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Psychiatric and neurological symptoms in schizophrenia and substance use disorder patients treated for 12-weeks with quetiapine

par

Simon Zhornitsky

Department de psychiatrie

Faculté de Médecine

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presentée par :

Simon Zhornitsky

a été evaluée par un jury composé des personnes suivantes :

Richard Warren, president-rapporteur

Stéphane Potvin, directeur de recherche

Emmanuel Stip, co-directeur de recherche

Sandra Boye, membre du jury

Christina Gianoulakis, examinateur externe

Valérie Mongrain, représentante de la Doyenne

Résumé

Contexte Autant dans une population schizophrène que non schizophrène, l'abus de substance a pour conséquence la manifestation de symptômes psychiatriques et neurologiques. Dans les présentes études cas-témoins, nous avons examiné les différences initiales ainsi que les changements suite au traitement de 12 semaines à la quetiapine au niveau de la sévérité de la toxicomanie et des symptômes psychiatriques et neurologiques chez 3 groupes distincts. Ces 3 groupes sont: des patients schizophrènes avec une toxicomanie (double diagnostic: DD), des patients schizophrènes sans toxicomanie concomittante (SCZ) et finalement, des toxicomanes non schizophrènes (SUD). Parallèlement, afin de nous aider à interpréter nos résultats, nous avons mené deux revues systématiques: la première regardait l'effet d'antipsychotiques dans le traitement de troubles d'abus/dépendance chez des personnes atteintes ou non de psychoses, la deuxième comparait l'efficacité de la quetiapine et sa relation dose-réponse parmi différents désordres psychiatriques. **Méthodes** Pour nos études cas-témoins, l'ensemble des symptômes psychiatriques et neurologiques ont été évalués via l'Échelle du syndrome positif et négatif (PANSS), l'Échelle de dépression de Calgary, l'Échelle des symptômes extrapyramidaux (ESRS) ainsi qu'avec l'Échelle d'akathisie de Barnes. **Résultats** À la suite du traitement de 12 semaines avec la quetiapine, les groupes SCZ et DD recevaient des doses de quetiapine significativement plus élevées (moyenne=554 et 478mg par jour, respectivement) par rapport au groupe SUD (moyenne = 150 mg par jour). Aussi, nous avons observé chez ces mêmes patients SUD une plus importante baisse du montant d'argent dépensé par semaine en alcool et autres drogues, ainsi qu'une nette amélioration de la sévérité de la toxicomanie comparativement aux patients DD. Par conséquent, à la fin de l'essai de 12 semaines, il n'y avait pas de différence significative dans l'argent dépensé en alcool et drogues entre les deux groupes de toxicomanes

or, les patients DD présentait, comme au point de départ, un score de toxicomanie plus sévère que les SUD. Étonnamment, aux points initial et final de l'étude, le groupe DD souffrait de plus de symptômes parkinsoniens et de dépression que le groupe SCZ. Par ailleurs, nous avons trouvé qu'initiallement, les patients SUD présentaient significativement plus d'akathisie, mais qu'en cours de traitement, cette akathisie reliée à l'abus/dépendance de cannabis s'est nettement améliorée en comparaison aux patients SCZ. Enfin, les patients SUD ont bénéficié d'une plus grande diminution de leurs symptômes positifs que les 2 groupes atteints de schizophrénie. **Conclusions** Bref, l'ensemble de nos résultats fait montre d'une vulnérabilité accentuée par les effets négatifs de l'alcool et autres drogues dans une population de patients schizophrènes. Également, ces résultats suggèrent que l'abus de substance en combinaison avec les états de manque miment certains symptômes retrouvés en schizophrénie. De futures études seront nécessaires afin de déterminer le rôle spécifique qu'a joué la quetiapine dans ces améliorations.

Mots clefs: Quétiapine, Schizophrenie, Toxicomanie, Symptoms extrapiramidales, Antipsychotique.

Résumé en Anglais

Background Psychiatric and neurological symptoms are consequences of substance abuse in schizophrenia and non-schizophrenia patients. The present case-control studies examined differences in substance abuse/dependence, and psychiatric symptoms and neurological symptoms in substance abusers with [dual diagnosis (DD) group] and without schizophrenia [substance use disorder (SUD) group] and in non-abusing schizophrenia patients (SCZ group) – undergoing 12-week treatment with quetiapine. Furthermore, two systematic reviews were conducted in order help explain our results. The first examined the usefulness of antipsychotics for the treatment of substance abuse/dependence in psychosis and non-psychosis patients. The second examined the dose-response and comparative efficacy of quetiapine across psychiatric disorders. **Methods** Psychiatric symptoms and neurological symptoms were evaluated with the Positive and Negative Syndrome Scale, the Calgary Depression Scale for Schizophrenia, the Extrapyramidal Symptoms Rating Scale, and the Barnes Akathisia Rating Scale. **Results** DD and SCZ patients were receiving significantly higher doses of quetiapine (mean=554 and 478mg per day, respectively), relative to SUD patients (mean=150mg per day). We found that SUD patients showed greater improvement in weekly dollars spent on alcohol and drugs and SUD severity, compared to DD patients. At endpoint, there was no significant difference in dollars spent, but DD patients still had a higher mean SUD severity. Interestingly, DD patients had significantly higher parkinsonism and depression than SCZ patients at baseline and endpoint. On the other hand, we found that SUD patients had significantly more akathisia at baseline, improved more than SCZ patients, and this was related to cannabis abuse/dependence. Finally, SUD patients improved more in Positive and Negative Syndrome Scale positive scores than DD and SCZ patients. **Conclusions** Taken together, our results provide evidence for increased vulnerability to

the adverse effects of alcohol and drugs in schizophrenia patients. They also suggest that substance abuse/withdrawal may mimic some symptoms of schizophrenia. Future studies will need to determine the role quetiapine played in these improvements.

Key words: Quetiapine, Schizophrenia, Substance use disorder, Extrapyramidal symptoms, Antipsychotic

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Liste des abbreviations

5-HT	5-hydroxytryptamine
6-OHDA	6-hydroxydopamine
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APA	American Psychiatric Association
ASI	Addiction severity index
AUS	Alcohol use scale
BAS	Barnes Akathisia Scale
BDI	Beck Depression Inventory
BIS	Barratt Impulsiveness Scale
BOLDER	BipOLar DEpRession study
BPRS	Brief Psychiatric Rating Scale
CDSS	Calgary Depression Scale for Schizophrenia
CNS	Central nervous system
CO	Carbon monoxide
CSAS	Chapman Social Anhedonia Scale
CYP1A2	Cytochrome P450 isoenzyme 1A2
DA	Dopamine
DD	Dual diagnosis
DRD4	Dopamine D4 receptor genotype
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
DUS	Drug-use scale

EMBOLDEN	Efficacy of Monotherapy SEROQUEL in BipOLar DEpressioN study
EPS	Extrapyramidal symptoms
ESRS	Extrapyramidal Symptoms Rating Scale
FEP	First-episode psychosis
FGA	First-generation antipsychotic
GABA	Gamma-Aminobutyric acid
GAD	Generalized anxiety disorder
GBD	Global Burden of Disease
GGT	Gamma-glutamyltransferase
HAM-D	Hamilton Depression Scale
HAM-A	Hamilton Anxiety Scale
HC	Healthy controls
IR	Regular oral formulation
ITT	Intention-to-treat population
L-DOPA	L-3,4-dihydroxyphenylalanine
LDL	Low-density lipoprotein
Li	Lithium
LOCF	Last observation carried-forward
LSD	Lysergic acid diethylamide
DVP	Divalproex
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major depressive disorder
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

NE	Norepinephrine
NET	Norepinephrine reuptake transporter
NMDA	N-Methyl-D-aspartate
OCD	Obsessive-compulsive disorder
OR	Odds-ratio
PAS	Psychoactive substances
PANSS	Positive and Negative Syndrome Scale for Schizophrenia
PET	Positron-emission tomography
SANS	Scale for the Assessment of Negative Symptoms
SCZ	Schizophrenia
SD	Single-diagnosis (or standard deviation)
SERT	Serotonin reuptake transporter
SGA	Second-generation antipsychotic
SIPD	Substance-induced psychotic disorder
SRI	Serotonin reuptake inhibitor
SSRI	Selective-serotonin reuptake inhibitor
SUD	Substance use disorder
TCA	Tricyclic antidepressant
THC	Delta-9-tetrahydrocannabinol
TLFB	TimeLine FollowBack procedure
XR	Slow-release oral formulation
VAS	Visual analogue scale
VTA	Ventral tegmental area

YBOCS	Yale-Brown Obsessive Compulsive Scale
YMRS	Young Mania Rating Scale

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1. Introduction

The lifetime prevalence of substance abuse/dependence in schizophrenia approaches 50% (Regier et al. 1990). Psychiatric and extrapyramidal (neurological) symptoms are consequences of substance abuse in schizophrenia and non-schizophrenia patients. The present case-control studies examined differences in substance abuse/dependence, and psychiatric and extrapyramidal symptoms in substance abusers with [dual diagnosis (DD) group] and without schizophrenia [substance use disorder (SUD) group] and in non-abusing schizophrenia patients (SCZ group) – undergoing 12-week treatment with quetiapine. Furthermore, two systematic reviews were conducted in order help explain our results. The first examined the usefulness of antipsychotics for the treatment of substance abuse/dependence in psychosis and non-psychosis patients. The second examined the dose-response and comparative efficacy of quetiapine across psychiatric disorders. Here, I will describe these reports and present additional data focusing on the SUD-alone group, and personality traits at baseline in the three groups. The data will be preceded by a general background on schizophrenia, antipsychotics, substance abuse/dependence, extrapyramidal symptoms, and the schizophrenia/SUD comorbidity.

Schizophrenia

1.1.1 Historical perspectives

Originally termed ‘dementia praecox’ (premature dementia), schizophrenia was first identified as a discrete illness by Dr. Emile Kraepelin in 1887 (Kyziridi, 2005). Kraepelin characterized the disorder as part of a process of incurable cognitive deterioration. The term ‘schizo (split) `phrenia (mind)’ was coined by Eugene Bleuler in 1907 – intending it to refer to a separation between perception, memory, thinking, and personality. Bleuler believed that Kraepelin`s definition was misleading because many schizophrenia patients did not exhibit a

pattern of progressive decline, and there was even partial or near-complete recovery in some cases (Kyziridi, 2005).

Bleuler was the first to classify schizophrenia symptoms as being `positive` (e.g. hallucinations, delusions) or `negative` (e.g. amotivation, blunted affect, asociality; Waters and Badcock, 2010). Another important characterization of schizophrenia symptoms was made by Kurt Schneider in 1959. He proposed the existence of core features or `first-rank` symptoms. These symptoms included third person auditory verbal hallucinations, loud (audible) thoughts (i.e. patients report that their own thoughts seem so loud that someone nearby could hear them), delusions of control (i.e. actions, intentions, and/or feelings are experienced to be under the control of some other force), and thought broadcasting (i.e. thoughts are believed to be accessible to others), insertion (i.e. thoughts are experienced as not being the patients' own) and withdrawal (i.e. thoughts experienced as actively extracted by others; Waters and Badcock, 2010). Together, these early characterizations greatly contributed to the notion of schizophrenia that we have today. Many of these early ideas (e.g. characteristic symptoms, positive/negative symptoms) have been carried forward in the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 1994).

1.1.2 Pharmacological hypotheses

There are at least four pharmacological hypotheses regarding the pathophysiology of psychosis: the serotonergic, cannabinoidergic, glutamatergic, and dopaminergic hypotheses. Serotonin was the first neurotransmitter to be implicated in the pathophysiology of psychosis (for review, see Pararelli et al. 2011). This was related to the discovery of the psychotomimetic effects of lysergic acid diethylamide (LSD), which acts as an agonist with high affinity for serotonergic 5-HT_{1-7} receptors (excluding 5-HT_3) and lower affinity for dopaminergic D_1-D_5 recepors (Woolley and Shaw, 1954; Porter et al. 1999; Nichols et al.

2002). Early studies revealed some similarities between schizophrenia and LSD-psychosis. For example, a comparison between 30 LSD-psychosis and 10 paranoid schizophrenia patients found that the former experienced more elation, disturbance in time sense, feeling of loss of control, body image changes, and somatic symptoms; however, suspiciousness was equal among the two groups (Langs and Barr, 1968). There is also evidence among 15 LSD-psychosis and 116 schizophrenia patients that the former reported significantly more visual illusions and hallucinations, but less auditory hallucinations. By contrast, some delusions were less common in patients with LSD-psychosis, possibly because of the frequency of insight into the abnormal nature of their perceptual symptoms (Hays and Tilley, 1973).

Administration of LSD to schizophrenia patients has been shown to produce aggravation of psychotic symptoms (Cholden et al. 1955). Because the effects of LSD are blocked by 5-HT_{2A} antagonists, it could be expected that these agents would have antipsychotic properties (Marek and Aghajanian, 1996). However, this has not entirely been the case. For instance, Meltzer et al. (2004) showed that haloperidol produced highly significant reductions in Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Syndrome Scale (PANSS) total scores ($p<0.001$), whereas the 5-$HT_{2A/2C}$ antagonist, SR46349B, produced barely significant reductions on these scales ($p=0.04$). Interestingly, analysis of subscales revealed that SR46349B did not produce significant reductions on the BPRS psychosis cluster score or the PANSS positive subscales, but it did produce significant improvements on the PANSS general ($p=0.03$) and PANSS negative ($p=0.04$) subscales. However, the greatest improvement with SR46349B versus placebo occurred on the Calgary Depression Scale for Schizophrenia (CDSS; $p=0.009$), suggesting that the benefit of SR46349B was of an antidepressant – rather than an antipsychotic – nature (Meltzer et al. 2004). These data coincide with the fact that drug development of the 5-HT_{2A} antagonist,

M10090, was stopped due to lack of efficacy versus established treatments schizophrenia (De Paulis, 2001).

The endogenous cannabinoid receptor system acts through retrograde transport as a functional autoreceptor for many neurotransmitter systems, including dopamine, opioids and gamma-aminobutyric acid (GABA; Meyer and Quenzer, 2005). Activation of cannabinoid type-1 receptors by tetrahydrocannabinol (THC) is associated with feelings of euphoria/mania, paranoia and hallucinations. For instance, there is evidence that cannabis-induced psychosis patients had significantly more hypomania and agitation at baseline and less affective flattening, incoherent speech, auditory hallucinations and hysteria, relative to paranoid schizophrenia patients, and many of these symptoms diminished after the individuals ceased cannabis use (Rottanburg et al. 1982). Surprisingly, both groups were equally given a diagnosis of paranoid schizophrenia at hospital admission. There is also evidence that cannabis-psychosis patients performed significantly better on tests of content of thought, forms of thought, and short-term memory, compared to bipolar mania and schizophrenia patients, whereas schizophrenia patients exhibited significantly more auditory hallucinations, relative to the other two groups (Imade and Ebie, 1991). Altogether, these studies indicate that cannabis psychosis and schizophrenia share a propensity towards paranoid thoughts and behaviours. Despite this association, however, Meltzer et al. (2004) did not find a significant difference between the CB_1 antagonist, SR141716, and placebo for positive or negative symptoms in schizophrenia.

Glutamate is the major excitatory neurotransmitter in the brain. Antagonism of ionotropic glutamate N-Methyl-D-aspartate (NMDA) receptors by drugs such as ketamine and phencyclidine produces neurological effects such as ataxia, drowsiness, and stupor, and at high doses, a lucid dream state (i.e. 'k-hole'; Muetzelfeldt et al. 2008). Due to the similarities between NMDA-antagonist intoxication and some symptoms of schizophrenia (e.g.

hallucinations, depersonalization, blunted affect, poverty of speech), it has been proposed that glutamate may play a role in schizophrenia psychopathology (Bubenikova-Valesova et al. 2008). In addition to their effects the NMDA receptor, both ketamine and phencyclidine display high affinity for D_2 receptors and moderate affinity for 5-HT_2 receptors, and the latter also binds to the dopamine transporter (Schiffer et al. 2003; Kapur and Seeman, 2001, 2002). Administration of ketamine to schizophrenia patients produced significant worsening of schizophrenia symptoms (as measured by BPRS total), which was mostly accounted for by changes in positive symptoms. Additionally, the ketamine-induced psychotic symptoms were similar to the patients` symptoms during active episodes of the illness (Lahti et al. 1995). These symptoms were partially, but not completely attenuated by concomitant treatment with haloperidol. Likewise, another study found haloperidol to significantly reduce symptoms of acute intoxication induced by ketamine (Giannini et al. 2000). These findings suggest that pro-dopaminergic activity is partially responsible for the aggravations in positive symptoms observed in ketamine-treated schizophrenia patients.

On the other hand, ketamine is not known to produce significant amounts of paranoia in normal subjects, and reports of ketamine-induced psychosis are rare. In the case of phencyclidine, there is evidence that – among 100 subjects with toxic psychosis – only 22 percent evidenced paranoid ideas, 12 percent depression, 5 percent fear/anxiety, and 3 percent suicidal ideation (McCarron et al. 1981). The low amount of schizophrenia symptoms in this phencyclidine sample were confirmed by a key comparison between cocaine- and phencyclidine-induced psychosis patients. The authors found that cocaine-induced psychosis predominantly included suspiciousness (17 of 22 patients), whereas phencyclidine-induced psychosis predominantly included perception of physical strength (12 of 22 patients) and divine spiritual experiences (6 of 22 patients). Furthermore, they found that patients taking phencyclidine would not report suspiciousness, but instead would report fear that bad things

might befall them, and fear of losing control or a sense of imminent dissolution of the self (Rosse et al. 1994).

The original as well as the most recent version of the dopaminergic hypothesis of schizophrenia posits that psychotic symptoms are caused by hyperactivity of the mesolimbic dopamine system (for review, see Howes and Kapur, 2009). The original hypothesis stemmed from the discovery in 1952 that chlorpromazine, a dopamine D_2 antagonist, was effective at treating positive symptoms in schizophrenia patients (Turner, 2007). To this day, antipsychotics remain the sole indicated treatment for the disorder. The case of pro-dopaminergic agents also favours this interpretation. Indeed, a review of classic studies found that the majority of patients exhibited an exacerbation of psychotic symptoms following acute treatment with amphetamine, whereas only 25% of controls exhibited such symptoms (Lieberman et al. 1987). Similarly, Laurelle (1998) reported that 47% of 34 schizophrenia patients who were challenged with amphetamine were classified as 'worseners', 41% were classified as 'no change', and 12% as 'improvers', in relation to PANSS positive symptoms. Compared with the no change, or the improver patients, the worsener patients displayed a significantly greater displacement of [123I]IBZM, suggesting enhanced striatal dopamine release. These studies provide evidence for dopaminergic hyperactivity in schizophrenia patients via increased presynaptic dopamine release. They also show that the dopaminergic hypothesis is the only model that can show significant changes in both directions in response to pharmacological challenge (i.e. improvement with antagonists and worsening with agonists). Finally, the data imply that NMDA antagonists do not share the same propensity to induce paranoia as serotonergic agonists (hallucinogens), cannabinoids, and psychostimulants. It may be that the latter agents produce paranoia through activation of common pathway(s) that are also affected in schizophrenia.

1.1.3 Symptomatology

Schizophrenia is the most disabling mental disorder, according to the global burden of disease study (Eaton et al. 2008). Schizophrenia patients suffer from positive, negative, and depressive symptoms (Tirupati et al. 2006; Villalta-Gil et al. 2006; Levine and Rabinowitz, 2007). The first decade of illness in schizophrenia is often characterized by repeated episodes of psychosis with varying levels of remission between episodes and increased disability following each episode (Tandon et al. 2009; Wyatt, 1991). Moreover, the bulk of functional deterioration tends to occur in the first five years after onset of schizophrenia, following which the illness typically progresses into a stable phase, wherein positive symptoms are decreased and negative predominate (Tandon et al. 2009).

Positive symptoms refer to symptoms that the majority of the population does not experience, but which are present in psychosis patients. They involve distortions of reality, including hallucinations (potentially in all five sensory modalities) and delusions (Tandon et al. 2009). To characterize the nature of hallucinations and delusions in schizophrenia, Mitchell and Vierkant (1991) conducted a study among 100 involuntarily hospitalized, paranoid schizophrenia patients. They found that auditory, visual, and tactile hallucinations were reported by 36, 7, and 3 patients, respectively. Command and non-command hallucinations were reported by 20 and 9 patients, respectively and they were often bizarre and threatening in nature. In addition, 49 patients reported delusions of persecution, 12 reported identity delusions, 9 reported possession delusions, 4 reported grandiose delusions and 4 reported Capgras Syndrome delusions (Mitchell and Vierkant, 1991). Another study by Mitchell and Vierkant (1989) examined delusions and hallucinations reported in the social histories of 150 schizophrenia patients admitted to a Texas hospital during the 1930s and of 150 patients admitted during the 1980s. Interestingly, the authors found that patients who were admitted during the 1930s exhibited the material deprivation and personal powerlessness

of the great depression in delusions of great wealth and hallucinations of positive 'special powers'. By contrast, patients in the 1980s exhibited an increased frequency of threatening hallucinations such visions of blood, snakes, and dead people of animals and command hallucinations to hurt, to kill, or to do 'perverse things'. These phenomena, according to the authors, suggest that the subcultural milieu of the 1980s had become more dangerous (Mitchell and Vierkant, 1989). Taken together, these data provide insight into the nature of hallucinations and delusions in schizophrenia patients and their association to the context in which they occur.

Negative symptoms consist of emotional, social and/or motivational deficits (Erhart et al., 2006; Stahl and Buckley, 2007). A recent study examining the factor structure of the Scale for the Assessment of Negative Symptoms (SANS) revealed a four-item structure consisting of affective flattening (e.g. paucity of expressive gestures, unchanging facial expression), alogia (e.g. poverty of content of speech, blocking), avolition-apathy (e.g. physical anergia, impersistence at work or school) and anhedonia-asociality (e.g. lack of relationships with friends and peers and lack of recreational interests and activities) (Rabany et al. 2011). In addition to negative symptoms, schizophrenia patients may exhibit depressive symptoms such as hopelessness, self-depreciation, guilty ideas of reference, morning depression and early wakening (Majadas et al. 2011). Interestingly, in the Rabany et al. (2011) study, the SANS total score showed a small negative correlation ($r = -0.184$; $p=0.05$) with Calgary Depressive Scale for Schizophrenia (CDSS) total score, supporting the notion that negative and depressive symptoms are separate constructs (despite a similarly sounding nomenclature). The occurrence of both negative and depressive symptoms has been termed the "emotion paradox" of schizophrenia, suggesting a disjunction between expression, perception and experience of emotion (Aleman and Kahn, 2005). For instance, there is evidence that patients with negative symptoms were less *expressive* than those without after viewing emotional films; however,

the former patients did not report *experiencing* less emotion to the films (Earnst and Kring, 1999). Consequently, it has been suggested that negative and depressive symptoms can co-exist in schizophrenia because levels of emotional experience may increase with the latter, whereas the ability to perceive emotional cues may diminish with the former (Aleman and Kahn, 2005).

1.1.4 Treatment

Antipsychotics attenuate positive symptoms in schizophrenia, and help improve outcomes, especially in the early stages of illness (Wyatt, 1991). For example, a pivotal study by May (1968) revealed that treatment with antipsychotics increased the rate of release from the hospital, reduced the length of hospital stay, and decreased the need for sedatives in newly admitted first-episode psychosis (FEP) patients, relative to psychotherapy or milieu therapy. Another study by Crow et al. (1986) showed that 46% of 120 FEP patients maintained on antipsychotics relapsed within two years, compared to 62% of patients on placebo and the chance of subsequent psychotic relapse was significantly increased in patients with a longer duration of untreated psychosis.

Apart from antipsychotics, there are a number of treatments that can partially improve outcomes among schizophrenia patients. In the May (1968) study, electroconvulsive therapy (ECT) was nearly as effective as neuroleptics for decreasing the duration of inpatient stay among schizophrenia patients. However, a more recent study revealed that the benefit from ECT was evident at 8 weeks, but it did not remain at the 6-month follow-up (Abraham and Kulhara, 1987). Similarly, while early data found that psychotherapy was ineffective with or without antipsychotics, more recent evidence has suggested that psychotherapy may significantly improve outcomes when paired with antipsychotics, particularly long-acting injectables (May, 1968; Hogarty et al. 1979; for review, see Zhornitsky and Stip, 2012). For

its part, repetitive transcranial magnetic stimulation has shown some promise as a treatment for positive and negative symptoms in schizophrenia, but results have been inconsistent (Lai et al. 2010; Barr et al. 2011). Unfortunately, however, none of these alternative treatments have come close to providing the same efficacy as antipsychotics for schizophrenia.

1.2 Antipsychotics

1.2.1 Typical vs. atypical

Following the discovery in 1952 that chlorpromazine has antipsychotic properties, there was finally a pharmacological treatment for schizophrenia; however, chlorpromazine and other `typical` antipsychotic drugs produced disturbing extrapyramidal or neurological side-effects such as parkinsonism, akathisia, dystonia and dyskinesia (Taylor, 2007). This was due to their potent antagonism of D_2 receptors located in the nigrostriatal dopamine system – a pathway that is heavily implicated in the capacity for voluntary movement (Tisch et al. 2004). However, new 'atypical' molecules would soon be developed that displayed lower affinity for D_2 receptors and did not produced large amounts of extrapyramidal symptoms.

The first widely used atypical antipsychotic was thioridazine (Boissier et al. 1959; Costall and Naylor, 1975). It is considered atypical because it produces an antipsychotic effect without a high propensity for inducing extrapyramidal symptoms. Thioridazine has a low-to-moderate affinity for D_1 and D_2/D_3 receptors, coupled with significant affinity for 5-$HT_{2A,}$ 5-$HT_{2C,}$ 5-$HT_{6,}$ 5-HT_7, α-1 adrenergic and histamine-H_1 receptors (Roth et al. 2004). Sulpiride was the second atypical antipsychotic to be developed (Carrère, 1968). It has low-to-moderate affinity for D_2/D_3 receptors and preferential binding to pre- (D2Short) versus post-synaptic D_2 receptors (D2Long; Pani and Gessa, 2002). Loxapine and clozapine were the next atypical antipsychotics to be marketed (Bishop and Gallant 1970; de Maio, 1972). Loxapine displays low-to-moderate affinity for D_1 and D_2/D_3 receptors and significant affinity for 5-HT_{2A}, 5-

HT_{2C}, 5-HT_6, 5-HT_7, $\alpha_{1\text{-}2}$, and H_1 receptors (Kroeze et al. 2002). Clozapine displays low-to-moderate affinity for D_1 and D_2/D_3 receptors and significant affinity for 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, 5-HT_7, $\alpha_{1\text{-}2}$, M_1, M_2, M_3, M_4, M_5 cholinergic, and H_1 receptors (Bolden, 1992; Roth et al. 2004). Subsequently, at least two other 'first-generation' atypical antipsychotics would follow: tiapride and melperone (Legrain, 1976; Kretzschmar et al. 1976). The former is a selective D_2/D_3 antagonist with a binding profile similar to sulpiride, and the latter displays low affinity for D_2/D_3, coupled with significant affinity for 5-HT_{2A}, and $\alpha_{1\text{-}2}$ receptors (Richelson and Souder, 2000; Burstein et al. 2005).

In the 1990s, companies developed new 'second-generation' drugs with a low propensity to produce extrapyramidal symptoms, beginning with amisulpride, and followed by risperidone, olanzapine, quetiapine, and ziprasidone (Mann et al. 1984; Janssen et al. 1988; Moore et al. 1992; Saller and Salama, 1993; Bench et al. 1993). Amisulpride shares with sulpiride and tiapride a selective affinity for D_2/D_3 receptors, and a preference for presynaptic D_2 receptors. Broadly speaking, the clinical and receptor-binding profile of olanzapine is similar to clozapine, the profile of quetiapine is similar to melperone, and the profiles of ziprasidone and risperidone are similar to thioridazine and loxapine (Richelson and Souder, 2000; Roth et al. 2004). Due to their marked affinity for serotonergic receptors, some of these atypical antipsychotics are also effective treatments for depression (for review, see Zhornitsky et al. 2011a, Pani and Gessa, 2002). In the case of sulpiride, tiapride and amisulpride, their preferential affinity for pre- over post-synaptic D_2 receptors at low doses leads to increased dopamine synthesis and turnover in dopamine terminal areas, thereby producing an antidepressant effect (Härnryd et al. 1984). Finally, their high affinity for noradrenergic receptors explains the anxiolytic/sedative properties associated with some atypical antipsychotics (Roth et al. 2004).

1.2.2 Side-effects

The broad spectrum of action of many atypical antipsychotics suggests that they should be associated with multiple side-effects. Antipsychotics with a moderate-to-high affinity for the D_2 receptor induce extrapyramidal and secondary negative symptoms, particularly when occupancy of striatal D_2 receptors reaches above 80% (Bobes et al. 2010; Uchida et al. 2011). In addition, due to their affinity for α-1 receptors, many antipsychotics produce sedation, orthostatic hypotension, and syncope. Furthermore, some atypical antipsychotics such as clozapine and olanzapine are associated with a high rate of metabolic disorders, possibly due to their antagonism of muscarinic M_3 receptors, which regulate insulin secretion from pancreatic islets (Gautam et al. 2010; Kong et al. 2010). Antagonism of muscarinic receptors is also believed to be responsible for symptoms of dry mouth, blurred vision, constipation, and confusion associated with these agents (Kozumplik et al. 2010). However, these properties also lead to a low rate of extrapyramidal symptoms, relative to D_2 affinity, because muscarinic M_4 receptors possess a regulatory effect on dopaminergic neurotransmission (Bymaster et al. 2003). Finally, prolactin elevation is a concern following treatment with typical antipsychotics and some substituted benzamides (amisulpride, but not tiapride and sulpiride) due to their selectivity/high affinity for D_2 receptors and preferential blockade of presynaptic D_2 receptors located on the anterior pituitary – a region that regulates prolactin secretion (Apud et al. 1987; Petty, 1999).

1.3 Substance abuse/dependence

Substance abuse is a term that that refers to pathological use of a medication or alcohol/illicit drugs that leads to significant impairment or distress and results in a failure to fulfill major role obligations at work, school or home; recurrent substance use in situations that are physically hazardous; recurrent substance-related legal trouble; and continued substance

abuse despite having substance-related social or interpersonal problems (APA, 1994). Substance abuse is more likely to be diagnosed in individuals that just began taking alcohol/drugs and it is often an early symptom of substance dependence.

In contrast to substance abuse, the DSM-IV definition of substance dependence relates more closely to the process of drug addiction (APA, 1994). For instance, one item requires the individual to exhibit tolerance as defined by a need for markedly increased amounts of the substance in order to achieve desired effect and diminished effectiveness with continued use. Another item requires the individual to exhibit symptoms of withdrawal and the need for more of the same substance to relieve or avoid withdrawal symptoms. Other items that may lead to a diagnosis of substance dependence include a persistent unsuccessful desire to reduce substance use and a habit of taking the substance in larger amounts or over a longer period than intended, and spending a great deal of time on activities necessary to obtain the substance, to use the substance and to recover from its effects (APA, 1994). The content of these items show that the DSM-IV definition of substance dependence is centred on processes surrounding alcohol/drug addiction (e.g. tolerance, withdrawal), whereas the definition of substance abuse is centered on substance-associated personal and societal harm. Interestingly, tolerance and withdrawal are no longer considered to be core features of substance dependence, although they remain part of its definition. New theories focus much more on loss of control, compulsive use and relapse.

1.3.1 Pharmacological mechanisms

All major drugs of abuse including psychostimulants, opiates, cannabis and alcohol are believed to produce their rewarding effects by increasing striatal dopamine levels (Meyer and Quenzer, 2005; Wise and Rompre, 1989). Cocaine produces its psychoactive effects by blocking the dopamine reuptake transporter, leading to large increases of dopamine in the

synaptic cleft, and at the affected synapses (Ritz et al. 1990). Amphetamine and methamphetamine produce their effects by being uptaken by monoaminergic transporters (mainly dopamine at low doses), wherein they provoke neurotransmitter release from the synaptic vesicles into the cytoplasm, and cause the transporters to function in a reverse direction to release neurotransmitters from the cytoplasm into the extracellular fluid (Ritz and Kuhar, 1989). In rats, amphetamine and cocaine elicit a locomotor response when injected directly into the ventral tegmental area (VTA) or nucleus accumbens (Chen and Reith, 1994; Meyer and Quenzer, 2005). Moreover, 6-hydroxydopamine (6-OHDA) lesions of these regions attenuate the locomotor-stimulating and reinforcing properties of systemically administered amphetamine and cocaine (Kelly et al. 1975; Koob et al. 1981; Roberts and Koob, 1982). During withdrawal, amphetamine and cocaine produce significant reductions in extracellular dopamine concentration in the ventral striatum, which can be observed behaviourally via increased thresholds to rewarding brain stimulation (Rossetti et al. 1992; Zhornitsky et al. 2010; Stoker and Markou, 2011).

Opiates such as heroin and morphine activate the endogenous opioid system, which plays a pivotal role in analgesia, reward, and body perception/sensory integration. These agents are agonists of μ, δ and κ-opioid receptors; however, they are more selective for the first subtype (Spetea et al. 2004). Both the μ and δ-receptor subtypes are believed to tonically inhibit dopamine. Activation of these sites increases VTA cell firing and dopamine release in the nucleus accumbens by inhibiting the (inhibitory) GABA cells found in VTA (Meyer and Quenzer, 2005). By contrast, activation of κ-opioid receptors exerts the opposite effect on the mesolimbic dopaminergic system. Specifically, higher doses of the psychotomimetic κ-agonist, salvinorin A, were found to significantly reduce dopamine levels in the caudate and putamen – an effect that was completely blocked by administration of the κ-antagonist, nor-binaltorphimine (Zhang et al. 2005). Here, the authors also found that the same doses of

salvinorin A caused conditioned place aversion and decreased locomotor activity, suggesting decreased reward system activity. On the other hand, there is evidence that nor-binaltorphimine potentiated decreases in dopamine release, conditioned-place aversion, and overt signs associated with morphine withdrawal (Spanagel et al. 1994).

Cannabis produces its psychoactive effects activating endogenous cannabinoid-type 1 (CB_1) receptors (Demuth and Molleman, 2006). Endocannabinoids are synthesized and released in response to depolarization of the postsynaptic cell due to influx of calcium. After they are released, these substances cross the synaptic cleft, activate presynaptic CB_1 receptors, and block calcium-mediated neurotransmitter release from the terminal (Demuth and Molleman, 2006). Cannabinoids produce their rewarding effects primarily by indirectly stimulating the dopamine and opioid neurotransmitter systems. Indeed, studies have shown that cannabinoids stimulate firing of dopamine neurons in the VTA and increase dopamine release in the nucleus accumbens (French et al. 1997; Sperlágh et al. 2009). Furthermore, there is evidence that that CB_1 antagonist, SR141716A, reduced self-administration of heroin in rats or mice and naltrexone, reduced THC self-administration in squirrel monkeys (Chaperon et al. 1998; Justinova et al. 2004). During withdrawal, there is evidence that THC produced reductions in dopamine cell activity and somatic symptoms, which were alleviated when rats were given more of the molecule (Diana et al. 1998).

Alcohol exerts its effects via a number of neurotransmitter pathways. Alcohol inhibits glutamate neurotransmission by reducing its effectiveness at NMDA receptors and reducing its release in a number of brain regions (Lovinger et al. 1989). During alcohol withdrawal, glutamate release is increased dramatically, leading to central nervous system (CNS) hyperexcitability, and potentially seizures. In addition, alcohol produces its psychoactive action by activating GABA receptors – an effect that is not surprising since alcohol shows cross-tolerance and cross-dependence with other GABA-receptor agonists such as

benzodiazepines and barbiturates (Allan et al. 1992; Toki et al. 1996). Indeed, there is evidence that manipulations that increase and decrease GABA also enhance and attenuate alcohol`s behavioral effects, respectively (Grobin et al. 1998). In addition to GABA, alcohol activates the opioidergic system, which plays a crucial role in the body's ability to relieve pain, and whose stimulation reverses the tonic inhibition that these receptors have on dopamine neurons, thereby leading to dopamine release (Meyer and Quenzer, 2005). Interestingly, alcohol consumption is attenuated in animals after administration of moderate and high doses of morphine, suggesting that the morphine displaces the alcohol from opioid receptors, thereby reducing its rewarding effects (Herz, 1997). Furthermore, alcohol augments the firing rate of dopaminergic neurons in the VTA and increases the amount of dopamine released into the nucleus accumbens (Tateno and Robinson, 2011). Finally, there is evidence that animals will self-administer alcohol directly into the VTA, and infusion of D_2 antagonists into the nucleus accumbens has been shown to reduce alcohol self-administration (Czachowski et al. 2001; Rodd-Henricks et al. 2000).

1.3.2 Treatment

Pharmacotherapies targeting the GABAergic system have been shown to be useful for the treatment of substance abuse/dependence. Benzodiazepines have long been used for the treatment of alcohol withdrawal due their ability to reduce withdrawal-induced seizures, and their ability to act as a substitution therapy in order to wean individuals off of alcohol (Koutsky and Sleten, 1963). However, these agents have a high addiction potential themselves, thus limiting their use among the substance use disorder population (Lalive et al. 2011). Indeed, there is evidence that while 15mg of diazepam reduced alcohol associations active problem drinkers, a lower dose (5mg) significantly increased the salience of alcohol

associations (Zack et al. 2006). In a similar vein, diazepam was found to significantly increase consumption of de-alcoholised beer among problem drinkers (Poulos and Zack, 2004).

Medications targeting the endogenous opioid system have had success in the treatment of opiate and alcohol abuse/dependence. For example, substitution therapy with oral methadone, a partial μ-opioid receptor agonist, has proven useful because of its ability to minimize withdrawal symptoms and wean patients off heroin (Mattick et al. 2009). Alternatively, naltrexone, a non-selective opioid-receptor antagonist, has been shown to reduce heavy drinking versus placebo in 19 of 27 (70%) clinical trials, presumably by attenuating the rewarding effects of alcohol (Pettinanti et al. 2006). However, the same study also found that only 9 of 25 (36%) trials found that naltrexone, was superior to placebo in improvement abstinence or 'any drinking'.

Studies suggest that targeting serotonergic and/or noradrenergic systems may help attenuate the effects of alcohol/drug intoxication and withdrawal. For instance, the dual serotonin and norepinephrine reuptake inhibitor, venlafaxine, significantly decreased the acute subjective effects of cocaine by 10-20% (Foltin et al. 2003). There is also evidence that the non-selective α-1/β-adrenergic receptor antagonist, carvedilol, attenuated increases in blood pressure and heart-rate induced by crack cocaine and decreased self-administration among users of crack cocaine (Sofuoglu et al. 2000). Additionally, the 5-HT_{2A} and 5-HT_{2C} antagonist, mirtazapine, attenuated withdrawal symptoms in amphetamine-dependant subjects (Shoptaw et al. 2009), and the beta-adrenergic antagonist, propanolol, decreased cocaine use in a subset of individuals with a high withdrawal severity (Kampman et al. 2001). Similarly, there is evidence that trazodone – a α-1 receptor antagonist – reduced symptoms of alcohol withdrawal and improved sleep quality post-detoxification (Karam-Hage and Brower, 2003; Borras et al. 2006). These preliminary findings attest to the potential of serotonergic and noradrenergic manipulation for the treatment of substance abuse/dependence.

Dopaminergic agents are intriguing targets for the treatment of SUDs because they directly target the mesolimbic dopamine system. Substitution therapy with dopamine agonists is one approach; however, they have addictive potential themselves. Experimental studies have found that sustained-release amphetamine reduced cocaine-associated subjective effects and drug-liking, and reduced breakpoint for cocaine self-administration among dependant individuals (Greenwald et al. 2010; Rush et al. 2010). There is also evidence that sustained-release amphetamine decreased the subjective and physiological effects of intranasal methamphetamine (Rush et al. 2011). Similarly, bupropion (a weak dopamine transporter inhibitor) reduced subjective effects and craving in methamphetamine-dependant individuals (Newton et al. 2006). Altogether, these data suggest that agonist substitution may be mildly effective for the treatment of SUDs.

1.3.2.1 Why treat with antipsychotics?

Another approach to pharmacotherapy of substance abuse/dependence is to block the rewarding effects of substances of abuse with atypical antipsychotics. In addition, many atypical antipsychotics possess significant anxiolytic and antidepressant efficacy due to antagonism of multiple serotonergic and noradrenergic receptor subtypes, suggesting that they may have the added benefit of alleviation of withdrawal, without the addictive potential of benzodiazepines and dopaminergic agonists (Roth et al. 2004). Animal models of reward have demonstrated that antipsychotics reverse cocaine-, amphetamine-, and morphine-induced decreases in threshold for rewarding brain stimulation and block the establishment of a conditioned place preference to alcohol, amphetamine, and cocaine (Yokel and Wise, 1976; Barrett et al. 1980; Winsauer et al. 2008; Arolfo and McMillen, 2000; Walker and Ettenberg, 2007). There is also evidence that antipsychotic agents block drug- and cue-induced reinstatement of responding on the drug-associated lever during self-administration of

cocaine, amphetamine, and heroin, and prevent the ability of amphetamine and heroin to reinstate operant runway behaviour (Ettenberg, 1990; Ettenberg et al. 1996; Gál and Gyertyán, 2006; Feltenstein et al. 2007).

Early studies in chronic alcoholics revealed that melperone was effective at reducing depression, tension, paranoia, craving and insomnia (Carlsson and Gullberg, 1978, Carlsson et al. 1979). Around the same time, tiapride began to gain interest for the treatment of alcohol withdrawal syndrome, particularly due to its ability to attenuate delirium tremens (Parent et al. 1978). More recently, quetiapine was found to reduce subjective intoxication, craving and sedation during alcohol administration, and alcohol cue-exposure (Ray et al. 2011). Similarly, there is evidence that clozapine decreased pleasant (i.e. expected 'high', 'rush') and unpleasant (paranoia and nervousness) responses to intranasal cocaine (Farren et al. 2000). As a whole, these experimental and short-term studies indicate that atypical antipsychotics may have promise for the treatment of SUDs via a reduction of intoxication or alleviation of craving and withdrawal.

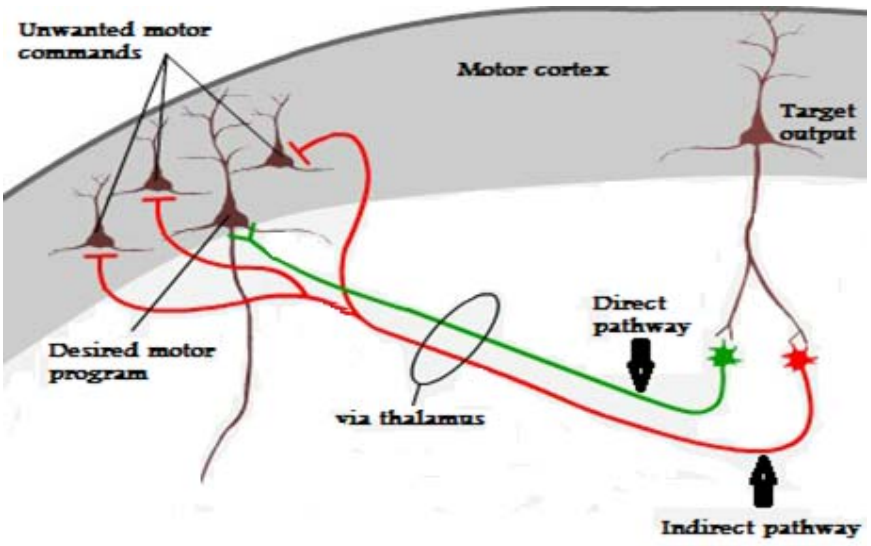
1.4 Extrapyramidal symptoms

Extrapyramidal symptoms refer to antipsychotic-induced disorders of movement. They include parkinsonism (e.g. resting tremor, bradykinesia), dyskinesia (e.g. involuntary movements of the body and face), dystonia (e.g. muscular contractions) and akathisia (e.g. subjective and objective restlessness). Parkinsonism is considered to be a hypokinetic disorder, whereas dyskinesia, dystonia, and akathisia are considered to be hyperkinetic disorders. Furthermore, extrapyramidal symptoms may be acute or tardive: the former may be transient, while the latter appears during long-term treatment (often after several years), and may be irreversible even after antipsychotics are discontinued (especially after treatment with typicals; Tarsy et al. 2011).

1.4.1 Neurobiology

Extrapyramidal symptoms are believed to occur because of antagonism of dopaminergic receptors in the basal ganglia (Feinberg and Snyder, 1975). The basal ganglia refer to several nuclei in the mesencephalon and diencephalon. They include the globus pallidus, striatum (putamen & caudate nucleus), subthalamic nucleus and substantia nigra (divided into pars compacta and pars reticulata). The basal ganglia form a network with the cortex and thalamus, and together, they regulate processes such as movement, cognition, and emotion. The striatum is the central input structure in this network and it receives numerous afferent connections from the cortex, thalamus, and substantia nigra pars compacta. The main output structures include the globus pallidus and substantia nigra pars reticulata, which project to the thalamus and brainstem (Tisch et al. 2004). The majority of neurons in the basal ganglia (~96%) are medium spiny neurons, which are inhibitory GABAergic neurons (Stolerman, 2010). In the basal ganglia neural network there are two major pathways (i.e. types of medium spiny neurons). Neurons in the 'direct', pathway facilitate the initiation and execution of voluntary movement and express mainly D_1 and presynaptic muscarinic M_4 receptors (Bymaster et al. 2003). Neurons in the 'indirect' pathway prevent unwanted motor commands from competing with voluntary movement and express mainly D_2 receptors. The role of dopamine is to keep the two pathways balanced and neurologically normal individuals are able to switch between the two pathways in a continuous, uninterrupted fashion. However, dysfunction of the direct and indirect pathways results in hypo- and hyperkinesia, respectively (Onla-or and Winstein, 2001).

Figure 1: Direct and indirect pathways of movement



Adapted from http://neuroscience.uth.tmc.edu/s3/chapter04.html

1.4.1.1 Parkinsonism

Drug-induced parkinsonism typically develops following several days to weeks of antipsychotic therapy due to blockade of dopaminergic receptors in the nigrostriatal pathway. The syndrome is characterized by poverty of movement (akinesia), slowness of movement (bradykinesia), rigidity, and resting tremor (frequency = 3-6Hz; Mattay and Casey, 2003). In monkeys, both D_1 and D_2 receptor antagonists have been evidenced to produce parkinsonism without tolerance, but the syndrome is more likely to develop with following treatment with the former (Lawrence et al. 1991; Casey, 1995). In schizophrenia, Kapur et al. (1995) showed that risperidone produced significant levels of parkinsonism when occupancy of striatal D_2 receptors reached above ~75%. Recently, a pooled analysis of 12 studies revealed a similar rate cut-off point of 78% D_2 occupancy for extrapyramidal symptoms as a whole (Uchida et al. 2011). It is likely that these overall estimates mainly reflect parkinsonism because akathisia, dyskinesia, and dystonia are rarer, and they show a weaker relationship to D_2

occupancy in positron-emission tomography (PET) studies (Kapur et al. 1995; Uchida et al. 2009).

Parkinsonism in schizophrenia can be treated by administration of anticholinergic drugs. Anticholinergics such as atropine and benztropine are believed to produce their antiparkinsonian effects via antagonism of M_4 receptors (Langmead et al. 2008). High levels of M_4 receptors are found in the striatum, cerebellum, and cerebral cortex, and on neurons in the 'direct' pathway. Interestingly, there is evidence that haloperidol-induced catalepsy was attenuated following treatment with scopolamine (an anticholinergic) in normal mice, but not in M_4 knockout mice (Karasawa et al. 2003). Similarly, Betz et al. (2007) showed that tropicamide (a moderately selective M_4 antagonist) suppressed the tremulous jaw movements (an animal model of parkinsonism) induced by the antipsychotic pimozide, and the muscarinic agonist pilocarpin. Moreover, tropicamide was equally as potent as atropine (a less selective anticholinergic) at reversing the effects of pilocarpin, but it was more potent at reversing the effects of pimozide, suggesting that M_4 antagonism was the moderating factor (Betz et al. 2007).

1.4.1.2 Dyskinesia

Tardive dyskinesia is a potentially irreversible syndrome characterized by abnormal involuntary orofacial and limb/trunk movements that normally emerge after long-term antipsychotic treatment (Gardos et al. 1987). Alternatively, pro-dopaminergic drugs (e.g. cocaine, amphetamine, L-DOPA) can induce dyskinesias (usually termed choreiform movements) during the acute and withdrawal phases, and especially after treatment with antipsychotics. The original hypothesis put forth to explain dyskinesia suggested that chemical denervation by antipsychotics led to striatal dopaminergic hyperactivity via upregulation and supersensitivty of the remaining dopamine receptors (Klawans and

Rubovitz, 1972). In support of this view, there is evidence that monkeys that underwent dopaminergic denervation (91-97%) of the basal ganglia with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exhibited significantly increased binding to D_2, but not D_1 receptors in this region (Graham et al. 1990). There is also evidence that oral dyskinesia induced by D_2 antagonists in monkeys was significantly reduced following treatment with the partial dopamine agonist, SDZ HAC-911 (Peacock and Gerlach, 1993). On the other hand, chronic treatment of monkeys with low or high doses of D_1 antagonists has been shown to induce mild acute dyskinesia, but there are no reports of tardive dyskinesia following treatment with these agents (Gerlach and Hansen, 1993; Lublin et al. 1994). Similarly, greater improvement in tardive dyskinesia was witnessed in the combined D_1 and D_2 antagonist treatment group, relative to monkeys who were treated with D_2 antagonists-alone (Peacock et al. 1999a,b). These findings imply that D_1 antagonism is a favourable property for antipsychotics to have when tardive dyskinesia is a concern.

Tardive dyskinesia is often exacerbated in schizophrenia patients following a reduction in dosages, suggesting that it may be a state of antipsychotic-withdrawal (Anand and Dewan, 1996; Tranter and Healy, 1998). In support, we recently showed that in patients who were switched to ziprasidone, abrupt discontinuation of typical antipsychotics resulted in elevated rates of dyskinesia, relative to patients who were slowly withdrawn from medication (Stip et al. 2010). We also found that patients, who were abruptly discontinued exhibited significantly less improvement on the BPRS, compared those who were slowly withdrawn. These data corroborate reports of an association between tardive dyskinesia and antipsychotic withdrawal-induced supersensitivity psychosis in the literature (Chouinard, 1991; Roy-Desruisseaux et al. 2011; Fallon and Dursun, 2011). In a similar vein, acute dyskinesia may be exacerbated by antipsychotic treatment – as illustrated by the case of a psychostimulant-naïve 7-year old boy who recently stopped taking risperidone and developed twitching

movements of his hands and feet, mouth movements, tongue protrusion, shoulder shrugging, and aggressive behaviour following initiation of methylphenidate (a dopamine transporter inhibitor; Hollis and Thompson, 2007).

Several pharmacological agents have been tried as treatment for tardive dyskinesia, including pro-dopaminergic drugs, dopamine depleting agents, and anticholinergics. However, none of these treatments has yielded consistently beneficial results and some may aggravate the syndrome. Consequently, once tardive dyskinesia becomes manifest it is important to reduce the risk of worsening symptoms by employing the lowest effective dose, switching to an atypical antipsychotic, or eventually discontinuing the medication, if possible (Mattay and Casey, 2003).

1.4.1.3 Dystonia

Dystonia is a hyperkinetic disorder of the basal ganglia that features prolonged muscle spasms (0.5-5 seconds) in agonist and antagonist muscles (Richter and Loscher, 1998). Dystonia can be classified in a number of different ways. Focal dystonia involves contractions of a specific body part, whereas generalized dystonia involves contractions of the entire body. Dystonia can be primary (i.e. characterized by lack of aetiology) or secondary (e.g. due to disease, lesions, and antipsychotics). Dystonia can be acute or tardive; the latter involves sustained abnormal postures and may persist for months or years after discontinuation of antipsychotic drugs (Mattay and Casey, 2003). Imaging studies have revealed that dystonia is often observed in stroke patients with lesions of the putamen, globus pallidus and thalamus (Mink, 1996). Additionally, there is evidence of decreased D_2-binding in the putamen of individuals with primary dystonia (Perlmutter et al. 1997). On the other hand, secondary dystonia is often the consequence of concomitant administration of psychostimulants and typical

antipsychotics, possibly due to dopaminergic supersensitivity (van Harten; et al. 1998; Evans et al. 2001).

In monkeys, studies show that D_1 antagonists produce dystonia when administered at high doses, as well as at low doses following pretreatment with D_2 antagonists; however, tolerance to this effect develops after a few days of treatment (Kistrup and Gerlash, 1987; for review, see Gerlach et al. 1996). Significantly, Peacock et al. (1999a) showed that tolerance to dystonia occurred during combined treatment with D_1 and D_2 antagonists in monkeys pretreated with D_2 antagonists; however, the tolerance disappeared when the former were discontinued and monkeys continued to receive the latter. Likewise, there is evidence that both SCH23390 (a selective D_1 antagonist) and raclopride (a selective D_2/D_3 antagonist) induced identical levels of dystonia and this effect was completely reversed by administration of biperiden (an anticholinergic) and LY171555 (a selective D_2 agonist; Kistrup and Gerlach, 1987). These studies indicate that antipsychotics that block D_1 (in addition to M_4) receptors may be preferred for individuals with a history of drug-induced dystonia.

1.4.1.4 Akathisia

Akathisia is the subjective feeling of restlessness, coupled with the presence of objective restlessness. Akathisia is described by patients as feeling uptight, anxious, and unable to relax, and it is associated with suicidal behaviour in schizophrenia (Barnes, 1989). Acute akathisia typically begins within hours to days following the onset of antipsychotic treatment. By contrast, tardive akathisia is differentiated by its persistence for months or years after discontinuation of antipsychotic therapy. Objective signs of akathisia include pacing, crossing and uncrossing the legs, rocking back and forth, and lifting the feet as if marching in place. Akathisia is often misdiagnosed as psychotic agitation, leading to an escalation of antipsychotic dose and aggravation of the initial symptoms (Mattay and Casey, 2003).

The pathophysiology is of akathisia is unclear; however, a number of neurotransmitters, including dopamine, serotonin, noradrenaline, acetylcholine and GABA have been implicated. This has stemmed from observations that akathisia is treated with beta-adrenergic blockers, anticholinergics, and benzodiazepines, and induced/aggravated by dopaminergic antagonists and serotonin transporter blockers (Sachdev and Brüne, 2000). Using PET, Farde (1992) demonstrated that akathisia, in response to D_1 and D_2 antagonism, was clinically indistinguishable between schizophrenia patients and healthy controls, and it occurred at similar levels of SCH-23390 and raclopride binding in basal ganglia (40-73%). The regions of basal ganglia may not be the only structures implicated in the pathophysiology of akathisia, however. For instance, case reports have evidenced reduced metabolic activity in the thalamus and cerebellum of a patient with antipsychotic-induced akathisia, and lesions of the prefrontal cortex in a patient with akathisia resulting from a traumatic brain injury (Silver and Yablon, 1996; Landgrebe et al. 2006). Unfortunately, however, experimental studies on this topic are rare and will need to be addressed by future research.

1.5 Schizophrenia and SUDs

Schizophrenia is associated with a nearly 50% lifetime prevalence of SUDs (excluding nicotine; Regier et al. 1990). In absolute numbers, patients who suffer from schizophrenia use alcohol and cannabis more frequently than cocaine. However, in relative numbers, cocaine abuse/dependence in schizophrenia is associated with the highest risk (odds ratio = 13), compared to the general population (Regier et al. 1990). Compared to non-abusing patients, dual diagnosis schizophrenia patients (DD) are more frequently hospitalized, non-compliant with treatment, suicidal, impulsive and violent, homeless and unemployed, and they have more legal and health problems (Mueser et al. 1998; Negrete, 2003). Moreover, there is

evidence that DD patients have more psychiatric and neurological symptoms, relative to non-abusing patients (Potvin et al. 2006a; Maat et al. 2008).

1.5.1 Psychiatric effects

Studies suggest that substance abuse is a major risk factor for the development of depression among the general public (Lynskey et al. 2004; Falck et al. 2006). In schizophrenia, a recent meta-analysis of 3283 patients revealed that DD patients experience more severe depressive symptoms compared to non-abusing patients (Potvin et al. 2007). In addition, substances of abuse can induce transient psychosis and anxiety that may be indistinguishable from schizophrenia and anxiety/panic disorders (Mauri et al. 2007; Lapworth et al. 2009). In the more serious case of psychosis, individuals may be diagnosed as having substance-induced psychotic disorder according to the DSM-IV if they include prominent delusions or hallucinations coupled with a lack of insight (Mathias et al. 2008).

Alcohol produces a range of effects depending on dose, including euphoria, anxiety, depression, psychotic reactions, stupor, and coma (West and Gossop, 1994; Jordaan et al. 2009). A recent comparison between alcohol-induced psychotic disorder and schizophrenia revealed that the former had significantly higher levels of depressive and anxiety symptoms, fewer negative and disorganized symptoms, better insight and judgment, and less functional impairment compared with patients with schizophrenia (Jordaan et al. 2009). In schizophrenia, there is evidence that patients with baseline paranoia or hallucinations reported an increase in these symptoms after drinking. Alcohol-abusing schizophrenia patients were also significantly more likely than those without schizophrenia to cite relief of depression and problems or worries as a reason for alcohol use (Pristach and Smith, 1996). Overall, there is evidence that alcoholism is associated with greater non-compliance, relapse, homelessness,

physical illness, suicidal behaviour, violence and hospital readmission in schizophrenia (Drake et al. 1989; Batki et al. 2009; Gerding et al. 1999; Rasanen et al. 1998).

THC intoxication is associated with feelings of euphoria/mania, anxiety and paranoia/hallucinations (D'Souza et al. 2004). In schizophrenia, an important experimental study demonstrated that THC transiently exacerbated a range of positive and negative symptoms (D'Souza et al. 2005). The positive symptoms induced in these patients were similar to their typical symptoms; the exacerbations were brief, modest, and occurred even though subjects were clinically stable, medication responsive and treated with therapeutic doses of antipsychotics. Analysis of negative symptoms revealed that patients were more blunted, less talkative, less spontaneous, and more internally preoccupied (D'Souza et al. 2005). With regards to long-term consequences of cannabis use, a 10-year follow-up study by Foti et al. (2010) revealed that lifetime cannabis use was associated with earlier onset of psychosis and increased positive symptoms, even after controlling for potential confounding variables. By contrast, there is evidence that the prevalence of suicidal attempts was increased in schizophrenia patients without cannabis use and they spent more time in hospital (Makkos et al. 2011). Similarly, a recent study of first-episode patients revealed that cannabis abusers had a significantly shorter duration of untreated psychosis and less negative symptoms, compared to non-abusing patients (Burns et al. 2010). As a whole, these findings may be reconciled if we assume that some cannabis abusers may represent a different (e.g. younger, male, lower illness severity) subpopulation of schizophrenia patients.

Cocaine use is associated with psychiatric symptoms in non-psychosis individuals that can be similar to those seen in schizophrenia (Caton et al. 2000; Mauri et al. 2007). Recently, a retrospective study of 674 cocaine users admitted to the emergency room found that psychiatric symptoms were the most frequent complaints (60.9%) associated with dependant and non-dependant cocaine use. Of these, the most common were anxiety (31.5%), agitation

(26.1%), paranoia (16.8%), psychosis (12.2%), depression (4.2%) and hallucinations (3.6%; Pavarin et al. 2011). In more severely dependent individuals – including those that use intravenous and smoked (crack) cocaine – psychotic symptomatology may be observed in nearly 90% of patients (Brady et al. 1991; Smith et al. 2009). In schizophrenia, research suggests that patients who abuse cocaine may have more hallucinations and depression/anxiety (Lysaker et al. 1994; Serper et al. 1995, 1999). There is also evidence that schizophrenia patients with a history of cocaine abuse/dependence are more depressed, relative to their non-abusing counterparts (Sevy et al. 1990). Similarly, a comparison between cocaine dependant patients with and without schizophrenia revealed that schizophrenia patients reported having significantly more energy, craving, depression and feeling worse and these differences were stable at the 72-hours follow-up (Carol et al. 2001). Taken together, the aforementioned studies show that alcohol, cannabis, and cocaine may induce schizophrenia-like psychiatric symptoms in non-psychosis individuals and aggravate these symptoms in schizophrenia patients.

1.5.2 Extrapyramidal effects

Alcohol and drugs of abuse may induce extrapyramidal symptoms in psychosis and non-psychosis patients. Alcohol acutely alters the functioning of the basal ganglia, and its long-term use produces anatomic and physiological changes in the striatum (Wang et al. 2000; Martinez et al. 2005; Sullivan et al. 2005). Among non-psychosis individuals, alcohol abuse was shown to produce enhanced body sway and action tremor during acute and protracted withdrawal (Bauer et al. 1993; Sullivan et al. 2010). Among schizophrenia patients, alcohol abuse was found to be related to more severe orofacial dyskinesia and akathisia (Duke et al. 1994). Moreover, there is evidence that inhalation of THC reduced raclopride binding in the ventral striatum and the precommissural dorsal putamen, suggesting an increase in dopamine

release (Bossong et al. 2009). In schizophrenia, current cannabis use and intravenous THC aggravated the presence of tardive dyskinesia, which is consistent with the dopaminergic supersensitivity hypothesis (Zaretsky et al. 1993; D'Souza et al. 2005). Alternatively, there is evidence that cannabis smoking may serve as a protective factor against the development of dyskinesia (Niehaus et al. 2008). Further research is needed to confirm these findings.

Long-term abuse of cocaine and amphetamine is associated with significant reduction in dopamine D_2 receptor availability in the striatum that may last for months after detoxification, similar to the striatal dopaminergic deficit observed in Parkinson's disease (Volkow et al. 2004). Studies in non-psychosis individuals have shown that cocaine abuse may produce extrapyramidal symptoms, including rigidity and Parkinsonian resting tremor—a symptom that has been shown to last as long as 12 weeks into abstinence (Bauer et al. 1993, 1996). Among schizophrenia patients, studies have revealed that cocaine use is a major risk factor for dystonia, parkinsonism, dyskinesia, and akathisia (Potvin et al. 2006a; Maat et al. 2008). Overall, a recent meta-analysis of studies investigating the effects of substance abuse on extrapyramidal symptoms in patients dually diagnosed with schizophrenia and SUDs revealed that these patients had more severe extrapyramidal symptoms, relative to non-abusing schizophrenia patients; an effect that was most prominent in dually diagnosed cocaine abusers (Potvin et al. 2009).

1.6 Hypotheses and research objectives

In the following sections, I will examine the results of the present trial which compared SUD outcomes as well as psychiatric and extrapyramidal (neurological) symptoms in substance abusers with and without schizophrenia, and in non-abusing schizophrenia patients at baseline, and after 12-weeks of treatment with quetiapine. This antipsychotic was chosen because it has previously been shown to improve substance use outcomes and psychiatric

symptoms in psychosis and non-psychosis patients (Potvin et al. 2004, 2006; Pinkofsky et al. 2005; Martinotti et al. 2008), while also producing little or no extrapyramidal symptoms (Weiden, 2007). Because this was a naturalistic study, the prescribed dose of quetiapine was determined by the treating physician.

The goal of this project was improve our understanding of the complex relationships between substance abuse and schizophrenia. It was also expected to help elucidate the clinical consequences of substance abuse in schizophrenia patients as well as their potential treatment by pharmacological means. Our hypothesis was that quetiapine treatment would result in improvements in substance abuse and clinical variables (psychiatric and neurological symptoms) across the groups. We also expected that improvements in substance use outcomes would be less pronounced in DD patients, relative to non-psychosis substance abusers (SUD arm). We made this hypothesis because of evidence that DD patients have a hard time quitting alcohol and/or drugs (Ziedonis et al. 2005). In order to contextualize the present study, I will present our supplementary data on outcomes in the SUD arm and on between the three groups at baseline. Moreover, I will examine findings from our systematic review on antipsychotics for the treatment of SUDs in patients with and without comorbid psychosis. We conducted this review to understand the impact of psychosis-status and substance-type on SUD outcomes – the latter issue being specifically important because of the inclusion of polysubstance abusers in the present trial. Second, I will examine findings from our systematic review on the dose-response and comparative efficacy and tolerability of quetiapine across psychiatric disorders. We conducted this review to understand the impact of quetiapine-dose on different psychiatric symptoms such as anxiety, depression, and psychosis and to understand the potential implications of the differences in prescribed quetiapine dose among the three groups in the present study.

2 Extrapyramidal symptoms in substance abusers with and without schizophrenia and in nonabusing patients with schizophrenia.

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Extrapyramidal symptoms in substance abusers with and without schizophrenia and in non-abusing patients with schizophrenia

Simon Zhornitsky[1]; Emmanuel Stip[1]; Tania Pampoulova[1,2]; Élie Rizkallah[1,2]; Olivier Lipp[1]; Lahcen Aït Bentaleb[1]; Jean-Pierre Chiasson[2]; Stéphane Potvin[1].

[1]Fernand-Seguin Research Centre, Department of Psychiatry, Faculty of Medicine, University of Montreal; Montreal, Canada

[2]Clinique du Nouveau-Départ; Montreal, Canada

Corresponding author

Stéphane Potvin
Centre de recherche Fernand-Seguin
7331 Hochelaga
Montreal, Quebec, Canada
H1N 3V2
Tel: (514) 251-4015
Fax: (514) 251-2617

2.1 Abstract

Background Extrapyramidal symptoms (EPS) such as parkinsonism, dystonia, dyskinesia, and akathisia are conditions of impaired motor function which are associated with chronic antipsychotic treatment in schizophrenia. In addition, EPS are often exacerbated by psychoactive substance (PAS) abuse, which is frequently observed in this population. Few studies, however, have investigated the contribution of PAS abuse on EPS in PAS-abusers without comorbid psychosis. ***Methods*** The present study compared the occurrence of EPS in outpatient schizophrenia patients with (DD group; n=36) and without PAS abuse (SCZ group; n=41) as well as in non-schizophrenia PAS abusers undergoing detoxification (SUD group; n=38). Psychiatric symptoms were measured using the Positive and Negative Syndrome Scale and the Calgary Depression Scale for Schizophrenia. Extrapyramidal symptoms were evaluated with the Extrapyramidal Symptoms Rating Scale and the Barnes Akathisia Scale. SUD diagnoses were complemented with urine drug screenings. ***Results*** We found that DD patients exhibited significantly more parkinsonian symptoms than SCZ patients and SUD individuals. Our sub-analyses revealed that cocaine and alcohol abuse/dependence was responsible for the increase in parkinsonism in DD patients. Additionally, we found that SUD individuals exhibited significantly more akathisia than the other two groups. In these latter individuals, sub-analyses revealed that alcohol and cannabis abuse/dependence was responsible for the increase in akathisia. ***Conclusion*** Our results suggest that PAS abuse is a contributor to EPS in individuals with and without schizophrenia.

Key words schizophrenia – substance use disorders – extrapyramidal symptoms – antipsychotics

2.2 Introduction

Schizophrenia is the most disabling psychiatric disorder, according to the Global Burden of Disease (GBD) study.[1] A major factor that contributes to occupational and social dysfunction in schizophrenia is poor treatment compliance.[2] Studies have shown that approximately two thirds of schizophrenia patients are only partially compliant or completely noncompliant with the medication they are prescribed, thereby greatly increasing the chances of psychotic relapse, rehospitalization and suicide.[2-4] Interestingly, a study by Garcia-Cabeza et al.[5] found that differences in negative subjective response to antipsychotic drugs and poor treatment compliance were strongly related to the presence of extrapyramidal symptoms (EPS) such as akathisia (subjective and observed restlessness), dystonia (muscular cramps), parkinsonism (resting tremor, bradykinesia, and rigidity) and tardive dyskinesia (repetitive and involuntary movements).[6,7] Although these symptoms may have disparate pathophysiologies, they have been found to occur during high levels of striatal dopamine D2 receptor occupancy by antipsychotics, which was also associated with worse subjective experience and increased substance abuse.[8,9,10,11]

The problem of antipsychotic-induced EPS is further compounded by the fact that schizophrenia is associated with a nearly 50% lifetime prevalence of substance use disorders (SUDs).[12] An aggravation of EPS via administration of antipsychotics and/or some psychoactive substances (PAS) such as alcohol, cocaine, amphetamine and cannabis is conceivable because these compounds have effects on the basal ganglia – a group of subcortical nuclei which are vital for voluntarily movement.[6] Cocaine and amphetamine stimulate striatal dopaminergic neurotransmission by blocking and reversing the dopamine transporter, respectively.[13] However, their long-term abuse is associated with significant reduction in dopamine D_2 receptor availability in the striatum that may last for months after detoxification,[14] similar to the striatal dopaminergic deficit observed in Parkinson's disease.[6]

Studies in non-psychosis individuals have shown that cocaine abuse may produce extrapyramidal symptoms, including rigidity[15] and parkinsonian resting tremor – a symptom that has been shown to last as long as 12 weeks into abstinence.[16,17] Conversely, there is evidence that prior regular use of amphetamines is common in patients with Parkinson's disease.[18] In schizophrenia patients, studies have revealed that cocaine use is a major risk factor for dystonia, parkinsonism, dyskinesia and akathisia.[19,20,21,22]

Alcohol acutely alters the functioning of the basal ganglia,[23] and its long-term use produces anatomic and physiological changes in the striatum.[24,25] In non-psychosis individuals, alcohol abuse was shown to produce enhanced body sway and essential tremor during acute and protracted withdrawal.[16,26] In schizophrenia patients, alcohol abuse was found to be related to more severe orofacial dyskinesia and akathisia.[27]

As for cannabis, there is evidence that inhalation of delta-9-tetrahydrocannabinol (THC) – the main psychoactive constituent of cannabis – reduced raclopride binding in the ventral striatum and the precommissural dorsal putamen, suggesting an increase in dopamine release.[28] In schizophrenia patients, current cannabis use[29] and intravenous THC[30] aggravated the presence of tardive dyskinesia. On the other hand, there is evidence that cannabis smoking may serve as a protective factor against the development of dyskinesia.[31] Altogether, our recent meta-analysis of studies investigating the effects of PAS abuse on EPS in patients dually diagnosed with schizophrenia and an SUD revealed that these patients had more severe EPS relative to non-PAS abusing schizophrenia patients; an effect that was most prominent in dually diagnosed cocaine abusers.[32] Unfortunately, one of the major problems with the studies conducted thus far has been the lack of a non-psychosis drug abuser group, thereby preventing researchers from elucidating the respective contributions of antipsychotics and drugs of abuse on EPS in schizophrenia. For this purpose, the present study is the first of its kind to

investigate EPS and PAS abuse in all three groups (i.e. dually-diagnosed schizophrenia patients, non-PAS abusing schizophrenia patients and non-psychosis PAS abusers).

2.3 Methods

Participants

Three groups of participants were recruited, namely: (i) patients with schizophrenia-spectrum disorders (schizophrenia, schizo-affective disorder, schizophreniform disorder); (ii) non-psychosis patients with SUDs in detoxification; and (iii) schizophrenia patients with comorbid SUDs. Psychiatric and SUD diagnoses were all based on DSM-IV criteria. Most SUD diagnoses were complemented with urine drug screenings (91% of patients). All participants signed a detailed consent form. The study was approved by the local ethics committee.

Patients in the dual-diagnosis schizophrenia group (DD; n=36) had one or more of the following substance use disorders (abuse or dependence): alcohol (n=19), cannabis (n=22), psychostimulants (cocaine and amphetamines) (n=11), hallucinogens (n=1) and phencyclidine (n=1), including 14 patients with poly-substance abuse/dependence. Substance abuse/dependence diagnoses were complemented with urine drug screenings. Patients were treated with one or more of the following antipsychotic: clozapine (n=1), olanzapine (n=22), risperidone (n=7), quetiapine (n=2), ziprasidone (1), haloperidol (n=4), flupenthixol (n=1) and other typical antipsychotics (n=6).

Non-PAS abusing schizophrenia patients (SCZ; n=41) were treated with one or more of the following antipsychotics: clozapine (n=7), olanzapine (n=9), risperidone (n=8), quetiapine (n=9), haloperidol (n=4), flupenthixol (n=2), and other typical antipsychotics (n=7).

As for non-psychosis substance-abusing patients (SUD; n=38), they had one or more of the following substance use disorders (abuse or dependence): (i) alcohol (n=25), cannabis (n=18), cocaine (n=12), amphetamines (n=4)**,** opiates (n=2), and benzodiazepines (n=1) – including 16 individuals with poly-substance abuse/dependence. Substance abuse/dependence diagnoses were complemented with urine drug screenings. No patient in the SUD group had a

history of antipsychotic treatment at the moment of testing. There were 3 cases of substance-induced psychosis in the SUD group; however, a reexamination of patients after 3 months revealed no cases of schizophrenia.

Clinical assessments

Psychiatric symptoms were measured using the Positive and Negative Syndrome Scale (PANSS)[33] and the Calgary Depression Scale for Schizophrenia (CDSS).[34] We chose the CDSS because it has previously been shown to exhibit little overlap with negative symptoms and EPS in schizophrenia[35,36] and because it is less likely to over-estimate depressive symptoms in dual-diagnosis schizophrenia, compared to other scales, as shown previously by our group.[37] For its' part, the PANSS has previously been used to measure positive symptoms in various psychiatric disorders,[38] including cases of drug-induced psychosis.[39] EPS were evaluated with the Extrapyramidal Symptoms Rating Scale (ESRS).[40] The ESRS provides a score for the patients' subjective appraisal of his symptoms, objective scores for parkinsonism, dystonia and dyskinesia. Akathisia was evaluated with the Barnes Akathisia Scale.[41] EPS were assessed by a well-trained physician (TP) with a unique expertise in psychiatry, neurology and addiction medicine. The screening of EPS was performed to distinguish EPS from symptoms resembling EPS. A particular effort was made to distinguish akathisia from pseudoakathisia; the latter being characterized by observed fidgety, restless movements without the subjective compulsion to move.[42] Likewise, a particular effort was made to distinguish parkinsonian resting tremor from essential tremor, commonly associated with alcohol withdrawal.[43] Finally, an experienced team of clinicians verified that DD patients were not intoxicated at the moment of clinical assessments.

Statistical analyses

Differences in EPS and psychiatric symptoms between the DD, SCZ and SUD groups were analyzed using one-way analyses of variance (ANOVA) with group as the independent variable. Multiple comparisons were performed and p-values were adjusted using a Bonferroni correction. The potential influence of confounding factors was analyzed with analyses of covariance (ANCOVA). Dichotomous variables were evaluated using Pearson's Chi-square test. The level of significance was set at $p<0.05$. Statistical analyses were performed using the Statistical Package for Social Sciences (version 14).

2.4 Results

Extrapyramidal symptoms

Between-group differences were found for parkinsonism, dyskinesia, and akathisia. Multiple comparisons revealed that DD (mean = 9.2 [13.5]) exhibited significantly more parkinsonism than SCZ patients (mean = 3.2 [3.9]; F= 4.711; p= 0.011). Dyskinesia was significantly higher in SCZ patients (mean = 1.6 [3.3]) than in SUD individuals (mean = 0.3 [1.0]; F= 3.755; p= 0.026). Akathisia was significantly higher in SUD individuals (mean = 1.4 [1.2]) than in SCZ patients (mean = 0.6 [1.2]; F= 4.321; p= 0.016). No between-group differences were found for subjective extrapyramidal symptoms.

Because we found that DD patients exhibited significantly more parkinsonism than SCZ patients, we performed sub-analyses to parcel out the contribution of specific PAS to these results. Sub-analyses revealed that the increase in parkinsonism in DD patients was related to alcohol (n=19) (F= 11.884; p= 0.001) and psychostimulants (n=11) (F= 14.618; p= 0.0001). Because we found that SUD individuals exhibited significantly more akathisia than SCZ patients, we performed sub-analyses to parcel out the contribution of specific PAS to these results. Sub-analyses revealed that the increase in akathisia was related to alcohol (n=25) (F= 4.187; p= 0.047) and cannabis (n=18) (F= 13.604; p=0.001).

Psychiatric symptoms

Between-group differences were found for PANSS positive, negative and total scores as well as for CDSS scores. Multiple comparisons revealed that DD patients had significantly higher PANSS positive scores (mean = 18.8 [4.8]) than SUD individuals (mean = 15.4 [5.2]; F= 4.498; p= 0.013). Both DD (mean = 16.4 [4.3]) and SCZ patients (mean = 18.7 [4.9]) had significantly higher PANSS negative scores than SUD individuals (mean = 13.6 [4.7]; F=10.966; p= 0.0001). PANSS total scores were significantly higher in DD patients (mean =

79.2 [10.3]) than in SUD individuals (mean = 69.5 [15.5]; F= 4.726; p= 0.011). CDSS scores were significantly higher in DD (mean = 7.2 [4.8]) and SUD individuals (mean = 6.7 [4.4]) SCZ patients (mean = 3.5 [3.8]; F= 8.440; p= 0.0001). No significant difference was found in PANSS general scores.

Socio-demographic variables

Between-group differences were found for age and number of hospitalizations. Multiple comparisons revealed that DD patients were significantly younger (mean [SD] = 31.4 [10.4]) than SCZ (mean = 37.8 [10.8]) and SUD individuals (mean = 37.9 [12.4]; F= 4.261; p= 0.016). DD patients (mean = 2.9 [3.0]) also had significantly fewer hospitalizations than SCZ patients (5.1 [4.8], respectively; t= -2.245; p= 0.028). SUD individuals spent on average significantly more dollars on PAS (mean = 795.6$ [1748.6]) than DD patients (mean = $82.3 [62.3]; F= 5.978; p= 0.017). DD and SCZ patients were outpatients, while SUD individuals were undergoing detoxification at an addiction treatment centre. The groups did not differ in terms of sex, ethnicity, psychiatric diagnosis, chlorpromazine equivalents, or anticholinergics (Table 1).

In order to control for potential confounding factors that may have contributed to our results, ANCOVAs were performed on significant socio-demographic variables (age and number of hospitalizations). The between-group differences in dyskinesia disappeared after using hospitalizations as a covariate (p=0.086). All other previously significant differences in EPS remained significant (all $p<0.05$).

2.5 Discussion

The present cross-sectional study is the first of its kind to examine EPS in dually-diagnosed schizophrenia patients, in non-PAS abusing schizophrenia patients and in non-psychosis PAS abusers. Analysis of EPS – our primary outcome measure – revealed that DD patients displayed significantly more parkinsonism compared to SCZ patients, while SUD individuals displayed significantly more akathisia than SCZ patients. In terms of parkinsonism, sub-analyses on specific PAS revealed that cocaine and alcohol abuse/dependence was significantly related to the severity of parkinsonian symptoms in DD patients. Consistent with our findings, previous studies in DD patients have shown cocaine use to be a major risk factor for parkinsonian symptoms. For example, Potvin et al.[21] found that compared to abstinent patients, DD patients displayed greater parkinsonism, which was significantly associated with cocaine use. Likewise, Maat et al.[22] demonstrated recent cocaine use to be significantly associated with the severity of parkinsonism in schizophrenia patients. For its part, alcohol was shown to produce parkinsonian-like symptoms in non-psychosis individuals during acute and protracted withdrawal.[16,26] Here, we report increased parkinsonian symptoms in alcohol abusing DD patients, relative to SCZ patients. Together, these data suggest that there is a compounding effect on parkinsonism as a result of alcohol and/or cocaine abuse and antipsychotic treatment in DD patients. It is also interesting that SUD individuals displayed significant amounts of parkinsonism, suggesting that PAS abuse and treatment with antipsychotics do not differ in their liability to produce parkinsonian symptoms – at least in the short-term.

In SUD individuals, we found significantly more akathisia relative to SCZ patients. Sub-analyses revealed that these symptoms were significantly related to alcohol and cannabis abuse/dependence. Previous studies in non-psychosis individuals have found alcohol withdrawal to be associated with the presence of restlessness[44] and psychomotor unrest.[45] In

addition to alcohol, our sub-analyses revealed that cannabis abuse was significantly associated with the presence of akathisia in SUD individuals. While not commonly associated with withdrawal symptoms in popular culture, heavy cannabis use has been shown to induce restlessness[46] and physical tension/agitation during withdrawal; symptoms which may last as long as 28 days.[47] Although the aforementioned studies did not distinguish between akathisia and pseudoakathisia, the present study did not score patients as having akathisia unless they complained of subjective restlessness, in addition to exhibiting observed, restless movements.[42] Consequently, our results confirm the presence of moderate amounts of 'true' akathisia in alcohol and cannabis withdrawal and suggest that this symptom may be more severe – at least transiently – than akathisia resulting from antipsychotic treatment (mostly atypicals, here).

Although counterintuitive, the finding that our SUD sample had more akathisia than our DD sample may be explained by the fact that the former individuals were undergoing detoxification, while the latter were active users. Moreover, DD patients in the present study spent significantly less money on PAS; a result that coincides with evidence that even infrequent use of small amounts of PAS can cause clinically relevant problems in individuals with schizophrenia[48] – possibly due to sensitization of their reward system.[49]

While previous studies have found abuse of PAS to be significantly associated with dyskinesia in DD patients[21,22,50], this was not found in the present study. Interestingly, it was our SCZ patients that exhibited the most severe dyskinesia. One explanation for these findings is that our SCZ sample was significantly older than our DD sample, and consequently, these patients are expected to have been treated with antipsychotics for longer periods of time. Indeed, after controlling for the number of hospitalizations (an indirect measure of duration of antipsychotic treatment), the differences in dyskinesia disappeared.

No between-group differences were found for dystonia. This is consistent with the results of our meta-analysis which found a non-significant effect size for dystonia.[32] It must also be considered that there was a low incidence of dystonia in our overall sample. In SUD individuals, there is evidence of dystonic reactions following concomitant administration of intravenous cocaine and high doses of the neuroleptic flupenthixol.[51] In the present study, however, the majority of schizophrenia patients (DD and SCZ groups) were treated with atypical antipsychotics, some of which bind more loosely to dopamine-D_2 receptors[52]; whereas SUD individuals were not undergoing antipsychotic treatment. Also noteworthy, both DD and SUD individuals were abusing mixed PAS, not stimulants specifically.

Analysis of between-group differences in schizophrenia symptoms revealed that DD patients exhibited the highest PANSS positive and total scores of the three groups. These results are consistent with previous studies showing that PAS-abusing schizophrenia patients are at a greater risk for psychotic relapse than abstinent patients.[32,53] Interestingly, the level of positive symptoms did not differ between SUD and SCZ patients. As such, this result confirms previous reports showing that psychotic reactions are common in patients with substance abuse/dependence.[54] On the other hand, despite the high PANSS positive scores in SUD subjects in the present study, only 3 out of 40 subjects in the SUD group responded to a diagnosis of substance-induced psychotic disorder. This may be explained by the fact that insight was still present in most SUD subjects, even when experiencing symptoms such as paranoia. In addition, it must be considered that the PANSS is not a diagnostic tool. While the strength of the PANSS is its reliability and its low risk of creating type II errors, the scale may lack specificity.[33] As for negative symptoms, the present study found that both DD and SCZ patients had significant amounts of negative symptoms, compared to SUD individuals – symptoms which may be resistant to antipsychotic treatment.[55] These results suggest that,

unlike positive symptoms, negative symptoms may be more unique to schizophrenia rather than arising due to PAS abuse.[56]

Finally, our results revealed that depression scores were significantly higher in DD and SUD individuals than in SCZ patients. Consistent with these results, previous studies found that DD patients have more depressive symptoms.[37,57,58] In a similar vein, there is evidence that mood disorders and SUDs are often comorbid with each other, suggesting that individuals may abuse PAS in order to relieve depressive symptoms or that PAS abuse may lead to the development and/or exacerbation of these symptoms.[59] Thus, our results add further support for a significant association between depression and abuse of PAS, both in psychosis and non-psychosis patients. Our results suggest that depressive symptoms are more strongly associated substance abuse than to schizophrenia – at least transiently. Assuredly, these results will need to be replicated by other groups.

Limitations

The present study has limitations. First, our DD and SUD samples differed in that the former were active PAS abusers, while the latter were undergoing detoxification. Additionally, the aforementioned groups differed in the amount of money spent on PAS, suggesting a different degree of abuse in these samples. The latter confound may be unavoidable, however, because schizophrenia only minimal quantities of PAS can cause clinically relevant changes in schizophrenia patients.[48] Moreover, although the increased frequency of parkinsonism in the DD group could be due to the presence of more clozapine-treated patients in the SCZ group, only 4 out of 7 patients were taking clozapine as their sole antipsychotic in the SCZ group; the other 3 patients were administered clozapine in combination with another antipsychotic. Finally, the lack of follow-up of the present study prevents us from revealing the temporal relationship of PAS-induced EPS and whether they are transient or stable in time.

Conclusion

Despite its limitations, the present study is the first of its kind to cross-sectionally examine EPS in the three groups (DD, SCZ and SUD). Indeed, all of the studies to date investigating the effects of antipsychotics and PAS on EPS in schizophrenia have lacked a group of antipsychotic-free non-psychosis PAS-abusers. Moreover, the present study contains a relatively large sample size (n=115) coupled with a careful clinical evaluation, paying particular attention to measuring EPS and not merely symptoms resembling EPS. We found that DD patients exhibit significantly more parkinsonian symptoms than SCZ patients and non-psychosis PAS abusers. Our sub-analyses revealed that cocaine and alcohol abuse/dependence was responsible for the increase in parkinsonism in DD patients. By contrast, we found that non-psychosis PAS abusers exhibit significantly more akathisia than the other two groups. In these latter individuals, sub-analyses revealed that alcohol and cannabis abuse/dependence was responsible for the increase in akathisia. In sum, our results demonstrate that PAS abuse is a contributor to EPS in individuals with and without schizophrenia. Future research should include a follow-up in order to elucidate the temporal relationship of PAS-induced EPS and to determine whether these symptoms are transient or stable through time.

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TABLE 1. *EPS, psychiatric symptoms, and sociodemographic variables*

Variable	DD group (n = 36)	SCZ group (n = 41)	SUD group (n = 38)	Statistics	Multiple comparison*
Extrapyramidal symptoms					
Subjective	4.1 (3.3)	4.3 (3.6)	5.9 (5.1)	$F = 2.138$; $P = 0.123$	–
Parkinsonism	9.2 (13.5)	3.2 (3.9)	6.1 (6.2)	$F = 4.711$; $P = 0.011$	DD > SCZ
Dystonia	0.3 (1.2)	0.3 (1.2)	0.5 (1.5)	$F = 0.091$; $P = 0.913$	–
Dyskinesia	0.6 (1.6)	1.6 (3.3)	0.3 (1.0)	$F = 3.755$; $P = 0.026$	SCZ > SUD
Akathisia	0.8 (1.0)	0.6 (1.2)	1.4 (1.2)	$F = 4.321$; $P = 0.016$	SUD > SCZ
Psychiatric symptoms					
PANSS-positive	18.8 (4.8)	17.4 (4.9)	15.4 (5.2)	$F = 4.498$; $P = 0.013$	DD > SUD
Negative	18.7 (4.9)	16.4 (4.3)	13.6 (4.7)	$F = 10.966$; $P = 0.0001$	DD > SUD SCZ > SUD
General	41.7 (6.0)	38.6 (8.7)	40.5 (8.7)	$F = 1.540$; $P = 0.219$	–
Total	79.2 (10.3)	72.2 (15.1)	69.5 (15.5)	$F = 4.726$; $P = 0.011$	DD > SUD
CDSS	7.2 (4.8)	3.5 (3.8)	6.7 (4.4)	$F = 8.440$; $P = 0.0001$	DD > SCZ SUD > SCZ
Socio-demographic variables					
Age	31.4 (10.4)	37.8 (10.8)	37.9 (12.1)	$F = 4.261$; $P = 0.016$	DD < SCZ DD < SUD
Sex	5 F, 31 M	13 F, 28 M	13 F, 25 M	$X^2 = 4.608$; $P = 0.1$	–
Ethnicity	33 Caucasian	36 Caucasian	36 Caucasian	$X^2 = 1.202$; $P = 0.548$	–
Psychiatric diagnoses	2 SF, 21 SCZ, 13 SA	2 SF, 28 SCZ, 11 SA	All nonpsychosis	$X^2 = 0.846$; $P = 0.655$	–
Weekly dollars spent on PAS	$82.3 (62.3)		$795.6 (1748.6)	$F = 5.978$; $P = 0.017$	–
Hospitalizations	2.9 (3.0)	5.1 (4.8)	–	$t = -2.245$; $P = 0.028$	–
Clinical setting	34 outpatients	38 outpatients	Detoxification	$X^2 = 0.098$; $P = 0.754$	–
Chlorpromazine equivalents (mg)	371.6 (344.9)	529.7 (492.9)	All antipsychotic-free	$t = -1.646$; $P = 0.104$	–
Anticholinergics	3	7	–	$X^2 = 1.296$; $P = 0.255$	–

CDSS, Calgary Depression Scale for Schizophrenia; DD, dual-diagnosis schizophrenia; F, female; M, male; PANSS, Positive and Negative Syndrome Scale; PAS, psychoactive substances; SA, schizoaffective disorder; SCZ, schizophrenia only; SF, schizophreniform disorder; SUD, nonpsychosis patients with substance use disorders.

*After Bonferonni correction.

3 Evolution of substance use, neurological and psychiatric symptoms in schizophrenia and substance use disorder patients: a 12-week, pilot, case-control trial with quetiapine

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S. Zhornitsky executed the research project, statistical analysis, and writing of the first draft.

Evolution of substance use, neurological and psychiatric symptoms in schizophrenia and substance use disorder patients: a 12-week, pilot, case-control trial with quetiapine

Simon Zhornitsky[1]; Emmanuel Stip[1]; Joelle Desfossés[1];Tania Pampoulova[1,2]; Élie Rizkallah[1,2]; Pierre-Paul Rompré[1]; Lahcen Aït Bentaleb[1]; Olivier Lipp[1]; Jean-Pierre Chiasson[2]; Alain Gendron[3]; Stéphane Potvin[1].

[1]Fernand-Seguin Research Centre, Department of Psychiatry, Faculty of Medicine, University of Montreal; 7331 Hochelaga St. Montreal, Quebec, H1N 3V2

[2]Clinique du Nouveau-Départ; 1110 Beaumont Ave. Montreal, Quebec, H3P 3E5

[3]AstraZeneca Pharmaceuticals; 1004 Middlegate Rd. Mississauga, Ontario L4Y 1S2

Corresponding author

Stéphane Potvin
Centre de recherche Fernand-Seguin
7331 Hochelaga
Montreal, Quebec, Canada
H1N 3V2
Tel: (514) 251-4015
Fax: (514) 251-2617

3.1 Abstract

Neurological and psychiatric symptoms are consequences of substance abuse in schizophrenia and non-schizophrenia patients. The present case–control study examined changes in substance abuse/dependence, and neurological and psychiatric symptoms in substance abusers with [dual diagnosis (DD) group, n=26] and without schizophrenia [substance use disorder (SUD) group, n=24] and in non-abusing schizophrenia patients (SCZ group, n=23) undergoing 12-week treatment with the atypical antipsychotic, quetiapine. Neurological and psychiatric symptoms were evaluated with the Positive and Negative Syndrome Scale, the Calgary Depression Scale for Schizophrenia, the Extrapyramidal Symptoms Rating Scale, and the Barnes Akathisia Rating Scale. At endpoint, DD and SCZ patients were receiving significantly higher doses of quetiapine (mean=554 and 478mg/day, respectively), relative to SUD patients (mean=150mg/day). We found that SUD patients showed greater improvement in weekly dollars spent on alcohol and drugs and SUD severity, compared to DD patients. At endpoint, there was no significant difference in dollars spent, but DD patients still had a higher mean SUD severity. Interestingly, DD patients had significantly higher parkinsonism and depression than SCZ patients at baseline and endpoint. On the other hand, we found that SUD patients had significantly more akathisia at baseline, improved more than SCZ patients, and this was related to cannabis abuse/dependence. Finally, SUD patients improved more in Positive and Negative Syndrome Scale positive scores than DD and SCZ patients. Taken together, our results provide evidence for increased vulnerability to the adverse effects of alcohol and drugs in schizophrenia patients. They also suggest that substance abuse/withdrawal may mimic some symptoms of schizophrenia. Future studies will need to determine the role quetiapine played in these improvements.

Key words schizophrenia – substance use disorder – paranoia – akathisia – quetiapine – cannabis

3.2 Introduction

Schizophrenia is the most disabling psychiatric disorder, according to the Global Burden of Disease study (Eaton et al., 2008). Important contributors to disability in schizophrenia are psychiatric (e.g., positive, negative, and depressive symptoms) and neurological symptoms (e.g., parkinsonism, dyskinesia, and akathisia; Patterson et al., 1998; Villalta-Gil et al., 2006; Aubin et al., 2009). Compounding these problems is the nearly 50% lifetime prevalence of substance use disorder (SUD) associated with schizophrenia (Regier et al., 1990). In non-psychotic individuals, substance use is associated with neurological and psychiatric symptoms (Mauri et al., 2007; Zhornitsky et al., 2010a). In schizophrenia patients, substance use has a negative impact on the course of the pathology. Compared to non-abusing patients, dual diagnosis (DD) schizophrenia patients are more frequently hospitalized, non-compliant with treatment, suicidal, impulsive and violent, homeless and unemployed, and they have more legal and health problems (Mueser et al., 1998; Negrete, 2003). Similarly, there is evidence that DD patients have more neurological and psychiatric symptoms than non-abusing schizophrenia patients (Bersani et al., 2005; Potvin et al., 2007, 2009; Harrison et al., 2008).

Current evidence suggests that atypical antipsychotic treatment is associated with improvements in psychiatric symptoms in schizophrenia (Lieberman et al., 2005; Lee et al., 2009; Nakamura et al., 2009). Due to these benefits, as well as their low propensity to induce neurological symptoms, atypical antipsychotics are increasingly being tried as treatments for substance abuse in psychotic and non-psychotic patients (for review, see Zhornitsky et al., 2010b). Indeed, previous studies in single- and DD patients suggest that atypical antipsychotics may lead to improvements in alcohol use disorder (Littrell et al., 2001; Martinotti et al., 2007, 2009). Some studies have also found atypical antipsychotics to improve cannabis use disorder in

DD patients (Green et al., 2003; van Nimwegen et al., 2008). However, irrespective of their efficacy for actually relieving substance abuse, we know very little about the effects of atypical antipsychotics on neurological and psychiatric symptoms when prescribed to substance abusers with or without comorbid psychosis. This is an important area of study because any residual symptoms and deficits may act as negative reinforcers to maintain the cycle of addiction (Koob and Le Moal, 2001), and may impair their social functioning and quality of life (Addington and Addington, 1997; Lahmek et al., 2009).

The present study examined substance use outcomes and neurological and psychiatric symptoms in substance abusers with and without schizophrenia and in non-abusing schizophrenia patients undergoing a 12-week treatment with the atypical antipsychotic quetiapine. This antipsychotic was chosen because it has previously been shown to improve substance use outcomes in psychotic and non-psychotic patients (Potvin et al., 2006a; Kampman et al., 2007; Martinotti et al., 2008; Rizkallah et al., 2010) and is an effective monotherapy for anxiety and depressive disorders (for review, see Zhornitsky et al., 2011), while also producing little or no neurological symptoms (Weiden, 2007). Importantly, this is the first study of its kind to trace the evolution of neurological and psychiatric symptoms in all three groups of patients undergoing a homogenous antipsychotic treatment. This study is complementary to earlier studies by Potvin et al. (2006a) and Rizkallah et al. (2010), which reported substance abuse and clinical outcomes for DD patients and non-schizophrenia substance abusers.

3.3 Methods

Participants

Three groups of participants were recruited, namely: (i) substance-abusing patients with schizophrenia-spectrum disorders (schizophrenia, schizoaffective disorder, schizophreniform disorder; DD group); (ii) non-psychotic substance abusers in detoxification (SUD group); and (iii) schizophrenia patients without comorbid substance abuse (SCZ group). Psychiatric and SUD diagnoses were by well-trained psychiatrists (Lahcen Aït Bentaleb, Olivier Lipp, and Emmanuel Stip) and physicians (Jean-Pierre Chiasson), and were all based on DSM-IV criteria. SUD diagnoses were complemented with urine drug screenings. In the SUD group, there were two diagnoses of borderline personality disorder and two diagnoses of substance-induced psychotic disorder (DSM-IV). All participants signed a detailed consent form. The study was approved by the local ethics committee.

For all three groups, exclusion criteria were: (i) patients already on clozapine or quetiapine; (ii) patients hospitalized in a psychiatric unit; (iii) pregnancy; (iv) female subjects of childbearing potential or inadequate contraception; and (v) clinically meaningful unstable, renal, hepatic, cardiovascular, respiratory, cerebrovascular, or other serious, progressive physical disease. For the DD and SCZ groups, patients were excluded if their total score on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was lower than 65. Adjuvant medications were allowed in all three groups.

Clinical assessments

Neurological symptoms were evaluated with the Extrapyramidal Symptoms Rating Scale (ESRS; Chouinard et al., 1980). Akathisia was evaluated with the Barnes Akathisia Scale (BAS; Barnes,

1989). Psychiatric symptoms were measured using the PANSS and the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1993). For more information on clinical assessments, refer to Potvin et al. (2006a).

SUD assessments

Quantities of substances used in the last week were also registered, using the TimeLine Follow-Back (TLFB) procedure (Sobell and Sobell, 1992). Quantities used were noted for all substances. Amount spent on substances was calculated based on the value market in Quebec province (Canada). To complement our evaluation of SUDs, urine screenings were performed on weeks 0 and 12, for cannabinoids, opiates, and psychostimulants. SUD severity was also evaluated using an adapted eight-item scale, based on DSM-IV criteria of substance dependence. Two trained students and a trained nurse scored [from 0 (no problem) to 5 (severe problem)] the patient's SUD severity on the following items: (1) loss of control; (2) time spent on PAS; (3) impact of SUDs on social life; (4) impact of SUDs on daily occupations; (5) physical impact of SUDs; (6) psychiatric impact of SUDs; (7) impact of SUDs on compliance; and (8) ability to enjoy pleasures other than substance use. For more information on SUD assessments, refer to Potvin et al. (2006a) and Rizkallah et al. (2010).

Statistical analyses

Baseline and endpoint differences between the DD, SCZ, and SUD groups were analyzed using one-way analyses of variance (ANOVA) with group as the independent variable. Changes in substance abuse, neurological and psychiatric symptoms were analyzed using mixed ANOVA with group as the independent variable and time as the repeated measure. Multiple comparisons

were performed using the Bonferroni correction. The influence of potential confounds on improvements in neurological and psychiatric symptoms were analyzed using analyses of covariance (ANCOVA). Dichotomous variables were evaluated using Pearson's Chi-square test. The level of significance was set at $p<0.05$. Last-observation carried forward (LOCF) was used. Statistical analyses were performed using the Predictive Analytics SoftWare (PASW; version 18).

3.4 Results

Participants

Thirty-one DD patients were prescribed quetiapine; of these, two were lost-to-follow-up and three dropped out due to side-effects (Figure 1.). Twenty-five SCZ patients were prescribed quetiapine; of these, two were lost-to-follow-up. Thirty-three SUD patients were prescribed quetiapine; of these, two were lost-to-follow-up, two dropped out due to side-effects, three dropped out due to relapse, and clinical data was missing for two patients. Therefore, LOCF analysis was available for 26, 23, and 24 patients in the DD, SCZ, and SUD group, respectively.

Sociodemographic variables

Significant differences were found for age ($F=5.5$, $p=0.006$), gender ($\chi2=7.1$, $p=0.03$), and quetiapine dose ($F=22.1$, $p=0.0001$) between the three groups (Table 1.). By contrast, no significant differences were found between the groups in ethnicity, psychiatric diagnosis, type of substance(s) used, number of hospitalizations, and baseline antipsychotic.

Substance use outcomes

Additionally, SUD patients had significantly higher SUD severity than DD patients at baseline ($F=11.3$, $p=0.002$), but DD patients had significantly higher SUD severity at endpoint ($F=14.7$, $p<0.001$; Table 2). Moreover, SUD patients spent significantly more dollars per week on alcohol and drugs at baseline ($F=11.1$, $p=0.002$), but there was no significant difference between the groups at endpoint. There was also a significant main effect of time for SUD severity ($F=106.4$, $p<0.001$) and dollars per week ($F=21.5$, $p<0.001$). Finally, SUD patients improved significantly

more than DD patients in SUD severity ($F=41.7$, $p<0.001$) and dollars per week ($F=16$, $p<0.001$).

Neurological symptoms

Dual diagnosis patients had significantly more parkinsonism than SCZ patients at baseline ($F=3.6$, $p=0.03$) and significantly more than SUD patients at endpoint ($F=4.2$, $p=0.02$; Table 3). In addition, SUD patients had significantly higher akathisia scores than SCZ patients at baseline ($F=3.1$, $p=0.05$), but not at endpoint. No significant differences were observed for dyskinesia at baseline or endpoint. Dystonia was not present in significant numbers in our sample (data not shown). Repeated measures analysis revealed that there was a main effect of time for parkinsonism ($F=9.5$, $p=0.003$) and akathisia ($F=6.9$, $p=0.01$), but not dyskinesia. Changes in parkinsonism and dyskinesia did not differ significantly between the groups. Akathisia improved significantly more from baseline to endpoint in SUD relative to DD and SCZ patients ($F=5.3$, $p=0.02$). The between-group differences in improvements in akathisia were no longer significant when changes in SUD outcomes were considered as covariates (p=n.s). Sub-analyses of drug-specific effects revealed that improvements in akathisia in SUD patients were particular to cannabis abusers ($F=7.2$, $p=0.01$). They also revealed that improvements in parkinsonism in DD patients were particular to stimulant abusers ($F=5.3$, $p=0.03$).

Psychiatric symptoms

At baseline ($F=13.7$, $p<0.001$) and endpoint, DD and SCZ patients had significantly higher PANSS negative scores compared to SUD patients ($F=23.6$, $p<0.001$; Table 4). In addition, depression scores were significantly higher in DD compared to SCZ patients at baseline ($F=3.2$,

p=0.05). Moreover, they were significantly higher in DD compared to SCZ and SUD patients at endpoint (F=5.7, p=0.005). No differences were observed in PANSS positive scores at baseline; however, PANSS positive symptoms were significantly higher in DD and SCZ patients at endpoint (F=16.9, p<0.001). Repeated measures analysis revealed that was a significant main effect of time for PANSS positive (F=38, p<0.001) and negative symptoms (F=28.7, p<0.001) as well as depression (F=36.6, p<0.001; Table 4). Changes in negative and depressive symptoms did not differ significantly between the groups (Table 4). However, PANSS positive symptoms improved significantly more in SUD patients from baseline to endpoint, compared to DD and SCZ patients (F=5.3, p=0.007). There was no effect of age, gender, and dose when these variables were entered into the ANCOVA model. However, the finding of a greater improvement in positive symptoms in SUD patients disappeared after changes in SUD severity in time were considered as a covariate (p=n.s).

3.5 Discussion

The present study aimed to examine changes in substance use, as well as neurological symptoms and psychiatric symptoms in substance abusers with and without schizophrenia and in non-abusing schizophrenia patients undergoing 12-week treatment with quetiapine We found that SUD patients had a higher mean SUD severity, spent significantly more dollars weekly on alcohol and drugs at baseline and showed greater improvement in these variables, compared to DD patients. Nevertheless, at endpoint, there was no significant difference in dollars spent, but DD patients still had a higher mean SUD severity. Interestingly, DD patients had significantly higher parkinsonism and depression than SCZ patients at baseline and endpoint. On the other hand, we found that SUD patients had significantly more akathisia at baseline, improved more than SCZ patients and this was related to cannabis abuse/dependence. Finally, there were no significant differences in PANSS positive scores between the groups; however, SUD patients improved more and the differences were significant at endpoint.

In the present study, we found that SUD patients improved more in terms of SUD outcomes than DD patients. One explanation for this result could be that SUD patients had a significantly higher SUD severity at baseline, leading to the greater improvement. In addition, our SUD group began the study in detoxification, whereas our DD group were active users, suggesting that it was easier for the former patients to quit alcohol and/or drugs. Alternatively, these results suggest that it may be more difficult for schizophrenia patients to reduce or quit their substance use (Ziedonis et al., 2005). Importantly, DD patients still had a higher mean SUD severity than SUD patients at endpoint, despite spending similar amounts on alcohol and drugs. This finding is consistent with reports that substance abuse can have negative consequences on schizophrenia patients even when they use small amounts, infrequently (Ziedonis et al., 2005). It

is also consistent with evidence of increased dopaminergic sensitivity in schizophrenia. Indeed, PET studies have reported increased D_2/D_3 occupancy in schizophrenia patients in response to amphetamine challenge, relative to healthy controls (Laruelle et al., 1996; Abi-Dargham et al., 1998).

In terms of EPS, we found that DD patients had elevated parkinsonism at baseline, relative to SCZ and SUD patients, despite using significantly smaller quantities of alcohol and/or drugs. At endpoint, DD patients still had elevated parkinsonism relative to the other two groups, although they were taking similar amounts of these substances relative to SUD patients. Interestingly, a subanalysis revealed that improvements in parkinsonism were only significant in abusers of psychostimulants in the DD group. Obviously, the increase in parkinsonism in DD patients, relative to SUD patients, may be attributed to the fact that schizophrenia patients concomitantly take antipsychotics, which may interact with psychostimulants to increase parkinsonism (Potvin et al., 2006b; Maat et al., 2008). Indeed – when given acutely – cocaine and amphetamine stimulate striatal dopaminergic neurotransmission by blocking and reversing the dopamine transporter, respectively. However, their long-term abuse is associated with significant reduction in dopamine D2 receptor availability in the striatum that may last for months after detoxification, similar to the striatal dopaminergic deficit observed in Parkinson's disease (Volkow et al., 2004). Taken together, these results suggest that schizophrenia patients are more vulnerable to develop parkinsonism than SUD patients, even when taking small amounts of psychostimulants.

An unexpected result of the present study is the elevated akathisia at baseline in SUD patients. Intriguingly, a subanalysis revealed that the improvements in akathisia were found in cannabis abusers, which is consistent with reports of restlessness and physical tension/agitation

among patients undergoing cannabis withdrawal (Kouri and Pope, 2000; Budney et al., 2003). Moreover, we found that akathisia improved significantly more in SUD patients, relative to SCZ patients, which is consistent with previous accounts of cannabinoid withdrawal. Overall, these results suggest that the endogenous cannabinoid system plays a role in the manifestation of akathisia, which may be related to its role in motor behavior (El Manira and Kyriakatos, 2010).

Analysis of psychiatric symptoms revealed that DD and SCZ patients had significantly more negative symptoms, relative to SUD patients at baseline and endpoint. This is consistent with evidence suggesting that negative symptoms are relatively unique to schizophrenia (Zhornitsky et al., 2010a). By contrast, we found that depressive symptoms were nearly twice as high in DD and over one and a half times higher in SUD compared to SCZ patients. This finding is in line with research showing that substance abuse is a risk factor for the development of depression (Lynskey et al., 2004; Falck et al., 2006; Pozzi et al., 2008) as well as with a meta-analysis of 3283 patients showing that addicted schizophrenia patients experience more severe depressive symptoms compared to non-abusing patients (Potvin et al., 2007). At study endpoint, depression scores were persistently elevated in DD patients. Taken together, these results are consistent with increased vulnerability in schizophrenia patients in response to drugs of abuse. Finally, at baseline – but not at endpoint – we found that all three groups had equally significant levels of positive symptoms, which is consistent with observations of elevated positive symptoms in non-schizophrenia substance abusers (Mauri et al., 2007; Lapworth et al., 2009). Interestingly, however, despite their high levels of positive symptoms, only two SUD patients responded to substance-induced psychosis criteria (SIPD; DSM-IV). Since the DSM-IV notes that a patient must have persistent delusions or hallucinations coupled with a lack of insight to be diagnosed with SIPD, we examined in more detail which PANSS positive items were most

elevated at baseline in our SUD group. We found that the most elevated items (mean score ≈3) were hostility, excitement and paranoia/suspiciousness; symptoms which may manifest during post-intoxication or withdrawal but do not signify the presence of SIPD, according to the DSM-IV (Unnithan and Cutting, 1992; West and Gossop, 1994; Rosenthal et al., 1998; Mathias et al., 2008). Moreover, the fact that positive symptoms showed greater improvement in SUD patients, relative to DD and SCZ patients, is likely linked to their greater improvement in substance abuse outcomes. Taken together, our findings suggest that paranoia is not a symptom which reliably distinguishes between schizophrenia and SUD patients, when the latter individuals are undergoing withdrawal.

Improvements in neurologic and psychiatric symptoms did not differ between DD and SCZ patients, meaning that DD patients can improve in time as much as SCZ patients, as long as they significantly decrease their drug consumption – a finding that is consistent with previous reports (Conley et al., 1998; Swartz et al., 2008). Thus, it is not necessarily true that DD patients are doomed to have a worse prognosis than SCZ patients (Mueser et al., 1998; Negrete, 2003); rather, our results suggest that similar rates of improvements in psychiatric symptoms can be expected when DD patients diminish their substance use. However, in DD patients who maintain their substance use, this could prove otherwise. Indeed, there is evidence from non-pharmacological studies that psychotic patients who maintain their substance use have more severe depression, more positive symptoms, poorer functional outcome, and greater rates of relapse at 1 year follow-up, relative to non-users and those who maintain abstinence (Turkington et al., 2009).

The present study contains both strengths and limitations. Importantly, this is the first study of its kind to trace the evolution of substance abuse, neurological and psychiatric

symptoms in DD, SCZ, and SUD patients undergoing a homogenous antipsychotic treatment. However, this pilot study was not powered to detect complex interactions between sociodemographic, psychiatric, neurologic, and SUD variables. The study is also limited because the design does not permit us to deduce whether or not quetiapine played a significant role in the improvements in psychiatric symptoms in SUD patients. Interestingly, there is evidence to suggest that low-dose quetiapine is a highly effective anxiolytic and antidepressant and may possess mild antipsychotic activity as well (Fabre et al., 1995; Arvanitis and Miller, 1997; Cutler et al., 2009; Bandelow et al., 2010; see Zhornitsky et al., 2011 for review). However, we entered dose into the ANCOVA model and it showed no significant effect for any of our results. Other potential confounds such as age and gender also did not affect our results. By contrast, SUD severity was a significant factor in the ANCOVA models and is likely related to the fact that our SUD patients were recruited when they entered into detoxification, whereas our DD patients were active users. Thus, differences in changes in neurological and psychiatric symptoms between SUD patients and the other two groups seem to be intoxication/withdrawal-related phenomena. Future studies should take more frequent measurements (e.g., every 3 weeks) of psychiatric symptoms and EPS, in order to better elucidate the temporal relationship in improvements of these variables. The contribution of quetiapine in the psychiatric and neurologic symptoms reported here will also need to be elucidated.

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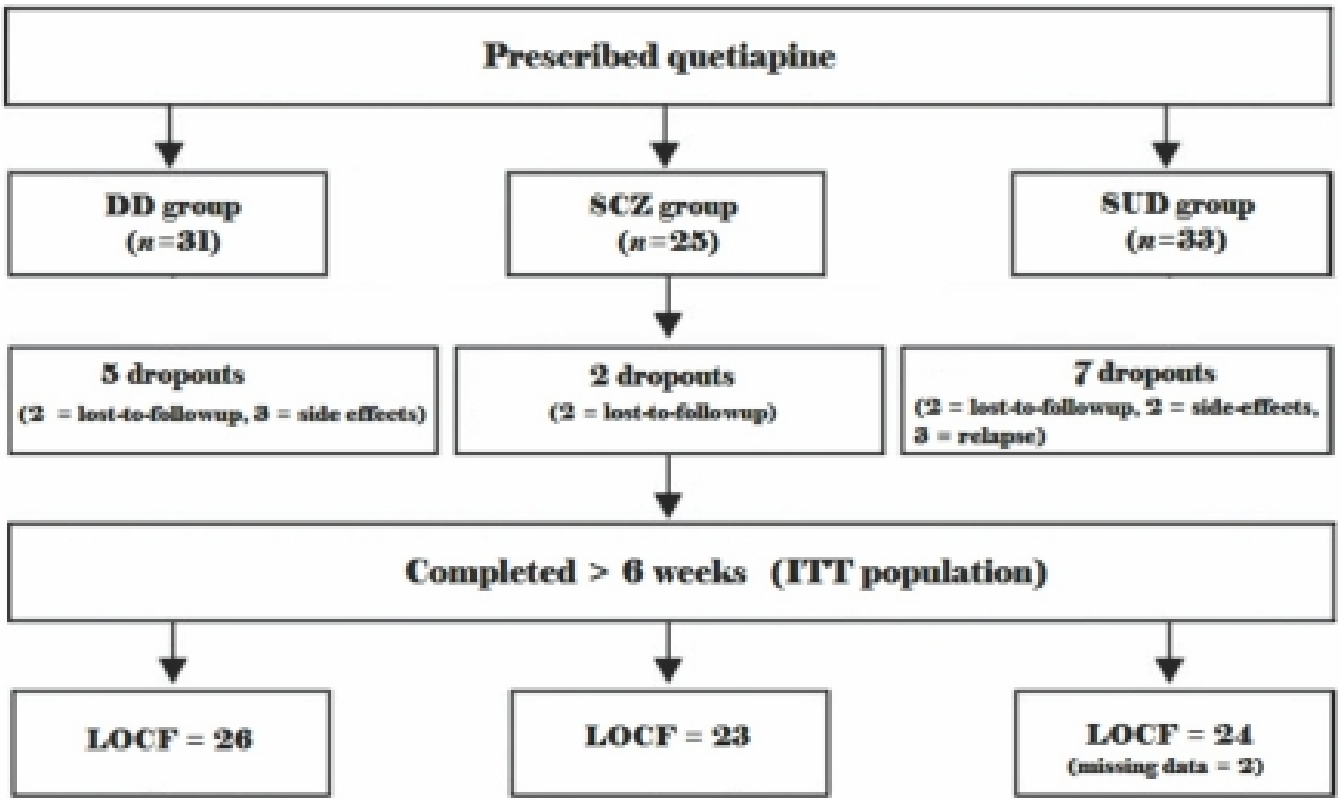
Figure 1. Participant disposition



ITT, intention-to-treat; LOCF, last-observation carried forward; DD, dual diagnosis group; SCZ, non-abusing schizophrenia group; SUD, non-schizophrenia substance abuser group.

Table 1: Sociodemographic variables

Variable (mean, SD)		**Statistics (multiple comparisons)***
Age (years)		
DD	30.5 (9.5)	F=5.5; p=0.006 (SCZ > DD)
SCZ	40.6 (12.4)	
SUD	37.5 (11)	
Gender		
DD	24 Male: 2 Female	χ^2=7.1, p=0.03
SCZ	15Male: 8 Female	
SUD	15Male: 9 Female	
Ethnicity		
DD	24 Caucasian: 2 other	χ^2=1, p=0.6
SCZ	20 Caucasian: 3 other	
SUD	20 Caucasian: 4 other	
Quetiapine dose (mg/d)		
DD	553.9 (254.9)	F=22.1; p=0.0001 (DD & SCZ > SUD)
SCZ	478.3 (272)	
SUD	150 (117.7)	
Hospitalizations		
DD	2.8 (3)	F=0.8; p=0.4
SCZ	3.6 (3.7)	
SUD	---	

Diagnosis DD SCZ SUD	 15SZ:9SA:2SF 13SZ:5SA:1SF ---	 χ^2=0.5, p=0.8
Baseline antipsychotic (atypical:typical:both:drug-free)[+] DD SCZ SUD	 18:4:3:1 14:4:0:3 ---	 χ^2=4, p=0.3
Alcohol abuse/dependence DD SCZ SUD	 12 YES: 14 NO --- 13 YES: 11 NO	 χ^2=0.3; p=0.6
Cannabis abuse/dependence DD SCZ SUD	 15 YES: 11 NO --- 15 YES: 9 NO	 χ^2=0.1; p=0.7
Stimulant abuse/dependence DD SCZ SUD	 9 YES: 17 NO --- 10 YES: 14 NO	 χ^2=0.3; p=0.6
Multi-substance abuse/dependence		

DD	10 YES: 16 NO	χ^2=2; p=0.2
SCZ	---	
SUD	14 YES: 10 NO	

SZ = schizophrenia; SA = schizoaffective disorder; SF = schizophreniform disorder; + = missing data for one subject in SCZ group; DD = dual diagnosis group, SCZ = non-abusing schizophrenia group, SUD = non-schizophrenia substance abuser group, *Bonferroni correction.

Table 2: SUD outcomes

Variable	**Baseline** (mean, SD)	**Endpoint** (mean, SD)	**Statistics (multiple comparisons*)**
SUD severity DD SUD	 22.1 (4.4) 28.3 (7.9)	 17.2 (7.7) 7.1 (10.4)	**Baseline:** F=11.3; p=0.002 **Time:** F=106.4; p<0.001 **Group x Time:** F=41.7; p<0.001 **Endpoint:** F=14.7; p<0.001
Dollars per week DD SUD	 93.4 (65.4) 467.1 (546.3)	 61.8 (60) 34 (72.7)	**Baseline**: F=11.1; p=0.002 **Time:** F=21.5; p<0.001 **Group x Time:** F=16; p<0.001 **Endpoint:** F=2.1; p=0.2

DD = dual diagnosis group, SCZ = non-abusing schizophrenia group, SUD = non-schizophrenia substance abuser group,

*Bonferroni correction.

Table 3: Neurological symptoms at baseline and endpoint

Variable	**Baseline** (mean, SD)	**Endpoint** (mean, SD)	**Statistics (multiple comparisons*)**
Parkinsonism			**Baseline:** F=3.6; p=0.03 (DD > SCZ)
DD	9.7 (14.1)	4.7 (5.9)	**Time:** F=9.5; p=0.003
SCZ	2.5 (2.6)	2.1 (2.4)	**Group x Time:** F=1.8; p=0.2
SUD	5.7 (6.9)	1.5 (3.4)	**Endpoint:** F=4.2; p=0.02 (DD > SUD)
Akathisia			**Baseline:** F=3.1; p=0.05 (SUD > SCZ#)
DD	0.7 (0.9)	0.4 (0.6)	**Time:** F=6.9; p=0.01
SCZ	0.6 (1.1)	0.7 (1.2)	**Group x Time:** F=5.3; p=0.02 (SUD > SCZ)
SUD	1.3 (1.2)	0.3 (0.7)	**Endpoint:** F=1; p=0.4
Dyskinesia			**Baseline:** F=2.7; p=0.07
DD	0.7 (1.8)	0.2 (0.7)	**Time:** F=1.1; p=0.3
SCZ	1.9 (3.4)	1.4 (3.3)	**Group x Time:** F=0.4; p=0.7
SUD	0.4 (1.1)	0.5 (1.3)	**Endpoint:** F=2.5; p=0.09

DD = dual diagnosis group, SCZ = non-abusing schizophrenia group, SUD = non-schizophrenia substance abuser group, *Bonferroni correction; # = LSD correction.

Table 4: Psychiatric symptoms at baseline and endpoint

Variable	**Baseline** (mean, SD)	**Endpoint** (mean, SD)	**Statistics (multiple comparisons*)**
PANSS positive			**Baseline:** F=1.4; p=0.3
DD	18.3 (4.3)	15.6 (4)	**Time:** F=38; p<0.001
SCZ	17.1 (4.3)	15.3 (4.3)	**Group x Time:** F=5.3; p=0.007 (SUD > DD & SCZ)
SUD	16.2 (5.4)	10 (2.7)	**Endpoint:** F=16.9; p<0.001 (DD & SCZ > SUD)
PANSS negative			**Baseline:** F=13.7; p<0.001 (DD & SCZ > SUD)
DD	19.5 (4.8)	16.4 (5)	**Time:** F=28.7 p<0.001
SCZ	17.1 (4.8)	16.4 (4.7)	**Group x Time:** F=2.3; p=0.1
SUD	12.5 (4.8)	8.9 (3.2)	**Endpoint:** F=23.6; p<0.001 (DD & SCZ > SUD)
Depression			**Baseline**: F=3.2; p=0.05 (DD > SCZ)
DD	6.8 (5)	3.9 (3.6)	**Time:** F=36.6; p<0.001
SCZ	3.6 (4.6)	1.2 (1.6)	**Group x Time:** F=1.1; p=0.4
SUD	6 (4.1)	1.8 (3.1)	**Endpoint:** F=5.7; p=0.005; (DD > SCZ & SUD)

DD = dual diagnosis group, SCZ = non-abusing schizophrenia group, SUD = non-schizophrenia substance abuser group, PANSS = Positive and Negative Syndrome Scale. *Bonferroni correction.

4 Clinical evolution of substance use disorder patients during treatment with quetiapine: a 12-week, open-label, naturalistic trial.

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Author roles:

S. Zhornitsky was involved in writing of the first draft and review and critique of the manuscript.

Clinical evolution of patients with substance use disorders during treatment with quetiapine: a 12-week, open-label, naturalistic trial.

Élie Rizkallah[1,2]; Emmanuel Stip[1]; Simon Zhornitsky[1]; Tania Pampoulova[1,2]; Alain Gendron[3]; Pierre-Paul Rompré[1]; Jean-Pierre Chiasson[2]; Stéphane Potvin[1].

[1] Fernand-Seguin Research Center, Department of Psychiatry, Faculty of Medicine, University of Montreal; Montreal, Canada

[2] Clinique du Nouveau-Départ; Montreal, Canada

Corresponding author

Stéphane Potvin
Centre de recherche Fernand-Seguin
7331 Hochelaga
Montreal, Quebec, Canada
H1N 3V2
Tel: (514) 251-4015
Fax: (514) 251-2617

4.1 Abstract

Objective Substance use disorders (SUDs) are associated with a variety of psychiatric disorders and mood and behavioural instability. Growing evidence suggests that the atypical antipsychotic quetiapine may be useful in the treatment of SUDs. The primary objective of the current open-label trial was to examine the effects of quetiapine on SUD outcomes in patients entering detoxification. **Methods** Thirty-three non-psychosis SUD patients participated. Patients received quetiapine for a 12-weeks beginning in detoxification. Craving, quantities used and psychiatric symptoms were evaluated on baseline and at end-point. Results Out of 33 recruited patients, 26 completed more than 9 weeks of treatment. Last observation carried forward analyses revealed that craving, SUD severity and quantities used improved during the study. Psychiatric and depressive symptoms also improved. **Conclusions** Our results cannot be attributed per se to the pharmacological effects of quetiapine due to the open-label design of the study; the small sample size involved and the fact that patients were involved in an intensive therapy program. Nevertheless, our results suggest that quetiapine may be helpful for the treatment of SUD patients entering detoxification. Controlled studies are warranted to determine whether these results are quetiapine-related.

Key words quetiapine – substance use disorders – psychiatric symptoms – detoxification – atypical antipsychotic

4.2 Introduction

Second-generation antipsychotics (SGAs) are attracting growing interest for the treatment of substance use disorders (SUDs). So far, SGAs have shown some benefit over first-generation antipsychotics (FGAs) for the treatment of SUDs in patients with schizophrenia or bipolar disorder. SGAs have also been tried in non-psychosis substance abusers, with mixed results.[1,2] Preliminary evidence suggests that among SGAs, quetiapine is associated with some of the most promising results, particularly during the period of detoxification.[3-7] During this period, SUD patients often develop psychiatric symptoms, including insomnia, depression, anxiety, and psychotic reactions.[8-9] Interestingly, in addition to its antipsychotic properties, quetiapine has been shown to possess significant sedative, anxiolytic and antidepressant effects.[10-11] It is perhaps due to these nonspecific effects (rather than owing to a specific mechanism such as methadone for heroin dependence) that quetiapine has been shown to be a beneficial treatment for withdrawal from a diverse range of addictive substances, such as stimulants, alcohol, and opiates.[4-6] Nevertheless, only a few retrospective studies have examined the potential efficacy of quetiapine in such a context.[4-6]

The primary objective of the current open-label, naturalistic trial was to examine the effects of quetiapine on SUD outcomes in patients with SUDs entering detoxification. Secondary objectives included the examination of clinical and tolerability outcomes.

4.3 Methods

Participants

Patients with SUD (abuse and/or dependence) (last 3 months) of alcohol, cannabis, cocaine and/or amphetamines were diagnosed, based on DSM-IV, by a physician trained in addiction medicine (JPC). SUD patients who were using one or multiple substances were included. Multiple substance abusers were included for three reasons: (i) abuse of multiple substances is very common;[12] (ii) its pharmacological treatment is an unmet clinical need raising growing concerns;[13] and (iii) the potential usefulness of quetiapine during detoxification may be attributed to general benefits (antipsychotic, anxiolytic, and antidepressant effects).[10-11] All patients signed a detailed informed consent form. The study was approved by the local scientific and ethics committee.

Exclusion criteria were: (1) patients already on quetiapine or clozapine; (2) pregnancy; (3) female subjects of childbearing potential without adequate contraception; (4) other axis-I psychiatric disorders such as bipolar disorder or schizophrenia spectrum disorders; and (5) any clinically meaningful unstable renal, hepatic, cardiovascular, respiratory, cerebrovascular disease or other serious, progressive physical disease. Diabetic patients were also excluded from the study. Patients were given quetiapine (IR or XR) for a 12-week open-label trial. Quetiapine was introduced when patients entered a 2- to 4- week detoxification program.

Along with their participation in the study, patients were administered one-to-two hours a week of individualized inpatient therapy for up to four weeks. Thirty-three patients with a diagnosis of SUD were recruited for inclusion in the trial. Out of the 33 recruited patients 26 completed more than 9 weeks of treatment. Seven patients were dropouts, for the following reasons: relapse (n=3), lost-to-follow-up without relapse (n=3), and medication not well-tolerated (n=1). Twenty-four patients completed the whole trial and two patients abandoned the study after 9 weeks. Both 9- and 12-week completers (26 patients) were

included in the last observation carried forward (LOCF) analyses. The mean dose of quetiapine at endpoint was 150mg ±113.8 [Note: Compliance to quetiapine was assessed via pill count and pharmacological records at the clinical setting]. Concomitant medications were allowed, except for other antipsychotics. Socio-demographic data, diagnostic data and data about medication for these patients are presented in Table 1.

Clinical assessments

To measure SUDs (all substances), several instruments were administered at baseline (week 0) and end-point (week 12). The craving of patients for their drug(s) of choice in the last week was assessed using a visual analog scale (VAS) (from 0 –no craving– to 100% -most intense craving imaginable). Quantities of substances used in the last week were also registered, using the TimeLine Follow-Back (TLFB) procedure.[14] Quantities used were noted for all substances. Amount spent on substances was calculated based on the value market in Quebec province (Canada). Apart from craving and substance use, SUD severity was measured with the Alcohol, and Drug Use Scales (AUS, and DUS) on baseline and end-point.[15] The AUS and DUS are five-point scales based on DSM-IV criteria for severity of disorder: 1=abstinence, 2=use without impairment, 3=abuse, 4=dependence and 5=severe dependence. To complement our evaluation of SUDs, urine screenings were performed on weeks 0 and 12, for cannabinoids, opiates, phencyclidine, and psychostimulants. In the case of alcohol, plasma gamma-glutamyltransferase (GGT) levels were assessed on baseline and at end-point.

Psychiatric and depressive symptoms were evaluated, with the Positive and Negative Syndrome Scale (PANSS)[16] and the Calgary Depression Scale for Schizophrenia (CDSS),[17] respectively, on baseline and at end-point, by a trained physician (TP). The PANSS was chosen because it was previously used to measure positive symptoms in SUD patients.[8,18] In addition, the PANSS is widely considered to be superior to the Brief Psychiatric Rating Scale

(BPRS) for measurement of negative symptoms, which are common during withdrawal from addictive substances.[8-9] Along with the PANSS, the CDSS was used because the present study was part of a larger study comparing substance abusers with and without schizophrenia and non-abusing schizophrenia patients.[19] However, the Beck Depression Inventory Second Edition (BDI-II)[20] was applied at baseline, and correlated significantly with the CDSS ($r=0.43$; $p=0.03$), suggesting that the latter scale can be reliably used to measure depressive symptoms in SUD patients without comorbid psychosis.

Statistical analyses

Changes in SUD outcomes, psychiatric symptoms, and medical variables during quetiapine treatment were evaluated using repeated-measures analyses of variance (ANOVAs). The level of significance was set at $p<0.05$ for all analyses.

4.4 Results

Substance use disorders

Of the 26 patients included in the LOCF analyses, alcohol was the drug of choice for 6 patients, cannabis for 14 patients, and stimulants for 9 patients. Nineteen patients used alcohol during the study, 15 patients used cannabis, and 12 used stimulants.

Overall, improvements on the AUS and the DUS, as well as a decrease in the weekly dollars spent on all substances were observed (Table 2). Craving for alcohol improved significantly over time on. Weekly money spent on alcohol significantly decreased from baseline to endpoint (84.2 [78.2] vs. 11.1 [25.3]; p=0.0001), but there was no change in plasma GGT levels (Table 2). Craving for cannabis (Table 2) and weekly money spent on cannabis significantly decreased from baseline to endpoint (178.7 [173.9] vs. 0.4 [1.1]; p=0.001). Likewise, craving for stimulants (Table 2) significantly diminished during quetiapine therapy from baseline to endpoint as did weekly money spent on stimulants (722.5 [628.7] vs. 50 [97.8]; p=0.002).

Twenty one positive urine screening were detected before treatment with quetiapine, such as amphetamine (n=2), cannabis (n=13) and cocaine (n=4). Only two positive screenings following treatment with quetiapine were noted: cocaine (n=2). Also noteworthy, before quetiapine, 5 patients required treatment with benzodiazepines, whereas only 1 patient still received such treatment at study end-point.

- insert Table 2 here -

Psychiatric symptoms

There were significant improvements from baseline in PANSS-positive, negative and general symptoms during quetiapine therapy. A significant improvement in depressive symptoms was also observed on the CDSS (Table 2).

Tolerability

Quetiapine was generally well tolerated and no patients developed cardiometabolic issues. The most frequent side-effects reported by the participants during the study were: somnolence (n=10), dizziness (n=7), dry mouth (n=5), constipation (n=4), headaches (n=5), fatigue (n=4), hypersalivation (n=2), sedation (n=4), palpitations (n=3), blurred vision (n=3) and jointure pain (n=2). No patient "misused" quetiapine.

Prolactin levels did not increase significantly during quetiapine therapy. No significant changes in heart rate were observed. Weight gain was, however, noticed during quetiapine therapy (Table 2).

4.5 Discussion

Results from this open-label, naturalistic trial, suggest that quetiapine may be beneficial for controlling withdrawal symptoms and promoting abstinence in non-psychosis patients with SUDs. During quetiapine therapy, SUD outcomes (quantities used & severity of SUDs and craving) significantly improved over time and this was corroborated by urine screenings. Although there was no correlation between changes in plasma GGT and reduced alcohol consumption, there is evidence that quetiapine may cause asymptomatic increase in liver enzymes,[21] which could explain this result.

Our findings are consistent with other reports of quetiapine's efficacy in the treatment of SUDs in psychosis and non-psychosis patients.[3-7,22,23] In psychosis patients, quetiapine was found to decrease severity of substance abuse and craving.[22,23] In non-psychosis patients, quetiapine decreased drinking in Type B alcoholics during post-detoxification.[3] Moreover, quetiapine decreased craving and promoted abstinence in alcohol and psychostimulant abusers during withdrawal.[5] Overall, the present study adds to the growing literature detailing the potential utility of this medication for the treatment of SUDs, especially during the period of detoxification. However, we cannot be certain whether the improvements were quetiapine-related, or whether they were due to the decrease in substance use as well as the psychotherapy that patients received.

The significant decrease in benzodiazepine use during treatment is worthy of mention. Although benzodiazepines are considered the drugs of choice for the treatment of acute alcohol withdrawal, their use as a long-term treatment of individuals with SUD is generally discouraged, because of potential cross-tolerance with alcohol and their potential of misuse.[24-26] Here, the anxiolytic effects of quetiapine may have rendered the use of benzodiazepines less necessary use, as previously reported by Pinkofsky et al.[6]

During quetiapine therapy, we observed improvements in positive, negative, general and depressive symptoms. Previous research found that quetiapine decreased depression, anxiety and agitation in patients undergoing detoxification.[6] Moreover, there is evidence that two weeks' quetiapine treatment improved positive, negative and depressive symptoms in individuals with cannabis and cocaine-induced psychosis.[8] As a whole, findings of the present study suggest that quetiapine may be beneficial for the treatment of psychiatric symptoms in substance abusers. Alternatively, psychiatric symptoms may have improved during the study simply because patients substantially decreased their substance use as well as their involvement in intensive therapy.

Quetiapine was generally well-tolerated among patients. No serious adverse events were reported, and only one subject did not tolerate the treatment. Prolactin did not increase during treatment. Patients significantly gained weight during the study, which may be quetiapine-related or due to an overall diminution of substance abuse. Taken together, these results are consistent with data showing that quetiapine is associated with low-to-moderate weight gain and little-to-no increase in prolactin.[27-29]

Conclusion

Our results cannot be attributed *per se* to the pharmacological effects of quetiapine, for three main reasons: (1) the open-label design of the study; (2) the small sample size involved; and (3) the fact that patients were involved in an intensive therapy program. Another limitation of the present pilot study is that we did not perform a correction for multiple comparisons, thus potentially leading us to commit a Type-I error(s). Finally, although the current study administered the CDSS – a scale used to measure depressive symptoms in schizophrenia – it correlated significantly with the BDI at baseline, suggesting that it can be used to measure depression in non-schizophrenia patients. Nevertheless, despite these limitations, the present

study is the first to prospectively administer quetiapine during detoxification, and the first to investigate the use of SGAs for cannabis use disorder in non-psychosis patients. Our results offer support for the potential benefits of quetiapine in the treatment of psychiatric symptoms associated with drug and alcohol withdrawal as well as in helping to maintain abstinence. This study encourages further evaluation of quetiapine in non-psychosis SUD patients during detoxification.

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Table 1: Participants' characteristics (n=26)

Age, in years (mean, SD)	36.6±11.1
Sex	17 Males, 9 Females
Ethnicity	24 Caucasian
Education level, in years	14.2 ± 2.5
Duration of SUDs	11.4 ±8.6
Psychiatric diagnoses	Borderline personality disorder (n=2) Substance-induced psychotic disorder (n=3)
SUD diagnoses	Alcohol abuse / dependence (n=12) Amphetamine abuse / dependence (n=2) Cannabis abuse / dependence (n=16) Cocaine abuse / dependence (n=9) MDMA abuse (n=1)
Adjuvant medications	Anticonvulsants (n=3) Antidepressants (n=5) Beta-blockers (n=2) Benzodiazepines (n=1)

MDMA= methylene-dioxy-methamphetamine; SUD= substance use disorder

Table 2: Substance use, psychiatric and tolerability outcomes during quetiapine therapy

Variable	**Baseline** (mean, SD)	**LOCF*** (mean, SD)	**Statistics**
Craving (visual analog scale) (n=26)			
Alcohol	69.2 (30.7)	21.7 (30.6)	F=11.5; p=0.02
Cannabis	75 (25.3)	15.7 (21.7)	F=41.8; p=0.0001
Stimulants	90.6 (19.4)	31.1 (33)	F=33.4; p=0.0001
Substance use (n=26)			
Mean $ (all substances)	498 (556)	31.4 (70.3)	F=22.1; p=0.0001
AUS	2.8 (1.4)	1.8 (0.9)	F=15; p=0.001
DUS	3.7 (1.5)	1.5 (0.8)	F=66.5; p=0.0001
Psychiatric symptoms (n=24)			
PANSS-positive	16.2 (5.4)	10 (2.7)	F=33.4; p= 0.0001
PANSS-negative	12.5 (4.8)	8.9 (3.2)	F=11.7; p= 0.002
PANSS-general	39.7 (8.9)	26.8 (9.6)	F=25; p= 0.0001
CDSS	6 (4.1)	1.8 (3.1)	F=17.2; p= 0.0001
Tolerability (n=24)			
Prolactin (µg/L)**	11.7 (7.1)	10.3 (10)	F=0.3; p=0.6
Heart rate (beats/min)	82 (15.3)	82.1 (18)	F=0.003; p=0.96
Weight (kg)	76.9 (17.7)	79 (17.4)	F=12.3; p=0.002
GGT (UI/L)**	75.4 (131)	39 (28)	F=2.3; p=0.15

**n=22; AUS= Alcohol Use Scale; CDSS= Calgary Depression Scale for Schizophrenia; DUS= Drug Use Scale; PANSS= Positive and Negative Syndrome Scale; SUDs= substance use disorders; *LOCF= last observation carried forward, $ = dollars spent on alcohol and drugs.

5 Sensation-seeking, social anhedonia, and impulsivity in schizophrenia and substance use disorder patients

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Sensation-seeking, social anhedonia and impulsivity in schizophrenia and substance use disorder patients

Simon Zhornitsky[1]; Élie Rizkallah[1,2]; Tania Pampoulova[1,2]; Jean-Pierre Chiasson[2]; Olivier Lipp[1]; Emmanuel Stip[1]; Stéphane Potvin, PhD[1].

[1]Department of Psychiatry, Faculty of Medicine, University of Montreal; Montreal, Canada

[2]Clinique du Nouveau-Départ; Montreal, Canada

Corresponding author

Stéphane Potvin
Centre de recherche Fernand-Seguin
7331 Hochelaga
Montreal, Quebec, Canada
H1N 3V2
Tel: (514) 251-4015
Fax: (514) 251-2617

5.1 Abstract

SUDs are associated with poor prognosis in schizophrenia and we do not yet have a good explanation for this frequent comorbidity. One hypothesis that has been advanced in the literature is that dual diagnosis patients may have a different personality profile than non-abusing schizophrenia patients. The present case-control study aimed to characterize levels of personality traits (sensation-seeking, social anhedonia, and impulsivity) in substance abusers with (DD group; n=31) and without schizophrenia (SUD group; n=39), relative to non-abusing schizophrenia patients (SCZ group; n=23) and healthy controls (n=25). Impulsivity was assessed using the Barratt Impulsivity Scale. Sensation-seeking was assessed using the Zuckerman Sensation Seeking Scale. Social anhedonia was assessed with the Chapman Social Anhedonia Scale. We found that sensation-seeking was significantly higher in DD and SUD, relative to SCZ patients. We found that social anhedonia was significantly elevated in DD and SCZ, relative to SUD patients and healthy controls. We found that impulsivity was significantly higher in DD, SCZ and SUD patients, compared to healthy controls. The results suggest that sensation-seeking is prominent in substance abuse (irrespective of schizophrenia), social anhedonia is prominent in schizophrenia (irrespective of substance abuse), and impulsivity is prominent in all three populations.

Key words: impulsivity, sensation seeking, social anhedonia, personality traits, schizophrenia, dual diagnosis, substance abuse

5.2 Introduction

Schizophrenia is a severely disabling psychiatric disease whose treatment is complicated by a nearly 50% prevalence of substance use disorder (SUD) in the United States (Regier et al., 1990). In non-psychosis individuals, SUDs are associated with increased psychiatric symptoms (Mauri et al., 2007; Zhornitsky et al., 2010a). In schizophrenia patients, SUDs have a negative impact on the course of the pathology. Compared to non-abusing patients, dually diagnosed schizophrenia patients are more frequently hospitalized, non-compliant with treatment, suicidal, impulsive and violent, homeless and unemployed, and they have more legal and health problems (Mueser et al., 1998; Negrete, 2003).

SUDs are associated with poor prognosis in schizophrenia and we do not have a good explanation for this frequent comorbidity. One hypothesis that has been advanced in the literature is that dual diagnosis (DD) patients may have a different personality profile than non-abusing schizophrenia patients (Gregg et al. 2007). Previous studies have revealed that DD patients differ from their non-abusing counterparts on measures of sensation-seeking and impulsivity, but not social anhedonia (Kwapil, 1998; Gut-Fayand et al. 2001; Dervaux et al. 2001). However, these studies suffered from two main limitations: they did not include a group of healthy controls and they did not include a group of non-psychosis SUD patients. The inclusion of these comparison groups may help us parcel the respective associations between schizophrenia, substance abuse and the aforementioned personality traits. This field of inquiry is important because personality trait measures may help tailor pharmacological and psychosocial intervention in these populations. For instance, there is evidence that atypical antipsychotics are beneficial for the treatment of alcoholism among Type B alcoholics – characterized by an early onset of drinking, greater severity of dependence and more impulsivity and psychiatric symptoms (Babor et al. 1992; for review see Zhornitsky et al. 2010b). Similarly, Conrod et al. (2000) found differential improvement in SUD outcomes

among non-psychosis female substance abusers who were matched to treatment based on levels of impulsivity, hopelessness, sensation-seeking, and anxiety-sensitivity.

In this context, the present case-control study aimed to characterize levels of personality traits (sensation-seeking, social anhedonia, and impulsivity) in substance abusers with and without schizophrenia, relative to non-abusing schizophrenia patients and healthy controls. Importantly, this is the first study to directly compare these traits in the four groups.

5.3 Methods

Four groups of participants were recruited, namely: (i) substance-abusing patients with schizophrenia-spectrum disorders (schizophrenia, schizoaffective disorder, schizophreniform disorder; DD group); (ii) non-psychosis substance abusers in detoxification (SUD group); (iii) schizophrenia patients with comorbid substance abuse (SCZ group) and; (iv) healthy controls (HC group). Psychiatric and substance use disorder diagnoses were by well-trained psychiatrists (OL, ES) and physicians (TP; JPC), and were all based on DSM-IV criteria. Substance use disorder diagnoses were complemented with urine drug screenings. All participants signed a detailed consent form. The study was approved by the local ethics committee.

For all three groups, exclusion criteria were: (i) patients already on clozapine or quetiapine; (ii) patients hospitalized in a psychiatric unit; (iii) pregnancy; (iv) female subjects of childbearing potential or inadequate contraception; and (v) clinically meaningful unstable, renal, hepatic, cardiovascular, respiratory, cerebrovascular or other serious, progressive physical disease.

Psychiatric symptoms (DD, SCZ and SUD groups) were measured using the PANSS and the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al. 1994). Impulsivity was assessed using the Barratt Impulsiveness Scale (BIS; a 34-item self-report; Patton et al. 1995). Sensation-seeking was assessed using the Zuckerman Sensation Seeking Scale (form V) (a 40-item self-report; Zuckerman, 1978; Loas et al. 2001). Social anhedonia was assessed with the Chapman Social Anhedonia Scale (CSAS; a 40-item self-report; Chapman et al. 1976).

Differences in socio-demographic variables and psychiatric symptoms between the DD, SCZ, SUD and HC groups were analyzed using one-way analyses of variance (ANOVA) with group as the independent variable. Changes in personality traits were analyzed using

repeated measures analysis of covariance (ANCOVA) with age as a covariate and group as the independent variable. Multiple comparisons were performed using the Bonferroni correction. Dichotomous variables were evaluated using Pearson's Chi-square test. The level of significance was set at $p<0.05$. Statistical analyses were performed using the Predictive Analytics SoftWare (PASW; version 18).

5.4 Results

Socio-demographic variables

Analysis of socio-demographic variables showed that individuals in the DD group were significantly younger than those in the SCZ and healthy control group (p=0.005); however, there were no significant differences in hospitalizations, diagnosis, and antipsychotic or substance class (Table 1).

Psychiatric symptoms

PANSS positive scores were 18.3 (4.6), 16 (4.4), and 15.3 (5.1) in the DD, SCZ and SUD groups respectively (p=0.04; DD > SUD); however, the difference did not remain significant after controlling for age in the ANCOVA. PANSS negative scores were 19.3 (4.8), 15.6 (4.7), 13.7 (4.7) in the DD, SCZ and SUD groups respectively (p<0.0001; DD > SUD). CDSS scores were 7.3 (4.9), 2.9 (4.4), 6.8 (4.3) in the DD, SCZ and SUD groups respectively (p=0.001; DD & SUD > SCZ).

Personality traits

Sensation-seeking total score was significantly higher in DD and SUD patients, compared to schizophrenia patients and significantly higher in SUD patients, compared to healthy controls (p<0.0001; Table 1). Social anhedonia score was significantly higher in DD and SCZ patients, relative to healthy controls (p=0.005; Table 1). Impulsivity total score was significantly elevated in DD, SCZ and SUD patients, relative to healthy controls (p<0.0001; Table 1). The results did not change after adding age as a covariate.

To check whether this confounded our results, we performed a correlation analysis (Pearson) on negative symptoms, depression, sensation-seeking, social anhedonia and impulsivity. There was only one significant correlation between negative symptoms and

social anhedonia (r=0.218; p=0.04). This result is unsurprising since many items on the PANSS negative subscale are concepts related to questions on the CSAS.

5.5 Discussion

In the present study, we found that sensation-seeking was significantly higher in DD and SUD, relative to SCZ patients. These findings are consistent with previous data showing associations between sensation-seeking and substance abuse, regardless of psychosis comorbidity (Ersche et al. 2010; Bizzarri et al. 2007, 2009; Dervaux et al. 2001, 2010a,b). Most importantly, Bizzarri et al. (2007) showed that sensation-seeking was significantly elevated in bipolar patients with substance abuse and in non-psychosis substance abusers, relative to healthy controls. Intriguingly, non-abusing bipolar patients exhibited a level of sensation-seeking that was higher than healthy controls, but lower than the two substance abusing groups. Here, we found that SCZ patients had significantly lower scores in the boredom susceptibility subscale of sensation-seeking, relative to healthy controls. These data suggest that (i) substance abusers with and without schizophrenia are characterized by abnormally high sensation-seeking, and (ii) non-abusing schizophrenia patients are characterized by abnormally low sensation-seeking.

We found that social anhedonia was significantly elevated in DD and SCZ, relative to SUD patients and healthy controls. A number of previous studies have established a link between social anhedonia and schizotypal personality traits and the development of schizophrenia-spectrum disorders. Indeed, there is evidence that subjects with social anhedonia exhibited higher schizotypal scores for interpersonal, paranoid, disorganized, and cognitive/perceptual dimensions, relative to controls (Rey et al. 2009). Likewise, Kwapil (1998) reported that 24% of subjects with high social anhedonia were diagnosed with schizophrenia-spectrum disorders at the 10-year follow-up, relative to only 1% of controls. By contrast, Dervaux et al. (2001) did not find a difference in physical anhedonia between schizophrenia patients with and without substance abuse. Here, the addition of the SUD and HC group suggests that anhedonia may actually play a role in dually diagnosed schizophrenia

patients, but to do so, it has to be coupled with sensation seeking, whereas anhedonia is not required in the SUD group. It may be that sensation-seeking is a way of counteracting anhedonia in some schizophrenia patients, may lead them to abuse drugs and/or alcohol. Taken together, these data show that social anhedonia is relatively unique to schizophrenia – irrespective of SUD comorbidity.

We found that impulsivity was significantly higher in DD, SCZ and SUD patients, compared to healthy controls. As such, our results are in accordance with previous studies that found elevated impulsivity in substance abusers without schizophrenia and in non-abusing schizophrenia patients, relative to healthy controls (Enticott et al. 2008; Ersche et al. 2010; Kaladjian et al. 2011; Duva et al. 2011). However – unlike previous studies – we did not find significant differences in impulsivity between substance abusers with and without schizophrenia. For example, Dervaux et al. (2010a,b) revealed significantly elevated levels of impulsivity in separate cohorts of alcohol and cannabis-abusing schizophrenia patients, compared to non-abusing schizophrenia patients. Similarly, Gut-Fayand et al. (2001) found significantly elevated levels of impulsivity in mixed substance abusers with schizophrenia, relative to non-abusing patients. The inability to find a difference between the groups may reflect a type-II error, since our SCZ group evidenced an impulsivity total score which was numerically lower than our DD and SUD groups. A larger sample size may have rendered the numerical difference statistically significant. Another potential reason is related to the fact that the BIS contains numerous cognitive items that may have obscured the results in our study. Consequently, experimental measures of impulsivity (e.g. response inhibition) are needed to confirm these findings.

Analysis of socio-demographic variables revealed that these DD patients were more likely to be younger, as shown previously in the literature (Wobrock et al. 2007; Koskinen et al. 2010). However, controlling for age did not influence our personality traits results.

Moreover, analysis of psychiatric symptoms revealed that DD patients had significantly more negative symptoms, relative to SUD patients. This is consistent with evidence suggesting that negative symptoms are relatively unique to schizophrenia (Zhornitsky et al. 2010a). By contrast, we found that depressive symptoms were over two times higher in DD and SUD patients, compared to SCZ patients. This finding is in line with research showing that substance abuse is a risk factor for the development of depression (Lynskey et al., 2004; Falck et al. 2006; Potvin et al., 2007).

Results of the present study suggest that sensation-seeking is prominent in substance abuse (irrespective of schizophrenia), social anhedonia is prominent in schizophrenia (irrespective of substance abuse) and impulsivity is prominent in all three populations. These results are limited because patients were using mixed substance. However, previous studies in the field suggest that personality profiles are not related to a specific substance (Dervaux et al. 2001, 2010a,b). As a whole, the findings may help tailor pharmacological and psychosocial intervention in these populations. Future studies will need to evaluate whether the personality profiles reported here reflect state or trait differences. It would also be interesting to verify if we can predict the development of substance abuse in schizophrenia based on the personality profiles reported here in longitudinal studies initiated during the prodrome of psychosis.

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Table 1: Personality traits, psychiatric symptoms, and socio-demographic variables

Variable (mean, SD)	**DD** **(n=31)**	**SCZ** **(n=23)**	**SUD** **(n=39)**	**HC** **(n=25)**	**Statistics**	**Multiple comparisons***
Personality traits						
Impulsivity						
Motor impulsivity	17.3 (8.2)	16.7 (8)	19.2 (8)	9.9 (5.3)	F=8; p<0.0001	DD, SCZ & SUD > HC
Cognitive impulsivity	22.5 (5.4)	19.8 (6.1)	21.2 (6.7)	14.6 (3.5)	F=9.8; p<0.0001	DD, SCZ & SUD > HC
Non-planning impulsivity	22.6 (5.7)	19 (5.6)	21.1 (7.5)	14.4 (4.8)	F=11.7; p<0.0001	DD, SCZ & SUD > HC
Total	62.4 (14.8)	55.6 (13.7)	61.3 (19.3)	37.9 (8.5)	F=15.1; p<0.0001	DD, SCZ & SUD > HC
Sensation-seeking						
Thrill-seeking	4.4 (2)	2.7 (1.7)	4.2 (2)	2.6 (2.1)	F=6.4; p<0.0001	DD & SUD > SCZ & HC
Experience-seeking	4.4 (1.8)	3.5 (1.3)	5.2 (1.6)	4.2 (2.3)	F=4.8; p=0.004	SUD > SCZ

Disinhibition	6.6 (1.8)	3.9 (1.2)	6.3 (2.2)	4.6 (1.9)	F=11.3; p<0.0001	DD & SUD > SCZ & HC
Boredom susceptibility	5.3 (2.1)	2.9 (1.7)	5.2 (2.2)	4.4 (1.9)	F=7.9; p<0.0001	DD & SUD > SCZ ; HC > SCZ
Total	20.6 (5.5)	13 (5.4)	21.1 (6.4)	15.9 (6.6)	F=11.7; p<0.0001	DD & SUD > SCZ ; SUD > HC
Social anhedonia	13.8 (7)	12.8 (6.9)	11.6 (5.9)	8 (4.2)	F=4.5; p=0.005	DD & SCZ > HC
Socio-demographic variables						
Age	30 (9.8)	39.9 (12.7)	37.8 (11.9)	40 (12.5)	F=4.6; p=0.005	DD > SCZ & HC
Gender	27M: 4F	14M: 9F	26M: 13F	16M: 9F	χ=5.9; p=0.1	---
Hospitalisations	2.8 (2.9)	2.8 (2.7)	---	---	F=0.5; p=0.9	---
Diagnosis	17SCZ:12SA:2SF	15SCZ:6SA:2SF	---	---	χ=1; p=0.6	---
Antipsychotic class	20AP:4TP:5BT:2DF	13AP:4TP:0BT:3DF	---	---	χ=4.5; p=0.2	---

Substance type						
Alcohol	15Y: 16N		25Y: 15N		χ=1.2; p=0.3	---
Cannabis	18Y: 13N		20Y: 19N		χ=0.3; p=0.6	
Stimulant	9Y: 22N		16Y: 23N		χ=1.1; p=0.3	

DD = dual-diagnosis schizophrenia; SCZ = schizophrenia only; SUD = non-psychosis patients with substance use disorders; HC = healthy controls; SA = schizoaffective disorder; SF = schizophreniform disorder; AP = atypical antipsychotic; TP = typical antipsychotic; BT = both; DF = drug-free; Y = yes; N = no; M = male; F = female; * = After Bonferroni correction

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S. Zhornitsky wrote the first draft, and contributed to the study design and systematic search.

Antipsychotic agents for the treatment of substance use disorders in patients with and without comorbid psychosis

Simon Zhornitsky[1]; Élie Rizkallah[1,2]; Tania Pampoulova[1,2]; Jean-Pierre Chiasson[2]; Emmanuel Stip[1]; Pierre-Paul Rompré[1]; Stéphane Potvin, PhD[1].

[1]Fernand-Seguin Research Centre, Department of Psychiatry, Faculty of Medicine, University of Montreal; Montreal, Canada

[2]Clinique du Nouveau-Départ; Montreal, Canada

Corresponding author

Stéphane Potvin
Centre de recherche Fernand-Seguin
7331 Hochelaga
Montreal, Quebec, Canada
H1N 3V2
Tel: (514) 251-4015
Fax: (514) 251-2617

6.1 Abstract

Substance dependence has serious negative consequences upon society such as increased health care costs, loss of productivity and rising crime rates. While there is some preliminary evidence that atypical antipsychotics may be effective in treating substance dependence, results have been mixed, with some studies demonstrating positive, and others negative or no effect. The present study was aimed at determining whether this disparity originates from the fact that reviewers discussed separately trials in patients with (DD) and without (SD) co-morbid psychosis. Using electronic databases we screened relevant literature leaving only studies which employed a randomized, double-blind, placebo-controlled or case-control design that had a duration of four weeks or longer. A total of 43 studies were identified; of these, 23 fell into the category of DD and 20 fell into the category of SD. DD studies suggest that atypical antipsychotics – especially clozapine – may decrease substance use in individuals with alcohol, and drug use disorders (mostly cannabis). SD studies suggest that atypical antipsychotics may be beneficial for the treatment of alcohol dependence – at least in some subpopulations of alcoholics. They also suggest that these agents are not effective at treating stimulant dependence and may aggravate the condition in some cases.

Key words: dual diagnosis, substance dependence, antipsychotic, schizophrenia, alcohol, stimulants, cannabis

6.2 Introduction

Abuse of psychoactive substances (PAS) such as stimulants, depressants and hallucinogens is currently one of the leading causes of crime, violence, disease, illness and death worldwide, and this places considerable burden upon economies via loss in productivity and increases in spending on health care and law enforcement.[1] For the PAS users, there is a high risk of developing psychiatric symptoms such as anhedonia, depression and anxiety during acute and protracted withdrawal.[2-5] In addition, abuse of some PAS has been shown to produce psychotic symptoms requiring treatment – symptoms which are often indistinguishable from those of schizophrenia.[6] Conversely, individuals with an already present mental illness are at an increased risk of developing substance use disorders (SUDs), the lifetime prevalence of which ranges from 25% in depression and anxiety disorders to 47% in schizophrenia and 56% in bipolar disorder.[7] In these psychosis patients, PAS abuse tends to exacerbate already-present psychiatric symptoms and is associated with poorer treatment outcome.[8] While psychiatric drugs may be useful in the treatment of psychiatric symptoms associated with SUDs, it remains to be seen whether they are effective at improving SUD outcomes.

Antipsychotics, drugs which are normally used to treat psychosis in schizophrenia and acute mania in bipolar disorder, have also shown promise in the treatment of SUDs and it has been presumed that these benefits are greater in dually diagnosed bipolar and schizophrenia patients.[12,13] This class of compounds is characterized by antagonism of dopamine (DA), a neurotransmitter that is implicated in the rewarding effects of drugs. For instance, animal models of reward have demonstrated that antipsychotics reverse cocaine-, amphetamine-, morphine and nicotine-induced decreases in threshold for rewarding brain stimulation,[14-17] increase responding for amphetamine and cocaine in the self-administration paradigm (indicative of decreased

rewarding efficacy)[18,19] and block the establishment of a conditioned place preference to amphetamine, ethanol, and cocaine.[20-22] Animal models of relapse have evidenced that antipsychotics block drug- and cue-induced reinstatement of responding on the drug-associated lever during self-administration of heroin, cocaine and amphetamine[23-25] and prevent the ability of heroin and amphetamine to reinstate operant runway behavior.[26,27]

PET studies show that all PAS increase DA release in the ventral striatum in humans.[28] For their part, all antipsychotics have been evidenced to block D_2 receptors in the striatum but recent evidence suggests that some newer antipsychotics may be distinguished by faster disassociation from D_2 receptors and this may be the reason why they are less likely to induce anhedonia and extrapyramidal symptoms (EPS).[29-31] In addition to dopaminergic antagonism, a number of antipsychotics act on other neurotransmitter systems such as serotonin (5-HT), norepinephrine (NE).[32,33] which may mediate heightened anxiety and depressive symptoms during acute and protracted withdrawal from PAS.[23,34,35] Such a broad spectrum of action makes antipsychotics theoretically useful because they may target a number of psychiatric symptoms such as craving, anxiety and depression in addition to blocking the rewarding efficacy of PAS. Indeed, some newer (atypical) antipsychotics have shown promise as monotherapies in the treatment of mood and anxiety disorders.[36-38] However, evidence for the utility of antipsychotics for the treatment of SUDs has not been conclusive – with some studies evidencing a decrease and others no effect or even an increase in SUD symptomatology. Reasons for these discrepancies may include the type of antipsychotic and the type of PAS as well as the presence of comorbid psychiatric symptoms.

Up to this point, the majority of reviews detailing the efficacy of antipsychotics for SUDs have only pooled studies of schizophrenia and bipolar patients and have included both controlled

as well as uncontrolled, open-label (switch design) trials and case reports.[12,39,40] The sole comprehensive review of the efficacy of antipsychotics in the non-psychosis population has focused on cocaine dependence.[41] The present review will examine randomized studies of antipsychotics in the treatment of SUDs in non-psychosis substance abusers (SD), as well as randomized and case-control studies (including retrospective studies) in psychosis dually-diagnosed (DD) substance abusers – simultaneously paying attention to antipsychotic and PAS type – with the aim of accounting for the aforementioned discrepancies that exist in the literature.

6.3 Methods

A systematic search was performed in the electronic databases PubMed and EMBASE using the key words "amisulpride OR antipsychotic OR aripiprazole OR chlorpromazine OR clozapine OR flupenthixol OR fluphenazine OR haloperidol OR neuroleptic OR olanzapine OR perphenazine OR risperidone OR tiapride OR quetiapine OR ziprazidone" AND "alcohol OR amphetamine OR cannabis OR heroin OR marijuana OR methamphetamine OR opiate OR phencyclidine OR substance abuse OR substance use disorder OR smoking OR nicotine". This search identified studies published between January 1, 1962 and June 1, 2009. Additionally, studies were identified by cross-referencing.

To be included in the review, studies had to address specifically the treatment of SUDs with antipsychotics. All psychosis patients (i.e. schizophrenia, schizoaffective, and bipolar disorder) with concomitant SUD were considered for inclusion in the DD group of studies. Treatment must have lasted longer than four weeks and outcomes must have been measured by craving, alcohol/drug use, and/or relapse. Only randomized studies were included in the SD group. In order to increase the number of studies measuring the efficacy of antipsychotics for the treatment of SUDs in DD patients, case-control studies comparing two or more antipsychotics (retrospective or prospective) with no randomization were also included. Case reports, open-label (switch design) and cross-sectional studies were excluded from both DD and SD analysis. Considering the methodological limitations of DD studies and the heterogeneity of substances included in both DD and SD studies, studies included in this review were not amenable to quantitative mete-analytic treatment.

6.4 Results

DD and SD study characteristics

A total of 43 studies were identified; of these, 23 fell into the category of DD and 20 fell into the category of SD. The 23 DD studies included 10 case-control and 13 randomized studies (Table 1; see Supplemental Table A for full table). Four of the studies in the DD group included primarily bipolar patients.[42-45] The remaining studies included primarily schizophrenia-spectrum disorders. Only two studies in the DD group employed a placebo-controlled design[42,43] and two studies had an open-label group receiving no medication.[44,46] Out of a total of 13 randomized studies in the DD group, ten were double-blind and three were open-label.[44,47,48] Four studies in the DD group were retrospective.[49-52] By contrast, 19 out of 20 studies in the SD group were placebo-controlled and all were double-blind and randomized (Table 2; see Supplemental Table B for full table).

DD results

Alcohol and drug use (mostly cannabis)

Five prospective DD schizophrenia studies investigated alcohol and drug use (mostly cannabis). A large 144-week case-control study (N=151) found that clozapine treatment was associated with significantly lower drinking severity, fewer days of alcohol use, a marginally significant reduction in severity of drug use (a majority of cannabis users) and greater remission.[53] Another large 144-week case-control study (N=362) found that patients compliant with atypicals (clozapine, risperidone and olanzapine) were significantly less likely to use alcohol and drugs (unspecified) compared to those compliant with typicals and those receiving no medication for 90 days.[46] Similarly, a large randomized trial (N=115) found that long-acting injectable risperidone was associated with significantly less alcohol and drug use (unspecified), lower

psychopathology, less EPS and better compliance with a SUD treatment program compared to zuclopenthixol depot.[48] Moreover, a case-control study found that patients receiving clozapine at the first 6-month period of substance abuse remission were significantly less likely to relapse to alcohol and drug use (a majority of cannabis users), compared to those receiving olanzapine, risperidone and typicals.[54] Finally, a case-control study comparing olanzapine to typicals found that olanzapine was associated with improvements in symptoms and psychosocial function; however, both treatments lead to significant decreases in alcohol use.[55]

Three retrospective studies in our sample investigated antipsychotic treatment of alcohol and drug use in schizophrenia patients. A retrospective study of clozapine versus risperidone in schizophrenia patients with alcohol and cannabis use disorders revealed that clozapine-treatment was associated with significantly lower rates of relapse at one year of treatment.[49] Another retrospective comparison found clozapine to be more effective than olanzapine, and olanzapine to be more effective than haloperidol for decreasing relapse in schizophrenia patients with alcohol use disorder.[51] Moreover, a larger retrospective comparison found that DD patients that were switched to or maintained on atypicals (primarily olanzapine and risperidone) evidenced significant decreases in alcohol and psychological addiction severity index (ASI) scores, compared to those who were treated with typicals.[52] However, in this study, multiple regression analysis revealed no significantly greater improvement in any ASI scores for those individuals who were switched to or maintained on atypicals.

A study that examined alcoholism in bipolar patients found that quetiapine add-on treatment significantly decreased depressive symptoms compared to placebo but was no better at reducing drinking variables.[42] On the other hand, a more recent pilot study by the same authors

found that quetiapine reduced heavy drinking days and increased treatment compliance compared to placebo.[43]

Two randomized double-blind studies specifically examined cannabis use in schizophrenia patients receiving olanzapine compared to risperidone. One found equal reductions in cannabis use and craving from baseline[56], while the other found equal reductions in cannabis craving and a preferential benefit of risperidone on craving.[57]

Finally, heroin use was examined in a prospective case-control trial of olanzapine, in combination with opioid agonists, in schizophrenia patients. Results demonstrated that olanzapine significantly reduced psychopathology and heroin use as well as improved treatment retention compared to haloperidol.[58]

Stimulants

Seven studies investigated antipsychotics for stimulant dependence in DD patients. One randomized, double-blind study failed to find a significant effect of olanzapine and risperidone on cocaine use and craving.[57] Another randomized double-blind trial found haloperidol to be associated with significantly less craving compared to olanzapine in cocaine-dependant schizophrenia patients.[59] A case-control trial of schizophrenia patients found that risperidone was associated with reduced psychopathology, less cue-elicited cocaine craving and lower rates of relapse compared to typical agents.[60] However, more recent randomized double-blind study by the same authors demonstrated olanzapine to significantly reduce cue-elicited craving but not cocaine use compared to typical antipsychotics.[61]

Two randomized studies found quetiapine treatment to be equally as efficient as risperidone[45] and more efficient than typicals at reducing stimulant craving in bipolar patients.[44]

On the other hand, a small placebo-controlled trial did not find any difference between quetiapine and placebo on cocaine use or craving in bipolar patients.[43]

Tobacco

Four studies examined the effects of atypical antipsychotics on cigarette smoking in schizophrenia patients. One open-label randomized study found that schizophrenia patients treated with atypicals exhibited significantly higher quit rates and lower expired CO than patients treated with typicals.[47] Additionally, a small double-blind trial, that randomized patients to high, medium and low (sub-therapeutic) doses of clozapine, found that those individuals with therapeutic plasma levels of clozapine evidenced reductions in cigarettes smoked and expired carbon monoxide (CO), compared to their haloperidol baseline.[62] A more recent study by the same team found that those patients randomized to higher doses of clozapine evidenced a significant decrease in the number of cigarettes smoked compared to their haloperidol baseline; however, biomarkers such as levels of nicotine, cotinine and expired CO were not significantly reduced as a function of clozapine dose.[63] On the other hand, a more recent attempt to replicate these results using a similar study design, found no significant effect of clozapine treatment on plasma cotinine levels (considered to be the most reliable biomarker of smoking decrease and abstinence) at any dose.[64] Finally, one retrospective study found that olanzapine and typicals were associated with a significantly lower completion rate and greater desire to smoke immediately after discharge from a SUD treatment program, compared to patients receiving risperidone and ziprasidone.[50]

SD results

Alcohol

Eleven studies investigated the effects of antipsychotics on alcohol use disorder in SD individuals. Olanzapine was found to significantly reduce cue-elicited craving and drinking when compared with placebo in a subset of individuals with the longer alleles of the DRD4 genotype (DRD4 L) but not in those with the shorter alleles (DRD4 S).[65] Similarly, quetiapine was found to reduce craving and drinking over placebo in Type B alcoholics but not in Type A alcoholics.[66] On the other hand, no difference between olanzapine and placebo was found in a study that did not differentiate between subsets of alcoholics.[67] Aripiprazole treatment was associated with the best outcomes of the atypical antipsychotics in undifferentiated alcoholics. One large placebo-controlled trial (N=295) found aripiprazole to significantly lower the amount of heavy alcohol consumption and alcohol dependence severity.[68] Another randomized, double-blind comparison of aripiprazole vs. naltrexone found treatment aripiprazole-treatment to be associated with a significantly longer abstinence time; however, naltrexone produced larger decreases in craving.[69] The sole study of amisulpride found that the D2/D3 antagonist increased alcohol craving and relapse as compared to placebo.[70] Tiapride, another substituted benzamide with affinity for D2/D3 receptors and atypical properties in preclinical models as well as a very low incidence of EPS in humans[71,72] was superior to placebo in preventing relapse and decreasing drinking in alcoholics with an anxious or depressive temperament[73] and in a group of undifferentiated alcoholics.[74] However, more recent, larger placebo-controlled trials (combined N=360), showed tiapride to increase relapse over placebo in undifferentiated alcoholics.[75,76] Finally, the only study in our sample investigating the use of flupenthixol decanoate for alcoholism found a significant increase in relapse in 281 alcoholics compared to placebo.[77]

Stimulants

A total of nine studies investigated antipsychotic treatment of stimulant dependence in SD individuals. One study of flupenthixol decanoate for the treatment of stimulant abuse found the antipsychotic to be superior to placebo for reducing crack cocaine use.[78] Five other placebo-controlled studies failed to find any significant differences in cocaine use or craving with either risperidone or olanzapine treatment.[79-83] However, risperidone increased depressive symptoms in one study.[80] Additionally, three placebo-controlled studies found atypical antipsychotics to significantly increase in stimulant use. In particular, an aggravation of drug use was found for olanzapine and cocaine,[84] risperidone (8mg/d) and cocaine[85] and aripiprazole and intravenous amphetamine.[86]

6.5 Discussion

DD studies

In DD studies, the biggest improvements in SUD outcome measures were observed for clozapine in DD patients with alcohol, and possibly, cannabis use disorders.[49,51,53,54] There was also evidence that treatment with other atypical antipsychotics such as quetiapine, olanzapine and risperidone may lead to improvements in alcohol and drug use (mostly cannabis).[43,46,48,51,54,56,57]. Interestingly, the largest placebo-controlled study in the DD group investigating alcohol use found no difference between quetiapine and placebo in bipolar patients.[42] However, it must be noted that in this study quetiapine was administered as add-on therapy to mood stabilizers, which makes it difficult to determine the effects of quetiapine alone on alcohol dependence.

Findings in DD patients need to be tempered by the fact that many of the studies in this group employed a case-control or retrospective design. One limitation of case-control and retrospective studies with clozapine may be that this medication is more likely to be tried in individuals who are non-responsive to treatment with other antipsychotics.[53] Overall, the difficulty in maintaining treatment compliance in DD patients renders finding large number of patients for randomized studies a hard task and precludes us from drawing causal relationships between atypical or typical treatment and SUDs. Nevertheless, of all the DD studies included in this review, the studies involving the largest sample sizes and having the longest duration of treatment were the clozapine studies. It is therefore difficult to rule out the results from these studies when evaluating the potential benefits of clozapine for SUD outcomes in DD patients.

The DD studies investigating atypical antipsychotic treatment of stimulant dependence showed reductions in craving[44,45,57,61] or no effect.[43,59] One possibility is that while these studies were randomized, many of them contained small sample sizes and may have lacked the power to

detect significant differences in stimulant use as a result of antipsychotic treatment. Providing support for this possibility, there is evidence that craving predicts relapse to a variety of PAS such alcohol, cocaine, tobacco and opiates.[88-91] However, despite these putative relationships, the effect of antipsychotics on stimulant dependence remains inconclusive.

Current research suggests that a pharmacokinetic interaction between cigarette smoking and specific antipsychotics may lead to increases in antipsychotic plasma levels and antipsychotic-induced side-effects, thereby making it difficult for patients to stop smoking. A study by Stuyt et al.[50] revealed that significantly more patients treated with olanzapine and typicals reported a desire to smoke immediately after discharge from a dual diagnosis treatment program, compared to those treated with risperidone and ziprazidone. The authors explained these data as being due to an induction of the cytochrome P450 isoenzyme 1A2 (CYP1A2) by cigarette smoke,[50] which has been shown to speed up metabolism of some atypicals such as clozapine, olanzapine, and typicals such as haloperidol, chlorpromazine, thiothixene and fluphenazine,[92,93] leading to as much as a 1.5-fold elevation in plasma clozapine levels when patients attempt to quit smoking.[94] By contrast, other studies that did not ask smokers to abstain from smoking (i.e. provided free unlimited cigarettes to patients) found clozapine to decrease[62,63] or to have no effect[64] on smoking. The only other study that we reviewed, which asked patients to abstain from smoking, revealed that significantly more patients on atypicals than typicals were willing to abstain from smoking for the entire duration of the 12-week trial[47]. Intriguingly, only two out of four of the agents in their atypical group are metabolized by CYP1A2, whereas all of the antipsychotics in the typical group are metabolized by CYP1A2.[92,93] As a whole, the preliminary positive evidence of atypicals for the treatment of tobacco dependence needs to be corroborated by future studies with larger sample sizes.

SD studies

Apart from two studies with aripiprazole that found improvements in alcohol dependence,[68,69] the majority of studies – which did not differentiate between subtypes of alcoholics – found both typical and atypical antipsychotics to increase relapse in SD individuals.[67,70,75-77] By contrast, other trials found atypical antipsychotics to be effective – but only in some subtypes of alcoholics. In particular, Kampman et al.[66] found that quetiapine decreased alcohol craving and drinking in Type B alcoholics, but not in Type A alcoholics – the former being characterized by an increased presence of psychopathology.[95] Another placebo-controlled trial found that tiapride decreased drinking and relapse in alcoholics with symptoms of anxiety and depression.[73] In addition, Hutchinson et al.[65] found that olanzapine decreased cue-elicited craving for alcohol and drinking over placebo; but only in individuals with the DRD4 L genotype. These results suggest that alcoholics with certain phenotypes and genotypes may be more likely to respond to treatment with atypical antipsychotics.

The studies which we reviewed suggest that typical and atypical antipsychotics are not effective treatments of stimulant dependence in SD individuals,[79-83] and may, in some cases, aggravate stimulant use. For example, risperidone was shown to aggravate cocaine use at high doses (8mg/day) in SD individuals[85] Another study found that olanzapine increased cocaine use compared to placebo.[84] In addition, aripiprazole was found to aggravate stimulant use in intravenous amphetamine users; causing a spike to 100% amphetamine-positive urine screens in the last 10 weeks of the study in aripiprazole-treated subjects.[86]

Surprisingly, the only study that has found improvements in stimulant use was involving flupenthixol decanoate.[78] While initial results showed that flupenthixol decreased cocaine use over placebo, a later publication revealed that 15% of patients treated with flupenthixol stopped

crack use due to the occurrence of severely distressing involuntary muscular restlessness (akathisia) after smoking crack-cocaine.[96] Similar EPS were found in a study of the effects of flupenthixol on subjective responses to intravenous cocaine.[97] In this 11-day study (which did not meet our inclusion criteria), individuals randomized to the high dose of flupenthixol evidenced a high rate of dystonic reactions (29%) and increased desire for the drug. In sum, the considerable number of SD studies reporting disturbing EPS and aggravations of stimulant use show that typical and atypical antipsychotics are not a clinically useful treatment for stimulant dependence in non-psychosis individuals.

Side-effects

The benefits of antipsychotics for treating SUDs in DD and SD individuals need to be weighed against the potential for noncompliance and relapse to substance abuse as a consequence of increased side-effects. Regardless of psychiatric comorbidity, antipsychotics may interact with PAS to increase EPS.[96-98] Moreover, smoking cessation may induce intoxication with clozapine, olanzapine and many typical agents, potentially leading to increased adverse effects.[94,99] During cases of alcohol withdrawal syndrome, treatment with antipsychotics has been found to be particularly dangerous because some of these compounds may lower seizure threshold.[100] Importantly, in DD patients, there is evidence that antipsychotic-induced side-effects are associated with noncompliance, psychotic relapse and elevated substance abuse.[101-104] Similarly, in SD individuals, there is evidence that antipsychotic-induced side-effects are associated with low treatment retention and elevated substance abuse.[85] These data demonstrate that clinicians involved in the treatment of DD patients should pay particular attention to interactions between

specific antipsychotics and PAS. They also suggest that antipsychotic treatment of SUDs in SD individuals may not outweigh the risk for harm.

Conclusion

DD studies suggest that atypical antipsychotics – especially clozapine – may decrease substance use in individuals with alcohol, and drug use disorders (mostly cannabis). SD studies suggest that atypical antipsychotics may be beneficial for the treatment of alcohol dependence – at least in some subpopulations of alcoholics. They also suggest that these agents are not effective at treating stimulant dependence and may aggravate the condition in some cases. Clinicians must bear in mind that antipsychotics are useful for the treatment of stimulant-induced psychotic disorders, but they must be cautious when using high doses of antipsychotics for the long-term treatment of SUD in stimulant abusers.

Further large-scale studies with long duration of treatment are required to measure the efficacy of clozapine on alcohol and cannabis dependence in DD patients. In addition, larger randomized trials are needed to determine the precise impact of atypical antipsychotics on stimulant dependence in DD patents. Finally, future studies should investigate which subgroups of SD alcoholics may benefit most from atypical therapy.

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Table 1: DD results

Study	*N*	Dx	Wks	SUD(s)	Treatment	R	D	P	Outcome(s)
Swanson et al. 2007[46]	362	SCZ	144	Alcohol + drugs	ATP vs. TYP vs. NA	N	N	N	ATP ↓ substance use
Drake et al. 2000[53]	151	SCZ	144	Alcohol + drugs	CLO vs. TYP	N	N	N	CLO ↓ substance use ↓ relapse
Brunette et al. 2006[54]	95	SCZ	96	Alcohol + drugs	CLO vs. ATP vs. TYP	N	N	N	CLO ↓ relapse
Petrakis et al. 2006[52]	249	SCZ	48	Alcohol + drugs	ATP vs. TYP	N	N	N	No difference
Rubio et al. 2006[48]	115	SCZ	24	Alcohol + drugs	RIS (inj) vs. ZUC (inj)	Y	N	N	RIS ↓ substance use
Green et al. 2003[49]	41	SCZ	48	Alcohol + cannabis	CLO vs. RIS	N	N	N	CLO ↓ relapse
Brunette et al. 2008[51]	86	SCZ	24	Alcohol	CLO vs. OLA vs. TYP	N	N	N	CLO ↓ relapse
Noordsy et al. 2001[55]	38	SCZ	24	Alcohol	OLA vs. TYP	N	N	N	Equal ↓ alcohol use
Brown et al. 2008[42]	102	BD	12	Alcohol	QTP	Y	Y	Y	No difference
Brown et al. 2010[43]	12	BD	12	Stimulants + alcohol	QTP	Y	Y	Y	QTP ↓ alcohol use
Brown et al. 2003[44]	24	BD	12	Stimulants	QTP vs. TYP vs. NA	Y	N	N	QTP ↓ craving
Nejtek et al. 2008[45]	94	BD	20	Stimulants	QTP vs. RIS	Y	Y	N	Equal ↓ craving
Smelson et al. 2002[60]	18	SCZ	6	Stimulants	RIS vs. TYP	N	N	N	RIS ↓ relapse ↓ craving

Smelson et al. 2006[61]	31	SCZ	6	Stimulants	OLA vs. HAL	Y	Y	N	OLA ↓ craving
Sayers et al. 2005[59]	24	SCZ	26	Stimulants	OLA vs. HAL	Y	Y	N	HAL ↓ craving
Akerele & Levin, 2007[57]	28	SCZ	14	Stimulants + cannabis	OLA vs. RIS	Y	Y	N	Equal ↓ cannabis use; RIS ↓ cannabis craving
van Nimwegen et al. 2008[56]	42	SCZ	6	Cannabis	OLA vs. RIS	Y	Y	N	Equal ↓ use ↓ craving
Gerra et al. 2007[58]	61	SCZ	12	Heroin	OLA vs. HAL	N	N	N	OLA ↓ use
Stuyt et al. 2006[50]	55	SCZ	144	Tobacco	OLA vs. RIS vs. ZIP vs. TYP	N	N	N	OLA + TYP ↑ craving
George et al. 2000[47]	44	SCZ	10	Tobacco	ATP vs. TYP	Y	N	N	ATP ↓ relapse ↓ use
McEvoy et al. 1995[62]	12	SCZ	12	Tobacco	CLO vs. HAL	Y	Y	N	Med + Hi CLO ↓ use
McEvoy et al. 1999[63]	55	SCZ	12	Tobacco	CLO vs. HAL	Y	Y	N	Med + Hi CLO ↓ use
de Leon et al. 2005[64]	38	SCZ	16	Tobacco	CLO vs. HAL	Y	Y	N	No difference

Table legend: ↑ = increase, ↓ = decrease, *N* = sample size (intent-to-treat population), dx = diagnosis (majority), wks = weeks, stimulants = amphetamines and/or cocaine, inj = injectable, SCZ = schizophrenia, BD = bipolar disorder, R = randomized, D = double-blind, P = placebo-

controlled, Med = medium dose, Hi = high dose, ATP = mixed atypicals, TYP = mixed typicals, CLO = clozapine, OLA = olanzapine, RIS = risperidone, QTP = quetiapine, ZIP = ziprasidone, ZUC = zuclopenthixol, HAL = haloperidol, NA = no medication.

Table 2: SD results

Study	*N*	Wks	SUD(s)	Treatment	R	D	P	Outcome(s)
Wiesbeck et al. 2001[77]	281	48	Alcohol	FLU (inj)	Y	Y	Y	FLU ↑ relapse
Shaw et al. 1987[73]	20	24	Alcohol	TIA	Y	Y	Y	TIA ↓ use ↓ relapse (anxio-depressive alcoholics)
Shaw et al. 1994[74]	54	24	Alcohol	TIA	Y	Y	Y	TIA ↓ use ↓ relapse
Gual et al. 2002[75]	81	24	Alcohol	TIA	Y	Y	Y	TIA ↑ relapse
Bender et al. 2006[76]	299	24	Alcohol	TIA	Y	Y	Y	TIA ↑ relapse
Marra et al. 2002[70]	71	24	Alcohol	AMI	Y	Y	Y	AMI ↑ relapse ↑ craving
Guardia et al. 2004[67]	60	12	Alcohol	OLA	Y	Y	Y	No difference
Hutchinson et al. 2006[65]	64	12	Alcohol	OLA	Y	Y	Y	OLA ↓ use ↓ craving (DRD4 L gene)
Kampman et al. 2007[66]	61	12	Alcohol	QTP	Y	Y	Y	QTP ↓ use ↓ craving (Type B subtype)
Anton et al. 2008[68]	295	12	Alcohol	APZ	Y	Y	Y	APZ ↓ use
Martionotti et al. 2009[69]	57	16	Alcohol	APZ vs. NAL	Y	Y	N	APZ ↓ relapse; NAL ↓ craving
Kampman et al. 2003[84]	30	12	Stimulants	OLA	Y	Y	Y	OLA ↑ relapse
Reid et al. 2005[83]	63	8	Stimulants	OLA	Y	Y	Y	No difference

Hamilton et al. 2009[81]	48	16	Stimulants	OLA	Y	Y	Y	No difference
Levin et al. 1999[79]	14	24	Stimulants	RIS	Y	Y	Y	No difference
Grabowski et al. 2000[85]	125	12	Stimulants	RIS	Y	Y	Y	Hi RIS ↑ use
Grabowski et al. 2004[82]	96	26	Stimulants	RIS	Y	Y	Y	No difference
Loebl et al. 2008[80]	31	12	Stimulants	RIS (inj)	Y	Y	Y	RIS ↑ depressive symptoms
Tiihonen et al. 2007[86]	36	20	Stimulants	APZ	Y	Y	Y	APZ ↑ use
Gawin et al. 1996[78]	54	6	Stimulants	FLU (inj)	Y	Y	Y	FLU ↓ use

Table legend: ↑ = increase, ↓ = decrease, *N* = sample size (intent-to-treat population), wks = weeks, stimulants = amphetamine and/or cocaine, inj = injectable, R = randomized, D = double-blind, P = placebo-controlled, Hi = high dose, OLA = olanzapine, RIS = risperidone, TIA = tiapride, APZ = aripiprazole, QTP = quetiapine, AMI = amisulpride, FLU = flupenthixol, NAL = naltrexone.

Supplemental Table A: DD results

Study	*N*	Dx	Wks	SUD(s)	Treatment (dose)	R	D	P	Outcome
Swanson et al. 2007[46]	362	SCZ	144	Alcohol + drugs	Atypicals (clozapine, olanzapine, risperidone) vs. typicals (NR) vs. no medication	N	N	N	Patients compliant with atypicals exhibited less substance use than those receiving no medication or those compliant with typicals or those noncompliant with antipsychotic medication.
Drake et al. 2000[53]	151	SCZ	144	Alcohol + drugs	Clozapine (NR) vs. typicals (NR)	N	N	N	Clozapine associated with significantly lower drinking severity, fewer days of alcohol use, reduction in severity of drug use and greater remission.
Brunette et al. 2006[54]	95	SCZ	96	Alcohol + drugs	Clozapine (484mg) vs. olanzapine or risperidone (NR) vs. typicals (NR)	N	N	N	Clozapine associated with significantly lower relapse rates than reference antipsychotics.
Petrakis et	249	SCZ	48	Alcohol +	Atypicals (olanzapine,	N	N	N	Those switched to or maintained on atypicals

al. 2006[52]				drugs	risperidone, quetiapine) vs. typicals (NR)				exhibited significant reductions in alcohol and psychological ASI scores; however, differences disappeared after controlling for potential confounding factors.
Rubio et al. 2006[48]	115	SCZ	24	Alcohol + drugs	Long-acting risperidone (47.2mg/15d) vs. zuclopenthixol depot (200mg/21d)	Y	N	N	Risperidone associated with significantly less alcohol and drug use and increased compliance with a SUD treatment program.
Green et al. 2003[49]	41	SCZ	48	Alcohol + cannabis	Clozapine (439mg) vs. risperidone (3.9mg)	N	N	N	Clozapine associated with significantly lower rates of relapse.
Brunette et al. 2008[51]	86	SCZ	24	Alcohol	Clozapine (488mg) vs. olanzapine (18mg) vs. typicals (405mg*)	N	N	N	Clozapine associated with significantly lower relapse rates than olanzapine and olanzapine associated with significantly lower relapse than typicals.
Noordsy et al. 2001[55]	38	SCZ	24	Alcohol	Olanzapine (15mg) vs. typicals (393mg*)	N	N	N	Equally significant reductions in drinking. Sample size of drug users too small to run a

									statistical analysis.
Brown et al. 2008[42]	102	BD	12	Alcohol	Quetiapine (300-600mg) vs. placebo	Y	Y	Y	No significant differences in drinking outcomes between groups.
Brown et al. 2010[43]	12	BD	12	Stimulants + alcohol	Quetiapine (429mg) vs. placebo	Y	Y	Y	No significant differences in cocaine use or craving. Quetiapine associated with significantly fewer heavy drinking days and longer time in treatment.
Brown et al. 2003[44]	24	BD	12	Stimulants	Quetiapine (394mg) vs. typicals (471mg*) vs. no medication	Y	N	N	No significant difference in cocaine and amphetamine use between groups. Quetiapine associated with significant reductions in craving.
Nejtek et al. 2008[45]	94	BD	20	Stimulants	Quetiapine (304mg) vs. risperidone (3mg)	Y	Y	N	Equally significant reductions cocaine and methamphetamine craving across groups.
Smelson et al. 2002[60]	18	SCZ	6	Stimulants	Risperidone (6mg) vs. typicals (522mg*)	N	N	N	Risperidone associated with significantly lower rates of relapse and less cue-elicited cocaine craving.

Smelson et al. 2006[61]	31	SCZ	6	Stimulants	Olanzapine (10mg) vs. haloperidol (10mg)	Y	Y	N	No significant difference in cocaine use between groups. Olanzapine associated with significantly less cue-elicited cocaine craving.
Sayers et al. 2005[59]	24	SCZ	26	Stimulants	Olanzapine (10-20mg) vs. haloperidol (10-20mg)	Y	Y	N	No significant difference in cocaine use between groups. Haloperidol associated with significantly less cocaine craving.
Akerele & Levin, 2007[57]	28	SCZ	14	Stimulants + cannabis	Olanzapine (20mg) vs. risperidone (9mg)	Y	Y	N	No significant reductions in cocaine use or craving. Risperidone associated with significantly less cannabis craving; equally significant reductions in cannabis use between groups.
van Nimwegen et al. 2008[56]	42	SCZ	6	Cannabis	Olanzapine (11mg) vs. risperidone (3mg)	Y	Y	N	Equally significant reduction in cannabis craving and use between groups.
Gerra et al. 2007[58]	61	SCZ	12	Heroin	Olanzapine (13mg) vs. haloperidol (9mg)	N	N	N	Olanzapine associated with significantly less heroin use and longer time in treatment.

Stuyt et al. 2006[50]	55	SCZ	144	Tobacco	Olanzapine (19mg) vs. risperidone (4mg) vs. ziprasidone (133mg) vs. typicals (NR)	N	N	N	Olanzapine and typicals associated with significantly more craving and lower completion rate of a SUD treatment program.
George et al. 2000[47]	44	SCZ	10	Tobacco	Atypicals (600mg*) vs. typicals (625mg*)	Y	N	N	Atypical antipsychotics associated with significantly higher quit rates and lower expired CO.
McEvoy et al. 1995[62]	12	SCZ	12	Tobacco	Clozapine (see McEvoy et al. 1999) vs. haloperidol (20mg)	Y	Y	N	Two highest clozapine plasma levels associated with significant reductions in number of cigarettes smoked and expired CO.
McEvoy et al. 1999[63]	55	SCZ	12	Tobacco	Clozapine (171mg, 414mg, or 551mg) vs. haloperidol (20mg)	Y	Y	N	Two highest clozapine plasma levels associated with significant reductions in cigarettes smoked.
de Leon et al. 2005[64]	38	SCZ	16	Tobacco	Clozapine (100mg, 300mg, or 600mg) vs. haloperidol (NR)	Y	Y	N	No significant effect of clozapine treatment on plasma cotinine levels.

Table legend: *N* = sample size (intent-to-treat population), dx = diagnosis (majority), dose = mean or fixed exit dose, wks = weeks, stimulants = amphetamines and/or cocaine, SCZ = schizophrenia, BD = bipolar disorder, R = randomized, D = double-blind, P = placebo-controlled, * = chlorpromazine equivalents, NR = not reported, CO = carbon monoxide.

Supplemental Table B: SD results

Study	*N*	Wks	SUD(s)	Treatment (dose)	R	D	P	Outcome
Wiesbeck et al. 2001[77]	281	48	Alcohol	Flupenthixol decanoate (10mg/14d) vs. placebo	Y	Y	Y	Flupenthixol associated with significantly higher relapse rates.
Shaw et al. 1987[73]	20	24	Alcohol	Tiapride (100mg) vs. placebo	Y	Y	Y	Tiapride associated with significantly lower drinking and relapse in alcoholics with symptoms of depression and anxiety.
Shaw et al. 1994[74]	54	24	Alcohol	Tiapride (100mg) vs. placebo	Y	Y	Y	Tiapride associated with significantly lower drinking and relapse.
Gual et al. 2002[75]	81	24	Alcohol	Tiapride (100mg) vs. placebo	Y	Y	Y	Tiapride associated with significantly higher relapse rates.
Bender et al. 2006[76]	299	24	Alcohol	Tiapride (100mg) vs. placebo	Y	Y	Y	Tiapride associated with significantly higher relapse rates.
Marra et al. 2002[70]	71	24	Alcohol	Amisulpride (50mg) vs. placebo	Y	Y	Y	Amisulpride associated with significantly higher relapse rates and craving.
Guardia et al.	60	12	Alcohol	Olanzapine (8mg) vs.	Y	Y	Y	No differences in drinking variables between groups.

2004[67]				placebo				
Hutchinson et al. 2006[65]	64	12	Alcohol	Olanzapine (5mg) vs. placebo	Y	Y	Y	Olanzapine associated with significantly less drinking and cue-elicited craving and in individuals with the DRD4 L genotype, but not in those with D4D4 S.
Kampman et al. 2007[66]	61	12	Alcohol	Quetiapine (400mg) vs. placebo	Y	Y	Y	Quetiapine associated with significantly less drinking and craving in Type B but not in Type A alcoholics.
Anton et al. 2008[68]	295	12	Alcohol	Aripiprazole (23mg) vs. placebo	Y	Y	Y	Aripiprazole associated with a significantly lower amount of heavy alcohol consumption and alcohol dependence severity.
Martionotti et al. 2009[69]	57	16	Alcohol	Aripiprazole (8mg) vs. naltrexone (50mg)	Y	Y	N	Aripiprazole associated with a significantly longer abstinence time; naltrexone associated with greater reductions in craving.
Kampman et al. 2003[84]	30	12	Stimulants	Olanzapine (10mg) vs. placebo	Y	Y	Y	Olanzapine associated with significantly more cocaine use and relapse.
Reid et al. 2005[83]	63	8	Stimulants	Olanzapine (10mg) vs. placebo	Y	Y	Y	No differences in cocaine use and craving between groups.

Hamilton et al. 2009[81]	48	16	Stimulants	Olanzapine (7mg) vs. placebo	Y	Y	Y	No differences in cocaine use and craving between groups.
Levin et al. 1999[79]	14	24	Stimulants	Risperidone (2mg) vs. placebo	Y	Y	Y	No differences in cocaine use and craving between groups.
Grabowski et al. 2000[85]	125	12	Stimulants	Risperidone (2mg vs. 4mg vs. 8mg) vs. placebo	Y	Y	Y	High dose of risperidone associated with more cocaine use and a 100% dropout rate; no differences between the moderate and low doses of risperidone and placebo.
Grabowski et al. 2004[82]	96	26	Stimulants	Risperidone (2mg vs. 4mg) vs. placebo	Y	Y	Y	No significant effect of risperidone, at any dose, on cocaine use.
Loebl et al. 2008[80]	31	12	Stimulants	Long-acting risperidone (25mg/14d) vs. placebo	Y	Y	Y	No significant effect of risperidone on cocaine use and craving. Significantly greater depression in the risperidone group.
Tiihonen et al. 2007[86]	36	20	Stimulants	Aripiprazole (15mg) vs. placebo	Y	Y	Y	Aripiprazole associated with significantly more intravenous amphetamine use than placebo.
Gawin et al.	54	6	Stimulants	Flupenthixol decanoate	Y	Y	Y	Flupenthixol associated with a reduction in crack

1996[78]				(10-20mg/14d) vs. placebo				cocaine use over placebo.

Table legend: *N* = sample size (intent-to-treat population), wks = weeks, stimulants = amphetamine and/or cocaine, dose = mean or fixed exit dose, R = randomized, D = double-blind, P = placebo-controlled.

7 Dose-response and comparative efficacy and tolerability of quetiapine across psychiatric disorders: a systematic review of the placebo-controlled monotherapy and add-on trials.

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Dose-response and comparative efficacy and tolerability of quetiapine across psychiatric disorders: a systematic review of the placebo-controlled monotherapy and add-on trials

Simon Zhornitsky[1]; Stéphane Potvin[1]; Hoda Moteshafi[1]; Simon Dubreucq[1]; Pierre-Paul Rompré[1]; Emmanuel Stip[1].

[1]Fernand-Seguin Research Centre, Department of Psychiatry, Faculty of Medicine, University of Montreal; Montreal, Canada

Corresponding author

Emmanuel Stip
Centre de recherche Fernand-Seguin
7331 Hochelaga
Montreal, Quebec, Canada
H1N 3V2
Tel: (514) 251-4015
Fax: (514) 251-2617

7.1 Abstract

The atypical antipsychotic, quetiapine, is frequently prescribed on-and off-label for the treatment of a variety of psychiatric disorders. Since quetiapine has variable affinity for dozens of receptors, its clinical effects should also show large variation as a function of dose and diagnostic category. The present review will attempt to elucidate the dose-response and comparative efficacy and tolerability (metabolic data) of quetiapine across psychiatric disorders. A systematic search was performed in the electronic databases PubMed and EMBASE using the key words "quetiapine" AND "placebo". Both monotherapy and add-on studies were included. A total of forty-one studies were identified. In unipolar and bipolar depression, studies found quetiapine to be consistently effective versus placebo, at doses of around 150¬300mg/d and 300-600mg/d, respectively. In bipolar mania, they found quetiapine to be consistently effective at doses of around 600mg/d. In acute exacerbation of schizophrenia, the majority of studies found quetiapine to be consistently effective at doses of around 600mg/d, however, a few large studies found no difference versus placebo. By contrast, quetiapine was found to be more consistently effective for stable schizophrenia. In obsessive-compulsive disorder (OCD), studies found quetiapine to be inconsistently effective doses of around 300mg/d. However, studies may have underestimated quetiapine`s efficacy for OCD due to concomitant administration of antidepressants and the utilization of treatment-refractory patients. In generalized-anxiety disorder, studies suggest that quetiapine is consistently effective at doses of around 150mg/d. Finally, analysis of metabolic tolerability data suggests that even low doses of quetiapine may lead to increases in weight gain and triglycerides across psychiatric disorders. Interestingly, however, quetiapine-induced elevations in LDL and total cholesterol seem to be restricted to schizophrenia patients.

Key words: quetiapine, schizophrenia, bipolar disorder, dose-response, depression, anxiety, cholesterol

7.2 Introduction

In recent years, atypical antipsychotics have been increasingly tried for the treatment of numerous psychiatric conditions such as schizophrenia, bipolar disorder, major depressive disorder and anxiety disorders. Among atypical antipsychotics, quetiapine is perhaps the most frequently used in the treatment of psychiatric disorders other than schizophrenia. Indeed, placebo-controlled studies have shown that quetiapine may be an effective monotherapy in bipolar mania and depression (Bowden et al. 2005; Calabrese et al. 2005), major depressive disorder (MDD; Weisler et al. 2009; Bortnick et al. 2010) and generalized anxiety disorder (GAD; Bandelow et al. 2010; Katzman et al. 2010). In addition, quetiapine was shown to be superior to placebo as augmentation therapy for obsessive-compulsive disorder (OCD; Vulink et al. 2009; Denys et al. 2004). Finally, uncontrolled studies have found quetiapine to be effective for borderline personality disorder (Adityanjee et al. 2008; Perrella et al. 2007).

With such a range of potential uses, quetiapine may very well be the "aspirin of psychiatry" (Stip, 2009). However, the mechanisms of action of quetiapine in the treatment of most of the aforementioned psychiatric disorders remain unclear. Quetiapine has affinity for dozens of receptors including histaminergic, noradrenergic, dopaminergic, serotonergic and cholinergic receptors (Bymaster et al. 1996; Schotte et al. 1996) – a characteristic that may be beneficial due to the high rate of comorbidity in psychiatry (Regier et al. 1990; Andrews et al. 2002). Since the affinity of quetiapine varies greatly from receptor to receptor, its clinical effects should also show large variation as a function of dose. Consequently, understanding the dose-response and comparative efficacy and tolerability of this medication across diagnostic categories is essential for optimally treating each disorder.

Interestingly, some recent reviews have questioned whether there are real therapeutic differences between high and low doses of quetiapine for schizophrenia (Sparshatt et al. 2008; Painuly, 2010). In addition, reviews on quetiapine`s dose-response have tended to focus on

the treatment of single psychiatric disorders; thus, not being able to compare its efficacy across diagnostic categories (Keating et al. 2007; McIntyre et al. 2009). The present review will examine placebo-controlled trials of quetiapine in order to elucidate the dose-response and comparative efficacy of this medication across psychiatric disorders. Dose- and diagnosis-related metabolic tolerability data will also be analyzed.

7.3 Methods

A systematic search was performed in the electronic databases PubMed and EMBASE using the key words "quetiapine" AND "placebo". Both monotherapy and add-on studies were included. This search looked for studies published between January 1, 1990 and October 1, 2010. Additionally, studies were identified by cross-referencing of review articles. Published abstracts were not included in the analysis. Moreover, both monotherapy and add-on studies were included due to the lack of monotherapy studies for some psychiatric disorders.

To be included in the review, studies must have contained a placebo-control group and addressed the treatment of adult psychiatric disorders with quetiapine. Fixed-and flexible-dose studies with a duration of three weeks or longer were included. Studies of quetiapine for psychosis/delirium/agitation in geriatric patients were excluded due to the inability of investigators to use higher than minimal doses when searching for efficacy. Similarly, the number of placebo-controlled studies of quetiapine for bipolar-spectrum disorder, social anxiety disorder and substance use disorders was too low to establish a dose-response, and consequently, they were also excluded from the present review.

Tolerability dose-responses were calculated by pooling fixed-dose studies of quetiapine monotherapy into three dose ranges (50-150mg, 300-400mg, 600-800mg). For each dose range, a weighted average of each tolerability mean value (e.g. weight gain, LDL cholesterol) was calculated for all relevant studies and adjusted for sample size. Tolerability

outcomes were separately calculated for schizophrenia and non-schizophrenia patients, since the former group may have poorer overall health (Druss and Rosenheck, 1997; Cradock-O'Leary et al., 2002). Immediate-and extended-release formulations (IR and XR) were pooled for the same dose. Maintenance trials were excluded from tolerability analyses to minimize variation in study length. Non-metabolic data were not analyzed because these results have recently been published by another group (Wang et al. 2010). Quetiapine was judged to be consistently effective when an overwhelming number of studies with large sample sizes attested to its efficacy, relative to placebo. Quetiapine was judged to be inconsistently effective when some large trials attested to its efficacy, but other important trials found no difference compared to placebo. Considering the heterogeneity of conditions (e.g. acute exacerbation vs. stable schizophrenia, refractory vs. non-refractory, augmentation vs. monotherapy), studies included in this review were not amenable to quantitative meta-analytic treatment.

7.4 Results

Description of studies

Forty-one studies were identified. Nine trials examined the treatment of unipolar depression with quetiapine (Table 1). Five trials examined the treatment of bipolar depression with quetiapine (Table 2). Three trials examined the treatment of GAD with quetiapine (Table 3). Eight trials examined the treatment of bipolar mania with quetiapine (Table 4). Ten trials examined the treatment of schizophrenia with quetiapine (Table 5). Finally, six trials examined quetiapine treatment of OCD (Table 6).

Quetiapine for unipolar depression

Four studies investigated quetiapine augmentation of unipolar depression. One eight-week trial of quetiapine IR (mean dose = 182mg/d) augmentation of SRIs for treatment-refractory major depressive disorder (MDD), with comorbid anxiety, found significantly greater reductions in Hamilton Depression Scale (HAM-D) and Hamilton Anxiety Scale (HAM-A) total scores in the quetiapine group, compared to the placebo group (McIntyre et al. 2007). Another 8-week study of quetiapine IR (mean dose = 47mg/d) of fluoxetine for MDD found that quetiapine was not superior at improving Montgomery-Åsberg Depression Rating Scale (MADRS) response and remission (however, it did improve sleep and anxiety subset over placebo; Garakani et al. 2008). Furthermore, a 10-week trial of quetiapine IR (mean dose = 148mg/d) augmentation of cognitive-behavioural therapy in treatment-refractory MDD found that quetiapine was superior to placebo at decreasing MADRS and HAM-D total scores at endpoint (Chaput et al. 2008). Additionally, a six-week study compared two doses of quetiapine XR (150 or 300mg/d) as adjuncts to SRIs. The authors found that 300mg was superior to placebo at decreasing MADRS total scores all time points, whereas 150mg was superior to placebo only in the first two weeks of the study. Finally, a six-week trial of quetiapine XR (150mg or 300mg/d) as augmentation to SRIs for MDD found both dose groups to improve in MADRS total scores at endpoint, relative to placebo (Bauer et al. 2009).

Five studies investigated quetiapine as monotherapy for MDD. An eight-week study found that quetiapine XR (mean dose = 162mg/d) significantly decreased MADRS and HAM-D total score versus placebo (Bortnick et al. 2010). Moreover, a six-week trial that compared monotherapy of MDD with three doses of quetiapine XR (50 or 150 or 300mg/d) demonstrated that all doses significantly decreased MADRS total scores at endpoint, relative to placebo (Weisler et al. 2009). However, only the 150mg and 300mg doses significantly decreased HAM-D total scores at endpoint. In addition, a six-week trial that compared quetiapine XR (150mg or 300mg/d) with duloxetine found that all active treatments reduced

MADRS total scores versus placebo (Cutler et al. 2009). However, differences between quetiapine and placebo were evident as early as week one, whereas the same could be said for duloxetine at week two. Additionally, the 300mg dose was superior to the 150mg dose in the proportion of MADRS remitters at week six and on some secondary efficacy measures (Cutler et al. 2009). Finally, a recent trial investigated quetiapine XR (mean dose = 177mg/d) as 52-week maintenance treatment in MDD patients (Liebowitz et al. 2010). The authors found that quetiapine significantly reduced the risk of recurrent depressive events and MADRS total scores at endpoint, compared to placebo.

Quetiapine for bipolar depression

Five large studies examined quetiapine as monotherapy for bipolar depression. One eight-week study found that quetiapine XR (300mg/d) was significantly better than placebo at decreasing MADRS total scores at endpoint (Suppes et al. 2010). In addition, two complementary eight-week trials (BOLDER I + II) found that quetiapine IR (300 or 600mg/d) was superior to placebo at decreasing MADRS total scores at endpoint. However, there were no significant differences between the two doses of quetiapine in either study (Calabrese et al. 2005; Thase et al. 2006). More recently, two complementary eight-week studies (EMBOLDEN I + II) found that quetiapine IR (300 or 600mg/d) was superior to lithium and paroxetine and placebo at reducing MADRS total scores at endpoint (Young et al. 2010; McElroy et al. 2010).

Quetiapine for bipolar mania

Five studies examined quetiapine augmentation of lithium or divalproex (Li/DVP) for bipolar mania. One three-week study found that augmentation of Li/DVP with quetiapine IR (mean dose = 504mg/d) resulted in greater decrease in Young Mania Rating Scale (YMRS) total

scores than with placebo (Sachs et al. 2004). In addition, a six-week trial found that quetiapine augmentation (mean dose = 492) of Li/DVP was associated with significant reduction in YMRS total scores compared to placebo (Yatham et al. 2004). Another six-week study by the same team found that augmentation of Li/DVP with quetiapine IR (mean dose = 455mg/d) resulted in significantly greater YMRS response rate but not change in YMRS total scores at endpoint (Yatham et al. 2007). Lastly, two large complementary studies examined the augmentation of Li/DVP with quetiapine IR (mean dose = 446mg and 519mg/d, respectively) for maintenance of bipolar I disorder (Vieta et al. 2008; Suppes et al. 2009). These trials demonstrated that the proportion of patients having a mood event (mania or depression) was significantly lower in the quetiapine than in the placebo group.

Three studies examined the monotherapy of bipolar mania with quetiapine. A 12-week study found that quetiapine IR (mean dose in responders = 618mg/d) and lithium equally reduced YMRS total scores at endpoint, relative to placebo (Bowden et al. 2005). Another 12-week study found that quetiapine IR (mean dose in responders = 559mg/d) and haloperidol decreased YMRS total scores at endpoint, relative to placebo. However, unlike quetiapine, haloperidol was more effective than placebo early in the study (McIntyre et al. 2007). In addition, a three-week trial found that quetiapine IR (median mode dose = 600mg/d) and paliperidone were equally superior to placebo at reducing YMRS total scores at endpoint (Vieta et al. 2010).

Quetiapine for schizophrenia

Four out of eight studies of quetiapine versus placebo for acute exacerbation of schizophrenia employed a fixed-dose design (Fabre et al. 1995; Arvanitis et al. 1997, Kahn et al. 2007; Lindenmayer et al. 2008). One small three-week trial of quetiapine IR (250mg/d) for schizophrenia found the medication to significantly decrease Brief Psychiatric Rating Scale

(BPRS) total scores relative to placebo (Fabre et al. 1995). Another study by the same team compared five doses of quetiapine IR (75, 150, 300, 600, or 750mg/d) with haloperidol (12mg/d) over six weeks for acute exacerbation of schizophrenia (Arvanitis et al. 1997). The authors found that 150, 300, and 600mg doses of quetiapine and haloperidol produced similarly significant reductions in BPRS total scores compared to placebo (however, the 750mg dose fared slightly worse). A larger six-week study compared quetiapine IR 400mg/d with quetiapine XR 400, 600 or 800mg/d and placebo for acute schizophrenia (Kahn et al. 2007). Results showed that all treatment groups evidenced significant reductions in Positive and Negative Syndrome Scale (PANSS) total scores compared to placebo. However, the largest differences versus placebo were found for the 600mg and 800mg groups, with no differences between them. Another six-week study compared quetiapine IR (300 or 600mg/d) with quetiapine XR (300, 600 or 800mg/d) for acute schizophrenia. The authors found that only those patients randomized to quetiapine XR 600mg evidenced a significant reduction in PANSS total scores, relative to placebo (Lindenmayer et al. 2008).

The remaining four studies investigated quetiapine for acute schizophrenia using a flexible-dose design (Borison et al. 1996; Small et al. 1997; Potkin et al. 2006; Canuso et al. 2009). One six-week study that examined quetiapine IR (mean dose = 307mg/d) for acute schizophrenia found a non-significant trend for reductions in BPRS total scores, relative to placebo (Borison et al. 1996). Another study by the same team, which compared patients treated with low (mean = 209mg/d) or moderate doses (mean = 360mg/d) of quetiapine IR for acute schizophrenia, found that only those patients randomized to the latter dosage evidenced significant reductions in BPRS total scores, compared to placebo (Small et al. 1997). A more recent study compared quetiapine IR (mean dose = 556mg/d) with risperidone (mean dose = 4.4mg/d) for acute exacerbation of schizophrenia (Potkin et al. 2006). The study included a two-week monotherapy phase followed by a four-week additive therapy phase. At the end of

the monotherapy phase, risperidone, but not quetiapine, was superior to placebo in decreasing PANSS total scores. Additionally, at the end of the additive therapy phase, a significantly lower percentage of risperidone-treated patients required the prescribing of additional antipsychotics (33%), compared to patients treated with quetiapine (53%) and placebo (59%). A similar trial that compared quetiapine IR (mean dose = 599mg/d) with paliperidone XR (mean dose = 9.8mg/d) for acute schizophrenia found that paliperidone, but not quetiapine, was superior to placebo at decreasing PANSS total scores at the end of the monotherapy phase (Canuso et al. 2009). At the end of the additive therapy phase, 42% of paliperidone, 51% of quetiapine and 62% of placebo-treated patients required additional antipsychotic treatment; a difference that emerged significant only for paliperidone relative to placebo.

Two studies examined quetiapine as treatment for clinically stable schizophrenia (Peuskens et al. 2007; Chen et al. 2010). In the first study, patients who were clinically stable on quetiapine XR for four months were randomized to receive quetiapine XR (mean dose = 669mg/d) or placebo for an additional 10 months. The authors found that quetiapine was associated with significantly longer time to relapse and lower relapse rates, relative to placebo (Peuskens et al. 2007). These findings were replicated by a more recent trial that switched positive symptom-free first-episode patients from their baseline antipsychotic to treatment with quetiapine IR (400mg/d) or placebo. The authors found that quetiapine was associated with a significantly lower rate of relapse after one year of treatment (Chen et al. 2010).

Quetiapine for OCD

All of the studies of quetiapine for OCD administered the medication as add-on therapy. Moreover, five out of six of these studies included patients who did not respond to previous treatment with SRIs. One group administered a fixed-dose of quetiapine IR (300mg/d) in an eight-week add-on therapy to SRIs (Denys et al. 2004). Their results showed a significantly

greater decrease in Yale-Brown Obsessive Compulsive Scale (YBOCS) total scores in the quetiapine group, relative to the placebo group. Similarly, a smaller, eight-week, single-blind trial of quetiapine IR (mean dose = 91mg/d) add-on to SRIs for refractory OCD found a significantly greater decrease in YBOCS total scores in the quetiapine group (Atmaca et al. 2002). On the other hand, a six-week trial failed to demonstrate an advantage for quetiapine IR (mean dose = 169mg/d) in decreasing YBOCS total scores, when administered as add-on to SRIs for refractory OCD (Carey et al. 2005). Another 16-week, add-on trial to selective serotonin reuptake inhibitors (SSRIs), did not show any benefits of quetiapine IR (mean dose = 215mg) versus placebo in the treatment of refractory OCD (Fineberg et al. 2005). Likewise, a 12-week trial of high-dose quetiapine (dose range = 400-600mg/d) as augmentation of SRIs did not find a significant difference between the treatment and placebo groups for refractory OCD (Kordon et al. 2008).

One study of quetiapine for OCD utilized non-treatment refractory patients. This 10-week trial found that quetiapine (dose range = 300-450mg/d) augmentation of citalopram was superior to placebo in decreasing YBOCS total scores at endpoint (Vulink et al. 2009).

Quetiapine for GAD

Two studies of quetiapine for GAD administered the medication as monotherapy. One of these was an eight-week study that investigated two fixed-doses of quetiapine XR (50mg or 150mg/d) versus paroxetine (20mg/d) (Bandelow et al. 2010). All active-treatments produced significant reductions in Hamilton Rating Scale for Anxiety (HAM-A) total scores at endpoint; however, the 150mg dose was associated with the largest and fastest improvement relative to placebo. Another study that evaluated quetiapine XR (mean dose = 163mg/d) as 52-week maintenance treatment for GAD demonstrated that quetiapine-treated patients had significantly reduced risk of anxiety symptom recurrence and a lower HAM-A total score

prior to the last anxiety event, relative to placebo (Katzman et al. 2010). On the other hand, a small study which administered quetiapine (mean dose = 121mg/d) as eight-week add-on therapy to paroxetine for treatment-refractory GAD found no difference between quetiapine and placebo in reduction of HAM-A scores at endpoint (Simon et al. 2008).

Tolerability

The mean duration of fixed-dose studies that were used to calculate the effect of dose and psychiatric diagnosis on metabolic tolerability outcomes was 7.3 (1.3) weeks. The pooled mean change (schizophrenia versus other diagnoses) in weight, triglycerides, LDL and total cholesterol for the fixed-dose studies is shown in Figures 1a-d. In general, a dose-dependent elevation was observed for weight and triglycerides in both schizophrenia and non-schizophrenia patients. By contrast, elevations of LDL and total cholesterol were observed uniquely for schizophrenia patients.

7.5 Discussion

The present review was aimed to elucidate the dose-response and comparative efficacy and tolerability of quetiapine across psychiatric disorders. In unipolar and bipolar depression, studies consistently found quetiapine to effective versus placebo, at doses of around 150-300mg/d and 300-600mg/d, respectively. In bipolar mania, they consistently found quetiapine to be effective at doses of around 600mg/d. In acute exacerbation of schizophrenia, the majority of studies consistently found quetiapine to be effective at doses of around 600mg/d, however, a few large studies found no differences versus placebo. By contrast, they consistently found quetiapine to be effective for stable schizophrenia. In OCD, studies did not consistently quetiapine to be effective doses of around 300mg/d. However, studies may have underestimated quetiapine`s efficacy for OCD due to concomitant administration of

antidepressants and the utilization of treatment-refractory patients. In GAD, studies consistently found quetiapine to be effective at doses of around 150mg/d, and while the number of studies is low, these results have been supported by as of yet unpublished studies (Atkinson et al 2008; Merideth et al 2008; Mezhebovsky et al. 2009). Finally, analysis of metabolic tolerability data suggests that even low doses of quetiapine may lead to increases in weight gain and triglycerides across psychiatric disorders. Interestingly, however, quetiapine-induced elevations in LDL and total cholesterol seem to be restricted to schizophrenia patients.

The efficacy of quetiapine in the treatment of depression has been a mystery for some time. Classically, drugs which have antidepressant properties are inhibitors of serotonergic (SERT) and/or noradrenergic (NET) transporters. Quetiapine has no affinity for SERT or NET but its principle active metabolite, N-desalkylquetiapine (norquetiapine), is a potent antagonist of NET (Jensen et al. 2008). In fact, the amount of NET occupancy in patients that are treated with quetiapine (150 or 300mg/d) is similar to that measured in patients that are treated with the TCA nortriptyline (Nyberg et al. 2007, 2008; Sekine et al. 2010). Whether or not NET inhibition can fully explain quetiapine`s antidepressant efficacy is unclear since norquetiapine also has high affinity for a number of serotonergic receptor subtypes such as 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C} and $5HT_7$ – all of which may have value as potential targets for new antidepressant drugs (Adell et al. 2005; Mnie-Filali et al. 2007). The fact that quetiapine significantly decreased MADRS scores a full one to two weeks before the dual SERT and NET inhibitor, duloxetine, may point to the presence of other antidepressant mechanisms (Cutler et al. 2009). Alternatively, in the Cutler et al. (2009) study, the main advantage of quetiapine over duloxetine and placebo was via an improvement in sleep, suggesting that histaminergic and/or adrenergic antagonism may be sufficient for observation of an early-onset anti-depressant effect.

Quetiapine`s efficacy for GAD at low doses is unsurprising since it is a potent antagonist of α-1 receptors, which regulate the response of the sympathetic nervous system and are a target of many TCAs (Stahl, 2008). In addition, norquetiapine is a potent partial agonist of $5HT_{1A}$ receptors, which are also activated by azapirones – a class of drugs with established efficacy for GAD (Chessick et al. 2006; Jensen et al. 2008). It is perhaps because of these mechanisms, in addition to NET antagonism, that quetiapine XR (150mg) was shown to significantly decrease HAM-A total scores a full one to two weeks before the SSRI, paroxetine (Bandelow et al. 2010). While quetiapine seems to have promise as a treatment for GAD, the overlap in receptor activity between quetiapine and many antidepressants may account for why studies of quetiapine augmentation of antidepressants for OCD have been mixed (Atmaca et al. 2002; Denys et al, 2004; Carey et al. 2005; Vulink et al, 2009). Likewise, the utilization of treatment-resistant patients may preclude the observation of a positive effect, due to the fact that these patients have already undergone numerous trials with other antidepressant drugs.

One possibility for why a few large studies did not find quetiapine to be superior to placebo for acute schizophrenia may be that studies used conventional titration (5-8 days), thereby underestimating quetiapine`s efficacy, especially in the first weeks of administration. However, although a preliminary study found rapid titration (3-4 days) to be superior in reducing PANSS total scores in schizophrenia patients (Pae et al. 2005), these findings were not replicated by a more recent and larger trial (Boidi and Ferro, 2007). Instead, it is more likely that quetiapine is a less effective antipsychotic overall, due to its low affinity and loose binding to dopamine D2 receptors (Kapur and Seeman, 2001), which may result in inadequate blockade of endogenous dopamine hyperactivity, which is believed to play an important role in the pathophysiology of positive symptoms in schizophrenia and mania in bipolar disorder (Cousins et al. 2009; Howes and Kapur, 2009). In the case of bipolar mania, quetiapine`s

loose binding to D_2 receptors may be sufficient to achieve consistent efficacy versus placebo, since even bipolar mania with psychotic features is associated with a lower mean severity of hallucinations and delusions compared to schizophrenia (Baethge et al. 2005). Like bipolar mania, stable schizophrenia should respond better to quetiapine treatment, compared acute schizophrenia, because it presumably requires less dopaminergic inhibition to attenuate positive symptoms. Indeed, two trials of stable schizophrenia did attest to the superiority of quetiapine in decreasing relapse rates, relative to placebo (Peuskens et al. 2007; Chen et al. 2010). Taken together, this evidence suggests that quetiapine may be more effective for stable, as opposed to acute schizophrenia.

A recent study by our group supports the interpretation that quetiapine may produce inadequate D2 blockade for the treatment of severe psychoses, even at high doses (Gallo et al. 2010). In that study, rats received three doses of quetiapine (i.p; 5mg, 10mg and 20mg/kg) before being tested in the intracranial self-stimulation paradigm – a powerful and validated model of mesolimbic dopaminergic activity (Wise and Rompre, 1989). Surprisingly, all doses of quetiapine produced an equally weak attenuation of reward (~20%; Gallo et al. 2010). On the other hand, there is evidence that mesolimbic reward attenuation by clozapine and haloperidol is dose-dependent and can reach ~45% and ~65%, respectively (Benaliouad et al. 2007). Supporting the finding that above-maximal doses of quetiapine are not more beneficial, a randomized, double-blind, eight-week trial by our group found no difference in reduction of PANSS total scores between patients treated with 800mg and 1200mg/d (Honer et al. in press) Taken together, our analyses suggest that quetiapine`s antipsychotic efficacy may be somewhat of an `all-or-nothing` response and is inconsistently efficacious for acute schizophrenia.

Analysis of tolerability outcomes suggests that quetiapine may produce elevations in body weight and triglycerides, even at minimal doses. Elevations in LDL and total cholesterol

were also observed but only in schizophrenia patients. These data are limited by the low number of studies using 50-150mg for schizophrenia, thereby preventing any meaningful direct comparisons at those doses. Nevertheless, the findings confirm the potential for weight gain and metabolic side-effects with quetiapine treatment (Simon et al. 2009). They also suggest a possible interaction between schizophrenia genes and quetiapine in increasing metabolic risk (Boston et al. 1996; Stahl et al. 2009). Intriguingly, a recent study found that antipsychotic-naive schizophrenia patients did not exhibit increased LDL and total cholesterol, relative to controls (Kirkpatrick et al. 2010). Unfortunately, however, it is yet unclear which mechanisms/genes may be responsible for the quetiapine-induced elevations in cholesterol in schizophrenia patients.

The present review is limited due to the inclusion of studies that administered quetiapine as augmentation therapy, rather than monotherapy. Quetiapine augmentation of antidepressants, for example, may limit interpretation of results since their mechanisms may overlap. Interpretation of studies that utilized patients who were resistant to treatment with antidepressants is problematic for the same reason. Similarly, in the treatment of bipolar mania, the majority of studies administered quetiapine as augmentation to mood stabilizers, which may have overestimated the efficacy of the medication as monotherapy for bipolar mania (especially in the case of bipolar mania with psychotic features). However, we chose to include augmentation studies because of the low number of monotherapy trials with quetiapine for certain psychiatric conditions. Additionally, monotherapy and add-on studies generally came to the same conclusions.

Overall, our review highlights the need for more monotherapy trials to be conducted in order to better elucidate the efficacy of quetiapine, especially in the case of severe psychoses and anxiety disorders. Moreover, the efficacy of quetiapine for both mania and depression

makes it an interesting treatment option for mood swings and behavioral instability in borderline personality disorder. Randomized controlled trials are warranted in the future.

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Table 1: Quetiapine for unipolar depression

Study	Diagnosis	*N* (*)	Weeks	Dose (mg/day)	Primary outcome(s)
Bauer et al. 2009	MDD (non-refractory)	487 (162)	6 wks	QTP XR (150, 300) + SRIs	QTP 300 & 150 > PBO
Bortnick et al. 2010	MDD (non-refractory)	299 (150)	8 wks	QTP XR (162#)	QTP > PBO
Cutler et al. 2009	MDD (non-refractory)	587 (147)	6 wks	QTP XR (150, 300) vs. DLX	QTP 300 > 150 > DLX > PBO
Garakani et al. 2008	MDD (non-refractory)	114 (57)	8 wks	QTP IR (47#) + FLX	No difference
Weisler et al. 2009	MDD (non-refractory)	700 (175)	6 wks	QTP XR (50, 150 ,300)	QTP 300 & 150 > 50 > PBO
Liebowitz et al. 2010	MDD (non-refractory, maintenance)	776 (388)	52 wks	QTP XR (177#)	QTP > PBO
Chaput et al. 2008	MDD	22 (11)	16 wks	QTP IR (148#)	QTP > PBO

	(refractory)				
El-Khalili et al. 2010	MDD (refractory)	432 (144)	8 wks	QTP XR (150 vs. 300) + SRIs	QTP 300 > 150 > PBO
McIntyre et al. 2007	MDD (refractory)	58 (29)	8 wks	QTP IR (182[#]) + SRIs	QTP > PBO

FLX = fluoxetine; DLX = duloxetine; PBO = placebo; MDD = major depressive disorder; SRIs = serotonin-reuptake inhibitors; > = order of significance relative to placebo; IR = immediate-release; XR = extended-release; * = mean per condition.

Table 2: Quetiapine for bipolar depression

Study	Diagnosis	*N* (*)	Weeks	Dose (mg/day)	Primary outcome(s)
Young et al. 2010 (EMBOLDEN I)	Bipolar depression	783 (196)	8 wks	QTP IR (300, 600) vs. Li	QTP 600 & 300 > Li & PBO
McElroy et al. 2010 (EMBOLDEN II)	Bipolar depression	700 (175)	8 wks	QTP IR (300, 600) vs. PRX	QTP 600 & 300 > PRX & PBO
Calabrese et al. 2005 (BOLDER I)	Bipolar depression	511 (170)	8 wks	QTP IR (300, 600)	QTP 600 & 300 > PBO
Thase et al. 2006 (BOLDER II)	Bipolar depression	467 (156)	8 wks	QTP IR (300, 600)	QTP 600 & 300 > PBO
Suppes et al. 2010	Bipolar depression	270 (135)	8 wks	QTP XR (300)	QTP > PBO

Li = lithium; PBO = placebo; PRX = paroxetine; MDD = major depressive disorder; > = order of significance relative to placebo; IR = immediate-release; XR = extended-release; * = mean per condition.

Table 3: Quetiapine for generalized-anxiety disorder

Study	Diagnosis	*N* (*)	Weeks	Dose (mg/day)	Primary outcome(s)
Simon et al. 2008	GAD (refractory)	22 (11)	8 wks	QTP IR (121[#]) + PRX	No difference
Bandelow et al. 2010	GAD (non-refractory)	866 (217)	10 wks	QTP IR (50, 150) vs. PRX	QTP 150 > 50 > PRX > PBO
Katzman et al. 2010	GAD (maintenance)	432 (216)	52 wks	QTP XR (163[#])	QTP > PBO

= mean dose; PRX = paroxetine; PBO = placebo; GAD = generalized anxiety disorder; > = order of significance relative to placebo; IR = immediate-release; XR = extended-release; * = mean per condition.

Table 4: Quetiapine for bipolar mania

Study	Diagnosis	*N* (*)	Weeks	Dose (mg/day)	Primary outcome(s)
McIntyre et al. 2005	Bipolar I	299 (100)	12 wks	QTP IR (559[#]) vs. HAL	HAL > QTP > PBO
Vieta et al. 2010	Bipolar I	486 (192)	3 wks	QTP IR (600[^])	PAL + QTP > PBO
Bowden et al. 2005	Bipolar I	302 (101)	12 wks	QTP IR (618[#]) vs. Li	QTP & Li > PBO
Sachs et al. 2004	Bipolar I	170 (85)	3 wks	QTP IR (504[#]) + Li/DVP	QTP > PBO
Yatham et al. 2004	Bipolar I	370 (185)	6 wks	QTP IR (492[#]) + Li/DVP	QTP > PBO
Yatham et al. 2007	Bipolar I	200 (100)	6 wks	QTP IR (455[#]) + Li/DVP	No difference

Vieta et al. 2008 (Trial 126)	Bipolar I (maintenance)	703 (352)	104 wks	QTP IR (446[#]) + Li/DVP	QTP > PBO
Suppes et al. 2009 (Trial 127)	Bipolar I (maintenance)	623 (312)	104 wks	QTP IR (519[#]) + Li/DVP	QTP > PBO

= mean dose; ^ = median dose; BSD = bipolar spectrum disorder; Li/DVP = lithium or divalproex; HAL = haloperidol; PBO = placebo; QTP = quetiapine; > = order of significance relative to placebo; * = mean per condition.

Table 5: Quetiapine for acute and stable schizophrenia

Study	Diagnosis	*N* (*)	Weeks	Dose (mg/day)	Primary outcome(s)
Fabre et al. 1995	Schizophrenia (acute)	12 (6)	3 wks	QTP IR (250)	QTP > PBO
Arvanitis et al. 1997	Schizophrenia (acute)	356 (51)	6 wks	QTP IR (75, 150, 300, 600, 750) vs. HAL	QTP 150, 300, 600 & HAL > 750 > PBO
Small et al. 1997	Schizophrenia (acute)	286 (95)	6 wks	QTP IR (209, 360[#])	Hi QTP > Lo & PBO
Borison et al. 1996	Schizophrenia (acute)	109 (55)	6 wks	QTP IR (307[#])	QTP > PBO [(p=0.07)]
Canuso et al. 2009	Schizophrenia (acute)	394 (131)	6 wks	QTP IR (599[#]) vs. PAL	PAL > QTP & PBO
Potkin et al. 2006	Schizophrenia (acute)	382 (127)	6 wks	QTP IR (524[#]) vs. RIS	RIS > QTP & PBO
Lindenmayer et al. 2007	Schizophrenia (acute)	532 (84)	6 wks	QTP XR (300, 600, 800) vs. QTP IR (300, 600)	QTP XR 600 > XR 300, XR 800, IR 300, IR 600 & PBO

Kahn et al. 2007	Schizophrenia (acute)	573 (115)	6 wks	QTP XR (400, 600, 800) vs. QTP IR (400)	QTP XR 800 & 600 > XR 400 > IR 400 > PBO
Chen et al. 2010	Schizophrenia (stable)	178 (89)	52 wks	QTP IR (400)	QTP > PBO
Peuskens et al. 2007	Schizophrenia (stable)	173 (87)	40 wks	QTP XR (669#)	QTP > PBO

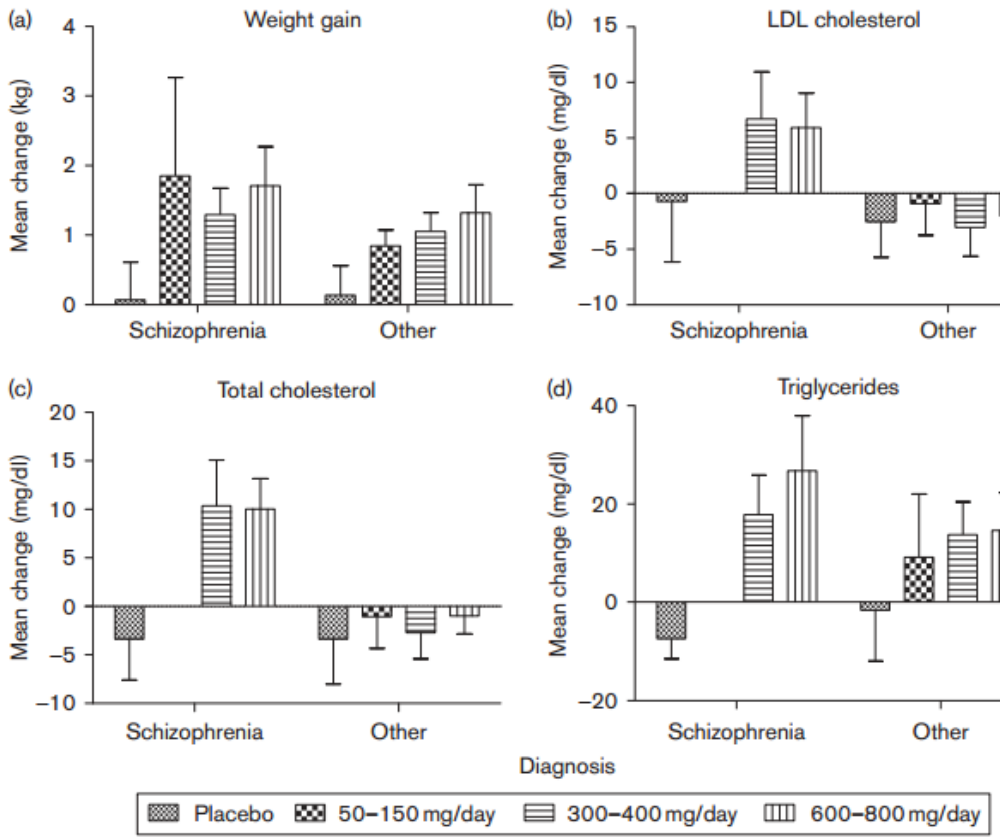
= mean dose; Hi = high dose; Lo = low dose; PBO = placebo; RIS = risperidone; PAL = paliperidone; XR = slow-release; IR = immediate-release; > = order of significance relative to placebo; IR = immediate-release; XR = extended-release; * = mean per condition.

Table 6: Quetiapine for obsessive-compulsive disorder

Study	Diagnosis	*N* (*)	Weeks	Dose (mg/day)	Primary outcome(s)
Vulink et al. 2009	OCD (non-refractory)	69 (35)	10 wks	QTP IR (300-450) + CTL	QTP > PBO
Kordon et al. 2008	OCD (refractory)	40 (20)	12 wks	QTP IR (400-600) + SRIs	No difference
Carey et al. 2005	OCD (refractory)	41 (21)	12 wks	QTP IR (169[#]) + SRIs	No difference
Denys et al. 2004	OCD (refractory)	37 (19)	8 wks	QTP IR (300) + SRIs	QTP > PBO
Atmaca et al. 2002	OCD (refractory)	27 (14)	8 wks	QTP IR (91[#]) + SRIs	QTP > PBO
Fineberg et al. 2005	OCD (refractory)	21 (11)	16 wks	QTP IR (215[#]) + SSRIs	No difference

= mean dose; PRX = paroxetine; PBO = placebo; SRIs = serotonin-reuptake inhibitors; CTL = citalopram; OCD = obsessive-compulsive disorder; > = order of significance relative to placebo; IR = immediate-release; * = mean per condition.

Fig. 1



(a–d) Mean change in metabolic outcomes after quetiapine treatment in schizophrenia and other psychiatric patients. Vertical lines denote standard deviation; (a) weight gain*:* schizophrenia: placebo (*N*=221); 50–150 mg (*N*=101); 300–400 mg (*N*=469); 600–800 mg (*N*=606); other*:* placebo (*N*=1279); 50–150 mg (*N*=947); 300–400 mg (*N*=1291); 600–800 mg (*N*=859); (b) low-density lipoprotein (LDL) cholesterol: schizophrenia: placebo (*N*=202); 50–150 mg=no data; 300–400 mg (*N*=417); 600–800 mg (*N*=501); other*:* placebo (*N*=924); 50–150 mg (*N*=947); 300–400 mg (*N*=931); 600–800 mg (*N*=511); (c) total cholesterol: schizophrenia: placebo (*N*=202); 50–150 mg=no data; 300–400 mg (*N*=417); 600–800 mg (*N*=501); other*:* placebo (*N*=931); 50–150 mg (*N*=947); 300–400 mg (*N*=937); 600–800 mg (*N*=511); (d) triglycerides: schizophrenia: placebo (*N*=202); 50–150 mg=no data; 300–400 mg (*N*=417); 600–800 mg (*N*=501); other: placebo (*N*=931); 50–150 mg (*N*=947); 300–400 mg (*N*=937); 600–800 mg (*N*=511).

8. General Discussion

Nearly half of all schizophrenia patients have had a substance use problem during their lifetime (Regier et al. 1990). Substance abuse/dependence in schizophrenia is associated with negative consequences for the patient and society as a whole. Studies have often found that DD patients exhibit more delusions, hallucinations and mood symptoms and they have higher rates of rehospitalisation, homelessness, medical problems and infectious diseases, violence, crime, and suicide (Negrete et al. 1986; Lysaker et al. 1994). Moreover, DD patients are significantly more likely to be noncompliant with antipsychotic treatment, leading to further deterioration in clinical and functional outcomes (Drake et al. 1989).

8.1 Extrapyramidal symptoms in substance abusers with and without schizophrenia and in non-abusing patients with schizophrenia (baseline analysis)

In order to understand what impact quetiapine may have on changes in psychiatric and extrapyramidal side-effects and substance abuse outcomes across the three groups, we must first examine their presence at baseline. In our baseline analyses of psychiatric symptoms, we found significantly elevated positive symptoms in DD patients, compared to SUD patients (Zhornitsky et al. 2010c). However, positive symptoms were still *clinically* elevated in our SUD group (mean = 15.4 on the PANSS). These results are in accordance with studies showing that substance abuse/dependence is associated with increased positive symptoms in schizophrenia patients and 'positive-like' (e.g. paranoia, excitement) symptoms in non-psychosis substance abusers (Serper et al. 1999; Mauri et al. 2007; Lapworth et al. 2009).

We also found elevated negative symptoms in DD and SCZ, compared to SUD patients. The results suggest that negative symptoms are relatively unique to schizophrenia, rather than arising due to substance abuse. Additionally, while we did not find a significant difference

between negative symptoms in DD and SCZ patients in the present study, a previous meta-analysis revealed that the former group may experience less negative symptoms (groups did not differ in age, sex, and positive/general psychopathology)(Potvin et al. 2006b). The differences in outcome between the two studies may reflect a type-II error due to the heterogeneous nature of substance(s) abused and low sample sizes involved.

Moreover, we found that depressive symptoms were nearly twice as high in DD patients and over one and a half times higher in SUD, relative in SCZ patients. This finding is in line with research showing that substance abuse is a risk factor for the development of depression (Lynskey et al. 2004; Falck et al. 2006). On the other hand, there is evidence that depressive symptoms may lead an individual to abuse substances in order to relieve the symptoms via negative reinforcement (Koob and Le Moal, 2008).

Our analyses of parkinsonism between the three groups revealed that SUD patients had (numerically) elevated scores at baseline (mean [SD] = 6.1 [6.2] on ESRS parkinsonism subscore), suggesting that substance abuse may produce parkinsonism independently of antipsychotics (at least transiently). Moreover, we found that DD patients evidenced increased parkinsonism scores at baseline, relative to SCZ patients (mean [SD] = 9.2 [13.5] vs. 3.2, respectively). In support, our previous meta-analysis (n=3479) showed that substance abuse is associated with augmented parkinsonism in DD patients, versus SCZ patients (Potvin et al. 2009). Further, we conducted a sub-analysis to see which substance(s) were responsible for this result. The sub-analysis showed that parkinsonism was significantly correlated with abuse of alcohol and psychostimulants, which is in accordance with previous studies showing that these substances elicit deleterious effects on the basal ganglia (discussed in the introduction). These data show that antipsychotics may interact with alcohol and psychostimulants to increase

parkinsonism in DD patients. We suspect that abuse of these substances also contributed to parkinsonism in SUD patients; however, we did not perform a sub-analysis in this group because they were not statistically different from DD or SCZ patients.

Unexpectedly, we found elevated akathisia at baseline in SUD patients, relative to the other two groups. This result is surprising because akathisia is a symptom that is classically associated with antipsychotic treatment. Importantly, our measure of akathisia included both subjective and objective components, which suggests the presence of 'true' akathisia (and not merely restlessness) in our SUD group. Moreover, a sub-analysis revealed that akathisia was related to alcohol and cannabis abuse which is consistent with reports of restlessness and physical tension/agitation during alcohol and cannabis withdrawal (West and Gossop, 1994; Kouri and Pope, 2000; Budney et al. 2003).

There were baseline differences in dyskinesia in our larger sample (SCZ > DD & SUD). They disappeared after entering hospitalizations into the ANCOVA. This may be explained by the fact that dyskinesia is a symptom that appears after prolonged antipsychotic treatment and our SCZ group was significantly older, relative to DD patients. Dystonia was not present in significant amounts in this study.

Altogether, the elevated positive and depressive symptoms and parkinsonism in DD patients is significant because DD patients were using significantly lower quantities of substances, compared to SUD patients (mean [SD] = 82.3 [62.3] vs. 795.6 [1748.6] dollars per week). Significantly, these findings support the notion that abuse of alcohol and drugs may induce clinically relevant aggravations in symptomatology in DD patients, even if they use small amounts, infrequently (Ziedonis et al. 2005). They also show that substances of abuse may

induce psychiatric and extrapyramidal symptoms in non-psychosis individuals, independently of schizophrenia diagnosis or antipsychotic treatment.

8.2. Evolution of substance use, neurological and psychiatric symptoms in schizophrenia and substance use disorder patients: a 12-week, pilot, case-control trial with quetiapine

We conducted our case-control trial for three main reasons. First, we asked whether differences in improvement would allow us to better understand the trajectory of symptoms in the 'real world setting'. Previous research among non-psychosis substance abusers revealed that they exhibited greater improvement in psychopathology following 2-week quetiapine treatment compared to non-abusing schizophrenia patients (Mauri et al. 2007). Second, we asked whether our analyses would allow us to divulge differences in the nature of the groups themselves. That is, are there differences that are innate to DD, SCZ and SUD patients, regardless of comorbid substance abuse/dependence (state vs. trait)? Previous research has shown that DD patients may have more depressive and less negative symptoms at baseline, compared to SCZ patients; however, follow-up studies of the groups undergoing a homogenous antipsychotic treatment are lacking (Conley et al. 1998; Potvin et al. 2007). Finally, we aimed to examine the impact of quetiapine on changes in substance abuse/dependence outcomes and psychiatric and extrapyramidal symptoms across the groups. This is an important question because (as discussed previously) quetiapine may have different levels of benefits for different groups of patients, depending on the level of comorbid psychiatric symptoms, as well as the dose prescribed. Our hypothesis was that quetiapine treatment would result in improvements in substance abuse and clinical variables (psychiatric and neurological symptoms) across the groups. We also expected

that improvements in substance abuse would be less pronounced in DD patients, relative to non-psychosis substance abusers.

In accordance with our hypothesis, we found that all three groups evidenced significant improvements in clinical and neurological variables with time, which is consistent with the existence of a placebo/practice effect in naturalistic studies of this kind (Goodwin, 2002). Likewise, we found that SUD patients had a higher mean SUD severity, spent significantly more dollars weekly on alcohol and drugs at baseline and showed greater improvement in these variables, compared to DD patients. At endpoint, there was no significant difference in dollars spent, but DD patients had a higher mean SUD severity. One explanation for the result that SUD patients improved more in substance abuse outcomes than DD patients may be that SUD patients had a significantly higher SUD severity at baseline, leading to the greater improvement. In support of this explanation, SUD severity was the only significant factor when entered in the ANCOVA model. The results could also be explained by the fact that our SUD group began the study in detoxification, whereas our DD group were active users, suggesting that it was easier for the former patients to quit alcohol and/or drugs. Alternatively, the results could suggest that it may be more difficult for schizophrenia patients to reduce or quit their substance use (Ziedonis et al. 2005). In addition, we found that DD patients had a higher mean SUD severity than SUD patients at endpoint, despite spending similar amounts on alcohol and drugs. These data are supported by evidence that substances of abuse can have deleterious consequences on schizophrenia patients, even when they use small amounts (Ziedonis et al. 2005) and evidence of increased D_2/D_3 occupancy in PET studies of schizophrenia patients in response to amphetamine challenge, relative to healthy controls (Laruelle, 2000). Together, these data support the dopaminergic supersensitivity model of schizophrenia.

We also found that SUD patients exhibited elevated PANSS positive symptoms at baseline and they improved more than the other two groups. This finding is consistent with results of Mauri et al. (2007). In that study, patients with schizophrenia, drug-induced psychosis, and borderline personality disorder were treated for two weeks with quetiapine. Their results revealed that positive symptoms in drug-induced psychosis individuals were similar to those seen in schizophrenia patients at baseline and they exhibited significantly more improvement by endpoint. However, in the present study, only two non-psychosis patients were diagnosed with substance-induced psychotic disorder (DSM-IV criteria). In order to receive this diagnosis, the DSM-IV requires the individual to present with persistent delusions or hallucinations and a lack of insight into the nature of these symptoms that cannot be accounted for by organic or functional psychosis. Consequently, we examined in more detail which PANSS positive items were most elevated at baseline in our SUD group and we found that the most elevated items (mean score ≈3) were hostility, excitement and paranoia/suspiciousness. The lack of substance-induced psychotic disorder diagnosis may be explained by the fact that insight was still present in most SUD subjects, even when experiencing symptoms such as paranoia as well as the lack of hallucinations and delusions (excluding paranoid delusions). Moreover, the finding that positive symptoms showed greater improvement in SUD patients, relative to DD and SCZ patients, is likely linked to their greater improvement in substance abuse outcomes. Taken together, our findings suggest that paranoia is not a symptom that reliably distinguishes between schizophrenia and SUD patients undergoing detoxification.

Analysis of PANSS negative symptoms revealed that they were significantly more elevated in DD and SCZ patients, relative to SUD individuals, and there was no significant difference in their improvement across the groups. Again, these results suggest that negative

symptoms are relatively unique to schizophrenia. However, non-psychosis individuals presenting with substance-induced psychosis may still exhibit significant levels of negative or 'negative-like' symptoms, which tend to return to baseline following cessation of substance use (Mauri et al. 2007).

CDSS scores were significantly elevated in DD and SUD patients at baseline, compared to SCZ patients; however, there was no difference in improvement between the groups. This latter finding is interesting because it suggests that some DD and SUD patients still had residual depressive symptoms, although they both significantly reduced their substance use over time. Furthermore, at study endpoint, CDSS scores (mean [SD] = 3.9 [3.6]) were persistently elevated in DD patients, despite being prescribed quetiapine – a clinically effective antidepressant. This finding may be explained by the fact that DD patients still had a significantly higher SUD severity at the end of the study. In addition, CDSS scores were (numerically) elevated in SUD patients versus SCZ patients (mean [SD] = 1.8 [3.1] vs. 1.2 [1.6], respectively). Taken together, these data suggest that depression is more strongly associated with substance abuse than schizophrenia – at least transiently – and should be considered a key target for the treatment of SUDs in psychosis and non-psychosis patients.

Parkinsonism was increased at baseline in DD, relative to SCZ patients and there was no significant difference in improvement between the groups. The lack of difference in improvement in parkinsonism may be attributed to the fact that all three groups were prescribed quetiapine. It may also be attributed to a type-II error because parkinsonism scores were lower in this SUD sample and variability was higher (mean [SD] = 5.7 [6.9]), relative to our larger baseline sample of SUD patients (described previously). Additionally, at endpoint, DD patients still had elevated parkinsonism, relative to the other two groups, although they were taking

similar amounts of substances, compared to SUD patients. As a whole, these data show that antipsychotics and substances of abuse may independently produce parkinsonism, but co-administration of the two may act in synergy to further elevate parkinsonism. Interestingly, a sub-analysis in DD patients revealed that improvements in parkinsonism were only significant in abusers of psychostimulants. This is unsurprising because cocaine abuse is associated with significant reduction in dopamine D_2 receptor availability in the striatum that may last for months after detoxification, similar to the striatal dopaminergic deficit observed in Parkinson's disease (Volkow et al. 2004). Moreover, this finding suggests that parkinsonism is more strongly associated with cocaine abuse than alcohol abuse, since our baseline sample found both to be associated with this symptom. Indeed, previous studies found high levels of Parkinsonian resting tremor in non-psychosis cocaine abusers, which contrasts with the (non-parkinsonian) active tremor found in alcoholics (Bauer et al. 1993, 1996).

Akathisia was significantly elevated in SUD patients and they improved significantly more, compared to the other two groups. Moreover, our sub-analysis showed that the improvement was correlated with the presence of cannabis use disorder, thus excluding the effects of alcohol, which were correlated with akathisia in our baseline sample. Consequently, we confirm the presence of ‘true’ akathisia during cannabis detoxification – a result that coincides with previous studies that evidenced objective restlessness as a consequence of cannabis withdrawal (Kouri and Pope, 2000; Budney et al. 2003). Although speculative, these results imply that the endogenous cannabinoid system is involved in the manifestation of akathisia, which may be associated with its role in motor behaviour (El Manira and Kyriakatos, 2010).

There were no significant differences at baseline or in terms of improvement in dyskinesia between the groups. Moreover, there were not a significant number of cases of dystonia observed in this study.

Overall, our results suggest that schizophrenia patients may be supersensitive to the effects of alcohol and drugs of abuse, as evidenced by the high SUD severity at endpoint in DD patients, despite spending similar amounts of money to obtain the substances. They also suggest that antipsychotics and substances of abuse interact in DD patients to increase parkinsonism, although they may both produce these symptoms independently of each other. In addition, they indicate that substance abuse/dependence is associated with increased depression in psychosis and non-psychosis substance abusers. Finally, our results suggest that substances of abuse may induce 'positive-like' symptoms and akathisia in non-psychosis SUD patients, independent of antipsychotic treatment or schizophrenia diagnosis. Unfortunately, we were not able to clarify the role of quetiapine in our results and quetiapine dose did not significantly affect any of our outcomes when entered as a covariate in the ANCOVA model.

8.3. Clinical evolution of substance use disorder patients during treatment with quetiapine: a 12-week, open-label, naturalistic trial

Before we can describe the impact of quetiapine on psychiatric and extrapyramidal symptoms in the three groups, we need to examine its impact on substance abuse as well as safety and tolerability outcomes. Analysis of safety/tolerability is crucial because these patients were undergoing detoxification and antipsychotic treatment may have potential health implications such as increased risk for seizures (Gillman and Lichtigfeld, 1990) and extrapyramidal reactions due to dopaminergic supersensitivity (Evans et al. 2001). In addition, we examined the effects of

quetiapine on substance use, and craving. Furthermore, although we did not include specific scales for the measurement of withdrawal symptoms, we recorded benzodiazepine use for each patient (prescribed for withdrawal).

Analysis of results of our SUD arm revealed that, during quetiapine therapy, substance use outcomes (quantities used and severity of SUDs and craving) significantly improved over time and this was corroborated by urine screenings. In addition, the present study was complementary to a study by Potvin et al. (2006b), which reports the results of our DD group. In that study, we found that the decreases in substance use were less prominent than reported here. This is important because it may explain why psychiatric and extrapyramidal symptom improvements differ between the DD and SUD groups. Furthermore, quetiapine was generally well tolerated and there were no new safety concerns that arose during either study and no interactions with substances of abuse were noted.

8.4. Sensation-seeking, social anhedonia and impulsivity in schizophrenia and substance use disorder patients

When investigating whether there are innate differences between substance abusers with and without schizophrenia, some authors have put forth the hypothesis that they may differ in terms of personality profile. Previous research has shown that DD patients may have more sensation-seeking and impulsivity (but not social anhedonia), compared to their non-abusing counterparts (Kwapil, 1998; Gut-Fayand et al. 2001; Dervaux et al. 2001). However, these studies suffered from two main limitations: they did not include a group of healthy controls and they did not include a group of non-psychosis SUD patients. The inclusion of these comparison groups may help us parcel the respective associations between schizophrenia, substance abuse and the

aforementioned personality traits. This field of inquiry is important because it may help tailor pharmacological and psychosocial intervention in these populations. For instance, there is evidence that quetiapine may be beneficial for the treatment of alcoholism among Type B (but not Type A) alcoholics – characterized by an early onset of drinking, greater severity of dependence and more antisocial traits and psychiatric symptoms (Babor et al. 1992). Similarly, among non-psychosis alcoholics with high levels of depression and anxiety, tiapride was effective at reducing alcohol use; however, other studies found tiapride to worsen outcomes in the general population of alcoholics (Shaw et al. 1987, Gual et al. 2002; Bender et al. 2007).

In this context, our baseline analysis revealed that sensation-seeking was significantly higher in DD and SUD, relative to SCZ patients. This finding is consistent with previous associations between sensation-seeking and SUDs (Dervaux et al. 2001, 2010a,b). In addition, we found that SCZ patients had significantly lower scores in the boredom susceptibility subscale of sensation-seeking, relative to healthy controls. These data suggest that substance abusers with and without schizophrenia are characterized by abnormally high sensation-seeking, and/or that non-abusing schizophrenia patients are characterized by abnormally low sensation-seeking.

We also found that social anhedonia was significantly elevated in DD and SCZ, relative to SUD patients and healthy controls. This finding is in accordance with previous studies that found a link between social anhedonia and schizotypal personality traits (Kwapil, 1998, Rey et al. 2009). Little data exists on social anhedonia in DD patients, but previous studies did not find elevated physical anhedonia in these individuals (Dervaux et al. 2001, 2010a,b). Together, the data show that social anhedonia is relatively unique to schizophrenia – irrespective of SUD comorbidity.

We found that impulsivity was significantly higher in DD, SCZ and SUD patients, compared to healthy controls. This finding is in accordance with studies showing elevated impulsivity in schizophrenia and SUD patients, relative to healthy controls (Enticott et al. 2008; Ersche et al. 2010; Kaladjian et al. 2011; Duva et al. 2011). However – unlike previous studies – we did not find significant differences in impulsivity between substance abusers with and without schizophrenia. The inability to find a difference in impulsivity between the groups may reflect a type-II error, since our SCZ group evidenced an impulsivity total score, which was numerically lower than our DD and SUD groups (mean [SD] = 55.6 [13.7], 62.4 [14.8], 61.3 [19.3], respectively). A larger *per group* sample size may have rendered the numerical difference statistically significant.

As a whole, the results suggest that sensation-seeking is prominent in substance abuse (irrespective of schizophrenia), social anhedonia is prominent in schizophrenia (irrespective of substance abuse) and impulsivity is prominent in all three populations. The findings may help tailor pharmacological and psychosocial intervention in these populations. Unfortunately, we were not able to answer the question whether these are state or trait differences because a low sample size prevented us from analyzing our follow-up data. Similarly, we were not able to perform analyses to determine if quetiapine had an effect on alcohol use as a function of personality traits (as suggested by Kampman et al. [2007]) because patients in the DD and SUD groups were using multiple substances, thereby rendering this type of analysis unfeasible.

8.5. Systematic review on antipsychotics for the treatment of SUDs in psychosis and non-psychosis patients

Due to the potential for serious consequences resulting from alcohol and drug abuse/dependence in schizophrenia, clinicians must carefully consider which antipsychotics are optimal for decreasing substance abuse among DD patients. Interestingly, although there is some evidence from randomized and case-control studies that atypical antipsychotic agents may be effective in treating substance dependence, results have been mixed, with some studies demonstrating positive and others negative or no effect. Previous reviews on the topic of antipsychotics for SUDs considered psychosis and non-psychosis patients separately or have included uncontrolled, open-label (switch design) trials and case reports (Wobrock and Soyka, 2009; Green et al. 2008). Consequently, we conducted a systematic review to determine whether the disparity originated from the fact that reviewers separately discussed trials in psychosis and non-psychosis patients (Zhornitsky et al. 2010a). In the context of our case-control trial with quetiapine, we aimed to better understand the effects of atypical antipsychotics in general, and quetiapine specifically, on substance use outcomes in psychosis and non-psychosis patients.

In the present systematic review, we examined both psychosis and non-psychosis patients and included only the best controlled studies (we included both randomized and case-control studies in the DD group in order to increase the number of studies), while simultaneously paying attention to the type of antipsychotic and substance of abuse.

A total of 43 studies were identified; of these, 23 fell into the category of DD (13 randomized and 10 case-control) and 20 into the category of SUD (all randomized). Studies in the DD category revealed atypical antipsychotics to generally be superior to (older) typicals for decreasing substance abuse and side-effects. The studies also indicated that atypical antipsychotics may improve alcohol and cannabis abuse/dependence use and craving and psychostimulant craving (but not use). Studies of atypical antipsychotics for tobacco dependence

were mixed and suggested the possibility of a pharmacokinetic interaction that may raise plasma levels (and side-effects) of antipsychotics when patients attempt to quit smoking. Studies of atypical antipsychotics for alcoholism in the SUD category were equally mixed, with some trials reporting that atypical antipsychotics aggravated alcohol abuse/dependence and others reporting that they may improve outcomes in the general population or particular subpopulations (e.g. individuals with higher baseline psychiatric symptoms and antisocial personality traits). As for psychostimulant abuse/dependence, studies either found no effect or they found that antipsychotics aggravated outcomes and/or produced disturbing extrapyramidal reactions (e.g. akathisia, dystonia, dyskinesia). Finally, specific antipsychotics were found to be more useful than others for reducing substance abuse – as was in the case of clozapine for alcohol and cannabis abuse/dependence (DD group). Similarly, aripiprazole, olanzapine and quetiapine showed promise over other antipsychotics (e.g. amisupride, tiapride, flupenthixol) in the treatment of alcoholism.

In the context of our case-control trial with quetiapine, these results suggest that we may expect more favorable outcomes for abusers of alcohol and cannabis in psychosis and non-psychosis groups, relative to abusers of psychostimulants. They also suggest that individuals with certain personality characteristics (e.g. impulsivity, sensation-seeking, anxiety/depression) may respond more favourably to quetiapine treatment in our study, relative to those without these characteristics (Carlsson and Gullberg, 1978; Shaw et al. 1987; Kampan et al. 2007). Finally, the results suggest that there is a potential for extrapyramidal reactions and increased substance use during antipsychotic treatment of psychostimulant abusers.

8.6 Systematic review on dose-response and comparative efficacy and tolerability of quetiapine across psychiatric disorders

Substance use disorders are often comorbid with psychiatric disorders such as depression, anxiety, and psychosis (Regier et al. 1990). Quetiapine itself is frequently prescribed on-label and off-label for the treatment of a variety of psychiatric disorders. As quetiapine has variable affinity for dozens of receptors, its clinical effects should also show a large variation as a function of dose and diagnostic category. This is an important topic of research since understanding the comparative efficacy of quetiapine across psychiatric disorders is crucial to properly treating DD patients who typically exhibit comorbid mood and anxiety disorders in addition to substance abuse/dependence. Previous reviews on quetiapine in psychiatry focused on the treatment of single disorders, and thus, were not able to compare the dose-response, efficacy and tolerability of this medication across psychiatric disorders (Keating and Robinson, 2007; McIntyre et al. 2009). Consequently, the present systematic review included placebo-controlled monotherapy and add-on trials in order to elucidate the dose-response and efficacy of quetiapine across psychiatric disorders (excluding substance abuse/dependence due to a lack of controlled trials) (Zhornitsky et al. 2011a).

A total of 41 studies were identified. Psychiatric disorders included schizophrenia (10 studies), unipolar depression (9 studies), bipolar mania (8 studies), obsessive-compulsive disorder (6 studies), bipolar depression (5 studies), and generalized anxiety disorder (3 studies). Studies revealed that quetiapine was most effective for generalized anxiety disorder (~150mg), unipolar (~150mg) and bipolar depression (~300-600mg), and bipolar mania (~600mg). However, studies of quetiapine for schizophrenia and obsessive-compulsive disorder produced inconsistent findings – with the most effective doses being ~600mg and ~300mg, respectively.

Additionally, by further subdividing studies of schizophrenia by psychosis severity, we found that quetiapine was most effective for stable, relative to acute schizophrenia.

In the context of our case-control trial with quetiapine, these data suggest a number of things. First, we may expect DD patients to exhibit less improvement in positive symptoms, relative to SCZ patients. This is because animal and human studies have demonstrated that quetiapine is a weak antipsychotic (Zhornitsky et al. 2010b, 2011a) and that substance abuse/dependence is associated with aggravations of positive symptoms in schizophrenia (Mauri et al. 2006; Swofford et al. 2000; Serper et al. 1999). Second, we may expect DD patients to exhibit more improvement in depression, compared to SCZ patients. This is because quetiapine is an efficient antidepressant for bipolar depression at similar doses which were prescribed in our study (DD and SCZ groups were given 554mg and 478mg of quetiapine, respectively), and because our meta-analysis revealed that DD patients have more depressive symptoms (Potvin et al. 2007), relative to non-abusing patients. Finally, dose-response analysis suggest that any improvements in positive symptoms in the SUD group may not be due to quetiapine because many patients were administered sub-antipsychotic doses (mean = 150mg [118]). On the other hand, quetiapine would still be expected to lead to improvement in depressive symptoms among SUD patients, since it may act as an antidepressant at doses as low as 50mg (although 150mg is optimal) (Zhornitsky et al. 2011a).

8.7 Strengths of studies

- These are the first studies of their kind to examine baseline difference and trace the evolution of substance abuse, psychiatric and extrapyramidal symptoms in DD, SCZ, and SUD patients undergoing a homogenous antipsychotic treatment (quetiapine in this case).

This is important because it allows us to parcel out the effects of substance abuse, antipsychotics and schizophrenia in DD patients.

- The studies are the first of their kind to measure and document both subjective and objective restlessness as a result of cannabis withdrawal.
- The inclusion of abusers of multiple substances (e.g. alcohol, cannabis, cocaine) may better reflect the 'real-world' setting.
- Our trial in non-psychosis SUD patients was the first study of its kind to prospectively administer quetiapine during detoxification.
- A large portion of our subjects were diagnosed with cannabis abuse disorder (alone or in conjunction with other substances; 16 out of 26 patients), making it the first trial to investigate the use of atypical antipsychotics for cannabis abuse/dependence in non-psychosis patients.
- Our study of personality traits is the first trial of its kind to compare sensation-seeking, impulsivity, and anhedonia in substance abusers with and without schizophrenia, in non-abusing schizophrenia patients and in healthy controls.

8.8 Limitations

- Our baseline and follow-up studies between the groups were not powered to detect complex interactions between socio-demographic, psychiatric, extrapyramidal, and SUD variables.
- Patients in the DD group were active users, while patients in the SUD group were undergoing detoxification. However, we were forced to do this due to the fact that acutely detoxifying schizophrenia patients may lead to clinical relapse and rehospitalisation.

- The inclusion of abusers of multiple substances may confound results and makes difficult for us to deduce respective the contribution of each substance. This is important because each substance has its own psychiatric effects and may be abused for different reasons, thereby potentially reflecting different subgroups of patients. However, while the overall sample size was adequate for a pilot trial (n=26), it was not large enough to separate out the effects of specific substances of abuse (e.g. alcohol, cannabis, cocaine). Because of the pilot nature of the trial, we did not correct for multiple comparisons, which may have led us to commit type I error(s).
- There were baseline differences in variables such as quetiapine dose, age, and gender between the three groups. However, we entered these variables into the ANCOVA model and they did not affect our results.
- Our results in non-psychosis SUD patients cannot be solely attributed to the pharmacological effects of quetiapine because of the study's open-label, switch design. That is, patients were aware of the medication they were taking and there was no control group of SUD individuals who were not treated by quetiapine. These confounds make it impossible to tell whether the improvements were simply due to participant bias and/or the passage of time.
- Patients were also involved in an intensive individual and group psychotherapy program, which may explain the improvements observed in the study.
- Our trial of quetiapine in non-psychosis patients used psychiatric and extrapyramidal scales for schizophrenia and did not include special scales to measure withdrawal from substances of abuse. This may limit the generalizability of the present findings to quetiapine treatment of other SUD populations undergoing withdrawal. However, it may

not have been a problem for depression because our sub-analysis found that CDSS scores correlated significantly with Beck Depression Inventory scores at baseline, suggesting that the former scale provides a valid measure of depression in non-psychosis patients.

- In our personality traits study, the lack of difference in impulsivity between the three groups may be related to the fact that the BIS contains numerous cognitive items that may have obscured the results in our study.

8.9 Epistemological coda

In the literature, a myriad of studies have compared schizophrenia patients with and without substance abuse/dependence. This has helped researchers to better understand the consequences of substance abuse in schizophrenia. However, to fully understand the schizophrenia-substance abuse comorbidity, studies must also compare dually diagnosed schizophrenia patients to non-psychosis substance abusers. This part is crucial because it allows researchers to parcel out the effects of psychosis and antipsychotics on DD outcomes and to answer questions such as, for example, Do schizophrenia patients become addicted quicker? Do they have a harder time to quit? Unfortunately, in the current literature, there are few studies which compared DD with SUD patients. This may be a challenging (but not impossible) task because the two groups might not use the same quantities or the same types of substances, which render the comparison difficult, despite its critical importance. Moreover, putting DD patients through detoxification may potentially have negative consequences on clinical relapse and rehospitalisation. Consequently, future studies should compare active users with active users, thereby avoiding the need to put DD patients through detoxification. Another challenge to comparing DD and SUD is the difficulty in choosing the scales that are equally valid in both groups. For example, does one

administer the PANSS (a schizophrenia scale) to non-psychosis SUD patients? Or does one use psychotomimetic scales, which are typically employed in studies with non-psychosis SUD patients? In order to overcome this issue, it is important to use a variety of scales (both psychosis and non-psychosis) in both groups. However, this may be a difficult task due to time/funding limitations. An alternative option may be to use scales that have been validated in both groups; however, up to this point, such scales are lacking. Clearly, more research is required to resolve these issues.

8.10 Implications for the pharmacotherapy of schizophrenia and SUDs

The results described herein have a number of implications for the treatment of schizophrenia and SUDs. In SUD patients, we found high levels of positive and depressive symptoms, and akathisia and parkinsonism at baseline, and these symptoms tended to return to normal after patients ceased their substance use. These data indicate that the clinical symptoms observed among SUD patients were mostly associated with symptoms of acute and protracted withdrawal from substances of abuse. They also suggest that substance abuse/dependence should be the primary target of treatment for these patients; however, because our SUD patients were receiving concomitant psychosocial therapy, we cannot attribute these benefits solely to quetiapine.

Our non-psychosis, SUD arm also provided preliminary information on the safety and efficacy of quetiapine in patients undergoing detoxification. While our study did not include specific alcohol and drug withdrawal scales, we did observe a decrease in the need for benzodiazepine prescriptions, which is important because benzodiazepines have a high abuse potential themselves and carry many of the same risks as alcohol such as withdrawal-induced delirium tremens, convulsions, and death (Albiero et al. 2012). In addition, we did not observe

any new safety or tolerability issues, apart from an asymptomatic increase in gamma-glutamyl transpeptidase. Elevation of this enzyme is considered to be a biomarker for alcohol abuse/dependence and liver disease. Previous research found that atypical antipsychotics produced an asymptomatic increase (27%) in gamma-glutamyl transpeptidase in the first month and after 6-months of treatment (23%), but significant elevations were rare (Atasoy et al. 2007). Consequently, in order to minimize safety risks, these results suggest the need to obtain baseline liver enzyme tests before administration of atypical antipsychotics to alcohol use disorder patients.

The relatively low number of side-effects and complications associated with quetiapine makes it an attractive candidate for the treatment of alcohol withdrawal at low doses. In animals, a review of the literature revealed that quetiapine and risperidone were most efficient among atypical antipsychotics at reducing signs of ethanol withdrawal such as locomotor hyperactivity, stereotyped behaviour, tremor, wet dog shakes, tail-stiffness, abnormal posture and gait, agitation and audiogenic seizures (Uzbay et al. 2011). In humans, there is a rich literature detailing the utility of atypical antipsychotics for the treatment of alcohol withdrawal syndrome (i.e. hallucinations, paranoia, agitation, anxiety, insomnia), which dates back to at least 1968 with thioridazine (Ehik, 1968). Atypical antipsychotics are usually administered in combination with anticonvulsants in this context to prevent the emergence of alcohol withdrawal-induced seizures (Croissant et al. 2009). Less evidence exists on atypical antipsychotics for withdrawal from drugs; however, a few retrospective studies found quetiapine to attenuate symptoms of opiate and amphetamine withdrawal in non-psychosis substance abusers (Pinkofsky et al. 2005; Sattar et al. 2004).

The benefits of antipsychotics for acute alcohol withdrawal may also theoretically extend to active alcoholics, since they should consistently re-experience symptoms of craving and withdrawal (Koob and LeMoal, 2008). Early studies in chronic alcoholics found that 2-week treatment with melperone (an atypical antipsychotic with a similar binding profile to quetiapine) improved muscular and nervous tension, depression, craving, emotional lability, somatization, ability to sleep, anxiety, paranoid ideation and presumed ability to work, relative to placebo (Carlsson and Gullberg, 1978; Carlsson et al. 1979). This was followed up by evidence that low-dose tiapride (100mg t.i.d for 6 months) reduced drinking, and neurotic symptoms, and produced gains in self-esteem, levels of expressed satisfaction with life situation, and use of health services (Shaw et al. 1987, 1994). By contrast, larger studies recently showed that treatment with low-dose tiapride or amisulpride over 6-months aggravated alcohol abuse/dependence in active alcoholics, and these findings could not be accounted for by differences in tolerability (Gual et al. 2002; Marra et al. 2002; Bender et al. 2007). It is unclear what may explain the aggravations, but one possibility is that substituted benzamides may lead to relapse because they induce dopamine release/exert a stimulatory effect at low doses due to their preferential blockade of presynaptic D_2 receptors (Schoemaker et al. 1997). However, quetiapine does not share a similar preference for pre- versus, post-synaptic D_2 receptors, and it possesses significant anxiolytic activity at low doses via antagonism of α-1 adrenergic receptors, which may have added benefit for alleviation of craving, and may explain why quetiapine has never been found to aggravate substance use disorder outcomes.

In DD patients, we observed comparatively high levels depression and parkinsonism at baseline, suggesting that an antipsychotic with significant antidepressant properties (or in conjunction with an antidepressant) and with a low tendency to produce extrapyramidal

symptoms should be ideal for be these patients. Quetiapine closely fits this profile. Quetiapine is not associated with large amounts of extrapyramidal symptoms due to its low affinity for D_2 receptors (Weiden, 2007), which should also minimize the possibility of extrapyramidal reactions when combined with substances of abuse such as psychostimulants (Evans et al. 2001). Moreover, quetiapine possesses significant antidepressant efficacy at low doses, possibly due to antagonism of multiple serotoninergic receptor subtypes (e.g. 5-HT_{2A}, 5-HT_{2C}, 5-HT_7) and antagonism of the norepinephrine transporter by its primary metabolite, norquetiapine (Jensen et al. 2008; for review, see Zhornitsky et al. 2011a).

On the other hand, while all groups showed improvement in parkinsonism and depression from baseline to endpoint in our study, DD patients still had significantly higher SUD severity, depression and parkinsonism scores at endpoint, which suggests that quetiapine may have helped, but that other (perhaps psychosocial) interventions are needed to wean the patients off alcohol and drugs and treat their residual psychiatric symptoms. Indeed, a systematic review of 45 experimental and quasi-experimental studies among DD patients showed that three types of interventions (group counselling, contingency management, and residential dual diagnosis treatment) exhibited consistent positive effects on SUD outcomes, whereas other interventions exhibited consistent positive effects on other areas of adjustment (e.g. case management enhanced community tenure and legal interventions increased treatment participation; Drake et al. 2008). In addition, a recent qualitative review revealed that psychosocial interventions (e.g. contingency management, modified 12-step programs, cognitive behavioural therapy and relapse prevention) are promising interventions for DD patients when they are well-coordinated, take a multidisciplinary and team approach, have specialist-trained personnel with accessible, 24-hour contact, and offer a variety of program types with long-term follow-up (Horsfall et al. 2009).

Taken together, these data suggest the possibility that the effects of pharmacotherapy in dual diagnosis schizophrenia are increased when combined with quality psychosocial interventions.

In DD and SUD patients, we found high levels of sensation-seeking and impulsivity at baseline, suggesting that these traits may be targets for psychosocial treatment. For example, Conrod et al. (2011b) randomized 364 alcohol drinking adolescents with elevated scores of impulsivity, sensation-seeking, anxiety-sensitivity and hopelessness to a control no-intervention condition or a two-session group coping skills intervention targeting one of the four personality risk factors. Their results showed short-term benefits (6-months) of the targeted interventions for quantity/frequency of drinking, and long-term benefits for problem drinking symptoms and alcohol-coping motives. The same authors also found benefits of targeted personality interventions for decreasing drug use (cannabis and cocaine) over a 24-month period in a randomized sample of 732 adolescents (Conrod et al. 2010). These studies offer support for the use of psychosocial interventions which target personality traits to decrease substance use in non-psychosis individuals. It would be interesting to see if the same would be true for DD patients.

In addition, our other systematic review of antipsychotics for SUDs in patients with and without comorbid psychosis revealed that quetiapine may be effective for treating Type-B alcoholics – characterized by earlier onset of drinking, more severe dependence and higher baseline antisocial traits and psychiatric symptoms (Kampman et al. 2007). However, here we did not subtype alcoholics because our subjects were abusers of multiple substances, not just alcohol, and consequently, this will be an important measure to include for future studies.

In DD and SCZ patients, we found high levels of social anhedonia, which is likely related to their negative symptoms. Indeed, the PANSS negative contains many items that are based on a

similar concept as social anhedonia (e.g. emotional and social withdrawal and poor rapport). It is unclear whether psychosocial interventions could be targets for treating social anhedonia since negative symptoms, in general, are considered refractory to treatment (Leucht et al. 2009).

8.11 Future directions

Future studies should include abusers of a single substance (e.g. alcohol only); however, in practice, we realize that it may be difficult to recruit patients with such strict criteria. Moreover, future studies should take more frequent measurements (e.g., every 3 weeks) of psychiatric and extrapyramidal symptoms, in order to better elucidate the temporal relationship in improvements of these variables. Nonetheless, regarding psychiatric symptoms, our results are consistent with those of Mauri et al. (2007), which showed that SUD individuals improved significantly more than schizophrenia patients after two weeks of treatment with quetiapine. In addition, future studies should compare improvements in DD and SUD patients who maintain their substance use and should include cue-elicited craving in order to have a more precise measurement of SUD outcomes. Finally, the contribution of quetiapine to changes in psychiatric and extrapyramidal symptoms reported here will need to be elucidated in randomized trials.

Our non-psychosis SUD arm encourages controlled evaluation of the safety and tolerability of quetiapine in non-psychosis SUD patients during detoxification, using specific withdrawal scales. Future studies with larger sample sizes may also want to separate alcoholics according to personality subtype as reported previously (Carlsson and Gullberg, 1978; Shaw et al. 1987; Kampman et al. 2007).

Future studies on personality traits between the three groups will need to evaluate whether the personality profiles reported here reflect state or trait differences. It would also be

interesting to verify if we can predict the development of substance abuse in schizophrenia based on the personality profiles reported here in longitudinal studies initiated during the prodrome of psychosis. Furthermore, future studies should include more measures of personality traits (e.g. anxiety-sensitivity, hopelessness), which have shown promise as targets for psychosocial interventions (Conrod et al. 2011a,b). Experimental measures (e.g. response inhibition) are needed to confirm impulsivity levels reported in this study.

8.12 Conclusion

In the present trial, we compared SUD outcomes as well as psychiatric and extrapyramidal (neurological) symptoms in substance abusers with and without schizophrenia, and in non-abusing schizophrenia patients at baseline, and after 12-weeks of treatment with quetiapine. In order to contextualize the present study, we presented supplementary data on our SUD arm-alone and on baseline personality traits between the groups. In addition, we conducted two systematic reviews of the literature: the first was on the effects of atypical antipsychotics on substance/dependence in patients with and without comorbid psychosis, and the second was on the dose-response and efficacy/tolerability of quetiapine across psychiatric disorders. The goal of this project was improve our understanding of the complex relationships between substance abuse and schizophrenia. It was also expected to help elucidate the clinical consequences of substance abuse in schizophrenia patients as well as their potential treatment by pharmacological means.

In the main trial, we found that SUD patients showed greater improvement in weekly dollars spent on alcohol and drugs and SUD severity, compared to DD patients. However, at endpoint, there was no significant difference in dollars spent, but DD patients still had a higher

mean SUD severity. Interestingly, DD patients also had significantly higher parkinsonism and depression than SCZ patients at baseline and endpoint. On the other hand, we found that SUD patients had significantly more akathisia at baseline, improved more than SCZ patients, and this was related to the presence of cannabis abuse/dependence. Finally, we found that SUD patients improved more in PANSS positive scores, relative to DD and SCZ patients.

Our supplementary data on the non-psychosis (SUD) arm contributed to preliminary evidence that quetiapine may be beneficial for the treatment of acute and protracted withdrawal from substances of abuse. Additionally, our baseline analysis of personality traits between the three groups and healthy controls revealed that sensation-seeking was associated with substance abusers, regardless of schizophrenia diagnosis, and social anhedonia was associated with schizophrenia, regardless of substance abuse/dependence diagnosis. In our first systematic review, we found a preferential benefit of atypical antipsychotics on alcohol vs. psychostimulant abuse/dependence. In our second systematic review, we found that quetiapine was an extremely effective antidepressant and anxiolytic at low doses, and a mild-to-moderate potency antipsychotic at high doses.

Altogether, our data provide evidence for increased vulnerability to the adverse effects of alcohol and drugs in schizophrenia patients, and they indicate that substance abuse/withdrawal may mimic some symptoms of schizophrenia. Moreover, the data suggest that quetiapine may have benefits for the treatment substance abuse/dependence and schizophrenia due to its significant anxiolytic and antidepressant and antipsychotic properties. Nonetheless, clinicians must be careful when prescribing antipsychotics for long periods of time to active substance abusers because there remains a possibility for these agents to cause harm. Lastly, our data suggest that psychosocial treatments (e.g. such as those targeting personality traits) may have

added benefit when combined with pharmacotherapy for the treatment of schizophrenia and SUDs.

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