Advances in Pharmacotherapy for Pediatric Anxiety Disorders

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Pharmacotherapy for Pediatric Anxiety Disorders

- What is known for:
  - acute treatment?
  - long-term treatment?
  - partial and non-responders to treatment?

- What is needed?

In her own words...

Mom, I need you to be there for me. I am getting pressure in the classroom. The work is making me nervous.

Even with the easy pluses - 1 + 1 = what? I say, “I can’t do this.” I want to run out of the classroom.

The work makes me nervous. My teacher has to slow down. She’s saying stuff too fast and I can’t catch up.

- 8 year old girl suffering from Anxiety

Childhood Anxiety Disorders

- Prevalence rates ranging 6% to 20%
- Anxiety disorders can be chronic or remit, and often lead to the onset of another anxiety disorder
- May develop:
  - Adult depression and anxiety
  - Substance abuse/dependence
  - Suicide

Keller, Lavori, Wunder, Beardslee, Schwartz, & Roth, (1992)
Compton, Thomas, Stinson, & Grant, (2007)
Childhood Anxiety Disorders

- The median age of onset is 11 years with an age range of 6 to 21 years of age
  [Kessler, Berglund, Demler, Jin, Merikangas, & Walters, (2005)]
- High comorbidity with another anxiety disorder, major depression, and/or disruptive behavior disorders
  [Biederman & Faraone, 2000; Cordero, Faggiero, & Angst, (2009)]

BENCHMARKS
Pediatric Drug Development

- 1997 – US Congress passes 6 month exclusivity
- 1997 – Research Units for Pediatric Psychopharmacology (RUPP)
- 2002 – Congress passes Best Pharmaceuticals for Children Act (BPCA): renewed exclusivity
- 2003 – Congress passes Pediatric Research Equity Act (PREA)

Multiple Anxiety Diagnoses

- Alprazolam (1-3.5 mg/day) > PBO (N=30, 8-17), 4 weeks
  [Simeon, Ferguson, Ruots, Robison, Gauthier, Dubois, & Wiggins (1992)]
- Fluvoxamine (100-300 mg/day) > PBO (N=128, 6-17), 8 weeks
  [RUPP Anxiety Study Group: Walkup, Labellarte, Riddle, Pine, Gendall, Klein, Davidson, McDuff, Hack, Koo, McCulley, Tugwalo, Fassentin, March, Compton, Robinson, Offlow, Poland, Vincent, Rice & Birmaher (2001)]
- Fluoxetine (20 mg/day) > PBO (N=74, 7-17), 12 weeks
  [Birmaher, Axelson, Monk, Kalas, Clark, Ehmann, Bridge, Hen & Brent (2003)]
- Fluoxetine > PBO for GAD, SOP
- Fluoxetine = PBO for SAD
- Venlafaxine ER (75-225 mg/day) > PBO (N=243, 8-17), 16 weeks
  [March, 2007]

Multiple Anxiety Diagnoses

- Paroxetine (10-50 mg/day) > PBO (N=322, 8-17), 16 weeks
  [Wagner, Mickey, Stein, Winderbaum, Caporini, Pesera, Gau, Davis, & MacHin (2000)]
- Venlafaxine ER (75-225 mg/day) > PBO (N=293, 8-17), 16 weeks
  [March, 2007]
Obsessive Compulsive Disorder

- Multiple positive studies of serotonin reuptake inhibitors and clomipramine:
  - Clomipramine - FDA approved to age 10 OCD
  - Fluvoxamine - FDA approved to age 8 OCD
  - Sertraline - FDA approved to age 6 OCD

Comparative Trials

- School Refusal
  - Imipramine (mean dose 182.3 mg/day) + CBT > PBO + CBT (p<0.001) (N=63, 12-18), 8 weeks

- Pediatric OCD Treatment Study
  - SRT (25-200 mg/day) + CBT > SRT = CBT > PBO (p<0.05) (N=112, 7-17), 12 weeks

  Excellent responder status: COMB=CBT>SERT=PBO and site differences

Comparative Trials

- OCD
  - GCBT = SRT (25-200 mg/day) (N=40, 9-17), 12 weeks

- Social Phobia
  - SET-C > Fluoxetine (20-80 mg/day) > PBO (p<0.001) (N=122, 7-17 yo), 12 weeks

Comparative Trials

- PTSD
  - TF-CBT + SRT (50-200 mg/day) = TF-CBT + PBO, (N=24, 10-17), 12 Weeks

  CGAS rating favored SRT group

- Child Anxiety Multimodal Study (CAMS)
  - CBT + SRT (25-200 mg/day) > SRT = CBT > PBO (p<0.001) (N=488, 7-17), 12 Weeks

  CGAS rating favored SRT group

Long-term Treatment

Multiple Anxiety Disorders:

- Rupp et al., 2002, 6-month open-label:
  - 94% of FVM responders maintained improvement

- Clark et al., 2005, 1 year fluoxetine follow up:
  - Fluoxetine responders maintained improvement
Long-term Trials

**Obsessive Compulsive Disorder:**
- DeVeagh-Geiss et al., 1992
  - Improvement maintained 1 yr extension of CMI
- Cook et al., 2001, follow up to March 1998
  - Maintained after 1 yr extension of SRT
- Asbahr et al., 2005
  - GCBT>SRT at 9 months

Comparative Long-term Trials

- Bernstein et al., 2001, 1 year follow up:
  - 64.1% met criteria for anxiety disorder
  - 33.3% met criteria for depressive disorder
- CAMS (ABCT, 2009)
  - The superiority of combined treatment is maintained over the 36 weeks

Safety Issues

Evaluating Safety

- Antidepressant treatment leads to more frequent adverse events as compared to placebo
- Issues with physical development and growth
- Activation reported more in children than adolescents
- Medication withdrawal symptoms

Risk Difference for Efficacy
- OCD - 19.8% ≡ NNT of 5
- Other anxiety disorders - 37.1% ≡ NNT of 3

Risk Difference for Suicidality
- 0.7% = NNH=143 significant overall
- OCD - 0.9%, NNH=280
- Other anxiety disorders - 0.7% NNH=140

Where we are now

**Medication Trials**
- SRI first line treatment
- If not responding consider a second SRI
- SNRI may be considered as second or third
- Always risk but consider the risk/benefit

**Comparative Trials**
- Effectiveness of CBT, medication, and combined treatment
- Differences in response between OCD and other anxiety disorders
- Challenges in delivering the treatments
Other Compounds

- **Memantine for OCD**
  Aboujaoude, Barry, & Gamel (2009); Stewart, Jenike, Hezel, Stack, Shuster, & Jenike (2008)

- **N-Acetylcysteine for Trichotillomania**
  Grant, Odlaug, & Kim (2009)

- **Riluzole for OCD & GAD**
  Coric, Taskiran, Pittenger, Wasylink, Mathalon, Saksa, Wu, Gueorguieva, Sanacora, Malison, & Krystal (2005); Grant, Lougee & Hirschtritt (2007)

- **Topiramate for OCD & GAD**
  Van Ameringen, Mancini, Patterson, & Bennett (2006)

Medication Augmentation of Psychotherapy

**D-cycloserine**
- N-methyl-D-aspartate (NMDA) receptor activity with a glycine binding site in basolateral amygdala
- DCS is a partial agonist of the glycine site
- May enhance extinction effects
- Meta-analysis lends support to the efficacy of DCS as an adjunctive treatment to exposure therapy.

(Nnorberg, Kyrios, Tolin, 2008)

What further research is needed?

- Treatment of partial and non-responders
- Augmentation and sequence strategies
- Timing of medication discontinuation to maintain gains and prevent relapse
- Evaluation of new compounds in pediatric populations

Ending on a good note………