Learning Objectives

By the end of the presentation, participants should be able to:

- Describe symptoms of a major depressive episode and interventions for depression based on symptom severity
- Describe 5 supportive strategies for primary care providers to implement in the office and list the top 4 medications choices for teens
- Identify risk factors for a suicide attempt including the role of non-suicidal self injury

Disclosures

- Research funding (sub-investigator)
  - Bristol Myers Squibb (Autism with aripiprazole)
  - Merck & Schering-Plough (Bipolar)
  - Supernus (ADHD + molindone)
  - Forest (memantine for autism)

- Committees
  - AACAP committee on Quality Issues
  - AACAP CME committee
  - AACAP Life Long Learning committee

Major Depressive Disorder

- Affect 2.6 million youth ages 6-17 annually
- 8.3% adolescents (M:F 1:2)
- 40-80% experience suicidal thoughts
- 35% of depressed youth will attempt suicide

Affects every facet of life - peers, family, school and general health

How depressive symptoms manifest:

- Mood: Depressed, irritable or labile mood
- Behavior
  - Low frustration tolerance, social withdrawal or somatic complaints
  - ⊖ interests (stop sports activities etc.) c/o boredom
- Vegetative symptoms
  - Fatigue or ⊖ energy, PMR or PMA
  - Sleep disturbance (often hypersomnia)
  - Weight or appetite change, failure to make wt gain
  - ⊖ concentration or indecisiveness
- Cognition
  - Feelings of worthlessness/hopelessness or inappropriate guilt
  - Thoughts of death or suicide

Criteria for Major Depressive Episode: depressed mood or anhedonia + 4 others

- S -
- I -
- G -
- E -
- C -
- A -
- P -
- S -
Criteria for Major Depressive Episode:
- depressed mood or anhedonia + 4 others
  - S - sleep, insomnia or hypersomnia
  - I - interests
  - G - guilt, feeling worthless or hopeless
  - E - energy
  - C - concentration
  - A - appetite
  - P - psychomotor retardation or agitation
  - S - suicidal thoughts or recurrent thoughts of death

Genetics
- Depression runs in families
- Monozygotic twin 76% concordance, raised separately 67% concordance
- Children with one depressed parent are 3x more likely to have MDD than children of non-depressed parents
- Need to ask about family history of bipolar disorder

Gathering History
- Best to interview both parent and youth
- Parents better at reporting behavioral disturbances & time course of symptoms
- Youth better at reporting on mood/anxiety/sleep
- Youth often have depressed mood or SI that parent is unaware of

Gathering History – youth self report
- Youth depression inventory-self admin scales
  - Children’s Depression Inventory (CDI)
  - CES-DC (public domain)
  - PHQ-9 (GLAD-PC toolkit, public domain; 73% sensitivity & 98% specificity)
- PHQ-2 questions scored on 3 point scale
  - “0” not at all and “3” nearly every day
  - Have you been feeling sad or depressed for the past 2 weeks?
  - Do you have a lack of pleasure in usual activities in past 2 weeks?
  - Score >3 sensitivity 74% and specificity 75%

Gathering History
- R/O neglect, abuse physical or sexual
- Recent stressors
- Anxiety symptoms
- Unusual thoughts, paranoia or psychotic symptoms
- Symptoms of mania now or past
  - need for sleep, hypersexuality or grandiosity
- FHx of suicides or bipolar disorder

Differential Diagnosis
Infectious
- Mononucleosis
- Influenza
- TB
- Hepatitis
- Syphilis
- HIV
- Subacute endocarditis

Neurologic
- Epilepsy
- CVA
- Multiple sclerosis
- Post-concussive states
- Subarachnoid hemorrhage
- Huntington’s disease
- Wilson’s disease
Differential Diagnosis (cont’d.)

Endocrine
- Diabetes
- Cushing’s disease
- Addison’s disease
- Thymus or thyroid
- Parathyroid
- Pituitary function

Others
- Lupus
- Porphyria
- Sodium
- Potassium
- Anemia
- Alcohol or drug abuse
- Meds-steroids, OCP, cimetidine, BDZ, antiHTN, aminophylline

Co-morbid psychiatric disease and differential
- 40-90% co-morbid conditions – dysthymia (often precedes MDD by a few years), anxiety disorder, disruptive behavioral disorders, ADHD or substance abuse
- Prediction of bipolar disorder:
  - Youth factors: early onset, PMR, psychotic features or drug induced hypomania
  - FHx of bipolar disorder or psychotic depression

Work-up
- History
- Physical exam
- CBC, CMP, TSH, UA, vit B12, vitamin D, UDS
- Consider other labs/tests as indicated: folate, RPR, HIV, ESR, ANA, EEG, MRI brain

Course of Major Depression
- Median duration of an episode 8 months in clinically referred youth, community samples 1-2 months
- 50% of pts have a recurrent MDE within 5 years. It is continuous with MDD in adulthood.
- 20-40% will develop bipolar disorder

Sequelaes
- Depression untreated affects social, emotional, cognitive and interpersonal skills
- Avg episode 7-9 months: long time in adolescent’s life
- High risk for nicotine & substance dependence, early teen pregnancy, physical illness
- As adults, higher suicide rates, more medical & psychiatric hospitalization, more impairment in work, family and social life

Treatment
- Psychoeducation
  - Parents
  - Youth
  - School
- Individual psychotherapy
  - Supportive
  - Cognitive Behavioral Therapy
  - Interpersonal Psychotherapy
- Family therapy
- Medication
Treatment Goals

- **Response** – significant reduction in symptoms or no symptoms for 2 weeks
- **Remission** – period of more 2 weeks but less than 2 months with few symptoms
- **Recovery** – absence of sx’s for more than 2 months

**Recovery is the goal**

Treatment recommendations: initial steps

- Positive screening for MDE and subsequent diagnosis
- Psychoeducation and treatment planning

**Mild depressive to moderate sx’s:**
- Active support and monitoring for 6-8 weeks

**Moderate to severe depressive sx’s:**
- Begin evidence based therapy or medication or both for 6-8 weeks

**Severe depressive sx’s:**
- Start medication and referral

AACAP practice parameters 2007 and GLAD-PC 2007

Psychoeducation

- All patients should receive
  - Information about symptoms and typical course with discussion about MDD (i.e. depression is a illness; not a sign of weakness; no one’s fault)
  - Discussion of treatment options
  - Placing patient in sick role temporarily may be helpful or temporary school accommodations
- No controlled trials with just psychoeducation, however, many pts improve with only education and supportive care

Supportive Treatment

- All patients should receive supportive treatment
  - For mild to moderate sx: may be all that is required
  - Meeting frequently to monitor progress
  - Active listening and reflection
  - Restoration of hope
  - Problem solving
  - Improving coping skills
  - Strategies for adherence
  - If not improving in 4 weeks, move to a more specific treatment

What to do in the office during active monitoring period?

- Rating scales (e.g. Child Depression Inventory, CES-DC or PHQ-9) to get baseline symptoms and track at follow up
- Mood diary
- Cognition/thought charts - negative thoughts in one column and a neutral thought in other column
- Prescribe pleasant activities and exercise
- Relaxation strategies

Emotions Thermometer

- 10 ______ suicidal thoughts
- 9 ______
- 8 ______
- 7 ______
- 6 ______
- 5 ______
- 4 ______
- 3 ______
- 2 ______
- 1 ______
- 0 ______ no depression
### Mood Monitoring Diary

List at least 1 activity each time frame and rate depression during that time using the emotions thermometer (10 worst; 0 no depression)

<table>
<thead>
<tr>
<th>Day</th>
<th>Morning</th>
<th>Afternoon</th>
<th>Evening</th>
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<tbody>
<tr>
<td>Monday</td>
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### Thought chart

<table>
<thead>
<tr>
<th>Initial negative thought</th>
<th>Neutral or more realistic thought</th>
<th>Emotion rating 0-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>I can’t do anything right and I’ll never amount to anything</td>
<td>I am not the best at organizing</td>
<td>5</td>
</tr>
<tr>
<td>Our team didn’t win all because of me</td>
<td>I did not play my best tonight nor did others</td>
<td>4</td>
</tr>
<tr>
<td>The entire day was pointless because I got a bad grade on the Math test</td>
<td>I’m disappointed in my math grade, but I did get all my homework done today</td>
<td>5</td>
</tr>
</tbody>
</table>

### Common Cognitive Distortions

- **Overgeneralizing** – making mountains from molehills “I’ll never amount to anything”
- **Catastrophizing** – “this is the worst thing could ever happen” or “I’ll never feel better”
- **Personalizing** – “when the teacher yelled at the class to be quiet, it was all my fault”
- **Selective abstraction** - focusing only on negative events “I did not get 100% on the test, only 98%”
- **Kitchen sinking** – gets overwhelmed as adds more issues to current problem

### Scheduling Pleasurable Activities

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### Things I can do to relax when upset

(identify ones that work for the youth)
- Walking or Running
- Weight lifting
- Playing a sport
- Listening to music/dance
- Read
- Do a puzzle
- Crafts
- Call a friend
- Talk to someone
- Take a hot shower
- Imagine a relaxing place in my mind
- Deep slow breathing

### Relaxation Strategies

- **Deep breathing**
  - Inhale for count of 5 & hold briefly
  - Exhale for count of 5
  - Repeat 5 times
- **Progressive muscle relaxation**
  - Begin with feet, contract muscles for count of 5 and slowly release
  - Move up the body through all muscle groups
- **Meditation** – many CDs and Apps available
What to do in the office during watchful waiting

- Use a rating scale to monitor sx’s
- Mood diaries
- Cognition charts - negative thoughts in one column and a neutral thought in other column
- Prescribe pleasant activities and exercise
- Relaxation strategies

Treatment Options

If has moderate to severe depression, start with more specific treatment OR if mild to moderate depression not improving after 4 weeks of supportive care (watchful waiting):

- Individual psychotherapy
  - Cognitive Behavioral Therapy
  - Interpersonal Psychotherapy
- Family therapy
- Medication

Severe depression – start meds and other referrals

Medication Treatment Options

- Selective Serotonin Reuptake Inhibitors
- Selective NE Reuptake Inhibitors
- Other antidepressants
- Tricyclic Antidepressants

- Typical duration of medication treatment – 6 to 12 months after response present. Relapse high if stop within 4 months of symptom improvement.

Medication - SSRIs

- *Fluoxetine (Prozac) - age 8
- Sertraline (Zoloft)
- Paroxetine (Paxil)
- Citalopram (Celexa)
- *Escitalopram (Lexapro) - age 12
- Fluvoxamine (Luvox)

*FDA approved for the treatment of MDD under age 18

Medication – SSRIss

- Early studies - struggled with high placebo response rates so medication could show efficacy

- Emslie (1997) – 1st study showing SSRI efficacy for adolescent depression (fluoxetine) - 58% fluoxetine response rate vs 32% placebo

Medication – SSRIss

- Treatment of Adolescents with Depression (TADS) JAMA 2004

- 439 adolescents with mod to severe depression treated with meds/CBT/PLC or med+CBT 12 wks
  - 71% response for Fluoxetine + CBT
  - 61% Fluoxetine alone
  - 43% CBT
  - 35% placebo

- 29% had suicidal thoughts at baseline

- By week 12, suicidal thoughts down to 10% of pts
Medication - SSRIs

- 
  Emeslie (2009) escitalopram vs. placebo
  12 weeks
  - Overall study negative.
  - Sub-analysis found it effective in the 12-17 aged patients, but not the younger cohort
For 12-17 year olds
- Response rates 64.3% ESC vs. 52.9% PLC
- Remission rates 41.6% ESC and 35.7% PLC

SSRIs - dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting dose</th>
<th>Dose increments</th>
<th>Typical target dose</th>
<th>Usual max dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>5-10mg</td>
<td>10-20mg</td>
<td>10-20mg kids</td>
<td>60mg</td>
</tr>
<tr>
<td>Sertraline</td>
<td>5-10mg</td>
<td>10mg</td>
<td>10-20mg</td>
<td>40mg</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>5-10mg</td>
<td>10mg</td>
<td>10-20mg</td>
<td>40mg</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5-10mg</td>
<td>5-10mg</td>
<td>10-20mg</td>
<td>40mg</td>
</tr>
</tbody>
</table>

SSRIs - dosing

- Typically once a day dosing in adults/teens
  - Morning for fluoxetine & sertraline
  - Evening for paroxetine, citalopram & escitalopram
- Pre-pubertal children metabolize more quickly - may need twice daily dosing
- Ensure an adequate trial before changing meds, maximum tolerated dose for at least 4-6 weeks

SSRIs - Common Side Effects

- Nausea and diarrhea – 5HT receptors numerous in gut, need to titration slowly, this side effect remits with exposure
- Headache – usually remits with time
- Agitation, impulsivity or activation – 3-8% pts
- Insomnia
- Fatigue or sedation (more common w/paroxetine, citalopram or escitalopram)
- Sexual side effects – low libido or anorgasmia

SSRIs – Side Effects of concern

- Increased bleeding time
- Serotonin syndrome – flushing, diarrhea, autonomic instability, muscle tremors or spasms & confusion
  - Do not use with St. John’s Wort, linezolid (Zyvox) or MAOIs. Caution with triptan migraine meds, ketorolac (Toradol) or propoxyphene (Darvon)
- Drug-drug interactions –
  - SSRIs inhibit P450 in the liver slowing metabolism of other meds. Inhibit conversion of Tylenol 3 to morphine (P450 2D6)
- Cardiac: do not use citalopram over 40mg/day QTC
- Suicidal thoughts - 4% of pts

SSRIs - predicting remission/relapse

- 50-60% of patients get response with 1st SSRI
- 30-40% of patients get into remission with 1st medication trial
- Predictors of remission include:
  - + FHx of depression
  - Early symptom response (within 4 weeks)
- Predictions of relapse:
  - Early age onset
  - Higher number of previous episodes
  - Symptom severity
  - Psychosis
Treatment of Adolescents with Depression (TADS)

- Follow up 5 years later N=196 pts (44.6% of original cohort)
- By 2 years, 96.4% had achieved recovery
  - Predicted by early response to meds
- By 5 years, 46.6% a recurrence

What about patients who do not respond to treatment?

Treatment Resistant Depression: TORDIA (2008)

- N=334 patients ages 12-18 yrs who had not responded to 12 weeks of an SSRI
- Switched to another SSRI or venlafaxine
- Or added CBT along with medication change
  - Adding CBT gave better response rate (54.8%) as compared to either medication change alone
  - No difference between change to a different SSRI or venlafaxine
- If patient does not respond to SSRI, add CBT (or psychotherapy) in next treatment step

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Medication Summary

- Most evidence for SSRIs treating ado MDD
- Meds considered first line
  - Fluoxetine (Prozac)
  - Sertraline (Zoloft)
  - Citalopram (Celexa)
  - Escitalopram (Lexapro)
- Treat for 6-9 months once symptoms have improved
- Goal to treat to remission (no sx’ s for > 2 months)

Medication-other

Few studies in newer antidepressants

- Bupropion (Wellbutrin) no RCTs in youth
- Mirtazapine (Remeron) 2 negative RCTs
- Venlafaxine (Effexor) 3 negative RCTs
- Dualoxetine (Cymbalta) 1 negative RCTs
- Trazadone (Desyrel)

- TCAs 11 DB-PC studies with TCA’s in adolescents → none more effective than placebo. Risk of cardiovascular adverse effect ↑HR, AV block, ↑QTc

Suicide

- 17% of adolescents think about suicide each year (CDC data)
- Thoughts of death are part of MDE
- 3rd leading cause of death in adolescents about 2,000 deaths per year
- 25% decline in suicide rate in 10-19 year range in past decade
FDA warning about +SI and antidepressant meds
- FDA reviewed 23 studies with 9 different meds - > 4,300 youth
- NO SUICIDES in these studies
- Adverse events reporting + SI or potentially dangerous behavior reported by 4% of pts on meds vs. 2% on placebo
- 17 of 23 studies asked about SI - no new SI or worsening of SI, actually decreased during treatment

Meta Analysis of 27 RCTs with SSRIs
- Studies were for MDD, OCD and non-OCD anxiety
- For MDD
  - NNT = 10
  - NNH = 112
- More effective and less SEs when treating OCD or non-OCD anxiety
  JAMA 2007

Suicide and SSRIs
- 2004 FDA black box warning for risk of suicide for all ages with ALL antidepressants
- Need to advise families about this risk and give crisis info
- 2004 FDA recommended
  - Weekly contact the first 4 weeks
  - Every other week through week 12
  - As indicated after week 12

Suicide and SSRIs
- FDA changed black box warning from specific monitoring to more general one:
  All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

Risk Factors for Suicide
- 90% teens who commit suicide have a mental illness (mood, substance, ADHD, PTSD)
- Hopelessness or significant anxiety
- Poor interpersonal problem solving skills
- Childhood physical or sexual abuse
- Same sex orientation
- Life stressors - conflict with parent or romantic interest
- Access to weapons
- ¼ - ½ who commit suicide have prior SA

Protective Factors
- Family cohesion
  - high degree of mutual involvement
  - shared interests
  - emotional support
- Religion
- Adaptive problem solving
Treating Adolescents Attempting Suicide (TASA)

Youth Most likely to re-attempt suicide
- Higher level of suicidal thoughts
- Higher level self-report of depressive symptoms especially hopelessness and anxiety
- 2 or more prior attempts
- Low lethality of index attempt
- History of maltreatment
- Low family cohesion
- Average time to re-attempt 6 weeks

What to assess regarding suicidal thoughts?
- What are the thoughts?
  - Preoccupation with morbid themes and death?
  - Passive wish to die?
  - Thoughts of harming self?
- Do you have intent to harm self or a plan?
- Have you acted on these thoughts at all?
- Have you done anything to hurt yourself?

What about self-harm?
- Is this cause for alarm?
- Called non-suicidal self-injury (NSSI)
  - Intentional destruction of one's body tissue without suicidal intent and for purposes which are not socially sanctioned
- Common methods:
  - 70%-90% of people who self-injure engage in skin cutting, scraping, or carving
  - 21.44% banging, bruising, and self-hitting
  - 15.35% burning

Epidemiology
- 10.15% teens have self-injured at least once
  - Most studies find 6-8% of teens and young adults reporting current, chronic self-injury
  - More common in clinical populations
- Self-injury typically begins at ages 12-15 years
- M=F lifetime rates, however females may engage in NSSI more often
- Females tend to cut; Males hit or bang
- More common in Hispanic or Native American in US studies. UK study found more in Asian decent

Course and Prognosis
- Occurs with a wide range of diagnoses
- Few longitudinal studies of NSSI exist
- Questions to be answered:
  - How many people stop NSSI and when?
  - Is NSSI a precursor to specific mental disorders?
  - How often does it lead to suicidal behavior?
- Some information on NSSI and suicide attempts from several large studies on depression in adolescents

TORDIA study

JAMA 2008

Pts ages 12-18 failed 2 month SSRI trial N=334

Switch SSRIs Placebo
47% improved

Switch SSRI + add CBT
Better outcome 54.8%

Switch to venlafaxine

Switch to venlafaxine + CBT
Better outcome 54.8%
TORDIA and SA/NSSI

- Baseline
  - 23.9% prior NSSI
  - 9.5% prior suicide attempt (SA)
  - 14% NSSI + SA
- The rate of SAs in youth with NSSI was more than double those without NSSI (37% vs. 15%) at study entry
- 24 week outcome
  - 13% with NSSI made a suicide attempt vs 3% with prior SA
  - Predictors of SA were NSSI & hopelessness

ADAPT study

- Original trial N=208 British teens with moderate to severe depression randomized to SSRI or SSRI + 12 weeks of CBT.
- Outcome at 28 weeks found no difference between treatment groups.
- Subsequent analysis looked at those at risk for suicide attempt

ADAPT: Suicide attempts & self injury

- N= 163 teens 11 to 17 years (mean age 14)
- Avg 67 weeks of depression
  - CDI score mean 59.9
- One month prior to the study
  - 28 (17%) had made SA
  - 58 (36%) had engaged in NSSI
- During the 28 weeks of the study
  - 50 (30%) youth made a SA
  - 60 (37%) youth engaged in NSSI

ADAPT summary

- Suicide attempt in 28 week f/u period
  - 30% made a SA, lower each month
  - Risk factors: +SI, depression severity, hopelessness, NSSI or SA in the month before baseline and impaired family functioning
  - *NSSI a stronger predictor of suicide attempt than a prior suicide attempt

- NSSI
  - 37% had self injury, lower each month
  - Risk factors: NSSI in month prior to study, depression severity, anxiety, hopelessness, female and younger age

Assessment of NSSI: Implications for intervention

- Age of onset
- Methods used for NSSI & access to those materials
- Frequency & interval from thoughts to action
- Last self-injury
- Location of injury and medical severity
- Thoughts before, during and after NSSI
- Function of behavior (intra or interpersonal)

Function of NSSI

- Most common are INTRAPersonal reasons
  1. To regulate emotions
    - Release emotions, calm down, stop numb feelings
    - Reduces high arousal emotions (anger, anxiety, frustration) more than low arousal (i.e. sadness)
  2. Self punishment
- Sometimes INTERPersonal
  - Interpersonal influence: “letting others know how I feel” “getting back at someone” or getting out of responsibilities
  - Peer bonding: “fitting in”
Assessment measures

- Self-Injurious thoughts and behavior interview (SITBI)
- Suicide Attempt Self Injury Interview SASII (Linehan)
- Suicide Behavior Questionnaire (SBQ Linehan)

Both Linehan assessment items online at http://blogs.uw.edu/brtc/publications-assessment-instruments/

Interventions for NSSI

- Few studies in adolescents looking at strictly NSSI
- Therapy that focuses on:
  - Emotion regulation
  - Problem solving
  - Improved self esteem

DBT, CBT or problem based

Research has repeatedly documented that people who engage in NSSI have more frequent & intense negative emotions as well as poorer global emotion regulation skills

General advice for families regarding SI or self harm

- No firearms in home
- Limit access to medication including OTC meds
- Remove access to parent’s medications
- Remove razors from bathroom or other sharps
- Increase supervision (e.g. keep doors open, limit peer contact to with adults present)
- Importance of seeking help if suicidal thoughts develop or worsen
- Crisis numbers, emergency room resources and 911

Summary

- Major depression occurs in 8% of adolescents
- Fast, easy screening scales available for primary care
- Treatment begins with psychoeducation
- Mild depression can respond to support
- Moderate depression tx starts with talk therapy or meds. Reassess the plan at 8 wk intervals
- Severe depression treatment likely to use meds or combination meds + therapy as first step

Summary

- Things that can help while waiting for referral or in supportive period include:
  - Mood monitoring charts
  - Scheduling pleasant activities
  - Monitoring cognitions and feelings
  - Relaxation training
- SSRIs are effective medications for MDD
  - Common SEs include GI upset, headache, agitation and sleep disturbance
  - Be careful of combining with other serotonergic medications
- Monitor for suicidality and non-suicidal self injury

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