

Depression in Childhood and Adolescence

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Depression - Defined

- Adjustment disorders with depressed mood:
Mild, self limiting & in response to clear stressor
- Depression NOS (“minor depression or subsyndromal depression):
Depressed mood or anhedonia, or irritability and up to 3 symptoms of major depression
- Dysthymia:
Chronic condition (1 year) & fewer symptoms than MDD
- Major Depression:
Depressed or irritable mood or anhedonia plus at least 5 other symptoms

Depression - Defined

Minor depression & Dysthymia:

- Functionally impairing
- Often precursors to major depression

Comorbidity is the rule:

- Anxiety frequently a precursor and companion
- ADHD – maybe co transmitted in some families
- Alcohol, drug & tobacco abuse in bidirectional relationship
- Conduct Disorder – especially in prepubertal samples

Depression in Childhood and Adolescence

- Depression in children and adolescents may have a more insidious onset than in adults, with irritability a more prominent feature than sadness.
- Depression may affect 2% of children and 4-8% of adolescents, with a peak incidence around puberty.
- It may be self-limiting, but about 40% of affected children experience a recurrent attack, a third of affected children will make a suicide attempt, and 3-4% will die from suicide.

Depression - Defined

Comorbidity may arise due to shared risk factors:

Example – depression, behavioral disorders & substance abuse may be due to common factors:

- Parental substance abuse
- Criminality
- Exposure to family violence
- Family Discord

Depression - Epidemiology

Population Prevalence:

- Point prevalence prepubertal children – 1-2%
- Point prevalence adolescents – 3-8%
- Lifetime prevalence end of adolescents – 8%

Gender Distribution & Puberty:

3:1 female to male ratio in adolescents (post puberty)

- Hormonal differences (estradiol & testosterone)
- Higher anxiety in females
- Increased interpersonal conflict
- Early-onset of puberty in girls – risk factor

Depression - Epidemiology

Age & Developmental Factors:

Prepubertal depression has separate risk factors:

- Behavioral problems
- Family adversity (family discord, parental criminality, substance abuse & antisocial disorder)
- Does not predict depression in adult life
- Infrequent— highly familial, multigenerational loading for depression with high rates of anxiety and bipolar disorder predicting recurrence in adolescence/adulthood

Depression - Epidemiology

Age & Developmental Factors:

Adolescence Onset Depression:

- More likely to be recurrent into adult life

Preschool Children with depression:

- Sad or irritable mood
- Anhedonia
- Low energy
- Changes in activity levels

Depression – Risk Factors

Genetic Factors

- Heritability 40 -65 %
- 2-4 Relative Risk in 1st degree relatives
- Co-transmission with anxiety
- Short-short allele for serotonin transporter

Cognitive Factors

- Depressed individuals show more negative/pessimistic view of self, world and future
- May predispose to depression when paired with stress

Depression – Risk Factors

Familial & Environmental Risk Factors

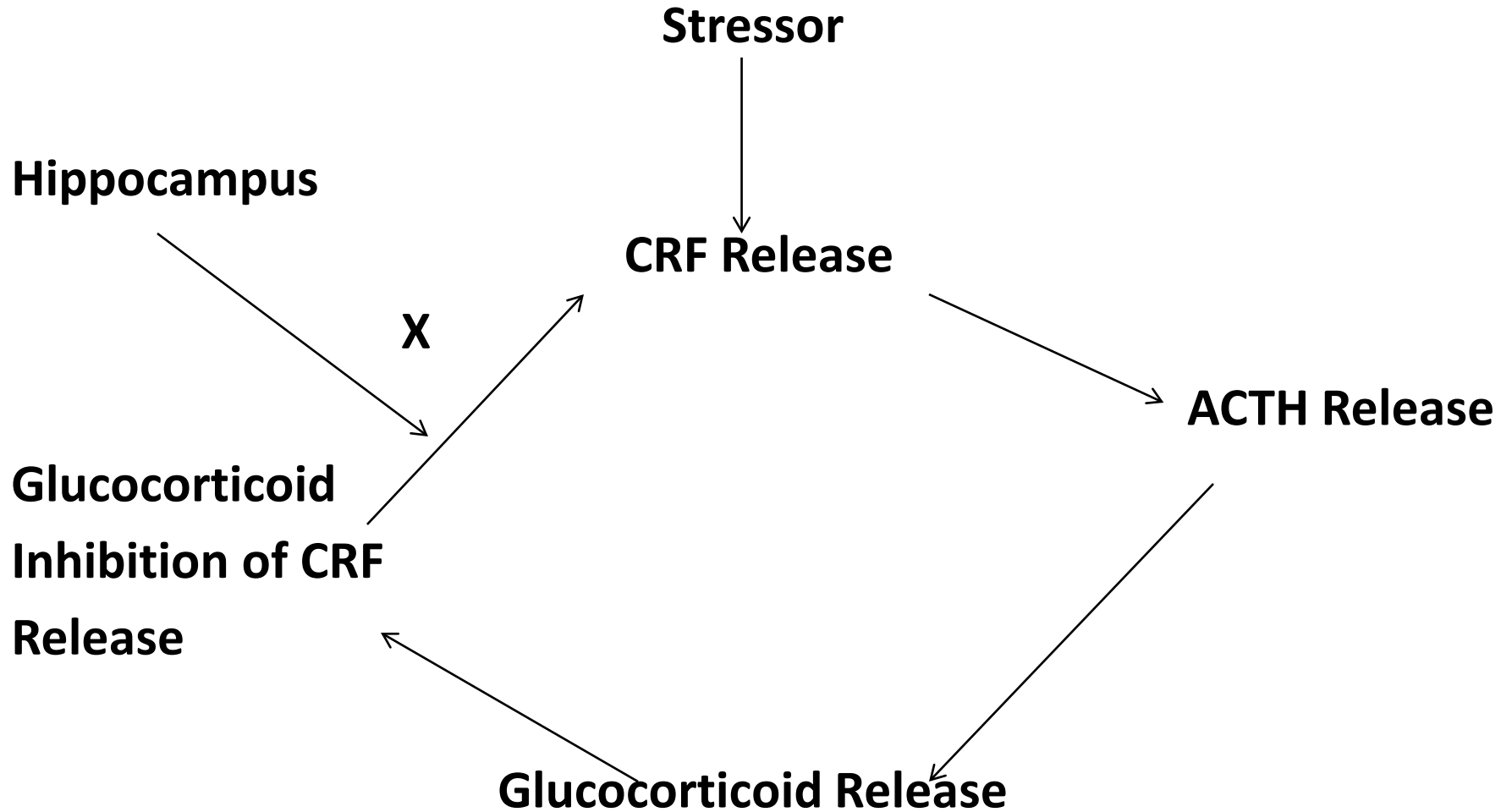
- Maternal Depression – complicated picture – both genetic risk but also passive and/or hostile interactions
- Neglect & Maltreatment – increase risk for depression and substance abuse, PTSD and suicide attempts
- Early loss and bereavement – risk for early and adult onset depression
- Protective – connection to family, school, nondeviant peer groups and parental behavioral and academic expectations

Neurobiology of Adversity

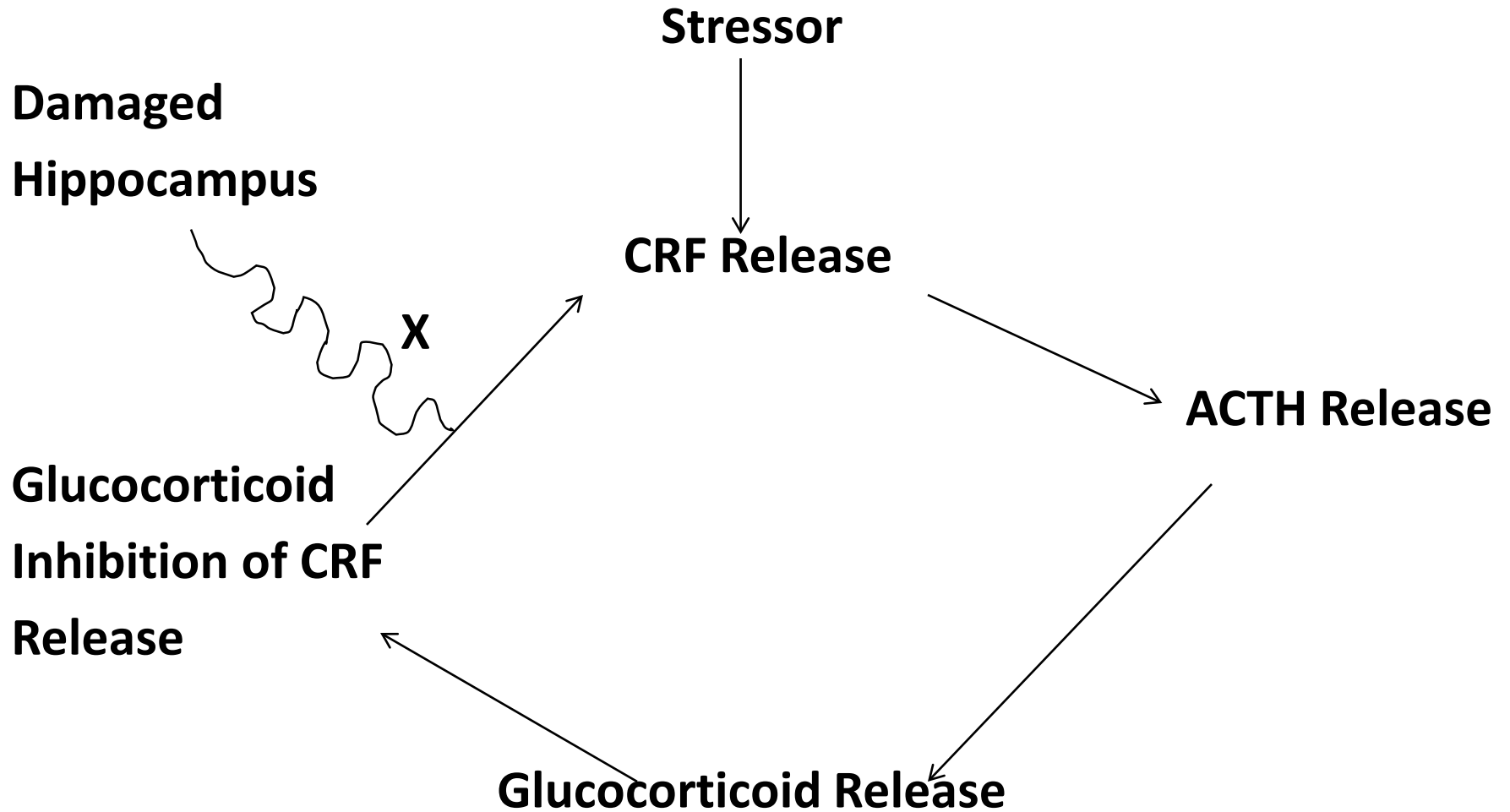
Childhood Adversity:

- May decrease 5HT receptor density in striatum
- May confer decreased sensitivity to negative feedback of glucocorticoids on HPA
- May sensitize individuals to develop more significant stress response to a given stressor

Stress and the HPA Axis
Normal Stress Response



Stress and the HPA Axis
Abnormal Stress Response



Depression – Course/Outcome

Episode Length & Recovery

- Mean length of episode – 3 to 6 months
- Longer episodes associated with
 - Comorbid anxiety, substance use, severity of depression and suicidality, Family discord
 - 20% of adolescents have greater than 2 year duration

Risk for Recurrence

- 40% recurrence at 2 years and 72% recurrence in 5 years
- Risk factors for recurrence: Lack of complete recovery, dysthymic baseline, poor social function, sexual abuse, family discord

Risk of Bipolar Course in Early Onset Depression: 10% - 20%

Depression – Management

Three empirically supported treatment of early onset depression:

1. Antidepressant Medication
2. Cognitive Behavioral Therapy
3. Interpersonal Therapy

In general less research on treatment of prepubertal children than Adolescents...

Treatment of C/A Depression

Psychotherapy

Large Meta-analysis (35 RTC's):

- Included CBT, IPT, Group, Individual, relaxation
- Effects for acute treatment are modest
- Outcomes better when youth is the informant
- No correlation b/t duration of tx and response
- Beneficial effects durable for months but not 1 year
- Also improved co-morbid anxiety but not externalizing symptoms

Treatment of C/A Depression

Treatment of Adolescent Depression

TADS Study

- FLX + CBT: 71% response
- FLX alone: 61%
- CBT alone: 43%
- Placebo: 35%
- SI present in 29% at baseline, all groups improved significantly

Treatment of C/A Depression

Antidepressants - History

- In 1980's case reports of positive responses of tricyclic antidepressants (TCA) in children and teens with depression.
- Widespread use of these agents ensued, then multiple double blind placebo controlled trials showed TCA's to be ineffective in children and adolescents
- In 1987 first positive trial of Fluoxetine was published, all serotonin reuptake inhibitors (SSRI's) gained widespread use
- In 2000's multiple negative trials of other SSRI's came to light
- In 2003, FDA issued warning on the use of Paxil in children due to increased SI
- In 2004, FDA required boxed warning of risk of increased SI with all antidepressants in children and teens (and young adults)

FDA Black Box

WARNING - SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in 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. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients less than 12 years of age.

Treatment of C/A Depression

Antidepressants – FDA Status

Fluoxetine

- FDA approved for MDD (8 – 18); OCD (7-18); Elective Mutism (6-12)

Escitalopram

- FDA approved MDD (≥ 12) – One negative study for MDD in children < 12

Sertraline

- FDA approved MDD (≥ 13); OCD (≥ 6)

Lithium

- FDA approved BPAD (≥ 6)

Not FDA Approved for use in Children & Adolescents

- Citalopram, Bupropion, Venlafaxine, Duloxetine, Paroxetine, TCA's, Lamotrigine, Buspirone

Paroxetine - FDA Status

Paroxetine:

Depression: The FDA recommends that paroxetine not be used in pediatric patients for the treatment of depression. Three well-controlled trials in pediatric patients with depression have failed to show therapeutic superiority over placebo; in addition, an increased risk for suicidal behavior was observed in patients receiving paroxetine when compared to other SSRIs (Dopheide, 2006).

Treatment of C/A Depression

Antidepressants – SSRI

Across RCT's

- Response rates are 40% - 70%
- Placebo response rates are 30% - 60%
- NNT is 10 (NNH 112)
- More likely to be statistically significant in adolescents (except with Fluoxetine)
- Fluoxetine – approved for use in children
- Fluoxetine - why more effective? – longer $t_{1/2}$ or better design of studies...

Treatment of C/A Depression

Antidepressants – Others

Negative Studies

- **TCA's**
- **Venlafaxine**
- **Mirtazapine**
- **Paroxetine**

Treatment of C/A Depression

Antidepressants – Side Effects

Most Common

- **GI symptoms**
- **Sleep Changes (insomnia, somnolence, vivid dreams, nightmares)**
- **Restlessness**
- **Diaphoresis**
- **Headache**
- **Akathisia**
- **Appetite changes (up and down)**
- **Sexual Dysfunction**

Treatment of C/A Depression

Antidepressants – Side Effects

- **Serotonin Syndrome (combo therapy) – agitation, confusion, hyperthermia**
- **Bleeding syndromes (bruising, epistaxis)**
- **Suicidality**

Behavioral Activation

- **Impulsivity**
- **Agitation**
- **Irritability**
- **Silliness**
- **3% - 8%**

Treatment of C/A Depression Antidepressants – Suicidality

Meta-Analysis

- Examined “suicidal adverse events” including ideation and attempts
- Risk Ratio for active treatment was 1.95 overall
- Translates to 1-3 spontaneously reported suicidal adverse event for 100 treated youth
- Few attempts and no completions
- Increased use of SSRI in adolescents coincides with decline in adolescent suicide

Treatment of C/A Depression

Antidepressants – Clinical Use

- **Doses are similar for children and adolescents as adults – except lower initial doses**
- **$T_{1/2}$ shorter in youth for Sertraline, Citalopram and bupropion SR – may need bid dosing**
- **Treat at “therapeutic doses” for 4 weeks**

Treatment of C/A Depression

Antidepressants – Clinical Use

- **Remission at 12-weeks is goal**
- **FDA recommends depressed youth be seen weekly of 1st 4 weeks then biweekly**
- **No data that monitoring affects adverse outcome of suicidal adverse effects**
- **Youth with h/o sexual abuse have lower response rates – role of adding psychotherapy**

Treatment of C/A Depression

Antidepressants – Clinical Use

- **Monitoring especially important for at-risk youth – current or prior suicidality, poor impulse control, substance use, family history of suicidality, history of sexual abuse**
- **Discontinuation is problematic (except with Fluoxetine) – seen as soon as 24 hours and after 6-8 weeks on medication**

Treatment of C/A Depression

Duration of Treatment

- **Rates of relapse high with both CBT and Medications**
- **Highest risk is within 4 months of symptomatic improvement**
- **Relapse rates “on” Fluoxetine 40% in 6 months versus placebo rate of 70%**
- **6-12 months of continued therapy is recommended for responders to acute treatment**

Treatment of C/A Depression

Psychotic Features

- **SSRI + Atypical Antipsychotic for psychotic depression in youth**
- **Vague or mild psychotic symptoms in a depressed child may respond to antidepressant alone**
- **Slow taper off antipsychotic with monotherapy is goal**
- **ECT option for adolescents**

Treatment of C/A Depression Bipolar Depression

- **Mild to Moderate depressed symptoms in patient with BPAD – consider psychotherapy before antidepressant**
- **Patients with psychotic features – higher risk for bipolar course**
- **If strong suspicion that course if bipolar – mood liability/strong family history – consider treating with lithium or lamotrigine**

Treatment of C/A Depression Comorbid Disorders

- **First treat disorder causing greatest distress and functional impairment (especially severe anorexia & serious substance dependence like cocaine, meth or IVDA)**
- **SUD – treat both as disorders worsen reciprocally; Adolescent RTC showed Fluoxetine reduced depressive and alcohol use**

Treatment of C/A Depression

Prevention

- **Programs targeting at-risk youth more effective – especially for females and older adolescents**
- **Treating depressed mothers – higher remission rates in depressed child**
- **Early-onset dysthymia and anxiety is risk for development of MDD**

Depression – Management

Cognitive Behavioral Therapy:

Predicated on observation that depressed individuals show:

- Distortions in thinking and information processing
- Emphasize negative aspect of situations
- Underemphasize the positive aspects of situations

Therapy:

Focuses on interrupting cycles of negative thinking, mood and maladaptive actions by:

- Cognitive restructuring
- Behavioral activation
- Skill building (problem solving, relaxation, assertiveness training)

Depression – Management

Interpersonal Therapy

Depression conceptualized as occurring in an interpersonal matrix

Therapy targets resolution of interpersonal stress associated with

Depression with components of:

- Education – psychoeducation, “limited sick role”, treatment contract
- Affect Identification – label & clarify and facilitate expression and monitoring of emotions
- Interpersonal Skill Building – modeling, use of therapeutic relationship as sample of interpersonal interaction, communication analysis, perspective taking, interpersonal problem solving & role playing

Treatment of C/A Depression

Psychotherapy

IPT

- Superior to twice-monthly supportive psychotherapy
- Most effective in moderate to severely depressed older teens
- Easy to disseminate