Serious Mental Illness and Trauma: A Literature Review and Issue Brief

Introduction.

The Adverse Childhood Experiences (ACE) study, conducted at Kaiser Permanente from 1995 to 1997[1], found very strong correlations between childhood trauma and a variety of health and social conditions in adulthood. Subsequent research has verified those relationships, examining a wide range of traumatic events and toxic stressors and an equally wide range of outcomes. Significant research attention is now focused on determining potential psychological and biological pathways of causation. However, the role of trauma in severe mental illnesses has remained controversial. One early research review[2] postulating a causal link between childhood trauma and psychosis was criticized for being premature, given methodological problems in the studies reviewed.[3] [4] In the past twelve years, a substantial body of literature has accumulated on this topic, including methodologically rigorous studies and several reviews and meta-analyses. The purpose of this paper is to summarize the current science on the relationship between trauma and serious mental illnesses.

SAMHSA defines "serious mental illness" as a "diagnosable mental, behavioral or emotional disorder (excluding developmental and substance use disorders) of sufficient duration to cause serious functional impairment in an individual's major life activities (going to work, school, interacting with family, etc.) Serious mental illnesses include major depression, schizophrenia, and bipolar disorder, and other mental disorders that cause serious impairment." [5] The current paper focuses primarily on these diagnosable conditions, as well as on "psychosis" and "psychotic symptoms," and is based on a literature review of research published between 2012 and 2017 (see accompanying annotated bibliography.)

Relationship between trauma and serious mental illnesses.

Evidence for an association between childhood trauma and serious mental illness is strong. There is little doubt that individuals with severe mental illnesses report child trauma at a much higher rate than the general population. For example, a large cross-sectional survey of child physical abuse in a representative sample of the U.S. population (National Epidemiological Survey on Alcohol and Related Conditions) found significantly increased adjusted odds ratios for a broad range of DSM-IV disorders, with a dose-response relationship between frequency of abuse and several adult psychiatric disorder groups.[6] A systematic review of four databases similarly found higher prevalence rates of physical and sexual abuse among people with severe mental illness compared to the general population.[7] Two recent meta-analyses have confirmed and quantified the association between childhood trauma and psychosis[8] and between childhood trauma and specific diagnostic categories.[9] Varese and colleagues found a significant association between adversity and psychosis across 36 patient-control, prospective and cross-sectional cohort studies, with an odds ratio of 2.8. They also found a dose-response relationship in nine of ten studies that tested for it. In a meta-analysis of studies comparing childhood trauma in patients with schizophrenia and non-psychiatric control subjects, Matheson et al found an odds ratio of 3.6, with similar results for all other major psychiatric disorders with the exception of anxiety disorders.

On the strength of this significant body of research, there is growing consensus that childhood trauma is a significant risk factor for serious mental illness. The question of whether there is a causal relationship

is less clear. Consistent dose-response relationships in large dataset analyses are suggestive. However, in order to establish a causal relationship, the possibility of reverse causality (i.e., early symptoms of psychosis increasing risk for childhood trauma) and genetic confounding must be ruled out. Prospective studies showing adverse experiences occurring before the onset of psychosis lend support for a causal hypothesis. In two prospective studies, Cutajar and associates[10] and Arseneault[11] and associates demonstrated that child trauma occurred before the onset of psychosis, but neither fully ruled out the possibility that early symptoms predated the exposure. A study by Kelleher and colleagues[12] found a bidirectional relationship (trauma predicting psychotic experiences over time and vice versa). However, even after making a number of strict adjustments to account for the bi-directionality, trauma was strongly predictive of psychotic experiences. In addition, they found evidence that cessation of traumatic experiences leads to a reduced incidence of psychotic experiences.

The genetic confounding hypothesis proposes that genetic risk affects both the likelihood of childhood trauma and that of psychosis, with trauma adding no additional impact. This hypothesis suggests that people at genetic risk for psychosis are more vulnerable to victimization because of traits associated with psychosis (e.g., poor social skills.) There is little available research evidence on this question, in part because it is difficult to accurately identify genetic risk for psychosis. However, several studies have shown strong and significant associations between child trauma and psychosis, even when controlling genetic factors. These results suggest a partial genetic mediation of environmental effects rather than a gene-environment confounding – i.e., if genetic factors increase risk for serious mental illness, exposure to trauma *further* increases risk.[13]

***Section summary**: Childhood trauma is a significant risk factor for serious mental illness, with meta-analyses showing that people with histories of childhood trauma are about three times as likely to be diagnosed with serious mental illness in adulthood as those without such histories. The question of causality is still under investigation. Dose-response relationships and the sequencing of events strongly suggest causality, but are not definitive. Studies controlling for genetic factors find child trauma confers significant additional risk. The most plausible explanation is a partial genetic mediation of the impact of trauma in the development of serious mental illness.*

Relationship between trauma and course of illness, severity, and treatment response.

Numerous studies suggest that traumatic experiences in childhood are associated with course of illness (onset, persistence and recurrence), symptom severity, and treatment response in serious mental illnesses. In a review of studies of childhood trauma and bipolar disorder, Aas and colleagues[14] found consistent indications that childhood trauma is associated with earlier onset, rapid cycling, psychotic features, lifetime episodes, and suicide attempts. Three relationships were replicated across multiple studies: age of onset, risk of suicide, and comorbid substance abuse. A recent meta-analysis of 30 studies[15] confirmed these relationships, finding patients with bipolar disorder and histories of child abuse, compared to patients with bipolar disorder but without child trauma histories, had greater severity of mania, depression and psychosis; greater co-morbidity with PTSD, anxiety disorders and alcohol use disorder; earlier age of onset; greater risk of rapid recycling; greater number of manic episodes; and higher risk of suicide attempts.

Similarly, there is evidence that childhood trauma is associated with both course of illness and treatment outcomes in depression. In two separate meta-analyses, Nanni et al found that childhood maltreatment is associated with elevated risk of developing recurrent and persistent depressive episodes and with lack of response or remission during treatment.[16] Several studies have found differential treatment response between people with depression who have trauma histories and those without. Adolescents with treatment-resistant depression who had histories of physical or sexual abuse showed poorer 12-week response to combination treatment (medication plus cognitive-behavioral therapy) when compared to those with no reported abuse history, even adjusting for other clinical predictors.[17] Similarly, Williams et al[18] showed poorer response to antidepressant medication in a large sample of adults with major depressive disorder who reported childhood abuse, particularly physical, emotional and sexual abuse before the age of seven, compared to those without such histories.

Research looking at groups with mixed diagnoses show similar results. Dvir et al[19] summarize several studies showing that patients with first episode psychosis who have experienced trauma have a different presentation at illness onset than those with no trauma exposure. In one of the few studies to compare the impact of traumatic events in childhood to those in adulthood, Stumbo et al[20] examined a group of adults diagnosed with a serious mental illness (including bipolar disorder, affective psychosis, schizophrenia or schizoaffective disorder). They found that adverse adult experiences were more important predictors of outcomes than adverse childhood experience. Adult exposure to trauma was associated with lower recovery scores, poorer quality of life, lower mental, physical and social functioning, and higher psychiatric symptom severity. There is also some evidence suggesting a relationship between childhood trauma and chronicity. Braehler et al [21] found that more severe childhood trauma was related to dissociative symptoms in all three groups (first-episode psychosis, chronic psychosis, and community controls) but that the relationship was strongest in the chronic group.

Not all studies have found a relationship between trauma and course of illness. Van Dam and colleagues[22] found a strong dose-response relationship between childhood trauma and psychosis, with abuse being more strongly associated with positive than negative symptoms. However, childhood trauma was not related to course of symptoms over three years. Similarly, there does not appear to be a strong relationship between trauma histories and severity or course of illness in obsessive-compulsive disorder. In a study of patients with obsessive-compulsive disorder, Visser and colleagues[23] found no association of trauma with measures of symptom severity or chronicity, although they did find a relationship with co-morbid affective disorders, substance use disorders, and eating disorders (but not to comorbid anxiety disorders.) They suggest that earlier inconsistent findings with this group could relate to the presence of comorbidity.

The literature linking individual types of childhood trauma to specific symptoms and clinical manifestations is less robust, although clearly suggestive. One study found that childhood sexual abuse was associated with hallucinations, while being brought up in a children's home was associated with paranoia.[24] A review of 44 studies found that unspecified neglect was most closely associated with mood and anxiety disorders, emotional abuse with personal disorders and schizophrenia, and physical neglect with personality disorders.[25] Severity of shutdown dissociation (the shutting down of sensory, motor and speech systems) in patients with schizophrenia spectrum disorder was related to number of childhood but not adult traumatic events, affected by both type and timing: Peak vulnerability occurred

at 13-14 years of age, with exposure to emotional neglect followed by emotional abuse having the strongest relationships.[26] In an exploratory study using qualitative techniques, Reiff and associates found that "trauma-related content" in adults with serious mental illnesses was higher in those with reported trauma histories than those without.[27] Clearly, the relationship between trauma and the course and severity of illness has important treatment implications. More research is needed to explore the relationship between specific types of trauma, age of occurrence, and clinical impact.

Section Summary. *There is robust evidence that traumatic experiences in childhood are associated with course of illness (onset, persistence and recurrence), symptom severity, and treatment response in bipolar disorder and depression, and possibly in other diagnostic categories. There is also evidence, although less robust, for relationships between specific forms of childhood trauma and specific symptoms and diagnoses. These relationships have clear clinical implications.*

Search for causal pathways and mediating variables.

While there is an emerging consensus about the strength of relationships between child trauma and the occurrence of serious mental illnesses, and growing evidence about relationships with course and severity of illness, the mechanisms through which these relationships occur are still largely unknown. Research is now focusing on psychological and biological pathways underlying these associations. A number of hypotheses have at least some supporting evidence.

Many theorists focus on the role of psychological processes in mediating the link between trauma and serious mental illness. Aas et al,[28] for example, found that "affective lability" statistically mediates the relationship between childhood trauma and severe or complex clinical expression of bipolar disorder. Van Winkel et al[29] summarize evidence that toxic stress and trauma can lead to a state of decreased self-value in relation to others, or even to state of social defeat. The social defeat notion is based in animal research showing that repeated attacks of a stronger intruder animal affects dopamine transmission, which is also implicated in the development of psychotic symptoms. Other possible psychological mediators mentioned by van Winkel include cognitive biases, ability to reflect a theory of mind, and a tendency to attribute negative events to external factors. Bentall and Fernyhough[30] postulate that early childhood trauma leads to low self-esteem, which, coupled with the inability to understand the intentions of others, leads to a tendency to anticipate social encounters as threats.

There is growing research on biological and neurobiological mechanisms that could underlie the trauma-psychosis link. Trauma and stress are known to cause changes in the stress-response and immune systems, including the inflammatory response; to affect the circadian system and sleep disorders; and to shorten telomeres. Any of these impacts could potentially affect the development of psychosis. A recent meta-analysis by Baumeister and colleagues[31] demonstrated that childhood trauma contributes to a pro-inflammatory state in adulthood, with specific inflammatory profiles depending on specific type of trauma. Danese and Baldwin[32] note that a systemic inflammatory response can affect brain development, behavior, and reactivity to subsequent stress, and ultimately risk for psychopathology.

Sensitization of the dopamine system is often suggested as a mechanism linking child trauma and psychosis. Van Winkel et al [33] review studies suggesting that early adversity results in exaggerated dopamine response to subsequent social stressors, and possibly also to recreational drug use. Although direct evidence linking early experience to stress-induced dopamine release is limited, changes in the dopamine response system have been reported in patients with psychosis.

Changes in the structure and functioning of the hypothalamic pituitary adrenal (HPA) axis have also received substantial attention due to the role the HPA axis plays in stress response. A meta-analysis[34] of patients diagnosed with schizophrenia and bipolar disorder showed elevated levels of morning cortisol, although the specific role of trauma could not be identified. Teicher et al[35] demonstrated a volume reduction in two important areas of the hippocampus in patients reporting childhood maltreatment, suggesting that exposure to early stress affects hippocampal development. Notably, the results were not mediated by histories of depression or PTSD. Other changes in the brain which may play a role in the link between trauma and psychosis include blunted reward-related brain activity[36] and effects on the fiber pathways that convey adverse experiences to frontal, temporal or limbic regions.[37] In addition, there is emerging evidence that prenatal exposure to toxic stressors, including alcohol and maternal seizures, may be a key component in the development of late-onset neuropsychiatric disorders.[38]

Another active area of research concerns the ways in which genetic mechanisms interact with early life trauma to influence the development of serious mental illnesses. Because most people exposed to child trauma do not develop psychotic symptoms, it is commonly assumed that underlying genetic vulnerability pays a role. For example, Cannon and colleagues[39] propose that exposure to prenatal or post-natal stressors interacts with genetic vulnerability to "prime the brain" to be more sensitive to stressors later in life. Research on gene-trauma interactions has had mixed results, with some studies showing evidence for an interaction and others not.[40] A recent meta-analysis on 31 datasets[41] examined the relationship between depression, childhood maltreatment or other stressful life events, and a gene thought to be associated with depression. They found a strong main effect for life stressors, no impact of the genotype, and no evidence of an interaction.

The most common explanation for the negative results is that the role of genes in mediating the development of serious mental illness is extremely complex. Recently, several researchers have drawn on epigenetics as a potential explanation for the apparent complexity in the expression of genetic vulnerability. Epigenetics refers to the regulation of genes through DNA methylation and chromatin structures, a process which is independent of genetic structure itself.[42] Research that focuses on DNA sequences would not be sensitive to epigenetic impacts. Diwadkar et al note that growing evidence fails to conclusively link individual genes to specific mental illnesses, and suggest that epigenetic effects during development may help to explain the negative results. Specifically, they suggest that mediation of the genes involved in the stress response may be involved.[43] Similarly, Bohacek and colleagues[44] review the epigenetic mechanisms involved in complex diseases and suggest that they may substantially account for the unexplained heritability of mental illnesses. Initial findings on the relationship of parenting and DNA methylation in children[45] and on the relationship of treatment response to epigenetic impacts on the HPA axis[46] [47] suggest that this avenue is worth pursuing.

Section summary. *Research is now focusing on psychological and biological pathways through which childhood trauma affects the development of serious mental illnesses. A number of hypotheses have been tested. While further research is needed, it appears that there are multiple biological systems involved, mediated by complex genetic/epigenetic mechanisms, and possibly operating through various psychological and cognitive consequences. The explanations discussed above are not mutually exclusive. Theories such as the traumagenic neurodevelopment model of psychosis[48] and the sociodevelopmental cognitive model of schizophrenia/psychosis[49] show great promise in bringing the different sub-fields together to expand our understanding of this issue.*

Implications

A recent Comment in the *Lancet*[50] suggests that childhood trauma may be "psychiatry's greatest public health challenge." The authors believe that evidence of a relationship between trauma and mental illness, including serious mental illness, is strong enough to warrant a major revamping of our mental health system. Taking a public health approach to serious mental illness would mean developing social policies acknowledging the impact of social determinants on the development of psychosis. It would also require implementing a full range of coordinated assessment, treatment and prevention interventions.

While specific causal connections remain to be worked out, it is clear that a sizeable percentage of people diagnosed with serious mental illnesses have experienced trauma. In addition to the convincing data on rates of childhood trauma in clinical populations, research has consistently shown that PTSD is highly co-morbid with serious mental illness.[51] Moreover, people with serious mental illness are at higher risk for additional trauma, including adult victimization as well as the traumatic impact of being given medication against one's will, being involuntarily detained, and experiencing threatening hallucinations.[52] It is certainly not surprising that this group experiences post-traumatic stress symptoms at higher rates than the general population.[53]

The National Institute for Health and Care Excellence (NICE), a group that sets standards of care in health and social services for the United Kingdom, has recently updated treatment guidance on psychosis and schizophrenia.[54] They recommend that all service users be routinely screened for PTS symptoms, and that trauma-based therapies be offered to those who screen positive. Others have recommended that all clients of mental health services, including those diagnosed with serious mental illnesses, be asked or given the opportunity to talk about childhood traumatic experiences,[55] and that they be provided with therapies addressing the traumatic experiences and targeting cognitive deficits or emotional dysregulation linked to trauma.[56] Clinicians are sometimes reluctant to address trauma because they believe self-disclosure is unreliable and/or that treatment for trauma may exacerbate psychotic symptoms. Recent research calls the unreliability of self-report into question, and a review of research on the use of trauma-specific therapies in patients with psychosis showed the interventions to be both safe and effective.[57] Experience in the field suggests that creating a "trauma-informed" clinical environment is an important first step in overcoming attitudinal barriers to addressing trauma.[58]

Studies documenting the relationship between childhood trauma and the onset, severity and course of illness raise another important clinical issue. Within several diagnostic categories, it appears that in patients with trauma histories, serious mental illnesses occur at an earlier age, manifest more severe symptoms and behaviors (including suicide), co-occur more often with other psychiatric illnesses, have more frequent and severe episodes, and respond less well to traditional treatments. In short, it appears that even with the same diagnosis, patients with trauma histories are less likely to do well, clinically, than those without. This raises the question of whether there are distinct sub-groups within diagnostic groups that might require different clinical guidelines and algorithms. While further research is clearly needed, Teicher et al[59] recently found support for this hypothesis, reviewing neurobiological findings for major depressive disorders, anxiety disorders and substance use disorders. Given the high human and social cost of treatment-resistant mental illness, this is a promising avenue to pursue.

There are also profound implications for primary and secondary prevention strategies. In contrast to the substance abuse field, little attention has been paid to the possibility of preventing serious mental illnesses. Knowing that trauma is a risk factor could change that. Read et al,[60] using the data from the Varese meta-analysis,[61] point out that a third of all new cases of adult psychosis could be prevented if six types of childhood adversity were eliminated. While it goes beyond the scope of this paper, many evidence-based prevention programs exist that could, if widely implemented, affect the population rates of these risk factors. The research reviewed here also raises the possibility of effective secondary prevention through interventions targeted at high-risk groups. Could rates of serious mental illness be reduced if children and adolescents exposed to trauma were given remedial assistance in coping with emotional dysregulation and other cognitive impacts of trauma *before* they developed prodromal symptoms of mental illness? Could chronicity be reduced if trauma-related issues were addressed when early symptoms first occur?

Responding to these questions and challenges will require a fundamental re-examination of our public mental health system, as well as the financial, regulatory and human resource structures that maintain it. The data suggest that it would be worthwhile to do so.

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