## EXPERT REVIEW

# Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education

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Childhood maltreatment is the most important preventable risk factor for psychiatric disorders. Maltreated individuals typically develop psychiatric disorders at an earlier age, have a more pernicious course, more comorbidities, greater symptom severity, and respond less favorably to treatments than non-maltreated individuals with the same primary DSM-5 diagnosis. Furthermore, maltreated individuals have alterations in stress-susceptible brain regions, hypothalamic-pituitary-adrenal response, and inflammatory marker levels not discernible in their non-maltreated counterparts. Hence, maltreated and non-maltreated individuals with the same primary DSM-5 diagnoses appear to be clinically and neurobiologically distinct. The failure to embody this distinction in DSM-5 has interfered with our ability to discover novel treatments, to recommend currently available treatments most likely to be efficacious, and has been a largely unrecognized confound that has thwarted our ability to identify the biological basis for major psychiatric disorders. Incorporating this distinction into DSM will help transform this sign and symptom-based classification system to a more etiologically informed nosology. We discuss several diagnostic alternatives and recommend the inclusion of a Developmental Trauma Disorder diagnosis for severely dysregulated individuals, of all ages, with numerous comorbidities, who experienced interpersonal victimization and disruptions in attachment, such as emotional maltreatment or neglect. For less severely affected maltreated individuals, we suggest using conventional diagnostic categories, such as major depression, but with an essential modifier indicating a history of childhood maltreatment, or early life stress, to delineate the ecophenotypic variant. Implementing this strategy should improve our ability to effectively diagnose and treat individuals with psychiatric disorders and to accelerate discovery.

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"The first step in wisdom is to know the things themselves; this notion consists in having a true idea of the objects; objects are distinguished and known by classifying them methodically and giving them appropriate names. Therefore, classification and name-giving will be the foundation of our science."—Carolus Linnaeus

## INTRODUCTION

This year, 2021, will mark a turning point in the COVID-19 pandemic. Let this year also herald a transformation in psychiatric practice, research, and education. Data supporting this shift have been growing at an exponential rate over the course of our careers and the findings are persuasive. While these discoveries are receiving increasing recognition and are being embraced by an expanding array of researchers and clinicians, many in our field remain unaware of the extent of these findings and their enormous implications. It is time for psychiatry to officially recognize these implications and to enact some essential changes.

What we will argue is that childhood abuse, childhood neglect, and other forms of childhood maltreatment (CM) or early life stress are not only the most important risk factors for many types of psychopathology, but they are critical experiential determinants that result in a cascade of molecular and neurobiological transformations that distinguish patients with maltreatment histories from their non-maltreated counterparts [1, 2]. This information is of utmost importance in treatment planning and should be a key factor in therapeutic algorithms [3]. Furthermore, the molecular and neurobiological effects of CM have been a largely unrecognized confound in psychiatric research studies and as such have been an enormous barrier to progress [4]. Recognizing the importance of CM by incorporating this information into our diagnostic nosology will enable us to better understand the epidemiology of psychiatric disorders and will help hasten the transition of the Diagnostic and Statistical Manual

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(DSM) [5] from an almost purely descriptive nosology into a more comprehensive classification system with an increasing focus on etiology and pathophysiology. Moreover, revising the DSM in this way will help us to provide better care for our patients and to substantially accelerate the rate and replicability of discovery.

There are several findings that we would like our colleagues to consider and understand.

## Prevalence

First, CM is highly prevalent. This is especially true for individuals with psychiatric disorders. For example, Struck et al. [6] recently reported that 15.0% of adult participants with no history of psychiatric illness reported having experienced any type of moderate-to-severe CM. In contrast, 56.1%, 56.3%, and 57.1 of individuals with schizophrenia/schizoaffective disorder, bipolar disorder, and major depression, respectively, reported this level of exposure. This was also true of 75.4% of individuals with persistent depressive disorders [6].

## Risk for psychopathology

Second, CM is the most important risk factor for many different psychiatric disorders in medically healthy individuals. It has been estimated that childhood adversity is responsible for 30%, 45%, 54%, 64%, and 67% of the population-attributable risk for anxiety disorders [7], childhood onset psychiatric disorders [7], depression [8], addiction to illicit drugs [9], and parenteral drug use [9], respectively. Furthermore, retrospectively reported exposure to five or more types of CM or household dysfunction increased the prospectively assessed risk of receiving an anxiolytic, antidepressant, antipsychotic, or mood stabilizer by 2.1-, 2.9-, 10.3-, and 17.3-fold, respectively [10].

## Types of childhood maltreatment

Third, there are many forms of CM and each, when studied independently, have been found to increase risk for psychiatric disorders [11, 12]. Furthermore, all types of maltreatment are associated with important differences in clinical presentation including: earlier onset; more severe symptoms; more pernicious course; increased risk for suicide; diminished quality of life and more psychiatric comorbidities [1, 2, 11]. When research began in earnest, 30–40 years ago, on the psychiatric consequences of CM, the focus was on sexual abuse and physical abuse as the most consequential types of CM. Recent studies that assess the psychiatric consequences of multiple types of maltreatment, including emotional abuse, emotional neglect, and physical neglect, have found that types of emotional maltreatment such as parental and peer verbal abuse are surprisingly consequential [13–15]. Verbal abuse entails insults, humiliation, threats to leave or hurt you, and proclamations such as "I wish you were never born" [13, 15, 16]. Emotional abuse and neglect have emerged in several studies as the most important risk factors for anxiety and depression [1, 6, 14, 17]. Hence, it is important to consider maltreatment broadly. In general, the more types of maltreatment reported, the greater the observed risk for psychopathology [8, 9].

A good working definition of CM has been published by the World Health Organization [18]:

> "Child maltreatment is the abuse and neglect that occurs to children under 18 years of age. It includes all types of physical and/or emotional ill-treatment, sexual abuse, neglect, negligence and commercial or other exploitation, which results in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power."

Note that a key factor in the definition is the betrayal of the child by an individual in a position of responsibility, trust, or power. This makes CM a particularly potent form of early life stress and it is CM rather than other stressors, such as natural disasters, that characteristically presents as antecedents to psychopathology [2]. This makes sense as parents, friends, and other responsible individuals can buffer the effects of stress on the developing child [19–21]. Hence, children can often endure great hardship if they feel protected and cared for. However, when the adversity is the product of their caretakers or peer group, it creates a stressor with far-reaching ramifications.

## Therapeutic response

Fourth, it is critical for psychiatrists to know that patients with histories of CM have a poorer response to most contemporary treatment modalities than non-maltreated individuals with the same primary DSM-defined diagnosis [3, 22–24]. For example, depressed individuals with CM often fail to adequately respond to treatment and are at markedly increased risk for developing recurrent and persistent depressive episodes [24]. Similarly, CM has been reported to moderate response to treatment in individuals with psychotic [23], substance abuse [25], and personality disorders [26]. The association between CM and therapeutic response was explored most extensively in the international Study to Predict Optimized Treatment for Depression, which was designed to identify pretreatment predictors of response to antidepressants that could change prescribing practices. Williams et al. [3] analyzed data from the 1008 adult participants with major depressive disorder (MDD) and 336 matched healthy controls enrolled in the trial. Briefly, they found that participants with MDD had a fourfold or higher rate of exposure to childhood abuse (sexual, physical, or emotional) than healthy controls. The experience of abuse at the age of 4–7 years contributed specifically and dramatically to lack of clinical response to one of three commonly prescribed antidepressants, with only 15.9% of participants reporting abuse within this temporal vulnerability window experiencing remission versus 84.1% of participants with no abuse history. Similarly, Lewis et al. [27] in the Treatment for Adolescents with Depression Study reported that neither fluoxetine, cognitive behavioral therapy (CBT), nor their combination was more effective than placebo in teens with a history of physical abuse, and that placebo actually appeared to be more effective than CBT in teens with histories of sexual abuse. CM has also been associated with a less favorable response to CBT [28], interpersonal psychotherapy [29, 30], and cognitive processing therapy [31] in adults. Interestingly, emotional abuse has often emerged as the specific type of maltreatment strongly associated with attenuated therapeutic response in a range of disorders [26, 28, 32].

In contrast, some treatments may be more effective in individuals with CM. Nemeroff et al. [22] reported that adults with chronic depression and early life stress had a more beneficial response to Cognitive Behavioral Analysis System of Psychotherapy (CBASP) than nefazadone and they appeared to have had a more favorable response to CBASP than chronically depressed individuals without early life stress. Likewise, O'Brien et al. [33] recently reported that participants with refractory depression and CM had a substantially better response to intravenous ketamine than refractory depressed individuals without CM. More data like these are desperately needed to guide treatment and an improved classification system will facilitate and empower this essential research.

## Neurobiological correlates

Fifth, CM is associated with substantial effects on brain structure, function, connectivity, and network architecture [4]. Consistent findings are smaller midsagittal area [34, 35] or decreased fractional anisotropy [36, 37] of the corpus callosum and lower hippocampal volume in adults [38, 39] but not necessarily in youths [34, 40]. CM is also associated with attenuated development of the anterior cingulate [41–43], orbitofrontal [39, 44, 45],

and dorsolateral prefrontal cortex [41, 45], and with enhanced amygdala response to threat [39, 46] and blunted striatal response to reward anticipation [47, 48].

Initially, researchers assumed that CM was damaging the developing brain. More likely it results in very specific phenotypic adaptations [4, 49]. This is illustrated in rigorously controlled unbiased whole brain analysis studies that assessed the structural consequences of exposure to specific types of CM. Briefly, exposure to parental verbal abuse was specifically associated with alterations in gray matter volume (GMV) in left auditory cortex [50] and with reduced integrity of the left arcuate fasciculus [51], which interconnects Broca and Wernicke's areas and is an important language pathway. Visually witnessing domestic violence, on the other hand, was specifically associated with reduced GMV in primary visual cortex [52] and reduced integrity of the inferior longitudinal fasciculus [53] that interconnects limbic and visual systems and plays an important role in our memory and emotional response to things we see. In contrast, penetrative sexual abuse was specifically associated with thinning of the portions of the somatosensory cortex in women responsible for sensation from the clitoris and surrounding genital area, while emotional abuse was associated with thinning in cortical regions relevant to self-awareness and self-evaluation [54]. In short, CM appears to result in neuroplastic adaptations that may protect a child living under abusive conditions by attenuating sensory processing of specific adverse experiences but may lead to the development of behavioral problems, such as sexual dysfunction, later in life [54].

Furthermore, there appear to be marked sex-related differences in the association between CM and brain structure, with greater reported differences in corpus callosum [55] and hippocampus [56] in maltreated males than females. There also appear to be specific sensitive periods when exposure to CM is associated with most significant alterations in structure [56, 57] and function [58]. For example, amygdala response to threatening visual stimuli was blunted in adults reporting exposure to physical maltreatment between ages 3–6 years but exacerbated in adults reporting exposure to peer emotional bullying at 13–15 years [58]. Again, these may be beneficial neuroplastic adaptations. A blunted fight-flight response may be beneficial in young children with parents who are episodically abusive and nurturing in order to maintain the attachment bond. By teenage years an enhanced fight-flight response may be beneficial, especially in adolescents experiencing bullying. However, a blunted amygdala response, later in life, is associated with impaired recognition of dangerous situations and increased risk for substance use disorders, while an exacerbated amygdala response is associated with increased risk for anxiety and depression [58, 59].

## Maltreated versus non-maltreated subtypes
Sixth, these CM-associated brain differences in stress-susceptible structures are present in maltreated individuals with psychiatric disorders but not necessarily in their non-maltreated counterparts [4, 60–63]. The most extreme example of this was a study by Poletti et al. [60] in which they used voxel-based morphometry to delineate anatomical differences between 206 participants with bipolar disorder, 96 participants with schizophrenia and 136 healthy controls. Morphometric differences from controls were only discernible in the schizophrenic and bipolar participants with moderate-to-high exposure to childhood adversity and not in those with low exposure. These findings, along with marked differences in treatment response and in clinical presentation, have led us to propose that maltreated and non-maltreated individuals with the same primary DSM diagnoses are clinically and neurobiologically distinct [2, 64] and represent a unique ecophenotype. In addition, individuals with the CM ecophenotype appear to have an array of molecular and physiological differences. These include abnormal hypothalamic-pituitary-

adrenal (HPA) axis and autonomic responses to stressors in the maltreated subtype, which are augmented in some [64] and blunted in other studies [65], likely due to differences in age as well as type and timing of exposure to CM [66]. Of critical interest is the finding that maltreated individuals with a variety of different disorders have elevated inflammatory marker levels [1, 67, 68]. Theories on the etiology of psychiatric disorders have often focused on HPA axis abnormalities and more recently on neuroinflammation, typically with no awareness that these abnormalities may be restricted to the CM subtype [69]. Furthermore, maltreatment is presumed to produce enduring biological change through an array of epigenetic modifications or by gene × experience × development interactions [1], which will also be specific to the maltreated subtype. Endeavoring to delineate the biological basis for psychiatric disorders without consideration of these critical subtype differences will almost certainly lead to conflicting results and replication failures.

## Neurobiology of resilience in the maltreated subtype
Seventh, although CM is a potent risk factor for many different psychiatric disorders there are a substantial number of individuals with CM histories who appear to be relatively resilient. We are referring to resilience here in a medical sense as absence of pathology or "better than expected outcome" following exposure to a potent risk factor [70]. Logically one might expect that the brains of these resilient individuals would show little if any of the aforementioned alterations in stress-susceptible regions or pathways. However, the whole complement of maltreatment-associated brain changes have been reported in maltreated individuals without overt psychopathology [4, 71]. This has led us, and others, to propose that asymptomatic MAL individuals are not unaffected but are effectively compensating through other neurobiological mechanisms [4, 71–74]. Ohashi et al. [75] reported that symptomatic and asymptomatic maltreated individuals had the same constellation of global brain network abnormalities, but the asymptomatic group could be reliably distinguished from the symptomatic maltreated group, and from unexposed controls, based on the connectivity of nine specific brain regions. This is an intriguing observation as it suggests that effective treatments for psychiatric disorders in individuals with CM may not require reversing the neurobiological effects of CM but may occur through altering connectivity in specific brain regions to bring the nodal network architecture of susceptible individuals into line with that of their more resilient counterparts [75, 76]. Of considerable interest is whether these are preexisting neurobiological differences that protect individuals from the psychiatric consequences of CM, or if they emerge over the course of time, and how they may be affected by protective factors and compensatory remedial environmental experiences [77, 78]. Overall, these findings indicate that moderate-to-severe CM is a transformative rather than normative event in even the relatively small percent of individual without psychiatric disorders who report this degree of exposure.

## IMPLICATIONS
There are five critical implications from these discoveries that we will enumerate and then discuss further below. First, it is essential that clinicians obtain a maltreatment history when assessing or treating individuals with psychiatric disorders. Because maltreatment is also a major risk factor for a host of medical disorders including cancer as well as heart, liver, digestive, and respiratory disease [79–81], one can argue that a maltreatment history should be an essential part of everyone's medical history. Second, as maltreated and non-maltreated cohorts with psychiatric disorders are so vastly different, this needs to be fully incorporated into our diagnostic nosology, preferably with a specific code to delineate the CM-associated ecophenotype. Third, we urge all investigators

conducting treatment trials for psychiatric disorders to collect data on CM and to analyze the data to indicate the extent to which CM moderates response. Perhaps the most effective way to do this would be for psychiatry and clinical psychology journals to strongly advocate this practice. Similarly, epidemiology and genetic risk studies would also benefit from inclusion of CM as a key biological variable. Fourth, clinical research studies on the biological basis of psychiatric disorders should, in almost all instances, collect data on CM as a key biological variable. Researchers would not consider conducting a study without controlling for the influence of sex or psychiatric medications. In general, maltreatment is a much more powerful confounding factor. Again, journals should take the lead in advocating this position along with the NIH. There may be situations when doing so would not be feasible (e.g., public datasets or autopsy samples without this information) and this should be noted in publications as a significant limitation. Fifth, as maltreatment is such a potent risk factor there should be a concerted effort to reduce exposure and a major effort to develop strategies to preempt the emergence of psychiatric disorders in youths who have been exposed. We encourage the NIMH, NIDA, NIAAA, and NICHD to make these high priority areas and for the field to place much more emphasis on prevention and preemption.

These recommendations may seem burdensome to researchers and clinicians who are unfamiliar with collecting and utilizing this information. Adequate data on exposure to maltreatment can be collected in a matter of minutes using any of a number of validated instruments with high test-retest reliability, such as the short form of the Childhood Trauma Questionnaire [82] or the Adverse Childhood Experiences scale (https://acestoohigh.com/got-your-ace-score/). We have included recommendations for researchers (S1, S2) and for clinicians (S3, S4) in the Supplementary materials on how to collect this information and how to incorporate it into their data analyses and clinical practice.

The absence of required specifiers for CM in the current formulation of the DSM distorts and impairs the value of many contemporary studies on the neurobiology, epidemiology, and treatment of psychiatric disorders. For example, a recently published [83], comprehensive analysis of risk factors for suicides in juveniles included over 7000 children and 910 suicides. Data were obtained from death certificates and Medicaid billing files. Although the ICD systems used to bill and indicate diagnoses have codes for exposure to child abuse (e.g., ICD-9CM 995.50-995.59; ICD-10CM T74.1-T74.9, and Z61.4-Z61.6), treating practitioners routinely use only ICD-9 and ICD-10 codes consistent with DSM-5 when evaluating and billing their patients. Based on the records used, this study found that youth suicide was most prominently associated with DSM-5 diagnoses of schizophrenia, depression, bipolar disorder, and substance use. However, most of the suicide decedents in the study did not have a recorded mental health diagnosis. Unfortunately, given this coding limitation, little was known about their exposure to CM and this factor was not mentioned, considered, or discussed in this study. This is a serious limitation that could markedly affect the analysis and interpretation of results as it has been reported that CM and household dysfunction account for up to 80% of the population-attributable risk for suicide attempts during childhood or adolescence [84]. Hence, we do not know if schizophrenia, depression, bipolar disorder, and substance abuse emerged as key risk factors because of the nature of the underlying disorder, or because of the very high prevalence of maltreatment within these diagnostic categories [6]. We can only know this by comparing incident rates in maltreated versus non-maltreated youths with these diagnoses. Knowledge of prior or ongoing CM would not only be important in studying the causes and epidemiology of youth suicide, it would be most useful in the clinic and among the most actionable considerations in the prevention of youth suicide if it emerges as a critical independent risk factor.

Another example is a recent paper on conceptual models and risk factors for treatment-resistant depression (TRD) [85]. A variety of potential biological factors were discussed in the article including activation of the inflammatory system, HPA axis disturbance, dysfunctional neuroanatomic circuits such as the default mode network, abnormal neural activity, and neurotransmitter dysfunction. Although abuse was briefly mentioned as a risk factor for TRD, there was no apparent understanding that CM may produce all of the aforementioned biological risk factors (e.g., inflammation [1, 67, 68], HPA axis disturbance [64, 86], dysfunctional neuroanatomic circuits [4, 87], abnormal neural activity [88–91], and neurotransmitter dysfunction [92–94]) as well as a host of critical clinical risk factors such as inadequate response to antidepressants [3]. Hence, the authors missed the opportunity to present a unified and parsimonious conceptual model for TRD.

## NOSOLOGICAL MODIFICATIONS

The thorniest question is how to modify psychiatric nosology. The need however is clear given the critically important clinical, molecular, and neurobiological differences between maltreated and non-maltreated individuals with the same primary diagnosis and the benefits of having information on exposure for epidemiological and clinical research purposes. Unfortunately, DSM-5 relegates CM to a brief section at the back of the volume (1, p. 715ff) under "Other Conditions That May Be the Focus of Clinical Attention" as an environmental condition, specifically "not (a) mental disorder" (and thus cannot be used for billing) and which "may be included in the medical record as useful information on circumstances that may affect the patient's care." Consequently, these codes are rarely utilized. ICD codes do have specific and well-defined CM categories, but because, at least in the USA, clinical records must be coded for billing using DSM diagnoses, it is not possible in epidemiologic studies using billing data to reliably translate less-detailed DSM-defined billing codes into more specific ICD diagnostic categories when CM is a consideration.

Post-traumatic stress disorder (PTSD) is often applied as a diagnostic label to individuals with mental illness secondary to CM, but the criteria actually required for a PTSD diagnosis are not met by most victims of CM. For example, Famularo et al. [95] found that only 35% of severely maltreated and psychologically traumatized children who were removed from parental custody due to the trauma actually met strict criteria for PTSD. This is not necessarily a matter of resilience. Kiser et al. [96] found that maltreated children and adolescents with psychiatric problems who did not meet criteria for PTSD actually exhibited more anxiety, depression, externalizing behaviors, and more overall problems than children who did. Similarly, psychiatrically hospitalized youth with CM but without PTSD were found to have more disrupted sleep than youth meeting criteria for PTSD [97]. Furthermore, they also responded more poorly to psychotherapy than traumatized youth meeting full criteria for PTSD [98]. These findings suggest that PTSD criteria formulated and validated in adults do not adequately describe the psychiatric impact of exposure to CM, and do not necessarily identify children most adversely affected by trauma let alone by other forms of maltreatment that do not fit the DSM definition of trauma. Furthermore, although some maltreated individuals do meet criteria for PTSD, this diagnostic coding does not indicate the existence of a CM history critical for research or epidemiologic purposes.

Similarly, a relatively small percentage of individuals with CM and severe psychopathology will meet criteria for complex PTSD (cPTSD), which has now been recognized as a distinct diagnostic category in ICD-11. Key criteria include the three PTSD requirements of reexperiencing, avoidance, and hypervigilance, as well as three disturbances in self-organization characterized by emotional

dysregulation, interpersonal difficulties, and negative self-concept. This diagnosis was formulated to capture the more complex clinical consequences of exposure to prolonged and extreme adversity, as seen in victims of persistent childhood sexual abuse, child soldiering, severe domestic violence, torture, genocide campaigns, or slavery [99]. While some individuals with CM histories will meet criteria for cPTSD, it is likely that individuals who experienced extreme adversity during childhood will have a different array of molecular and neurobiological alterations than individuals who have experienced extreme adversity in adulthood and these groups may well respond differently to treatment. Hence, neither PTSD nor cPTSD provide the clarity that a comprehensive nosology requires.

A more maltreatment-centric possibility is Developmental Trauma Disorder (DTD), which has been proposed as a diagnostic category for youths who have experienced CM and other forms of childhood adversity and who experience dysregulation in three spheres—emotional/somatic, attentional/behavioral, and relational/self-identity [100]. This proposed diagnosis is structured like PTSD with a requisite criterion A exposure but unlike PTSD (which focuses on threat of death, serious injury, or sexual violence), it requires both interpersonal victimization (physical or sexual assault, witnessing domestic violence) and disrupted attachment with a primary caregiver (prolonged separation, neglect, emotional abuse). In general, youths who meet criteria for this proposed disorder experienced poly-victimization have an average of 5.3 different DSM diagnoses on structured interview and have very high scores for dysregulation as well as externalizing and internalizing symptoms on the Child Behavioral Checklist [100]. In short, DTD identifies a relatively small but seriously impaired subset of youths with CM and psychopathology. This is an appealing unitary diagnostic category and the failure to include it in DSM-5 should be rectified.

The need for a unitary diagnostic label for maltreated youths with severe mental health problems, and the inadequacies of current DSM classification, were highlighted in a recent report issued by key committees from the American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry [101]. They used the term "complex trauma" to describe the effects of exposure during childhood to multiple or chronic traumatic events, or to severe, pervasive, or prolonged maltreatment, which result in a wide range of behavioral, cognitive, and emotional alterations that do not fit easily into common diagnostic categories and require a "thoughtful and parsimonious formulations rather than a laundry list of diagnoses." This report also notes that abnormal "behaviors…in the presence of ongoing danger are not pathologic but a normal stress response" and "there is little value in a pharmacotherapy trial for possible comorbidities until the danger has been mitigated." In short, approaching behavior problems in youth from within the current DSM paradigm can lead to inattention to ongoing CM and misguided attempts at medication management.

Unfortunately, there is a trend to label youths exposed to "complex trauma" with DTD and to label adults with the same childhood exposure with cPTSD. This makes little sense as the actual diagnostic criteria proposed for these two disorders are distinctly different. We believe that it would make more sense clinically and neurobiologically to have one diagnostic category, such as DTD, for individuals who experienced "complex trauma" during childhood (with or without adult exposure) and another diagnostic category, such as cPTSD, for individuals who experienced "complex trauma" during adulthood but not childhood.

Most individuals with CM and psychopathology, however, will not meet criteria for DTD. Some of these individuals will have experienced DTD criterion A exposure but will not manifest the three required forms of dysregulation, or they may have experienced only one part of the criterion A exposure, such as emotional abuse. Maltreated individuals who do not meet DTD criteria will typically have fewer DSM diagnoses and may have less severe psychopathology than those with DTD [100]. Major depression with a comorbid anxiety disorder, or substance use disorders, or bipolar disorder is typical clinical presentation of maltreated individuals who do not meet DTD criteria. For these individuals we recommended, as a first step, a moderate revision to the DSM, to add the specifier "With Maltreatment History" or "With Early Life Stress" to their primary DSM diagnosis to recognize that these individuals are part of a distinct maltreatment-related subtype or ecophenotype [2, 64].

## CONCLUSIONS

DSM-5, as we are well aware, is a work in progress and that a medical classification system that focuses entirely on signs and symptoms without regard to etiology, pathophysiology, or theory will misconstrue pathophysiologically heterogeneous disorders with similar clinical presentations as unitary, and unitary disorders that can present in distinctly different ways as heterogeneous [102]. Revising the DSM to acknowledge the critical role of CM would be a quantum step forward in the development of an etiologically informed classification system. Indeed, we predict that recognizing CM as an etiological agent that can produce ecophenotypic variants of major psychiatric disorders or DTD may prove to be as pivotal for psychiatry as germ theory has been for internal medicine. At the very least this will provide an opportunity to explore the common phenomenon that patients who have been abused respond poorly to standard pharmacologic and psychotherapeutic treatment and allow a more expansive exploration of treatments specific for the sequelae of CM. In addition, being able to specifically diagnose patients with post CM disorders will facilitate identification of the complimentary state—resilience—and catalyze more research into that phenomenon. Heightened attention to CM-associated diagnoses will also better inform public policy and needs to be a critical component in the education and training of mental health professionals.

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## AUTHOR CONTRIBUTIONS
JBG and CBN conceived the idea and wrote the initial drafts. MHT wrote the final drafts and supplementary materials with input from the other co-authors.

## ADDITIONAL INFORMATION
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