Reducing the Anxiety of Pediatric Anxiety
Part 2: Treatment

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Disclosure

I have no financial interest or other relationships with any vendor, manufacturer, or company of any product.

I will be discussing off-label use of antidepressants in pediatric populations.

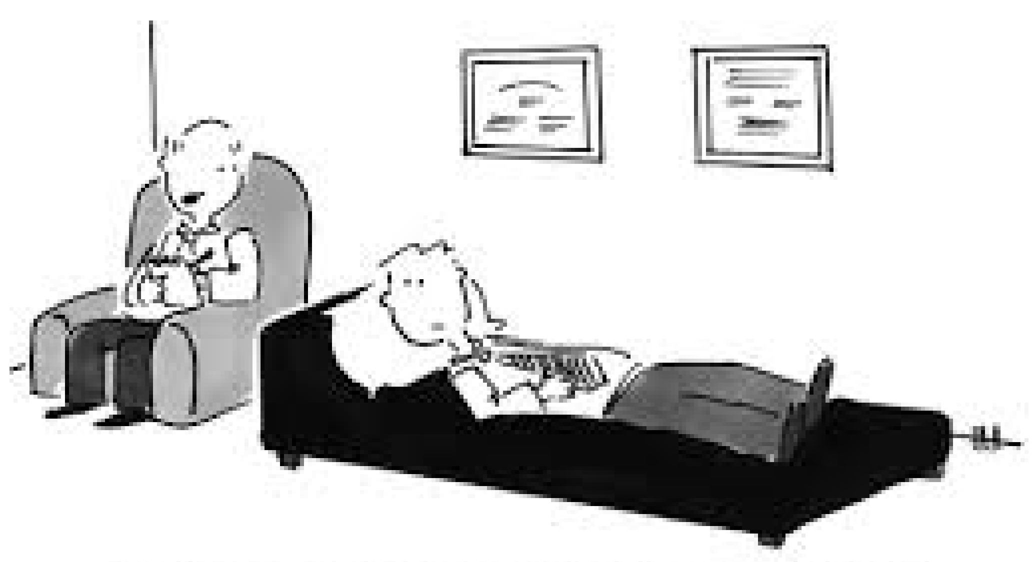
Objectives

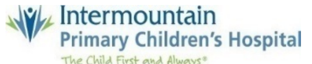
- Review overall anxiety treatment options
- Review therapy techniques and options
- Discuss role of medications, including specifics of antidepressant management

Anxiety Treatment

- Usually involves therapy +/- medications
- Treatment planning should consider:
  - Severity of illness
  - Age of patient
  - Provider availability / affordability
  - Child and family attitudes

Therapy

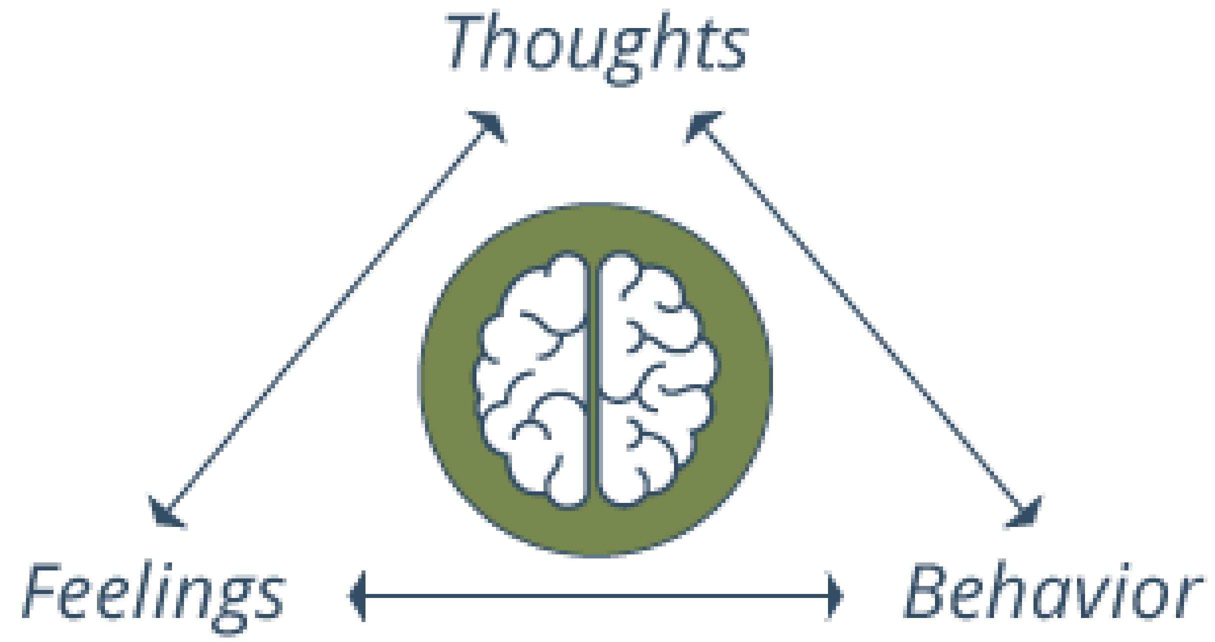


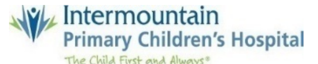


Therapy

- Cognitive behavioral therapy
- Psychodynamic therapy
- Supportive therapy
- Parent-child interactive therapy

Cognitive Behavioral Therapy





Cognitive Behavioral Therapy

- Psychoeducation
- Skills training
- Cognitive restructure
- Controlled exposure
- Relapse prevention

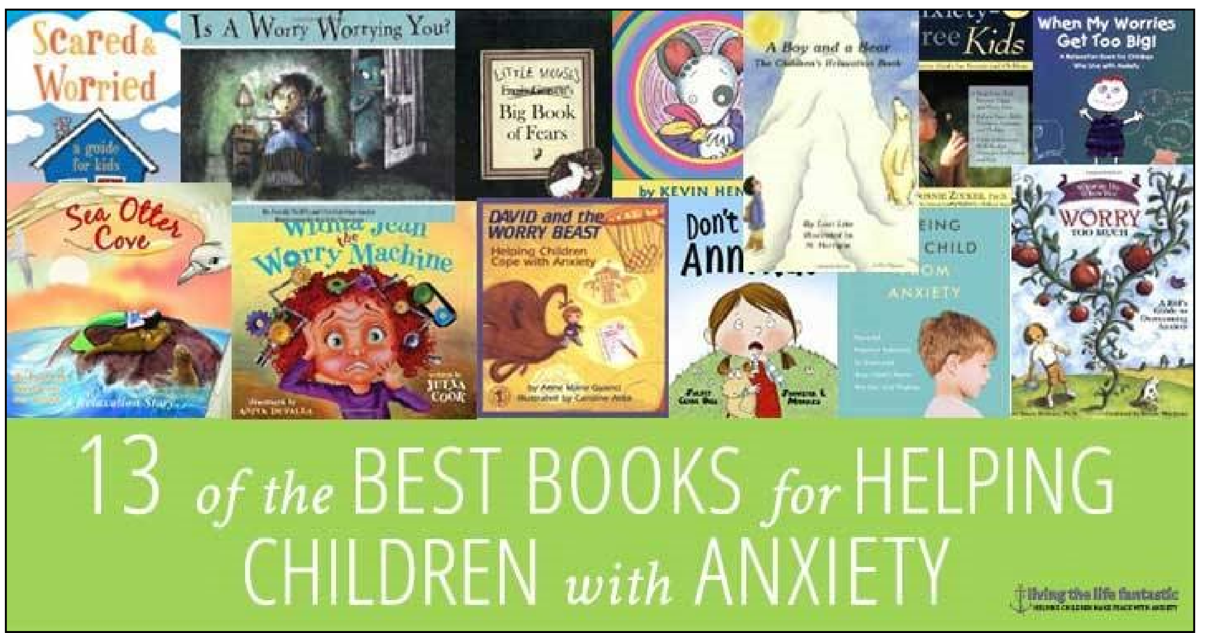
Cognitive Behavioral Therapy

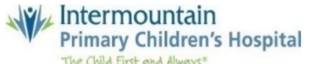
- Efficacy clearly established in:
  - Separation anxiety, generalized anxiety, panic disorder, specific phobias, OCD, PTSD (adaptation), social phobia, selective mutism
  - Down to age 7, with adaptations down to age 4
- Moderators of treatment outcomes:
  - Poorer response when high caregiver burden
  - Family not involved with younger children

Cognitive Behavioral Therapy

- Specific treatments with most evidence
  - Coping Cat (ages 7-13), C.A.T (14-17), Parent-child CBT (4-7)
- Typically 12-20 weekly session of face-to-face
- Some evidence for group CBT for social phobia
- Therapist-guided, internet-based CBT showing promise

Self-Help Strategies





Medications

Medications

- Overall evidence still limited
- SSRIs medication of choice, followed by SNRIs
- Can also consider TCAs, buspirone, hydroxyzine, other antidepressants, benzodiazepines
- Meds have less efficacy and more side effects in younger ages
- NNT = 3 with broad anxiety, 6 with OCD, 10 with MDD

Broad Anxiety Disorders

- SSRIs
  - Sertraline, fluoxetine, paroxetine, fluvoxamine with positive placebo-controlled RCTs
  - Fluoxetine with one negative study
  - No RCTs with citalopram or escitalopram
- SNRIs
  - Venlafaxine with mixed results
  - Duloxetine with positive RCT (only FDA approval)

Broad Anxiety Disorders

- Benzodiazepines
  - Alprazolam and clonazepam with mixed results
- TCAs
  - Impramine RCT negative
  - Clomipramine RCTs mixed
- Others
  - Buspirone RCT failed to separate from placebo
  - No RCTs with mirtazapine, bupropion, etc.

Treatment: CAMS study

- RCT sponsored by NIMH,
  - 12-wk placebo-controlled
- 488 patients with separation, GAD, or social phobia, ages 7-17
- Randomized to 4 groups
  - CBT and sertraline
  - Sertraline alone
  - CBT alone
  - Placebo

Ref: Walkup et al, NEJM(2008)

CAMS Study Results

- Percent improved in anxiety:

CBT and sertraline	81%
CBT alone	60%
Sertraline alone	55%
Placebo	24%

- Adverse events uncommon; less in the CBT groups, but equal between sertraline and placebo
- Medication response may be quicker

Obsessive Compulsive Disorder

- Placebo-controlled RCTS
  - Positive results for multiple SSRIS (sertraline, fluoxetine, fluvoxamine, paroxetine)
  - Positive results for clomipramine
- POTS study
  - Both sertraline and CBT alone superior to placebo
  - Combination of CBT and sertraline most effective

Post Traumatic Stress Disorder

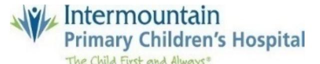
- Limited data on psychopharmacologic approaches
- One large RCT of sertraline failed to separate from placebo
- Strong evidence for the utility of therapeutic interventions

Risks of Antidepressants

- Side effects are common
  - GI symptoms (nausea, diarrhea)
  - Appetite changes (wt gain, anorexia)
  - Sleep changes (drowsiness, insomnia)
  - Headache
  - Sexual dysfunction
- Adverse effects are rare

Antidepressant Adverse Responses

	Symptoms	Incidence	When occurs
Suicidality	Self-harm acts/ thoughts	2%	1-4 weeks
Activation	Inner restlessness, irritability, agitation	3-10%	2-6 weeks
Mania	euphoria, decreased need for sleep	1-5%	2-4 weeks
Discontin-uation	Nausea, insomnia, irritability, parasthesias	4-18%	1-7 days of stopping
Serotonin syndrome	Confusion, restlessness, fever, hyperthermia, hypertonia	<1%	Adding serotonergic medication



Antidepressants and Suicidality

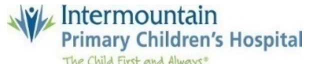
- Black Box Warning (2004)
  - Warning of increased risk of suicidality in pediatric pts taking antidepressants.
- FDA Analysis of short-term RCTs
  - Average risk of spontaneous suicidal thinking / behavior on drug was 4% vs. 2% on placebo
- Toxicology studies
  - 0-6% of suicides had antidepressants in blood
  - 25% had active prescriptions for antidepressants
- Epidemiological Studies
  - Regional increases in SSRI use associated with decreases in youth suicide rates

Antidepressants: Which to choose?

- 1st - SSRI (fluoxetine, sertraline, fluvoxamine, citalopram, escitalopram)
  - Side effect profile
  - Drug-drug interactions
  - Duration of action
  - Positive response to a particular SSRI in first-degree relative
- 2nd - Another SSRI (above + paroxetine OR duloxetine?)
- 3rd - Alternative antidepressants or antianxiolytic
  - Duloxetine, venlafaxine, buspirone, benzodiazepines

SSRI Comparison Chart

Medication	Half-life	Drug interaction potential	More common side effects
Citalopram	35 hrs	low	sexual SE, long QT
Escitalopram	30 hrs	low	perhaps fewer
Fluoxetine	2-4 days	high	agitation, nausea
Fluvoxamine	16 hrs	high	agitation, insomnia
Paroxetine	20 hrs	high	sexual, weight gain, sedation, anticholinergic
Sertraline	26 hrs	moderate	diarrhea, nausea



Commonly Used Antidepressants

Medication	FDA indication in Youth
Citalopram	
Escitalopram	≥12 years with MDD
Fluoxetine	≥8 years with MDD ≥7 years with OCD
Fluvoxamine	≥8 years with OCD
Paroxetine	
Sertraline	≥6 years with OCD
Duloxetine	≥7 years with GAD
Venlafaxine	

Antidepressant Dosing Chart

Medication	Starting Dose (mg/d)	Increments (mg)	Effective Dose (mg)	Maximum Dose (mg)
Citalopram	10	10	20	40
Escitalopram	5	5	10	20
Fluoxetine	10	10-20	20	60
Fluvoxamine	25	25	50-100	200
Paroxetine	10	10	20	60
Sertraline	25	12.5-25	50-100	200
Duloxetine	30	30	60	120
Venlafaxine	37.5	37.5-75	150	225

Pharmacogenetics Testing

- Different labs test for different genes, use different methods, and use different interpretation guidelines
- Do not take indication/ use into account
- Do not take drug interactions into account
- Based on single gene interactions only
- No evidence that use of these tests include clinical outcomes

Action	Drug Impacted	Clinical Interpretation	Gene	Genotype	Phenotype
✓	**Antipsychotics:** Aripiprazole (Abilify®), Brexpiprazole (Rexulti®), Iloperidone (Fanapt®), Pimozide (Orap®)	**NORMAL RESPONSE EXPECTED**	CYP2D6	*4/*10	Intermediate Metabolizer
✓	**Antipsychotics:** Haloperidol (Haldol®)	**NORMAL RESPONSE EXPECTED**	CYP2D6	*4/*10	Intermediate Metabolizer
✓	**Antipsychotics:** Perphenazine	**NORMAL RESPONSE EXPECTED**	CYP2D6	*4/*10	Intermediate Metabolizer

Action	Drug Impacted	Clinical Interpretation	Gene	Genotype	Phenotype
✗	**Antipsychotics:** Risperidone (Risperdal®)	**CONSIDER ALTERNATIVES** (e.g., quetiapine, olanzapine, clozapine)	CYP2D6	*4/*10	Intermediate Metabolizer
✗	**Antipsychotics:** Thioridazine (Mellaril®)	**CONSIDER ALTERNATIVES**	CYP2D6	*4/*10	Intermediate Metabolizer
✗	**Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs):** Venlafaxine (Effexor®)	**CONSIDER ALTERNATIVES** (e.g., citalopram, sertraline)	CYP2D6	*4/*10	Intermediate Metabolizer

Initial Treatment

Titrate SSRI to effective dose

After 6-8 weeks

Partial Improvement

Increase med to max dose

Add therapy

Explore poor adherence, comorbidites

Consider augmentation

No Improvement

Reassess diagnosis

Add therapy

Switch to another SSRI

Improvement

Continue meds for 6-12 months after resolution

Anxiety Treatment

- Therapy is gold standard
- In younger children and milder anxiety:
  - Therapy alone, involving parent
- In older children and more severe anxiety:
  - CBT +/- SSRI
  - Combination treatment seems to be optimal
  - Family involvement

When to Consult Psychiatry?

- Diagnosis unclear
  - High comorbidities
  - Concern for bipolar or psychosis
- Treatment failure
  - Failure of two SSRIs (and/or SNRI)
  - Adverse reactions

Take Home Points

- Therapy (CBT) is first line treatment.
- Antidepressants (SSRI and SNRI) are effective.
- Combined therapy and antidepressants seem to most effective.
- Benefits of antidepressants clearly outweigh the risks in more severe illness and older ages

Resources

www.aacap.org (AACAP practice parameters, parent handouts)

www.aap.org/commpeds/dochs/mentalhealth/ (AAP literature on anxiety)

www.effectivechildtherapy.com (Society of Clinical Child & Adolescent Psychology information on evidence-based therapies and how to choose a therapist)