton Rating Scale for Depression; CES–D, Centre for Epidemiological Studies –Depression Scale; CBCL, Child Behaviour Checklist; MFQ, Mood and Feelings Questionnaire; BDI, Beck Depression Inventory; CGAS, Children's Global Assessment Scale; NA; not applicable; SIQ–Jr, Suicidal Ideation Questionnaire – Junior High School Version; Kiddie–SADS–PL, Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Present and Lifetime version.
a. Mean values relate to entire sample.

**Table DS2** Interventions

| | Treatment for Adolescents with Depression Study (2004)[3] | Clarke *et al* (2005)[13] | Melvin *et al* (2006)[15] | Adolescent Depression Antidepressant and Psychotherapy Trial (2007)[14] | Treatment of SSRI-Resistant Depression in Adolescents (2008, 2009)[12,17] |
|---|---|---|---|---|---|
| CBT in combined treatment | Individual manualised CBT, 2 parent-only sessions and 1–3 joint parent–child sessions depending on need in acute phase | Individual manualised brief CBT plus medication adherence work and consultation between therapist and prescriber. Parents offered separate monthly informational sessions | Individual manualised CBT, family and companion sessions for parents offered | Individual manualised CBT, parental participation at end of session encouraged | Individual manualised CBT, 3–6 sessions included parents |
| Combined treatment, *n* | 107 | 77 | 25 | 105 | 166 (CBT + any antidepressant) |
| Intensity and length of treatment | 50–60 min weekly individual sessions over first 12 weeks plus 2 parent and 1–3 family sessions. At 12 weeks, partial responders given 6 sessions weekly, full responders 3 biweekly sessions. After week 18, 3 6-weekly sessions to 36 weeks | 60 min sessions, 5–9 sessions in acute phase, and telephone consultation and up to 6 optional sessions offered as needed in continuation phase | 50 min weekly sessions, 2 of which were family sessions. Maintenance of 3-monthly booster sessions. Total duration 20 weeks | 55 min sessions, weekly for 12 weeks, then fortnightly for 12 weeks, with a final session at 28 weeks | 12 sessions over first 12 weeks, plus 3 extra sessions if judged necessary |
| Number of individual CBT sessions offered and mean number attended | 12 sessions offered at 12 weeks; at 36 weeks, 21 in partial responders, 18 in full responders. Mean number at 12 weeks 11; not reported at 36 weeks | Maximum 9 sessions (5 attended) in acute phase; no additional sessions requested in continuation phase over and above telephone consultation | 12 weekly sessions of acute treatment (11 attended) plus 3 booster sessions (<1 attended) | 19 sessions offered. Mean number attended by 12 weeks 7; by 28 weeks 11 | 12 (8 attended) |
| Type of therapist | CBT therapists who were either masters or doctoral level clinicians with experience of CBT for depression and/or CBT with youths | Masters degree level psychologists with previous CBT experience | Mostly psychologists, 2 general practitioners, and a social worker with previous CBT experience | Psychiatrists with agreed competence prior to study (taped session ratings). Also CBT therapists (mostly doctoral level psychologists) treated 30 participants | Masters degree level therapists with prior experience in CBT |
| Adjunct therapy | Adjunct services for attrition prevention permitted for all participants, up to 4 sessions. Combined treatment included all elements of CBT and fluoxetine alone arms, but no other routine psychosocial care | All participants could receive any non-study healthcare services (treatment as usual) | 20 participants received additional treatment (antidepressants or psychological treatment) elsewhere at the end of the acute phase | 'Treatment as usual' also given as necessary to all participants by CAMHS practitioners | All participants also received 3 sessions of family psychoeducation with clinicians, established supportive treatment allowed to continue maxium fortnightly |
| Medication | Fluoxetine. Current psychotropic medication not permitted at trial entry | SSRI. Adjunct medication permitted | Sertraline. Current psychotropic medication not permitted at trial entry, but 14 participants received antidepressants elsewhere after acute treatment | Fluoxetine primary SSRI (89%), adjunct medication permitted | Randomised to venlafaxine, fluoxetine, paroxetine or citalopram depending on previous treatment Adjunctive medications if necessary |
| *n* | 109 | 75 | 26 | 103 | 168 (any antidepressant) |
| Dose | Flexible dosing schedule 10 mg/day increased if necessary to 60 mg/day. Mean dose 28 mg for CBT group, 33 mg for SSRI alone group at 12 weeks | Not specified. 181 (s.d. = 246) days of psychotropic medication in CBT arm *v.* 309 (s.d. = 489) days in control arm | Flexible dose design, 25 mg to maximum of 100 mg/day | Flexible dose regime. Fluoxetine begun at 10 mg/day and increased up to maximum of 60 mg/day. Mean dose was 30 mg for both groups | Flexible dose design. Mean doses were 34 mg for SSRI, 205 mg for venlafaxine |

*(continued)*

**Table DS2** *(continued)*

| | Treatment for Adolescents with Depression Study (2004)[3] | Clarke *et al* (2005)[13] | Melvin *et al* (2006)[15] | Adolescent Depression Antidepressant and Psychotherapy Trial (2007)[14] | Treatment of SSRI-Resistant Depression in Adolescents (2008.2009)[12,17] |
|---|---|---|---|---|---|
| Duration | 12 weeks acute treatment, then responders and partial responders in active treatment arms entered 24-week maintenance phase | 'Treatment as usual' over 1 year | 12 weeks acute treatment, then maintenance treatment for 6 months | 28 weeks | 12 weeks |
| Number of sessions offered/attended in SSRI-alone arm | 6 sessions offered at 12 weeks, then every 6 weeks to 36 weeks (total 10 sessions offered). Mean number attended at 36 weeks not reported | Sessions offered unspecified. 5 mental health sessions attended over year | Reviewed weekly initially; once dose established reviewed every 2–3 weeks. 7 sessions attended over 18 weeks | 9 offered over 28 weeks, mean number attended 7 | Weekly for 4 weeks, then fortnightly to 12 weeks (total offered 8). Number attended not specified |
| Adverse events | At 12 weeks, treatment with fluoxetine showed an elevated risk of psychiatric adverse events (11% *v.* 5.6% fluoxetine + CBT *v.* 4.5% placebo *v.* 0.9% CBT). 3 cases of hypomania with fluoxetine, one with fluoxetine + CBT, one on placebo. Spontaneously reported physical adverse events occurred more commonly with fluoxetine and fluoxetine + CBT, but CBT had significantly greater scores on a self-report checklist. At 36 weeks, suicidal events were more common with fluoxetine compared with fluoxetine + CBT: 14.7% *v.* 8.4% (CBT 6.3%) | Not specified | 6% ($n = 6$) discontinued medication because of adverse events. Most common: fatigue, concentration, insomnia, drowsiness, restlessness. No medication change as a result of emergence or exacerbation of suicidality or mania | 59% reported side-effects in SSRI arm, 62% in combined arm. 0.5% ($n = 1$) considered to be severe (seizure possibly related to medication). Most common: headache, tiredness, nausea, reduced appetite, dry mouth, restlessness. No significant differences in suicidality between arms | No differences between treatments for adverse events, including for suicidality and self-harm. Sleep difficulties and irritability were the only psychiatric adverse events that occurred in at least 5% of participants. One episode of hypomania. There were more non-psychiatric adverse events (skin and cardiovascular problems) with venlafaxine *v.* SSRIs. Also, adolescents with higher suicidal ideation and receiving venlafaxine reported more self-harm. |
| Follow-up assessments | 6, 12, 18, 36 weeks | 6, 12, 26 and 52 weeks | 12 weeks, 9 months | 6, 12 and 28 weeks | 12 weeks |

CBT, cognitive–behavioural therapy; CAMHS, Child and Adolescent Mental Health Services; SSRI, selective serotonin reuptake inhibitor.

**Table DS3** Quantitative outcomes at 12 weeks[a]

| | Newer-generation antidepressant alone | | | Combined treatment | | | Newer-generation antidepressant minus combined | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | Mean | s.d. | *n* | Mean | s.d. | MD | WMD | 95% CI | *P* | $\tau^2$ | $I^2$, % |
| *Children's Depression Rating Scale – Revised (CDRS–R)* | | | | | | | | | | | | |
| ADAPT | 101 | 61.0 | 11.8 | 101 | 62.8 | 12.4 | −1.80 | | −5.14 to 1.54 | | | |
| TADS | 97 | 36.8 | 12.7 | 95 | 33.4 | 11.9 | 3.35 | | −0.13 to 6.83 | | | |
| TORDIA[b] | 168 | 38.1 | 12.9 | 166 | 36.9 | 13.9 | 1.20 | | −1.68 to 4.08 | | | |
| Combined CDRS–R | | | | | | | | | | | 3.32 | 55 |
| Fixed effect | | | | | | | | 0.89 | −0.96 to 2.74 | 0.35 | | |
| Random effect | | | | | | | | 0.90 | −1.88 to 3.68 | 0.53 | | |
| Hamilton Rating Scale for Depression | | | | | | | | | | | | |
| Clarke *et al* | 61 | 8.4 | 6.7 | 61 | 8.2 | 6.6 | 0.20 | | −2.16 to 2.56 | | | |
| Mood and Feelings Questionnaire | | | | | | | | | | | | |
| ADAPT | 99 | 21.6 | 14.8 | 100 | 22.7 | 15.4 | −1.10 | | −5.30 to 3.10 | | | |
| Beck Depression Inventory | | | | | | | | | | | | |
| TORDIA | 168 | 38.1 | 12.9 | 166 | 36.9 | 13.9 | −0.05 | | −2.79 to 1.79 | | | |
| Reynolds Adolescent Depression Scale (RADS) | | | | | | | | | | | | |
| TADS | 97 | 60.6 | 17.0 | 90 | 56.0 | 16.4 | 4.60 | | −0.18 to 9.38 | | | |
| Melvin *et al* | 26 | 72.9 | 16.8 | 25 | 71.6 | 18.3 | 1.28 | | −8.38 to 10.90 | | | |
| Combined RADS | | | | | | | | 3.95 | −0.33 to 8.23 | 0.07 | | |
| Centre for Epidemiological Studies – Depression Scale | | | | | | | | | | | | |
| Clarke *et al* | 61 | 16.6 | 9.6 | 61 | 15.7 | 11.3 | 0.90 | | −2.82 to 4.62 | | | |
| Children's Global Assessment Scale | | | | | | | | | | | | |
| ADAPT | 100 | 50.7 | 12.1 | 101 | 52.1 | 14.3 | −1.40 | | −5.06 to 2.26 | | | |
| TADS | 98 | 62.1 | 11.9 | 95 | 66.6 | 11.9 | −4.49 | | −7.85 to −1.13 | | | |
| TORDIA[b] | 168 | 63.3 | 11.9 | 166 | 65.1 | 11.8 | −1.80 | | −4.34 to 0.74 | | | |
| Clarke *et al* | 61 | 63.7 | 9.6 | 61 | 65.5 | 10.0 | −1.80 | | −5.82 to 1.68 | | | |
| Combined CGAS | | | | | | | | −2.32 | −3.90 to −0.74 | 0.004 | | |
| Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA) | | | | | | | | | | | | |
| ADAPT | 101 | 18.0 | 7.5 | 101 | 17.1 | 8.3 | 0.90 | | −1.28 to 3.08 | | | |
| TADS | 86 | 10.9 | 6.4 | 83 | 9.5 | 6.0 | 1.37 | | −0.49 to 3.23 | | | |
| Combined HoNOSCA | | | | | | | | 1.17 | −0.24 to 2.59 | 0.10 | | |
| Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Present and Lifetime version – suicidality | | | | | | | | | | | | |
| ADAPT[c] | 100 | 0.50 | 1.00 | 101 | 0.60 | 1.20 | −0.10 | | −0.41 to 0.21 | | | |
| Suicidal Ideation Questionnaire – Junior High School Version (SIQ–Jr) | | | | | | | | | | | | |
| TADS | 97 | 14.8 | 17.4 | 90 | 12.5 | 16.5 | 2.28 | | −2.57 to 7.13 | | | |
| TORDIA[b] | 168 | 31.4 | 17.5 | 166 | 31.7 | 20.2 | −0.30 | | −4.36 to 3.76 | | | |
| Melvin *et al* | 23 | 24.2 | 26.9 | 24 | 23.2 | 20.2 | 1.03 | | −12.62 to 14.68 | | | |
| Combined SIQ–Jr | | | | | | | | 0.77 | −2.26 to 3.81 | 0.62 | | |

MD, mean difference; WMD, weighted mean difference; ADAPT, Adolescent Depression Antidepressant and Psychotherapy Trial; TADS, Treatment for Adolescents with Depression Study; TORDIA, Treatment of SSRI-Resistant Depression in Adolescents.
a. Heterogeneity measures $\tau^2$ and $I^2$ equal zero unless shown.
b. TORDIA scores are mean of 2 arms, i.e. selective serotonin reuptake inhibitor alone + venlafaxine alone *v.* selective serotonin reuptake inhibitor + cognitive–behavioural therapy and venlafaxine + cognitive–behavioural therapy
c. ADAPT total suicidality score: mean of threshold scores for the 5 items (0 not present, 1 present).