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Environmental Risk and Protective Factors and Their Influence on the Emergence of Psychosis

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Abstract

Environmental risk and protective factors in schizophrenia play a significant role in the development and course of the disorder. The following article reviews the current state of evidence linking a variety of environmental factors and their impact on the emergence of psychotic disorders. The environmental factors include pre- and perinatal insults, stress and trauma, family environment, and cannabis use. The review of evidence is followed by case examples and clinical applications to facilitate the integration of the evidence into clinical practice.

Keywords

Risk and protective factors; schizophrenia; prodromal states; psychosis; environmental factors; perinatal trauma; stress; family environment; cannabis use

Schizophrenia is a highly heritable disorder with a strong genetic basis, yet numerous studies have highlighted the pivotal role that environmental factors play in the development and course of the disorder. Concordance rates of monozygotic twins are around 50%, with the remaining variance attributed to environmental factors, such as pre/perinatal complications, stress/trauma, winter/spring births, family environment, and cannabis (Brown, 2011). Genetic effects are thought to interact with environmental factors by making some individuals more sensitive to environmental stressors (Rutter, Pickles, Murray, & Eaves, 2001). While genetic risk factors are difficult to identify, environmental risks are ripe for early identification and targeted interventions. In order to advance our understanding of the environmental conditions that interact with genetic risk to make individuals more likely to develop schizophrenia, researchers have made efforts to identify individuals at risk for developing psychosis, prior to its full onset. Such “clinical high risk” (CHR) individuals have relatively high rates of conversion to psychosis (35% over 2.5 years; Cannon, *et al.*, 2008; Ruhrmann, *et al.*, 2010). The CHR syndrome is primarily characterized by the presence of attenuated psychotic symptoms and/or genetic risk and functional deterioration (Yung & McGorry, 1996). A growing body of literature has begun to examine the impact of environmental risk and protective factors in CHR youth. The current article will review the

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evidence linking risk and protective environmental factors to the development of psychosis in clinical high-risk (CHR) patients and discuss interventions that can target known environmental risk factors in early psychosis. Specifically, we will discuss early environmental risk factors for psychosis that affect pre- and perinatal development as well as later environmental risk factors, including the family environment, stress/trauma, and substance use, particularly cannabis.

PRE- AND PERINATAL NEURODEVELOPMENT

Obstetric Complications

Fetal Hypoxia—Fetal hypoxia is an obstetric complication caused by oxygen deficiency to the tissues of the fetus that may lead to severe complications in prenatal growth and metabolism. Various birth-related events have been linked to fetal hypoxia, including emergency cesarean section, bleeding during pregnancy, and preeclampsia (Cannon, *et al.*, 2000), and direct cues of hypoxia include blue-ish skin at birth and requiring resuscitation, among others (Dalman, Allebeck, Cullberg, Grunewald, & Koster, 1999). Fetal hypoxia has been shown to have the strongest association with schizophrenia onset when compared to microbial agents, fetal maldevelopment, maternal smoking, or other obstetric complications in epidemiological studies (Cannon, 1997). However, risk for later schizophrenia related to fetal hypoxia is restricted to individuals with a family history of psychosis; hypoxic events in offspring of healthy parents confer no additional risk for psychosis beyond that of the general population (Cannon, *et al.*, 2000). *In utero* oxygen deprivation has been hypothesized as a mechanism contributing to the anatomical changes in the brain associated with patients with schizophrenia and their unaffected first degree relatives (Cannon, 1997). There is evidence of hypoxia-related ventricular enlargement and reduction in gray matter volume (Cannon, *et al.*, 2002; Mittal, Ellman, & Cannon, 2008) in frontal, temporal, and parietal cortices, areas that are implicated in executive function (i.e., planning, inhibition of impulses, abstract thinking, etc.), working memory, and spatial ability, to name a few.

Maternal Infection—Maternal infection has been shown to increase risk for schizophrenia in at least three ways: 1) increased fetal exposure to neurotoxins, 2) increased antibodies during prenatal periods, and 3) latent alterations in neuromaturation that occur around the time of puberty. Seminal work by Mednick (Mednick, Machon, Huttunen, & Bonett, 1988) studied mothers who acquired a viral influenza in Finland during their 2nd trimester, and reported that their offspring had significantly higher prevalence of schizophrenia. Other studies have replicated this finding and have also implicated other bacterial and viral infections across all trimesters of pregnancy in elevating schizophrenia risk, including upper respiratory infections (Mortensen, *et al.*, 1999), genital tract infections (Babulas, Factor-Litvak, Goetz, Schaefer, & Brown, 2006), toxoplasmosis (Yolken, *et al.*, 2001), and measles and rubella (Rimon, Nishmi, & Halonen, 1978).

However, it may not be the pathogenic microbial agents (e.g., influenza) that lead to increased risk for schizophrenia *per se*, but the activated immune response (Gilmore & Jarskog, 1997). Indeed, the exposure to cytokines, messengers of the immune system that orchestrate the inflammatory response, disrupts dopamine and other neurotransmitter systems relevant to schizophrenia. In addition, some (Zuckerman, Rehavi, Nachman, & Weiner, 2003) but not all (Meyer, *et al.*, 2008) research suggests that maternal infection works additively with pathological pubertal neuromaturation.

Paternal Age—Johanson (1958) was the first to suggest that advanced paternal age was a risk factor for schizophrenia. More recently, a study using data from the Collaborative Perinatal Project showed that increased paternal age was related to increased risk for the development of schizophrenia, and that the risk was 3-fold for fathers over the age of 55

(Ellman, Huttunen, Lonnqvist, & Cannon, 2007). Another large-scale study conducted on 638 individuals with schizophrenia in Israel showed that each decade of life in fathers increased the risk for developing schizophrenia by approximately 1.5 times in offspring (Malaspina, *et al.*, 2001). Brown and colleagues (Brown, *et al.*, 2002) supported this finding, and added that there is a dose-dependent association between paternal age and risk for schizophrenia. Commonly suggested mechanisms for the role of parental age have been epigenetic in nature, where *de novo* mutations (i.e., alterations in sperm-producing cells that were not inherited from either parent) contribute to abnormalities in gene expression (Flanagan, *et al.*, 2006; Malaspina, 2001). Additionally, evidence from animal models has shown that accumulated exposure to toxins (e.g., air pollution in urban environments) over the course of the lifetime is correlated with DNA damage and mutations (Yauk, *et al.*, 2008). Further, these pathological changes have been suggested to increase with age (Rutten & Mill, 2009), making toxic influences more detrimental to older fathers. Therefore, lifestyle changes that encourage minimized exposure to known environmental toxins may reduce the risk for schizophrenia.

Malnutrition—Maternal malnutrition occurring during times of famine has been implicated in the elevated risk for schizophrenia (St Clair, *et al.*, 2005; Susser & Lin, 1992). Two studies of populations that experienced large-scale, well-demarcated famine in The Netherlands (1944–1945) and China (1959–1961) suggest that nutritional stability is necessary for optimal neurodevelopment. Potential mechanisms linking prenatal malnutrition to schizophrenia include changes in the gene expression of mothers, where a shortage of nutrients influences neurodevelopment. Typically, these nutrients exist in the diet as folate (B vitamins), proteins, essential fatty acids, and vitamins A and D. Deficiencies of B vitamins can lead to accumulated high levels of the potentially dangerous amino acid, homocysteine (Miller, Nadeau, Smith, & Selhub, 1994), and elevated levels of homocysteine have been found in patients with schizophrenia (Haidemenos, *et al.*, 2007). Notably, supplementation with B vitamins or the nutrient trimethylglycine reduces the concentration of homocysteine in the bloodstream (van Guldener & Stehouwer, 2001). In addition, vitamin D deficiency may result from dietary deprivation, and also from a shortage of sunlight exposure. Not surprisingly, vitamin D deficiencies are among the most prevalent nutrient deficiencies due to seasonal and latitude constraints, and winter/spring births (Torrey, Miller, Rawlings, & Yolken, 1997) and higher global latitudes (Davies, Welham, Chant, Torrey, & McGrath, 2003) have been associated with elevated prevalence rates of schizophrenia. It should be noted, however, that maternal psychological distress typically co-occurs with nutritional deprivation and may confound these results. The influence of early stressors on psychosis risk, namely through dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis, are discussed below.

STRESS AND TRAUMA

While clinicians have long observed an apparent link between stress or trauma and psychosis in their patients, several recent lines of research support the idea that both significant trauma and everyday stress are important environmental factors influencing the emergence, expression and course of psychosis. A common diagnostic question that arises when adolescents present with both a trauma history and recent emergence of psychotic/subpsychotic symptoms is whether the youth is showing early signs of schizophrenia or whether the psychotic-like symptoms are “just” a consequence of the trauma (i.e. complex post-traumatic stress disorder). In this section we review emerging evidence suggesting a connection between trauma and psychosis that transcends diagnostic boundaries.

A number of studies have now established a relationship between early trauma and later psychosis. Adult schizophrenia patients report higher rates of childhood trauma than the

general population and children who experience trauma are at higher risk for later developing attenuated and fully psychotic symptoms in both adolescence and adulthood, especially auditory hallucinations, and especially in cases of maltreatment with an intention to harm (Arseneault, *et al.*, 2011); (Read, van Os, Morrison, & Ross, 2005 for a review). Early trauma may interact with other environmental risk factors, as individuals in a population cohort study who were exposed to high levels of trauma prior to age 16 and reported cannabis use by age 19 were more likely to have clinician-rated and self-reported psychotic-like symptoms at follow-up at age 19 (Konings, *et al.*, 2011). Finally, children exposed to trauma or bullying are more likely to report psychotic-like symptoms at age 12, even after controlling for genetic risk for psychosis (Arseneault, *et al.*, 2011). Although these studies do not establish a causal link between trauma and psychosis, they contribute support to the theory that trauma experiences may raise the risk of developing psychosis in adolescence.

The few available CHR studies that assess childhood trauma suggest a very high rate, including our own sample, estimated at 70% – 83%, with diagnosed PTSD rates of 15%–21% (Bechdolf, *et al.*, 2010; Loewy, Pearson, Stuart, Mathalon, & Vinogradov, 2011; Thompson, *et al.*, 2009). In these studies, total trauma exposure was associated with positive symptom severity at baseline (Thompson, *et al.*, 2009) and CHR patients with a sexual abuse history were more likely to have converted to a full psychotic disorder 1–2 years later (Bechdolf, *et al.*, 2010). These data suggest that trauma experiences are extremely common in putatively prodromal patients, may be related to positive symptom severity and conversion, and should be inquired about routinely, even when overt PTSD symptoms are not present.

More recently, investigators have begun examining the impact of everyday stress on full and attenuated psychosis. Fully psychotic patients who have experienced childhood trauma reported increased negative affect and psychotic symptoms in response to daily stress, compared to psychotic patients without childhood trauma (Lardinois, Lataster, Mengelers, Van Os, & Myin-Germeys, 2011), and a genetic polymorphism has been found to mediate the relationship between daily stressors and momentary increases in psychotic symptoms (Collip *et al.*, 2011). Adolescents with schizotypal personality disorder (SPD), who also develop full psychosis at an elevated rate of 21% by 2.5 years, have reported a greater number of total, independent and undesirable life events compared to healthy adolescents, and report more distress in response to daily hassles (Tessner, Mittal, & Walker, 2011; Woods *et al.*, 2009). Additionally, frequency of daily stressors predicted an increase in positive symptoms one year later. In another study, CHR youth had lower levels of stressful life events and similar levels of daily hassles as an age-matched healthy control group, but nonetheless reported being more distressed by events and used different coping strategies (Phillips, Edwards, McMurray, & Francey, 2011). Altogether, these studies suggest that stress reactivity is heightened in adolescents with attenuated and full psychosis, triggering fluctuations of psychotic symptoms, and may be influenced by both genetic and environmental risk factors. Given that CHR patients have been found to report even higher stress levels than first-episode psychosis patients (Pruessner, Iyer, Faridi, Joobor, & Malla, 2011), reducing stress and improving coping in CHR youth may be especially important targets for intervention.

One hypothesis linking trauma/stress and psychosis is based upon animal models of stress sensitization/ dysregulation, proposing that early trauma causes dysregulation of the primary neurobiological stress response system, the hypothalamic-pituitary-adrenal (HPA) axis, with downstream effects on the neural systems implicated in psychosis (Walker & Diforio, 1997). Numerous studies have now demonstrated dysregulated HPA-axis activity in schizophrenia (Walker, Mittal, & Tessner, 2008 for a review) and in CHR groups (Garner, *et al.*, 2005;

Walker & Bollini, 2002; Walker, Walder, & Reynolds, 2001; Yee, *et al.*, 2007), with some suggestion that higher cortisol levels predict conversion to full psychosis (Walker, *et al.*, 2010). Although the exact molecular mechanisms linking early stress and psychosis are not fully clear, there is sufficient evidence to suggest that early and/or chronic stress or trauma contribute significantly to psychotic symptom expression.

Complicating the relationship of early trauma and emerging psychosis in adolescence is the fact that illusions, hallucinations and suspiciousness are common features of PTSD. In fact, 46% of sexual assault victims have been found to experience hallucinations (Kilcommons, Morrison, Knight, & Lobban, 2008) and 40% of veterans with combat-related PTSD report psychotic symptoms, mostly auditory hallucinations (David, Kutcher, Jackson, & Mellman, 1999), spurring the suggestion that a subtype of PTSD be recognized, “Posttraumatic stress disorder with secondary psychotic symptoms” (Sautter, *et al.*, 2003). Given this complex relationship between trauma and psychosis, especially in teens, trauma should be a focus of thorough assessment in CHR patients, and psychotic-like symptoms should be thoroughly assessed in adolescents with trauma histories. In either case, patients need to be followed over time to determine whether psychotic-like symptoms will resolve once the trauma has been treated, or whether they will continue to progress into full psychosis. Regardless of which outcome develops, psychological interventions that focus on normalizing and de-catastrophizing symptoms will serve to reduce the distress that can accompany these experiences and that may otherwise put the young person at risk for worsening psychosis.

Development of psychological interventions for traumarelated psychotic symptoms is a small, but rapidly growing area, with evidence from case studies and series, rather than randomized controlled trials (for a review, see Bendall, Jackson, & Hulbert, 2010). These approaches tend to focus on cognitive models of hallucinations as intrusions (Kinderman, 2011) and delusional interpretations (Turkington, Bryant, & Lumley, 2011). Formulation-based cognitive behavioral therapy for psychosis links earlier life experience and recent stressors with the emergence of psychotic symptoms in an explanatory model that helps normalize experiences for patients (Callcott, Dudley, Standart, Freeston, & Turkington, 2011). Reframed as an expression of psychological distress, psychotic symptoms may be clearly linked to trauma experiences from the beginning of treatment, or linked after some exploration between patient and clinician. These approaches can be used with psychotic-like experiences of all severity levels, making them ideal for CHR youth. For example, a formulation for an adolescent who was previously bullied as a child and now has persecutory ideation might be that previous experiences taught him to watch closely for threats by peers, and now, under stress, his mind may understandably be over-vigilant and perceive threat where there is none. Further discussion would link alternative interpretations of perceived threat to different emotional reactions: noticing a classmate laughing with friends in the hallway can be interpreted as “he said something mean and they’re laughing at me,” which leads to feelings of fear and anger, while an interpretation of “they’re laughing at a joke, he’s a funny guy” may lead to an urge to engage with others socially. By definition, CHR adolescents have some level of insight about the reality of their symptoms and may be easier to engage in this type of reality-testing work.

In order to reduce overall stress/distress, general stress management techniques and medications targeting stress and anxiety may also be useful. Identifying the “optimum” level of stress may seem difficult with CHR adolescents, but it is critical to encourage engagement in age-appropriate social and scholastic or employment activities without overwhelming patients and triggering a worsening of symptoms. This is an iterative process that must be individualized for each patient: there is no clear guideline for what level of stress CHR teens can tolerate. It may take time, but an expectation of eventual recovery and

full engagement in school/work and social activities is a very reasonable goal, one that keeps teens on track developmentally to a self-sufficient young adulthood.

FAMILY ENVIRONMENT

Evidence from adoption (Tienari, *et al.*, 2003), expressed emotion (Butzlaff & Hooley, 1998; Kavanagh, 1992), and treatment studies (Miklowitz, 2003) have shown that the family environment has a significant impact on the development and course of schizophrenia. One of the most compelling studies showing the risk and protective effects of the family environment on the development of psychosis is a longitudinal, population-based adoption study conducted in Finland. The benefit of adoption studies is that the biological parents are not the rearing parents, thus allowing for an independent evaluation of gene-environment interaction. In this study, adopted-away offspring of mothers with a schizophrenia-spectrum disorder were compared to adopted-away offspring of biological mothers without a schizophrenia spectrum diagnosis. Psychiatrists who were blind to the illness status of the biological mothers evaluated the adoptive family environments. The environments were then characterized as healthy or unhealthy, thus allowing for a 2x2 comparison of high versus low genetic risk in relation to unhealthy versus healthy family environments. Unhealthy family environments were defined as highly critical, conflictual and exhibiting boundary problems. Among adoptees with a high genetic risk and an unhealthy rearing environment, 36% developed a psychotic disorder, while only 6% of those with high genetic risk reared in a healthy environment developed psychosis. Among adoptees with low genetic risk, the family environment did not contribute to the risk for psychosis. While these findings demonstrate the strong effect family environmental stress can have on heightening risk for developing a psychotic disorder in genetically vulnerable individuals, the equally important finding is the degree to which a healthy environment was able to protect at-risk individuals from developing a psychotic disorder. Further, the family environment only had an effect on genetically vulnerable individuals, demonstrating that the family environment alone cannot *cause* schizophrenia.

Another aspect of the family environment that has been shown to influence patient outcomes is Expressed Emotion (EE), a measure of the emotional temperament and familial interactions of the home environment. "High EE" environments are characterized by critical, hostile, or emotionally overinvolved (EOI) families. Emotional overinvolvement refers to the family behaviors that are overly protective, unusually self-sacrificing, and exhibiting exaggerated emotional responses. Examples of EOI include a father who chooses not to leave the house to look after his son (age 21 and going to school); a mother who says she is so consumed with her concern for her daughter that she spends the night in her 16 year old daughter's room. She goes on to explain she sleeps in her daughter's room out of fear that she won't hear her daughter calling for her if she needs something in the middle of the night. While one can see that EOI, at least in its extreme form, can infuse stress in the home environment, particular situations might warrant a higher degree of involvement. It is important to consider the age of the patient and the severity of symptoms. For instance, in the example above, it might be appropriate for a parent to sleep in her daughter's room if there is a suicide risk OR, it might be appropriate for a parent to remain at home to manage a recent worsening of symptoms. One question to ask when assessing whether the degree of EOI is appropriate is how sustainable is this behavior? Is the family system able to maintain the accommodations to care for their loved one and successfully manage the stress that stems from those accommodations? And lastly, how useful is that change in supporting the loved one? Further questions to ask the young person and the family should focus on gauging the emotional temperament of the home, determining whether there are established boundaries, assessing communication styles (argumentative, intrusive, avoidant), and lastly, learning how the family solves problems. Questions may include: To what degree do you

consider your family environment critical, conflictual? How does the family typically deal with conflict? Are rules and expectations clear? Do family members enjoy being around one another?

High EE family environments have consistently been linked to poor outcomes among patients with schizophrenia (Butzlaff & Hooley, 1998; Kavanagh, 1992) and recently have been shown to impact the longitudinal course of CHR symptoms and psychosocial functioning (O'Brien, *et al.*, 2006; Schlosser, *et al.*, 2010). Individuals with schizophrenia living in high-EE family environments experience greater likelihood of psychiatric relapse (65% relapse within 1 year) while low-EE environments are protective against relapse (35% relapse within 1 year). CHR youth living in high-EE environments experience a worsening of attenuated psychotic symptoms while those living in warm and optimally-involved family environments experience improved functioning over time, even after controlling for baseline symptoms (Schlosser *et al.*, 2010). Given this information, it is important for treatment providers to be aware of the presence of high-EE and factors that increase the risk for high-EE attitudes. Signs that a family environment might be characterized as high EE are a high degree of conflict, criticism, and overinvolvement. Additionally, family members rated as having high-EE attitudes are more likely to assume that their mentally ill loved one has more control over his/her symptoms (Hooley & Campbell, 2002). For instance, a high-EE family member may express more critical comments if she thinks that her son is "being lazy" rather than experiencing negative symptoms. Clinicians can survey primary caregiver beliefs about the extent of control their loved ones have over their illness, with greater attributions of control being more highly associated with high-EE environments.

Due to the large body of evidence linking the family environment to psychosis outcomes, it is not surprising that family-based treatments are indicated for schizophrenia patients. Specifically, family interventions (in combination with pharmacological treatment) that include psychoeducation, communication skills, and problem-solving have been shown to be highly protective against relapse (6–12 month rates on average ~12.5%) whereas schizophrenia patients not receiving those types of interventions experience relapse rates around 42% (McFarlane, Dixon, Lukens, & Lucksted, 2003; Miklowitz, 2003). There have been fewer family-based intervention studies conducted in CHR populations; however some preliminary evidence suggests that, as in schizophrenia, family interventions have the potential to improve patient outcomes (O'Brien, *et al.*, 2007). Two multi-site randomized controlled trials, one using a family focused treatment model, and one using a psychoeducational multi family group model, are currently being conducted in CHR populations (Family Focused Treatment for Prodromal Youth study and the Early Detection and Intervention for the Prevention of Psychosis Program), and will likely provide more evidence supporting the use of family-based treatments.

Taken together, these studies have far-reaching clinical implications, suggesting that the family environment is a critical target for intervention with CHR youth. All family interventions for schizophrenia-spectrum disorders begin with psychoeducation, which can include a review of the symptoms that comprise the at-risk syndrome and common comorbid symptoms (e.g. anxiety, depression), differentiating normative adolescent behavior from symptoms, and a discussion about the role of stress in the clinical course. The clinician should emphasize the importance of maintaining a low-key family environment and to be mindful of the possibility of worsening symptoms in the presence of increased stress. Some parents might respond to this information with uncertainty about the appropriate level of expectations they can place on their loved one. It is important to emphasize a balanced approach in which expectations are maintained, but adjusted based on the young person's age and phase of illness. Further, families often feel a tremendous amount of guilt and responsibility for their loved one's illness. It is critical to inform families that while they

have the ability to have an effect, they are not the cause of the symptoms. One can cite research about the etiology of psychosis and point to the evidence showing that the family environment alone cannot cause an individual to develop psychosis.

In summary, the psychoeducational sessions are meant to provide sufficient information to the family to encourage a more effective, low-stress family system. While psychoeducation is a critical component of treatment for CHR youth, it is often not enough to lead to longstanding change. The most effective family-based treatments combine psychoeducation with communication skills training and structured problem solving. Communication skills focus on positive listening behaviors (active listening) and constructive verbal communication (validating the other person's feelings). Structured problem solving includes a methodical approach designed to maintain a low-key problem-solving environment to encourage a more effective approach to solving conflicts. For a more detailed review of recommended approaches to working with families of CHR youth, refer to Schlosser and colleagues (in press) and McFarlane and colleagues (2003). If it is not feasible to provide communication skills training and structured problem solving, it is nonetheless valuable to involve the family in the treatment plan. Involving family members in the treatment will not only encourage a healthy family environment, it will likely improve outcomes for CHR youth.

CANNABIS USE

Cannabis use is common in patients with psychosis, with some studies finding lifetime use of cannabis in more than 80% of patients (Barnett, *et al.*, 2007), and abuse rates varying from 11% (Green, Young, & Kavanagh, 2005) to 50.8% (Barnett, *et al.*, 2007). Since cannabis use is potentially one of the few modifiable psychosis risk factors there is a clear need to understand the relationship between psychosis and cannabis use. Although it is established that cannabis use can bring on transient psychotic symptoms in users (D'Souza, *et al.*, 2000), it remains unclear whether cannabis use can cause the emergence of a psychotic disorder. For patients diagnosed with a psychotic disorder, cannabis use can worsen the course of illness, increase the risk for relapse (Linszen, Dingemans, & Lenior, 1994), and generate more positive symptoms (Grech, Van Os, Jones, Lewis, & Murray, 2005), even after adjusting for confounding factors. Furthermore, this association seems to be dose-dependent, with more chronic and heavy use leading to more adverse consequences (Zammit, *et al.*, 2007). More recent evidence from longitudinal studies suggests that adolescent cannabis use increases risk for psychosis in young adulthood, particularly in youth with a genetic risk for psychosis (Caspi, *et al.*, 2005). Nonetheless, the direction of causality between cannabis use and psychosis remains the subject of debate.

Three directions of causality have been suggested by Hambrecht and Häfner (2000): (1) Prior to the onset of psychosis, cannabis use causes the emergence of psychotic symptoms, especially in vulnerable individuals, and (2) the self-medication model, which assumes that the causality has the opposite direction, with patients using cannabis in an attempt to reduce or cope with symptoms of schizophrenia, or (3) the simultaneous use of cannabis and psychotic symptoms are coincidental, with causality being attributed to an unknown third factor. There has been evidence supporting all three directions of causality (Ferdinand, *et al.*, 2005; Hambrecht & Häfner, 2000), and uni-causality between cannabis use and psychosis seems unlikely. However, studies looking at temporal association between cannabis use and psychosis have shown that a large percentage of patients with psychosis began cannabis use before the emergence of positive symptoms (Ferdinand, *et al.*, 2005; Linszen, *et al.*, 1994), therefore lending support to the hypothesis that cannabis use interacts with a genetic predisposition for psychosis to lower the threshold for the development of psychosis.

Compelling evidence for cannabis as a risk factor in the development of psychosis comes from prospective cohort studies that have demonstrated increased psychosis risk in cannabis users in young adulthood, with heavy users being more likely to develop psychosis during a 21 year follow up period (McGrath, *et al.*, 2010). Risk for developing psychosis seems to be highest amongst those users who had a predisposition for psychotic symptoms (indicated by self reported psychotic symptoms) at baseline. However, cannabis use also elevates risk in those individuals without a baseline predisposition (van Os, *et al.*, 2002; van Os, *et al.*, 2005). Furthermore, cannabis use has been linked to worsening of attenuated psychotic symptoms (Corcoran, *et al.*, 2008), earlier onset of those symptoms (Dragt, *et al.*, 2010), and higher risk for conversion to full psychosis among CHR patients (Cadenhead & Kristensen, 2007). However, results have not been uniform across studies, and several studies have been unable to establish a link between cannabis use and conversion to psychosis (Phillips *et al.* 2002) or severity of attenuated psychotic symptoms (Machielsen, van der Sluis, & de Haan, 2010).

Most prospective cohort studies examining the relationship between substances and psychotic symptoms have focused on cannabis use, given its high rate of use in the general population. However, the list of substances that induce psychotic symptoms is well-known, including a variety of stimulants and hallucinogens (e.g. methamphetamine, PCP), and even alcohol (Johns, *et al.*, 2004). However, since alcohol is often used in combination with other substances, establishing if alcohol use is a risk factor in the development of psychosis, independent of other substances, is challenging (Barkus & Murray, 2010). Assessing cannabis and other substance use should obviously be integrated in every assessment of CHR syndromes. Psychoeducation about cannabis use and risk for psychosis is a critical intervention.

Case Study

A. was a sixteen year old male referred for a CHR syndrome evaluation by his school counselor after expressing concern about feeling “paranoid”. A. was a high school student, who lived with his parents in a suburb of San Francisco. He held a part-time job as a sales associate in a local bookstore, and he had recently become increasingly suspicious of his coworkers, thinking they were talking negatively about him, and sabotaging his ability to productively work by misplacing his supplies. A. had started using cannabis socially during his freshman year in high school, but his use had increased significantly one year ago when he and his family moved to California, and he was now smoking cannabis on a daily basis. His cannabis use caused significant conflict between A. and his parents, who felt that A.’s suspiciousness was not part of a prodromal syndrome, but caused by his use. A. had tried to discontinue cannabis use on two previous occasions because he felt cannabis use made him forgetful and interfered with motivation. His longest period of abstinence was one month. When questioned about his use during the intake assessment he stated that cannabis helped relieve the anxiety associated with the mistrust he felt towards his coworkers. It also became clear that cannabis use was normative in A.’s social circle, and that social gatherings almost inevitably lead to use.

The clinical vignette describes several common issues that arise when addressing cannabis use in an adolescent CHR population. First, patients often find that cannabis use relieves the anxiety or depression associated with prodromal symptoms; second, cannabis use is perceived as an integral part of the patient’s social landscape; and third, the cannabis use is a point of much contention between adolescents and their parents. When addressing cannabis use with CHR adolescents, psychoeducation about the relationship between cannabis use and (attenuated) psychotic symptoms is essential. Psychoeducation can be effective in reducing cannabis use in a psychotic population (Edwards, *et al.*, 2006). However, psychoeducation alone is rarely enough, and efforts should be made to allow the patient to

recognize the possible link between his/her cannabis use and (attenuated) psychotic symptoms. Motivational interviewing, a client-centered approach aimed at increasing motivation for change through a variety of techniques can be useful in this process (Miller & Rollink, 2002). Although cannabis use might temporarily alleviate distress caused by CHR symptomatology, patients report that it often also increases the intensity of attenuated or full psychotic symptoms themselves. Sometimes patients voice concerns about effects of use that might not be directly linked to positive symptoms, such as A's concerns in the vignette above about cannabis use interfering with motivation and memory. If this is the case, the patient's self-generated concerns about use can be elaborated, and discussed. Since cannabis is often used socially, and a perceived increase of social role functioning is cited as a common reason for cannabis use in a psychotic population (Addington & Duchak, 1997), exploring coping mechanisms that the patient can use to decrease or discontinue cannabis use in social situations can be helpful. An intervention aimed at reducing cannabis use in the CHR population incorporating some of the above described techniques was found to significantly reduce cannabis use (Bucci, *et al.*, 2010).

Families are often an essential component in successfully reducing cannabis use in adolescents. In the vignette above A.'s parents thought cannabis was to blame for A.'s suspiciousness, and therefore discontinuing use would also mean the discontinuation of symptoms. Discussing the parent's apprehension regarding the CHR syndrome diagnosis and praising them for taking steps towards early intervention can be helpful in reducing tension that surrounds the diagnosis. In the case of A. it was pointed out that his suspiciousness was still present during his periods of abstinence, and that it is unlikely that a discontinuation of use would also mean full remission of symptoms. However, it was emphasized that discontinuing cannabis use might reduce the intensity of symptoms now, and possibly prevent A.'s symptoms worsening over time. Family therapy adjunctive to A.'s individual therapy was suggested to advance communication and reduce tension between A. and his family.

Overall, there is a growing body of evidence that points to cannabis use as a risk factor for psychosis, especially in those individuals with a pre-existing genetic or environmental vulnerability for developing psychosis. Therefore, cannabis use should be strongly discouraged by adolescents with CHR syndromes. Psychoeducation about the risks associated with cannabis use should be a routine part of working with CHR patients, even those patients who are currently not using cannabis.

CONCLUSION

We have reviewed a number of risk and protective factors shown to impact the emergence of psychotic disorders. A common thread throughout was the emphasis that no single environmental factor is likely sufficient to cause a psychotic disorder. Rather, genetic vulnerabilities and environmental risk factors add and/or interact to trigger psychosis in adolescence and young adulthood. It is this fact, along with the typical medium-term conversion rates of 35% or less in CHR groups that make psychosocial interventions so compelling. Evidence of the importance of environmental factors in risk for psychosis is growing rapidly, presenting a host of opportunities for prevention and early intervention.

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