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The link between schizophrenia and substance use disorder: A unifying hypothesis

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ABSTRACT

Substance use disorders occur commonly in patients with schizophrenia and dramatically worsen their overall clinical course. While the exact mechanisms contributing to substance use in schizophrenia are not known, a number of theories have been put forward to explain the basis of the co-occurrence of these disorders. We propose here a unifying hypothesis that combines recent evidence from epidemiological and genetic association studies with brain imaging and pre-clinical studies to provide an updated formulation regarding the basis of substance use in patients with schizophrenia. We suggest that the genetic determinants of risk for schizophrenia (especially within neural systems that contribute to the risk for both psychosis and addiction) make patients vulnerable to substance use. Since this vulnerability may arise prior to the appearance of psychotic symptoms, an increased use of substances in adolescence may both enhance the risk for developing a later substance use disorder, and also serve as an additional risk factor for the appearance of psychotic symptoms. Future studies that assess brain circuitry in a prospective longitudinal manner during adolescence prior to the appearance of psychotic symptoms could shed further light on the mechanistic underpinnings of these co-occurring disorders while identifying potential points of intervention for these difficult-to-treat co-occurring disorders.

1. Introduction

Schizophrenia is a severe psychiatric disorder that affects 1% of the population worldwide. Patients with schizophrenia are quite vulnerable to substance use disorders (Regier et al., 1990; Stinson et al., 2006); according to the Epidemiological Catchment Area study, 47% of patients with schizophrenia have serious problems with drug or alcohol use during their lifetime compared to 16% of the general population. Regarding specific substances: tobacco, alcohol, cannabis and cocaine use disorders occur commonly in patients with schizophrenia (Mueser et al., 1990; Volkow, 2009), with lifetime prevalence ranging from 60 to 90% for cigarette smoking, as well as 21–86% for alcohol (Volkow, 2009), 17–83% for cannabis (Degenhardt and Hall, 2001; DeQuardo et al., 1994; Dixon et al., 1991; Hambrecht and Hafner, 1996; Karam et al., 2002; Mueser et al., 1995; Perala et al., 2007; Peralta and Cuesta, 1992; Ringen et al., 2008; Volkow, 2009) and 15–50% for cocaine use (Chambers et al., 2001; Mueser et al., 1990) – rates at-least three-times greater than those in the general population (Regier et al., 1990). Importantly, in this population, such high rates of substance use disorders are problematic: co-occurring substance use disorder has been associated with clinical exacerbations, non-compliance with treatment, poor global functioning, violence, suicide and increased rates of relapse and re-hospitalization (DeQuardo et al., 1994; Dickey and Azeni, 1996; Henquet et al., 2010; Juckel et al., 2006; Kivlahan et al., 1991; Knudsen and Vilmar, 1984; Linszen et al., 1994; Negrete and Knapp, 1986; Peralta and Cuesta, 1992; Regier et al., 1990; Sayers et al., 2005; Smith et al., 1997; Swendsen et al., 2011; Treffert, 1978; van Dijk et al., 2012). Given this, two key questions arise: 1) How do we explain the link between schizophrenia and substance use disorder? And 2) Why do patients with schizophrenia use substances when their use is associated with a general worsening of the course of schizophrenia (DeQuardo et al., 1994; Dickey and Azeni, 1996; Juckel et al., 2006; Linszen et al., 1994; Sayers et al., 2005; Smith et al., 1997; Swendsen et al., 2011; van Dijk et al., 2012)?

2. Prevalent theories regarding substance use in schizophrenia

As reviewed by Green et al. (2007), a number of theories have been advanced over the past 20 years to explain the association between substance use disorder and schizophrenia.

The diathesis-stress model (sometimes referred to as the "two-hit" model) posits a neurobiologic vulnerability interacting with an

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environmental stressor (which could include substance use) that leads to schizophrenia (Fowles, 1992). A related model (the cumulative risk factor hypothesis) suggests that individuals with schizophrenia have an increased risk of substance use disorder because of the cumulative effects of poor cognitive, social, educational and vocational functioning, in the presence of poverty, victimization and deviant social environments (Mueser et al., 1990).

The self-medication hypothesis suggests that substance use in patients with schizophrenia is based on the wish to lessen symptoms or decrease side effects of antipsychotic treatment (Khantzian, 1997). While the notion of self-medication is plausible, most studies have reported no (or very limited) relationship between symptoms of schizophrenia and substance use, or between medication side effects and use (DeQuardo et al., 1994).

An alternative, biologically-based theory, at times referred to as a "primary addiction hypothesis" (Chambers et al., 2001) or a "reward deficiency syndrome" (Green et al., 1999), suggests that both schizophrenia and substance use disorders share a common pathophysiology in overlapping neural circuits, and that substance use may be related to a dysfunction of the brain reward circuit in patients with schizophrenia.

These competing hypotheses are not necessarily mutually exclusive. First, even the "reward deficiency syndrome" hypothesis suggests that patients may be self-medicating their reward deficiency through their use of substances (Green et al., 1999). Furthermore, while the increased use of substances prior to onset of psychosis may arise as a result of reward related dysfunctions in prodromal states, it is also possible that cognitive deficits and negative symptoms during this prodrome may in fact be ameliorated by the substance use (Jones et al., 2016; Kristensen and Cadenhead, 2007). Moreover, the high rates of substance use in first-degree relatives may arise from trait-based abnormalities in reward circuitry, or from potential "self-medication" of sub-threshold symptoms that might be present in these relatives (Smith et al., 2008; Stone et al., 2001). One way to begin to differentiate between these hypotheses could involve assessing the effects of reducing substance use in these patients (as suggested by Chambers (2010). In an interesting investigation in this special issue, Boggs et al. (2017) suggested that acute or prolonged abstinence or resumption of tobacco smoking produces minimal effects on cognition or schizophrenia symptoms, presenting an evidence-based challenge to the "self-medication" hypothesis. Another study in this issue by Rabin and colleagues showed that abstinence from cannabis use improved depressive symptoms in patients with schizophrenia (Rabin et al., 2017).

While each of these models has commonsense appeal, it has not been clear to this point which of them is most strongly supported by on-going research. In the remainder of this paper, we review the existing research findings toward the development of a unifying hypothesis that may contain and further elucidate all of the existing theories.

3. Which comes first? Epidemiology of substance use and schizophrenia

It is clear that lifetime rates of substance use disorders are elevated (above that in the general population) in patients with psychotic disorders (Kendler et al., 1996), including those in their first psychotic episode (Arranz et al., 2015). Reports of rates of substance use in patients with first episode psychosis range from 30 to 70% (Abdel-Baki et al., 2017). Di Forti and colleagues suggest that for many, the substance use begins before the psychosis: they showed that patients presenting with first episode psychosis were more likely to be daily cannabis users and to have smoked cannabis for more than 5 years when compared to healthy controls (Di Forti et al., 2009); and Weiser et al. (2004) noted that patients with schizophrenia have a higher rate of tobacco smoking prior to the onset of schizophrenia compared to those without schizophrenia. Moreover, a number of investigators have suggested that adolescent cannabis, and potentially tobacco, smoking increases the risk of schizophrenia (Gage and Munafo, 2015a, 2015b; Kendler et al., 2015).

Regarding cannabis, a recent meta-analysis reaffirmed its potential role: higher rates of cannabis use were associated with an increased risk of psychosis in a dose-dependent fashion, where heavy users had a 4-fold risk and moderate users had a 2-fold risk of developing psychosis (Marconi et al., 2016). While this does not necessarily indicate causality, premorbid cannabis use is associated with an earlier age of onset of psychotic symptoms (Donoghue et al., 2014; Stefanis et al., 2013), and the relationship between age of onset of cannabis use and age of onset of psychosis seems to be linear– with one study showing a 7–8 year gap between cannabis use and the initiation of psychotic symptoms (Stefanis et al., 2013). Moreover, while there is typically a gender gap in the age of onset of psychotic symptoms, with men showing symptoms earlier than women (Eranti et al., 2013), this gender gap is abolished by cannabis use (Donoghue et al., 2014).

Others have assessed whether cannabis use (especially during adolescence) is a significant risk factor for developing schizophrenia later in life. Fergusson et al. (2003) reported that individuals with cannabis use disorder at the ages of 18 and 21 had significantly higher rates of psychosis when compared to non-cannabis using participants (Fergusson et al., 2003), and Arseneault et al. (2002) found that adolescents using cannabis at the age of 15 were more likely to develop a schizophreniform disorder by the age of 26 when compared to non-using adolescents, even when controlling for prior psychotic symptoms. Lastly, Schubart and colleagues demonstrated that cannabis use at the age of 12 was associated with a nearly 5-fold increase in odds of being hospitalized for psychosis later in life (Schubart et al., 2011). As discussed below, these studies raise the question of whether adolescent cannabis use can interfere with adolescent brain development, leading to an increased risk of schizophrenia (Rais et al., 2008).

Clearly, however, while adolescent cannabis use is a significant risk factor for psychosis, other environmental and biological factors also influence the risk of developing schizophrenia (Green and Glausier, 2016). For instance, childhood trauma and cannabis use appear to interact synergistically to heighten the risk of psychosis later in life (Gage et al., 2016a). In addition, of course, not all individuals who develop schizophrenia use cannabis (or other substances) before the development of their initial symptoms of psychosis. The well-known study of Hambrecht and Hafner (2000), for example, indicated that while the onset of cannabis use often occurs prior to reports of the first positive symptom, patients with schizophrenia could be divided into 3 distinct groups based on cannabis use and *any* prodromal symptoms (Hambrecht and Hafner, 2000). The study described a subset of patients using cannabis several years prior to the first signs of schizophrenia, while another subset experienced initial psychotic symptoms and began using cannabis at approximately the same time. Finally, a third subset of patients began using cannabis after the onset of schizophrenic symptoms. Hambrecht and Hafner divided these subsets into a "vulnerability" group, a "stress" group, and a "coping" group, respectively. Consequently, while adolescent cannabis use may be a risk factor for later schizophrenia development, it may only be so in a subset of people (Hambrecht and Hafner, 2000). Moreover, adolescent tobacco smoking has also been suggested as a possible risk factor for schizophrenia (Kendler et al., 2015). Interestingly, a meta-analysis found that adolescent alcohol exposure did not alter the age of onset of psychosis (Large et al., 2011). These findings emphasize the importance of studying the effects of substance use during adolescence, and their potential interaction with schizophrenia and co-occurring substance use disorders.

4. Enduring effects of adolescent drug exposure

While adolescent substance use may contribute to the risk for psychosis (Di Forti et al., 2009), drug use during this vulnerable developmental period also enhances vulnerability for continued substance

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