

Best Evidence Statement (BEST)

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Treatment of children and adolescents with Major Depressive Disorder (MDD) during the Acute Phase

Clinical Question

P (population/problem)	Among children and adolescents 6 to 17 years of age diagnosed with MDD
I (intervention)	what pharmacotherapy and psychotherapy
C (comparison)	compared to placebo
O (outcome)	improves symptoms and functionality in family, educational and social domains?

Target Population Children and adolescents 6 to 17 years of age diagnosed with MDD

Excluding children with bipolar disorders, psychotic disorders, and schizophrenia

Objective of acute phase is symptomatic response and ultimately full symptom remission with treatment maintenance and continuation being the consolidation response of treatment to help avoid relapse and reoccurrence of another episode.

Recommendation(s)

All MDD Patients

1. It is recommended that the severity (brief, uncomplicated, mild, moderate or severe) of the child's or adolescent's MDD be the basis of the treatment decision (*Brent 2008 [2a], Local Consensus [5], Hughes 2007 [5a]*). (See algorithm)

Brief or Mild/Uncomplicated MDD

2. It is recommended that supportive therapy be the initial treatment for children and adolescents with brief, uncomplicated and/or mild depression continuing for 4 to 8 sessions until remission (*Brent 2008 [2a], Local Consensus [5], Birmaher 2007 [5a], Hughes 2007 [5a], NICE 2005 [5a]*)
Note 1: Supportive Psychotherapy – Includes but not limited to active listening and reflection, restoration of hope, problem solving, coping skills, and strategies for maintaining participation in treatment, psychoeducation, and family and school involvement (*Birmaher 2007 [5a]*).

Note 2: It is not warranted to prescribe antidepressant medication for the initial treatment of children and young people with mild depression (*Hughes 2007 [5a], NICE 2005 [5a]*).
3. It is recommended for non-responders to supportive therapy that psychotherapy and/or pharmacotherapy be offered/trialed in children and adolescents with mild depression. Possible therapies are:
 - a. Depression Specific Therapy (*Local Consensus [5]*)
 - b. Cognitive Behavioral Therapy (CBT) or
 - c. Interpersonal Psychotherapy (IPT)
(*Klein 2007 [1a], Brent 2008 [2a], Local Consensus [5], Birmaher 2007 [5a], Hughes 2007 [5a], NICE 2005 [5a]*).
Note: Psychotherapy appears to be more effective for youth ages 12 to 18 years (*Watanabe 2007 [1b]*).

d. Antidepressant/SSRI monotherapy (Fluoxetine, Escitalopram, Citalopram, or Sertraline) alone or with psychotherapy (*Williams 2009 [1a], Brent 2008 [2a], Local Concensus [5], Birmaher 2007 [5a], Hughes 2007 [5a], NICE 2005 [5a]*).

Note 1: Avoid antidepressant medication for initial treatment for children and adolescents with mild depression (*NICE 2005 [5a]*).

Note 2: Begin antidepressants/SSRIs at lowest dose, titrating up and down based upon effectiveness and tolerance of side effects (*Hughes 2007 [5a], NICE 2005 [5a]*).

Note 3: Treatment with antidepressants may be administered alone until the child is amenable to psychotherapy or treatment can be combined from the beginning if appropriate (*Birmaher 2007 [5a]*).

Moderate or Severe MDD

4. It is recommended children and adolescents with moderate or severe MDD begin antidepressants/SSRIs as first-line treatment with the addition of Depression Specific Therapy, CBT or IPT as clinically necessary. Possible antidepressants are:

- a. Fluoxetine (*Hetrick 2007 [1a], Wallace 2006 [1a], Whittington 2004 [1b], March 2004 [2a], Barton 2009 [5a]*)
- b. Escitalopram (*Local Concensus [5]*)
- c. Citalopram (*Williams 2009 [1a], Wallace 2006 [1a], Cheung 2005 [1a], Cheung 2006 [1b]*)
- d. Sertraline (*Hetrick 2007 [1a], Cheung 2005 [1a], Whittington 2004 [1b]*)
(*Hetrick 2007 [1a], Cheung 2005 [1a], Brent 2008 [2a], Cheung 2008 [3b], Ambrosini 1999 [4b], Local Concensus [5], Hughes 2007 [5a], NICE 2005 [5a]*).

Note 1: Combined psychotherapy with fluoxetine has been effective for some adolescents (*Williams 2009 [1a], Kratochvil 2006 [2a], March 2004 [2a], Barton 2009 [5a]*).

Note 2: Medication choice is collaborative decision/agreement between clinician, patient, and family, based upon such things as patient/family history, preferences, response to medication(s), and other considerations. (*Hughes 2007 [5a]*).

Note 3: Begin SSRIs at lowest dose, titrating upward and back down based upon effectiveness and tolerance of side effects (*Hughes 2007 [5a], NICE 2005 [5a]*).

Note 4: When a patient responds to medication(s) with symptom remission, maintain treatment for 6 months (*Hughes 2007 [5a], NICE 2005 [5a]*).

5. It is recommended that medication dosage be lowered or medication switch to one of the following alternate antidepressant/SSRI if patient does not experience adequate clinical improvement or have satisfactory symptom response or medication tolerance to initial antidepressant/SSRI treatment. Alternate antidepressants/SSRIs include:

- a. Fluoxetine,
- b. Citalopram
- c. Sertraline
- d. Escitalopram
- e. Paroxetine (adolescents only – not approved for children) (*Cheung 2005 [1a], Berard 2006 [2a], Keller 2001 [2a]*)
(*Whittington 2004 [1b], Local Concensus [5], Hughes 2007 [5a], NICE 2005 [5a]*).

6. It is recommended that treatment be augmented with one of the following for children and adolescents showing only a partial response to SSRI treatment and/or having not yet achieved remission:

- a. Lithium (*Nierenberg 2006 [2a]*)
- b. Quetiapine (*Olver 2008 [4b], Pathak 2005 [4b]*)
- c. Bupropion (*Glod 2003 [3b]*)
- d. Mirtazapine (*Haapasalo-Pesu 2004 [3b]*)
- e. Risperidone (*Local Concensus [5]*)
- f. Venlafaxine (benefit among adolescents not children) (*Cheung 2006 [1b], Emslie 2007 [2a]*)
(*Emslie 2007 [2a], Local Concensus [5], Hughes 2007 [5a]*).

Or switch to one of the following along with Depression Specific Therapy/CBT therapy:

- a. Bupropion (*Glod 2003 [3b]*)
- b. Mirtazapine (*Haapasalo-Pesu 2004 [3b]*)
- c. Venlafaxine (benefit among adolescents not children) (*Cheung 2006 [1b], Emslie 2007 [2a]*)
- d. Duloxetine
(*Brent 2008 [2a], Local Concensus [5], Hughes 2007 [5a]*).

All MDD Patients on Medications

7. It is recommended patients taking antidepressants/SSRIs be closely monitored by health care providers, family and caregivers for emergent suicidality, hostility, agitation, mania, and unusual changes in behavior, especially within the first few months of treatment or when dosage is adjusted (*Lock 2005 [5], Birmaher 2007 [5a], Hughes 2007 [5a], NICE 2005 [5a]*).

Note: A balance of benefit and harm includes consideration that treatment with antidepressants decreases the likelihood of actual suicides even though an increase in suicide behavior and thoughts has been documented in clinical trials (*Williams 2009 [1a], Bridge 2007 [1a], Lock 2005 [5]*).

8. It is recommended that once a patient responds and achieves depressive symptom remission, medication be continued at least 6 to 12 months at full therapeutic dose and be seen at least every 3 months during continuation of treatment to monitor for relapse and suicide ideation (*Nierenberg 2006 [2a], Cheung 2008 [3b], Hughes 2007 [5a]*).
9. It is recommended that antidepressants, except fluoxetine, be discontinued slowly (*Birmaher 2007 [5a], Hughes 2007 [5a], NICE 2005 [5a]*).
10. It is recommended that tricyclic antidepressants not be used in children and adolescents (*Bauer 2002 [5], Birmaher 2007 [5a], Hughes 2007 [5a], NICE 2005 [5a]*).

Discussion/summary of evidence

A review of the literature regarding treatment of major depressive disorders in children and adolescents revealed a practice parameter from the American Academy Child and Adolescent Psychiatry, an updated US Preventive Service Task Force Recommendation Statement on Screening and Treatment for Major Depressive Disorder in Children and Adolescents, a clinical guideline from the National Institute for Health and Clinical Excellence, a conference consensus medication treatment algorithm, and a Cochrane review as well as numerous meta-analysis, systematic reviews, and RCTs (*Williams 2009 [1a], Usala 2008 [1a], Bridge 2007 [1a], Hetrick 2007 [1a], Cheung 2006 [1b], Brent 2008 [2a], March 2007 [2a], March 2004 [2a], Local Concensus [5], Barton 2009 [5a], Hughes 2007 [5a], NICE 2005 [5a]*). Meta-analyses have consistently found that fluoxetine is efficacious in treating MDD in pediatric populations (*Williams 2009 [1a], Bridge 2007 [1a], Hetrick 2007 [1a], Cheung 2005 [1a]*). Per the Cochrane review by Hetrick SSRIs are effective treatments for adolescent depression (*Hetrick 2007 [1a], Local Concensus [5]*). The grade of the evidence is moderate quality for similar interventions with varying efficacy for MDD (*Williams 2009 [1a], Usala 2008 [1a], Bridge 2007 [1a], Cheung 2006 [1b], Brent 2008 [2a], Birmaher 2007 [5a], Hughes 2007 [5a]*). There are many limitations in the trials carried out leading to less than definitive answers for those caring for children and adolescents with MDD (*Hetrick 2007 [1a], Whittington 2004 [1b]*).

The authors of the systematic reviews and meta-analyses along with the local clinical consensus experts, having repeatedly looked at the same RCTs' findings, support the use of selected antidepressants in the treatment of children and adolescents with MDD (*Williams 2009 [1a], Usala 2008 [1a], Bridge 2007 [1a], Hetrick 2007 [1a], Whittington 2004 [1b], Brent 2008 [2a], March 2007 [2a], Local Concensus [5], Birmaher 2007 [5a], Hughes 2007 [5a], NICE 2005 [5a]*). The evidence for the antidepressants, SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRI), is inconsistent, but when pooled there is significance in benefit of reduction in depressive symptoms (*Williams*

2009 [1a], Usala 2008 [1a], Hetrick 2007 [1a], Cheung 2005 [1a], Cheung 2006 [1b], Whittington 2004 [1b], Brent 2008 [2a], Jureidini 2004 [5], NICE 2005 [5a]). The difficulty lies in the methodological shortcomings of the studies preventing interpretation of the efficacy of the SSRIs (Williams 2009 [1a], Usala 2008 [1a], Cheung 2005 [1a], Watanabe 2007 [1b], Cheung 2006 [1b], Brent 2008 [2a]). Several treatment strategies used in clinical practice such as the Texas Treatment Algorithm were not tested in children, yet are being used effectively in practice today (Brent 2008 [2a], Local Consensus [5]).

Data indicate that about 60% of adolescents achieve adequate symptom response with initial SSRIs, leaving 40% with inadequate response (Hetrick 2007 [1a], Brent 2008 [2a]). The combination of CBT and medication has been found to be superior to CBT or medication alone for achieving remission or reduction of symptoms (Klein 2007 [1a], Brent 2008 [2a], March 2007 [2a], Kennard 2006 [2a], TADS Team 2005 [2a], Vitiello 2008 [5]). Fluoxetine alone or in combination has been shown to accelerate improvements in depression (TADS Team 2005 [2a]). In the Adolescent Depression, Antidepressants and Psychotherapy Trial (ADAPT), no difference was found by adding CBT to patients already receiving SSRIs (Goodyer 2007 [2a]). The cardinal study, Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial, led clinicians to switch to alternate SSRIs or venlafaxine, and CBT when initial SSRIs were not effective (Brent 2008 [2a]). Along with these findings and consistent with the initial Treatment for Adolescents with Depression Study (TADS) results Asarnow concluded the addition of CBT yields benefit even among the most severely ill youth when first and second stages of treatment are not effective (Asarnow 2009 [2a], March 2007 [2a], TADS Team 2005 [2a], March 2004 [2a], Vitiello 2008 [5], Barton 2009 [5a]). In fact, not only did TADS demonstrate clinically meaningful improvements but also the combination of fluoxetine and CBT produced the greatest improvement as long-term treatment and help prevent relapse in symptoms of MDD (March 2007 [2a], TADS Team 2005 [2a], March 2004 [2a]). The differences in some of these study findings are attributed to differences in sample participants and study designs (Klein 2007 [1a], Brent 2009 [5]).

Watanabe et al conducted a systematic review of 27 studies of patients (6 to 18 years) suffering from mild to moderate depressive symptoms, the authors concluded CBT and IPT alone were more effective than no treatment, wait-listing or attention placebo at post-treatment and may be effective for up to 6 months (Watanabe 2007 [1b]). Trials involving psychotherapy showed greater symptom reduction compared to other controlled conditions (Williams 2009 [1a]). Psychotherapy is the treatment for depressed youths in the short term, but augmenting psychotherapy with antidepressant therapy could improve the effectiveness of psychotherapy (Watanabe 2007 [1b], TADS Team 2005 [2a]).

For patients with mild MDD supportive therapy is equally efficacious than CBT or IPT (Birmaher 2007 [5a]). Current RCT's reveal up to 60% of children and adolescents with MDD, respond to placebo (Birmaher 2007 [5a]), with more severe MDD requiring CBT, IPT and antidepressants.

Health Benefits, Side Effects and Risks

Benefits

- 60% of children and adolescents with MDD respond to placebo, indicating any level of care provides positive outcome (Bridge 2007 [1a], Cheung 2005 [1a], Berard 2006 [2a])
- 15 to 30% respond to brief supportive treatment (Goodyer 2007 [2a], Renaud 1998 [2a])
- SSRIs are an effective treatment for adolescent depression (Hetrick 2007 [1a])
- Supportive therapy is effective for mild MDD as is CBT and IPT (Birmaher 2007 [5a])
- Patients are more likely to benefit from antidepressant treatment than commit suicide (Williams 2009 [1a], Bridge 2007 [1a], Cheung 2005 [1a], Hughes 2007 [5a]), risk and benefit need to be weighed by clinicians (Williams 2009 [1a]) due to the risk of suicide ideation tied to SSRIs.
- All treatment arms of TADS were effective in reducing suicide ideations (Emslie 2006 [2a]).

- During the 1990s the number of suicides decreased among youths in the United States as the number of antidepressant prescriptions increased (Hughes 2007 [5a]).
- CBT therapy appears to minimize persistent suicidal ideations and behaviors (TADS Team 2005 [2a], Barton 2009 [5a]).
- Antidepressants/SSRIs have been well tolerated by pediatric population with few short-term side effects (Hetrick 2007 [1a], Cheung 2005 [1a], Local Consensus [5]).

Adverse events

- None of the psychotherapy studies in Watanabe's systematic review reported adverse effects (Watanabe 2007 [1b]).
- Adverse events for SSRIs include suicide ideations – passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior, yet no suicide deaths occurred in any of the trials of this systematic review (Williams 2009 [1a]). Patients treated with fluoxetine therapy show more clinically significant suicidal ideation than those treated with CBT or combination, CBT and fluoxetine (TADS Team 2005 [2a]).
- Overall SSRIs were well tolerated with the main side effects including headache, diarrhea, nausea, vomiting, fatigue, insomnia, agitation, irritability and behavioral changes (anxiety, hostility and impulsivity) (Hetrick 2007 [1a], Cheung 2005 [1a], Cheung 2008 [3b]).
- Side effects can be addressed with dose titration or medication change and appear to subside with time (Donnelly 2006 [2a], Birmaher 2007 [5a], Hughes 2007 [5a])

Risks

- Increased risk of suicide which is the 3rd leading cause of death among those 15 to 24 years of age and 6th leading cause of death among those 5 to 14 years of age (Barton 2009 [5a]).
- Treating youth with antidepressants leads to a 1 to 3% increase in suicidal ideation and/or behavior (Williams 2009 [1a], Cheung 2005 [1a], Watanabe 2007 [1b])
- Difficulty differentiating disease process from adverse events of treatments, including medications when suicide attempts are made while on SSRIs (Williams 2009 [1a], Cheung 2005 [1a]) and difficulty drawing conclusions about the association between suicide related events and SSRIs (Williams 2009 [1a])
- Since the FDA's "black box warning" the number of SSRI prescriptions decreased and the number of suicides increased (Hughes 2007 [5a])
- Patients may be at risk for relapse and need to be assessed for residual symptoms of depression (Hughes 2007 [5a]).

References/citations

1. **Ambrosini, P. J. et al.:** Multicenter Open-Label Sertraline Study in Adolescent Outpatients With Major Depression. *J Am Acad Child Adolesc Psychiatry*, 38(5): 566-572, 1999, [4b] _____.
2. **Asarnow, J. R. et al.:** Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. *Journal of the American Academy of Child & Adolescent Psychiatry*, 48(3): 330-9, 2009, [2a] _____.
3. **Barton, B.:** Screening and treatment for major depressive disorder in children and adolescents: US Preventive Services Task Force Recommendation Statement. *Pediatrics*, 123(4): 1223-8, 2009, [5a] _____.
4. **Bauer, M.; Whybrow, P. C.; Angst, J.; Versiani, M.; and Moller, H. J.:** World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 2: Maintenance treatment of major depressive disorder and treatment of chronic depressive disorders and subthreshold depressions. *World J Biol Psychiatry*, 3(2): 69-86, 2002, [5] _____.
5. **Berard, R. et al.:** An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. *Journal of Child & Adolescent Psychopharmacology*, 16(1-2): 59-75, 2006, [2a] _____.

6. **Birmaher, B. et al.:** Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry*, 46(11): 1503-26, 2007, [5a] [_____](#) 
7. **Brent, D. et al.:** Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA*, 299(8): 901-13, 2008, [2a] [_____](#) 
8. **Brent, D. A., and Maalouf, F. T.:** Pediatric depression: is there evidence to improve evidence-based treatments? *J Child Psychol Psychiatry*, 50(1-2): 143-52, 2009, [5] [_____](#) 
9. **Bridge, J. A.; Iyengar, S.; Salary, C. B.; Barbe, R. P.; Birmaher, B.; Pincus, H. A.; Ren, L.; and Brent, D. A.:** Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials.[see comment]. *JAMA*, 297(15): 1683-96, 2007, [1a] [_____](#) 
10. **Cheung, A.; Kusumakar, V.; Kutcher, S.; Dubo, E.; Garland, J.; Weiss, M.; Kiss, A.; and Levitt, A.:** Maintenance study for adolescent depression. *J Child Adolesc Psychopharmacol*, 18(4): 389-94, 2008, [3b] [_____](#) 
11. **Cheung, A. H.; Emslie, G. J.; and Mayes, T. L.:** Review of the efficacy and safety of antidepressants in youth depression. *J Child Psychol Psychiatry*, 46(7): 735-54, 2005, [1a] [_____](#) 
12. **Cheung, A. H.; Emslie, G. J.; and Mayes, T. L.:** The use of antidepressants to treat depression in children and adolescents. *CMAJ*, 174(2): 193-200, 2006, [1b] [_____](#) 
13. **Donnelly, c. l. m. d.; WAGNER, K. D. M. D., Ph.D.; Rynn, m. m. d.; Ambrosini, p. m. d.; Landau, p. m. d.; YANG, R. P. D., and; and WOHLBERG, C. J. M. D., Ph.D.:** Sertraline in Children and Adolescents With Major Depressive Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 45(10): 1162-1170, 2006, [2a] [_____](#) 
14. **Emslie, g. j. m. d.; Findling, r. l. m. d.; Yeung, p. p. m. d.; KUNZ, N. R. P. D.; and LI, Y. P. D.:** Venlafaxine ER for the Treatment of Pediatric Subjects With Depression: Results of Two Placebo-Controlled Trials. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46(4): 479-488, 2007, [2a] [_____](#) 
15. **Emslie, g. m. d. et al.:** Treatment for Adolescents With Depression Study (TADS): Safety Results. *Journal of the American Academy of Child & Adolescent Psychiatry*, 45(12): 1440-1455, 2006, [2a] [_____](#) 
16. **Glod, C. A. et al.:** Open trial of bupropion SR in adolescent major depression. *Journal of Child & Adolescent Psychiatric Nursing*, 16(3): 123-30, 2003, [3b] [_____](#) 
17. **Goodyer, I. et al.:** Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomised controlled trial. *BMJ*, 335(7611): 142, 2007, [2a] [_____](#) 
18. **Haapasalo-Pesu, K. M.; Vuola, T.; Lahelma, L.; Marttunen, M.; Haapasalo-Pesu, K.-M.; Vuola, T.; Lahelma, L.; and Marttunen, M.:** Mirtazapine in the treatment of adolescents with major depression: an open-label, multicenter pilot study. *Journal of Child & Adolescent Psychopharmacology*, 14(2): 175-84, 2004, [3b] [_____](#) 
19. **Hetrick, S.; Merry, S.; McKenzie, J.; Sindahl, P.; and Proctor, M.:** Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database Syst Rev*, (3): CD004851, 2007, [1a] [_____](#) 
20. **Hughes, C. W. et al.:** Texas Children's Medication Algorithm Project: update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. *J Am Acad Child Adolesc Psychiatry*, 46(6): 667-86, 2007, [5a] [_____](#) 
21. **Jureidini, J. N.; Doecke, C. J.; Mansfield, P. R.; Haby, M. M.; Menkes, D. B.; and Tonkin, A. L.:** Efficacy and safety of antidepressants for children and adolescents. *BMJ (Clinical Research Ed.)*, 328(7444): 879-883, 2004, [5] [_____](#) 
22. **Keller, M. B. et al.:** Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*, 40(7): 762-72, 2001, [2a] [_____](#) 
23. **Kennard, B. D.; Stewart, S. M.; Hughes, J. L.; Jarrett, R. B.; and Emslie, G. J.:** Developing cognitive behavioral therapy to prevent depressive relapse in youth. *Cognitive and Behavioral Practice*, 15(4): 387-399, 2008, [4b] [_____](#) 
24. **Kennard, B. P. D. et al.:** Remission and Residual Symptoms After Short-Term Treatment in the Treatment of Adolescents With Depression Study (TADS). *Journal of the American Academy of Child & Adolescent Psychiatry*, 45(12): 1404-1411, 2006, [2a] [_____](#) 
25. **Klein, J. B.; Jacobs, R. H.; and Reinecke, M. A.:** Cognitive-behavioral therapy for adolescent depression: a meta-analytic investigation of changes in effect-size estimates.[see comment]. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46(11): 1403-13, 2007, [1a] [_____](#) 
26. **Kratochvil, C. et al.:** Acute time to response in the Treatment for Adolescents with Depression Study (TADS).[see comment]. *Journal of the American Academy of Child & Adolescent Psychiatry*, 45(12): 1412-8, 2006, [2a] [_____](#) 
27. **Local Consensus:** During BEST development time frame. [5] [_____](#) 
28. **Lock, J.; Walker, L. R.; Rickert, V. I.; and Katzman, D. K.:** Suicidality in adolescents being treated with antidepressant medications and the black box label: position paper of the Society for Adolescent Medicine. *J Adolesc Health*, 36(1): 92-3, 2005, [5] [_____](#) 
29. **March, J. et al.:** Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*, 292(7): 807-20, 2004, [2a] [_____](#) 
30. **March, J. S. et al.:** The Treatment for Adolescents With Depression Study (TADS): long-term effectiveness and safety outcomes. *Arch Gen Psychiatry*, 64(10): 1132-43, 2007, [2a] [_____](#) 
31. **NICE, N. I. f. H. a. C. E.:** Depression in Children and Young People: Identification and management in primary, community and secondary care. 2005, [5a] [_____](#) 
32. **Nierenberg, A. A. et al.:** A Comparison of Lithium and T3 Augmentation Following Two Failed Medication Treatments for Depreaaon: A STAR*D Report. *Am J Psychiatry*, 163(9): 1519-1530, 2006, [2a] [_____](#) 

33. **Olver, J. S. et al.:** Quetiapine augmentation in depressed patients with partial response to antidepressants. *Human Psychopharmacology*, 23(8): 653-60, 2008, [4b] .
34. **Pathak, S.; Johns, E. S.; Kowatch, R. A.; Pathak, S.; Johns, E. S.; and Kowatch, R. A.:** Adjunctive quetiapine for treatment-resistant adolescent major depressive disorder: a case series. *Journal of Child & Adolescent Psychopharmacology*, 15(4): 696-702, 2005, [4b] .
35. **Renaud, J.; Brent, D. A.; Baugher, M.; Birmaher, B.; Kolko, D. J.; and Bridge, J.:** Rapid response to psychosocial treatment for adolescent depression: a two-year follow-up. *Journal of the American Academy of Child & Adolescent Psychiatry*, 37(11): 1184-90, 1998, [2a]  .
36. **TADS Team, T.:** The Treatment for Adolescents With Depression Study (TADS): Demographic and Clinical Characteristics. *Journal of the American Academy of Child & Adolescent Psychiatry*, 44(1): 28-40, 2005, [2a]  .
37. **Usala, T.; Clavenna, A.; Zuddas, A.; and Bonati, M.:** Randomised controlled trials of selective serotonin reuptake inhibitors in treating depression in children and adolescents: a systematic review and meta-analysis. *European Neuropsychopharmacology*, 18(1): 62-73, 2008, [1a] .
38. **Vitiello, B. M. D. et al.:** Cognitive-Behavioral Therapy to Prevent Relapse in Pediatric Responders to Pharmacotherapy for Major Depressive Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 47(12): 1395-1404, 2008, [5] .
39. **Wallace, A. E.; Neily, J.; Weeks, W. B.; and Friedman, M. J.:** A cumulative meta-analysis of selective serotonin reuptake inhibitors in pediatric depression: did unpublished studies influence the efficacy/safety debate? *Journal of Child & Adolescent Psychopharmacology*, 16(1-2): 37-58, 2006, [1a] .
40. **Watanabe, N.; Hunot, V.; Omori, I. M.; Churchill, R.; and Furukawa, T. A.:** Psychotherapy for depression among children and adolescents: a systematic review.[see comment]. *Acta Psychiatrica Scandinavica*, 116(2): 84-95, 2007, [1b] .
41. **Whittington, C. J.; Kendall, T.; Fonagy, P.; Cottrell, D.; Cotgrove, A.; and Boddington, E.:** Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet*, 363(9418): 1341-1345, 2004, [1b] .
42. **Williams, S. B.; O'Connor, E. A.; Eder, M.; and Whitlock, E. P.:** Screening for child and adolescent depression in primary care settings: a systematic evidence review for the US Preventive Services Task Force. *Pediatrics*, 123(4): e716-35, 2009, [1a]  .
43. **Winters, N. C.; Collett, B. R.; and Myers, K. M.:** Ten-year review of rating scales, VII: scales assessing functional impairment. *J Am Acad Child Adolesc Psychiatry*, 44(4): 309-38; discussion 339-42, 2005, [5a]  .

Note: Full tables of evidence grading system available in separate document:

- Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality (abbreviated table below)
<http://groups/ce/NewEBC/EBCFiles/Table-EvidenceLevels.pdf>
- Grading a Body of Evidence to Answer a Clinical Question
<http://groups/ce/NewEBC/EBCFiles/GradingBodyOfEvidence.pdf>
- Judging the Strength of a Recommendation (abbreviated table below)
<http://groups/ce/NewEBC/Judgingthestrengthofarecommendation.pdf>

Table of Evidence Levels (see note above)

<i>Quality level</i>	<i>Definition</i>
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

<i>Strength</i>	<i>Definition</i>
“Strongly recommended”	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
“Recommended”	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.
Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.	
<ol style="list-style-type: none"> 1. Grade of the Body of Evidence (see note above) 2. Safety / Harm 3. Health benefit to patient (<i>direct benefit</i>) 4. Burden to patient of adherence to recommendation (<i>cost, hassle, discomfort, pain, motivation, ability to adhere, time</i>) 5. Cost-effectiveness to healthcare system (<i>balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis</i>) 6. Directness (<i>the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome]</i>) 7. Impact on morbidity/mortality or quality of life 	

Supporting information

Introductory/background information

Major depressive disorder affects up to 10% of youth with the incidence in children having been estimated at 2% and adolescents increasing up to 8%. Untreated depressive disorders result in impairment in schools, interpersonal relationships, occupational adjustment, and increases the risk of suicide (Brent 2008 [2a]). Suicide ranks third as a cause of death among adolescents in the United States of America. The risk of suicide and morbidity from untreated depression is far greater than the risk of taking antidepressants (Winters 2005 [5a]).

Symptom remission is the goal of treatment for MDD, but it is estimated at least 40% of youth do not experience symptom relief during treatment (Hetrick 2007 [1a], Brent 2008 [2a]). Relapse rates range from 30 % to 40% within 1 to 2 years after acute treatment (Kennard 2008 [4b]). Pharmacotherapy has been shown to reduce symptoms rapidly in the acute phase; however children and adolescents often report ongoing residual

symptoms and often relapse. CBT has been shown to prevent relapse, increase wellness, helping patients to develop skills to promote and sustain well-being (*Kennard 2008 [4b]*).

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Search strategy

1. Original Search

depression.mp. **OR** major depression.mp. **OR** exp Depressive Disorder, Major/
Antidepressant and each individual antidepressant and drug: Fluoxetine, Citalopram, Sertraline,
Escitalopram, Paroxetine, Lithium, Bupropion, Mirtazapine, Risperidone, and Venlafaxine
Selective Serotonin Reuptake Inhibitors (SSRIs)
Cognitive Behavioral Therapy (CBT) or Interpersonal Psychotherapy (IPT)

Limits:

- english language
- "child (6 to 12 years)" or "adolescent (13 to 18 years)"
OR *pediatr* \$/* **OR** *child* \$/* **OR** *adolesc* \$/* **OR** *teen* \$/*
- (guideline or meta analysis or practice guidelines or systematic review).pt. or "the cochrane library".jn. or
"cochrane database of systematic reviews".jn.

2. Additional articles – identified from reference lists, systematic reviews, and clinicians

Applicability issues

Psychotherapies are not readily available (*Williams 2009 [1a]*, *Usala 2008 [1a]*, *TADS Team 2005 [2a]*).
Although findings to date are promising, existing treatments are not entirely effective (*Klein 2007 [1a]*).

Applicable Outcome Measures

Percentage of follow-up patients with depression who demonstrate an improvement in their symptom and function status from initial assessment to their most recent assessment (as assessed by QIDS-17).

Percentage of patients who were diagnosed with a new episode of depression and treated with antidepressant medication, who remained on antidepressant medication for at least 180 days (if medication tolerated).

Copies of this Best Evidence Statement (BEST) are available online and may be distributed by any organization for the global purpose of improving child health outcomes. Website address: <http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/default.htm>
Examples of approved uses of the BEST include the following:

- copies may be provided to anyone involved in the organization's process for developing and implementing evidence based care;
- hyperlinks to the CCHMC website may be placed on the organization's website;
- the BEST may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents; and
- copies may be provided to patients and the clinicians who manage their care.

Notification of CCHMC at HPCEInfo@cchmc.org for any BEST adopted, adapted, implemented or hyperlinked by the organization is appreciated.

Additionally for more information about CCHMC Best Evidence Statements and the development process, contact the Health Policy & Clinical Effectiveness office at: 513-636-2501 or HPCEInfo@chmcc.org.

[as appropriate, substitute *Center for Professional Excellence/Research and Evidence-based Practice office at CPE-EBP-Group@chmcc.org* for the contact information. If the BEST was developed by another group, the appropriate contact information ought to be substituted.]

Note

This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

Reviewed by Cincinnati Children's Hospital Medical Center Evidence Federation

Appendix Treatment Algorithm

