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Is Epigenetic Stress the Link Between Childhood Maltreatment and Borderline Personality Disorder?

Janet Charoensook, M.D.

Borderline personality disorder will affect approximately 18 million Americans in their lifetime (1). The 12-month prevalence of borderline personality disorder in the United States is 1.6% (2). Roy R. Grinker introduced borderline personality disorder to the academic community in the 1960s, with the first effort to define the syndrome, while Otto Kernberg wrote a series of papers introducing “borderline personality organization” and its treatment to the psychoanalytic community (3, 4). The *DSM-5* defines borderline personality disorder as “a pattern of instability in interpersonal relationships, self-image, and affects, and marked impulsivity” (5).

There are multiple studies that indicate that childhood maltreatment, specifically sexual abuse, is both commonly reported in and strongly associated with borderline personality disorder, with symptoms of the personality disorder, such as derealization or dysphoria, predictive of childhood abuse (6–8). Some speculate that this may just be bias in recall, dependent on the population sampled and its retrospective nature, or whether the child’s difficult temperament led to some form of neglect (9). However, Johnson and colleagues (10) found that individuals with a history of childhood physical abuse, sexual abuse, or neglect were four times as likely to have a personality disorder in early adulthood compared with individuals who did not, even when difficult temperament, parental education, and mental health were controlled for. They further suggested that sexual abuse was “associated with elevated borderline [personality disorder] symptoms” (10). Childhood maltreatment, maladaptive parenting, and biological predisposition are all possible mechanisms that under-

lie the relationship between childhood maltreatment and borderline personality disorder (10). The present review aims to highlight the recent research on another possible explanation for an association between childhood maltreatment and borderline personality disorder: epigenetic modifications secondary to early-life stress.

THE HYPOTHALAMUS-PITUITARY-ADRENAL (HPA) AXIS AND STRESS RESPONSE

The HPA, consisting of the paraventricular nucleus (PVN) of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland, is the essential component of one’s stress response. Stress activates the HPA. The principal regulator of the HPA, corticotropin-releasing factor, is released from the PVN and induces the downstream release of adrenocorticotrophic hormone (ACTH) (11, 12). ACTH targets the adrenal cortex whereby it stimulates glucocorticoid synthesis and secretion. Glucocorticoids play a wide variety of physiologic roles. Most important to epigenetic stress is that glucocorticoids are a prominent regulator of HPA activation via negative feedback (13). Succinctly, stress induces the release of glucocorticoids, and high levels of circulating glucocorticoids then inhibit the axis upstream.

EPIGENETIC CHANGES

Epigenetics is the heritable modification of gene expression influenced by our environment. DNA methylation, histone modifications, and micro-RNA activity are mechanisms of silencing gene expression (14). Early-life stresses can cause DNA methylation, modifying gene expression, resulting in dysregulation of the HPA axis (15–17).

THE GLUCOCORTICOID RECEPTOR GENE *NR3C1*

Weaver and colleagues (18, 19) found that positive maternal care in rodents resulted in epigenetic modification—DNA methylation of certain CpG sites of exon 1_f of the promoter of the glucocorticoid receptor gene *NR3C1*—inhibiting HPA activation, reducing stress, and, in a sense, programming their young’s response to stress (18–21). Simply, quality care reduces stress in the young.

Whereas quality care leads to epigenetic modifications that reduce stress, glucocorticoid receptor gene *NR3C1* can also be a target of early-life stress because increased methylation of its promoter region in exon 1_f (the human homolog of the aforementioned rodent exon 1_f) has been documented in both patients with a history of childhood trauma and patients with borderline personality disorder (22–24).

THE RELATIONSHIP BETWEEN *NR3C1* METHYLATION AND BORDERLINE PERSONALITY DISORDER

In the first study to show an association between various types of childhood maltreatment and increased methylation of *NR3C1* in humans, Perroud and colleagues (22) recruited 101 patients from an intensive dialectical-behavior therapy center and found that sexual abuse significantly correlated with *NR3C1* methylation status when compared with non-sexually abused counterparts. The majority of the patients were females (94.06%) in their 30s, who were diagnosed with borderline personality disorder and suffered from comorbid major depressive disorder (73.26%), alcohol use disorder (61.3%), and substance use disorder (51.6%).

Childhood maltreatment was quantified using the Childhood Trauma Questionnaire (CTQ). The CTQ assesses five types of self-reported trauma: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse. The scores are correlated to cut-off points to determine severity: none, low, moderate, and severe.

NR3C1 methylation status was determined by DNA extracted from leukocytes. Perroud et al examined exon 1_F because increased methylation in this location was 1) shown by Oberlander and colleagues (25) to be a possible link between prenatal maternal mood and an infant's modified HPA stress reactivity and 2) shown by McGowan and colleagues (26) to be associated with subsequent decreased hippocampal *NR3C1* gene expression in suicide victims with a history of childhood abuse. The *NR3C1* exon 1_F gene sequence also includes a nerve growth factor inducible protein A (NGFI-A) binding site that regulates gene transcription, but the CpG sites that have been extensively studied do not include this site (22). NGFI-A is highly expressed in young rodents that received quality maternal care (27).

There was a positive correlation between the severity of childhood maltreatment (amount and frequency) and *NR3C1* methylation (22). The CpG sites studied by Perroud and colleagues and McGowan and colleagues had increased methylation in those with childhood sexual abuse (22, 26). Perroud and colleagues suggested that increased methylation occurred in specific areas located near recognition elements for NGFI-A, since the NGFI-A binding site is upstream of the CpG sites studied, but the significance remains unknown (22, 25, 26).

For each type of maltreatment, there was significant association with increased methylation. Participants with childhood sexual abuse had increased methylation compared with counterparts who did not; the more severe the abuse, the higher the methylation status (22). There was also highly significant association between methylation status and emotional abuse (22). This is important to note because the literature tends to gravitate toward examination of sexual abuse; emotional abuse is an equally

important factor and can be just as predictive (22).

Perroud and colleagues were unable to correlate the degree of methylation to borderline personality disorder severity (22). Additionally, McGowan and colleagues used postmortem hippocampal samples of suicide victims, while Perroud and colleagues used peripheral blood (22, 26). Thus, the results by Perroud and colleagues cannot be readily applied to genetic expression in the brain.

Martin-Blanco and colleagues (23) aimed to correlate methylation status with borderline personality disorder severity. They recruited 281 patients with borderline personality disorder from specialized inpatient units that treat the disorder and examined 1) the genomic DNA extracted from their peripheral leukocytes, 2) their history of previous hospitalizations, 3) their self-injurious behaviors, and 4) their self-reported childhood trauma via the CTQ. They examined the same eight CpG sites (22, 25, 26). Similar to the study by Perroud and colleagues, the participants were predominantly female (85%), with a mean age of 29 years (23). The authors found that there was a “significant positive correlation” between *NR3C1* methylation status and childhood physical abuse (23). There was significant association between methylation of specific sites—CpG 1, 2, and 3—and physical abuse and emotional neglect ($p=0.08$); methylation of CpG 6 correlated to emotional abuse (23). Additionally, the authors noted a significant association between methylation and clinical severity as measured by the Revised Diagnostic Interview for Borderlines, self-injurious behaviors, and past hospitalizations (23).

Radtke and colleagues (24) examined 46 participants, mainly adolescents and young adults, recruited via advertisement and compensated monetarily, and found a statistically significant correlation between methylation of a CpG site (cg17860381) within exon 1_F in lymphocytes, childhood maltreatment, and symptoms of borderline personality disorder. Their statistical analysis indicated that childhood maltreatment and cg17860381 methylation were both significant predictors for the symptoms of the disorder and its intensity; however, they did not detail the specific symptoms (24).

THE SEROTONIN 3A RECEPTOR 5-HT_{3A}R

The serotonin 3A receptor (5-HT_{3A}R) has a role in cortical circuit formation, HPA function, and regulation of acute stress-induced HPA activity, and it factors into anxiety, fear, anxiety-related behaviors, and cognition and regulates corticotropin-releasing hormone in the central amygdala (28, 29). Considering its multifaceted nature, 5-HT_{3A}R has piqued the interest of researchers.

Perroud and colleagues (30) also studied 5-HT_{3A}R and, specifically, the single-nucleotide polymorphism (SNP) rs1062613, leading to a C to T polymorphism, which has been implicated in bipolar disorder (31). The methylation of multiple CpG sites in the glucocorticoid response element region (CpG3II, CpG2III, CpG5III) has been associated with childhood maltreatment, especially physical abuse, while methylation in other sites (CpG2III, CpG4III) is increased in patients with a history of suicide attempt, previous hospitalization, and substance dependence (30). These findings suggest that there are multiple receptors affected by epigenetic modification in response to environmental stressors, such as physical abuse, and may contribute to high-risk behaviors.

Furthermore, these epigenetic modifications may be additive, since those with the resultant CC genotype from the rs1062613 SNP demonstrated the highest level of methylation at CpG2III in the presence of childhood maltreatment (32). This additive effect decreases 5-HT_{3A}R expression, which functions in emotional processing during stress.

CONCLUSIONS

There has been a shift in ongoing borderline personality disorder research from identifying “vulnerability genes” to identifying genes that can be influenced by the environment and contribute to adult psychopathology (33). While further epigenetics and genetic research awaits, the studies reviewed here can help us to understand how early-life traumatic stress produces molecular changes that correlate with adult personality pathology.

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KEY POINTS/CLINICAL PEARLS

- In a community-based longitudinal study of 639 youths and their mothers between 1975 and 1993 that also controlled for difficult temperament, parental education, and mental health, individuals with a history of childhood physical abuse, sexual abuse, or neglect were four times more likely to have a personality disorder in early adulthood compared with individuals who did not have such history.
- Epigenetics, consisting of DNA methylation, histone modifications, and micro-RNA activity, is a mechanism of gene expression influenced by the environment.
- Glucocorticoid receptor gene *NR3C1* is a target of early-life stress because increased methylation of its promoter region in exon 1_F has been documented in both patients with a history of childhood trauma and patients with borderline personality disorder.
- In one study, patients who had suffered from childhood maltreatment, especially physical abuse, had high rates of DNA methylation of specific CpG sites in the glucocorticoid response element region of the 5-HT_{3A}R, which may be associated with the frequency of suicide attempts and hospitalizations.

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Advancing Clinical Care and Medical Understanding in a Resource-Limited Setting: Lessons From the Aro Village Project in the Wake of the Affordable Care Act

Elisa Nabel, B.A.

The three largest facility providers of inpatient psychiatric services in the United States are not hospitals: they are general prisons (1). The prevalence of mental illness in the criminal systems arose following a failure to fund federally approved mental health care programs in the 1960s as a dearth of resources failed to match the ensuing care demand from public inpatient hospital closures (2). Indeed, the high prevalence of mental illness in prisons is a reflection of an under-resourced medical system (3).

Are there any alternatives to this medical onus given the pecuniary realities?

Although developed over 50 years ago in colonial Nigeria, Dr. Thomas Lambo's Aro Village Project addressed head on health care dilemmas we face today to conciliate moralistic concerns about space, funding, and resources for mental health care with financial limitations. Colonial officials considered resources for psychiatric care too costly. However, Lambo, the first Nigerian psychiatrist, created a form of preferable mental health care by innovating, at the seams of politics, health care systems design and medical treatment. The Aro Village Project provides a historical example of how the enormous societal cost of psychiatric care can be mitigated by making intelligent and affordable investments in the way mental health care is delivered.

THE ARO VILLAGE PROJECT: EXPANDING ACCESS TO PSYCHIATRIC CARE IN A RESOURCE-LIMITED SETTING

With moralistic and pragmatic concerns about the asylum-based system

that legally institutionalized the large and growing population of homeless mentally ill in the village of Abeokuta, Nigeria, the local colonial government decided in 1949 to invest in a new mental hospital that could treat, rather than contain, its occupants (4). Land was purchased, and the then resident Dr. Lambo was recruited to direct the anticipated care program. However, in following discussions, the new facility proved more costly than anticipated (5). Construction was delayed.

In 1954, 5 years after the initial planning meeting, Dr. Lambo, having graduated, arrived at Aro Mental Hospital and sought to create a care system despite the few pieces in place (6). He converted the completed employee housing quarters into a day hospital complex (see Figure 1) and addressed patient housing by turning to the abutting village space of Aro where he asked villagers to rent out rooms in their homes to patients.

The ensuing Aro Village Project enabled overnight care through a micro-economic project that deflected responsibility for patient care to the hospital, even though it was located in a physically separate place. As villagers feared the renowned violent behavior of the anticipated patients, Lambo installed a 24/7 village nursing station, placing health care workers within arm's reach. Furthermore, he mandated a family member to live with and assist each patient as a prerequisite for patient intake, assuring villagers in opening their homes. Villagers often forwarded the rent received from the patients to the hospital to expand its electrical and plumbing system, providing Aro with unprecedented electrical lighting and running water.

The hospital also benefitted from this arrangement, as it improved the accessibility of clinical services at diminished costs. After providing electricity and water, the hospital recycled rent revenue by creating loans for families

FIGURE 1. The Day Clinic for the Aro Village Project^a



^a The photograph shows the inaugural building at the Aro Mental Hospital, originally intended as colonial staff quarters, which was converted into a day clinic for the Aro Village Project that treated several hundred patients each year. In 1957, the clinic moved directly into the village. Photograph taken by Elisa Nabel, 2011.

to renovate their homes, increasing the patient capacity of the village. Furthermore, villagers accepted labor as a form of payment and thus created a more flexible patient payment system. The Aro Village Project offered care to Nigerian psychiatric patients for the first time since being envisioned by colonial officers.

THE CLINICAL VILLAGE: ENHANCING PATIENT CARE THROUGH SYNERGY OF PSYCHIATRIC TREATMENT AND DELIVERY STRUCTURES

The Aro Village Project outgrew its immediate use as a temporary means for medical access and developed into a new standard of care that continues to be modeled (7). The improvements to patient care grew from Lambo's deliberate efforts to respond to patient's voiced preferences to avoid visits to the hospital (8). The joint efforts of family members, villagers, and nurses facilitated a clinical village environment that helped patients avoid the hospital. Family caretakers accompanied patients to and from appointments, maintained the patients' living space, and engaged in family therapy sessions. Village elders coordinated patient care, which could include any combination of psychoanalysis, medications, and electroconvulsive shock therapy (9). Treatment providers also worked with traditional healers to guide group activities. Nurses were continually stationed to provide assistance in the villages (10). In 1956, roughly 300 patients sought vacancies in the village, while over 200 beds in the hospital remained empty. In response, a new day clinic was built directly into the village in 1957 (11).

This approach transformed societal preferences for treating mental illness and experiences of psychiatric care. In 1955, within the 60-mile radius surrounding Aro, for every patient admitted to Aro, 15 were cared for at home. By 1958, three times as many patients were brought to the Aro Village Project as the number of patients who were attended at home (12).

FROM MADNESS TO MENTAL ILLNESS: HOW THE ARO VILLAGE PROJECT TRANSFORMED SOCIETAL EXPERIENCES OF "WÉRE"

The Aro Village Project garnered social support by reshaping Nigerian understandings about *wére*, the Yoruba term often translated as madness. Prior to the Aro Village Project, attempts to cure *wére* entailed beating patients with a "medical whip" (13). Employing medical interventions, particularly psychotropic drug therapy, Lambo gained local reputation as "the man who carried a magic stick" (personal communication with Charles Femi Jegede, May 2011). Social integration of *wére* also played a crucial role in altering perceptions of madness (14). Lambo's mentee who trained in the village noted rapid destigmatization, "because the news went around that patients who had been roaming the streets for years were now living with villagers with no problem" (personal communication with Michahel Olatawura, May 2011). The theory that *wére* was a curable mental affliction took root. Just as the introduction of psychotropics affected possibilities for care, they also enabled a reinterpretation of the nature of mental illnesses.

PRINCIPLES DEMONSTRATED: ACCESS, QUALITY, AND SOCIAL RESPONSIVENESS DESPITE LOW RESOURCES

The Aro Village Project demonstrates three main principles of efficacious mental health care despite resource restraints

applicable to psychiatric health care reform in the United States today: access, quality, and social responsiveness (15, 16). That is, mental health care should be financially and geographically attainable and provided in a way that helps patients cope with their own mental health impairments. Furthermore, mental health care should be culturally appropriate and socially appealing. First, Aro improved access to mental health care through flexible payment systems and continual expansion depending on medical demand. Following the Affordable Care Act, fee-per-service models, even on a sliding care, continue to place a large financial burden on patients (17, 18). A patient-centered medical home model, already shown to reduce hospitalizations and costs in a primary health care setting, could also apply to mental health systems in severe cases (19). Additionally, access for lower acuity cases to medical homes could be extended by coupling this health care reform with methods of health care payment that take population health into consideration (20). Second, non-negotiable guidelines that were patient-centered and driven ensured that quality remained protected at Aro. Valuing services by patient outcomes can delineate minimum care standards; these can be feasibly enacted by incentivizing and financing bundle packages within our current health care system (21). Finally, the Aro Village care system was socially integrated in a financially stable manner, and thus it allowed both participants in the system and the general population to benefit from the arrange-

KEY POINTS/CLINICAL PEARLS

- Dr. Thomas Lambo's Aro Village Project successfully tackled health care problems we face today to address concerns about space, funding, and resources for high-quality mental health care in the face of significant financial limitations.
- Investments working at the interfaces of politics, health care systems design, and medical treatment created a form of preferable mental health care that mitigated government and societal costs of psychiatric care.
- Development of psychiatric care systems that are socially responsive can reduce societal stigma of mental illness.
- This historical example of health care systems innovation demonstrates how mental health care access can be improved through flexible payment systems and creative restructuring of delivery structures that relate to medical demand.

ment in a way that was tangible. Programs that focus on socially integrating patients with mental illness can reduce the demand for care reliant on confinement. As the Aro Village Project demonstrates, creating synergy between patients' social incentives, disease-related needs, and medical supply can be harnessed creatively to produce an affordable, sustainable, and effective psychiatric care system despite competing demands of a large illness burden and financial constraint.

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Persistent and Long-Term Neuropsychiatric Implications of Cannabis Use in Adolescents

David S. Mathai, B.S.

As society grapples with questions regarding the legality and safety of cannabis, it is particularly important to consider epidemiological trends and the implications of cannabis use in younger populations. A remarkable 78% of first-time users are between the ages of 12 and 20 years old (1). The annual U.S. Monitoring the Future Survey demonstrates an ongoing, significant decrease in perceived risk that high school students attribute to cannabis use (2). Further evidence suggests that patterns of substance abuse are highly correlated with perceptions of risk (3). The adverse effects of acute cannabis intoxication vary among users but are well-characterized by responses such as impaired short-term memory, impaired motor coordination, altered judgment, paranoia, and psychosis at higher doses (4). The persistent and long-term neuropsychiatric consequences of cannabis use in humans have proven more challenging to investigate, but there is a growing body of recent scientific literature that addresses these concerns. It is noteworthy that the potency of recreationally available strains has also climbed significantly over time (5). The purpose of the present article was to examine the basis for increased adolescent vulnerability to chronic effects of cannabis use, specifically in the domains of cognition, psychosis, and addiction.

BASIS FOR HEIGHTENED VULNERABILITY

Brain development and maturation processes begin in utero and continue significantly through the early decades of life (see reference 6 for a review). Component processes include neuronal migration and differentiation, synaptogenesis,

axon formation, dendritic proliferation, myelination, pruning, apoptosis, and other changes, all potentially at risk of disruption with early-onset cannabis use. The effects of delta 9-tetrahydrocannabinol (THC), the major psychoactive constituent of cannabis, are known to be mediated by activity at cannabinoid receptors located in the CNS. Cannabinoid receptors mature in adolescence (7) and are highly distributed in critical brain regions such as the prefrontal cortex, anterior cingulate cortex, basal ganglia, hippocampus, amygdala, and cerebellum (8). Various endogenous cannabinoids have been identified as ligands with innate cannabinoid receptor activity, and numerous animal studies suggest that this endocannabinoid system is involved in the regulation of key neurodevelopmental processes that occur through adolescence and may be disrupted by exogenously administered cannabinoids (9). Moreover, neuroimaging studies comparing the brains of adolescent chronic cannabis users and healthy control subjects point to structural and functional alterations that are apparent soon after initiation of drug use and persist even after months of abstinence (10). These studies do not necessarily indicate causation; however, the negative effects of cannabis on functional connectivity in adults are more notable if use begins at young ages (11). Taken together, this evidence makes a strong case for concern over adolescent cannabis use.

COGNITION

Impaired verbal learning and memory have been consistently observed in chronic cannabis users in cross-sectional studies, including adolescent populations (12–14). Evidence for working

memory impairment has been mixed, but studies have also differed in the specific tasks employed and in subjects' history of cannabis use. There is strong and largely consistent evidence for attention deficits associated with chronic cannabis exposure in adolescents (see reference 15 for a review). Prior cannabis use appears to impair executive function in an age-dependent, dose-responsive manner, and adolescent-onset cannabis users demonstrate more severe and persistent cognitive impairment than adult-onset users (9, 16–19). Whether there is recovery of impairment with prolonged abstinence remains a topic of debate (see reference 15 for a review).

Prolonged, heavy cannabis use has been associated with an amotivational state (20–22), which may predict impaired learning and educational underachievement. A well-known study by Meier et al. (19) observed a longitudinal 8-point decline in IQ among heavy, adolescent-onset cannabis users, which was not restored by cessation. However, these findings have been challenged due to the possibility of other confounding variables in repeat analyses (23). An analysis of two longitudinal twin sibling studies also did not find a significant IQ decline between frequently using and non-using twins, where frequent cannabis use was defined as 30 or more times of lifetime use (24).

PSYCHOSIS

Psychosis outcomes in relation to cannabis use are at times poorly defined, but Ranganathan et al. (25) argues for characterization based on timing, duration, and resolution. Within this framework, cannabinoids have been associated with acute-onset psychosis through intoxica-

tion that resolves without clinical intervention, acute-onset psychosis that persists beyond intoxication and requires clinical intervention, and chronic psychotic disorders that emerge later in life, also requiring intervention. A review by Radhakrishnan et al. (6) concluded that the connection between cannabis and varieties of psychosis meets many but not all of the criteria for causality, passing measures such as the existence of a temporal relationship between cannabis use and psychosis, a dose-responsive effect, biological and experimental plausibility, and consistency in findings. However, a causal relationship has been questioned due to an absence of specificity and strength of association. Other factors may also play an important role; for example, variants of the *AKT1* and *COMT* genes, which are involved in dopamine signaling and metabolism, have been proposed as significant moderators of the risk of psychotic disorder with adolescent cannabis exposure (26, 27). These findings ultimately point to significantly greater risk of psychosis associated with adolescent-onset use. Another epidemiological review by Gage et al. (28) proposes that while it is challenging to establish causality without further evidence, the significant cannabis-psychosis relationship still merits attention and public health action.

ADDICTION

Around 30% of all cannabis users may develop some degree of problem use, which can lead to dependence, and in severe cases takes the form of addiction (29). There is laboratory evidence of tolerance to the effects of THC (30) and clinical evidence of a withdrawal syndrome—commonly characterized by symptoms such as anger, aggression, irritability, anxiety, decreased appetite or weight loss, and sleep difficulties—that complicates abstinence in users trying to quit (31). Theories of addiction suggest that repeated drug use disrupts prefrontal cortex function and results in behavioral changes that contribute to problem use, specifically in areas of emotional regulation, inhibitory control, salience attribution, maintenance of motivational arousal, and self-aware-

KEY POINTS/CLINICAL PEARLS

- Cannabis use is significant in adolescent populations, although the persistent and long-term neuropsychiatric consequences of early use are not well understood.
- There is evidence for increased vulnerability to the effects of cannabis use in adolescents, due to ongoing brain development and maturation.
- Increasing literature supports long-term cognitive impairment, psychosis, and addiction related particularly to adolescent-onset cannabis use.
- While further study is needed, current policy and public health efforts should account for our current scientific understanding of these outcomes.

ness (32). Moreover, epidemiological studies report an age-dependent, dose-response relationship between prior cannabis use, impaired executive control (16), and development of cannabis use disorder (33–35). In perspective, individuals who use cannabis before the age of 18 are four to seven times more likely than adults to develop problem use (36). Among cannabis-related admissions to substance abuse treatment facilities in the United States, 81% of use was initiated by age 16 (37).

CONCLUSIONS

While we are still in the early stages of understanding the effects of cannabis on the developing brain, there is a growing body of scientific literature that supports various long-term consequences of adolescent-onset cannabis use relating to cognitive impairment, psychosis, and addiction. Rather than thinking of these deficits as unique outcomes, it may be useful to consider such dysfunction as a shared product of disrupted neurodevelopment, and early impairments in cognition may very well underlie manifestations of psychosis and patterns of problematic drug use that characterize addiction. Still, much of the existing evidence is based on observational studies that are ultimately limited in generalizability. Going forward, it will be important to build on converging evidence across disciplines to better characterize the relationship between cannabis and chronic neuropsychiatric outcomes. Furthermore, a greater understanding of moderating variables and risk factors will be paramount to guiding effective public health efforts. Finally, it is unclear

to what extent the public is aware of the implications of adolescent cannabis use. An accurate and informed opinion of cannabis must be a part of the emerging conversation on recreational consumption and effective drug policy.

At the time this article was accepted for publication, David Mathai was a fourth-year medical student at Baylor College of Medicine, Houston. He will begin his psychiatry residency on June 26, 2017, at Baylor College of Medicine.

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Accounting for the Social Determinants in Psychiatric Care Delivery

Ralph H. de Similien, M.D., M.S., M.Ed.

Patients with psychiatric illnesses have unique existential challenges that affect their health and lives tremendously. Notorious among these challenges are those emanating from the social environments in which they are born, work, learn, live, worship, age, and play. Termed “social determinants” in modern literature (1–3), these challenges are remnants of human-, society-, and organization-made disparities transmitted from past unequal structural arrangements of resource distribution and socioeconomic inequalities. Examples of social determinants include adverse early-life events, poor education, poor access to health care, chronic unemployment, poverty, discrimination, and food and material insecurity, among others. Defined as “the cause of the causes” of poor health and unfavorable health outcomes (3, 4)—mental health included—social determinants can present serious impediments to patients’ therapeutic end-result and also can lead to poor compliance to treatment for major psychiatric illnesses. By virtue of the limitations they place on patients’ lives, the circumstances they force patients to live under, and the decisions they force patients to make daily, social determinants can hence be a serious handicap to psychiatric care and recovery from psychiatric illness, including substance abuse.

CASE VIGNETTE: PART I

“Ms. Z” is a 45-year-old woman who is HIV positive, homeless, never-married, childless, unemployed, and illiterate living in a shelter, with no formally diagnosed psychiatric disorder. She walked into the outpatient men-

tal health clinic requesting help with chronic heroin use. She has been “an addict,” she said, since the age of 17, having been exposed to heroin while living on the streets after running away from a sexually abusive stepfather at home. With no education and no skills, as a way of supporting her habit, Ms. Z started prostituting herself shortly after leaving home. In the city jail, she became a familiar figure for various charges, including prostitution, shoplifting, possession with intent to sell, assault, etc., for which she served a combined 15 years. While under our care, she was treated for opioid use disorder with buprenorphine/naloxone maintenance therapy in addition to weekly group cognitive-behavioral therapy. She did well initially on this treatment regimen for the first 6 weeks. However, around the end of that period, she started testing positive for opiates again.

Psychiatric illnesses—and any illness for that matter—do not exist in a psychological or physiological vacuum. They can result as a consequence of stressors: physiological, neurological, psychological, biological, sociological, environmental, etc. Termed “allostatic loads” (5–8)—the physiological cost of chronic social and environmental stressors—they can have enormous consequences on overall emotional health when they exist in excess (i.e., “allostatic overload” [5, 6, 8]). Not all patients carry identical allostatic loads; this difference in the allostatic load burden and its eventual consequence can lead to what Dr. Michael Marmot, former chair of the World Health Organization Commission on Social Determinants of Health, referred to as the health gradient: whereby those at

the bottom of the socioeconomic ladder fare much worse in terms of health compared with those at the top (1, 2, 9, 10). In other words, social status and relative economic standing matter to overall health and persistence of illnesses in that they bear what Dr. Marmot later coined the status syndrome (10). Simply put, a patient from a limited socioeconomic background who is homeless and living on the street, with a history of multiple incarcerations, is not going to approach her treatment recommendations the same way as a patient from an affluent background presenting with the same chief complaint. Neither will she approach her treatment compliance the same way. Thus, the overall health of the two will differ.

Because these patients bring unique social determinant challenges from their environments to the psychiatric table of care, some of these challenges have to be tackled simultaneously with the psychiatric disorder if a productive therapeutic outcome is to be expected. Such dual approach is deemed necessary because the nature of these patients’ illnesses can be, at times, socioenvironmental in origin. As such, the “ecological context” (11) in which the psychiatric illness and recovery take place (i.e., the background story) can be as important a factor in the attainment of successful treatment outcomes as the psychotropic medications themselves.

CASE VIGNETTE: PART II

Ms. Z was recently kicked out of the shelter, unable to find meaningful work given her criminal record and poor education, and, cornered by the effects of her adverse early-life events,

she resorted to old habits to maintain a “stable” existence.

The cumulative effect of the social determinants can limit the social and economic options of those affected by them. Ms. Z’s initial treatment failure, when seen in this light, was no more than a manifestation of the end result of the effects of her disadvantageous, deeply layered, and limited socioeconomic circumstances. In other words, her state of poverty and environment were contributing to her relapse and could not be ignored. We had to start looking at the ecological context in which her treatment was taking place and begin to examine our therapeutic shortcomings in terms of the effects of these social determinants on her daily life and therapeutic progress.

We first had to integrate and coordinate her care back to HIV treatment. We also referred her to a long-term inpatient detoxification program, while simultaneously helping her secure stable housing and employment with the help of our social worker. Ms. Z is still aiming to get back on her feet as we attempt to help her lift the layers of limitations these social determinants have imposed on her life. Nonetheless, we note improvements over the subsequent months following her inpatient detoxification treatment program: she has started to regularly attend her weekly group therapy, remains compliant to her treatment regimen, and has thus far been testing negative for substances of abuse.

Our approach to Ms. Z’s opioid use disorder treatment necessitated some maneuvering that went beyond the one-size-fits-all substance use disorder treatment protocol we are all too familiar with. Being overly focused on these treatment protocols and other classic treatment conventions, more often than not, leads physicians—psychiatrists included—to overlook the social environment (12) (the physical, social, and cultural milieus within which our patients function daily) contributing to the patient’s present state and health. Through years of studying, we have been trained to view patient care from a top-down disease-based model that has its lim-

KEY POINTS/CLINICAL PEARLS

- Social determinants are existential challenges originating from the environments in which people are born, work, learn, live, worship, age, and play.
- Social determinants are remnants of human-, society-, and organization-made socioeconomic injuries transmitted from past unequal structural arrangements and socioeconomic inequities.
- Social determinants can contribute to psychiatric illness through allostatic load and allostatic/overload: the physiological cost of chronic social and environmental stresses.

its. One such limit is that it fails to take into account the effects of social determinants on patients’ overall health, compliance to treatment, and functionality. This model neglects to make allowance for the social and economic stressors that have been reported to play both direct and indirect roles in disease development (5, 6, 8). In the case of Ms. Z, the social determinants were affecting her treatment participation and had to be accounted for in the treatment protocol to achieve better and longer-lasting therapeutic outcomes. Of course, this does not imply that her initial treatment failures were singularly the result of our not taking the social determinants into account in her treatment protocol. Nonetheless, not having seriously considered them was undoubtedly one factor in a multifactorial web of causation leading to the shortcoming of our initial therapeutic effort. Perhaps, this is not the end of Ms. Z’s substance abuse story. Perhaps, the final answers will come, in the next few months or years, as to the definite effect of our therapeutic approach on her long-term treatment outcome. Perhaps they will not. Nonetheless, we currently hail her abstinence from substances, even if briefly, as a great milestone on her road to recovery from opioid use disorder.

CONCLUSIONS

The learning point from Ms. Z’s case is that social and economic factors do matter when addressing recovery from substance abuse and other psychiatric illnesses (3, 11, 13). As exis-

tential burdens, social determinants, in and of themselves, can lead to psychiatric distress and dysfunction through their effects on the decisions they force patients to make and the life they force patients to live. Because social determinants mortgage the patients’ emotional well-being, they can lead to poor treatment compliance, worse therapeutic outcome, and significant psychoaffective end results. Addressing the social determinants in our patients’ lives forces us physicians to bear witness to the daily, chronic, negative consequences of health care disparity and socioeconomic inequality, which are issues physicians are not presently comfortable handling. While we are not trained to be social workers, being aware of social determinants and making appropriate referrals early in treatment can be significant to the therapeutic alliance and long-term therapeutic end results. Screening for these socioeconomic needs that are negatively affecting the health of our patients and guiding them to the correct path to local resources can help them overcome such disparities. Failure on this account can easily derail a well-thought-out therapeutic plan. In other words, social determinants should never be ignored in the development of the therapeutic plan for our patient’s optimal psychiatric care.

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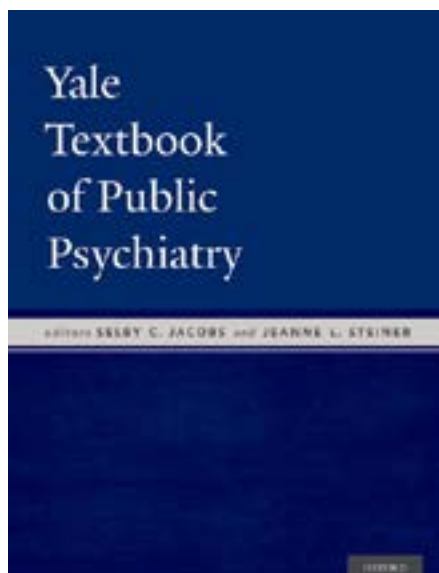
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Yale Textbook of Public Psychiatry

Rishi Sawhney, M.D.

The *Yale Textbook of Public Psychiatry* is a tremendous feat, as it is the first textbook geared toward the rapidly growing field of public psychiatry, a field that has only become more relevant with all the changes occurring in the United States health care system. This textbook is available in hardcover and eBook. It includes contributions from 74 faculty members and is edited by Selby C. Jacobs, M.D., Professor Emeritus of Psychiatry and former Director (and CEO) of the Connecticut Mental Health Center in New Haven, and Jeanne L. Steiner, D.O., Medical Director of the Connecticut Mental Health Center in New Haven and Director of the Yale Fellowship in Public Psychiatry.

The book begins by defining public psychiatry as “that part of the practice of psychiatry that is 1) financed by the general funds of state departments of mental health or 2) by reimbursement income from entitlements such as Medicaid” (pp. 1–2). As described in the book, “public psychiatry uses not only a clinical perspective while caring for the individual service user, but also a population perspective” (p. 2). In order to help explain how both states and the federal government work together to create a public psychiatry system, the textbook weaves in the experiences, challenges, and systems in place for the Connecticut mental health system throughout the various topics and chapters.



Edited by Selby Jacobs and Jeanne Steiner.
New York, Oxford University Press, 2016, 312 pp, \$125.00 (hardcover)

The textbook covers various topics from a public psychiatry perspective and details evidence-based approaches for topics such as substance use disorders, child psychiatry, outpatient care, and inpatient care while also including topics of growing importance like recovery-oriented practice, integrated health care, and early intervention and prevention for psychosis. Thus, it is an introduction to the field of public psychiatry but is also valuable to residents entering the fields of addiction psychi-

atry, child psychiatry, hospital-based psychiatry, forensic psychiatry, community psychiatry, and global mental health, as it details the systems in place in those fields.

This book is a vital asset to both general residency training programs and public psychiatry fellowship training programs. It concisely educates readers on many topics that can be confusing, hard to teach, and sometimes lacking as part of training despite their importance, such as delivery models of health care, financing of health care, and the basics of Medicaid and Medicare.

As a resident starting public psychiatry fellowship next year, I found the book enjoyable and a pleasure to read. It easily explains so many different topics and simultaneously generates enthusiasm and hope regarding how the system of public psychiatry has improved and the continued possibilities for system improvements. In a time of ongoing change due to the Affordable Care Act of 2010 and its unknown future, as this law is being threatened to be repealed, this textbook is an invaluable resource in understanding why the system is the way it is and offers solutions for the implementation of evidenced-based practices in the mental health care system going forward.

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Inside Out

Sabina Bera, MD., M.S.

“Emotions can’t quit, genius!” (1)

Although our species has described emotions for thousands of years, the neuronal labyrinth that forms them remains elusive. In early adolescence, striking changes take place as the maturation of cortical connections occur, affecting an individual’s ability to cope with, understand, and reflect upon such emotions (2). The recent children’s film *Inside Out*, directed by Pete Docter, takes on the ambitious task of capturing this complexity in the mind of a preadolescent girl named Riley.

In the film, there are five emotions represented as distinct characters: Joy, Sadness, Fear, Disgust, and Anger. These emotions live in the mind’s “Headquarters” and have access to the main control panel, which dictates Riley’s affect and actions.

In the beginning of the film, we witness Riley’s first psychosocial stressor. Her family moves from Minnesota to California, where her father has accepted a demanding new job. Riley has difficulty adapting to her new home and forms her first important sad memory while crying in front of her new class. After Joy’s precarious attempt to prevent more sad memories fails, both Joy and Sadness are unwittingly sucked into a memory tube, leaving them lost in Riley’s brain.

The film follows Joy and Sadness as they find their way back to Headquarters, taking the viewer through Riley’s stages of development. Viewers feel sadness themselves as Riley’s imaginary friend Bing Bong—reminiscent of her preoperational stage—sacrifices himself



to propel Joy toward Headquarters and wastes away in the Land of Forgotten Memories. Riley, who grows apathetic without Joy and Sadness in Headquarters, makes an attempt to run back to Minnesota. The film closes with Sadness returning Riley’s important memories and subsequently teaching Riley about the importance of incorporating the entire spectrum of emotions, bringing her back home to the warm embrace of her family.

Inside Out achieves the impressive feat of depicting emotions in a way that is accessible to young children. More importantly, the film demonstrates the benefit of expressing emotions, as well as the dangers of repressing them.

I couldn’t help but think of my own patients while watching this film. Al-

though Riley has an unremarkable developmental history, no medical or psychiatric problems, and a strong support system, she experiences difficulty coping with periods of transition and stress. Our younger patients face additional adversities: they struggle with neurodevelopmental disorders such as intellectual disabilities, autism, or attention deficit hyperactivity disorder. As psychiatrists, we are challenged with processing our own versions of Joy, Sadness, and other emotions with children who have experienced trauma, bullying, or unstable family structure.

Experiences in early life are thought to be a source of psychopathology by many highly regarded psychoanalysts. Riley’s resilience equips her for the upcoming conflicts she may experience in puberty. *Inside Out* implores us to make this a reality for our own young patients, perhaps by encouraging acceptance of the complete spectrum of their emotions, communicating the danger involved in restricting them, and realizing the same emotions connect us all to one another.

Dr. Bera is a second-year resident in the Department of Psychiatry at UCLA-Kern, Kern Medical, Bakersfield, Calif.

REFERENCES

1. Docter P: *Inside Out* [Film]. Directed by Pete Docter. Emeryville, Calif, Pixar Animation Studios/Walt Disney Pictures, 2015
2. Martin A, Volkmar F, Lewis M: *Lewis’s Child and Adolescent Psychiatry*. Edited by Martin A, Volkmar F. Philadelphia, Lippincott Williams & Wilkins, 2007, pp 287–288

Residents' Resources

Here we highlight upcoming national opportunities for medical students and trainees to be recognized for their hard work, dedication, and scholarship.

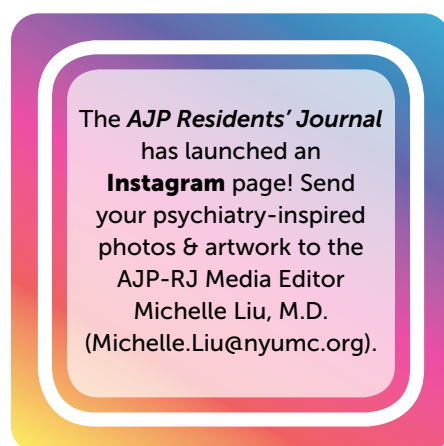
**To contribute to the Residents' Resources feature, contact Oliver Glass, M.D., Deputy Editor (glassol@ecu.edu).*

JUNE DEADLINES

Fellowship/Award, Organization, and Deadline	Brief Description and Eligibility	Contact and Website
American Academy of Child and Adolescent Psychiatry (AACAP) Educational Outreach Program (EOP) for General Psychiatry Residents AACAP Deadline: June 30, 2017	The EOP provides the opportunity for general psychiatry residents to receive a formal overview to the field of child and adolescent psychiatry, establish child and adolescent psychiatrists as mentors, and experience the AACAP Annual Meeting in Washington, DC, October 23–October 28, 2017 <ul style="list-style-type: none"> General psychiatry residents who are AACAP members or have pending AACAP membership. 	AACAP Assistant Director of Training and Education E-mail: training@aacap.org Phone: 202-587-9663 https://www.aacap.org/aacap/Awards/Resident_and_ECP_Awards/AACAP_Educational_Outreach_Program_for_General_Psychiatry_Residents.aspx
AACAP Educational Outreach Program for Child and Adolescent Psychiatry (CAP) Residents AACAP Deadline: June 30, 2017	The EOP provides the opportunity for child and adolescent psychiatry residents to receive a formal overview to the field of child and adolescent psychiatry, establish child and adolescent psychiatrists as mentors, and experience the AACAP Annual Meeting in Washington, DC, October 23–October 28, 2017. <ul style="list-style-type: none"> Child and adolescent psychiatry fellows who are AACAP members or have pending AACAP membership. 	AACAP Assistant Director of Training and Education E-mail: training@aacap.org Phone: 202-587-9663 http://www.aacap.org/AACAP/Awards/Resident_and_ECP_Awards/AACAP_Educational_Outreach_Program_for_CAP_Residents.aspx

JULY DEADLINES

Fellowship/Award, Organization, and Deadline	Brief Description and Eligibility	Contact and Website
Webb Fellowship Program Academy of Psychosomatic Medicine (APM) Deadline: July 1, 2017	This fellowship is designed to support residents and fellows in psychosomatic medicine at an early stage in their career. One-year appointments in which each fellow will have a designated mentor and present a paper at the Annual Meeting. Financial support will be provided for each fellow's organizational membership for one year and for Annual Meeting registration fees. <ul style="list-style-type: none"> PGY-3 psychiatry resident or psychosomatic fellow. 	N/A http://www.apm.org/awards/webb-fship.shtml
Trainee Travel Award APM Deadline: July 1, 2017	To encourage psychosomatic fellows, residents, and medical students to join APM, attend the Annual Meeting. A limited number of monetary awards are given to help offset the cost of attending the Annual Meeting. <ul style="list-style-type: none"> Medical students, residents, and fellows. 	N/A http://www.apm.org/awards/trainee-travel.shtml



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The Residents' Journal accepts manuscripts authored by medical students, resident physicians, and fellows; attending physicians and other members of faculty cannot be included as authors.

To submit a manuscript, please visit <http://mc.manuscriptcentral.com/appi-ajp>, and select a manuscript type for *AJP Residents' Journal*.

1. **Commentary:** Generally includes descriptions of recent events, opinion pieces, or narratives. Limited to 500 words and five references.
2. **History of Psychiatry:** Provides a historical perspective on a topic relevant to psychiatry. Limited to 500 words and five references.
3. **Treatment in Psychiatry:** This article type begins with a brief, common clinical vignette and involves a description of the evaluation and management of a clinical scenario that house officers frequently encounter. This article type should also include 2–4 multiple-choice questions based on the article's content. Limited to 1,500 words, 15 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.

4. **Clinical Case Conference:** A presentation and discussion of an unusual clinical event. Limited to 1,250 words, 10 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
5. **Original Research:** Reports of novel observations and research. Limited to 1,250 words, 10 references, and two figures. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
6. **Review Article:** A clinically relevant review focused on educating the resident physician. Limited to 1,500 words, 20 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
7. **Drug Review:** A review of a pharmacological agent that highlights mechanism of action, efficacy, side-effects and drug-interactions. Limited to 1,500 words, 20 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.

8. **Perspectives in Global Mental Health:** This article type should begin with a representative case or study on psychiatric health delivery internationally, rooted in scholarly projects that involve travel outside of the United States; a discussion of clinical issues and future directions for research or scholarly work should follow. Limited to 1,500 words and 20 references.
9. **Arts and Culture:** Creative, nonfiction pieces that represent the introspections of authors generally informed by a patient encounter, an unexpected cause of personal reflection and/or growth, or elements of personal experience in relation to one's culture that are relevant to the field of psychiatry. Limited to 500 words.
10. **Letters to the Editor:** Limited to 250 words (including 3 references) and three authors. Comments on articles published in the *Residents' Journal* will be considered for publication if received within 1 month of publication of the original article.
11. **Book and Movie Forum:** Book and movie reviews with a focus on their relevance to the field of psychiatry. Limited to 500 words and 3 references.

Upcoming Themes

If you have a submission related to the themes shown, contact the Section Editor listed below the topic. **Please note that we will consider articles outside of the theme.**

If you are interested in serving as a **Guest Section Editor** for the *Residents' Journal*, please send your CV, and include your ideas for topics, to Rachel Katz, M.D., Senior Deputy Editor (rachel.katz@yale.edu).

Forensic Psychiatry

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Treating Patients With Comorbid Substance Use Disorders

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