Early-Life Trauma and Depression

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Disclosures

• Neither I nor any member of my immediate family has a financial relationship or interest (currently or within the past 12 months) with any proprietary entity producing health care goods or services consumed by, or used on, patients related to the content of this CME activity

• I do not intend to discuss an unapproved/investigative use of a commercial product/device
Overview

- Background information: early-life trauma and depression
- Findings on depression phenotypes: early-life trauma vs. other causes
- Clinical and research implications
Childhood Trauma

- Parental separation
- Parental death
- Physical/mental illness of caretaker
- Exposure to domestic violence
- Natural disasters and political instability
- Childhood maltreatment
  - abuse (emotional, physical, sexual)
  - neglect (emotional, physical)
Maltreatment Statistics

3.6 Million* referrals of maltreatment to CPS involving 6.6 Million children*

61% referrals screened in (become reports) 39% referrals screened out

2.2 million reports received a disposition

63% Professional 19% Nonprofessional 19% Unclassified >100% due to rounding

3.2 million children received either an investigation or alternative response

702,000 victims* Includes 1,580 fatalities*

410,448 victims received postresponse services

147,462 victims received foster care services

2,498,000 non-victims

890,889 non-victims received postresponse services

94,457 non-victims received foster care services

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DHHS, ACF 2016

Maltreatment - Perpetrators

Exhibit 5-D Perpetrators by Relationship to Their Victims, 2012

- Parent: 80.3%
- Nonparent: 16.5%
- Unknown: 3.1%

Percentage of Parents by Parental Type:
- Biological Parent: 88.5%
- Stepparent: 3.9%
- Unknown Parental Type: 7.0%
- Adoptive Parent: 0.7%

Percentage of all Perpetrators: Total = 100%

Based on data from tables 5-5 and 5-6.

DHHS; ACF 2012
Early-Life Trauma: Sequelae

- Physical
  - impaired development, medical illnesses

- Behavioral
  - delinquency, aggression, suicidality

- Psychological
  - impaired social competence, emotional regulation and cognition, psychopathology

- Biological
  - alterations in autonomic reactivity, stress response and brain structure and function
Impact of Early-Life Trauma

- Effects of early-life trauma can be long-lasting and occur in multiple systems
  - progressive physical, cognitive and emotional development
  - dramatic changes in brain development
  - stress during neuronal plasticity can result in persistent sensitization of the neurobiological systems to mild stress
Maltreatment: Depression Risk

Teicher & Sampson, Am J Psychiatry 2013;170:1114–1133
One-year Incidence of Major Depression

Percent Clinically Depressed

Age

Depression: Age, Sex and Puberty

Hankin et al., J Abnorm Psychol 2015; 124: 803-816
Pediatric Depression: Sequelae

- Suicidal behavior
- Risk for recurrent episodes
- Risk for other psychopathology
- Persistence into adult life
- Psychosocial difficulties
  - interpersonal problems
  - early pregnancy
  - school dropout
  - unemployment
Is depression associated with maltreatment different from depression without maltreatment?
Phenotypes: Clinical Differences

- Depression + maltreated phenotype
  - earlier onset of depression
  - more severe symptoms
  - higher rates of comorbidity
  - more chronic and recurrent episodes
  - greater risk for suicidality
  - poorer response to treatment
Normal LHPA Response

Response in Early Adversity
Hypothalamic-Pituitary-Adrenal (HPA) Axis Assessment
HPA Response to Stress in Depression

Rao et al., Biological Psychiatry 2008;64:521-526
ELA Effects on HPA in Depression

Rao et al., Biological Psychiatry 2008;64:521-526

ELA = early-life adversity
Depression Risk and HIPP Size

Hippocampal Volume (% of TBV)

Normal  High-Risk  Depressed

Left  Right

HIPP = hippocampus
Rao et al., Biological Psychiatry 2010;67:357-364
Effect of ELA on HIPP Size

Left Hippocampal Volume (% of TBV)

- Normal
- High-Risk
- Depressed

ELA (-)  ELA (+)
Effects of FH and ELA on HIPP

![Graph showing the effects of Family History (FH) and Electrolyte Abnormalities (ELA) on Left Hippocampal Volume (% of TBV). The graph compares the volume for Family History (+) and Family History (-) with and without ELA.](image-url)
Adversity-HIPP: Depression Risk

Rao et al., Biological Psychiatry 2010;67:357-364
Maltreatment & White Matter Tracts

Huang et al., Neuropsychopharmacology 2012;37:2693-2701
Intrinsic Functional Connectivity

Rao et al., unpublished data
Emotion Regulation Neural Circuit

Wilcox et al., Am J Psychiatry 2016;173:344-361
Fronto-Limbic Circuit: Go/No-Go Task

Hare et al., Biol Psychiatry 2008;63:927-9345
Maltreatment Effects on Fronto-limbic Circuit

Amygdala Response

ACC/PFC Response
Trauma Effects on Amygdala Response

Grant et al., J Psychiatr Res 2011;45:886-895
Maltreatment: AMG-PFC Connectivity

Birn et al., Depress Anxiety 2014;31:880-892
Depression: Self-Referential Thinking

Yoshimura et al., J Affect Disord 2010;122:76-85
Depression: AMG-PFC Connectivity

Johnstone et al., J Neurosci 2007;27:8877-8884
Maltreatment Effects on Risk-taking Behavior

Risky Choice

Reaction Times
Maltreatment Effects on Reward-processing Circuitry

Ventral Striatal Response

Selection Phase

- Low-Risk Selection
- High-Risk Selection

- NC
- MDD
- MDD+MALTX

Feedback Phase

- win
- No-Win

- NC
- MDD
- MDD+MALTX

Ventral Striatal Response Selection Phase

Ventral Striatal Response Feedback Phase
Anhedonia: Reward Circuitry

Adapted from Simon et al., Schizophr Res 2010;118:154-156
Maltreatment Effects on Response to Treatment of Depression

Nemeroff et al 2003; PNAS 100:14293-14296
Interim Summary

- Depression due to early-life trauma may be a different phenotype
  - different clinical profile
  - different neurobiology
  - different treatment response
Next Steps

• Develop and test treatments based on differential neurobiological profiles
• Test whether the treatments affect observed neurobiological deficits
Neurofeedback: AMG Downregulation

Paret et al., Front Behav Neurosci 2014;8:299
Tx Effects on Self-Referential Thinking

Neurofeedback: Positive Memories

Zotev et al., Neuroimage Clin 2016;11:224-238
Can social policy affect changes in neurobiology?
Cortisol: 24-Hour (Diurnal) Pattern

Social Support Effects on HPA Axis

Bernard et al., Arch Pediatr Adolesc Med 2010;164:438-443
Summary

• Early-life trauma increases the risk for depression and other problems
• Trauma interacts with genetic factors to induce neurobiological changes and increase risk for psychopathology
• Neurobiological deficits can be altered by social policy and other interventions
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