Increasing Your Confidence in Treating Pediatric Depression and Anxiety

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I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial services discussed in this CME activity.

Feeling confident with what you recommend

• What might happen without treatment?
• What treatments work?
  • Data in the literature
  • Clinical experience*
  • Availability of treatment*

• * Call us! 1-866-599-PALS (7257)
Depression

Some statistics to consider

- Adolescent depression affects 12-25% of adolescents
- Onset prior to age 12 linked to poor functioning, suicide attempts, more lifetime depression, psychiatric comorbidity.
- Generally associated with poor academic, social, and health outcomes; substance abuse, early pregnancy and parenthood, and increased healthcare costs
- Suicide is the 2nd leading cause of death for our youth ages 10-24
- More teenagers and young adults die from suicide than from cancer, heart disease, AIDS, birth defects, stroke, pneumonia, influenza, and chronic lung disease, COMBINED
- Despite these statistics, 80% of adolescents do not receive appropriate treatment

The Natural History of Depression

- 1580 high school students 14-18 yo
- Mean age of onset of first episode of MDD was 14.9
- MDE duration mean 26.4 weeks, median 8.0 weeks
  - Previous studies: Mean 32-36 weeks, median 16 weeks
- Relapse:
  - 5% within 6 months
  - 12% within a year
  - 33% within 4 years
  - Previous studies: 20% relapse in 1 year, 40% in 2 years
Screening Tools for Depression

**PHQ-9A (Adolescent)**
- A normed for ages 12-18
- Score of 11 has a sensitivity (89.5%) and specificity (77.5%)
- Similar to those in adults
- PHQ-9A scores reflect severity
  - Mild: 5-10
  - Moderate: 11-14
  - Moderately Severe: 15-19
  - Severe: >20

**Short Mood and Feelings Questionnaire (SMFQ)**
- Can be used in children ages 6-17
- Child and parent report in combination have the greatest efficiency in predicting depression severity
- Combined scores (parents+child)>10 concerning for depression
- Individually have concern if:
  - Child score>7
  - Parent score>4


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The Treatment of Adolescents with Depression Study (TADS)

**Design**
- 439 12-17 y.o. with MDD
- Fluoxetine, CBT, combo, or placebo
- 12 weeks blinded, 24 weeks unblinded

**Results**
- Rates of response (12 weeks):
  - Combo 71.0%>fluoxetine 60.6%>CBT 43.2%>placebo 34.8%
- Suicidal thinking in 29% at baseline, improved significantly in all 4 groups but greatest improvement in combo at 12 wks
- Suicidal events by 36 weeks:
  - Fluoxetine 14.7%>combo 8.4% or CBT 6.3%

1. TADs Study Team. *JAMA* 2004;292(7), 807
2. March et al. *Arch Gen Psych* 2007; 64(10):1132

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TADS 1 yr follow-up

At one year follow-up benefits persisted
TADS - Conclusions

- Treatment of depression with fluoxetine alone or in combo with CBT accelerates response
- Adding CBT to meds enhances the safety of meds
- Therefore, combined treatment superior to monotherapy

Initial treatment of depression

- Mild/uncomplicated/brief
  - Psychoeducation
  - Supportive management - active listening and reflection, restoration of hope, problem solving, coping skills, and strategies for maintaining participation in treatment
  - Case management — environmental stressors in family and school
- Moderate
  - CBT (or IPT)
  - Consider SSRI – not responding, not ready for therapy
- Severe/suicidal ideation
  - CBT (or IPT) and SSRI

Which SSRI to start with?

- Fluoxetine – multiple positive RCTs, FDA approved 8 and up
  - Very little SI signal in controlled studies
  - Long half life means no withdrawal symptoms from missed doses
  - Covered by all plans, and available generic
  - Available in once a week dosing:
    - Start patient on short acting fluoxetine and stabilize at 20 mg dose
    - Then stop fluoxetine 20 mg/day and start fluoxetine 90 mg/week capsule 7 days after last 20 mg dose
  - Caution: Medication interactions
Fluoxetine in the press this year!

August 2016 Lancet article by Cipriani et al. “Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis”.

- Meta-analysis of 34 RCT’s for the acute treatment of MDD, included 5260 patients
- For SSRI monotherapy for depression in adolescents, Fluoxetine is the only antidepressant with statistically significant change from placebo
- Take home: Fluoxetine should be first line treatment if choosing an SSRI for a depressed teen with moderate-to-severe depression without access to psychotherapy or who is not responding to therapy alone

Which SSRI to start with? (cont.)

- Sertraline* – 1 positive RCT
- Citalopram* – 1 positive RCT
  - Caution: QT prolongation, doses over 40 mg not recommended and caution advised with other QT prolonging medication or meds/conditions that would decrease citalopram metabolism
- Escitalopram – 1 mixed result RCT (only adolescent subset positive), FDA approved 12 and up

* Not FDA approved for depression treatment <18

Medicating Major Depression

- Start low, go slow
- Change one medicine at a time
- Use the full dose range, wait 4-6 weeks before each increase
Predictors of poor response to SSRIs with/without CBT

- Depression severity and chronicity
- Hopelessness
- Suicidal ideation
- Family conflict
- Functional impairment
- History of abuse
- Non-suicidal self injury (NSSI)
- Older age and lower family income (TADS study)
- Comorbidity (TADS)

Treatment of Resistant Depression in Adolescents (TORDIA)

- Design
  - 334 12-18 y.o. with MDD that had not responded to 2 mo on SSRI
  - Switch to: (1) 2nd SSRI, (2) 2nd SSRI and CBT, (3) venlafaxine, (4) venlafaxine and CBT
    - 12 weeks blind, 12 more open
- Results
  - Rates of response (12 weeks)
    - CBT plus either med 54.8%, med alone 40.5%
    - No difference in response between 2nd SSRI and venlafaxine
- Adverse Effects
  - No differential treatment effects on SI
  - More AEs with venlafaxine
    - Increase diastolic BP and pulse
    - Skin problems
    - Associated with a higher rate of self-harm adverse events in those with higher SI

TORDIA - Conclusions

- For adolescents with depression not responding to first SSRI:
  - Continued treatment results in remission in approximately 1/3 of patients
  - Eventual remission is evident within the first 6 weeks in many
  - Earlier intervention may be important
  - Switch to 2nd SSRI just as efficacious as a switch to venlafaxine
    - SSRI had fewer adverse effects
  - Combo of CBT + new med > new med alone
After two SSRIs don’t work - depression

- Venlafaxine*
  - Combo of 2 RCTs (2ndary analysis) showed positive effect for adolescents
- Cymbalta*
  - 1 open label safety study
- Bupropion*
  - Open label positive studies in adolescents
- Mirtazapine*
  - Open label positive study in adolescents
- Tricyclic antidepressants*
  - Serious side effects, fatal in overdose
- Meta-analysis – not superior over placebo in kids
- Other augmenting agents*

*Not FDA approved for depression treatment <18

Switching antidepressants

- Cross taper vs. switch over
- Potential concerns:
  - Discontinuation syndrome
  - Relapse of partially treated symptoms
  - Side effects to new medication
  - Medication interactions
    - Serotonin syndrome
    - P450 2D6
      - fluoxetine and paroxetine strongly inhibit it, most commonly used antidepressants are substrates
  - Time to get to therapeutic dose of new med
  - Complexity of instructions
Antidepressant medication in adults: Switching and discontinuing medication, Hirsch and Birnbaum, UpToDate Feb 13. 2012.  Accessed 8/13/12

Alternative Treatments

- **Exercise**
  - 2006 Cochrane review found 28 RCTs, 4 highest quality showed small benefit for adults with MDD
  - J Consult Clin Psychol 2010; 78: 268-272
  - Prospective longitudinal study on youth with MDD: increased physical activity in those (11-15 yrs) who increased by 10% or more after 6-12 months.
  - 2006 Cochrane review 2006; 78: 268-272
  - J Consult Clin Psychol 2010; 78: 268-272: increased physical activity in teens (11-15 y/o) who increased by 10% for each additional type of activity

- **Bright light therapy**
  - Bright light therapy effective in adults with non-seasonal MDD both as monotherapy and in combination with fluoxetine
  - Small RCT in JAMA Psychiatry 2019;73(1):56-63
  - 28 adolescents in RTC improved on BDI with light therapy compared to placebo

- **Omega-3 fatty acids**
  - RCT in Am J Psychiatry 2006; 163(6): 1098
  - 20 patients showed improved with omega-3 monotherapy

- **St. John's wort**
  - www.nccam.nih.gov/health/stjohnswort
  - Inconsistent data in adults only, no RCT's in youth
  - Drug interactions: can potentiate serotonergic drugs and increase risk of serotonin syndrome

- **SAM-E**
  - One positive systematic review in adults, no RCT's in youth

- **5-Hydroxytryptophan (5HTP)**
  - Mixed results in adults, no RCT's in youth

- **Glutamine**
  - No RCT's in youth

- **Vitamin D**
  - No RCT's in youth

- **Reiki**
  - Positive RCT in Psychiatry Research 2016; 239: 325-330
  - No benefit in trial, compared CBT, Reiki and waitlist, and showed CBT > Reiki > waitlist
Once things stabilize...

- Treatment should be continued for 6 to 12 months during the continuation phase
  - Patients typically seen at least monthly, depending on clinical status, functioning, support systems, environmental stressors, motivation for treatment, and the presence of comorbid psychiatric or medical disorders.
- General rule of thumb: the longer it takes to recover or the higher the # of recurrences, the longer the period of maintenance.
  - ≥2 episodes of depression, 1 severe episode, or chronic episodes should have maintenance treatment for > 1 yr.

Anxiety

The natural history of anxiety

- Harvard/Brown Anxiety Research Project
  - Adult patients of psychiatric clinics
    - Remission at one year
      - Panic disorder - ~40%
      - Panic disorder with agoraphobia - ~15%
      - Social phobia - ~7%
      - GAD - ~10-15%
    - Remission at 8 years
      - Panic disorder - ~70-75%
      - Panic disorder with agoraphobia - ~35-40%
      - Social phobia - ~30%
      - GAD - 45-55%
The natural history of anxiety

- Cumulative Probability of Relapse after 8 years
  - Panic disorder ~20-60% (gender variable)
  - Panic disorder with agoraphobia ~40-50%
  - Social phobia ~30%
  - GAD ~40%

- Important points
  - Anxiety disorders are chronic in majority of men and women
  - Patients who experienced remission were more likely to improve during first 2 years

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Child/adolescent Anxiety Multimodal Study (CAMS)

- Design
  - 488 7-17 y.o. with SAD, GAD or SP
  - 14 sessions of CBT, sertraline, combo, or placebo
  - 12 weeks

- Results
  - Very much or much improved:
    - 80.7% combo
    - 59.7% CBT
    - 54.9% sertraline
    - 23.7% placebo
  - Pediatric anxiety rating scale, similar results
  - SI no more frequent in sertraline than placebo, no suicide attempts

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CAMS - Conclusion

- CBT and sertraline both work, combo of the two has superior response rate
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- CBT and sertraline both work, combo of the two has superior response rate

The Pediatric OCD Treatment Study (POTS)

- Design
  - 112 7-17 y.o. with OCD
  - Sertraline, CBT, combo, or placebo
  - 12 weeks
- Results
  - Improvement in CY-BOCS
    - Combo > CBT = sertraline > placebo
  - Clinical remission
    - Combo 53.6%
    - CBT 39.3%
    - Sertraline 21.4%
    - Placebo 3.6%
  - No patient became suicidal or made an attempt
- Conclusion
  - Youth with OCD should begin with CBT or CBT plus SSRI

Screening Measures for Anxiety—SCARED (child and parent versions)

- Free, ages 9-17
- Broad screen for global anxiety
- Also has subscales for specific anxiety diagnoses
- Brief version for tracking over time
- Available in several languages
Additional screeners for anxiety

- SPENCE Children’s Anxiety Scale [http://scaswebsite.com]
  - Free, has child, parent and teacher scales
  - Ages 3-17
  - Available in many (28+) languages
  - 44 item measure for child and 38 item measure for parent
  - Screens for somatization, panic, GAD, separation anxiety and social phobia

- GAD7
  - Free
  - Brief, only 7 questions
  - Validated for ages 14 and up
  - Scores 0-21 with >5 (mild), >10 (moderate), >15 (severe)
  - Total score >10 should trigger extended evaluation


Initial treatment of anxiety

- Mild
  - CBT (or other therapy)

- Moderate
  - CBT
  - Consider SSRI—esp. if not responding, not ready for therapy

- Severe
  - CBT and SSRI


Anxiety Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Strength Form</th>
<th>Oral bioavailability</th>
<th>Active ingredients</th>
<th>Common dose range (mg/day)</th>
<th>NTRC approved?</th>
<th>FDA approved?</th>
<th>Off-label use</th>
<th>Efficacy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>20, 40 mg tablets</td>
<td>75%</td>
<td>Fluoxetine</td>
<td>20-80</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>Start with 20 mg and increase by 10 mg every week up to 80 mg</td>
</tr>
<tr>
<td>Nortriptyline (Pamelor)</td>
<td>25, 100 mg tablets</td>
<td>70%</td>
<td>Nortriptyline</td>
<td>25-150</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>Increase slowly by 25 mg every week up to 150 mg</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>20, 40 mg tablets</td>
<td>60%</td>
<td>Paroxetine</td>
<td>20-60</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>Start with 20 mg and increase by 10 mg every week up to 60 mg</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>50 mg tablets</td>
<td>60%</td>
<td>Sertraline</td>
<td>50-200</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>Start with 50 mg and increase by 50 mg every 2-4 weeks up to 200 mg</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>75 mg tablets</td>
<td>50%</td>
<td>Venlafaxine</td>
<td>75-375</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>Start with 75 mg and increase by 75 mg every 2-4 weeks up to 375 mg</td>
</tr>
<tr>
<td>Vortioxetine (悯乐)</td>
<td>5, 10, 15 mg capsules</td>
<td>90%</td>
<td>Vortioxetine</td>
<td>5-20</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>Start with 5 mg and increase by 5 mg every week up to 20 mg</td>
</tr>
</tbody>
</table>

* Recommended: Use with caution or discontinue if seizures occur. HH: Consider in patients with a history of seizures or those with a family history of seizures.
After two SSRIs don’t work - anxiety

- Venlafaxine* (Effexor XR) – 2 positive RCTs combined in one to get benefit
  - Side effect profile makes this a 2nd tier option
- Mirtazapine* (Remeron) – no controlled trials
  - Consider if need sedation and appetite stimulation
- Buspirone* (BuSpar) – 2 negative RCTs in youth with GAD
- Benzodiazepines*
  - Have not shown efficacy in RCTs with youth
  - Risk of tolerance and dependence
  - Used for severe anxiety - adjunctively & short term
- Beta-blockers* - no controlled trials
  - Used for performance anxiety
- Benzodiazepines*
  - Hydroxyzine used as an adjunctive, often for insomnia/anticipatory anxiety

Tricyclic antidepressants

- Comparative shown to be efficacious in OCD, FDA approved ≥ 10yo
- Tricyclic side effects, cardiovascular risk of toxicity with overdose
  *Not FDA approved for anxiety treatment <18


Other common concerns and recent updates

Sleep Troubles

- Commonly impacted by both depression and anxiety
- Impact from SSRIs
  - Serotonergic REM suppression may cause decreased dream frequency
  - Increased periodic limb movements of sleep
  - Vivid dreams
- Sleep hygiene
- CBT-Insomnia
- Sleep meds: no medication labeled for insomnia in children by FDA
  - Melatonin: 3-5 mg, 1 hour before bedtime
  - Diphenhydramine: 12.5-25 mg starting dose, max 50 mg QHS, short term only
  - Trazodone: 25-50 mg QHS, max 200 mg QHS
    - Inhibits CYP 2D6, use with caution with fluoxetine or paroxetine, it may decrease their effect
Discussing the black box warning

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicide thoughts or behavior in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of an antidepressant for 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. The available data from placebo-controlled studies of depression in children, adolescents, and adults do not provide a basis for differential risk assessment.

Beforeinitiation, it should be recognized that antidepressants can cause serious adverse reactions including overdose in children and adults, and may be prescribed appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Therefore, while antidepressant treatments may be considered, the need for careful observation and communication with the prescriber: PRINCIPAL FINDINGS: In pediatric patients with MDD and Obsessive-Compulsive Disorder (OSD),
Black box warning, recent meta-analyses

- Bridge et al, JAMA. 2007;297:1683-1696
  - Meta-analysis of 27 RCTs for antidepressants relative to placebo for pediatric MDD and anxiety (OCD and non-OCD)
  - Results:
    - Overall small but increased risk of treatment-emergent suicidal ideation/suicide attempt
    - Pooled risk of suicidal ideation/suicide attempt for each indication were all less than 1%
    - Depending on treatment indication, NNT ranges from 3 to 10, while NNH via emergence of suicidal ideation/suicide attempt ranges from 112 to 200
Black box warning, recent meta-analyses (cont.)

• Conclusions:
  • Relative to placebo, antidepressants are efficacious for pediatric MDD and anxiety disorders
  • Effects strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD.
  • Benefits of antidepressants appear to be much greater than risks from SI/suicide attempt across indications
  • Comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.
  • "We believe that the strength of evidence presented here supports the cautious and well monitored use of antidepressant medications as one of the first-line treatment options"
Refusal to engage in therapy

- Help him/her learn more about what therapy really is
  - http://www.dartmouthcoopproject.org/TeenMental/Cognitive_Behavioral_PT.html
- Educate patient and family on the benefits of therapy
- Remind him/her that therapists are different, therapies are different, and the future experience may be nothing like the past
- Suggest starting with self-guided therapy
- Take a motivational stance

Motivational Interviewing

- Goal is to increase motivation to change
- Change talk is elicited from patient, rather than imparted by provider
- Has shown effectiveness in many types of behavior change, including
  - Adults with obesity
  - Teens with substance use
- Can be used at any point in treatment

MI Principles and Strategies

- Express empathy
- Develop discrepancy
- Avoid argumentation
- Roll with resistance
- Support self-efficacy
- Ask open-ended questions
- Listen reflectively
- Affirm
- Summarize
- Elicit self-motivational statements
Motivational Interviewing

- Brief Negotiation
  - http://www.motivationalinterview.org

Self-guided therapy (depression and anxiety)

- For parents:
  - Freeing Your Child from Anxiety: Powerful, Practical Solutions to Overcome Your Child’s Fears, Worries, and Phobias (Tamar Chansky)
  - Freeing Your Child from Negative Thinking: Powerful Practical Strategies to Build a Lifetime of Resilience, Flexibility, and Happiness (Tamar Chansky)
  - The Depressed Child: Overcoming Teen Depression (Kaufman)

- For children:
  - What to Do When You Worry Too Much: A Kid’s Guide to Overcoming Anxiety (Haistiner and Matthews)
  - What to Do When Your Brain Gets Stuck (Huebner)
  - Taking Depression to School (2002) (Kathy Khalsa)
  - Where’s Your Smile, Crocodile? (Clair Freedman)

Self-guided therapy (depression and anxiety)

- For adolescents/young adults:
  - Mastery of Your Anxiety and Worry: Workbook (Craske and Barlow)
  - Mastery of Your Anxiety and Panic: Workbook (Barlow and Craske)
  - Riding the Wave Workbook (Pincus et al)
  - Feeling Good: The New Mood Therapy (David Burns)
  - Relaxation Exercises
    - http://www.dartmouthcoopproject.org/TeenMental/using_relaxation_TN.html
    - http://palforkids.org/docs/Care_Guide/Anxiety_Care_Guide.pdf (Relaxation Therapy Tip Sheet)
  - Depression Self Care
    - http://www.dartmouthcoopproject.org/TeenMental/teen-resources.html
Useful Apps: mood and anxiety

- **Positive Penguins**: educational app to help kids understand why they feel the way they do and help them challenge their negative thinking
  - [http://positivepenguins.com/](http://positivepenguins.com/)
- **Breathe2Relax**: app designed by the National Center for Telehealth & Technology to teach breathing techniques to manage stress
- **Worry Box**: app to track worries
- **Bellybio**: interactive, guided deep breathing
- **Optimism**: mood tracking app

Useful apps: sleep

- **Bedtime meditations for kids**: guided meditations
- **Deep Sleep with Andrew Johnson**: guided progressive muscle relaxation to target anxiety and insomnia
- **isleep**: guided meditations with music for sleep

Questions?