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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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use. Some of the commonly used substances (e.g., tobacco, alcohol and cannabis) in patients with schizophrenia are associated with increased risk for future substance use if use is initiated in adolescence (Chadwick et al., 2013; Kandel and Kandel, 2014; Levine et al., 2011). While the neurodevelopmental consequences of drug exposure during adolescence are not fully understood, previous epidemiological and pre-clinical investigations provide valuable clues regarding the long-term changes in addiction vulnerability arising from this exposure.

Tobacco use usually begins during adolescence, and this exposure is associated with increased risk for the development of cocaine, marijuana, heroin and alcohol use in adulthood (Grant et al., 2004; Strong et al., 2016). The causal direction of these associations is not entirely known, primarily due to a potential confound that needs to be considered in the context of the "gateway drug" hypothesis: that the development of another drug use after early exposure to a drug could reflect a common or shared liability for drug use and that this liability, rather than the exposure to the first drug, could increase the risk of progression to the use of another drug. The causal direction is further complicated since animal studies of the long-term effects of adolescent nicotine exposure on future drug use have produced mixed results (Alajaji et al., 2016; Pomfrey et al., 2015; Spear, 2016). However, exposure to nicotine during adolescence may produce long-term epigenetic changes that may increase susceptibility to the initiation and continued use of tobacco and other substances (Kandel and Kandel, 2014).

Alcohol use also begins in adolescence (Swendsen et al., 2012), and this early exposure predisposes users to future risk for an alcohol use disorder as well as other cognitive and reward-related dysfunctions (Nguyen-Louie et al., 2015). While the interaction between adolescent alcohol exposure and risk for schizophrenia has not been explicitly studied in patients, a recent study suggested that alcohol use in adolescence predicted future co-occurring mental health and poly-substance use disorders (Salom et al., 2016). A substantial body of preclinical literature has also suggested that alcohol exposure in adolescence promotes suboptimal decision-making, amplifies the incentive value of reward-predictive cues and produces long-lasting changes in alcohol's activation of brain reward circuitry (Boutros et al., 2015; Clark et al., 2012; Liu and Crews, 2015; McClory and Spear, 2014; Spoelder et al., 2015; Vetreno and Crews, 2015).

Cannabis use during adolescence increases the risk for life-time cannabis dependence from 9% to 16%, and even higher to 25–50% among daily adolescent users (Volkow et al., 2014). While it is debated whether cannabis serves as a "gateway" drug, associations between adolescent cannabis use and use of illicit and novel psychoactive substances have been reported (Agrawal et al., 2004a, 2004b), and longitudinal studies have suggested that regular or heavy cannabis use is associated with an increased risk of using other illicit drugs (Khan et al., 2013; Lynskey et al., 2003). Moreover, these findings have been supported by preclinical studies suggesting increased vulnerability for future drug use in rats exposed to cannabinoids during adolescence (e.g., increased intake of heroin, morphine, cocaine and WIN-55212 [a synthetic cannabinoid agonist] (Chadwick et al., 2013; Dow-Edwards and Izenwasser, 2012; Ellgren et al., 2007; Rodriguez-Arias et al., 2016)). While the enduring effects of adolescent drug exposure on future risk of co-occurring schizophrenia and substance use disorder is important, it needs to be considered in the context of genetic predisposition or susceptibility that might be related to the risk for schizophrenia.

5. Genetic underpinnings of schizophrenia and co-occurring substance use disorder

Based on epidemiological data and family studies, it appears clear that genetic factors significantly influence susceptibility to schizophrenia. The concordance rate for schizophrenia in monozygotic twins is 40–50% (Cariaga-Martinez et al., 2016; Schwab and Wildenauer, 2013). Genetic factors are also thought to play a role in the susceptibility to develop schizophrenia and a co-occurring substance use disorder. Indeed, polygenic risk scores for schizophrenia are also associated with cannabis use, cocaine use, nicotine use, and severe alcohol use (Carey et al., 2016).

It appears that gene x environment interactions generate risk of schizophrenia and co-occurring substance use disorders. Three distinct genes, encoding brain-derived neurotrophic factor (*BDNF*), catechol-*O*-methyltransferase (*COMT*), and protein kinase B (*AKT*), have garnered the most attention for their relationship with both schizophrenia and substance use. While polymorphisms of *BDNF* (rs6265 and rs103411), involved in synaptic plasticity and the activity of dopamine (Guillin et al., 2001; Hartmann et al., 2001), are not associated with alcohol dependence alone, they are strongly associated with schizophrenia and co-occurring alcohol dependence, suggesting that these *BDNF* variants may be important in the co-occurrence of these disease states (Cheah et al., 2014).

A particular allele of *COMT*, which influences catecholamine metabolism, has been implicated in schizophrenia (see Apud and Weinberger, 2007 for review). Specifically, the *COMT* Val/Val allele, associated with reduced dopamine function in the prefrontal cortex (PFC), results in increased risk for developing endophenotypes related to schizophrenia, but not necessarily the development of the disease (Ira et al., 2013). Environmental factors, however, can interact with *COMT* genotypes to impact the risk of psychosis development. Caspi and colleagues demonstrated a significant interaction between the *COMT* Val/Val allele and adolescent (but not adult) cannabis use to predict adult psychosis, suggesting that two risk factors, a particular *COMT* polymorphism and adolescent cannabis use, together can increase the risk of psychosis (Caspi et al., 2005). This finding, however, has not been replicated by subsequent investigations (Kantrowitz et al., 2009). Moreover, since *BDNF* and *COMT* are implicated in a number of genome wide associations studies of other psychiatric disorders, the associations between these genes and schizophrenia and co-occurring substance use disorder could arise as a result of pleiotropy (an effect of gene on multiple traits resulting in an effect on the outcome, but not via the behavior/trait displaying a significant association), and, thus, must be interpreted with caution.

AKT, a serine/threonine protein kinase involved in protein synthesis, synaptic plasticity and cell proliferation, (Scheid and Woodgett, 2001), is reduced in post-mortem brains of patients with schizophrenia (Emamian et al., 2004; Kalkman, 2006; Swiech et al., 2008). Interestingly, one study found an interaction between *AKT* polymorphisms and cannabis use in the risk of developing psychosis (Di Forti et al., 2012). Specifically, *AKT* C/C (but not T/T) allele carriers were 7 times more likely to develop psychosis if they used cannabis on a daily basis. Moreover, van Winkel and colleagues showed that patients with schizophrenia who used cannabis regularly had poorer cognitive performance if they carried the *AKT* C/C allele when compared to T/T allele carriers (van Winkel et al., 2011). Like *BDNF* and *COMT* polymorphisms, it may be that the *AKT* gene confers risk for schizophrenia development when environmental risk factors, specifically cannabis use, are also present. However, such associations, requiring the presence of genetic risk and developmental substance use, do not rule out the possibility of a shared susceptibility or reverse causality, and require further investigation to assess the causal directions in complex disorders such as schizophrenia.

An interesting finding from the Psychiatric Genomics Consortium 2 genome wide association study showed that a variant in the nicotinic acetylcholine receptor *CHRNA5-A3-B4* gene cluster (previously associated with heaviness of smoking in smokers in the Tobacco Genetics Consortium study (2010)) reached genome-wide significance (Schizophrenia Working Group of the Psychiatric Genomics, 2014), suggesting shared genetic architecture between schizophrenia and cigarette smoking. This is further corroborated by a study in this special issue by Hartz and colleagues showing that a statistically significant genetic correlation exists between schizophrenia and various smoking phenotypes (e.g., cigarettes per day, nicotine dependence) (Hartz et al., 2017). Moreover, a recent pre-clinical study suggests the

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contribution of genetic variation within *CHRNA5* may mediate both schizophrenia and nicotine use through a shared hypofrontality phenotype (Koukouli et al., 2017), making it important to study the circuit-based correlates of these co-occurring disorders.

Recent studies have also used a Mendelian randomization approach to begin to assess the causal direction of the effects of substance use on schizophrenia. While the impact of initiation of cannabis and cigarette smoking on the risk for schizophrenia has been suggested by this technique (Gage et al., 2016b; Gage and Munafo, 2015a, 2015b; Vaucher et al., 2017), a recently published finding also suggests that there is stronger evidence supporting the hypothesis that schizophrenia genetic risk predicts cannabis initiation (Gage et al., 2016b). This is consistent with the increased risk for substance use in non-psychotic relatives of patients with schizophrenia (Smith et al., 2008; Stone et al., 2001) and suggests that even though the substance use arises prior to the onset of psychotic symptoms, there may be pre-existing vulnerabilities to initiating substance use associated with the risk for schizophrenia.

6. Brain reward circuit dysfunction as a missing link?

One manifestation of the genetic susceptibility to schizophrenia may be dysfunction within brain circuits involved in reward and motivation (specifically the mesocorticolimbic dopamine circuitry) that may drive both the initiation and continued use of substances. Reward processing in healthy subjects is related to dopaminergic activity in the ventral striatum (Boehme et al., 2015; Deserno et al., 2015; Schlagenhauf et al., 2013), which may be impaired in patients. Thompson et al. (2013) found that patients with schizophrenia and a co-occurring substance use disorder have decreased striatal dopamine release; the authors suggested that this decreased release might be due to the substance use history in these patients. Importantly, the authors also suggested that in such patients, there might be a hypersensitive dopamine system (as observed via the changes in positive symptoms in response to amphetamine); we propose that this hypersensitivity may further contribute to their vulnerability toward substance use.

Abnormal reward processing has been studied in patients with schizophrenia using functional magnetic resonance imaging. In medication-naïve patients, a reduction of activity has been described in the ventral striatum during reward anticipation, and with reward outcomes (Esslinger et al., 2012; Juckel et al., 2006; Nielsen et al., 2012; Schlagenhauf et al., 2009). Abnormal reward processing in patients is also known to correlate with symptoms of the disease, e.g., severity of positive symptoms has been correlated with reduced ventral striatal activity during reward anticipation (Esslinger et al., 2012; Nielsen et al., 2012; Simon et al., 2015), with reduced prefrontal cortical activity between favorable and unfavorable outcomes (Schlagenhauf et al., 2009), and with over-activation of the midbrain to neutral cues (Romaniuk et al., 2010). Moreover, negative symptoms have been correlated with reduced ventral striatal activity in reward anticipation (Juckel et al., 2006; Simon et al., 2010) and decreased response to reward in both putamen (Waltz et al., 2009) and ventral striatum (Gradin et al., 2013). Interestingly, a recent study also assessed neural responses to cigarette smoking cues in smokers with schizophrenia, and found that patients with schizophrenia showed greater activation of a region within the brain reward circuit (i.e., ventromedial prefrontal cortex) in response to smoking cues compared to smokers without a psychiatric comorbidity (Potvin et al., 2016), suggesting that drug rewards may produce amplified responses in these patients.

In addition to the studies noted above related to task based brain activity, a few recent studies have demonstrated reduced resting-state functional activity in patients with co-occurring nicotine addiction between insula and anterior cingulate cortex (Moran et al., 2013; Moran et al., 2012), and in patients with co-occurring cannabis use disorder and schizophrenia between nucleus accumbens and frontal cortical regions of the brain reward circuit (Fischer et al., 2014). The Fischer study also demonstrated that smoked cannabis or oral THC partially ameliorated the hypoconnectivity, suggesting that cannabis use may be an effort by patients to correct dysfunctional brain reward circuitry (Fischer et al., 2014), consistent with both the reward deficiency syndrome and primary addiction hypotheses.

Developmental dysfunction of the hippocampus and frontal cortex may form the mechanistic underpinnings of this brain reward circuit dysfunction, as proposed by Chambers et al. (2001). The hippocampus not only plays a key role in the modulation of dopaminergic activity within the nucleus accumbens, but also mediates the integration of information in the nucleus accumbens. Although the nucleus accumbens receives diverse synaptic input (Finch, 1996), the hippocampus ultimately drives these neurons to respond (O'Donnell and Grace, 1995). The hippocampus has also been shown to induce neuroplasticity in the nucleus accumbens (Mulder et al., 1998), providing more evidence that abnormal hippocampal development and activity can have both long term and immediate effects in accumbal development and information processing. Developmental abnormalities in both the hippocampus and prefrontal cortex may lead to overall dopaminergic hypersensitivity of the mesolimbic system (Weinberger and Lipska, 1995), whereby reduced inhibitory control of the nucleus accumbens (Weinberger and Lipska, 1995) can lead to disinhibition of accumbal outputs to thalamocortical loops driving behavior associated with motivational states (Lavin and Grace, 1994). This disinhibition may result in impaired reward learning such as the persistent interpretation of rewards as novel or the inability to tune out irrelevant stimuli (Gray et al., 1992). These developmental abnormalities in the interplay between the hippocampus, prefrontal cortex and nucleus accumbens may produce motivational deficits consistent with long-term substance abuse (without the prior drug exposure), while facilitating the reinforcing effects of substances, consistent with the dopaminergic hypersensitivity observed in dual diagnosis patients (Thompson et al., 2013).

Suggestions that developmental dysfunction of the hippocampus leads to a reward circuit dysfunction gets further validation in a rodent model of preadolescent hippocampal lesioning – the neonatal ventral hippocampal lesion rat (NVHL rat), in which normal hippocampal signaling (particularly to the frontal cortex and the nucleus accumbens) is altered during development (Lipska and Weinberger, 2000; Tseng et al., 2009). NVHL rats not only exhibit a schizophrenia-like phenotype, but they also have a dysregulated reward circuit. Importantly, they also demonstrate increased consumption of (and increased behavioral sensitization to) substances commonly used by patients, e.g., cocaine (Chambers et al., 2013; Chambers et al., 2010; Chambers and Taylor, 2004), nicotine (Berg and Chambers, 2008; Berg et al., 2014), methamphetamine (Brady et al., 2008) and alcohol (Berg et al., 2011; Conroy et al., 2007; Jeanblanc et al., 2015). Data from research on this animal model suggest that brain reward circuit dysfunctions increase the vulnerability for substance use in patients with schizophrenia, which combined with potentially accentuated reinforcing properties of the substances, may make patients with schizophrenia especially vulnerable to initiating substance use. While the developmental time-course of these deficits are not known, the epidemiological evidence regarding higher rates of substance use in adolescents prior to the onset of schizophrenia (as well as in non-psychotic first degree relatives (Smith et al., 2008; Stone et al., 2001) suggests that these dysfunctions may predate the onset of psychosis.

7. Effects of antipsychotics on substance use and reward

An important related issue concerns the effects of antipsychotic medication on substance use in this population. Most antipsychotics do not lessen substance use in patients with schizophrenia, with one exception – clozapine has been shown in many (albeit still preliminary) studies to do so across a variety of substances (e.g., alcohol, cannabis, tobacco) (Brunette et al., 2011; Brunette et al., 2006; Brunette et al., 2008; Buckley et al., 1999; Drake et al., 2000; George et al., 1995; Lee et al., 1998; Wu et al., 2013; Zimmet et al., 2000). Related to this,

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Mesholam-Gately et al. (2014) have observed, in a population of substance using patients with schizophrenia that in comparison with other antipsychotics, clozapine strengthens the hedonic experience associated with olfactory stimuli. Moreover, Machielsen et al. (2014), assessing the effects of clozapine versus risperidone in patients with schizophrenia and cannabis use disorder, suggested that clozapine may be more efficacious at reducing cannabis use due to its ability to modulate attentional bias to drug cues and its actions on reducing activation within the brain reward circuit. Green et al. (1999) have hypothesized that clozapine's unusual effects may relate to its weak dopamine D2 receptor blockade, coupled with its ability to potentiate the action of norepinephrine in the brain, which together may ameliorate the brain reward circuit dysfunction in these patients.

8. A unifying hypothesis

Converging lines of evidence, as reviewed here, support a shared vulnerability for substance use in patients with (and in those at risk for developing) schizophrenia. Genetic risk (driven especially by genes encoding catecholaminergic signaling within the brain) or an early environmental insult (exemplified by the neonatal ventral hippocampal lesion rat model of schizophrenia) may lead to a dysfunctional mesocorticolimbic brain reward circuit. Such a dysfunctional circuit may lead pre-psychotic adolescents to use substances at greater rates than other adolescents, and the substance use itself may both trigger the onset of schizophrenia and lead to continued substance use. And lastly, even if substance use does not begin prior to the onset of psychosis, the dysregulated circuitry of these individuals leads them to continue to have a high rate of initiation of substance use – and to continue such use once it begins – despite the adverse consequences of use.

This hypothesis aims to unify epidemiological, genetic and neurobiological evidence from both basic and clinical investigations, and offers a potential roadmap for understanding the link between substance use disorders and schizophrenia. Future prospective longitudinal studies (e.g., the on-going Adolescent Brain Cognitive Development Study of the National Institute on Drug Abuse) looking at markers of neurobiological function (e.g., functional brain imaging) prior to the appearance of psychotic symptoms in adolescents who use substances could help uncover the mechanistic underpinnings of these co-occurring disorders. We would suspect that those using substances in adolescence who go on to develop schizophrenia would begin to show potential dysfunctions in brain reward circuitry (e.g., hypoconnectivity, dopamine hypersensitivity) prior to the onset of schizophrenia and substance use during adolescence. Lastly, since substance use disorders and schizophrenia may arise from a common susceptibility in these patients, targeting these disorders together may improve overall outcomes for these difficult-to-treat patients, as suggested by the integrated dual diagnosis treatment framework (Drake et al., 1998).

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Contributors

Dr. Khokhar was responsible for the formulation of the concept of the review in consultation with Dr. Green. All authors contributed to the writing of the review.

Conflict of interest

In the past three years, Dr. Alan Green has received research grants from Alkermes, Novartis and Janssen, and he has also owned stock in Pfizer, Johnson & Johnson and Mylan. He has served as an (uncompensated) consultant to Otsuka and Alkermes, and as a member of a Data Monitoring Board for Lilly. Moreover, he is a co-inventor of one patent (and another patent application) regarding treatment of substance abuse. The other authors do not have any conflicts to disclose.

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