Best Practices in Treating Pediatric Anxiety and Depression

Leslie Hulvershorn, MD, MSc
Chief, Pediatric Mood Disorders
Riley Hospital for Children
Indiana University School of Medicine

Objectives

- Identify useful tools to screen for anxiety and depression in children and adolescents
- Utilize best practices, either through provision of care or referral, in the treatment of pediatric anxiety and depression

Outline

- **Depression Diagnoses/Phenomenology**
- **Etiology/Risk Factors**
- **Epidemiology**
- **Diagnostic Controversies**
- **Treatments: Focus on Psychopharmacology**
- **Black Box Warning**
- **Anxiety Disorders**

Referrals

Why treat adolescent depression?

- Earlier onset heralds more severe and persistent course: need for early positive experience with treatment and identification of early triggers
- Adverse *short term* effects: school performance, educational attainment, relationships
- Adverse *long term* effects: Physical health, adult functioning
- 11-27 fold increase in suicide (3rd leading cause of death in 14-19 year olds)

Types of Mood Disorders

- **Adjustment Disorder:** occur in response to a clear stressor
- **Other Specified Depression (vs. Depression unspecified):** depressed mood, anhedonia or irritability + up to 3 symptoms of MDD
- **Persistent Depressive Disorder:** lasts **at least 1 year**
- **Major Depression (5/9):** sad/**irritable** mood or anhedonia + social withdrawal, worthlessness, guilt, suicidal thoughts/behavior, sleep changes, decreased motivation, poor concentration, increased/decreased appetite
- **"Double Depression":** PDD + MDD
- **Psychotic Features:** hallucinations, delusions

Depression Screening

- Screening: Adolescent Symptom Inventory or PHQ-2
- Severity Rating: PHQ-9 or Child Depression Rating Scale
- Diagnostic Interview: KSADS—must determine episodicity

Differences in the adolescent approach

- Interview parents and kids: together and separate
- Adolescents more likely to be aware of affective symptoms than parents (opposite for externalizing disorders)
- Expect fewer threshold symptoms/disorders
- Anticipate more medication side effects
- May see less buy in to therapy

Clinical Manifestations

PERSISTENT & PERVASIVE:

- Sadness
- Anhedonia
- Boredom
- Irritability
- Unresponsive to pleasurable activities/interactions with others
- Physical symptoms
- DEVELOPMENTAL DERAILMENT

Comorbidities

- 80-90% have comorbidities
- Anxiety Disorders
- ADHD (genetic co-transmission)
- Substance use disorders (bidirectional causality)
- Conduct Disorder (prepubertal)

Risk Factors

- Subthreshold depressive symptoms
- Shared with externalizing disorders and substance use disorders
- Parental substance use/depression/antisocial behavior
- Exposure to violence/neglect/maltreatment
- Early attachment failures: Family discord
- # lifetime stressors
- Genetics: 40-65% concordance rates (adolescent form is more highly heritable; short form of 5-HT transporter)
- 2-4 fold increased risk for depression with first degree relatives with depression

Epidemiology

- Point Prevalence: 1-2% of children, 3-8% of adolescents
- Lifetime prevalence in adolescence: 20%
- Pre-pubertal 1:1gender ratio (female : male)
- Post-pubertal 3:1gender ratio (female : male)
- Risk of recurrence: 72% within 5 years

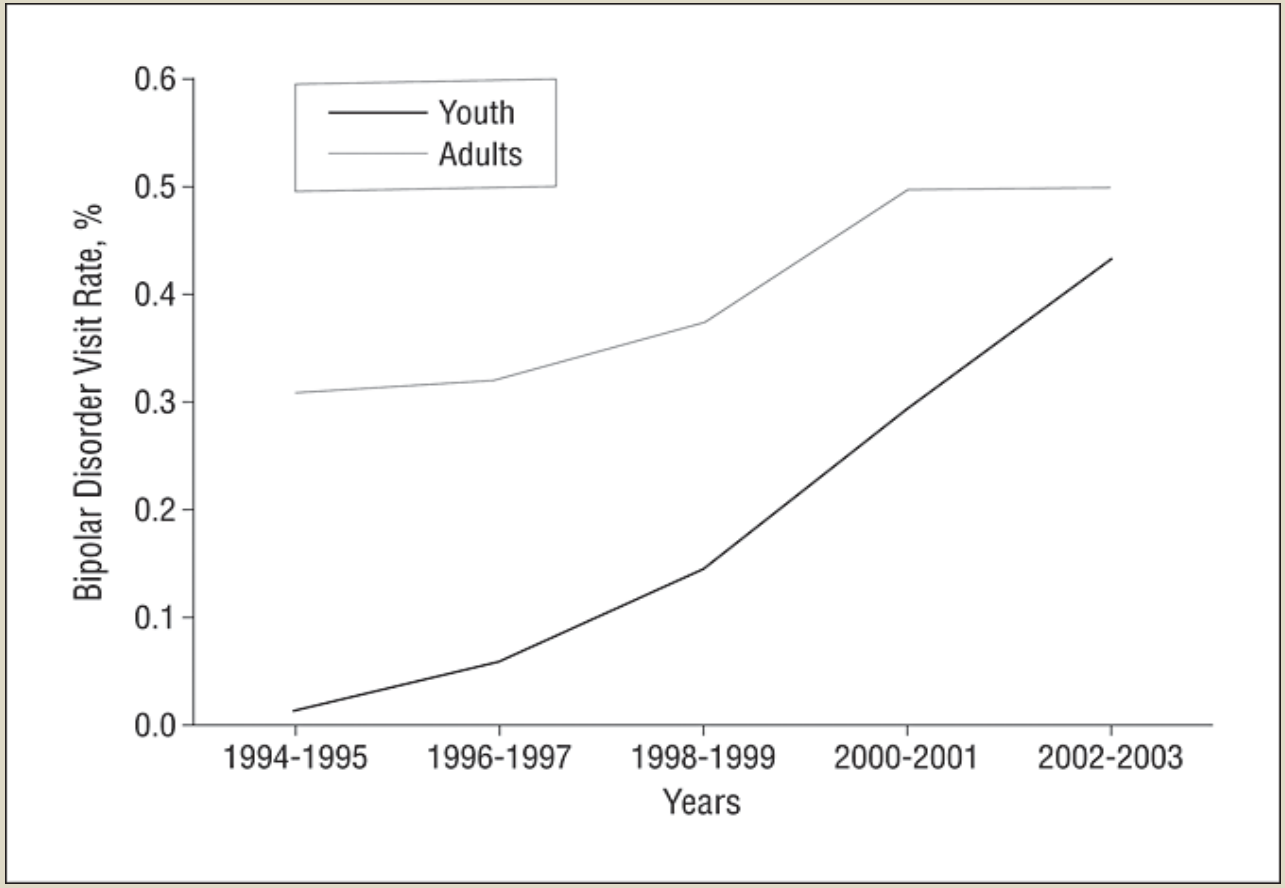
Depressed vs Normal Teens

- Ups and downs are typical
- Mood disorder = Functional impairment
- Intense, long lasting (3-8 months)
- Different than usual mood

Concerns for bipolar disorder

- Hypomania or mania: weeks not hours!
- Strong family history
- Not terribly dangerous to give SSRI
- 10% of early onset depression may turn into bipolar disorder

What about bipolar disorder?



Disruptive Mood Dysregulation Disorder

A. The disorder is characterized **by severe recurrent *temper outbursts* in response to common stressors.**

1. The temper outbursts are manifest verbally and/or behaviorally, such as in the form of verbal rages, or physical aggression towards people or property.

2. The reaction is grossly out of proportion in intensity or duration to the situation or provocation.

3. The responses are inconsistent with developmental level.

B. *Frequency*: The temper outbursts occur, on average, three or more times per week.

C. *Mood between temper outbursts:*

1. Nearly every day, the mood between temper outbursts is persistently negative (irritable, angry, and/or sad).

2. The negative mood is observable by others (e.g., parents, teachers, peers).

D. *Duration*: Criteria A-C have been present for at least 12 months. Throughout that time, the person has never been without the symptoms of Criteria A-C for more than 3 months at a time.

E. The temper outbursts and/or negative mood are present in at least two settings (at home, at school, or with peers) and must be severe in at least in one setting.

F. Chronological age is at least 6 years (or equivalent developmental level).

G. The onset is before age 10 years.

H. In the past year, there has never been a distinct period lasting more than one day during which abnormally elevated or expansive mood was present most of the day for most days, and the abnormally elevated or expansive mood was accompanied by the onset, or worsening, of three of the "B" criteria of mania (i.e., grandiosity or inflated self esteem, decreased need for sleep, pressured speech, flight of ideas, distractibility, increase in goal directed activity, or excessive involvement in activities with a high potential for painful consequences; see pp. XX). Abnormally elevated mood should be differentiated from developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation.

I. The behaviors do not occur exclusively during the course of a Psychotic or Mood Disorder (e.g., Major Depressive Disorder, Dysthymic Disorder, Bipolar Disorder) and are not better accounted for by another mental disorder (e.g., Pervasive Developmental Disorder, post-traumatic stress disorder, separation anxiety disorder). (Note: This diagnosis can co-exist with Oppositional Defiant Disorder, ADHD, Conduct Disorder, and Substance Use Disorders.) The symptoms are not due to the direct physiological effects of a drug of abuse, or to a general medical or neurological condition.

Treatment of Adolescent Mood Disorders

Evidence Based Treatments for MDD

- Antidepressants
- Cognitive Behavior Therapy (CBT)
- Interpersonal Therapy (IPT)
- Psychodynamic Psychotherapy
- Repeated Transcranial Magnetic Stimulation (rTMS)
- ECT
- MAXIMIZE PROTECTIVE FACTORS: Positive connections to family and school, reasonable parental behavioral and academic expectations, healthy, non-deviant peer group

What if you can't find a therapist?

- Providing parental support
- Recognizing and treating parental mental illness
- Educating patients about depression
- Problem solving
- Attending to recent family or peer group conflicts
- Dealing with comorbidity
- Liaising with schools and other agencies
- Empathic reflective approach
- Advice on nutrition and diet, exercise, sleep hygiene

MDD Algorithm

- Mild Depression: family education, supportive counseling, problem solving
- Moderate: therapy or medications
- Severe: Combination therapy (medications + therapy)
- Try for 6 weeks and then reassess

Evidence for SSRI: Cochrane Review

- 19 trials, 3335 participants
- Healthier than clinical populations: excluded comorbid and suicidal cases
- Remission 38% on placebo, 44.% on SSRI
- Suicidality: 25% on placebo, 40% on SSRI

Hetrick et al 2012

MDD Medications

- Start with fluoxetine: 10mg x 1 week then 20 mg x 3 weeks (see weekly for first 4 weeks; every 2 weeks for next 4)
- If still depressed, increase every 4 weeks
- Target dose: 40-80 mg
- Switch to another SSRI after 8 weeks if no response
- Augment (Wellbutrin XL) if partial response after achieved target dose
- Reasons for antidepressant failure: noncompliance, rapid metaboliser, substance use, comorbid diagnoses, medical issues

Antidepressants

- Fluoxetine: 41-61% response to fluoxetine *v* 20-35% response to placebo, FDA approved for ages 8 and up
- Lexapro approved for MDD ages 12-17
- FDA does not recommend Paroxetine
- Shorter half lives than in adults

Therapy vs Meds: Cochrane Review

- 10 studies, n=1235. LIMITED EVIDENCE
- Mainly no differences between treatments
- Immediately post-intervention: antidepressants favored therapy (68% remitted vs 54%)
- Immediately post-intervention: combined treatment favored antidepressants (66% remitted vs 58%)
- Combined treatment NOT more effective than therapy alone
- Suicidal ideation (immediately and 6-9 months later): higher in medication group (13% vs 4%)

TADS

- 12 weeks
- CBT alone (43% response) vs fluoxetine alone (61% response) vs CBT + fluoxetine (71%) vs placebo (35%)
- CBT accelerated response, reduced suicidality

ADAPT (UK)

- 12 weeks
- Fluoxetine alone (61% “much or very much improved”) vs fluoxetine + CBT (53% “much or very much improved”)
- No added benefit of CBT

TORDIA: Treatment Resistent

- Adolescents not responding to an adequate trial of an SSRI
- Switch to: (1) a different SSRI (paroxetine, citalopram, fluoxetine) (2) a different SSRI + CBT (3) venlafaxine (4) venlafaxine + CBT
- CBT + medication (54%) better than med switch alone (40.5%)
- No difference between SSRI (47%) or venlafaxine (48%)
- More side effects with venlafaxine

BP Depression

Summary of Levels of Evidence

	Bipolar I Disorder, Manic or Mixed, *Without Psychosis*	Bipolar I Disorder, Manic or Mixed *With Psychosis*	Bipolar Depressive Episode
Lithium	A & B	A & B	B & C
Divalproex	B & C	B & C	C
Carbamazepine	B	B	ND
Oxcarbazepine	D	D	ND
Topiramate	C	C	ND
Clozapine	C	C	ND
Risperidone	B & C	B & C	ND
Olanzapine	B & C	B & C	B
Quetiapine	B & C	B & C	B
Ziprasidone	B & C	B & C	ND
Aripiprazole	B & C	B	ND
Selective serotonin reuptake inhibitors	NA	NA	C[a]
Bupropion	NA	NA	D
Lamotrigine	C	C	B & D

Note: Level A data consist of child/adolescent placebo-controlled, randomized clinical trials. Level B data consist of adult randomized clinical trial. Level C data consist of open child/adolescent trials and retropective analysis. Level D data consist of child/adolescent case reports or the panel consensus as to recommend current clinical practices. ND = no data; NA = not applicable.

[a] May be mood destabilizing.

Preventing Relapse: Meds or therapy

- Cochrane Review: 9 trials, n= 882
- Lower rates of relapse/recurrence with antidepressant treatment (41% vs 67% for placebo) in 3/3 trials
- "Little evidence to conclude which type of treatment approach prevents relapse"

Cox GR et al 2012

Pharmacogenetic Screening: Cytochrome and 5HT Transporter Polymorphisms

- GeneSightRx
- “Psychotropic Panel”
- “ADHD Panel”

Pharmacogenetic Results

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH CAUTION AND WITH MORE FREQUENT MONITORING
citalopram(Celexa®)	amitriptyline(Elavil®) [1,5]	doxepin(Sinequan®) [1]
desvenlafaxine(Pristiq®)	bupropion(Wellbutrin®) [1]	duloxetine(Cymbalta®) [7]
escitalopram(Lexapro®)	clomipramine(Anafranil®) [3,5]	fluvoxamine(Luvox®) [7]
selegiline(Emsam®)	desipramine(Norpramin®) [1,5]	mirtazapine(Remeron®) [3]
sertraline(Zoloft®)	fluoxetine(Prozac®) [1]	
	imipramine(Tofranil®) [1,5]	
	nortriptyline(Pamelor®) [1,5]	
	paroxetine(Paxil®) [1]	
	trazodone(Desyrel®) [1]	
	venlafaxine(Effexor®) [1]	

Antipsychotics

USE AS DIRECTED	USE WITH CAUTION	USE WITH CAUTION AND WITH MORE FREQUENT MONITORING
fluphenazine(Prolixin®)	aripiprazole(Abilify®) [1]	
iloperidone(Fanapt®)	chlorpromazine(Thorazine®) [7]	
quetiapine(Seroquel®)	clozapine(Clozaril®) [3]	
ziprasidone(Geodon®)	haloperidol(Haldol®) [1]	
	olanzapine(Zyprexa®) [3]	
	perphenazine(Trilafon®) [1]	
	risperidone(Risperdal®) [1]	
	thioridazine(Mellaril®) [7]	
	thiothixene(Navane®) [7]	

[1]: Serum level may be too high, lower doses may be required.

[2]: Serum level may be too low, higher doses may be required.

[3]: Difficult to predict response because of multiple gene variations.

[4]: Genotype suggests less than optimal response.

[5]: Blood levels may be outside of optimal range.

[6]: Use of this drug is associated with an increased risk of side effects.

[7]: Serum level may be too low in the presence of CYP1A2 inducers. See pages three and four for additional information.

The Black Box: Antidepressants and “Suicidality”

Antidepressants and "Suicidality"

- In 2003 the FDA noted concerns for increased suicidality with Paroxetine in pediatric patients
- FDA Meta-analysis: 23 industry sponsored and 1 NIMH trial (suicidal thoughts/behavior were not systematically screened for)
- Of 4,582 pediatric patients, there were no deaths.
- 1 study showed slight increased risk toward "suicidality" (OR=1.6) in kids, others did not
- In adults antidepressants are protective or neutral (OR < 1)

Antidepressants and “Suicidality”

- Autopsy studies show that teens who kill themselves rarely have used SSRIs in the prior 2 weeks
- Since SSRIs were approved for use in teens in 1998, suicide rates have dropped
- Increase in suicides in 2004 after 2003 black box warning
- 10-11 times more patients will respond to antidepressants than demonstrate “suicidality”
- NNT=10; NNH=143

Meta-analysis: 41 Trials of Fluoxetine and Venlafaxine

"For youths, no significant effects of treatment on suicidal thoughts and behavior were found, although depression responded to treatment. No evidence of increased suicide risk was observed in youths receiving active medication."

(Gibbons et al, 2012)

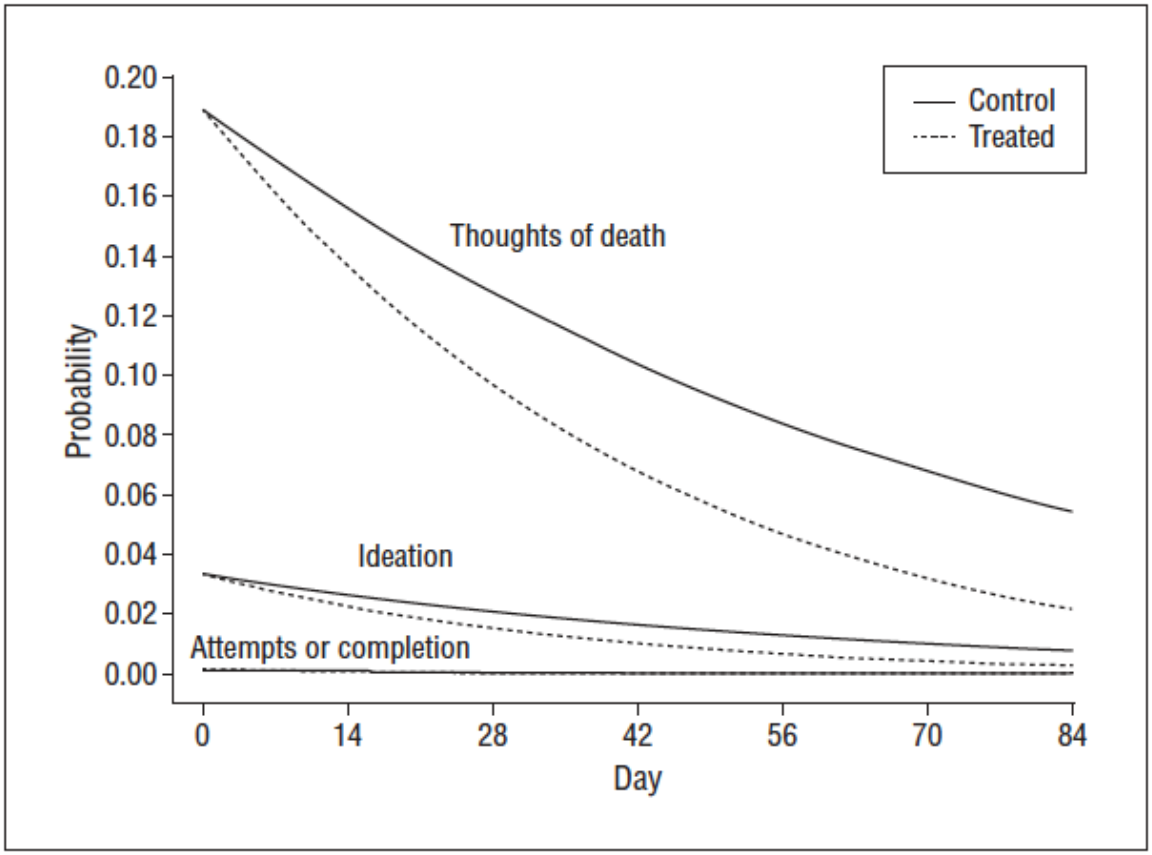


Figure 1. Probabilities of suicide risk in adult and geriatric fluoxetine hydrochloride and venlafaxine hydrochloride studies. Solid lines indicate estimated probabilities for control patients receiving placebo; dashed lines, estimated probabilities for treated patients; thoughts of death curves, "wishes he or she were dead or any thoughts of possible death to self" or worse; ideation curves, "suicide ideas or gestures" or worse; and attempts or completion curves, "suicide attempts or suicides."

Summary

- Mood disorders are common in adolescence and moderate and severe forms should be aggressively treated
- Therapy and medication management should be pursued for most patients, although therapists are hard to find
- SSRIs are effective and necessary treatments for depression
- Youth with bipolar disorder are the minority of cases you will see

Anxiety Disorders in Youth

- Generalized Anxiety Disorder: CBT (Coping Cat) +/ SSRI
- PTSD: TF-CBT +/- SSRI, Prazosin, Alpha agonist
- OCD: Exposure and Response Prevention + SSRI (high dose)
- Selective Mutism: Exposure Therapy (Brave Buddies) +/- SSRI (low dose)
- Separation Anxiety: CBT + SSRI

Clinical Referrals/Information

- Call Riley Clinic: (317) 944-8162
- Email me directly: lhulvers@iupui.edu
- http://www.aacap.org/cs/Depression.ResourceCenter