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Unique Effects of Clozapine: A Pharmacological Perspective

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Abstract

Schizophrenia is a heterogenous and severe neuropsychiatric disorder that affects nearly 1% of the population worldwide. Antipsychotic drugs are the mainstay of treatment, but not all patients with schizophrenia respond to treatment with these agents. Clozapine, the first atypical antipsychotic, is a highly effective medication for patients with schizophrenia who do not respond to other antipsychotics. Although clozapine tends not to produce extrapyramidal symptoms, other side effects of the drug (e.g., agranulocytosis, myocarditis, seizures) limit its widespread use. This chapter reviews clozapine's unique clinical effects and unusual pharmacological profile. In addition to its effects in treatment resistant schizophrenia, clozapine has been shown to decrease suicidality, which occurs at an increased rate in patients with schizophrenia. Still preliminary, but consistent data, also suggest that clozapine limits substance use in these patients, an important effect since substance use disorders are common in patients with schizophrenia and are associated with a poor outcome, including an increased risk for suicide and poor response to treatment. We have suggested, from animal studies, that clozapine's apparent ability to limit substance use may occur through its actions as a weak dopamine D2 receptor antagonist, a potent norepinephrine α-2 receptor antagonist and a norepinephrine reuptake inhibitor. Using animal models, we have built combination of agents toward creation of safer clozapine-like drugs to reduce substance use in these patients. Future research into the mechanisms of action of clozapine toward the development of safe clozapine-like agents is of great public health importance.

Introduction

Schizophrenia is a heterogenous and complex neuropsychiatric disorder that affects nearly 1% of the population worldwide and includes a composite of positive, negative and cognitive symptom domains (Andreasen, 2000). The introduction of the antipsychotic drugs, beginning with chlorpromazine in the 1950s dramatically changed the nature of treatment

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Foreword:

We are delighted to contribute this article in honor of Solomon H. Snyder. I (Alan I. Green) was the first medical student to work in his laboratory, just fifty years ago, in the early months of 1967. Sol was then, as he has remained, an inspirational figure, encouraging a naïve student, a history major in college, that he had a talent for scientific research. Sol's many contributions to neuropsychopharmacology, including toward an early understanding of the action of antipsychotic drugs, as noted in the following article, while extraordinary, are at least equaled by his unique ability to launch the careers of dozens of productive scientists. While I have tried over these many years to capture the Snyder gift for inspiration, I have learned that there is only one Sol.

for patients with this severe disorder. Moreover, the realization that effective antipsychotics blocked the dopamine D2 receptor contributed to the development of the dopamine hypothesis of schizophrenia (Snyder, 1976). The seminal paper noting a correlation between potency at the dopamine D2 receptor and clinical potency (Creese, Burt, & Snyder, 1976) further cemented the notion that search for a potent dopamine receptor antagonist was the holy grail for optimal treatment of schizophrenia. The major side effects of the antipsychotics, extrapyramidal symptoms (e.g., muscle rigidity, tremor, tardive dyskinesia), were assumed to be a necessary fellow traveler with an effect antipsychotic drug. The use of chlorpromazine and the medications that followed, all potent dopamine D2 receptor antagonists, allowed many patients to be discharged from asylums, and led to the development of the community mental health center movement. Nonetheless, it was recognized early on that while the antipsychotics were effective, many patients had only a partial response, and for a substantial component of the population of patients with schizophrenia, these “miracle drugs” had almost no effect. This situation seemed to change with the (re)introduction of clozapine, an “atypical” antipsychotic, in 1989 (J. Kane, Honigfeld, Singer, & Meltzer, 1988; J. M. Kane & Correll, 2016; Meltzer, 1997). This chapter will trace the use of clozapine, discuss its unique clinical applicability, and address aspects of its pharmacology that may contribute to its unusual and striking clinical effects.

History of Clozapine

Clozapine was first discovered in 1959 by scientists at Wander Laboratories, who were screening tricyclic compounds for anti-depressant activity and were surprised to discover drugs with a chemical structure comparable to the tricyclic anti-depressants but with antipsychotic properties (Naheed & Green, 2001). Since the prevailing thought at the time was that extrapyramidal side-effects were required for antipsychotic efficacy, clozapine was considered “atypical” or “defective,” which limited initial interest in the compound (Burns, 2001). In the early 1970s, however, Stille and Hippius challenged the prevailing extrapyramidal symptom dogma with data derived from studies in patients given clozapine demonstrating that its antipsychotic efficacy was not dependent on the development of these symptoms (Stille, Lauener, & Eichenberger, 1971). Moreover, they noted that this atypical antipsychotic (which did not produce obvious extrapyramidal effects) had excellent clinical efficacy across multiple symptom domains.

As the use of clozapine spread in Europe, a troubling side effect began to limit its popularity. In a trial in Finland, 16 patients developed agranulocytosis, and 8 of them died from overwhelming infections (de la Chapelle, Kari, Nurminen, & Hernberg, 1977; Idanpaan-Heikkila, Alhava, Olkinuora, & Palva, 1975). Because of this report, use of clozapine was dramatically reduced and research on the drug was stopped. Although it was essentially pulled from the market, some humanitarian use of clozapine continued, especially for patients unresponsive to other drugs, with very careful blood monitoring. Moreover, reports surfaced that many patients that had been responsive to clozapine relapsed when the drug was stopped, increasing the interest in determining whether there was a safe way to use the drug while managing the risk of agranulocytosis (Naheed & Green, 2001).

The publication by Kane et al (1988) , funded by Sandoz, which now owned clozapine, dramatically changed the landscape for use of the drug. This careful investigation of patients who were refractory to other antipsychotics demonstrated the superior efficacy of clozapine over chlorpromazine for such patients – with demonstrated superiority in terms of positive and negative symptoms of psychosis, along with the development of minimal extrapyramidal side effects. Moreover, the frequent blood monitoring within the study demonstrated a way to use clozapine safely.

Sandoz used the findings of the Kane et al (1988) study to support an application to the FDA for use of clozapine in treatment-resistant schizophrenia, with a requirement for blood testing to monitor for the risk for agranulocytosis. With such careful use, including the cessation of use at the first sign of possible agranulocytosis, the rate of agranulocytosis has been reported to be 0.38% (Schulte, 2006).

The re-introduction of clozapine in 1989 dramatically changed the treatment approach for patients with refractory psychosis–suddenly there was a medication that for many at least seemed to decrease psychosis and allow them to be treated as outpatients. With its more widespread use, however, many other potential side effects of clozapine were noted, including weight gain, diabetes, myocarditis and seizures, that, combined with the requirement for frequent blood monitoring, tended to limit the use of this most interesting drug to a very narrow range of patients (Flanagan, 2008; Hodge & Jespersen, 2008). To this day, clozapine is seriously under-prescribed by psychiatrists, with estimates suggesting that only 5–20% of clozapine-eligible patients receive clozapine treatment (Olfson, Gerhard, Crystal, & Stroup, 2016). After the introduction of clozapine, many other “atypical” agents were developed; nonetheless, none of them have met the standard of clozapine for efficacy. This, coupled with the decline in clozapine use over time, has emphasized the need for revisiting the pharmacology of clozapine, and bringing attention back to a drug that may be our best option in treating a variety of schizophrenia and schizophrenia-related disorders.

Clozapine broke the mold of the first generation antipsychotics and displayed clinical efficacy without a potent dopamine D2 receptor blockade and thereby reduced risk for the extrapyramidal side-effects (Fakra & Azorin, 2012). While clozapine still remains the most effective antipsychotic, its mechanisms of action remains elusive (Wenthur & Lindsley, 2013). Attempts to create structurally related compounds have not produced agents that match clozapine’s efficacy. Clozapine is an agent that seems to serendipitously benefit from actions across various neurotransmitter systems. Imaging and pharmacological studies suggest that while typical antipsychotics show high striatal dopamine receptor binding, clozapine does not (Mamo et al., 2004) but seems to be having its effects not only through dopamine receptors, but also at serotonergic, noradrenergic and glutamatergic receptors (Meltzer, Matsubara, & Lee, 1989; Sur et al., 2003). The effects of clozapine have considerably advanced our understanding of the mechanistic underpinnings of schizophrenia, and have given rise to other atypical drugs that act, for example, at serotonin 5-HT2A as well as dopamine D2 receptors (Janssen et al., 1988). Clozapine’s blockade of norepinephrine alpha 2 receptors has also been thought to contribute to its activity (Baldessarini, Huston-Lyons, Campbell, Marsh, & Cohen, 1992; Breier et al., 1994) as have its possible modulatory actions on dysfunctional glutamatergic system (Olney, Newcomer, &

Farber, 1999). In the latter half of this chapter, we will further delineate the pharmacological actions of clozapine with the goal of reconstructing clozapine-like agents for use in indications in which clozapine shows clear superiority over other antipsychotic medications. Prior to that, however, we will describe three special populations of patients with schizophrenia, in which clozapine has demonstrated a unique efficacy, those with: treatment resistance; suicidality; and co-occurring substance use disorders.

Treatment-resistant schizophrenia

As many as 30% of patients with schizophrenia are resistant to treatment with antipsychotic medications (Conley & Kelly, 2001), meaning they show no or partial clinical response to at least two different antipsychotic medications. Treatment-resistant schizophrenia is associated with an increased risk of substance use, suicidal ideation, and a poorer quality of life (Kennedy 2014), and attempts to develop therapies for treatment-resistant schizophrenia have been elusive. But clozapine is uniquely effective in its ability to improve clinical outcomes in patients with treatment resistance schizophrenia. As mentioned above, Kane and colleagues (1988) first evaluated the efficacy of clozapine for treatment resistant schizophrenia. In this controlled clinical trial, patients with schizophrenia (who had a history of poor response to previous trials of antipsychotics) were treated with the typical antipsychotic haloperidol for 6 weeks, and those who failed to show a significant clinical response were then randomly assigned to clozapine or chlorpromazine treatment for another 6 weeks (J. Kane et al., 1988). The patients treated with clozapine showed significantly greater improvements in Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions (CGI) scale scores compared to those treated with chlorpromazine.

Since this iconic study, subsequent experiments have corroborated the findings from Kane and colleagues. For instance, in a randomized double-blind study of the efficacy of clozapine compared to haloperidol, a typical antipsychotic, treatment resistant patients receiving clozapine had significantly lower psychotic symptoms as measured by the Positive and Negative Syndrome Scale (PANSS), as well as fewer days hospitalized for psychiatric complaints, compared to those receiving haloperidol (Rosenheck et al., 1997). A meta-analysis of 12 controlled studies also confirmed that clozapine was more efficacious in reducing psychotic symptoms in patients with treatment resistant schizophrenia, as well as decreasing the risk of extrapyramidal side-effects, compared to typical antipsychotic medications (Chakos, Lieberman, Hoffman, Bradford, & Sheitman, 2001). Moreover, two large-scale clinical trials (Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE] in the US, and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study [CUtLASS] in the UK) both demonstrated that clozapine is the most effective antipsychotic for patients with schizophrenia unresponsive to treatment with other antipsychotic drugs (including those developed after the introduction of clozapine)(Jones et al., 2006; Lewis et al., 2006; Lieberman et al., 2005; Naber & Lambert, 2009). Thus, based on the available data, clozapine continues to be considered the “gold-standard” for patients with treatment resistant schizophrenia, although it continues to be underutilized in general clinical practice.

There has been interest in discovering indicators of preferential response to clozapine that might allow its use prior to multiple treatment trials with other antipsychotics, thus to identify predictors of treatment resistance. Significant predictors of a favorable response to clozapine treatment include younger age, more severe symptoms (as evidence by more days hospitalized for psychiatric reasons prior to schizophrenia diagnosis), a previous suicide attempt, affective symptoms and use of antidepressant medications (Wimberley et al., 2016). Interestingly, treatment resistant schizophrenia has been associated with reduced cortical thickness, including areas of the frontal, parietal, temporal, and occipital lobes (Zugman et al., 2013), which may have clinical relevance as a neural indicator of treatment resistant schizophrenia and minimize the delay between diagnosis and appropriate antipsychotic treatment. Nonetheless, these imaging data have not, to this point been, directly linked to preferential response to clozapine.

Some of the biologic characteristics of treatment resistant schizophrenia may also hint at the possible mechanism behind the efficacy of clozapine. For instance, treatment resistant patients have been demonstrated to have reduced dopamine synthesis (rather than hyperactivity seen in other patients) in the striatum compared to non-resistant patients (Demjaha, Murray, McGuire, Kapur, & Howes, 2012), suggesting that treatment resistant patients may have a distinct form of schizophrenia that is mediated by dysregulated neurotransmitter systems beyond dopamine. Moreover, given the wide spectrum pharmacological action of clozapine, its relatively low affinity for the dopamine D2 receptor, as well as its actions in glutamatergic, serotonergic and noradrenergic systems (Wenthur & Lindsley, 2013), the capacity of clozapine to treat patients with treatment resistant schizophrenia may be linked to the ability of clozapine to alter more than just dopamine synthesis.

Nonetheless, since the precise mechanisms underlying the effectiveness of clozapine for treatment resistant schizophrenia are still poorly understood, some research has also aimed to identify how clozapine treatment alters neurobiological functioning in these patients. Reduced frontal cortical metabolic activity has been consistently associated with an increased response to clozapine treatment (Chung & Remington, 2005), suggesting the frontal cortex may be an important region involved in clozapine’s efficacy. In an attempt to determine the effects of clozapine on cortical metabolic activity, Molina and colleagues (2005) evaluated resting neural metabolic activity in treatment resistant patients prior to and 6 months after clozapine treatment. Clozapine treatment was associated with reductions in prefrontal cortical metabolic activity, as well as reduced basal ganglia metabolic activity. Interestingly, reductions in basal ganglia metabolic activity were associated with reductions in negative symptoms, while reductions in positive symptoms were associated with increased in metabolic activity in the visual cortex. In a follow-up study by these authors, clozapine treatment was associated with enhanced activity in the cingulate cortex, insula, and hippocampus during a cognitive task compared to risperidone treatment (Molina et al., 2008). Thus, clozapine’s unique ability to correct deficits in cortical and limbic regions compared to other antipsychotic medications may be related to its efficacy in treatment resistant patients, but substantially more work is required to fully understand the mechanisms underlying clozapine’s effectiveness for this indication and others.

Suicidality

Patients with schizophrenia are at a significantly high risk for suicide, as approximately 50% of patients attempt suicide, compared to only 1% in the general population, and 10% of patients with schizophrenia die from suicide (Meltzer et al., 2003; Meltzer & Baldessarini, 2003). In an early trial in treatment resistant patients, clozapine treatment was associated with significantly fewer suicide attempts compared to patients treated with typical antipsychotics (Spivak et al., 1998). Later, in the seminal InterSePT trial (International Suicide Prevention Trial), a randomized, international study comparing suicidal behavior in patients at risk of suicide who were treated with either clozapine or olanzapine (thought to be the most effective agent secondary to clozapine), Meltzer and colleagues (2003) showed that suicidal behavior was significantly reduced in patients treated with clozapine compared to those treated with olanzapine. Specifically, fewer clozapine-treated patients attempted suicide and clozapine patients required fewer hospitalizations and rescue interventions related to suicide. A retrospective study looking at inpatients with schizophrenia corroborated these findings; prior to clozapine treatment the rate of suicidal behavior among these patients was 28%, which was reduced to 3% during clozapine treatment (Modestin, Dal Pian, & Agarwalla, 2005). Interestingly, in a subset of patients, discontinuation of clozapine resulted in an increase in suicidal behavior to 18%. Lastly, a small study of 3 patients with schizophrenia further demonstrated that the effects of clozapine discontinuation on suicidal behavior; abrupt discontinuation of clozapine treatment due to side-effects in these patients were rapidly followed by suicide (Patchan, Richardson, Vyas, & Kelly, 2015). Thus, clozapine is exceptionally effective in reducing the risk of suicide in patients with schizophrenia, compared to both typical and atypical antipsychotic medications.

Depression is common in patients with schizophrenia, with up to 80% of patients experiencing depressive symptoms, and is associated with a poorer quality of life, increased risk of both relapse and suicide (Nakajima et al., 2015). The CATIE trial, mentioned above, found that clozapine was more effective than quetiapine in reducing depressive symptoms in patients (Nakajima et al., 2015). Yet, the CATIE trial also found no significant differences between clozapine, olanzapine, and risperidone in reducing symptoms of depression in patients with schizophrenia. Thus, the unique ability of clozapine to reduce suicidal behavior in patients with schizophrenia may not be entirely due to its antidepressant effects.

Little is known regarding the mechanisms behind clozapine’s efficacy in reducing suicidal behavior, but it may be related to clozapine’s effects on norepinephrine, a neurotransmitter thought to be involved in the emergence of depression and commonly targeted by antidepressant medications (Delgado & Moreno, 2000). Indeed, early work by our group giving clozapine to patients with treatment refractory schizophrenia showed that clozapine dramatically and chronically enhances peripheral norepinephrine levels (A. I. Green et al., 1993), which is not observed with haloperidol (Green et al, 1993), or with other typical antipsychotic medications (Spivak et al., 1998). Moreover, other atypical agents, such as risperidone, which also block the norepinephrine α-2 receptor, do not elevate peripheral norepinephrine levels to the extent of clozapine (See, Fido, Maurice, Ibrahim, & Salama, 1999). Moreover, Breier et al (1994) noted a relationship between elevated norepinephrine

levels and overall response to clozapine. Thus, the ability of clozapine to alter neurotransmitter systems other than dopamine, especially clozapine-induced increases in norepinephrine levels, may be partly associated with clozapine's ability to reduce depression (and suicidal behavior) in patients with schizophrenia. Another potential mechanism for the reduction in suicidal behavior by clozapine may be related to clozapine's apparent ability to reduce substance use in patients with schizophrenia, since substance use in these patients is associated with a risk for suicide. Previous studies have suggested that limiting substance use in dual diagnosis patients with schizophrenia may limit suicide since suicidal ideation has been shown to be greater among patients who are currently misusing substances, compared with past or non-substance misusers (Hunt et al., 2006; Kamali et al., 2000). Moreover, our unpublished secondary analyses of the data from the InterSePT study, showing that clozapine was efficacious in reducing the initiation of substance use in patients with schizophrenia who are at a high risk for suicide, suggests another unique subpopulation that would benefit from clozapine.

Substance use in schizophrenia

In still preliminary studies, clozapine does seem to have the unusual ability (among antipsychotics) of decreasing substance use in patients with schizophrenia and co-occurring substance use disorder. The Epidemiologic Catchment Area (ECA) study in the late 1980s made it clear that individuals with schizophrenia have a high rate of substance use disorder, particularly alcohol, cannabis and cocaine – estimated to be 4.6 times the rate in the background population (Regier et al., 1990). Moreover, the rate of tobacco smoking is known to be 70 – 90% in patients with schizophrenia, in face of the decreasing rate of tobacco smoking in the general US population (falling below 20%) (Hartz et al., 2014; Kalman, Morissette, & George, 2005). In fact, it has been estimated that 44% of all cigarettes in the US are smoked by less than 5% of the population – mainly those with severe psychiatric disorders (Lasser et al., 2000). Use of alcohol, cannabis and cocaine have a negative effect on the course of schizophrenia, as defined by increased rates of hospitalization, decreased compliance with medication, increased violence and suicide, and overall increased societal costs (DeQuardo, Carpenter, & Tandon, 1994; Dickey & Azeni, 1996; Henquet et al., 2010; Juckel et al., 2006; Kivlahan, Heiman, Wright, Mundt, & Shupe, 1991; Knudsen & Vilmar, 1984; Linszen, Dingemans, & Lenior, 1994; Negrete & Knapp, 1986; Peralta & Cuesta, 1992; Regier et al., 1990; Sayers et al., 2005; Smith, Barzman, & Pristach, 1997; Swendsen et al., 2012; Treffert, 1978; van Dijk, Koeter, Hijman, Kahn, & van den Brink, 2012).

While the typical antipsychotic drugs (e.g., haloperidol) have clear therapeutic efficacy in treating psychosis in patients with schizophrenia, they do not appear to reduce substance use in patients with schizophrenia and substance use disorder (A. I. Green, Noordsy, Brunette, & O'Keefe, 2008), and may even lead to further use (Bedard, Maheux, Levesque, & Samaha, 2013). Atypical antipsychotics, on the other hand, seem to have varying effects on substance use. While most atypical antipsychotics have modest efficacy toward reducing substance use, we and others have shown that clozapine, unlike typical antipsychotics, appears to substantially decrease alcohol and substance use in this population (Albanese, Khantzian, Murphy, & Green, 1994; Buckley, Thompson, Way, & Meltzer, 1994; Drake, Xie, McHugo,

& Green, 2000; Marcus & Snyder, 1995; Wu, Chen, & Lee, 2013; Zimmet, Strous, Burgess, Kohnstamm, & Green, 2000) and also prevent relapse to alcohol use in those whose alcohol use has remitted (Brunette, Drake, Xie, McHugo, & Green, 2006). The observation that clozapine might decrease substance use was first reported in the mid-1990s, with a series of case reports, retrospective surveys and one naturalistic study (Akerman, Brunette, Noordsy, & Green, 2014; Albanese et al., 1994; Buckley et al., 1994; Drake et al., 2000; Marcus & Snyder, 1995; Wu et al., 2013; Zimmet et al., 2000). The naturalistic study noted a dramatic improvement of alcohol abuse (as well as cannabis use) in patients who had been given clozapine vs. those remaining on a standard (typical) antipsychotic (Drake et al., 2000). Nonetheless, only one randomized trial has been published – involving a small sample of patients with schizophrenia and cannabis use disorder, which indicated that clozapine treatment was associated with a decrease in cannabis use, as compared to treatment with other antipsychotics (Brunette et al., 2011). Thus, the data on clozapine's effects on decreasing substance use are consistent, although a definitive study has not yet been done.

Many studies have investigated whether other atypical antipsychotics share clozapine's ability to limit comorbid alcohol/substance use disorders in patients with schizophrenia. (A. I. Green et al., 2008). While some data exist regarding possible effects of quetiapine, olanzapine and aripiprazole, the overall consensus is that none of the typical or atypical agents also consistently limit substance use in these patients (Akerele & Levin, 2007; Beresford et al., 2005; Brown, Jeffress, Liggin, Garza, & Beard, 2005; Brunette, Dawson, O'Keefe, Buckley, & Green, 2009; A. I. Green et al., 2008; Warsi, Sattar, Bhatia, & Petty, 2005).

Basis of substance use disorder in schizophrenia

In the remainder of this article, we will focus on schizophrenia and co-occurring substance use disorder to begin to delineate the potential basis of the unusual effects of this drug – leading to the possible development of a safer clozapine-like agent. While the story is still unfinished and much research needs to be done, the theories of the basis of the co-occurrence of schizophrenia and substance use disorder may provide some clues. The four main theories of comorbid schizophrenia and substance abuse are the self-medication hypothesis; the cumulative risk factor hypothesis; the stress diathesis theory; and the primary addiction hypothesis.

A common clinical explanation for the use of alcohol and other substances in patients with schizophrenia invokes the "self-medication hypothesis", where the alcohol/substance abuse relates to an attempt by the patient to self-medicate negative symptoms or the extrapyramidal side effects of antipsychotics (Khantzian, 1997; Siris, 1990). While the self-medication hypothesis has some intuitive appeal, the available data do not provide evidence to support this as a causal explanation for the use of alcohol/substances in patients with schizophrenia (Buchanan, Strauss, Breier, Kirkpatrick, & Carpenter, 1997; Cantwell et al., 1999; Hambrecht & Hafner, 1996; Kovasznay et al., 1997; Linszen et al., 1994; Lysaker, Bell, Beam-Goulet, & Milstein, 1994). Substance use, actually, tends to be less common in patients with primarily negative symptoms, and even first episode patients, including those not treated with antipsychotic medications, frequently use substances (Batki, Leontieva,

Dimmock, & Ploutz-Snyder, 2008; Brunette et al., 2017; Buchanan et al., 1997; Tomassi et al., 2017).

The cumulative risk factor hypothesis posits that patients with schizophrenia are more likely to have a substance use problem when combined with certain environmental factors such as socioeconomic status and accessibility to drugs (Mueser et al., 1990). Rosenthal (1970) proposed a similar concept, the stress diathesis theory or the “two-hit” model. Schizophrenia is widely accepted to have an important genetic component, and Rosenthal theorized that genetic factors predicted a risk for disease, but when combined with an environmental stressor (including substance use), could manifest into schizophrenia (Fowles, 1992; Pruessner, Cullen, Aas, & Walker, 2017). Some studies support the diathesis-stress theory with interactions observed between substance (especially cannabis) use and an earlier age of onset of schizophrenia and psychosis (I. W. Green & Glausier, 2016; Linszen et al., 1994).

The fourth hypothesis is the primary addiction hypothesis (Chambers et al., 2001) also known as reward deficiency syndrome hypothesis (Green et al., 1999). Both animal and human studies (in an animal model of schizophrenia and in patients with schizophrenia) find dysfunction in the dopamine-mediated brain reward circuit (Chambers, 2007; Chambers, Krystal, & Self, 2001; Chambers et al., 2013; Fischer, Whitfield-Gabrieli, Roth, Brunette, & Green, 2014; Thompson et al., 2013), which could underlie both schizophrenia and substance abuse (Khokhar, Dwiel, Henricks, Doucette, & Green, 2017).

Our theoretical neurobiologic formulation (A.I. Green, Zimmet, Strous, & Schildkraut, 1999), consistent with Chambers et al., (Chambers et al., 2001) and others (Nisell, Nomikos, & Svensson, 1995) suggests that a high rate of substance use disorders in patients with schizophrenia may be secondary to biological dysfunctions within the dopamine–mediated mesocorticolimbic “brain reward” pathways. Many studies suggest that negative symptoms in patients with schizophrenia are related to reduced activity in dopamine neurons projecting from the ventral tegmental area into the prefrontal cortex (i.e., mesocortical neurons) (Grace, 1991; Moghaddam & Sesack, 1996; Weinberger, 1987). At the same time, other midbrain DA neurons projecting from the ventral tegmental area to the nucleus accumbens (i.e., mesolimbic neurons), which are themselves regulated by neural projections from the prefrontal cortex (Au-Young, Shen, & Yang, 1999; Moghaddam & Sesack, 1996; Pycock, Kerwin, & Carter, 1980), are thought to be hyperactive, leading to the positive symptoms of psychosis (Grace, 1991). Both of these dopaminergic pathways (particularly the mesolimbic) are key elements in the brain reward circuit that is thought both to mediate pleasure, contentment and motivation within everyday life (Fibiger & Phillips, 1988; Gardner, 1997) and to be the locus for the reward-based effects of substances of abuse (Hyman, Malenka, & Nestler, 2006). Interestingly, our group and others have shown in behavioral studies that patients with schizophrenia have impaired olfactory hedonic processing (Folley & Park, 2010; Mesholam-Gately, Gibson, Seidman, & Green, 2014) and we (Fischer et al., 2014) and others have demonstrated a brain reward circuit deficit (including decreased functional connectivity between the nucleus accumbens and the prefrontal cortex) in fMRI studies of such patients.(Fischer et al., 2014; Juckel et al., 2006; Moran, Sampath, Kochunov, & Hong, 2013; Moran, Sampath, Stein, & Hong, 2012; Nielsen, Rostrup, Wulff, Bak, Broberg, et al., 2012; Nielsen, Rostrup, Wulff, Bak, Lublin, et al., 2012; Wint et al., 2005).

This theory (A.I. Green et al., 1999) also proposed that the substances themselves, due to their common action of potentiating dopamine activity, might normalize the brain reward circuit dysfunction while at the same time exacerbating symptoms in the patients. Pilot data has shown that individuals with comorbid cannabis use disorder and schizophrenia have significantly lower resting-state functional activity between the nucleus accumbens and prefrontal cortical brain reward circuit regions when compared to a control group, and that either smoked cannabis or Δ^9-tetrahydrocannabinol (THC) substantially ameliorates the abnormal connectivity. (Fischer et al., 2014).

Pharmacology of Clozapine: Building a safer clozapine?

Why does clozapine limit substance use in patients with schizophrenia – and does it lead to clues about building a safer clozapine-like agent? Clozapine's unique clinical effects (secondary to its broad pharmacological profile that includes a relatively weak blockade at dopamine D2 receptors) may in part involve release of dopamine in the prefrontal cortex (Devoto et al., 2003; A.I. Green et al., 1999). Moreover, because of the apparent modulation of the subcortical mesolimbic dopamine system by the prefrontal cortex (A.I. Green et al., 1999; Moghaddam & Sesack, 1996) the release of dopamine by clozapine in the prefrontal cortex may also result in a decrease of dopamine release in the mesolimbic system, which, when added to its (albeit weak) D2 receptor blocking effects, may contribute to its antipsychotic potential and its ability to reduce substance use (A.I. Green et al., 1999; Moghaddam & Sesack, 1996; Pycock et al., 1980). This combined with our original work on clozapine, where we were struck by the dramatic elevation of plasma norepinephrine in patients treated with the drug, as compared to those treated with haloperidol (A. I. Green et al., 1993), and based on the original work from Svensson et al., (2003), we hypothesized that clozapine might improve the reward dysfunction and thereby making patients less likely to use substances (A. I. Green, Burgess, Dawson, Zimmet, & Strous, 2003; A.I. Green et al., 1999). Thus far, two sets of data seem to suggest this is the case. Machielsen and colleagues recently demonstrated that clozapine (as compared to risperidone) reduces craving for cannabis and decreases insula activation during a cannabis attentional bias task (Machielsen, Veltman, van den Brink, & de Haan, 2014, 2017). Moreover, we showed that clozapine improves olfactory hedonic tone, as compared to typical antipsychotics, in patients with schizophrenia and co-occurring substance use disorder (Mesholam-Gately et al., 2014).

Our group has attempted to deconstruct the pharmacological actions of clozapine related to its effect on substance use in patients with schizophrenia, following up on our theoretical paper suggesting the importance of the ratio of norepinephrine α2 to dopamine D2 receptor blockade (A.I. Green et al., 1999). To do this, we developed a series of studies in rodents, primarily using the Syrian golden hamster and the alcohol preferring P rat. In these studies, we focused most directly on clozapine's weak dopamine D2 receptor blockade, its potent norepinephrine α2 receptor blockade and the ability of clozapine to dramatically increase norepinephrine levels in plasma and brain (Chau, Gulick, Xie, Dawson, & Green, 2010; A. I. Green et al., 1993; A. I. Green et al., 2004; Khokhar, Chau, Dawson, & Green, 2015) to understand its ability to reduce alcohol drinking in patients and in our rodent models.

We first showed that like patients with schizophrenia, acute and chronic treatment with clozapine (and not haloperidol) could reduce alcohol drinking in the Syrian golden hamster and the alcohol preferring P rat (Chau et al., 2010; Chau et al., 2013; A. I. Green et al., 2004). These early studies established the predictive validity for these models in testing the effects of antipsychotic agents since clozapine reduced alcohol drinking whereas haloperidol did not. Moreover, discontinuation of clozapine treatment resulted in a gradual increase in alcohol drinking toward baseline levels (A. I. Green et al., 2004). Lastly, the reductions in alcohol drinking were not accompanied by decreases of sucrose, water or food consumption suggesting that the effects of clozapine were specific to alcohol drinking (Chau et al., 2010). Our subsequent work showed that it was the weak antagonism of dopamine D2 receptors by clozapine that contributed to its ability to reduce alcohol drinking in the hamster (Chau et al., 2011). This was done by adding raclopride (a potent dopamine D2 receptor antagonist) to clozapine; the addition of raclopride significantly blunted clozapine's ability to reduce alcohol drinking in the Syrian golden hamster (Chau et al., 2011).

Beyond its actions on dopamine receptors, however, it may be clozapine's actions on the noradrenergic system, which, when added to (or related to) its ability to release dopamine in the prefrontal cortex, may be of greatest importance in understanding its unique clinical profile, including its effects on alcohol/substance use in patients with schizophrenia. As noted above, clozapine produces striking elevations of NE in the plasma (Breier et al., 1994; A. I. Green et al., 1993) and CSF (Leiberman et al., 1991) in patients, and our findings suggest that this may be explained both by its α-2 receptor antagonism (Ashby & Wang, 1996) as well as its ability to block the reuptake of norepinephrine following synaptic release (Khokhar et al., 2015; Yoshimura et al., 2000). Clozapine's actions on norepinephrine may be particularly relevant given the suggestions that norepinephrine may potentiate functioning of the dopamine-mediated "reward system" by decreasing the "noise" of basal firing patterns (i.e., by slowing and deregularizing firing) in ventral tegmental area dopamine neurons (with resultant increase in signal detection) (Grenhoff & Svensson, 1989; Nisell et al., 1995). Even as we began to understand the effects of clozapine related to its ability to reduce substance use, however, we were still not able to use this information to inform treatment. This led to a line of translational research in our laboratory related to designing improved medications for use in this difficult to treat population.

Specifically, we have attempted to reconstruct some of the actions of clozapine, using other antipsychotics currently available on the market. In the first of these studies, we showed that the addition of the norepinephrine reuptake inhibitor desipramine to risperidone (an atypical antipsychotic that is a potent dopamine D2 receptor antagonist, as well as a potent norepinephrine α-2 receptor antagonist but does not reduce substance use in patients or in our animal models) significantly improved risperidone's ability to reduce alcohol drinking in the Syrian golden hamster (Gulick, Chau, Khokhar, Dawson, & Green, 2014). In this study, low doses of risperidone were used to approximate the weak dopamine D2 blockade seen with clozapine. Following up on these findings with another related atypical antipsychotic, paliperidone, the primary metabolite of risperidone, with similar effects on dopamine and noradrenergic systems, we showed that the addition of desipramine to paliperidone resulted in significant decreases in alcohol drinking in the Syrian golden hamster; consistent with this, the combination of paliperidone and desipramine also markedly reduced alcohol

drinking in the alcohol preferring rat, resulting in almost a complete inhibition of initiation of alcohol drinking in the P rat (Chau, Khokhar, Gulick, Dawson, & Green, 2015). In these studies, neither the desipramine, nor the low doses of paliperidone alone, were sufficient to reduce alcohol drinking significantly, but the combination of the two drugs was able to do so, suggesting that modulation through both the dopaminergic and noradrenergic mechanisms is required for this effect. Lastly, our recently published findings with iloperidone, an antipsychotic with an α-2/D2 receptor antagonism ratio similar to that of clozapine (Kalkman & Loetscher, 2003), shows remarkable efficacy for reducing alcohol drinking in the hamster (almost to the same extent as clozapine), and this effect can be enhanced by the addition of desipramine, but not idazoxan (an α-2 antagonist) (Khokhar & Green, 2016). The lack of additional effect of idazoxan suggests that since iloperidone acts as a potent norepinephrine α-2 receptor antagonist, the further addition of another α-2 antagonist does not enhance iloperidone's ability to reduce alcohol drinking. Lastly, this reconstruction approach has also shown that even a typical antipsychotic that lacks any ability to reduce alcohol drinking by itself, haloperidol, can be converted to an agent that does so by the addition of desipramine and idazoxan (Khokhar et al., 2015). In this study, a low dose of haloperidol was combined with norepinephrine reuptake inhibition as well as alpha-2 antagonism, and this combination resulted in significant decreases in alcohol drinking in the hamster.

Based on these findings, we have begun to translate the theoretical clozapine reconstruction approach to clinical trials, where we have recently shown that a combination of quetiapine (a weak dopamine D2 receptor antagonist, whose primary metabolite, desalkylquetiapine, is a norepinephrine reuptake inhibitor) and mirtazapine (a norephinephrine α-2 receptor antagonist) significantly reduced alcohol in heavy drinkers (Brunette, Akerman, Dawson, O'Keefe, & Green, 2016). Planned studies by our group will test the effects of other clozapine-like combinations on alcohol and substance use in patients with schizophrenia, while further animal research is aiming to identify the exact neural underpinnings of substance use in this population toward new treatment development to improve outcomes for these patients.

Conclusion

Given the disturbing side effect profile of clozapine, however, even with its superior efficacy for treatment resistant schizophrenia, for suicidality in patients with schizophrenia and its apparent ability to decrease substance use in these patients, its use is limited (only around 5% of patients with schizophrenia use clozapine). Many post clozapine agents that have been introduced since the mid-1990s provide little evidence that any of them are as effective as clozapine for refractory psychosis, for dealing with suicidality or for decreasing substance use in patients with schizophrenia. Our focus on the "balance" of noradrenergic and dopaminergic actions of clozapine appears to give clues to its unusual effect in decreasing substance use. Whether this research, enabled by the availability of animal models of alcohol drinking, applies as well to clozapine's unique effects on treatment refractory patients or in those at risk of suicide is not clear. Our own research program is beginning to move into study of animal models of schizophrenia to provide further clues (Khokhar & Todd, 2017). Without question, though, given the unique clinical effects of clozapine, as well as its

continued underutilization, future research aimed at creating clozapine-like agents as well as studying the neurobiological underpinnings of clozapine's efficacy are of great public health importance.

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Conflict of Interest: In the past three years, Dr. Alan Green has received grants from Alkermes, Novartis and Janssen to support research studies, and he has served as an (uncompensated) consultant to Otsuka and Alkermes, and as a member (uncompensated) 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.

References

Akerele E, & Levin FR (2007). Comparison of olanzapine to risperidone in substance-abusing individuals with schizophrenia. Am J Addict, 16(4), 260–268. doi:10.1080/10550490701389658 [PubMed: 17661193]

Akerman SC, Brunette MF, Noordsy DL, & Green AI (2014). Pharmacotherapy of Co-Occurring Schizophrenia and Substance Use Disorders. Curr Addict Rep, 1(4), 251–260. doi:10.1007/s40429-014-0034-7 [PubMed: 27226947]

Albanese MJ, Khantzian EJ, Murphy SL, & Green AI (1994). Decreased substance use in chronically psychotic patients treated with clozapine. Am J Psychiatry, 151(5), 780–781.

Andreasen NC (2000). Schizophrenia: the fundamental questions. Brain Res Brain Res Rev, 31(2-3), 106–112. [PubMed: 10719138]

Ashby CR Jr., & Wang RY (1996). Pharmacological actions of the atypical antipsychotic drug clozapine: a review. Synapse, 24(4), 349–394. doi:10.1002/(SICI)1098-2396(199612)24:4<349::AID-SYN5>3.0.CO;2-D [pii] 10.1002/(SICI)1098-2396(199612)24:4<349::AID-SYN5>3.0.CO;2-D [PubMed: 10638826]

Au-Young SM, Shen H, & Yang CR (1999). Medial prefrontal cortical output neurons to the ventral tegmental area (VTA) and their responses to burst-patterned stimulation of the VTA: neuroanatomical and in vivo electrophysiological analyses. Synapse, 34(4), 245–255. [PubMed: 10529719]

Baldessarini RJ, Huston-Lyons D, Campbell A, Marsh E, & Cohen BM (1992). Do central antiadrenergic actions contribute to the atypical properties of clozapine? Br J Psychiatry Suppl (17), 12–16.

Batki SL, Leontieva L, Dimmock JA, & Ploutz-Snyder R (2008). Negative symptoms are associated with less alcohol use, craving, and "high" in alcohol dependent patients with schizophrenia. Schizophr Res, 105(1-3), 201–207. doi:10.1016/j.schres.2008.06.020 [PubMed: 18701256]

Bedard AM, Maheux J, Levesque D, & Samaha AN (2013). Prior haloperidol, but not olanzapine, exposure augments the pursuit of reward cues: implications for substance abuse in schizophrenia. Schizophr Bull, 39(3), 692–702. doi:10.1093/schbul/sbs077 [PubMed: 22927669]

Beresford TP, Clapp L, Martin B, Wiberg JL, Alfers J, & Beresford HF (2005). Aripiprazole in schizophrenia with cocaine dependence: a pilot study. J Clin Psychopharmacol, 25(4), 363–366. [PubMed: 16012280]

Breier A, Buchanan RW, Waltrip RW 2nd, Listwak S, Holmes C, & Goldstein DS (1994). The effect of clozapine on plasma norepinephrine: relationship to clinical efficacy. Neuropsychopharmacology, 10(1), 1–7. doi:10.1038/npp.1994.1 [PubMed: 8179790]

Brown ES, Jeffress J, Liggin JD, Garza M, & Beard L (2005). Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. The Journal of clinical psychiatry, 66(6), 756–760. [PubMed: 15960570]

Brunette MF, Akerman SC, Dawson R, O'Keefe CD, & Green AI (2016). An open-label pilot study of quetiapine plus mirtazapine for heavy drinkers with alcohol use disorder. Alcohol, 53, 45–50. doi:10.1016/j.alcohol.2016.02.006 [PubMed: 27256763]

Brunette MF, Dawson R, O'Keefe C, Buckley P, & Green AI (2009). An open label study of quetiapine in patients with schizophrenia and alcohol disorders. Ment. Health Subst. Use, 2(3), 203–211.

Brunette MF, Dawson R, O'Keefe CD, Narasimhan M, Noordsy DL, Wojcik J, & Green AI (2011). A randomized trial of clozapine vs. other antipsychotics for cannabis use disorder in patients with schizophrenia. Journal of Dual Diagnosis, 7(1-2), 50–63. doi:10.1080/15504263.2011.570118 [PubMed: 25914610]

Brunette MF, Drake RE, Xie H, McHugo GJ, & Green AI (2006). Clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. Schizophr Bull, 32(4), 637–643. doi:10.1093/schbul/sb1003 [PubMed: 16782758]

Brunette MF, Mueser KT, Babbin S, Meyer-Kalos P, Rosenheck R, Correll CU, … Kane JM (2017). Demographic and clinical correlates of substance use disorders in first episode psychosis. Schizophr Res. doi:10.1016/j.schres.2017.06.039

Buchanan RW, Strauss ME, Breier A, Kirkpatrick B, & Carpenter WT Jr. (1997). Attentional impairments in deficit and nondeficit forms of schizophrenia. Am J Psychiatry, 154(3), 363–370. doi:10.1176/ajp.154.3.363 [PubMed: 9054784]

Buckley P, Thompson P, Way L, & Meltzer HY (1994). Substance abuse among patients with treatment-resistant schizophrenia: characteristics and implications for clozapine therapy. Am J Psychiatry, 151(3), 385–389. [PubMed: 8109646]

Burns MJ (2001). The pharmacology and toxicology of atypical antipsychotic agents. J Toxicol Clin Toxicol, 39(1), 1–14. [PubMed: 11327216]

Cantwell R, Brewin J, Glazebrook C, Dalkin T, Fox R, Medley I, & Harrison G (1999). Prevalence of substance misuse in first-episode psychosis. Br J Psychiatry, 174, 150–153. [PubMed: 10211169]

Chakos M, Lieberman J, Hoffman E, Bradford D, & Sheitman B (2001). Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry, 158(4), 518–526. doi:10.1176/appi.ajp.158.4.518 [PubMed: 11282684]

Chambers RA (2007). Animal Modeling and Neurocircuitry of Dual Diagnosis. Journal of Dual Diagnosis, 3(2), 19–29. doi:10.1300/J374v03n02_04 [PubMed: 20585464]

Chambers RA, Krystal JH, & Self DW (2001). A neurobiological basis for substance abuse comorbidity in schizophrenia. Biol Psychiatry, 50(2), 71–83. doi:S0006322301011349 [pii] [PubMed: 11526998]

Chambers RA, McClintick JN, Sentir AM, Berg SA, Runyan M, Choi KH, & Edenberg HJ (2013). Cortical-striatal gene expression in neonatal hippocampal lesion (NVHL)-amplified cocaine sensitization. Genes, brain, and behavior, 12(5), 564–575. doi:10.1111/gbb.12051

Chau DT, Ahmed J, Wang TT, Xie H, Dawson R, & Green AI (2011). Raclopride lessens the ability of clozapine to suppress alcohol drinking in Syrian golden hamsters. Neuropharmacology, 61(4), 646–652. doi:S0028-3908(11)00187-0 [pii] 10.1016/j.neuropharm.2011.05.007 [PubMed: 21619888]

Chau DT, Gulick D, Xie H, Dawson R, & Green AI (2010). Clozapine chronically suppresses alcohol drinking in Syrian golden hamsters. Neuropharmacology, 58(2), 351–356. doi:10.1016/j.neuropharm.2009.10.006 [PubMed: 19895824]

Chau DT, Khokhar JY, Dawson R, Ahmed J, Xie H, & Green AI (2013). The comparative effects of clozapine versus haloperidol on initiation and maintenance of alcohol drinking in male alcohol-preferring P rat. Alcohol, 47(8), 611–618. doi:10.1016/j.alcohol.2013.10.002 [PubMed: 24280363]

Chau DT, Khokhar JY, Gulick D, Dawson R, & Green AI (2015). Desipramine enhances the ability of paliperidone to decrease alcohol drinking. J Psychiatr Res, 69, 9–18. doi:10.1016/j.jpsychires.2015.07.010 [PubMed: 26343589]

Chung C, & Remington G (2005). Predictors and markers of clozapine response. Psychopharmacology, 179(2), 317–335. doi:10.1007/s00213-005-2174-x [PubMed: 15717209]

Conley RR, & Kelly DL (2001). Management of treatment resistance in schizophrenia. Biol Psychiatry, 50(11), 898–911. [PubMed: 11743944]

Creese I, Burt DR, & Snyder SH (1976). Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science, 192(4238), 481–483. [PubMed: 3854]

de la Chapelle A, Kari C, Nurminen M, & Hernberg S (1977). Clozapine-induced agranulocytosis. A genetic and epidemiologic study. Hum Genet, 37(2), 183–194. [PubMed: 885538]

Delgado PL, & Moreno FA (2000). Role of norepinephrine in depression. The Journal of clinical psychiatry, 61 Suppl 1, 5–12.

Demjaha A, Murray RM, McGuire PK, Kapur S, & Howes OD (2012). Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. Am J Psychiatry, 169(11), 1203–1210. doi:10.1176/appi.ajp.2012.12010144 [PubMed: 23034655]

DeQuardo JR, Carpenter CF, & Tandon R (1994). Patterns of substance abuse in schizophrenia: nature and significance. J Psychiatr Res, 28(3), 267–275. [PubMed: 7932286]

Devoto P, Flore G, Vacca G, Pira L, Arca A, Casu MA, … Gessa GL (2003). Co-release of noradrenaline and dopamine from noradrenergic neurons in the cerebral cortex induced by clozapine, the prototype atypical antipsychotic. Psychopharmacology (Berl), 167(1), 79–84. [PubMed: 12632247]

Dickey B, & Azeni H (1996). Persons with dual diagnoses of substance abuse and major mental illness: their excess costs of psychiatric care. American Journal of Public Health, 86(973–977). [PubMed: 8669521]

Drake RE, Xie H, McHugo GJ, & Green AI (2000). The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. Schizophr Bull, 26(2), 441–449. [PubMed: 10885642]

Fakra E, & Azorin JM (2012). Clozapine for the treatment of schizophrenia. Expert Opin Pharmacother, 13(13), 1923–1935. doi:10.1517/14656566.2012.709235 [PubMed: 22803789]

Fibiger HC, & Phillips AG (1988). Mesocorticolimbic dopamine systems and reward. Ann N YAcad Sci, 537, 206–215.

Fischer AS, Whitfield-Gabrieli S, Roth RM, Brunette MF, & Green AI (2014). Impaired Functional Connectivity of Brain Reward Circuitry in Patients with Schizophrenia and Cannabis Use Disorder: Effects of Cannabis and THC. Schizophr Res, Sep;158(1-3), 176–182. doi:j.schres.2014.04.033

Flanagan RJ (2008). Side effects of clozapine and some other psychoactive drugs. Curr Drug Saf, 3(2), 115–122. [PubMed: 18690989]

Folley BS, & Park S (2010). Relative food preference and hedonic judgments in schizophrenia. Psychiatry Res, 175(1-2), 33–37. doi:10.1016/j.psychres.2008.07.026 [PubMed: 19931919]

Fowles DC (1992). Schizophrenia: diathesis-stress revisited. Annu Rev Psychol, 43, 303–336. doi:10.1146/annurev.ps.43.020192.001511 [PubMed: 1539945]

Gardner EL (1997). Brain reward mechanisms In Lowinson J, Ruiz P, Millman R, & Langrod J (Eds.), Substance Abuse: a Comprehensive Texbook (pp. 61–85). Baltimore: Williams & Wilkins.

Grace AA (1991). Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience, 41(1), 1–24. [PubMed: 1676137]

Green AI, Alam MY, Sobieraj JT, Pappalardo KM, Waternaux C, Salzman C, … Schildkraut JJ (1993). Clozapine response and plasma catecholamines and their metabolites. Psychiatry Res, 46(2), 139–149. [PubMed: 8483973]

Green AI, Burgess ES, Dawson R, Zimmet SV, & Strous RD (2003). Alcohol and cannabis use in schizophrenia: effects of clozapine vs. risperidone. Schizophr Res, 60(1), 81–85. [PubMed: 12505141]

Green AI, Chau DT, Keung WM, Dawson R, Mesholam RI, & Schildkraut JJ (2004). Clozapine reduces alcohol drinking in Syrian golden hamsters. Psychiatry Res, 128(1), 9–20. [PubMed: 15450910]

Green AI, Noordsy DL, Brunette MF, & O'Keefe C (2008). Substance abuse and schizophrenia: pharmacotherapeutic intervention. J Subst Abuse Treat, 34(1), 61–71. doi:10.1016/j.jsat.2007.01.008 [PubMed: 17574793]

Green AI, Zimmet SV, Strous RD, & Schildkraut JJ (1999). Clozapine for comorbid substance use disorder and schizophrenia: do patients with schizophrenia have a reward-deficiency syndrome that can be ameliorated by clozapine? Harv Rev Psychiatry, 6(6), 287–296. [PubMed: 10370435]

Green IW, & Glausier JR (2016). Different Paths to Core Pathology: The Equifinal Model of the Schizophrenia Syndrome. Schizophr Bull, 42(3), 542–549. doi:10.1093/schbul/sbv136 [PubMed: 26392629]

Grenhoff J, & Svensson TH (1989). Clonidine modulates dopamine cell firing in rat ventral tegmental area. Eur. J. Pharmacol, 165, 11–18. [PubMed: 2569981]

Gulick D, Chau DT, Khokhar JY, Dawson R, & Green AI (2014). Desipramine enhances the ability of risperidone to decrease alcohol intake in the Syrian golden hamster. Psychiatry Res, 218(3), 329–334. doi:10.1016/j.psychres.2014.04.038 [PubMed: 24836200]

Hambrecht M, & Hafner H (1996). Substance abuse and the onset of schizophrenia. Biol Psychiatry, 40(11), 1155–1163. [PubMed: 8931919]

Hartz SM, Pato CN, Medeiros H, Cavazos-Rehg P, Sobell JL, Knowles JA, … Genomic Psychiatry Cohort, C. (2014). Comorbidity of severe psychotic disorders with measures of substance use. JAMA Psychiatry, 71(3), 248–254. doi:10.1001/jamapsychiatry.2013.3726 [PubMed: 24382686]

Henquet C, van Os J, Kuepper R, Delespaul P, Smits M, Campo JA, & Myin-Germeys I (2010). Psychosis reactivity to cannabis use in daily life: an experience sampling study. Br J Psychiatry, 196(6), 447–453. [PubMed: 20513854]

Hodge K, & Jespersen S (2008). Side-effects and treatment with clozapine: a comparison between the views of consumers and their clinicians. Int J Ment Health Nurs, 17(1), 2–8. doi:10.1111/j.1447-0349.2007.00506.x [PubMed: 18211398]

Hunt IM, Kapur N, Windfuhr K, Robinson J, Bickley H, Flynn S, … Homicide by People with Mental, I. (2006). Suicide in schizophrenia: findings from a national clinical survey. J Psychiatr Pract, 12(3), 139–147. [PubMed: 16732132]

Hyman SE, Malenka RC, & Nestler EJ (2006). Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci, 29, 565–598. [PubMed: 16776597]

Idanpaan-Heikkila J, Alhava E, Olkinuora M, & Palva I (1975). Letter: Clozapine and agranulocytosis. Lancet, 2(7935), 611.

Janssen PA, Niemegeers CJ, Awouters F, Schellekens KH, Megens AA, & Meert TF (1988). Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin-S2 and dopamine-D2 antagonistic properties. J Pharmacol Exp Ther, 244(2), 685–693. [PubMed: 2450200]

Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, … Lewis SW (2006). Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry, 63(10), 1079–1087. doi:10.1001/archpsyc.63.10.1079 [PubMed: 17015810]

Juckel G, Schlagenhauf F, Koslowski M, Wustenberg T, Villringer A, Knutson B, … Heinz A (2006). Dysfunction of ventral striatal reward prediction in schizophrenia. Neuroimage, 29(2), 409–416. doi:10.1016/j.neuroimage.2005.07.051 [PubMed: 16139525]

Kalkman HO, & Loetscher E (2003). alpha2C-Adrenoceptor blockade by clozapine and other antipsychotic drugs. European journal of pharmacology, 462(1-3), 33–40. [PubMed: 12591093]

Kalman D, Morissette SB, & George TP (2005). Co-morbidity of smoking in patients with psychiatric and substance use disorders. Am J Addict, 14(2), 106–123. doi:10.1080/10550490590924728 [PubMed: 16019961]

Kamali M, Kelly L, Gervin M, Browne S, Larkin C, & O'Callaghan E (2000). The prevalence of comorbid substance misuse and its influence on suicidal ideation among in-patients with schizophrenia. Acta Psychiatr Scand, 101(6), 452–456. [PubMed: 10868468]

Kane J, Honigfeld G, Singer J, & Meltzer H (1988). Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry, 45(9), 789–796. [PubMed: 3046553]

Kane JM, & Correll CU (2016). The Role of Clozapine in Treatment-Resistant Schizophrenia. JAMA Psychiatry, 73(3), 187–188. doi:10.1001/jamapsychiatry.2015.2966 [PubMed: 26841681]

Khantzian EJ (1997). The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. Harv Rev Psychiatry, 4(5), 231–244. doi:10.3109/10673229709030550 [PubMed: 9385000]

Khokhar JY, Chau DT, Dawson R, & Green AI (2015). Clozapine reconstructed: Haloperidol's ability to reduce alcohol intake in the Syrian golden hamster can be enhanced through noradrenergic modulation by desipramine and idazoxan. Drug and alcohol dependence, 152, 277–281. doi:10.1016/j.drugalcdep.2015.04.003 [PubMed: 25979645]

Khokhar JY, Dwiel LL, Henricks AM, Doucette WT, & Green AI (2017). The link between schizophrenia and substance use disorder: A unifying hypothesis. Schizophr Res. doi:10.1016/j.schres.2017.04.016

Khokhar JY, & Green AI (2016). Effects of iloperidone, combined with desipramine, on alcohol drinking in the Syrian golden hamster. Neuropharmacology, 105, 25–34. doi:10.1016/j.neuropharm.2016.01.017 [PubMed: 26796639]

Khokhar JY, & Todd TP (2017). Behavioral predictors of alcohol drinking in a neurodevelopmental rat model of schizophrenia and co-occurring alcohol use disorder. Schizophr Res. doi:10.1016/j.schres.2017.02.029

Kivlahan DR, Heiman JR, Wright RC, Mundt JW, & Shupe JA (1991). Treatment cost and rehospitalization rate in schizophrenic outpatients with a history of substance abuse. Hosp Community Psychiatry, 42(6), 609–614. [PubMed: 1864571]

Knudsen P, & Vilmar T (1984). Cannabis and neuroleptic agents in schizophrenia. Acta Psychiatr Scand, 69(2), 162–174. [PubMed: 6142585]

Kovasznay B, Fleischer J, Tanenberg-Karant M, Jandorf L, Miller AD, & Bromet E (1997). Substance use disorder and the early course of illness in schizophrenia and affective psychosis. Schizophr Bull, 23(2), 195–201. [PubMed: 9165630]

Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, & Bor DH (2000). Smoking and mental illness: A population-based prevalence study. JAMA, 284(20), 2606–2610. [PubMed: 11086367]

Leiberman J, Johns C, Pollack S, Bookstein P, Cooper T, Ladorola M, & Kane J (1991). Biochemical effects of clozapine in cerebrospinal fluid of patients of schizophrenia In Tammiga C & Schultz S (Eds.), Schizophrenia Research (pp. 341–349). New York: Raven Press.

Lewis SW, Barnes TR, Davies L, Murray RM, Dunn G, Hayhurst KP, … Jones PB (2006). Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull, 32(4), 715–723. doi:10.1093/schbul/sbj067 [PubMed: 16540702]

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, … Clinical Antipsychotic Trials of Intervention Effectiveness, I. (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med, 353(12), 1209–1223. doi:10.1056/NEJMoa051688 [PubMed: 16172203]

Linszen DH, Dingemans PM, & Lenior ME (1994). Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry, 51(4), 273–279. [PubMed: 8161287]

Lysaker P, Bell M, Beam-Goulet J, & Milstein R (1994). Relationship of positive and negative symptoms to cocaine abuse in schizophrenia. J Nerv Ment Dis, 182(2), 109–112. [PubMed: 8308528]

Machielsen MW, Veltman DJ, van den Brink W, & de Haan L (2014). The effect of clozapine and risperidone on attentional bias in patients with schizophrenia and a cannabis use disorder: An fMRI study. Journal of psychopharmacology, 28(7), 633–642. doi:10.1177/0269881114527357 [PubMed: 24646809]

Machielsen MW, Veltman DJ, van den Brink W, & de Haan L (2017). Comparing the effect of clozapine and risperidone on cue reactivity in male patients with schizophrenia and a cannabis use disorder: A randomized fMRI study. Schizophr Res. doi:10.1016/j.schres.2017.03.030

Mamo D, Kapur S, Shammi CM, Papatheodorou G, Mann S, Therrien F, & Remington G (2004). A PET study of dopamine D2 and serotonin 5-HT2 receptor occupancy in patients with schizophrenia treated with therapeutic doses of ziprasidone. Am J Psychiatry, 161(5), 818–825. doi:10.1176/appi.ajp.161.5.818 [PubMed: 15121646]

Marcus P, & Snyder R (1995). Reduction of comorbid substance abuse with clozapine. Am J Psychiatry, 152(6), 959.

Meltzer HY (1997). Treatment-resistant schizophrenia--the role of clozapine. Curr Med Res Opin, 14(1), 1–20. doi:10.1185/03007999709113338 [PubMed: 9524789]

Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, … International Suicide Prevention Trial Study, G. (2003). Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry, 60(1), 82–91. [PubMed: 12511175]

Meltzer HY, & Baldessarini RJ (2003). Reducing the risk for suicide in schizophrenia and affective disorders. The Journal of clinical psychiatry, 64(9), 1122–1129. [PubMed: 14628990]

Meltzer HY, Matsubara S, & Lee JC (1989). Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. J Pharmacol Exp Ther, 251(1), 238–246. [PubMed: 2571717]

Mesholam-Gately RI, Gibson LE, Seidman LJ, & Green AI (2014). Schizophrenia and co-occurring substance use disorder: reward, olfaction and clozapine. Schizophr Res, 155(1-3), 45–51. doi:10.1016/j.schres.2014.03.002 [PubMed: 24685823]

Modestin J, Dal Pian D, & Agarwalla P (2005). Clozapine diminishes suicidal behavior: a retrospective evaluation of clinical records. The Journal of clinical psychiatry, 66(4), 534–538. [PubMed: 15816798]

Moghaddam B, & Sesack SR (1996). Cellular interactions in the prefrontal cortex: a major focus of schizophrenia research In Dickstein L, Riba M, & Oldham J (Eds.), American Psychiatric Press Review of Psychiatry (pp. 351–372). Washington, D.C.: American Psychiatric Association.

Molina V, Gispert JD, Reig S, Sanz J, Pascau J, Santos A, … Palomo T (2005). Cerebral metabolic changes induced by clozapine in schizophrenia and related to clinical improvement. Psychopharmacology, 178(1), 17–26. doi:10.1007/s00213-004-1981-9 [PubMed: 15365682]

Molina V, Tamayo P, Montes C, De Luxan A, Martin C, Rivas N, … Dominguez-Gil A (2008). Clozapine may partially compensate for task-related brain perfusion abnormalities in risperidone-resistant schizophrenia patients. Prog Neuropsychopharmacol Biol Psychiatry, 32(4), 948–954. doi:10.1016/j.pnpbp.2007.12.028 [PubMed: 18262704]

Moran LV, Sampath H, Kochunov P, & Hong LE (2013). Brain circuits that link schizophrenia to high risk of cigarette smoking. Schizophr Bull, 39(6), 1373–1381. doi:10.1093/schbul/sbs149 [PubMed: 23236076]

Moran LV, Sampath H, Stein EA, & Hong LE (2012). Insular and anterior cingulate circuits in smokers with schizophrenia. Schizophr Res, 142(1-3), 223–229. doi:10.1016/j.schres.2012.08.033 [PubMed: 23021898]

Mueser KT, Yarnold PR, Levinson DF, Singh H, Bellack AS, Kee K, … Yadalam KG (1990). Prevalence of substance abuse in schizophrenia: demographic and clinical correlates. Schizophr Bull, 16(1), 31–56. [PubMed: 2333480]

Naber D, & Lambert M (2009). The CATIE and CUtLASS studies in schizophrenia: results and implications for clinicians. CNS Drugs, 23(8), 649–659. doi:10.2165/00023210-200923080-00002 [PubMed: 19594194]

Naheed M, & Green B (2001). Focus on clozapine. Curr Med Res Opin, 17(3), 223–229. doi:10.1185/0300799039117069 [PubMed: 11900316]

Nakajima S, Takeuchi H, Fervaha G, Plitman E, Chung JK, Caravaggio F, … Graff-Guerrero A (2015). Comparative efficacy between clozapine and other atypical antipsychotics on depressive symptoms in patients with schizophrenia: analysis of the CATIE phase 2E data. Schizophr Res, 161(2-3), 429–433. doi:10.1016/j.schres.2014.12.024 [PubMed: 25556080]

Negrete JC, & Knapp WP (1986). The effects of cannabis use on the clinical condition of schizophrenics. NIDA Res Monogr, 67, 321–327. [PubMed: 3092086]

Nielsen MO, Rostrup E, Wulff S, Bak N, Broberg BV, Lublin H, … Glenthoj B (2012). Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. Arch Gen Psychiatry, 69(12), 1195–1204. doi:10.1001/archgenpsychiatry.2012.847 [PubMed: 22868877]

Nielsen MO, Rostrup E, Wulff S, Bak N, Lublin H, Kapur S, & Glenthoj B (2012). Alterations of the brain reward system in antipsychotic naive schizophrenia patients. Biol Psychiatry, 71(10), 898–905. doi:10.1016/j.biopsych.2012.02.007 [PubMed: 22418013]

Nisell M, Nomikos GG, & Svensson TH (1995). Nicotine dependence, midbrain dopamine systems and psychiatric disorders. Pharmacol Toxicol, 76(3), 157–162. [PubMed: 7617539]

Olfson M, Gerhard T, Crystal S, & Stroup TS (2016). Clozapine for Schizophrenia: State Variation in Evidence-Based Practice. Psychiatr Serv, 67(2), 152. doi:10.1176/appi.ps.201500324 [PubMed: 26522679]

Olney JW, Newcomer JW, & Farber NB (1999). NMDA receptor hypofunction model of schizophrenia. J Psychiatr Res, 33(6), 523–533. [PubMed: 10628529]

Patchan KM, Richardson C, Vyas G, & Kelly DL (2015). The risk of suicide after clozapine discontinuation: Cause for concern. Ann Clin Psychiatry, 27(4), 253–256. [PubMed: 26554366]

Peralta V, & Cuesta MJ (1992). Influence of cannabis abuse on schizophrenic psychopathology. Acta Psychiatr Scand, 85(2), 127–130. [PubMed: 1543037]

Pruessner M, Cullen AE, Aas M, & Walker EF (2017). The neural diathesis-stress model of schizophrenia revisited: An update on recent findings considering illness stage and neurobiological and methodological complexities. Neurosci Biobehav Rev, 73, 191–218. doi:10.1016/j.neubiorev.2016.12.013 [PubMed: 27993603]

Pycock CJ, Kerwin RW, & Carter CJ (1980). Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. Nature, 286(5768), 74–76. [PubMed: 7393327]

Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, & Goodwin FK (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA, 264(19), 2511–2518. [PubMed: 2232018]

Rosenheck R, Cramer J, Xu W, Thomas J, Henderson W, Frisman L, … Charney D (1997). A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. N Engl J Med, 337(12), 809–815. doi:10.1056/NEJM199709183371202 [PubMed: 9295240]

Sayers SL, Campbell EC, Kondrich J, Mann SC, Cornish J, O'Brien C, & Caroff SN (2005). Cocaine abuse in schizophrenic patients treated with olanzapine versus haloperidol. J Nerv Ment Dis, 193(6), 379–386. [PubMed: 15920378]

Schulte P (2006). Risk of clozapine-associated agranulocytosis and mandatory white blood cell monitoring. Ann Pharmacother, 40(4), 683–688. doi:10.1345/aph.1G396 [PubMed: 16595571]

See RE, Fido AA, Maurice M, Ibrahim MM, & Salama GM (1999). Risperidone-induced increase of plasma norepinephrine is not correlated with symptom improvement in chronic schizophrenia. Biol Psychiatry, 45(12), 1653–1656. [PubMed: 10376128]

Siris SG (1990). Pharmacological treatment of substance-abusing schizophrenic patients. Schizophr Bull, 16(1), 111–122. [PubMed: 1970669]

Smith CM, Barzman D, & Pristach CA (1997). Effect of patient and family insight on compliance of schizophrenic patients. J Clin Pharmacol, 37(2), 147–154. [PubMed: 9055141]

Snyder SH (1976). The dopamine hypothesis of schizophrenia: focus on the dopamine receptor. Am J Psychiatry, 133(2), 197–202. doi:10.1176/ajp.133.2.197 [PubMed: 1251927]

Spivak B, Roitman S, Vered Y, Mester R, Graff E, Talmon Y, … Weizman A (1998). Diminished suicidal and aggressive behavior, high plasma norepinephrine levels, and serum triglyceride levels in chronic neuroleptic-resistant schizophrenic patients maintained on clozapine. Clin Neuropharmacol, 21(4), 245–250. [PubMed: 9704166]

Stille G, Lauener H, & Eichenberger E (1971). The pharmacology of 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo(b,e)(1,4)diazepine (clozapine). Farmaco Prat, 26(10), 603–625. [PubMed: 5157543]

Sur C, Mallorga PJ, Wittmann M, Jacobson MA, Pascarella D, Williams JB, … Conn PJ (2003). N-desmethylclozapine, an allosteric agonist at muscarinic 1 receptor, potentiates N-methyl-D-aspartate receptor activity. Proc Natl Acad Sci U S A, 100(23), 13674–13679. doi:10.1073/pnas.1835612100 [PubMed: 14595031]

Svensson TH (2003). Alpha-adrenoceptor modulation hypothesis of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry, 27(7), 1145–1158. doi:S0278-5846(03)00222-7 [pii] 10.1016/j.pnpbp.2003.09.009 [PubMed: 14642973]

Swendsen J, Burstein M, Case B, Conway KP, Dierker L, He J, & Merikangas KR (2012). Use and abuse of alcohol and illicit drugs in US adolescents: results of the National Comorbidity Survey-Adolescent Supplement. Arch Gen Psychiatry, 69(4), 390–398. doi:10.1001/archgenpsychiatry.2011.1503 [PubMed: 22474107]

Thompson JL, Urban N, Slifstein M, Xu X, Kegeles LS, Girgis RR, … Abi-Dargham A (2013). Striatal dopamine release in schizophrenia comorbid with substance dependence. Mol Psychiatry, 18(8), 909–915. doi:10.1038/mp.2012.109 [PubMed: 22869037]

Tomassi S, Tosato S, Mondelli V, Faravelli C, Lasalvia A, Fioravanti G, … Group GU (2017). Influence of childhood trauma on diagnosis and substance use in first-episode psychosis. Br J Psychiatry. doi:10.1192/bjp.bp.116.194019

Treffert DA (1978). Marijuana use in schizophrenia: a clear hazard. Am J Psychiatry, 135(10), 1213–1215. [PubMed: 29496]

van Dijk D, Koeter MW, Hijman R, Kahn RS, & van den Brink W (2012). Effect of cannabis use on the course of schizophrenia in male patients: a prospective cohort study. Schizophr Res, 137(1-3), 50–57. [PubMed: 22313726]

Warsi M, Sattar SP, Bhatia SC, & Petty F (2005). Aripiprazole reduces alcohol use. Can J Psychiatry, 50(4), 244. [PubMed: 15898470]

Weinberger DR (1987). Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry, 44(7), 660–669. [PubMed: 3606332]

Wenthur CJ, & Lindsley CW (2013). Classics in chemical neuroscience: clozapine. ACS Chem Neurosci, 4(7), 1018–1025. doi:10.1021/cn400121z [PubMed: 24047509]

Wimberley T, Stovring H, Sorensen HJ, Horsdal HT, MacCabe JH, & Gasse C (2016). Predictors of treatment resistance in patients with schizophrenia: a population-based cohort study. Lancet Psychiatry, 3(4), 358–366. doi:10.1016/S2215-0366(15)00575-1 [PubMed: 26922475]

Wint D, Dreher J, Furman D, Koch P, Kohn P, Egan M, … Berman KF (2005). Altered Cerebral Processing of Reward Uncertainty in Patients with Schizophrenia While Medication-Free and on Atypical Neuroleptics. Neuropsychopharm, 30(Suppl 1), S262.

Wu BJ, Chen HK, & Lee SM (2013). Do atypical antipsychotics really enhance smoking reduction more than typical ones?: the effects of antipsychotics on smoking reduction in patients with schizophrenia. J Clin Psychopharmacol, 33(3), 319–328. doi:10.1097/JCP.0b013e31828b2575 [PubMed: 23609378]

Yoshimura R, Yanagihara N, Hara K, Terao T, Nakamura J, Ueno S, … Izumi F (2000). Inhibitory effects of clozapine and other antipsychotic drugs on noradrenaline transporter in cultured bovine adrenal medullary cells. Psychopharmacology, 149(1), 17–23. [PubMed: 10789878]

Zimmet SV, Strous RD, Burgess ES, Kohnstamm S, & Green AI (2000). Effects of clozapine on substance use in patients with schizophrenia and schizoaffective disorder: a retrospective survey. J Clin Psychopharmacol, 20(1), 94–98. [PubMed: 10653215]

Zugman A, Gadelha A, Assuncao I, Sato J, Ota VK, Rocha DL, … Jackowski AP (2013). Reduced dorso-lateral prefrontal cortex in treatment resistant schizophrenia. Schizophr Res, 148(1-3), 81–86. doi:10.1016/j.schres.2013.05.002 [PubMed: 23721966]