Université de Montréal

La comorbidité schizophrénie – toxicomanie: modèles cliniques et neurobiologiques, et traitement pharmacologique.

Par Stéphane Potvin

Programme de Sciences biomédicales

Faculté de médecine

Thèse présentée à la Faculté des études supérieures

en vue de l'obtention du doctorat

en Sciences biomédicales

Décembre 2006

Université de Montréal

Faculté des études supérieures

Cette thèse :

La comorbidité schizophrénie – toxicomanie:

modèles cliniques et neurobiologiques,

et traitement pharmacologique.

présentée par :

Stéphane Potvin

a été évaluée par un jury composé des personnes suivantes :

Président-rapporteur : Gabriella Gobbi

Directeur de recherche : Emmanuel Stip

Membre du jury : Pierre-Paul Rompré

Examinateur externe : Raymond Tempier

Représentant de la Faculté de médecine : Louis-Éric Trudeau

Résumé

La toxicomanie est hautement prévalente chez les schizophrènes et elle est associée à de multiples conséquences négatives, telles qu'une fréquence accrue de rechutes psychotiques et d'épisodes dépressifs. Les raisons motivant les schizophrènes à consommer demeurent toutefois méconnues. Selon l'hypothèse de l'automédication, les schizophrènes consommeraient en vue de soulager leurs symptômes négatifs. Pour évaluer cette hypothèse, nous avons réalisé une méta-analyse d'études comparant les symptômes négatifs de schizophrènes avec et sans toxicomanie. Nous avons découvert que les schizophrènes toxicomanes présentent une symptomatologie négative moins sévère. Dans ce prolongement, nous avons entrepris une étude en imagerie par résonance magnétique fonctionnelle, comparant des schizophrènes avec et sans toxicomanie, soumis à des stimuli émotionnels. Relativement au groupe non-toxicomane, les schizophrènes toxicomanes ont rapporté des réponses émotionnelles et des activations corticales accrues. Tout comme la méta-analyse, ces résultats renforcent l'hypothèse d'une symptomatologie négative moins sévère chez les patients toxicomanes. Similairement, nous avons étudié la cognition de schizophrènes avec et sans toxicomanie. Nous avons observé une meilleure performance cognitive (mémoire explicite) chez le groupe toxicomane.

Ces résultats posent un problème d'interprétation. En effet, la nature transversale des études réalisées ne permet pas de déterminer si la toxicomanie soulage certains symptômes des schizophrènes (automédication), ou encore une symptomatologie négative/cognitive moins sévère prédispose davantage la toxicomanie.

Ce qui vaut pour les symptômes négatifs/cognitifs ne semble pas valable pour les symptômes extrapyramidaux (SEP). En effet, dans une étude transversale comparant les SEP de schizophrènes avec et sans toxicomanie, le groupe toxicomane a présenté davantage de SEP.

Peu d'études pharmacologiques ont été réalisées auprès des schizophrènes toxicomanes. Récemment, des données préliminaires ont suggéré que la clozapine et la quétiapine soulagent les *craving* des schizophrènes. Ces médicaments antipsychotiques partagent certaines propriétés pharmacologiques et cliniques qui ont leur importance dans le présent contexte. Dans la mesure où les schizophrènes recherchent une automédication, il est pertinent d'observer que ces antipsychotiques induisent peu de SEP, qu'ils ont des effets thymorégulateurs, et qu'ils soulagent les symptômes négatifs/cognitifs. Nous avons donc réalisé une étude ouverte auprès de schizophrènes toxicomanes, traités à la quétiapine. Une amélioration a été observée sur le plan de la toxicomanie, des symptômes psychiatriques, des SEP et de la cognition. Ces résultats suggèrent que la quétiapine soulagerait la toxicomanie des schizophrènes, tout en conservant ses propriétés cliniques. Par ailleurs, nous avons observé que l'adaptation sociale et l'anhédonie, mesurées à l'entrée de l'étude, étaient des variables prédictives de l'évolution de la consommation de substances psychoactives et la sévérité de la toxicomanie dans le temps. Ces résultats suggèrent un lien complexe entre les symptômes négatifs, l'environnement social et la toxicomanie des schizophrènes.

Enfin, nous avons observé que des taux élevés d'anandamide – un cannabinoïde endogène - dans le plasma en début d'étude prédisent une consommation accrue de substances psychoactives et une plus grande sévérité de la toxicomanie en fin d'étude chez les patients schizophrènes. Ce résultat suggère que

la sensibilité des schizophrènes aux substances psychoactives (c'est-à-dire leur propension accrue à développer une toxicomanie et leur sensibilité accrue aux effets néfastes de ces substances) serait liée à des perturbations des endocannabinoïdes, ce qui pourrait ouvrir de nouvelles pistes de traitement pharmacologique.

L'ensemble des données accumulées au cours des travaux inclus dans la thèse accréditent les principaux modèles de la comorbidité « schizophrénie – toxicomanie », et laissent espérer qu'une meilleure compréhension des causes et des conséquences de cette comorbidité pave la voie à de meilleurs traitements.

Mots clés

Comorbidité – schizophrénie – toxicomanie – automédication – anhédonie – cognition – symptômes extrapyramidaux – méta-analyse – imagerie par résonance magnétique fonctionnelle – cannabinoïdes endogènes

Abstract

Substance use disorders (SUD) are highly prevalent in schizophrenia and are associated with multiple negative consequences, such as psychotic relapses and depressive episodes. However, the reasons motivating substance use in schizophrenia remain poorly understood. According to the self-medication hypothesis, schizophrenia patients use psychoactive substances (PAS) to relieve their negative symptoms. To test this hypothesis, we performed a meta-analysis of studies measuring negative symptoms in schizophrenia patients with and without SUD, using the Scale for the Assessment of Negative Symptoms. We found that dual diagnosis patients have less severe negative symptoms. In the same vein, we also conducted a functional magnetic resonance imaging study of schizophrenia patients with and without SUD, exposed to emotional stimuli. Relative to the non-addiction group, dual diagnosis patients displayed stronger emotional reactions and greater cortical activations. In par with the meta-analysis, these results support the hypothesis of lesser negative symptoms in dual diagnosis schizophrenia. Similarly, we investigated cognition in schizophrenia patients with and without SUD, and observed a better cognitive performance (explicit memory) in dual diagnosis patients.

The previous results must be interpreted cautiously. Indeed, the cross-sectional nature of our studies does not allow to determine whether SUD relieve certain schizophrenia symptoms (self-medication), or whether less severe negative/cognitive symptoms predispose to SUD.

We also studied extrapyramidal symptoms (EPS) in dual diagnosis patients. Unlike negative and cognition, we found more severe EPS (mainly parkinsonian signs) in schizophrenia patients with SUD, relative to patients without SUD. This

result adds to the prevailing literature describing multiple negative consequences of SUD in schizophrenia.

Few pharmacological studies have been conducted in dual diagnosis schizophrenia. Recently, preliminary data have shown benefits of clozapine and quetiapine among these patients. Clozapine and quetiapine share pharmacological and clinical properties relevant in the present context. Insofar as schizophrenia patients use PAS as some form of self-medication, it is noteworthy that these antipsychotics induce little EPS; that they exert a positive impact on mood; and they are efficient for negative/cognitive symptoms. We thus conducted an open-label trial involving schizophrenia patient with comorbid SUD, treated with quetiapine. We observed improvements in SUD, psychiatric symptoms, EPS and cognition. These results suggest that quetiapine may relieve SUD in schizophrenia, while retaining its usual clinical efficacy. In addition, we found in this study that baseline social adjustment and anhedonia were predictors of consumption and SUD severity in time. This latter result suggests that there may be complex interactions between negative symptoms, social environment and SUD in schizophrenia.

Lastly, we discovered that elevated baseline plasmatic levels of anandamide, an endogenous cannabinoid, predict increased PAS consumption and greater substance abuse severity in schizophrenia at endpoint. This finding suggests that the sensitivity of schizophrenia patients to PAS (e.g. their increased propensity to develop a SUD and their enhanced sensitivity to the negative consequences of PAS) may be linked to endocannanoid disturbances. If replicated, this result may have implications for the pharmacological treatment of SUD in schizophrenia.

The results of the studies included in the present thesis are in par with the main models of the "schizophrenia – SUD" comorbidity, and they entail a better

understanding of the causes and consequences of SUD in schizophrenia, which may help define better treatment approaches of this comorbidity.

Key words

Comorbidity – schizophrenia – substance use disorders – self-medication – anhedonia – cognition – extrapyramidal symptoms – meta-analysis – functional magnetic resonance imaging – endogenous cannabinoids

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2-AG = 2-arachidonylglycerol

5-HT = 5-hydroxy-tryptamine (serotonin)

ACC = anterior cingulate cortex

AC-PC axis = anterior commissure – posterior commissure

AEA = anandamide

ANCOVA = analyse de covariance

ANOVA = analysis of variance

ATV = aire tegmentaire ventrale

AUS = Alcohol Use Scale

BA = Brodmann area

BAS = Barnes Akathisia Scale

β = standardized regression coefficient

BD = bipolar disorder

BPRS = Brief Psychiatric Rating Scale

CANTAB = Cambridge Neuropsychological Test Automated Battery

CB_1 = cannabinoid-1 receptor

CB_2 = cannabinoid-2 receptor

CBE = cannabinoïdes endogènes

CDSS = Calgary Depression Scale for Schizophrenia

CIHR = Canadian Institute of Health Research

CNS = central nervous system

COC = cocaine

CPFm = cortex prefrontal médian

CSF = cerebrospinal fluid

D_2 = récepteurs dopaminergiques D_2 (dopamine-D_2 receptors)

DD = dual diagnosis / double diagnostic

Δ = % of change from baseline to end-point

Δ^9-THC = delta-9-tetrahydrocannbinol

df = degree of freedom

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders – 4th edition

DUS = Drug Use Scale

ECB = endogenous cannabinoids

EPI = Echoplanar images

EPS = extrapyramidal symptoms

ESRS = Extrapyramidal Symptoms Rating Scale

F = female

FAAH = fatty acid amid hydrolase

FAEA = bioactive fatty acid ethanolamides

fMRI = functional magnetic resonance imaging

FRSQ = Fond de la recherche en Santé du Québec

GGT = gamma-glutamyltransferase

IIT = Investigator Initiated Trial

IRAOS = Interview for the Retrospective Assessment of the Onset and Course of Schizophrenia and Other Psychoses

IRMf = imagerie par résonance magnétique fonctionnelle

LOCF = last observation carried forward

MOT = motor screening

MNI = Montreal Neurological Institute

mPFC = medial prefrontal cortex

NAc = nucleus accumbens

NE = norepinephrine

OEA = oleylethanolamide

PACS = Penn Alcohol Craving Scale

PAL = paired associates learning

PANSS = Positive and Negative Syndrome Scale

PAS = psychoactive substances

PCP = phencyclidine

PEA = palmitylethanolamide

PET = positron emission tomography

POLY = alcohol and cannabis

PPAR-α = peroxisome-proliferator-activated receptor-alpha

r = correlation coefficient

R^2= % of variance of the dependent variable explained by the model

RSEB = Rating Scale for Emotional Blunting

SA = schizoaffective disorder / trouble schizoaffectif

SANS = Scale for the Assessment of Negative Symptoms

SAPS = Scale for the Assessment of Positive Symptoms

SCID-IV = Structured Clinical Interview for DSM-IV

SCZ = schizophrenia / schizophrénie

SD = standard deviation

SEM = standard error of the mean

SEP = symptômes extrapyramidaux

SNpc = substantia nigra pars compacta

SPA = substances psychoactives

SPECT = single photon emission computed tomography (tomoscintigraphie)

SPM = Statistical Parametric Mapping

SPSS = Statistical Package for Social Sciences

SSTICS = Subjective Scale to Investigate Cognition in Schizophrenia

SUD = substance use disorders

SWM = spatial working memory

TAL = Talairach coordinates

THC = cannabis

TLFB = TimeLine Follow-Back

VAS = visual analog scale

χ^2 = chi-square

Remerciements

Je désire remercier le Dr Emmanuel Stip pour son engagement à terminer les projets entamés malgré des circonstances humaines difficiles, pour la productive plate-forme de recherche qu'il met à la disposition des étudiants, de même que pour sa passion de la recherche, sa sensibilité clinique et son sens aigu de la liberté. Je désire également remercier Alain Gendron, pour son enthousiasme, son support inconditionnel, et le fait qu'il soit toujours fiable; Dr Roch-Hugo Bouchard, sans qui le projet n'aurait pu être complété dans les délais prévus; Pierre-Paul Rompré, pour la sagesse de ses conseils; Daniele Piomelli, pour le caractère unique de son expertise scientifique; Dr Olivier Lipp, pour sa courtoisie, sa disponibilité et ses pertinents commentaires; Dr Robert Élie, parce qu'il sait marier statistiques et philosophie; Dr Adham Mancini, pour sa curiosité, sa persévérance et son coloré sens de l'humour; Dr Tania Pampoulova, sans laquelle le quotidien de la recherche manquerait de poésie; Amir Sepehry, pour son enthousiasme et sa persévérance; Lise Fournier, pour son constant souci du travail bien fait; Marc-André Sirois, pour son sens de la camaraderie; et Mimi Dumont, pour son écoute. Enfin, j'ai une pensée bien particulière pour le Dr Jean-Yves Roy, que je salue ici pour ses remarquables qualités de visionnaire et de bâtisseur, mais surtout, pour son irremplaçable amitié.

Dédicace

Cher Jean-Yves,

Le 27 avril 2004, tu nous as quitté sur la pointe des pieds, laissant inachevés quelques projets auxquels tu tenais de tout cœur: d'abord, la Clinique Cormier-Lafontaine, spécialisée dans les comorbidités « psychiatrie et toxicomanie », dont tu as été le fondateur, mais également une plateforme de recherche brisant les habituels critères d'exclusion des études sur la schizophrénie et la toxicomanie. Tel un métaphysicien forçant la porte d'entrée de la science, tu venais à peine de reprendre le goût de la recherche, toi qui avais incidemment débuté ta carrière dans le domaine. Au moment de nous quitter, tu étais sur une lancée, alors que plusieurs projets de recherche pointaient à l'horizon. Les articles inclus dans la présente thèse consignent l'achèvement de certains de ces projets. Ces travaux, qui gravitent autour de la comorbidité « schizophrénie – toxicomanie », ne répondent probablement pas à tes interrogations les plus existentielles, leurs résonances anthropologiques, leur portée éthique. Mais ils ont au moins le mérite de répondre à la promesse que nous avons tenu à ton endroit: celle de poursuivre tes projets dans le respect de ta mémoire.

Chapitre introductif

Le présent chapitre introductif constitue une synthèse d'une série d'articles et de chapitres théoriques rédigés par notre groupe sur les liens complexes entre la schizophrénie et la toxicomanie (voir bibliographie).

1.1. La comorbidité schizophrénie – toxicomanie

Malgré l'existence de travaux précurseurs au cours des années 1970, l'intérêt contemporain porté à la comorbidité toxicomanie[1] / santé mentale se cristallise lors de la publication des recherches de McLellan et de son groupe au début des années 1980 (McLellan et al., 1981a; McLellan et al., 1981b). L'intuition clinique de l'école de Philadelphie était claire: plusieurs des toxicomanes qui ne répondaient pas aux tentatives de rétablissement étaient, en fait, porteurs d'un trouble psychiatrique co-occurrent. Ce n'est que peu à peu que l'on a pu apprécier l'impact novateur de cette perspective. Il a fallu, entre autres, compléter un certain nombre d'études épidémiologiques (Kessler et al., 1997, 1994) avant de constater à quel point cette co-occurrence n'avait rien de fortuit ni de banal. Ces travaux, à leur tour, ont mis en lumière l'ampleur de la comorbidité schizophrénie – toxicomanie à laquelle nous nous intéressons ici: près de la moitié des patients souffrant de schizophrénie – 47 % selon l'étude de Regier (1990) – vont abuser ou dépendre au cours de leur vie de l'une ou l'autre des substances psychoactives (SPA), cette catégorie incluant l'alcool mais excluant la nicotine. On découvre que ces patients consomment, dans l'ordre

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[1] Pour des fins de concision, le terme « toxicomanie » est ici employé, et il désigne un abus ou une dépendance pour l'une ou l'autre des principales substances psychoactives.

décroissant, de l'alcool, du cannabis et de la cocaïne (de l'héroïne en Europe). Si la haute prévalence à vie de la toxicomanie chez les patients souffrant de schizophrénie fait l'objet d'un consensus, il importe toutefois de mentionner que la prévalence et le type de substances varient passablement d'une étude à l'autre, en fonction du continent (Amérique versus Europe), du milieu urbain ou rural, et de l'environnement (contexte clinique versus population générale) où l'étude est réalisée (Dixon, 1999; Kavanagh et al., 2002; Mueser et al., 2001; Regier et al., 1990).

Dans la littérature, trois modèles principaux ont été proposés en vue de rendre compte de la fréquente co-occurrence de la toxicomanie chez les patients schizophrènes: (i) le modèle de vulnérabilité, selon lequel la toxicomanie serait un facteur de déclenchement de psychoses latentes et un facteur d'aggravation de psychoses manifestes (ici, la cause est la toxicomanie et la conséquence est la psychose [toxicomanie → psychose]) (Andreasson et al., 1989,1987; Arsenault et al., 2002); (ii) le modèle de l'automédication, qui suggère que le schizophrène aurait recours aux SPA en vue de soulager certains symptômes clés, tels que les symptômes négatifs (ici, psychose → toxicomanie) (Khantzian, 1997,1985); (iii) le modèle de facteurs communs, selon lequel des facteurs communs à la psychose et à la toxicomanie (exemples : personnalité, environnement, gènes, neurotransmetteurs, etc.) serait à l'origine de la psychose et de la toxicomanie (Chambers et al., 2001; Tsapakis et al., 2003).

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[2] Pour des fins de concision, le terme « schizophrène » est ici employé, et il désigne un patient souffrant de schizophrénie.

De ces trois modèles, le modèle de la vulnérabilité est celui qui a reçu le plus d'appui empirique depuis que la comorbidité schizophrénie – toxicomanie fait l'objet de recherches cliniques. Une vingtaine d'années de recherche dans le domaine enseigne que la toxicomanie chez les schizophrènes s'accompagne d'une panoplie de conséquences néfastes. En effet, comparativement aux schizophrènes non-toxicomanes, les schizophrènes toxicomanes possèdent les caractéristiques suivantes (Negrete, 2003; Mueser *et al.*, 1998): (i) ils font davantage de rechutes psychotiques et sont plus fréquemment hospitalisés; (ii) ils prennent moins régulièrement leur médication; (iii) ils ont plus de problèmes de logement et d'emploi; (vi) ils sont plus violents et criminalisés; (vii) ils sont plus dépressifs et suicidaires; et (viii) ils ont plus de problèmes de santé. Il est également possible que les schizophrènes toxicomanes aient davantage de déficits cognitifs et de signes extrapyramidaux, mais la littérature à ce sujet demeure controversée, d'autant plus que certaines études rapportent moins de déficits cognitifs et de signes extrapyramidaux chez les patients comorbides (à ce sujet, voir les sections *1.2.1.3* et *1.2.1.4*).

Les meilleures évidences en faveur du modèle de vulnérabilité proviennent des études épidémiologiques portant sur la consommation de SPA – en particulier le cannabis – comme facteur de risque dans le développement de troubles psychotiques endogènes, incluant la schizophrénie.

De celles-ci, la plus citée est celle d'Andreasson et de son groupe (1987), une vaste étude prospective menée auprès de 45 570 conscrits de l'armée suédoise de 1969 et 1970. À la consultation des dossiers médicaux de ces conscrits 15 ans plus tard, le risque de développer la schizophrénie s'est avéré 2.9 fois plus élevé chez les plus grands consommateurs de cannabis de leur cohorte. Depuis, des critiques sévères ont été adressées à cette étude charnière (Hall & Degenhardt, 2000). Par

exemple, l'étude ne contrôlait pas l'influence d'autres SPA, comme les amphétamines, et elle ne documentait pas les traits de personnalité antérieurs à la conscription. Les collaborateurs d'Andreasson ont tenté, depuis, de répondre à ces critiques, reprenant leurs analyses statistiques premières (Zammit et al., 2002; Allebeck et al., 1993; Andreasson et al., 1989). Plus récemment, d'autres études longitudinales ont été entreprises par d'autres groupes, mieux contrôlées cette fois. De façon générale, ces études *prospectives* démontrent que la consommation de cannabis accroît, à terme, la fréquence de *symptômes* psychotiques observés chez les consommateurs (Fergusson et al., 2003; Arsenault et al., 2002), davantage qu'elle n'accroît le fréquence des *diagnostics* de psychose (van Os et al., 2002). Reprenant les études longitudinales publiées jusqu'en 2004, deux méta-analyses ont récemment estimé que le risque relatif (« odds ratio ») de développer des symptômes psychotiques est de 2.1 à 2.9 fois plus élevé chez les consommateurs de cannabis (Henquet et al., 2005; Semple et al., 2005).

1.2. Pourquoi les schizophrènes consomment-ils des SPA ?

Si le modèle de vulnérabilité reçoit une certaine corroboration empirique et que ce modèle décrit bien les conséquences de la toxicomanie chez les schizophrènes, ce modèle explique mal pourquoi autant de patients schizophrènes semblent apprécier des SPA. Aussi, la plupart des auteurs se réfèrent aux deux autres modèles (automédication et facteurs communs) afin d'expliquer cette préférence.

1.2.1. La perspective de l'automédication

Systématisée par Khantzian au cours des années 1980 et 1990, l'hypothèse de l'automédication postule que le recours aux SPA par le schizophrène représente une

tentative de soulagement de sa maladie (Khantzian, 1997, 1985). Lorsque l'on tente d'expliquer la consommation des schizophrènes, c'est la plupart du temps à cette construction que l'on fait appel. Il faut dire qu'elle signale un important virage: alors que les psychodynamiciens ont tendance à interpréter la consommation de SPA comme une recherche effrénée de plaisir, l'hypothèse de l'automédication renverse la perspective et met plutôt l'emphase sur l'évitement de la souffrance. Selon la littérature, le schizophrène chercherait à obtenir, en ayant recours à la substance, un soulagement de ses symptômes négatifs, ses affects anxio-dépressifs et ses déficits cognitifs.

1.2.1.1. Les symptômes négatifs

Les évidences préliminaires suggèrent que les symptômes négatifs joueraient un rôle primordial dans la comorbidité schizophrénie – toxicomanie. D'abord, il a été démontré, en contexte de laboratoire, que les amphétamines soulagent les symptômes négatifs de la schizophrénie (Mathew & Wilson, 1989). Par ailleurs, des études cliniques ont démontré que les schizophrènes dépendants du cannabis ou de la cocaïne ont des symptômes négatifs moins sévères que les schizophrènes abstinents (Bersani et al., 2002; Serper et al., 1995). D'autre part, il a été démontré que les schizophrènes toxicomanes ont un meilleur ajustement prémorbide (Arndt et al., 1992). De plus, les schizophrènes répondant aux critères du « syndrome déficitaire » du DSM-IV ont une moindre propension à consommer des SPA (Kirkpatrick et al., 2003, 1996). Par contre, il importe de souligner qu'un nombre non négligeable d'études ne mettent pas de telles différences en lumière (Kamali et al., 2000; Drake & Wallach, 1989).

L'ambiguïté de tels résultats invite à investiguer les symptômes négatifs dans leur hétérogénéité. Parmi l'ensemble de ces symptômes, l'*anhédonie* et l'*émoussement de l'affect* s'imposent assurément comme des candidats de choix. En effet, depuis les travaux classiques de Chapman, l'anhédonie et l'émoussement de l'affect sont considérés comme étant de bons prédicteurs d'une prédisposition à la schizophrénie (Mishlove & Chapman, 1985; Chapman et al., 1980). Ainsi habité par une absence interne d'émotions et de plaisir, le schizophrène serait particulièrement vulnérable aux effets renforçants des SPA. Incidemment, le groupe de Green et Zimmet (1999), l'un des rares à tabler sur l'apport des neurosciences, postule que le schizophrène pourrait souffrir d'un syndrome déficitaire de la récompense (" reward deficiency syndrome "). Sur le plan empirique, la recherche de plaisir (et/ou le soulagement de l'anhédonie) est justement l'une des raisons de consommer les plus fréquemment invoquées par les schizophrènes toxicomanes (Gearon et al., 2001).

Parmi les symptômes négatifs, le *retrait social* représente une autre piste d'investigation invitante. Il est en effet permis d'imaginer que le schizophrène recourre aux pouvoirs désinhibiteurs des SPA afin de compenser ses difficultés de socialisation (Potvin et al., 2003a). En accord avec cette hypothèse, certaines études cliniques ont démontré que les schizophrènes toxicomanes ont de meilleures aptitudes sociales *subjectives* (Carey et al., 2003; Mueser et al., 2000), malgré le fait que leurs conditions sociales *objectives* sont généralement détériorées (exemple: le travail).

En dépit de résultats préliminaires prometteurs, on ne saurait conclure à la validité de l'hypothèse de l'automédication. Selon cette perspective, le fait de consommer apporte un soulagement symptomatique. Mais il demeure possible que ce soit l'inverse qui soit vrai, à savoir qu'une symptomatologie négative moins sévère

puisse prédisposer aux conduites addictives. Selon Mueser et al. (2000) par exemple, les schizophrènes ayant de moindres symptômes négatifs seraient davantage susceptibles à la toxicomanie en raison de meilleures aptitudes sociales. Comme ils le notent, pour s'inscrire dans le mode de vie de la toxicomanie, il faut être en mesure de socialiser avec les vendeurs de drogues, de même que les pairs consommateurs. Mais avant de départager le primaire du secondaire en ce domaine, il importe d'abord d'établir que les schizophrènes toxicomanes ont effectivement moins de symptômes négatifs.

Par ailleurs, il est intrigant d'observer qu'aucune étude en imagerie cérébrale n'a été entreprise en vue d'investiguer la question. Selon un modèle animal bien connu (voir section 1.2.2.), un dysfonctionnement du système mésocorticolimbique serait associé à la schizophrénie. Plus précisément, une hypoactivité du cortex préfrontal médian (CPFm), semblerait sous-tendre les symptômes négatifs de la schizophrénie (Grace, 1993). Les études en imagerie cérébrale menées chez les schizophrènes tendent à supporter cette hypothèse, qu'il s'agisse d'études mesurant l'activité cérébrale au repos (Liddle, 1996; Liddle et al., 1992) ou celle observée en cours de traitement émotionnel. En effet, chez le volontaire sain, le rôle du CPFm dans le traitement des émotions de base (la tristesse, la peur, la colère, etc.) a été démontrée à l'occasion d'une récente méta-analyse de Phan et al. (2004, 2002). Par contre, des données préliminaires recueillies en imagerie cérébrale (tomographie par émission de positrons et résonance magnétique) démontrent des activations atténuées du CPFm chez les schizophrènes, en réponse à des stimuli émotionnels tant positifs (appétitifs) que négatifs (aversifs) (Fahim et al., 2004; Takashaki et al., 2004; Paradiso et al., 2003). Dans la mesure où les schizophrènes toxicomanes ont moins de symptômes négatifs que les schizophrènes abstinents, on devrait donc s'attendre à

une relative préservation du fonctionnement du CPFm chez les patients comorbides, soumis à des stimuli de nature émotionnelle.

1.2.1.2. Les affects anxio-dépressifs

Nombre de cliniciens préfèrent attribuer l'usage comorbide de SPA par les schizophrènes à une tentative de régulation d'*affects* tels que la dépression, le stress et l'anxiété (Blanchard et al., 2000). À l'origine de l'idée de la prépondérance des affects, il y a une observation clinique commune: en thérapie, les schizophrènes invoquent régulièrement le soulagement des états anxio-dépressifs comme la raison de leur usage des SPA (Addington et Duchak, 1997; Dixon et al., 1991). À l'appui de cette intuition clinique, il existe des données probantes à l'effet que le stress constitue un facteur de rechute tant dans la schizophrénie (Walker et Diforio, 1997) qu'en toxicomanie (Goeders, 2003). Par ailleurs, des recherches indiquent, d'une part, que les schizophrènes toxicomanes sont plus dépressifs que les autres schizophrènes (Cuffel & Chase, 1994; Brady et al., 1993), et d'autre part, qu'il existe une corrélation positive entre la dépression et la consommation de SPA – surtout l'alcool – chez les schizophrènes (Blanchard et al., 1999; Strakowski et al., 1994). Bien que ces résultats soient séduisants, leur interprétation reste des plus délicates. En effet, une telle corrélation ne permet pas d'établir que la dépression observée soit la cause de l'abus de SPA. En fait, il se peut fort bien que l'inverse soit vrai, c'est-à-dire que l'abus de substances soit la cause de la dépression observée. De fait, chez patients déprimés (mais non-psychotiques), on assiste généralement à une résorption de 80% des syndromes dépressifs, après une période de désintoxication à l'alcool d'une durée d'un mois (Liappas et al., 2002; Brown et al., 1995).

1.2.1.3. La cognition

La recherche neuropsychologique effectuée au cours de la dernière décennie a permis d'établir que 70 à 75 % des schizophrènes présentent des déficits cognitifs, affectant principalement l'attention soutenue, les fonctions exécutives, la fluidité verbale, la mémoire verbale, ainsi que la mémoire de travail (Goldberg & Green, 2002; Stip, 1996). Or, ces déficits cognitifs constituent de meilleurs prédicteurs d'intégration sociale que les symptômes positifs de la schizophrénie (Green, 1996).

Toujours selon l'hypothèse de l'automédication, les schizophrènes consommeraient des SPA dans le but de corriger, ne serait-ce que partiellement, ces déficits cognitifs (Potvin et al., 2003a). Ici comme dans le cas des symptômes négatifs, le raisonnement inverse peut également être défendu. Afin de maintenir le mode de vie de la toxicomanie, les schizophrènes doivent être minimalement en mesure de socialiser et de mettre en application des stratégies d'organisation (Joyal et al., 2003). En ce sens, les schizophrènes les plus prédisposés à la toxicomanie seraient les patients présentant une relative préservation de la fonction cognitive.

Peu d'études ont documenté l'impact neurocognitif des drogues d'abus chez les schizophrènes. Jusqu'ici, certains groupes ont démontré que les schizophrènes toxicomanes ont moins de déficits cognitifs, comparés aux schizophrènes abstinents (Carey et al., 2003; Joyal et al., 2003; Potvin et al., 2005a; Stirling et al., 2005). Cependant, la plupart des études n'ont pas documenté de telles différences (Pencer & Addington, 2003; Addington & Addington, 1997; Cleghorn et al., 1991), alors que d'autres études ont mis en relief davantage de déficits cognitifs chez les schizophrènes consommateurs (Liraud & Verdoux, 2002) – surtout en ce qui a trait à la cocaïne (Serper et al., 2000a, 2000b). Le caractère contradictoire des résultats obtenus jusqu'ici semble donc supporter à la fois le modèle d'automédication et le

modèle de vulnérabilité. Le Tableau 1 donne des informations plus détaillées des résultats décrits jusqu'ici dans la littérature.

Tableau 1: La cognition des patients souffrant de schizophrénie avec ou sans toxicomanie co-occurrente.

Auteurs	Population	SPA	Résultats
Addington & Adddington, 1997	33 SCZ 33 DD	Surtout alcool et cannabis	Pas de différences entre les groupes
Allen et al., 1999	217 SCZ 54 DD	Alcool	Plus de déficits cognitifs chez le groupe DD
Barnes et al., 2006	110 SCZ 42 DD	Surtout cannabis et alcool	Pas de différences entre les groupes
Bowie et al., 2005	17 SCZ 18 DD	Alcool	Plus de déficits mnésiques chez le groupe DD
Carey et al., 2003	56 SCZ & trouble bipolaire	Toxicomanie présente (n=15); toxicomanie à vie (n=26) (surtout alcool et cannabis)	Meilleur fonctionnement cognitif global chez le groupe DD
Cleghorn et al., 1991	38 DD 25 SCZ	Cannabis, surtout	Pas de différences entre les groupes
Cooper et al., 1999	24 SCZ 25 DD	Cocaïne	Pas de différences entre les groupes
Herman et al., 2004	43 SCZ 46 DD	Surtout alcool et cannabis	Moins de déficits exécutifs dans le groupe DD
Joyal et al., 2003	16 DD 14 SCZ	Non spécifiées	Meilleures fonctions exécutives et fluidité verbale dans le groupe DD
Liraud & Verdoux, 2002	35 SCZ 42 troubles de l'humeur	Alcool (n=21) Cannabis (n=21)	Cannabis <> plus de déficits d'attention sélective
Nixon et al., 1996	13 SCZ 13 DD	Alcool	Pas de différences entre les groupes

Pencer & Addington, 2003	138 SCZ 128 DD	Surtout alcool et cannabis	Pas de différences entre les groupes
Serper et al., 2000a	42 SCZ 21 DD	Cocaïne	Plus de déficits de mémoire verbale chez les abuseurs de cocaïne
Serper et al., 2000b	35 SCZ 21 DD	Cocaïne	Idem
Sevy et al., 2001	91 SCZ 27 DD	Surtout alcool et cannabis	Meilleur quotient intellectuel chez le groupe DD
Sevy et al., 1990	35 SCZ 16 DD	Cocaïne	Meilleure mémoire verbale mais moindre attention soutenue chez les SCZ
Smelson et al., 2003a	24 DD 23 SCZ	Cocaïne	Plus de déficits attentionnels et moins de dextérité motrice dans le groupe DD
Smelson et al., 2002	16 DD 17 SCZ	Cocaïne (abstinence de 72 heures)	Moins de déficits attentionnels et plus grande rapidité psychomotrice dans le groupe DD
Stirling et al., 2005	Psychose (n=69)	Avec ou sans cannabis	Cannabis <> meilleur fonctionnement cognitif
Thoma et al., 2006	9 SCZ 9 DD	Alcool	Plus de déficits cognitifs chez le groupe DD

DD= double diagnostic: schizophrénie et toxicomanie; SCZ= schizophrénie

1.2.1.4 Les symptômes extrapyramidaux

Toujours selon l'hypothèse de l'automédication, les schizophrènes seraient portés à consommer des SPA en vue d'obtenir un soulagement des effets secondaires associés à la prise d'antipsychotiques, surtout les symptômes extrapyramidaux (SEP): signes parkinsoniens, dystonie, dyskinésie et akathisie. Sur le plan empirique, peu d'études ont été entreprises en vue d'évaluer l'impact des SPA sur les SEP expérimentés par les schizophrènes. À ce jour, les résultats ont été contradictoires, décrivant à la fois

plus et moins de SEP chez les schizophrènes toxicomanes, comparés aux schizophrènes abstinents (Potvin et al., 2006a; Duke et al., 1994; Van Harten et al., 1998; Soni et al., 1991). À l'instar des résultats des études évaluant la cognition des schizophrènes toxicomanes, la littérature portant sur les symptômes extrapyramidaux des patients comorbides supportent à la fois les modèles d'automédication et vulnérabilité.

1.2.2. Les facteurs neurobiologiques communs à la psychose et la toxicomanie

Depuis quelques années, un certain nombre de psychologues et de psychiatres mettent en doute la validité de l'hypothèse de l'automédication, en raison des faiblesses suivantes:

- L'hypothèse de l'automédication suggère qu'une fois la schizophrénie contrôlée, la consommation de substances psychoactives devrait s'endiguer. Dans les faits, seuls les programmes thérapeutiques ciblant à la fois la psychose et la toxicomanie se révèlent efficaces.
- Les schizophrènes toxicomanes sont généralement peu observants, tant au traitement psychosocial que pharmacologique.
- La consommation de substances psychoactives accroît l'incidence des rechutes psychotiques (Hunt et al., 2002; Linszen et al., 1994). Or, les rechutes induites par les SPA ne découragent pas les schizophrènes de consommer.

Aussi, un nombre croissant de cliniciens et de chercheurs préfère concevoir la comorbidité schizophrénie – toxicomanie sous l'angle de facteurs communs à la psychose et la toxicomanie, tels que les traits de personnalité (Dervaux et al., 2001; Gut-Fayand et al., 2001), l'environnement social (Mueser et al., 2000) et plus particulièrement, des perturbations de systèmes spécifiques de neurotransmission.

1.2.2.1 La sensibilisation dopaminergique

Au lieu de concevoir, comme Khantzian, la toxicomanie comme une réponse secondaire à un symptôme primaire de la schizophrénie, la neurobiologie, en retraçant la voie biologique commune de la schizophrénie et de la toxicomanie, le système mésolimbique de récompense, incite plutôt à penser que la sensibilité aux SPA serait elle-même endogène (primaire) à la pathologie (Chambers et al., 2001). La neurobiologie propose, comme alternative à la perspective de l'automédication, un modèle qui repose sur une compréhension du mode d'action des amphétamines et de leurs effets adverses.

Dans leur usage courant, les amphétamines produisent un état généralisé de vigilance (euphorie, attention accrue, hyperactivité, etc.). Leurs effets contrastent en particulier avec l'émoussement de l'affect, l'apathie, et les autres symptômes négatifs de la schizophrénie. Pourtant, il arrive que les amphétamines induisent en certaines circonstances d'authentiques psychoses, ce que Young et Scoville observent pour la première fois en 1938. À la suite de cette observation, des études sont entreprises au cours des années 1960 et 1970, lesquelles reproduisent expérimentalement la psychose amphétaminique chez des volontaires sains (Angrist et al., 1970 ; Griffith et al., 1969). Ces états psychotiques surgissent à la suite d'une administration répétée de l'amphétamine à dose constante, qui engendre une augmentation graduelle des effets de la substance, ce que l'on désigne comme étant un phénomène de *sensibilisation* (effets plus marqués pour une même dose).

De façon générale, la psychose amphétaminique reproduit très bien les *symptômes positifs* de cette psychopathologie (lignée schneiderienne, *hallucinations auditives* prédominantes). Avant tout, cette psychose reproduit fidèlement les idées

délirantes de nature paranoïde du schizophrène, de sorte que les cliniciens peuvent aisément la confondre avec la *schizophrénie paranoïde* (Potvin et al., 2005b).

L'administration aiguë d'amphétamines chez le rongeur facilite la libération de dopamine dans le système mésolimbique de récompense, lequel se projette de l'aire tegmentaire ventrale (ATV) au nucleus accumbens (NAc) (Gardner, 1997). Après l'administration répétée de l'amphétamine à dose constante, produisant une hypersensibilité aux effets des psychostimulants, on observe une libération accrue de dopamine dans le système de récompense, qui serait elle-même secondaire à une diminution de la libération de dopamine dans le système mésocortical, lequel se projette de l'ATV au cortex préfrontal. Suivant ce modèle animal, l'*hypo*dopaminergie *mésocorticale* pourrait rendre compte de des symptômes négatifs et des déficits cognitifs frontaux de la schizophrénie, alors que l'*hyper*dopaminergie *mésolimbique* serait associée aux symptômes positifs (Grace, 1993); ainsi, la symptomatologie positive serait un état endogène de sensibilisation. [Chez l'humain, les données de la génétique et de la tomographie par émission de positrons (TEP) tendent à confirmer les deux volets de l'hypothèse dopaminergique de la schizophrénie. D'une part, la libération striatale de dopamine en réponse à l'administration d'amphétamines en contexte expérimental est deux fois plus prononcée chez les schizophrènes que chez les sujets sains, surtout en phase aiguë de la psychose (Laruelle et Abi-Dargham, 1999). D'autre part, il existe une corrélation négative entre la régulation à la hausse (*up regulation*) des récepteurs dopaminergiques D_1 dans le cortex préfrontal des patients schizophrènes et leur performance lors des tâches cognitives mesurant les fonctions exécutives (Abi-Dargham, 2002). Enfin, une association a été démontrée entre la schizophrénie et le

polymorphisme de la catéchol-O-méthyltransférase, l'enzyme de dégradation des catécholamines dans le cortex préfrontal (Glatt et al., 2003)].

Lorsqu'il y a une sensibilisation aux amphétamines, on observe donc une *hyper*dopaminergie dans le système de récompense (Pierce & Kalivas, 1997). Or, la majorité des substances psychoactives facilitent, chez l'animal, la libération de dopamine dans ce système (Wise & Rompré, 1989), ce qui semble également être le cas chez l'humain (Boileau et al., 2003; Drevets et al., 2001; Sell et al., 1999). Ces observations suggèrent que le schizophrène serait vulnérable à la récompense induite par les drogues d'abus.

De tous les modèles animaux de la schizophrénie, le plus valide est le modèle de la lésion néonatale de l'hippocampe ventral développé par Lipska et Weinberger (1993). Lorsqu'on effectue une telle lésion, le rongeur lésé affiche, une fois adulte, une sensibilité aux effets du stress, des déficits cognitifs réminiscents de la mémoire de travail humaine, des comportements de retrait social, de même qu'une hypersensibilité aux effets *locomoteurs* des amphétamines (Lipska et Weinberger, 2000). Plus spécifiquement, des recherches récentes démontrent que les rongeurs ainsi lésés s'auto-administrent davantage la cocaïne que les rongeurs sans lésion (Chambers & Self, 2002). Ce qui accrédite l'idée d'une sensibilité du schizophrène aux effets des drogues d'abus.

1.2.2.2 La sérotonine

Outre l'hypothèse dopaminergique, une hypothèse impliquant la sérotonine dans la pathophysiologie de la schizophrénie a été formulée, laquelle repose sur les observations suivantes (Gouzoulis-Mayfrank et al., 1998; Miyamoto et al., 2003; Moghaddam et Krystal, 2003): (i) les hallucinogènes (la psilocybine, le diéthylamide

de l'acide lysergique ou LSD) sont des agonistes des récepteurs 5-HT_{1A} et 5-HT_{2A} de la sérotonine et ils produisent des effets psychotomimétiques [Note : La ressemblance des ces effets avec la phénoménologie de la shizophrénie ne fait toutefois pas consensus (à ce sujet, voir Potvin et al., 2005b)]; (ii) les antipsychotiques de seconde-génération (clozapine, olanzapine, quétiapine et rispéridone) possèdent une affinité supérieure pour les récepteurs 5-HT_{2A} que pour les récepteurs D_2 de la dopamine; (iii) les études post mortem montrent une diminution de la densité corticale des récepteurs 5-HT_{2A} dans la schizophrénie [Note : Cette observation n'a pas été répliquée fidèlement dans les études *in vivo* d'imagerie cérébrale (Lewis et al., 1999)]; et enfin (iv), il existe un lien entre les polymorphismes du gène du récepteur 5-HT_{2A} et la schizophrénie.

Que la sérotonine soit impliquée ou non dans la pathophysiologie de la schizophrénie, elle semble impliquée dans les mécanismes d'action des antipsychotiques de seconde génération (Meltzer et al., 2003; Kapur et Remington, 1996). Chez l'animal, la sérotonine et la dopamine ont des effets généralement opposés. Par exemple, les inhibiteurs sélectifs de la recapture de la sérotonine (ISRS) et les agonistes 5-HT_{2A} inhibent la libération de dopamine dans le striatum et le cortex préfrontal. À l'inverse, l'ajout d'un antagoniste 5-HT_{2A} de forte puissance (*high potency*) à un antagoniste D_2 de faible puissance (*low potency*) facilite la libération de dopamine, notamment dans le cortex préfrontal. Comme ils ont une plus forte affinité pour 5-HT_{2A} que D_2 (voir Tableau 4), les antipsychotiques de seconde génération faciliteraient l'activité dopaminergique dans le cortex préfrontal, et produiraient ainsi leurs effets bénéfiques sur les symptômes négatifs et les déficits cognitifs frontaux de la schizophrénie (nous y reviendrons).

Le rôle de la sérotonine dans le développement de la toxicomanie et dans son traitement est l'un des plus difficiles à cerner. Certes, l'alcool module le récepteur 5-HT_3 de la sérotonine (Johnson et al., 1999), et la cocaïne facilite la libération de sérotonine dans la fente synaptique en bloquant l'activité de son transporteur (Sora et al., 2001). Cela dit, hormis des évidences préliminaires montrant que l'ondansétron, un antagoniste 5-HT_3, soulage les appétences (*craving*) pour l'alcool (Johnson et al., 1999), les médicaments agissant sur la sérotonine (les ISRS, en particulier) se sont avérés inefficaces dans le traitement de l'alcoolisme et de la dépendance à la cocaïne (Torrens et al., 2005).

À notre connaissance, aucun groupe n'a suggéré que la propension à la toxicomanie des schizophrènes pourrait être due à des perturbations de la neurotransmission sérotoninergique. Par contre, un certain nombre de groupes ont suggéré que l'efficacité présumée des antipsychotiques de seconde génération dans le traitement de la toxicomanie des patients schizophrènes serait attribuable à leur action sur les récepteurs de la sérotonine (voir Section 1.3).

1.2.2.3 Les cannabinoïdes endogènes

D'autres systèmes de neurotransmission peuvent agir à titre de courroie biologique entre la schizophrénie et la toxicomanie. Parmi ces systèmes, celui des cannabinoïdes endogènes apparaît commun l'un des systèmes les plus prometteurs. Relayant les effets du cannabis dans le cerveau, ce système, comme nous allons le voir, semble être dysfonctionnel dans la schizophrénie. Il est d'autant plus pertinent que le cannabis est la substance la plus fréquemment consommée chez les schizophrènes traités à l'Hôpital Louis-H Lafontaine (données d'archives non publiées).

L'idée d'un lien entre les effets du cannabis et la santé mentale, la psychose en particulier, n'est pas nouvelle. Elle remonte vraisemblablement aux travaux de Moreau de Tours en 1845 (Moreau de Tours, 1845). De fait, le cannabis peut produire, chez les consommateurs sains, des effets qui s'apparentent au monde de la psychose en général, et de la schizophrénie en particulier. D'abord, le cannabis porte atteinte à la mémoire de travail (Iversen, 2000), laquelle est perturbée chez le schizophrène. De plus, le cannabis produit des illusions perceptuelles (paradigme d'inversion binoculaire) similaires à celles observées chez le schizophrène (Emrich et al., 1997). Le cannabis, à certaines doses, peut même induire de la dépersonnalisation (Mathew et al., 1999), un symptôme qui n'est pas rare chez le schizophrène.

En de rares occasions, le cannabis peut induire d'authentiques psychoses transitoires, qui s'apparentent passablement à la schizophrénie. D'une durée maximale de deux semaines, le trouble psychotique induit par le cannabis se caractérise par des délires francs (paranoïa, grandiosité, etc.), de la dépersonnalisation, des éléments d'hypomanie, une légère désorganisation de la pensée, un léger émoussement de l'affect et des symptômes de la lignée de Schneider (intrusion et diffusion de la pensée). Cette psychose s'accompagne parfois d'hallucinations, tout autant visuelles qu'auditives. On ignore toutefois si le cannabis provoque ces troubles psychotiques seulement chez des sujets qui présentent préalablement des traits schizotypiques, ou s'il peut aussi provoquer de tels épisodes chez des consommateurs sans vulnérabilité.

Dans ses effets chroniques, le cannabis semble provoquer un syndrome amotivationnel, lequel ressemble aux symptômes négatifs de la schizophrénie. Tel que décrit cliniquement, ce syndrome s'accompagne d'apathie, de passivité,

d'indifférence, d'un manque d'ambition ainsi que d'une perte d'intérêt. On ignore cependant si ce syndrome est le produit direct des neuroadaptations induites à long terme par le cannabis ou s'il n'est pas plutôt le reflet d'une certaine contre-culture de l'oisiveté (Johns, 2001).

Des études naturalistes confortent également l'idée d'une parenté entre les effets du cannabis et les symptômes de la schizophrénie. Très récentes, ces études démontrent qu'il existe une corrélation positive entre la consommation de cannabis et la schizotypie (Dumas et al., 2002; Verdoux et al., 2002). De façon générale, plus un sujet consomme régulièrement du cannabis, plus il présente un ensemble de traits associés à la schizophrénie, que ce soit des aberrations perceptives, de l'anhédonie, des pensées magiques ou du retrait social. Reposant sur des statistiques corrélationnelles, ces études ne permettent toutefois pas de déterminer si les traits schizotypiques observés sont primaires ou secondaires à la consommation de cannabis. Il demeure en effet possible que ces sujets, ayant des traits schizotypiques, soient prédisposés à consommer davantage de cannabis.

Comparativement à la population générale, le risque de développer un trouble de consommation de cannabis (abus/dépendance) est environ six fois plus élevé chez le schizophrène (Regier et al., 1990). Cependant, les raisons qui motivent les schizophrènes à consommer continuent de nous échapper. La recherche de nature prospective indique seulement que la fréquence de rechutes psychotiques et d'hospitalisations est plus élevée chez les schizophrènes consommateurs que chez les abstinents (Linszen et al., 1994). Depuis la parution de vastes études populationnelles, nombre de chercheurs pensent même que la consommation chronique de cannabis serait un facteur de risque dans le développement des troubles psychotiques, incluant la schizophrénie. Reprenant les études longitudinales publiées

jusqu'en 2004, deux méta-analyses ont estimé que le risque relatif (« odds ratio ») de développer des symptômes psychotiques est de 2.1 à 2.9 fois plus élevé chez les consommateurs de cannabis (Henquet et al., 2005; Semple et al., 2005).

La robustesse de l'association schizophrénie – cannabis suggère que des facteurs biologiques pourraient rendre compte, partiellement du moins, de celle-ci. La récente découverte du système des cannabinoïdes endogènes (CBE), sur lequel agit le cannabis, rend aujourd'hui possible un tel ordre d'explication. Composé d'au moins deux neuromédiateurs lipidiques, l'anandamide (arachidonlyléthanolamide) et le 2-arachidonylglycerol (2-AG), ainsi que d'un minimum de deux récepteurs, CB_1 et CB_2, le système des CBE est l'un des plus abondants dans le système nerveux central (SNC). On détecte, notamment, de fortes concentrations des récepteurs CB_1 dans des régions aussi diverses que les aires associationnistes du cortex (incluant le cortex préfrontal), l'hippocampe et ses structures associées, l'amygdale ainsi que les noyaux gris centraux (incluant le nucleus accumbens). Par ailleurs, on l'identifie, quoique en moindres concentrations, dans le thalamus, l'hypothalamus, le cervelet, et surtout, dans les aires de la perception de la douleur (nociception). Quant à CB_2, on le trouve surtout en périphérie, dans le système immunitaire, mais on le retrace également dans les cellules gliales du système nerveux central (Ameri, 1999).

Ainsi distribué, ce système serait impliqué à la fois dans les fonctions cognitives supérieures, la mémoire à court terme, le contrôle inhibiteur du mouvement, le soulagement de l'anxiété, les états d'hédonie, ainsi que dans la protection neuronale, la nociception, la thermorégulation et la stimulation de l'appétit. En périphérie, ce système serait impliqué dans le soulagement des inflammations et dans les phénomènes d'immunosuppression (Martin et al., 2002).

En plus de relayer les effets pharmacologiques du cannabis, le système des CBE pourrait être impliqué dans la physiopathologie de la schizophrénie. Quoique préliminaires, certaines observations militent en faveur de cette hypothèse :

- Le système des CBE est fortement concentré dans des régions cérébrales qu'on estime perturbées chez le schizophrène, comme le cortex préfrontal, l'hippocampe ainsi que les noyaux gris centraux.
- Les taux d'anandamide mesurés dans le liquide céphalo-rachidien sont environ deux fois plus élevés chez les schizophrènes que chez les volontaires sains (Giuffrida et al., 2004; Leweke et al., 1999).
- Une étude *postmortem* indique que la densité des récepteurs CB_1, mesurée à l'aide de la tomographie à positrons, est altérée dans le cortex préfrontal dorsolatéral des schizophrènes (Dean et al., 2001).
- Il y aurait une association entre la schizophrénie et le polymorphisme du gène encodant CB_1 (Ujike et al., 2002; Leroy et al., 2001). Fait intéressant: dans l'étude de Ujike et al. (2002), l'association a été seulement observée avec les schizophrènes souffrant d'une toxicomanie.

Cette littérature émergente, suggérant l'existence d'anomalies du système des cannabinoïdes endogènes dans la schizophrénie, laisse présager que les perturbations de ce système, qui relaie dans le cerveau les effets du cannabis, pourraient contribuer à la sensibilité des schizophrènes aux effets du cannabis (Dean et al., 2001; Potvin et al., 2005d; van Os et al., 2002), et possiblement aux autres SPA.

1.2.2.4 Autres systèmes de neurotransmission

Glutamate: L'hypothèse d'un hypofonctionnement des récepteurs N-méthyl-D-asparte (NDMA) du glutamate est l'une des hypothèses pathophysiologiques les plus importantes de la schizophrénie[3]. Cette hypothèse repose sur une série d'observations bien étayées (Javitt et Zukin, 1991; Jentsch et Roth, 1999; (Krystal et al., 1994;): (i)

la phencyclidine (PCP), un antagoniste NMDA, peut produire des psychoses toxiques transitoires chez les consommateurs et une exacerbation psychotique chez les schizophrènes; (ii) des études expérimentales démontrent que l'administration de la kétamine chez des volontaires sains produit des manifestations reproduisant fidèlement les symptômes négatifs et les déficits cognitifs frontaux de la schizophrénie (Note: Le cas des symptômes positifs est controversé.); (iii) les agonistes NMDA (glycine et D-sérine) seraient partiellement efficaces dans le traitement des symptômes négatifs de la schizophrénie (Tuominen et al., 2006); (iv) chez l'humain comme chez l'animal, les anesthésiques dissociatifs facilitent la libération de dopamine dans le striatum; et enfin (v), il y a co-transmission glutamatergique dans les neurones à monoamines, incluant les neurones à dopamine (Trudeau 2003). [Il est à noter que les études menées à l'aide de la TEP ont produit des résultats équivoques en ce qui a trait à des anomalies des récepteurs NMDA dans la schizophrénie (Moghaddam et Krystal, 2003)].

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[3] De plus en plus d'évidences mettent également en relief des anomalies de la neurotransmission cholinergique dans la schizophrénie, impliquant notamment les récepteurs nicotiniques α_7 de l'acétylcholine (références). Il a été suggéré qu'en fumant la cigarette, les patients souffrant de schizophrénie tenteraient de corriger ce fonctionnement anormal du système cholinergique. Des variables liées au tabagisme ont été mesurées dans l'étude pharmacologique décrite dans l'article V de la présente thèse, mais ces variables ont été incluses au mémoire de maîtrise de Nancy Légaré, intitulé « L'effet de la quétiapine sur le profil tabagique des patients schizophrènes ». Aussi, le présent exposé introductif ne fait pas mention des perturbations cholinergiques associées à la schizophrénie.

En plus de relayer dans le SNC les effets des dissociatifs anesthésiques, la neurotransmission glutamatergique serait également impliquée dans les effets de l'alcool, qui module les récepteurs NMDA (Johnson et Ait-Daoud, 1999). À notre connaissance toutefois, aucun groupe n'a postulé que la neurotransmission glutamatergique contribuerait à la sensibilité des schizophrènes pour l'une ou l'autre des SPA. En revanche, rien n'exclut que la sensibilisation dopaminergique, à laquelle certains auteurs attribuent la propension à la toxicomanie des schizophrènes, pourrait être elle-même secondaire à des perturbations glutamatergiques (Chambers et al., 2001).

Opioïdes endogènes: Le système des opioïdes endogènes se compose de trois transmetteurs (l'endorphine, l'enképhaline et la dynorphine) qui se lient à trois principaux récepteurs (*mu*, *delta* et *kappa*) (Borg et Kreek, 2003; Léonard et Vallée, 2002). Les opioïdes endogènes jouent un rôle important dans le système de récompense. Les opiacés produisent une libération de dopamine dans le striatum ventral, indirectement, en agissant comme agonistes des récepteurs *mu* localisés sur des interneurones GABAergiques[4] dans l'ATV (Borg et Kreek, 2003). Quant à l'alcool, son effet renforçateur semble en partie relayé par un effet modulateur sur les opioïdes endogènes (Johnson et Ait-Daoud, 1999). Chez l'humain, ces évidences pré-cliniques se sont traduites par des traitements pharmacologiques dont l'efficacité a été démontrée. En effet, la dépendance et le sevrage aux opiacés sont traités à l'aide de thérapies de substitution (méthadone, buprénorphine) agissant comme agonistes

[4] GABA= acide amino-gamma-butyrique

(partiels) des récepteurs mu (Léonard et Vallée, 2002). De plus, la naltrexone, un antagoniste des récepteurs opioïdergiques a une utilité démontrée dans la prévention des rechutes à l'alcool (Johnson et Ait-Daoud, 1999; Modesto-Lowe et Van Kirk, 1999). Si les évidences actuellement disponibles mettent en relief un rôle fondamental des opioïdes endogènes dans la toxicomanie (surtout dans le cas de l'alcool et des opiacés), en revanche, il n'existe aucune preuve rigoureuse à l'effet que ce système serait dysfonctionnel dans la schizophrénie. En effet, les études ayant mesuré – dans les années 1980 – les taux d'endorphines dans le plasma et dans le liquide céphalo-rachidien chez les schizophrènes ont produit des résultats contradictoires, de même que les études pharmacologiques avec la naltrexone (pour une revue, voir Potvin et al., 2005d).

1.3. Le traitement pharmacologique

D'un point de vue neurobiologique, la schizophrénie et la toxicomanie semblent impliquer des perturbations communes du système de récompense. Au moins trois séries d'observations militent en ce sens: (i) comme il a été démontré chez l'animal et maintenant chez l'être humain, la plupart des SPA facilitent la libération de dopamine dans le système de récompense (Potvin et al., 2005c); (ii) un état d'hyperdopaminergie dans le système de récompense est impliqué dans le processus pathophysiologique des symptômes positifs de la schizophrénie (Laruelle & Abi-Dargham, 1999); (iii) les antipsychotiques, de première ou seconde génération, améliorent les symptômes positifs de la pathologie en bloquant l'activité dopaminergique dans ce même système (Kapur, 2003).

Bloquant les récepteurs D_2 de la dopamine, les antipsychotiques (surtout l'halopéridol et le flupenthixol) diminuent le comportement d'auto-administration de

SPA (surtout la cocaïne) chez le rongeur (Soyka & DeVries, 2000). Quand vient le temps d'évaluer ce potentiel anti-addictif chez l'être humain, il importe toutefois de distinguer les effets des antipsychotiques chez les toxicomanes porteurs ou non d'une psychose associée, car la psychose – la schizophrénie en particulier – semble correspondre à un état endogène de sensibilisation. Au cours des dernières années, des études rigoureuses ont été entreprises auprès de toxicomanes non-psychotiques, en vue d'évaluer le potentiel anti-addictif d'antipsychotiques tels que l'amisulpride, le flupenthixol, l'olanzapine et la rispéridone (Tableau 2). Étonnamment, la plupart de ces études ont mis en relief soit une absence d'effets anti-addictifs ou encore des effets pro-addictifs. Seule exception à la règle: lorsque comparé à la désipramine, le flupenthixol, un antagoniste mixte D_1/D_2, s'est avéré efficace dans le traitement de la cocaïnomanie. Cependant, il a été découvert ultérieurement que les patients traités au flupenthixol avaient arrêté la cocaïne principalement en raison de sévères réactions d'akathisie (Gawin et al., 1996).

Ces résultats paradoxaux mettent en lumière les limites des modèles animaux de la toxicomanie, qui s'intéressent principalement aux effets aigus des SPA. À ce titre, il est intéressant de noter que l'administration *aiguë* de l'halopéridol, avant et pendant la période d'habituation aux stimulants, *atténue* leurs effets renforçateurs, alors que son administration *chronique*, dans les mêmes conditions, *augmente* au contraire leurs propriétés renforçatrices (Kosten, 1997; Kosten et al., 1996; LeDuc & Mittleman, 1993).

Tableau 2. L'impact des antipsychotiques chez les toxicomanes non-psychotiques

Auteurs	Type d'étude	Médication(s)	Patients	Durée	Résultats
Grabowski et al., 2000	Double insu	Rispéridone Vs placebo	125 cocaïnomanes	12 semaines	Plus de problèmes de rétention avec le rispéridone (2 & 8 mg)
Grabowski et al., 2004	Double insu	Rispéridone Vs placebo	120 cocainemanes	26 semaines	Pas de différences entre le rispéridone et le placebo
Guardia et al., 2004	Double Insu	Olanzapine vs placebo	60 alcooliques	12 semaines	Pas de differences dans les taux de rechute
Kampman et al., 2003	Double insu	Olanzapine Vs placebo	30 cocaïnomanes	12 semaines	Olanzapine → plus faible taux d'abstinence
Khalsa et al., 1994	Double insu	Flupenthixol Vs désipramine	63 cocaïnomanes ("crack")	6 semaines	Diminution des *craving* pour la cocaïne
Marra et al., 2002	Double Insu	Amisulpride Vs placebo	71 alcooliques	6 mois	Amisulpride → plus de rechutes et de *craving* / plus faible taux d'abstinence
Wiesbeck et al., 2001	Double insu	Flupenthixol Vs placebo	281 alcooliques	6 mois	Flupenthixol → plus de rechutes

1.3.1. L'efficacité des antipsychotiques chez les psychotiques toxicomanes

En raison de leur fort antagonisme D_2, les antipsychotiques conventionnels comme l'halopéridol devraient être utilisés dans le traitement de la toxicomanie des schizophrènes. Dans l'ensemble, on observe toutefois que l'usage thérapeutique de l'halopéridol, mais également des autres antipsychotiques conventionnels

n'améliorent pas le profil de consommation des schizophrènes (Dixon et al., 1991; Brady et al., 1990). Parmi les antipsychotiques conventionnels, le flupenthixol, un antipsychotique possédant des propriétés anti-dépressives, a démontré des résultats encourageants. Une étude pilote ainsi que deux études ouvertes, menées auprès de petits échantillons, ont rapporté des résultats suggérant que le flupenthixol pourrait soulager la toxicomanie de ces patients (Soyka et al., 2003; Levin et al. 1998; Schilkrut et al., 1988).

Jusqu'ici les résultats les plus prometteurs chez les schizophrènes toxicomanes ont été obtenus avec la clozapine (Tableau 3). Prototype des antipsychotiques dits atypiques, la clozapine a ceci de particulier qu'elle réduit généralement, mais augmente parfois, les effets renforçateurs de la cocaïne chez l'animal (Roberts & Vickers, 1984; Kosten & Nestler, 1994; Vanover et al., 1993; Loh et al., 1992) et le cocaïnomane (Farren et al., 2000). Faisant échos à ces observations, plusieurs études de cas, ainsi que des observations naturalistes suggèrent que la clozapine pourrait contrer l'abus de substances psychoactives chez les psychotiques toxicomanes (Tsuang et al., 1999; Lee et al., 1998; Buckley, 1998; Albanese et al., 1994; Yovell & Opler, 1994). Cela semble corroborer par deux études rétrospectives et deux études prospectives menées auprès de schizophrènes toxicomanes (Brunette et al., 2006; Green et al., 2003; Zimmet et al., 2000; Drake et al., 2000). La littérature suggère que la clozapine serait particulièrement efficace dans le traitement du tabagisme chez les schizophrènes (McEvoy et al., 1999, 1995a; George et al., 1995), contrairement à l'halopéridol, qui semble en promouvoir l'abus (McEvoy et al., 1995b). Cependant, la seule étude à double insu menée à ce jour n'a pas démontré de profil avantageux de la clozapine dans le traitement du tabagisme des schizophrènes (de Leon et al., 2005).

Partageant des propriétés cruciales avec la clozapine (voir Tableau 4), l'olanzapine, la rispéridone et la quétiapine ont montré des résultats eux aussi prometteurs, à l'occasion d'études ouvertes. Récemment, trois études mieux contrôlées sont venues accréditer ces résultats encourageants: (i) dans une étude à double insu menée auprès de 31 schizophrènes dépendants à la cocaïne, l'olanzapine s'est avérée supérieure à l'halopéridol, au terme d'un traitement de 6 semaines, dans le soulagement des *craving* (ou appétences) induits par des indices (« cues ») évoquant les effets de la cocaïne (Smelson et al., 2006); (ii) dans une étude à double insu menée auprès de 24 schizophrènes abuseurs de cocaïne, le traitement à l'olanzapine (26 semaines) s'est accompagné d'une *diminution* de la proportion de dépistages urinaires positifs de benzoylecgonine (métabolite de la cocaïne), alors que le traitement à l'halopéridol s'est accompagné d'une *augmentation* des dépistages urinaires positifs. Paradoxalement toutefois, le groupe traité à l'halopéridol présentait moins d'appétences à la fin de l'étude que les patients sous olanzapine (Sayers et al., 2005); (iii) une étude a comparé l'évolution de 24 patients psychiatriques (incluant 22 psychotiques), dépendants aux psychostimulants, et traités avec un antipsychotique de première génération. Après randomisation, 12 patients ont poursuivi leur traitement, alors qu'il fut arrêté chez les 12 autres patients. Dans ce second groupe, la quétiapine a été introduite au besoin chez 8 patients. Au terme des 12 semaines de traitement, une réduction significative des *craving* était noté chez ces 8 patients, mais pas dans l'autre groupe, ni chez les 4 patients non traités (Brown et al., 2003).

Au fil des ans, ces résultats prometteurs des antipsychotiques de seconde génération auprès des schizophrènes toxicomanes ont pavé la voie à un effort de

modélisation théorique des bénéfices potentiels des "atypiques" auprès de la clientèle comorbide.

Tableau 3: L'impact de clozapine, l'olanzapine et la quétiapine chez les patients souffrant de psychose et de toxicomanie.

CLOZAPINE

Auteurs	Type d'étude	Population	Durée	Résultats
Brunette et al., 2006	Prospective (clozapine vs autres anti-psychotiques)	95 SCZ/SA : Substances mixtes	10 ans	Clozapine → moins de rechutes
Drake et al., 2000	Prospective	34 SA: alcool (n=22) drogue (n=13)	6-36 mois	"On" vs "off" clozapine → ↓ de la sévérité de l'alcoolisme
De Leon et al., 2005	Double insu (haloperidol)	38 SCZ : Tabagisme	Donnée manquante	Pas d'amélioration
George et al., 1995	Rétrospective	18 SCZ : Tabagisme	Moyenne de 14 mois	Moindre usage de tabac
Green et al., 2003	Rétrospective (clozapine vs rispéridone)	41 SCZ: Alcool & cannabis	> 1 an	Clozapine → plus haut taux d'abstinence
McEvoy et al., 1995a	Ouverte	12 SCZ	12 semaines	12% de réduction de consommation
McEvoy et al., 1999	Ouverte	35 SCZ	12 semaines	11% de réduction
Procyshyn et al., 2002	Étude comparative (tabagisme)	14 SCZ / SA : rispéridone avec ou sans clozapine		Clozapine → plus faibles taux de monoxyde de carbone
Zimmet et al., 2000	Rétrospective	43 SCZ: 18 alcool /	> 3 ans	Réduction de la consommation

		3 cannabis 12 cocaïne 22 polytoxico		chez plus de 85 % des patients

OLANZAPINE

Bano et al., 2001	Programme de méthadone	21 SCZ: cocaïne et héroïne	14 mois	Moindre consommation de cocaïne chez 11 patients
Littrell et al., 2001	Étude pilote	30 SCZ: alcool et cocaïne	12 mois	Rémission complète chez 21 patients
Noorsdy & O'Keefe, 1999	Pilote	67 psychotiques	6 mois	Réduction de 15 à 20 % de la sévérité de la toxicomanie
Noorsdy et al., 2001	"switch" (avec psycho-thérapie)	52 psychotiques: alcool (n=30) drogue (n=22)	6 mois	Baisse significative de la sévérité de la toxicomanie
Sayers et al., 2005	Double insu (haloperidol)	24 SCZ: Cocaïne	26 semaines	Moins de déspistage urinaires positifs mais plus de *craving*
Smelson et al., 2006	Double insu (haloperidol)	31 SCZ: Cocaïne	6 semaines	Moins de *craving* induits par des indices (« cues »)

QUÉTIAPINE

Brown et al., 2003	Randomisée (typique vs quétiapine)	22 psychotiques 2 dépressifs: cocaïne et amphétamines	12 semaines	Réduction significative des *craving*

Brown et al., 2002; Longoria et al., 2004	Ouverte (quétiapine en adjuvant)	Trouble bipolaire (n=17): cocaine (alcool)	12 semaines	Réduction significative des *craving* et de l'argent dépensé

RISPÉRIDONE

Smelson et al., 2002b	Comparative (rispéridone vs typiques)	18 SCZ: cocaïne	6 semaines	Rispéridone <> moins de *craving* pour la cocaïne

Note: Le tableau 3 n'inclut pas les multiples études de cas publiées sur le sujet.
SCZ = schizophrénie; SA = trouble schizoaffectif

1.3.2. Hypothèses neuropharmacologiques

Comme le démontre le Tableau 4, la clozapine, l'olanzapine, la rispéridone et la quétiapine sont des médications qui possèdent une affinité pour un nombre élevé de récepteurs pharmacologioques. Étant donné cette complexité, plusieurs hypothèses ont été proposées en vue de rendre compte du caractère « atypique » des ces antipsychotiques, et de façon similaire, de leur efficacité présumée chez les patients comorbides.

Tableau 4: Le profil d'affinités de l'halopéridol, de la clozapine, l'olanzapine et la quétiapine

	D1	D2	D4	$5HT_{1a}$	$5HT_{2a}$	$5HT_3$	α_1	α_2	H_1	M
Cerveau du rongeur[1-5]										
Halopéridol	+++	++++	+++	Nil	++	Nil	++	Nil	Nil	Nil
Clozapine	+(+)	++	+++	+	+++	++	+++	++	+++	+++(+)
Olanzapine	++	+++	++(+)	(+)	+++(+)	++	+++	++	+++	+++
Quétiapine	+	+(+)	Nil	+	++	++	+++	(+)	++(+)	+(+)
Rispéridone	+(+)	+++	+++	+(+)	++++	Nil	+++	+++	+++	Nil
Cerveau humain: études postmortem[6]										
Halopéridol	---	+++	---	+	++	---	+++	+	+(+)	Nil
Clozapine	---	++(+)	---	++	+++	---	+++	+++	+++	+++
Olanzapine	---	+++	---	+	+++(+)	---	++(+)	+(+)	++++	+++
Quétiapine	---	+	---	++(+)	++	---	+++	++	+++	+
Rispéridone	---	+++	---	++	++++	---	+++	+++	+++	Nil

D_1= récepteur dopaminergique D_1; D_2= récepteur dopaminergique D_2; D_4= récepteur dopaminergique D_4; $5\text{-}HT_{1a}$= récepteur $5\text{-}HT_{1a}$ de la sérotonine; $5\text{-}HT_{2a}$= récepteur $5\text{-}HT_{2a}$ de la sérotonine; $5\text{-}HT_3$= récepteur $5\text{-}HT_3$ de la sérotonine; α_1= récepteur α_1 de la norépinéphrine; α_2= récepteur α_2 de la norépinéphrine; H_1= récepteur H_1 de l'histamine; M= récepteurs muscariniques

++++: très forte affinité (< 1 nM); +++: forte (1-20 nM); ++: modérée (21-150 nM); +: faible (150-1000 nM); nil= absence d'affinité (> 1000 nM)

[1] Arnt & Skarsfeldt, 1998; [2] Schotte et al., 1996; [3] Ashby & Wang, 1996; [4] Bymaster et al., 1996; [5] Saller & Salama, 1993; [6] Richelson & Souder, 2000

1.3.2.1. Sélectivité mésolimbique

Le système de récompense semble impliqué dans la pathophysiologie de la schizophrénie et de la toxicomanie. Or, un certain nombre de paradigmes expérimentaux (exemple: paradigme de l'hyperdépolarisation) (pour plus d'informations, voir Potvin et al., 2003b), développés chez l'animal, démontrent que la clozapine, l'olanzapine et la quétiapine agisse de façon préférentielle sur ce système, au détriment du système nigrostriatal, dont les neurones dopaminergiques se projettent de la "substantia nigra pars compacta" (SNpc) jusqu'au néo-striatum (putamen et noyau caudé) (Cooper et al., 1996). De façon similaire, des données préliminaires obtenues chez l'humain démontrent que l'occupation des récepteurs D_2 par la clozapine ou la quétiapine est supérieure dans le système limbique que dans le

striatum, alors que l'occupation de ces récepteurs par l'halopéridol est équivalente dans ces régions (Stephenson et al., 2000).

1.3.2.2. Dissociation rapide de D_2

Conformément à leur sélectivité mésolimbique, les antipsychotiques de seconde génération (surtout la clozapine et la quétiapine) induisent peu ou pas, dans la pratique clinique, de symptômes extrapyramidaux (SEP), une observation maintenant corroborée par voie de méta-analyse (Geddes et al., 2000). Or, les schizophrènes consomment possiblement en vue de soulager ces effets secondaires désagréables (dysphorie et SEP) (Schneier & Siris, 1987). L'action préférentielle sur le système de récompense apparaît comme une condition nécessaire au traitement de la toxicomanie du schizophrène. Il importe toutefois que cette action soit bénéfique, et non pas dommageable. Depuis les travaux classiques de Wise chez le rongeur, on soupçonne que les antipsychotiques tels que l'halopéridol, en raison de leur fort antagonisme D_2, induisent de l'anhédonie ou une perte de motivation (Wise, 1982, 1985). Cela ne semble pas être le cas avec la clozapine (Wiley, 1990). Incidemment, la dysphorie induite par les neuroleptiques pourraient être l'un des déclencheurs de l'abus de substances chez le schizophrène (Voruganti & Awad, 2004; Voruganti et al., 1997). Or, les antipsychotiques atypiques, incluant la clozapine, l'olanzapine, le rispéridone et la quétiapine, produisent moins de dysphorie que les antipsychotiques conventionnels (Voruganti et al., 2000). De surcroît, la clozapine soulagerait l'anhédonie des schizophrènes (Miller et al., 1994), ce qui semble moins clair en ce qui concerne l'olanzapine, le rispéridone et la quétiapine (Tollefson & Sanger, 1997; Borison et al., 1996). Finalement, il a été démontré, à l'aide de la tomoscintigraphie (imagerie SPECT) qu'il y a une corrélation positive entre l'occupation des récepteurs

D_2 et la propension d'un antipsychotique à induire de la dysphorie chez le schizophrène. Plus précisément, la dysphorie est principalement observée quand l'occupation de D_2 est supérieure à 78 % (Bressan et al., 2002; Seeman, 2002). La plupart des antipsychotiques de seconde génération (surtout la clozapine et la quétiapine) ont une occupation de D_2 inférieure à celle des antipsychotiques conventionnels (Gefvert et al., 2001; Nordström et al., 1995). Tout semble indiquer que ce serait dû au fait que ces antipsychotiques se dissocient plus rapidement de D_2 (Kapur et al., 2000; Kapur & Seeman, 2000; Seeman & Tallerico, 1999). En somme, ce caractère pulsatile pourrait protéger le système de récompense de la même façon qu'il semble protéger le système extrapyramidal (Küfferle et al., 1997) [Note : Ces études en imagerie cérébrale n'avaient pas la résolution spatiale nécessaire pour distinguer la partie ventrale du striatum, liée à la dysphorie, de la partie dorsale, laquelle est liée aux SEP].

1.3.2.3 Le système des cannabinoïdes endogènes

Hormis la dopamine, d'autres neurotransmetteurs jouent un rôle clé dans l'effet renforçateur des SPA, incluant les opioïdes et les cannabinoïdes endogènes (Wise et al., 2002). Comme nous l'avons vu précédemment, le système des cannabinoïdes endogènes semblent fonctionner anormalement dans la schizophrénie, alors que les évidences relatives aux opioïdes endogènes sont contradictoires. À notre connaissance, aucun antipsychotique n'agit directement sur les récepteurs cannabinoïdes. Toutefois, il a été récemment démontré que la clozapine, contrairement à l'halopéridol, modulait la sensibilité des récepteurs CB_1 dans le noyau accumbens (Sundram et al., 2005). Partant de ce constat, Sundram et ses collègues (2005) ont émis l'hypothèse que la clozapine pourrait produire ses effets

bénéfiques chez les schizophrènes toxicomanes en modulant l'activité des cannabinoïdes endogènes dans le système de récompense.

1.3.2.4. Le récepteur 5-HT$_3$ de la sérotonine

Rien, dans ce qui précède, ne suggère que la clozapine, l'olanzapine et la quétiapine constitueraient d'authentiques médications anti-addictives. À ce jour, seuls la naltrexone (un antagoniste des récepteurs opioïdes) et à un moindre degré l'ondansetron (un antagoniste sélectif 5-HT$_3$) se sont avérées de véritables médications anti-addictives. Il s'agit de deux médicaments dont l'efficacité a été démontrée chez le rongeur, qui soulagent les appétences pour l'alcool (Johnson et al., 2002 ; Volpicelli et al., 1995). De façon notable, tant Wilkins que Buckley postulent que des antagonistes 5-HT$_3$ pourraient aider les schizophrènes toxicomanes (Buckley 1998; Wilkins, 1997). En droite lignée avec cette hypothèse, il y a lieu de remarquer que la clozapine, l'olanzapine et la quétiapine agissent spécifiquement sur ce récepteur, contrairement aux antipsychotiques conventionnels (Bymaster et al., 1996). Mentionnons toutefois que l'affinité de ces trois antipsychotiques pour 5-HT$_3$ est modérée (voir Tableau 4). De plus, si l'olanzapine agit à titre d'antagoniste sur ce récepteur (Bymaster et al., 2001), il reste à établir si la clozapine et la quétiapine sont des agonistes ou des antagonistes de ce même récepteur. Le fait qu'ils agissent sur ce récepteur représente néanmoins une avenue de recherche prometteuse.

1.3.3. L'automédication

Jusqu'ici, l'emphase a été mise sur le système de récompense, ce qui présuppose que les schizophrènes consomment des SPA en raison de leur sensibilité aux effets renforçateurs de ces psychotropes. Mais au lieu d'approcher la comorbidité

schizophrénie – toxicomanie en termes de renforcement *positif*, la plupart des auteurs adopte plutôt l'hypothèse d'automédication de Khantzian, qui se base sur le concept de renforcement *négatif*. Selon cette hypothèse, les schizophrènes n'abuseraient pas des substances psychoactives en vue d'éprouver du plaisir mais dans le but de soulager le malaise associé à leur symptomatologie (Khantzian, 1997). Plus précisément, les schizophrènes tenteraient de soulager leurs symptômes négatifs, leurs affects anxio-dépressifs et leurs déficits cognitifs.

1.3.3.1. Les symptômes négatifs

Dans la mesure où l'hypothèse de Khantzian est vraie, la supériorité de la clozapine par rapport à l'halopéridol dans le traitement des symptômes négatifs, maintenant confirmée par méta-analyse (Chakos et al., 2001), pourrait représenter un avantage dans le traitement des schizophrènes toxicomanes. Dans le cas de l'olanzapine et du rispéridone, une évidence grandissante suggère que ces antipsychotiques seraient plus efficaces que les antipsychotiques conventionnels dans le traitement de ces symptômes (Tollefson & Sanger, 1997; Bhana et al., 2001; Davis & Chen, 2002). En ce qui a trait à la quétiapine, même si sa supériorité demeure à démontrer (Arvinitis et al., 1997), cette médication semble corriger les patrons d'activation cérébrale, mesurés en imagerie par résonance magnétique fonctionnelle (IRMf), des schizophrènes en cours d'une tâche de traitement émotionnel (Stip et al., 2005).

La modélisation animale suggère qu'une hypoactivité du système mésocortical (voir section 1.2.2.) serait à l'origine des symptômes négatifs de la schizophrénie (Davis, 1991; Weinberger, 1987). Conformément à leur efficacité clinique, des données robustes démontrent que la clozapine, l'olanzapine et le rispéridone facilitent la libération de dopamine dans le cortex préfrontal chez

l'animal, contrairement aux neuroleptiques conventionnels comme l'halopéridol (Volonté et al., 1997; Heidbreder et al., 2001; Westerink et al., 1998). Notons que dans le cas de la quétiapine, une étude sur deux démontre un tel effet (Volonté et al., 1997; Ichikawa et al., 2002).

1.3.3.2. Les affects anxio-dépressifs

Lorsqu'on leur demande, les schizophrènes rapportent consommer en vue de soulager leurs affects négatifs (stress, anxiété et dépression) (Addington & Duchak, 1997; Dixon et al., 1991). Incidemment, la clozapine, l'olanzapine et la quétiapine exercent une action bénéfique sur l'humeur des schizophrènes, ce qui ne semble pas être le cas avec les neuroleptiques traditionnels (Tollefson et al., 1998; Breier et al., 1999; Purdon et al., 2001; Davis & Chen, 2002). Cette propriété de la clozapine, l'olanzapine, le rispéridone et la quétiapine peut être attribuée au fait que ces antipsychotiques affectent plusieurs récepteurs de la sérotonine (5-HT) et de la norépinéphrine (NÉ), et qu'ils exercent un effet modulateur sur les hormones du stress (Hatzimanolis et al., 1998; Cohrs et al., 2004).

1.3.3.3. La cognition

Les antipsychotiques de première génération ont généralement peu d'effets bénéfiques sur la cognition. En raison de leur fort antagonisme des récepteurs D_2 de la dopamine au niveau du striatum, ces antipsychotiques pourraient avoir un impact délétère sur la mémoire procédurale. Qui plus est, ces antipsychotiques nécessitent régulièrement la prescription concomitante d'anticholinergiques, en raison des effets extrapyramidaux qu'ils induisent. Or, les anticholinergiques sont généralement néfastes pour la cognition, en particulier pour la mémoire.

La recherche psychopharmacologique suggère que les antipsychotiques atypiques auraient, au contraire, un impact positif sur la cognition des schizophrènes. Prototype de ces antipsychotiques, la clozapine a été évaluée pour son impact neurocognitif chez les schizophrènes, à l'occasion d'une quinzaine d'études pharmacologiques. De façon générale, cette littérature suggère que la clozapine serait efficace dans le traitement des déficits de fluidité verbale (surtout), de vitesse motrice et des fonctions exécutives, mais également de la mémoire verbale (Meltzer & McGurk, 1999; Keefe et al., 1999). Par contre, la clozapine aurait un impact négatif sur la mémoire de travail verbale. Dans le cas de l'olanzapine, les améliorations cognitives les plus substantielles sont notées du côté des fonctions exécutives. Cet antipsychotique semble améliorer, par ailleurs, la fluidité verbale, la mémoire verbale et la mémoire visuelle, mais également l'attention des schizophrènes (Sharma et al., 2003; Stip et al., 2003; Bilder et al., 2002). En ce qui a trait au rispéridone, cet antipsychotique améliore les fonctions exécutives, la mémoire de travail, l'attention et la mémoire verbale, mais également la vitesse motrice. Cet antipsychotique ne corrige toutefois pas les déficits de fluidité verbale. Par ailleurs, la rispéridone pourrait être néfaste à la mémoire procédurale, en raison de sa forte affinité pour D_2 (Harvey et al., 2003; Kasper & Resinger, 2003). À l'instar des autres atypiques, l'impact neurocognitif de la quétiapine semble avantageux, même s'il est moins bien documenté (Velligan et al., 2002; Purdon et al., 2001). La quétiapine semble exercer un effet bénéfique sur la fluidité verbale et l'attention, mais également les fonctions exécutives et la mémoire verbale.

Si on se fie à la littérature préliminaire publiée jusqu'ici, il demeure difficile de prédire si les antipsychotiques de seconde génération possèdent bel et bien des propriétés anti-addictives. En revanche, ces médicaments s'avèrent d'utiles agents

pharmacologiques en vue de mettre à l'épreuve, de façon prospective, la validité de l'hypothèse de l'automédication, en raison de leur efficacité dans le traitement des symptômes négatifs, des déficits cognitifs et des affects anxio-dépressifs.

Objectifs de la thèse

Objectifs généraux

Au moment d'entreprendre les travaux inclus dans cette thèse, il existe trois grandes séries de données probantes par rapport à la comorbidité « schizophrénie – toxicomanie » étant reconnues par la majorité des chercheurs dans le domaine :

1) la prévalence à vie d'un trouble de consommation (abus ou dépendance) de l'une ou l'autre des principales substances psychoactives est élevée dans la schizophrénie ;
2) la toxicomanie chez les patients schizophrènes est associée à une panoplie de conséquences néfastes: rechutes psychotiques, hospitalisations, épisodes dépressifs, idées suicidaires, problèmes d'observance, criminalité, problèmes de logement, d'emploi et de santé, etc. ;
3) les services intégrés traitant à la fois la schizophrénie et la toxicomanie sont plus efficaces que les traitements parallèles ou séquentiels.

Si l'on aborde les relations entre schizophrénie et toxicomanie du point de vue de la recherche clinique, il peut y avoir deux grandes approches académiques. L'une de ces approches entreprend d'examiner un aspect très spécifique, restreint, mais qui a finalement du mal à rendre compte d'une relation qui est en fait très complexe. L'autre approche est favorable à un regard plus large, envisageant les pièces d'un puzzle qui n'ont pas tendance à se rassembler facilement, en raison de paradigmes différents, de technologies éloignées ou de disciplines (la psychiatrie et la toxicomanie) généralement imperméables les unes par rapport aux autres. Les deux approches comportent leur lot d'avantages et d'inconvénients. Le côtoiement de mes maîtres, qui sont demeurés des cliniciens tout en oeuvrant en recherche, m'ont incité à choisir la seconde approche. Celle-ci reflète la complexité de saisie d'une double

condition qui tient compte d'un construit approximatif (hétérogénéité de la schizophrénie), d'une versatilité dans l'usage des substances psychoactives (hétérogénéité des substances), et d'une difficulté liée à la faisabilité des essais cliniques dans le domaine. Dans ce contexte, nous avons décidé d'entreprendre une série de travaux par rapport à cinq enjeux précis relatifs à la comorbidité schizophrénie – toxicomanie, où il y avait un manque de données probantes ou un manque de consensus parmi les cliniciens et chercheurs dans le domaine, au moment d'entreprendre nos travaux. Ces cinq enjeux sont les suivants :

1) les patients souffrant de schizophrénie et de toxicomanie ont-ils des symptômes négatifs moins sévères que les patients non-toxicomanes ?
2) les patients souffrant de schizophrénie et de toxicomanie ont-ils plus ou moins de déficits cognitifs ?
3) les patients avec un double diagnostic ont-ils davantage de symptômes extrapyramidaux ?
4) les antipsychotiques de seconde génération soulagent-ils la toxicomanie des patients avec un double diagnostic ?
5) existe-t-il, sur le plan neurobiologique, un dénominateur commun entre la schizophrénie et la toxicomanie, impliquant la dopamine, les cannabinoïdes endogènes et/ou les hormones du stress ?

Objectifs par articles

Les 7 articles inclus dans la présente thèse explorent l'un ou l'autre de ces cinq enjeux.

1[er] article Potvin S, Sepehry AA, Stip E. A meta-analysis of negative symptoms in dual diagnosis schizophrenia. *Psychological Medicine* 2006; 36(4):431-40.

Objectif: Déterminer si les schizophrènes toxicomanes ont moins de symptômes négatifs que les schizophrènes non-toxicomanes, par voie d'une méta-analyse

d'études transversales évaluant les symptômes négatifs à l'aide de la « Scale for the Assesment of Negative Symptoms ». (voir Enjeu #1)

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2e article Potvin S, Mancini-Marië A, Fahim C, Mensour B, Stip E. Processing of social emotion in patients with schizophrenia and substance use disorder. *Social Neuroscience*; Accepté

Objectifs: (i) Déterminer si les schizophrènes toxicomanes ont une plus forte réaction émotionnelle en réponse à des stimuli émotionnels de nature sociale; (ii) vérifier à l'aide de l'imagerie par résonance magnétique fonctionnelle si cette réaction accrue se traduit par de plus grandes activations du cortex préfrontal. (voir Enjeu #1)

*

3e article Potvin S, Briand C, Prouteau A, Bouchard RH, Lipp O, Lalonde P, Nicole L, Lesage A, Stip E. CANTAB explicit memory is less impaired in addicted schizophrenia patients. *Brain and Cognition* 2005; 59 (1): 38-42.

Objectif: Déterminer si les schizophrènes toxicomanes ont plus ou moins de déficits cognitifs que les schizophrènes abstinents, à l'occasion d'une étude transversale où la cognition est mesurée à l'aide de la batterie CANTAB (Cambridge Neuropsychological Tests Automated Battery). (voir Enjeu #2)

*

4e article Potvin S, Pampoulova T, Mancini-Marië A, Lipp O, Bouchard RH, Stip E. Increased extrapyramidal symptoms in patients with schizophrenia and a comorbid substance use disorder. *Journal of Neurology, Neurosurgery and Psychiatry* 2006; 77 (6): 796-8. (voir Enjeu #3)

Objectif: Déterminer si les schizophrènes toxicomanes ont davantage de symptômes extrapyramidaux que les schizophrènes non-toxicomanes, à l'occasion d'une étude transversale.

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5e article Potvin S, Stip E, Lipp O, Mancini-Marië, Élie R, Demers MF, Roy MA, Bouchard RH, Gendron A. Quetiapine in patients with schizophrenia-spectrum and substance use disorders: an open-label trial. *Current Medical Research & Opinion* 2006; 22 (7): 1277-1285. (voir Enjeu #4)

Objectif: Dans la perspective de l'automédication, mettre à l'épreuve la quétiapine, un antipsychotique de seconde génération, chez des schizophrènes toxicomanes, à l'occasion d'une étude ouverte d'une durée de 12 semaines. Au moment d'entreprendre cette étude, les meilleures évidences chez les patients avec un double diagnostic sont celles obtenues avec la clozapine, mais ce médicament s'accompagne d'un risque de développer de l'agranulocytose. Dans ce contexte, nous avons plutôt décidé de mettre à l'épreuve la quétiapine, car elle présente un profil pharmacologique analogue à la clozapine (dissociation rapide de D_2; ratio 5-HT_{2A}/D_2, agonisme $5HT_{1A}$) et qu'elle a des effets similaires sur les symptômes négatifs, la cognition et les affects anxio-dépressifs, sans induire de symptômes extrapyramidaux. De plus, nous avions des résultats préliminaires suggérant une efficacité potentielle de la quétiapine dans le traitement de la dépendance au cannabis (voir Annexe II).

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6e article Potvin S, Lipp O, Roy MA, Demers MF, Bouchard RH, Stip E. Predictors of substance abuse and psychiatric symptoms in addicted schizophrenia patients. *Psychopathology*; Soumis (voir Enjeu #1)

Objectifs: À l'occasion d'une étude prospective de 12 semaines menée auprès de patients avec un double diagnostic, identifier les prédicteurs cliniques de l'évolution

de la toxicomanie dans le temps; inversement, déterminer si la toxicomanie est un prédicteur de l'évolution clinique des patients.

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7e article Potvin S, Kouassi E, Lipp O, Roy MA, Demers MF, Bouchard RH, Gendron A, Arista G, Piomelli D, Stip E. Endogenous cannabinoids in patients with schizophrenia and substance use disorder during quetiapine therapy. *Psychopharmacology;* Soumis (voir Enjeu # 5)

Objectif: Conformément à l'hypothèse d'une sensibilité biologique des schizophrènes aux effets des substances psychoactives, déterminer si les perturbations du système des cannabinoïdes endogènes dans la schizophrénie permettent de prédire l'évolution de la toxicomanie chez ces patients. En plus de relayer les effets du cannabis dans le cerveau, des évidences suggèrent que le système des cannabinoïdes endogènes est dysfonctionnel dans la schizophrénie. Renforçant l'intérêt de ce système, des données non publiées montrent que le cannabis est la substance psychoactive la plus fréquemment consommée par les patients souffrant de schizophrénie traités à l'hôpital Louis-H Lafontaine[1].

[1] Au moment d'entreprendre les travaux de la thèse, deux systèmes biologiques avaient été proposés comme dénominateur commun neurobiologique à la schizophrénie et à la toxicomanie : le système dopaminergique et les cannabinoïdes endogènes. Dans nos séries de travaux, nous n'avons pas exploré le rôle de la dopamine, car cela aurait nécessité un examen de tomographie par émission de positrons, ce qui aurait entraîné des frais supplémentaires substantiels. Par ailleurs, nous avons mesuré les taux de cortisol des patients, mais plusieurs échantillons ont été perdus pour des raisons pratiques.

1er article

A meta-analysis of negative symptoms in dual diagnosis schizophrenia.

Stéphane Potvin, Amir Ali Sepehry, Emmanuel Stip.

Centre de recherche Fernand-Seguin, Hôpital Louis-H Lafontaine; Department of Psychiatry, Faculty of Medicine, University of Montreal.

Running title

Negative symptoms in dual diagnosis schizophrenia

Corresponding author

Emmanuel Stip; MD, MSc, CSPQ; Centre de recherche Fernand-Seguin; 7331 rue Hochelaga; Montréal, Québec, Canada; H1N 3V2; Tél : (514) 251-4015; Fax: (514) 251-2617; [redacted]

Abstract

Background According to the self-medication hypothesis, schizophrenia patients would abuse psychoactive substances to get a relief from their negative symptoms. Studies testing the self-medication hypothesis in dual diagnosis (DD) schizophrenia have not been conclusive, with some studies showing that dual diagnosis patients experience less negative symptoms, whereas other studies have failed to detect such differences. One potential confounding factor for this discrepancy lies in the diverse scales used to evaluate the negative symptoms. A systematic quantitative review of the literature using computerized search engines has been undertaken. **Methods** Studies were retained in the analysis if: (i) they assessed negative symptoms using the SANS; (ii) groups of schizophrenia patients were divided according to substance use disorders (alcohol, amphetamines, cannabis, cocaine, hallucinogens, heroin and phencyclidine). **Results** Attainable published studies were screened. According to our inclusion criteria, 18 possible studies emerged. Data from 11 studies were available for mathematical analysis. A moderate effect size (Total N= 1135; 451 DD; 684 single diagnosis; adjusted Hedges's g= -0.470; p= 0.00001) was obtained, within a random-effect model, suggesting that DD patients experience less negative symptoms. Groups did not differ in age, sex, and positive/general psychopathology. **Conclusions** Using narrow criteria (e.g. SANS), the results of this meta-analysis show that schizophrenia patients with a substance use disorder experience less negative symptoms than abstinent schizophrenia patients. As such, these results suggest either that substance abuse relieves the negative symptoms of schizophrenia or that the patients with less negative symptoms would be more prone to substance use disorders.

Introduction

The lifetime prevalence of substance use disorders (SUD) in schizophrenia is close to 50% (Regier *et al.* 1990). SUD in schizophrenia are associated with depression, suicide, impulsivity, criminality, homelessness, unemployment, non-compliance, and health problems (Mueser *et al.* 1998). Khantzian (1987) was the first to suggest that schizophrenia patients would abuse psychoactive substances to get a relief from their negative symptoms, especially anhedonia. Since then, the validity of the "self-medication hypothesis" has remained a topic of debate among researchers. For instance, Mueser *et al* (1998) and Blanchard *et al* (2000) have openly rejected an association between negative symptoms and SUD in schizophrenia. Others have observed that the link between negative symptoms and addiction may be exclusive to cocaine (Negrete, 2003; Lysaker *et al.* 1994). Contributing to this confusion, evidence gathered so far has been somewhat contradictory. Some studies have reported that dual diagnosis (DD) schizophrenia patients experience less negative symptoms, compared to abstinent (SCZ) patients (Compton *et al.* 2004; Goswami *et al.* 2004; Serper *et al.* 1999). Yet, other studies have failed to document such a difference (Addington & Addington, 1997; Gut-Fayand *et al.* 2001).

One potential confounder lies in the diverse scales used to assess negative symptoms in those studies. Clinical investigations have used the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1983), home-made scales, along with numerous other scales. To control for this potential confounder, we performed a meta-analysis of cross-sectional studies evaluating the negative symptoms of DD and SCZ patients

using the SANS. Providing a detailed and comprehensive psychiatric evaluation of negative symptoms (30 items grouped into 5 symptom complexes), the SANS was chosen because the scale includes an "anhedonia" item, which is not the case for the BPRS or the PANSS. According to the self-medication hypothesis, anhedonia would be the primary symptoms targeted by schizophrenia patients when they abuse drugs (Khantzian, 1997). In addition, studies using the SANS are usually designed so to emphasize negative symptoms as a primary variable, since this scale is specific to negative symptoms, whereas other scales (e.g. BPRS & PANSS) assess broad schizophrenia symptoms. Lastly, the SANS includes the least confounding cognitive items (e.g. "abstraction" & "stereotyped thinking" in the PANSS); accordingly, factor analyses show that 4 out of 5 SANS sub-scales (exception: "attention" item) load for the negative factor (Buchanan & Carpenter, 1994).

Methods

Search

A search of computerised literature databases (PubMed & PsycInfo) was conducted, using the following keywords: "schizophrenia", "alcohol", "amphetamine", "cannabis", "cocaine", "hallucinogens", "heroin", "marijuana", and "phencyclidine". Studies were also identified by cross-referencing of included studies. A consensus has been reached between authors on the studies retained or discarded, based on the following inclusion and exclusion criteria (only published studies were included).

Study selection

Inclusion of: 1) Patients with a schizophrenia spectrum disorder: schizophrenia, schizoaffective disorder, and schizophreniform disorder; 2) Schizophrenia patients

with and without a comorbid SUD (abuse or dependence) (current or lifetime); 3) Psychoactive substances: alcohol, amphetamines, cannabis, cocaine, hallucinogens, heroin, or phencyclidine (PCP); 4) Negative symptoms assessed with the SANS; 5) Studies published between January 1st 1983, the year when the SANS was validated, and December 31 2004.

Exclusion of: 1) Patients with an affective (bipolar/unipolar) psychotic disorder and patients suffering from toxic psychoses; 2) Schizophrenia patients whose primary substance of abuse/dependence is either tobacco or benzodiazepine.

Quality assessment

Each study responding to our inclusion criteria was evaluated for their methodological quality. Using a consensual approach, an inter-rater agreement was performed between authors for each study, and a score on a scale from 1 to 5 was provided. In their evaluation, raters were guided by the following methodological criteria: 1) *Diagnosis* Interview > chart review (1 point); 2) *Diagnostic criteria* DSMI > ICD > Research Diagnostic Criteria (1 point); 3) *Diagnostic subtype (schizophrenia)*: balanced > not (1 point); 4) *SUD*: specific PAS > mixed PAS (1 point); 5) Abuse/dependence > regular use (1 point); 6) Current SUD > lifetime (1 point); 7) *Urine toxicology* Screenings > no (1 point); 8) *Sample size* N over 100 > N under 100 (1 point); 9) *Symptoms* Known > unknown scale; no differences between the groups > differences (1 point); 10) *Sex*: All males > no differences between the groups > differences (1 point); 11) *Age*: No differences between the groups > differences (1 point); 12) *Socio-demographic data (e.g. marital status)*: balanced > not (2 points); 13) *Antipsychotic medications*: Controlled dosage > not (1 point); 14) *Psychiatric setting* Exclusively inpatient or outpatient > mixed (1 point).

In order to decrease variability in scores, the total score obtained for each study on a total of 15 was amended to a total score on a scale from 1 to 5.

Data extraction & quantitative data synthesis

Two reviewers independently extracted data; disagreements were resolved by discussion. Using Comprehensive Meta-Analysis (Borenstein & Rothstein, 1999), effect size estimates of the differences in negative symptoms between DD and SCZ patients were calculated. Effect size estimates were calculated from means and standard deviation (SANS total score) for each group of subjects: schizophrenia patients with and without SUD. Within a random effect model, effect size estimates were derived using Hedges's g (Cooper & Hedges, 1994), which provides unbiased effect sizes adjusted for sample size. Random effect models, being more stringent than fixed effect models, allow population-level inferences (DerSimonian & Laird, 1986). The direction of the effect size was negative if DD patients showed a lower score on the SANS (a lower score means less negative symptoms) than SCZ patients.

For one study (Salyers & Mueser, 2001), the SANS scores were provided for "alcohol" and "drug use" sub-groups. Further, the SANS subscale scores were provided but not the SANS total score. In order to calculate the effect size for this study, the SANS sub-scale scores of both groups (alcohol use group and drug use group) were collapsed, to generate the total SANS score for one group (alcohol/drug use group).

To control for age, sex and symptoms, relevant data (N, mean and SD) of the DD and the SCZ groups of each study were gathered. In the case of age and symptoms, a weighted average of means and SD has been produced for all studies, adjusted for sample size, using D-STAT (Johnson, 1989). An independent 2-sample

T test was then performed. For sex, a chi-square test was applied for all studies. For some studies, BPRS *total* scores were not available, only BPRS subscale scores. These were collapsed (average of means and SD), also using D-STAT.

Homogeneity of effect size estimates

It is only legitimate to aggregate effect size estimates when effect sizes are homogenous. Thus, we have calculated the Q statistic for the effect size estimates of the studies included in meta-analysis. Studies introducing variability were excluded, so that the distribution of the statistic becomes non-significant ($p< 0.1$).

Results

Study characteristics

A total of 2843 studies were identified. 2667 studies were discarded based on the evaluation of the abstract and 159 studies on the evaluation of the article, according to the following reasons: 1) type of article (e.g. review, historical overview, book, book chapter, case report, dissertation and letter-to-the editor) (1065 studies); 2) type of study (e.g. theoretical biology, epidemiology, survey, therapeutic programs and government report) (353 studies); 3) type of population (e.g. toxic psychosis, psychotic depression, delirium and bipolar disorder) (908 studies); 4) study design (e.g. no DD group & no SCZ group) (301 studies); 5) negative symptoms were not assessed (112 studies); 6) negative symptoms were assessed with a scale other than the SANS (e.g. BPRS, PANSS, Manchester Scale, Present State Examination) (73 studies) (Note: Two studies (Osher *et al.* 1994; Drake *et al.* 1989) used a modified case manager version of the BPRS/SANS to assess negative symptoms; thus, these

were not considered for meta-analysis.) ; 7) studies on schizophrenia patients dependent on tobacco (14 studies).

18 articles responded to our search criteria (Table 1). Out of 18 studies identified, SANS results were not available for 5 studies (after contacting authors for missing data). Thus, 13 articles were available for meta-analysis, for a total sample size of 1 260 schizophrenia patients (505 DD and 755 SCZ). However, this set of studies was heterogeneous (Q= 19.435; p= 0.079). Two studies contributed significantly to this heterogeneity of effect size estimates (Bühler *et al.* 2002,; DeQuardo *et al.* 1994). In the case of DeQuardo *et al* (1994), SUD diagnoses were based on a chart review. As for Bühler *et al* (2002), their study assessed substance abuse/dependence using the IRAOS (Interview for the Retrospective Assessment of the Onset and Course of Schizophrenia and Other Psychoses) (Bühler *et al.* 2002). After removal of these two outlying studies, the dataset of 11 studies was no longer heterogenous (Q= 3.912; p= 0.951).

Table 1: Cross-sectional studies of single and dual diagnosis schizophrenia patients using the SANS.

Authors	PAS	Current/ Lifetime SUD	SUD criteria	Study Score (0 – 5)	Population (specifics)	Age	Sex	SANS	SANS Sub-scales	Psychosis Scale	Follow-up Testing	Included /excluded
Allen *et al*, 2000	Alcohol	Lifetime	DSM-III-R	2	Inpatients	DD group Older	All males	Yes	NA	BPRS	No	Included
Arndt *et al*, 1992	Mixed	Lifetime	DSM-III	---		No Diff.	More males In DD group	NA	NA[1]	SAPS (NA)	No	Excluded
Bersani *et al*, 2002a *	Cannabis	Current	DSM-IV [2] Use/abuse	3	Inpatients	DD group Younger	All males	Yes	Yes	Multiple	No	Included
Bersani *et al*, 2002b *	Cannabis	Current	DSM-IV [3] Use/abuse	2	Inpatients	No Diff.	All males	Yes	Yes	SAPS	No	Included
Bühler *et al*, 2002	Mixed	Lifetime	Retro -spective	---	1st episode	No Diff.	No Diff.	Yes	Yes		Before/after	Excluded
Conley *et al*, 1998	Mixed	Lifetime	DSM-III-R	4	Inpatients	No Diff.	No Diff.	Yes	Yes	BPRS	Before/after	Included
DeQuardo *et al*, 1994	Mixed	Current	Chart review	---	Psychosis Exacerbation	No Diff.	No Diff.	Yes	NA	BPRS	Before/after	Excluded
Dixon et al, 1991	Mixed	Current	DSM-III-R	2	Inpatients	No Diff.	No Diff.	Yes	Yes	BPRS	Discharge	Included
Goswami, 2004	Mixed	Current	DSM-IV	4	Outpatients	No Diff.	All males	Yes	Yes	SAPS	No	Included
Kovasznay *et al*, 1997	Mixed	Lifetime	DSM-III-R	---	Outpatients	Median age	More males In DD group	NA	NA	BPRS	6-month follow-up	Excluded
Peralta *et al*, 1992	Cannabis	Current	DSM-III-R	2.5	Inpatients	No Diff.	No Diff.	Yes	Yes	SAPS	No	Included
Rabinowitz *et al*, 1998	Mixed	Lifetime	DSM-III-R	---	1st admission	NA	NA	NA		SAPS BPRS	No	Excluded
Salyers & Mueser, 2001	Alcohol & mixed	Current	Users vs Non-users	2.5	Maintenance Therapy [4]	DD group Younger	More males In DD group	Yes	Yes [5]	BPRS (4 subscales)	No	Included
Serper *et al*, 1999	Cocaine	Current	DSM-III-R	3.5	Emergency Presentation	DD group Younger	No Diff.	Yes	Yes	BPRS SAPS	No	Included
Serper *et al*, 1995	Cocaine	Current	DSM-III-R	3.5	Emergency Presentation	DD group Younger	No Diff.	Yes	NA	BPRS SAPS	Before/after	Included
Sevy *et al*, 2001	Mixed	Lifetime	RDC	2.5	Inpatients (1st episode)	No Diff.	More males In DD group	Yes [6]	NA	Other scale	No	Included
Swofford *et al*, 1996	Mixed	Current	DSM-III-R	---	Outpatients	DD group Younger	All males	NA		BPRS SAPS	No	Excluded
Zisook *et al*, 1992	Mixed	Lifetime	DSM-III-R	---	Outpatients	No Diff.	More males in DD group	NA			No	Excluded

NA= not available; No Diff.= no differences between the DD and SCZ groups; RDC= Research Diagnostic Criteria

[1] Anhedonia subscale scores reported; [2] Scores for users and abusers reported together; [3] Scores for users and abusers reported separately; [4] Following hospitalization /relapse in the last 3 months; [5] SANS three-factor model; [6] SANS without attention subscale (* an overlap of data between these two studies cannot be excluded)

Quantitative data synthesis

11 studies were included in the first composite analysis. Within a random-effect model, a moderate and significant negative effect size (Total N= 1 135; DD group= 451; SCZ group= 684; adjusted Hedges's g= -0.470; p= 0.00001) was obtained, suggesting that DD patients would experience less negative symptoms. These 11 studies were weighted according to their methodological quality score (see Methodology section). After weighting of the studies, a moderate effect size was also obtained (Table 2).

Table 2. Meta-analysis of SANS data in DD and SCZ patients.

Citation	N1	N2	Effect	-1,00 -0,50 0,00 0,50 1,00	Lower	Upper	PValue
Allen	22	11	-,767		-1,548	,013	,041
Bersani, 2002a	54	71	-,585		-,950	-,220	,001
Bersani, 2002b	25	25	-,482		-1,060	,095	,090
Conley	23	37	-,650		-1,195	-,104	,016
Dixon	40	43	-,475		-,918	-,031	,032
Goswami	22	22	-,497		-1,116	,122	,101
Peralta & Cuesta	23	72	-,386		-,865	,093	,108
Salyers & Mueser	168	236	-,380		-,580	-,180	,000
Serper, 1995	15	22	-,596		-1,292	,100	,078
Serper, 1999	32	54	-,701		-1,158	-,244	,002
Sevy	27	91	-,289		-,725	,146	,186
Random Combined (11)	**451**	**684**	**-,470**		**-,593**	**-,347**	**,000**

SCZ-ADD **SCZ**

Secondary analyses were performed in order to rule out the potential impact of psychiatric setting (inpatients/outpatients), SUD course (current/lifetime), pattern of substance use (DSM SUD/regular use), therapeutic intervention (before/after), and SANS calculation (all 5 subscales). The results obtained from these secondary analyses were consistent with the results obtained in the composite analysis (Table 3).

Table 3. Secondary analyses.

Analysis	Number of studies	DD group (N)	SCZ group (N)	Effect Size (Hedges's g)	95% Confidence interval	P-value
Inpatients [1] (exclusively)	9	261	426	-0.527	-0.688 / -0.365	0.00001
SUD [2] (not regular use)	9	219	377	-0.508	-0.684 / -0.333	0.00001
Current Use / abuse [3]	8	123	129	-0.447	-0.582 / -0.313	0.00001
SANS with 5 sub-scales [4]	9	256	357	-0.560	-0.728 / -0.392	0.00001
Baseline (exclusively) [5]	10	411	641	-0.469	-0.598 / -0.341	0.00001
Follow-up (exclusively) [6]	3	78	102	-0.228	-0.645 / 0.190	0.28422
Males (exclusively) [7]	4	123	129	-0.569	-0.826 / -0.313	0.00001

[1] Excluded: Goswami et al., 2004; Salyers & Mueser, 2001; [2] Excluded: Bersani et al., 2002a; Salyers & Mueser, 2001; [3] Excluded: Allen et al., 2000; Conley et al., 1998; Sevy et al., 2001; [4] Excluded: Salyers & Mueser, 2001; Sevy et al., 2001; [5] Excluded: Dixon et al., 1991; [6] Included: Conley et al., 1998; Dixon et al., 1991; Serper et al., 1995; [7] Included: Allen et al., 2000; Bersani et al., 2002a, 2002b; Goswami et al., 2004

A posteriori analyses

Two sets of *a posteriori* analyses were carried out. First, we were interested in evaluating the impact of the type of PAS abused on our results. As mentioned in the introduction, some authors have observed that the differences in negative symptoms between DD and SCZ patients would apply exclusively to schizophrenia patients with a cocaine use disorder. To test the validity of this assumption, we divided the 11

studies included in the meta-analysis, based on the type of PAS assessed. 2 studies were specific to alcohol, 3 studies to cannabis, and 2 studies to cocaine (Table 1). For alcohol, a low-to-moderate and *non-significant* effect size (Total N= 396; DD group= 149; SCZ group= 247; adjusted Hedges's g= -0.38; p= 0.09) was obtained. However, for cannabis, a moderate and significant effect (Total N= 270; DD group= 102; SCZ group= 168; adjusted Hedges's g= -0.51; p= 0.0001) was obtained. This was also true for cocaine (Total N= 123; DD group= 47; SCZ group= 76; weighted Hedges's g= -0.67; p= 0.0004) (Table 4).

Table 4: SANS in schizophrenia with alcohol, cannabis or cocaine addiction.

PAS	DD group (N)	SCZ group (N)	Effect Size (Hedges's g)	95% Confidence interval	P-value
Alcohol (2 studies) [1]	149	247	-0.38	-0.82/0.06	0.09
Cannabis (3 studies) [2]	102	168	-0.51	-0.76/-0.25	0.0001
Cocaine (2 studies) [3]	47	76	-0.67	-1.05/-0.29	0.0006

[1] Allen et al., 2000; Salyers & Mueser, 2001; [2] Bersani et al., 2002a, 2002b; Peralta & Cuesta, 1997; [3] Serper et al., 1999; Serper et al., 1995.

A second subset of *a posteriori* analyses were performed, focusing on the SANS subscales. The SANS sub-scale scores were available for 7 studies (Table 2). The SANS sub-scale scores for these 7 studies were pooled together. For 3 subscales (alogia, anhedonia and avolition), a moderate and significant effect size was obtained, with the highest effect size being observed for the "anhedonia" subscale (Table 5). For the "flat affect" subscale, a low-to-moderate effect size was obtained, and a low effect size was noticed in the case of the "attention" subscale (Table 5).

Table 5: SANS subscales in single and dual diagnosis schizophrenia (7 studies)[1].

PAS	DD group (N)	SCZ group (N)	Effect Size (Hedges's g)	95% Confidence interval	P-value
SANS Alogia	219	324	-0.46	-0.64/-0.29	0.00001
SANS Anhedonia	219	324	-0.52	-0.69/-0.34	0.00001
SANS Attention	219	324	-0.25	-0.43/-0.08	0.0049
SANS Avolition	219	324	-0.41	-0.59/-0.24	0.00001
SANS Flat affect	219	324	-0.36	-0.53/-0.18	0.0001
SANS Total	219	324	-0.40	-0.48/-0.32	0.00001

[1] Bersani et al., 2002a, 2002b; Conley et al., 1998; Dixon et al., 1991; Goswami et al., 2004; Peralta & Cuesta, 1997; Serper et al., 1999.

Psychopathology

To control for symptoms, BPRS, PANSS, and SAPS scores were separately pooled, for the DD and SCZ groups of available studies. Out of 11 studies, 10 studies reported psychopathology scores with one or more of the following scales (Table1):

BPRS: 7 studies reported the BPRS scores of patients (Table 1). Using the BPRS, no differences in general symptoms were identified between the DD and SCZ groups (DD group: N= 354; BPRS score=14.95 ± 4.21; SCZ group: N= 474; BPRS score= 15.47 ± 5.2).

SAPS: 6 studies reported the SAPS scores of patients (Table 1). Using the SAPS, no differences in positive symptoms were identified between the DD and SCZ groups (DD group: N= 171; SAPS score= 31.88 ± 16.93; SCZ group: N= 266; SAPS score= 30.44 ± 25.02).

PANSS: One study reported the PANSS scores of patients (Table 1). Using the PANSS, no differences in general symptoms were identified between the DD and SCZ groups (DD group: N= 54; PANSS score= 91.3 ± 14.9; SCZ group: N= 71; PANSS score= 92.8 ± 19.8).

Independently of the scale used, no overall differences in (global/positive) symptoms were observed between the DD and SCZ groups.

Socio-demographic data

It has been repetitively reported that DD patients are younger and more frequently males than SCZ patients (Ries *et al.* 2000; Swofford *et al.* 2000). To control for such confounding factors, age and sex data were separately pooled, for the DD and SCZ groups of available studies.

Age: 10 out of 11 studies reported the age (mean and SD) of patients (Table 1). Available data were pooled together. No differences in terms of age were observed between the DD and SCZ groups (DD group: N= 411; 32.51 years ± 7.36; SCZ group: N= 641; 33.56 ± 8.39).

Sex: Sex ratio was provided in the same 10 studies (Table 1). Available data were pooled together. No significant differences between the DD and SCZ groups were observed (DD group: N= 411; 345 males (83.9%); SCZ group: N= 641; 458 males (71.5%); x^2= 13.5; p= 0.14).

To further control for sex, we regrouped 4 studies where patients were all males (Table 1). A last analysis was performed on these 4 studies. Within a random-effect model, a moderate and significant negative effect size (Total N= 252; DD group= 123; SCZ group= 129; adjusted Hedges's g= -0.57; p= 0.00001) was obtained (Table 3).

Discussion

The aim of this study was to perform a meta-analysis of cross-sectional studies assessing negative symptoms in single and dual diagnosis schizophrenia patients using the SANS. The meta-analysis was carried in order to verify the assumption suggesting that dual diagnosis schizophrenia patients would experiences less negative symptoms, compared to abstinent schizophrenia patients. Out of 18 possible articles identified in our electronic search, 11 studies were included in the meta-analysis (Table 1). Within a random effect model, a moderate and significant negative effect size was obtained. Similar results were obtained after the 11 studies were weighted according to their methodological quality (on a scale from 1 to 5) (Table 2). As such, these results suggest that addicted schizophrenia patients with a SUD would experience fewer negative symptoms than abstinent schizophrenia patients.

To gain a better understanding of the relationship between negative symptoms and addiction in schizophrenia, *post-hoc* analyses were performed on the SANS subscales. After pooling the data from 7 studies, a moderate and significant negative effect size was obtained for 3 subscales (alogia, anhedonia and avolition), with the highest effect size being observed for the "anhedonia" subscale. For the "flat affect" subscale, a low-to-moderate effect size was obtained, and a low effect size was noticed in the case of the "attention" subscale (Table 5). These results have methodological relevance, since they stress the importance, when testing negative symptoms in DD patients, of choosing a scale comprising the "anhedonia item" while limiting cognitive items. Further, these results reinforce our decision of retaining only studies using the SANS.

As mentioned previously, it has been suggested that the differences in negative symptoms between DD and SCZ patients would only apply to schizophrenia patients with a cocaine use disorder. To test the validity of this assumption, we divided the 11 studies included in the meta-analysis, based on the type of PAS assessed. 2 studies were identified on alcohol, 3 studies on cannabis, and 2 studies on cocaine (see Table 1). For cannabis, a moderate and significant effect size was obtained. This was also true for cocaine. However, in the case of alcohol, the observed effect size was non-significant, apart from being low-to-moderate (Table 4). These findings suggest that schizophrenia patients who misuse cocaine, and also cannabis, but not alcohol, experience fewer negative symptoms than abstinent patients. However, it must be taken in consideration that the sample size of the *a posteriori* analyses on specific PAS involved small samples; therefore, no decisive conclusion can be drawn from them.

To our knowledge, this is the first meta-analysis to investigate negative symptoms in dual diagnosis schizophrenia, despite twenty years of clinical research on this widely debated topic. Also of interest, the meta-analysis is performed on an important sample size (1135 patients), using the best scale available (SANS) to evaluate the negative symptoms of schizophrenia. Further, the meta-analysis provides preliminary evidence that 7 potential confounding factors (age, sex, positive/general symptoms, psychiatric setting, SUD course, substance use pattern and follow-up) do not impact on the global result of less negative symptoms in dual diagnosis schizophrenia.

The current meta-analysis has 3 main limitations. Despite homogeneity in effect size estimates, the clinical heterogeneity of the studies included in the meta-analysis can not be under-estimated (Table 1). Further, despite the numerous controls

performed in the meta-analysis, it can not be ruled out that our results could be explained by a non-controlled confounding factor, such as depression or antipsychotic medication. In addition, a publication bias might have skewed our results, since positive results tend to be published more consistently than negative ones. Of the 3 studies not available, two reported (not statistically) that there were no differences in negative symptoms between DD and SCZ patients (Rabinowitz *et al.* 1998; Swofford *et al.* 1996), while one study only reported that DD patients had less "anhedonia symptoms" than SCZ patients (Arndt *et al.* 1992).

The findings of the current meta-analysis must be considered with caution. Our results are certainly consistent with the self-medication hypothesis conceptualized by Khantzian, especially since the strongest effect size estimate was observed with the "anhedonia" subscale. By taking PAS, schizophrenia patients would relieve their negative symptoms. On neurobiological grounds, the negative symptoms of schizophrenia have been associated with a dopaminergic deficit in the prefrontal cortex (PFC) (Finlay, 2001; Grace, 1993). Despite their diverse mechanisms of action, PAS share the common property of acutely increasing dopamine release in this system (Devous *et al.* 2001; Gardner *et al.* 1997; Volkow *et al.* 1996). By taking PAS, schizophrenia patients would be self-medicating their prefrontal dopaminergic deficit.

However, the self-medication hypothesis is associated with numerous flaws, which have been reviewed by many authors (Potvin *et al.* 2003; Blanchard *et al.* 2000; Mueser *et al.* 1998). For instance, schizophrenia patients with a SUD are poorly compliant with medication (ironically) and they relapse frequently without ceasing PAS use. It is noteworthy that our results are also consistent with the reverse explanation, namely that schizophrenia patients with less negative symptoms would

be more prone to SUD. In this vein, Kirkpatrick *et al* (1996) demonstrated that the deficit syndrome of schizophrenia is related to less substance use. Arndt *et al* (1992) also found that addicted schizophrenia patients have better pre-morbid adjustment levels.

The fact that a difference in negative symptoms was observed between DD and SCZ patients, whether DD patients were current or lifetime abusers, is of relevance to the debate on the self-medication hypothesis. This result suggests, to the very least, that the observed differences in negative symptoms do not depend on the acute effects of PAS. Unless PAS have long-term effects on negative symptoms, this result could also call into question the self-medication hypothesis and favor the reverse explanation, namely that patients with fewer negative symptoms are more prone to SUD. In the future, longitudinal studies will be required to resolve this debate.

In conclusion, the results of this meta-analysis show that dual diagnosis schizophrenia patients experience fewer negative symptoms than abstinent schizophrenia patients. As such, these results suggest either that substance abuse relieves the negative symptoms of schizophrenia or that the patients with less negative symptoms would be more prone to SUD. Alternatively, a factor yet to be identified could underscore this relationship.

Acknowledgment

The authors would like to thank Dr Conley, Dr Sanders, and Dr Häfner who generously provided their data. Declaration of interest: None.

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2e article

Processing of social emotion in patients with schizophrenia and substance use disorder: a fMRI study

(**Running title:** Dual diagnosis schizophrenia: a fMRI study)

Stéphane Potvin [1,2,3], Adham Mancini-Marïe [1,2,3], Cherine Fahim [1,2,4], Boualem Mensour [5], Emmanuel Stip [1,2,6]

1 Fernand-Seguin Research Center, Department of psychiatry, University of Montreal

2 Louis-H Lafontaine Hospital, Department of psychiatry, University of Montreal

3 Biomedical Sciences Program, Faculty of Medicine, University of Montreal

4 Department of Neurological Sciences, Faculty of Medicine, University of Montreal

5 Department of Radiology, Centre Hospitalier de l'Université de Montréal (CHUM), University of Montreal

6 Department of Psychiatry, Faculty of Medicine, University of Montreal

Word count 237 (abstract) & 3921 (text body)

Corresponding author

Emmanuel Stip, Centre de recherche Fernand-Seguin, 7331, rue Hochelaga, Montréal (Québec) H1N 3V2 CANADA Tel: (514) 251-4015; Fax: (514) 251-2617; Email: emmanuel.stip@umontreal.ca

Abstract

Background The lifetime prevalence of substance use disorders among schizophrenia patients is close to 50%. The negative consequences of substance abuse in schizophrenia are well documented, but the aetiology of this comorbid condition remains unknown. Mounting evidence suggests that dual diagnosis patients have fewer negative symptoms and better social skills, compared to non-abusing patients. We hypothesized that schizophrenia patients with substance use disorder (SCZ-SUD) would display increased cerebral activations in response to socio-emotional stimuli, relative to patients with no SUD (SCZ). **Methods** Schizophrenia patients (DSM-IV criteria) were divided into two groups: patients with (n =12) and without (n=11) substance use (alcohol and/or cannabis). Using functional magnetic resonance imaging (fMRI), patients were scanned during passive viewing of an emotional film excerpt with social content. **Results** Loci of activation were identified in the right mPFC (BA 10) and the right supramarginal gyrus (BA 40) in SCZ-SUD patients, and in the left pons in SCZ patients. Relative to SCZ patients, increased loci of activation were found in the right superior parietal cortex (BA 7) and the left medial prefrontal cortex (BA 10) in SCZ-SUD patients, which reported higher subjective emotional experience on a self-report scale. **Conclusions** To our knowledge, this is the first fMRI study to assess social emotions in dual diagnosis schizophrenia. Our results suggest that socio-emotional processing may be less impaired in dual diagnosis, which recruited brain regions seemingly involved in "social cognition". Further studies on the topic are warranted.

Key words

Schizophrenia – substance use disorders – social emotions – medial prefrontal cortex – functional magnetic resonance imaging

1. Introduction

Epidemiological investigation has revealed that the lifetime prevalence of substance use disorders (SUD) among schizophrenia patients is close to 50% (Kavanagh, McGrath, Saunders, Dore, & Clark, 2002; Regier et al., 1990). In decreasing order, schizophrenia patients abuse alcohol, cannabis and cocaine. These psychoactive substances (PAS) have a negative impact on the course and treatment of the pathology, which translates into a higher incidence of psychotic relapses, depressive episodes, homelessness, unemployment, as well as legal and health problems (for a review, (Mueser, Drake, & Wallach, 1998).

Although the clinical consequences of SUD among patients with schizophrenia are well documented, the reasons that motivate drug intake among these patients remain unclear, although preliminary, some evidence suggests that negative symptoms play a key role in the etiology of the schizophrenia – addiction comorbidity (Potvin, Stip, & Roy, 2003). Of interest, it has been shown that schizophrenia patients addicted to cannabis or cocaine have fewer negative symptoms (Bersani, Orlandi, Kotzalidis, & Pancheri, 2002; Serper et al., 1995), as confirmed by a recent meta-analysis (Potvin, 2005). When compared to abstinent ones, addicted schizophrenia patients also have better social skills (Carey, Carey, & Simons, 2003) and better pre-morbid adjustment levels (Arndt, Tyrrell, Flaum, & Andreasen, 1992). Moreover, it has been demonstrated that the DSM-IV deficit syndrome of schizophrenia is related to less substance use (Kirkpatrick et al., 1996; Kirkpatrick, Messias, & Tek, 2003).

Whether these differences are the cause or the consequence of substance abuse in schizophrenia remains a matter of debate. Because of their pharmacological effects, PAS may relieve the negative symptoms (anhedonia & blunted affect), as a form of "self-medication" (Khantzian, 1997). Alternatively, schizophrenia patients with fewer negative symptoms could be more prone to SUD, since emotionally withdrawn patients are less likely to sustain the social lifestyle of substance abuse (Joyal, Halle, Lapierre, & Hodgins, 2003; Mueser et al., 2000). Primary or secondary to substance abuse, the socio-emotional differences between schizophrenia patients are likely to have a biological component. Therefore, the present study sought to explore socio-emotional processing in dual diagnosis schizophrenia, using functional magnetic resonance imaging (fMRI).

In the last decade or so, positron emission tomography (PET) and fMRI studies have targeted the neurophysiological substrates of emotions, including social emotions (e.g. attachment, sadness, grief, "empathy", etc.). A complex array of frontal and limbic structures have been linked to basic emotions, including the anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), insula, amygdala and basal ganglia (Murphy, Nimmo-Smith, & Lawrence, 2003; Phan, Wager, Taylor, & Liberzon, 2002; Phan, Wager, Taylor, & Liberzon, 2004). As for social emotions, an emerging literature highlights the contribution of prefrontal (ACC, mPFC & OFC), limbic (amygdala), but also parietal structures (Farrow et al., 2001; Gundel, O'Connor, Littrell, Fort, & Lane, 2003b; Norris, Chen, Zhu, Small, & Cacioppo, 2004; Ruby & Decety, 2004). In schizophrenia patients, emotional processing has been studied to a lesser extent but preliminary results point to deficits in prefrontal and limbic neural activity (Paradiso et al., 2003; Takahashi et al., 2004).

To investigate socio-emotional processing, a film depicting an emotionally laden social interaction was shown to schizophrenia patients with and without SUD. We hypothesized that the passive viewing of the film would elicit a stronger socio-emotional response among dual diagnosis patients, relative to patients with no history of SUD. The other objective of the study was to explore the neural correlates underlying this difference.

2. Materials and Methods

2.1 Participants

Based on DSM-IV criteria, all subjects were diagnosed with schizophrenia, and they were further divided into two groups: patients with and without substance use. The local scientific and ethics committees approved the research program.

Twelve patients with SUD (last 18 months) versus eleven patients without SUD (lifetime) did participate in the study after signing a detailed written informed consent form. The schizophrenia – substance use group (SCZ-SUD) and the schizophrenia group without substance use (SCZ) matched for socio-demographic data: age, sex, age of onset, years of education, and lifetime tobacco consumption (Table 1).

Patients were stabilized on one or more antipsychotic medication(s) (Table 1). The effects of antipsychotic medication of cerebral activity were considered through dose equivalency estimation to 100mg/d of chlorpromazine (Woods, 2003). Using SPSS, we conducted a Mann-Whitney U-test, and found no significant difference between the 2 groups (SCZ-SUD: 425 ± 260.7; SCZ: 367.5 ± 350.6; U= 66; NS).

2.2 Psychiatric assessments

Psychiatric assessments included the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987), the Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington, Maticka-Tyndale, & Joyce, 1992) and the Rating Scale for Emotional Blunting (RSEB) ((Abrams & Taylor, 1978). Criteria for entry into the study were a DSM-IV diagnosis of schizophrenia, and no concomitant axis-I or axis-II disorders other than substance use. Patients with medical or neurological diseases were not included in the study.

Through chart review of inpatient and outpatient psychiatric medical records, patients were screened for SUD diagnoses, established by ES and other psychiatrists on the ward. Diagnoses were determined using DSM-IV criteria of substance abuse and dependence. In addition, two raters (AM-M and SP) scored the severity of the patients' substance use on a scale from 1 to 5 (1=abstinent; 2=use without impairment; 3=substance abuse; 4=substance dependence; 5=severe dependence), using the Alcohol Use Scale and the Drug Use Scale (Drake et al., 1990). An inter-rater agreement was performed between the two raters to validate the substance use scores, using a consensual approach. The raters based their judgment upon the following data extracted from medical files: toxic psychoses, psychotic relapses/hospitalizations secondary to drug intake, positive urine screenings, detoxifications, drug intoxications, legal and health problems associated with substance use, as well as the number and types of substances consumed.

Patients were divided into two groups (SCZ-SUD versus SCZ), according to SUD diagnoses and substance use severity scores (SCZ-SUD: >2 versus SCZ: ≤ 2) (Table 1). Patients in the SCZ-SUD group were diagnosed with one or more of the following SUD (abuse or dependence) (last 18 months): alcohol only (n=2), cannabis only (n=5), alcohol plus cannabis (n=5).

There was no direct evaluation of withdrawal or intoxication symptoms, but a trained team (clinical, radiologist and trained personnel) able to detect acute withdrawal or intoxication symptoms evaluated the patients prior to scanning. One month prior to the scan session, none of the SCZ-SUD patients were regular users, defined as daily or "binge" consumption (Note: One patient with positive drug urine screening in his medical chart for that time span was excluded).

Table 1: Participants

	SCZ-SUD group (n=12)	**SCZ group (n=11)**	**Statistics**
Sociodemographic data			
Age	25.5 years ± 5.2	28.7 years ± 9.3	U=0.516 (p=0.688)
Sex	8 males; 4 females	8 males; 3 females	χ^2=0.1 (p=0.752)
Age of onset	21.7 years ± 2.1	22.1 years ± 5.4	U=57 (p=0.577)
Education level	10.4 years ± 2.5	10.4 years ± 4.2	U=65 (p=0.950)
Antipsychotic medication	Haloperidol (n=3) Olanzapine (n=4) Quetiapine (n=2) Risperidone (n=4) Zuclopenthixol (n=1)	Clozapine (n=1) Haloperidol (n=1) Olanzapine (n=3) Risperidone (n=7) Zuclopenthixol (n=2)	
Substance use data			
SUD diagnoses * (abuse/dependence)	cannabis (n=10) alcohol (n=5) (last 18 months)	No SUD diagnosis (lifetime)	---
AUS & DUS composite score (0 to 5 scale)	4.1 (mean) (range: 3 – 5)	1.5 (range: 1 – 2)	---
Tobacco	11 smokers	9 smokers	χ^2=0.491 (p=0.484)

AUS= Alcohol Use Scale; DUS= Drug Use Scale; SUD = substance use disorder;

* Diagnoses established by psychiatrists on the ward

2.3 Behavioral procedures

Blood-oxygen-level-dependent (BOLD) signal changes were measured while subjects viewed film excerpts used to transiently induce either a negative socio-emotional (activation) state or an emotionally neutral (reference) state. Film excerpts were presented through goggles connected to a MR-compatible video system (Resonance Technology, Van Nuys, CA, USA). The presentation of the film excerpts took the form of a boxcar design according to the following sequence: neutral film excerpt (shown for 180 s), then a rest period during which subjects viewed a blue cyan screen (for 18 s), and finally, the socio-emotional film excerpt (also shown for 180 s). The order of presentation of the film excerpts was counter-balanced across subjects. The socio-emotional film depicted the death of a father in presence of his young son, wife, friends and colleagues (Figure 1) or an emotionally charged confrontation between a husband and wife. The film excerpts were extracted from the film "The champ" (1979). These excerpts have been validated by Gross & Levenson (1995) (Gross, 1995) and have been used in several studies involving healthy volunteers and psychiatric patients (Christie & Friedman, 2004; Eugene et al., 2003; Stip et al., 2005). The emotionally neutral film excerpt depicted various human activities (e.g. gardening, carpentry, etc.). Film excerpts were chosen to elicit social emotions because of their dynamic nature. Compared to the static pictures usually used in emotion studies (Lane, Reiman, Ahern, Schwartz, & Davidson, 1997), these clips offered a better mirror of real-life situations. To asses the subjective responses of the subjects to the stimuli, immediately at the end of the run, subjects were asked to rate verbally on a visual analog subjective rating scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotional reaction ever

felt in one's lifetime) the intensity of emotional reaction felt during the viewing of the socio-emotional film excerpt. To avoid a confounding effect of inattention to the film excerpts, we verified that patients in both groups (SCZ-SUD versus SCZ) did not differ on the PANSS "attention item" (Table 2). Also, a short briefing about the film contents was performed after the scanning session.

Figure 1: Clip excerpts from the film "The Champ" (1979)

2.4 Image acquisition and Analysis

Echoplanar images (EPI) were acquired on a 1.5 Tesla system (Magnetom Vision, Siemens Electric, Erlangen, Germany). Twenty-eight slices (5mm thick) were acquired every 2.65 s in an inclined axial plane, aligned with the AC-PC axis. These

T2* weighted functional images were acquired using an EPI pulse sequence (TE = 44 ms, Flip = 90°, FOV = 215 mm, Matrix = 64 x 64, Voxel size = 3.36mm X 3.36mm X 5mm). Following functional scanning, high-resolution data were acquired via a Tl-weighted three-dimensional volume acquisition obtained using a gradient echo pulse sequence (TE=44ms, Flip=12° FOV=250mm, Matrix=256x256, Voxel size=0.94 mm^3).

Data were analyzed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Images for all subjects were realigned to correct for artefacts due to small head movements. The gradient-recalled echo-planar sequence that we used is associated with large static magnetic field inhomogeneities commonly found near air/tissue interfaces (Cordes, Turski, & Sorenson, 2000). These inhomogeneities can create artefacts like signal loss and voxel shifts in the ventral frontal, medial temporal, and inferior temporal regions (Song, 2001). To correct for this disadvantage, Cordes et al. (Cordes et al., 2000) proposed using masking to recover signal loss by adjusting the refocusing gradient amplitude in the slice-select direction. This procedure is an automated computer algorithm that partitions echo-planar images into regions of recoverable signal intensities using a histogram analysis and determines each region's proper refocusing gradient amplitude. The effectiveness of this method is demonstrated by recovering signal voids in the orbitofrontal cortex, parahippocampal/amygdala region, and inferior visual association cortex near the cerebellum. In addition, masking proved to be useful for fMRI studies in inhomogeneous areas that require high temporal resolution such as the amygdala and the orbitofrontal cortex. (Song, 2001). Accordingly, a mask was applied to the slices of the mean EPI image which presented signal loss. This procedure was implemented for every subject. All

volumes were realigned to the first volume of each session to correct for subject motion and were spatially normalized to the standard space defined by the Montreal Neurological Institute (MNI) template. Images were then convolved in space with a three-dimensional isotropic gaussian kernel (6mm FWHM) to improve the signal-to-noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization.

For the statistical analysis, the time series of the images were convolved with the delayed box-car function, which approximates the activation patterns. Effects at each and every voxel were estimated using the general linear model. Voxel values for the contrasts of interest yielded a statistical parametric map of the t statistic (SPM *t*), subsequently transformed to the unit normal distribution (SPM Z).

A "fixed-effects model" was implemented to contrast the brain activity associated with the viewing of the socio-emotional film and that associated with the viewing of the emotionally neutral film (Socio-Emotional minus Neutral). This "fixed-effects model" produced individual contrast images, which were used as raw data for the implementation of a "random-effects model", which takes into account inter-subject variance and permits population-level inferences (Friston, 1997). Within such "random-effects model", and using these individual contrast images, one-sample t-tests were used to measure, voxel by voxel, the mean BOLD response produced by the Socio-Emotional minus Neutral contrast for each group of patients (SCZ & SCZ-SUD). In addition, two-sample t-tests were carried out, voxel-by-voxel, to directly compare the mean BOLD response between the two groups of subjects (SCZ-SUD group minus SCZ group and SCZ group minus SCZ-SUD group) with regard to the Socio-Emotional minus Neutral contrast. For these exploratory analyses, a probability threshold of an uncorrected $p<0.001$ was used. Only clusters

showing a spatial extent of at least five contiguous voxels were kept for image analysis. Coordinates of activation were converted from MNI coordinates to Talairach and Tournoux (Talairach, 1988) coordinates using the mni2tal algorithm (M. Brett, Cambridge, MA, http://www.mrc-cbu.cam.ac.uk/Imaging). Contrast images were overlaid onto a group mean anatomy image provided by SPM for viewing.

For psychiatric data (e.g. PANSS), statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS), version 10.0. Considering the limited sample size of this study, comparisons between the two groups were performed using the Mann-Whitney U-test, a nonparametric equivalent to the independent samples Student's t-test, which is based on rankings of the data. For dichotomous variables (e.g. sex), comparisons between the two groups were performed with the chi-square test. Significance tests were two-tailed, and the α level for rejecting the null hypothesis was set at 0.05.

3. Results

3.1. Psychiatric data

On a clinical level, the Mann-Whitney U-test was performed in order to differentiate the psychiatric profile of the patients in the two groups (Table 2). For positive symptoms (PANSS) ($p= 0.781$) and depression (CDSS) ($p= 0.684$), no significant differences were noticed. On the PANSS negative sub-scale, a non significant trend was observed ($p= 0.095$). However, patients in the SCZ-SUD group reported less emotional blunting as asssessed by the RSEB.

3.2. Self-report data

In keeping with one of our hypotheses, it was shown that patients in the SCZ-SUD group reported higher subjective emotional experience on a self-report scale (from 0 to 8), compared with patients in the SCZ group (p= 0.011) (Table 2). Of interest, a positive correlation was found across groups between self-report data and substance use scores (Pearson's r= 0.507; p= 0.014). Noteworthy, for all patients (both groups), emotional valence was negative and the dominant emotion was sadness.

Table 2: Comparative psychiatric data

	SCZ-SUD group		**SCZ group**			
	Mean	*SD*	*Mean*	*SD*	*Mann-Whitney U*	*p-value*
*Subjective Report **	*4.7*	*2.6*	*1.6*	*2.1*	*25*	*0.011*
Positive PANSS	22.6	5.1	21.4	7.7	61.5	0.781
Negative PANSS	20.6	8.9	27.5	8.8	39.0	0.095
RSEB	10.6	2.1	19.7	2.8	33.5	0.044
General PANSS	44	11.9	47.9	8.1	48	0.267
Attention	3	0.9	2.9	1.4	57.5	0.581
Total PANSS	87.2	21.3	96.7	18.2	51	0.355
Depression	5.3	4.4	6.0	4.6	59.5	0.684

* On a self-report scale from 0 (absence of any emotional reaction) to 8 (strongest emotional reaction ever felt in one's lifetime); RSEB=Rating Scale for Emotional Blunting

3.3. fMRI results

3.3.1. One-sample t-tests (Socio-Emotional minus Neutral)

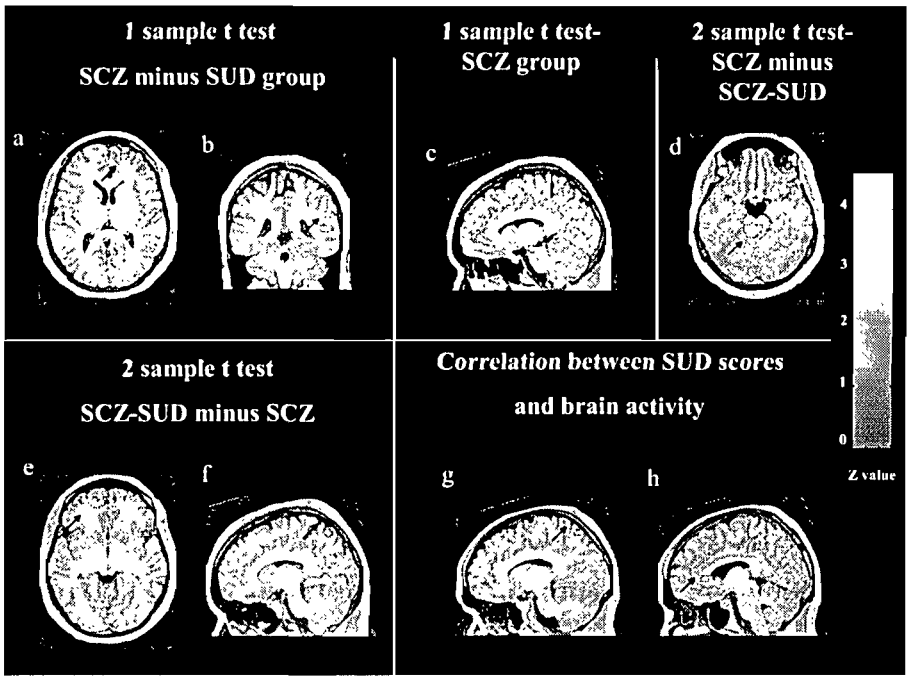
In the SCZ-SUD group, significant loci of activation were identified in the right mPFC (BA 10) and the right supramarginal gyrus (BA 40). In the SCZ group, significant loci of activation were observed only in the left pons (Table 3) (Figure 2).

Table 3: Socio-Emotional minus Neutral: exploratory analyses

			TAL coordinates				
Region of activation	**Brodmann area**	**Voxels**	**x**	**y**	**z**	**z score**	**p***
SCZ-SUD group: 1-sample T test							
A. Right mPFC	10	9	21	59	5	3.25	0.001
B. Right supramarginal gyrus	40	13	62	-39	35	3.14	0.001
SCZ group: 1-sample T test							
C. Left pons		20	-9	-15	-14	3.44	0.0001
SCZ-SUD group minus SCZ group: 2-sample T test							
F. Right precuneus cortex	7	6	12	-61	58	3.22	0.001
E. Left mPFC	10	19	-21	55	-8	2.85	0.002
SCZ group minus SCZ-SUD group: 2-sample T test							
D. Left & right Pons		178	0	-33	-16	3.08	0.001

mPFC = medial prefrontal cortex; p* = uncorrected

Figure 2. Significant BOLD activation during socio-emotional *minus* neutral condition.



a= right medial prefrontal cortex (BA10) (z=5); b= right supramarginal gyrus (BA40) (y=–39); c= left pons (x=–9); d= pons (z=–16); e= (left medial prefrontal cortex (BA10) (z=–8); f= right precuneus cortex (BA7) (x=12); g= right precuneus cortex (BA7) (x=12); h= right anterior cingulate cortex (BA24) (x=6)

To explore potential differences in cerebral activations related to particular PAS, exploratory sub-analyses were performed in patients abusing cannabis only (THC group; n=5) versus patients abusing alcohol and cannabis (POLY group; n=5). Both groups displayed similar patterns of cerebral activity in the medial prefrontal and temporo-parietal cortices (Table 4).

Table 4: Cerebral activations in the POLY and THC groups (Socio-Emotional minus Neutral).

Region	BA	Voxels	Talairach coordinates			z-score	p *
			x	y	z		
POLY group: 1-sample t-test							
Right supramarginal gyrus	40	31	65	-28	35	3.08	0.001
Right superior frontal gyrus	10	11	21	58	3	2.80	0.003
Right middle frontal gyrus	10	15	30	62	11	2.62	0.004
THC group: 1-sample t-test							
Right supramarginal gyrus	40	32	39	61	49	4.06	0.0001
Left angular gyrus	39	10	-45	-56	50	3.90	0.0001
Right middle gyrus	10/11	11	30	52	-8	3.47	0.0001
Left middle gyrus	10	35	-24	58	-5	3.11	0.001
Right superior frontal gyrus	9	34	21	51	25	2.63	0.004

BA = Brodmann area; * p = uncorrected

3.3.2. Two-sample t-tests (Socio-Emotional minus Neutral)

When the SCZ group was subtracted from SCZ-SUD group, significant loci of activation were observed in the right superior parietal cortex (BA 7). Loci of activation were also noted in the left mPFC (BA 10), close to significance. When the SCZ-SUD group was subtracted from the SCZ group, significant loci of activation were found in the pons (Table 3) (Figure 2).

3.3.3. Correlation analyses between fMRI and substance use scores

Within a random effect model, correlation analyses were conducted between scores on Alcohol and Drug Use Scales (composite score) and BOLD signal increases across groups of patients (SCZ-SU & SCZ). A positive correlations was found in the right superior parietal cortex (BA 7) (TAL coordinates: x=12 y=-61 z=58; p=0.001 z= 3.23; 9 voxels). A positive correlation close to significance was also noticed in the right ACC (BA 24) (TAL: x=6 y= 26 z= 1; p= 0.002; z= 2.81; 42 voxels) (Table 5).

Table 5: Correlation analyses (across groups)

Correlation between ROI and substance use severity score*							
Region of activation			**Talairach coordinates**				
	Brodmann area	**Voxels**	**x**	**y**	**z**	**z score**	**p****
G. Right precuneus cortex	BA 7	9	12	-61	58	3.23	0.001
H. Right ACC	BA 24	42	6	26	1	2.81	0.002

* composite score for AUS & DUS; p** = uncorrected; ACC= anterior cingulate cortex

Discussion

This study was conducted for two purposes: 1) to test the hypotheses that schizophrenia patients with SUD would experience stronger emotional reactions during the passive viewing of a film depicting a social interaction with a negative emotional content, relative to schizophrenia patients without SUD; and 2) to explore the neural correlates underlying this difference in socio-emotional processing. On a

clinical level, dual diagnosis patients did not differ from SCZ patients in terms of positive, negative and depressive symptoms, but displayed less blunted affect symptoms. As it was hypothesized, SCZ-SUD patients had a stronger emotional response during the passive viewing of the film. Neurally, significant loci of activation in the right mPFC (BA 10) and the right supramarginal gyrus (BA 40) were found in the SCZ-SUD group. In the SCZ group, significant loci of activation were observed only in the pons, which has been involved in the autonomic responses (bodily states) associated with emotional experience (Critchley, Mathias, & Dolan, 2001). Further, no significant loci of activation were found in the SCZ-SUD group in the superior parietal cortex, even if significant loci of activation were detected in this region when the SCZ group was subtracted from the SCZ-SUD group. Finally, positive correlations were found across groups (SCZ-SUD & SCZ patients) between substance use scores and loci of activation in the right superior parietal cortex (BA 7), and also the right ACC (BA 24).

According to a recent meta-analysis carried out by Phan et al. (Phan et al., 2002), the mPFC has been the most consistently activated region in the functional brain imaging studies of emotion, irrespective of valence. Considering the general role of the mPFC in emotion, Lane et al. (Lane, Fink, Chau, & Dolan, 1997) and Reiman et al. (Reiman et al., 1997) have proposed an involvement of the mPFC in the self-representation of emotional state. Consistent with this view, the mPFC has been recently found to be the most frequently activated region in tasks assessing "social cognition" (e.g. theory of mind) (Gallagher et al., 2000; Gundel, O'Connor, Littrell, Fort, & Lane, 2003a; Lou et al., 2004; Vogeley & Fink, 2003).

The temporo-parietal cortex has been traditionally associated with higher cognitive functions such as semantics, reading and arithmetics (Menon, Rivera,

White, Glover, & Reiss, 2000). As for the superior parietal cortex (BA7), it has been mostly associated with decision-making and autobiographic memory (Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; Harrington et al., 2004). Although the role of these regions in emotional processing has been poorly studied, an emerging neuroimaging literature consistently shows that these regions, like the mPFC, are recruited in social cognitive functions, such as "theory of mind" (Gallagher et al., 2000; Saxe & Kanwisher, 2003; Vogeley et al., 2001).

Although no significant loci of activation were found in the ACC in the SCZ-SUD group, a positive correlation was observed between activations in this region and the substance use scores across groups. Along with the mPFC, the ACC has been one of the brain regions the most consistently involved in emotional processing, across paradigms (Phan et al., 2002). Interestingly, the ACC mediates motivated behavior, and dysfunctions in this region are associated with apathy (Mega, 2001). The relationship found in the current study between the ACC and substance use scores is consistent with animal and human data showing substance use disorders to be mediated by the motivational circuit (Goldstein & Volkow, 2002; Koob & Le Moal, 2001).

Interestingly, differences in brain activity between SCZ and SCZ-SUD patients did not involve limbic structures, but mostly regions closely involved in social cognition. This general pattern makes it plausible that dual diagnosis patients displayed a greater emotional reaction, because they were more likely to figure out the mental states of the characters depicted in the film excerpts.

To our knowledge, this is the first study to assess social emotions in dual diagnosis schizophrenia using fMRI. We found less socio-emotional impairment in dual diagnosis patients, a result consistent with recent evidence showing that dual

diagnosis patients have fewer negative symptoms and better social skills (Carey et al., 2003; Joyal et al., 2003; Potvin et al., 2003), compared to non-abusing patients. Also, the study adds to the growing body of data relating the negative/cognitive symptoms of schizophrenia to the functioning of the prefrontal cortex. According to animal and human data, a *hypoactivity* in the mPFC underscores the negative/cognitive symptoms of schizophrenia (Finlay, 2001; Grace, 1993). Our results suggest that the functioning of the mPFC is more preserved in dual diagnosis patients. They also strengthen the notion that the mPFC is involved in the processing of basic emotions (happiness, sadness, fear, etc.), as shown in recent meta-analyses (Phan et al., 2002).

The principal weakness of the study lies in the method (chart review) used to evaluate substance use. Still, 52% of schizophrenia patients in the selected sample were substance abusers, a result clearly in line with the epidemiological data showing that the lifetime prevalence of SUD among patients with schizophrenia is close to 50% (Kavanagh et al., 2002; Regier et al., 1990). Also, the study did not include a control group of healthy volunteers. However, neuroanatomical and neurophysiological studies have demonstrated brain differences between schizophrenia patients and normal controls (Kasai et al., 2002), which make comparison between their cerebral activation difficult, using fMRI. Nevertheless, healthy volunteers have been investigated with our emotional paradigm, using fMRI. These studies have produced reported widespread loci of loci of activation in various brain regions, including regions similar to our ROIs (Britton, Taylor, Berridge, Mikels, & Liberzon, 2006; Eugene et al., 2003; Goldin et al., 2005). Also, it must be considered that the objective of the study was to provide a greater understanding of the schizophrenia – substance use comorbidity. It was not the purpose to differentiate

the single or dual diagnosis patients from the general population. Another limitation is heterogeneity of antipsychotic medications, which we cannot exclude, even after control for chlorpromazine equivalence. Further, patients were not directly evaluated for intoxication or acute withdrawal before the scanning session. Lastly, the heterogeneity of psychoactive substances (alcohol & cannabis) used by the SCZ-SUD patients make it difficult to draw firm conclusions from our observations. However, it is noteworthy that our exploratory findings showed similar loci of activations in cannabis-abusing versus alcohol and cannabis-abusing patients.

Our results must be interpreted cautiously, since the current study design does not allow to conclude whether a relative preservation of socio-emotional processing has lead patients to substance use or whether substance use has modulated the patients' social emotions, as predicted by the self-medication hypothesis. Although alcohol and cannabis have been shown to activate the mPFC and the ACC, the actual knowledge on alcohol and cannabis does not support a positive impact of these substances on the temporo-parietal and superior parietal cortices (Ameri, 1999; Weiss & Porrino, 2002). Based on these observations, it seems unlikely that the entire activations found in the SCZ-SUD group were secondary to substance use.

The results of this fMRI study suggest that socio-emotional processing is less impaired in schizophrenia patients with SUD. Whether this relative preservation is primary or secondary to substance use remains to be determined. The current findings have potential therapeutic implications. If socio-emotional processing is relatively spared in dual diagnosis patients, it might be successful to encourage them to engage in social activities with less negative consequences than drug consumption. On neurobiological grounds, group differences did not involve limbic structures but prefrontal, temporo-parietal and superior parietal cortices, which have all been linked

to "social cognition". In the future, it would be of interest to specifically investigate "social cognition" in dual diagnosis schizophrenia, using fMRI.

Acknowledgment This study was supported by grants from the Fonds de la Recherche en Santé du Québec (FRSQ), AstraZeneca Pharmaceuticals, University of Montreal Eli Lilly Chair of Schizophrenia Fund and the Canadian Institute of Health Research (CIHR). The authors would like to thank Lahcen Aït Bentaleb M.D., Pierre Lalonde M.D., Marcel Wolfe M.D. and Jean M'Pania M.D. for their assistance in patient recruitment.

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3e article

CANTAB explicit memory is less impaired in addicted schizophrenia patients.

Stéphane Potvin [1]; Catherine Briand [1]; Antoinette Prouteau [3]; Roch-Hugo Bouchard [4]; Olivier Lipp [2]; Pierre Lalonde [2]; Luc Nicole [2]; Alain Lesage [1]; Emmanuel Stip [1].

[1] Centre de recherche Fernand-Seguin, Hôpital Louis-H Lafontaine

[2] Hôpital Louis-H Lafontaine, University of Montreal

[3] Department of psychiatry, University Victor Segalen

[4] Centre de recherche Université Laval Robert-Giffard

Corresponding author
Emmanuel Stip, MD, M.Sc, CSPQ; Centre de recherche Fernand-Seguin; 7331, rue Hochelaga; Montreal, Quebec, Canada; H1N 3V2; Tel: (514) 251-4015; Fax: (514) 251-2617; E-mail address: [redacted]

Abstract

It has been suggested that in order to sustain the lifestyle of substance abuse, addicted schizophrenia patients would have less negative symptoms, better social skills, and less cognitive impairments. Mounting evidence supports the first two assumptions, but data lacks regarding cognition in dual diagnosis schizophrenia. 76 schizophrenia outpatients (DSM-IV) were divided into two groups: with (n= 44) and without (n= 32) a substance use disorder. Motor speed and visuospatial explicit memory were investigated using CANTAB. As expected, dual diagnosis patients showed a better cognitive performance. Our results suggest either that substance abuse relieves the cognitive deficits of schizophrenia or that the patients with less cognitive deficits are more prone to substance abuse.

Key words

Schizophrenia; substance use disorders; explicit memory; psychomotor processing; subjective cognition; CANTAB; SSTICS

Acknowledgments

This study was supported by the Fonds de la Recherche en Santé du Québec (FRSQ) and AstraZeneca Pharmaceuticals.

Introduction

Epidemiological studies show that the lifetime prevalence of substance use disorders (SUD) is close to 50% among schizophrenia patients. Psychoactive substances (alcohol, cannabis and cocaine) exert a negative impact on the course of the pathology. Compared to abstinent patients, addicted schizophrenia patients relapse more frequently, they are more depressed and suicidal, they engage more often in criminal activities, and they are more frequently homeless and unemployed (Mueser et al., 1998).

It has been suggested that in order to find, acquire, and sustain alcohol and/or drug use, schizophrenia patients would have better social skills, less negative symptoms, and better cognitive functioning than abstinent patients (Joyal et al., 2003). Supporting this assumption, it has been shown that schizophrenia patients addicted to cannabis or cocaine have less severe negative symptoms (Bersani et al., 2002; Serper et al., 1995). When compared to abstinent ones, dual diagnosis patients also appeared to have a better pre-morbid adjustment (Arndt et al., 1992). They also seemed to have better social functioning (Côté et al., 1997). Further, it has been shown that the DSM-IV deficit syndrome of schizophrenia is related to less substance abuse (Kirkpatrick et al., 1996).

Regarding cognition of dual diagnosis schizophrenia, robust evidence is lacking. Recently, Carey et al. (2003) have shown that dual diagnosis patients suffer from less global cognitive impairments. Joyal et al. (2003) obtained similar results but their sample size was small (total n= 30). The current study was undertaken in order to further strengthen the preliminary evidence supporting the hypothesis of a better cognitive functioning in dual diagnosis patients. To find, acquire, and sustain alcohol and/or drug use, we hypothesized that dual diagnosis patients would have

less deficits in explicit memory. A fronto-temporal function, explicit memory is significantly impaired among schizophrenia patients, and it is an important predictor of their social and occupational functioning (Hoff & Kremen, 2003).

Methods

Participants

Recruited from a convenient sample, participants were 76 outpatients with schizophrenia (SCZ) or schizoaffective disorder (SA), diagnosed using the Structured Clinical Interview for DSM-IV (SCID-IV). The assessment was approved by the local ethics committee. All subjects gave informed consent.

The study was cross-sectional. According to DSM-IV criteria, participants were divided into two groups: with and without a current SUD (last six months). 44 patients were included in the dual diagnosis (DD) group and 32 patients were included in the single diagnosis schizophrenia (SCZ) group. Patients (n= 44) from the DD group suffered from one or more of the following SUD (abuse/dependence): alcohol (20 patients), cannabis (28 patients), cocaine (12 patients), other substance (5 patients), and poly-addiction (17 patients). The two groups of patients were matched for age, sex, diagnosis subtype, ethnicity, education level, and duration of illness. However, the two groups differed in terms of antipsychotic medication. Patients in the DD group were more frequently treated with typical antipsychotics, compared to patients from the SCZ group (Table 1).

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was administered in order to measure severity of symptoms. Compared to patients from the SCZ group, DD patients showed more severe positive, general and total symptoms. But no differences emerged for negative symptoms (Table 1).

Table 1. Comparative socio-demographic data.

	DD group (n = 44)	SCZ group (n = 32)
Age (years)	31.4 ± 11	34.3 ± 11.1
Females	8	7
Males	36 (81.8 %)	25 (78.1 %)
Diagnosis subtype	34 (77.7 %)	26 (81.2 %)
Schizophrenia	10	6
SA disorder		
Ethnicity	41	32
Caucasian	3	0
Other		
Education level (years)	11.4 ± 2.2	11.3 ± 2.3
Duration of illness (months)	90.9 ± 104.5	109.6 ± 117.4
Antipsychotics	38 (86 %)	32 (100 %)
Atypical	18 (40.9 %)	6 (18.7 %)
Typical [a]		
PANSS	16.7 ± 6.3	13.4 ± 4.9
Positive [b]	17.8 ± 7.3	17.2 ± 6.8
Negative [c]	37.8 ± 13	30.4 ± 8.2
General [d]	72.2 ± 24.4	61 ± 16.6
Total [e]		

SA= schizoaffective
[a] χ^2= 32; p= 0.0001; [b] t= 2.540; p= 0.013; [c] t= 0.354; p= 0.725; [d] t= 3.015; p= 0.004; [e] t= 2.378; p= 0.020

Assessments

DD and SCZ patients were assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Fray et al., 1996), a series of computerised tasks. The tests were run on computers with touch-sensitive colour monitors. Patients were

asked to respond by simply touching the screen with a finger. Patients first completed a « motor screening task » (MOT), an index of psychomotor speed, which familiarized them with the testing procedure. In this screening task, patients are asked to place a finger on a flashing cross. After completion of this task, patients completed the « paired associates learning » (PAL) task.

The PAL task is designed to assess visuo-spatial explicit memory. During the PAL task, patients are asked to remember up to eight pattern-location associations. Patients are instructed that the white boxes presented on the screen will open up one by one, in a random order. Their task is to look for coloured patterns in the boxes, and to remember which pattern belongs in which box. On the first stage, only one box contains a coloured pattern. This initial stage is followed with another stage with one pattern, then two stages with two patterns each, two patterns with three patterns each, one stage with six patterns, and a last stage with eight patterns (one pattern by box). On each trial of every stage, if the patients' choices are incorrect, the boxes are re-opened successively. For each stage, patients are allowed up to nine reminding phases. If they fail all the phases (for a given stage), the task is stopped.

Performance was scored using five indices: (i) *First trial memory score* : the total number of patterns correctly located, on the first trial, summed across the eight stages (range: 0 – 26) (ii) *Stages completed* (range : 1 – 8); (iii) *Stages completed on first trial* (range: 1 – 8); (iv) *Total errors*: the total number of incorrect placements, summed across the eight stages; *Total trials* (maximal score = 10 trials by stage).

The patients' cognitive complaints were assessed with the Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS) (Stip et al., 2003). The questionnaire was developed to explore the subjective appreciation of patients for cognitive domains that have been repetitively shown to be impaired in schizophrenia.

The 21 Likert-type questions of the scale cover four cognitive areas: attention, executive functions, memory and praxia. Each question describes a specific cognitive problem, and the patients are instructed to indicate the frequency with which it occurs in their life (4= very often; 3= often; 2= sometimes; 1= rarely; 0= never).

Statistical analysis

The patients' cognitive performance on the CANTAB PAL and MOT tasks, as well as on the SSTICS, were analysed using one-way analyses of variance (ANOVA) with group as the independent variable. Unpaired T tests were used to analyse potential socio-demographic differences between the DD and the SCZ groups. Dichotomous variables were evaluated using chi-square tests. *A posteriori* correlation analyses were performed using Pearson's test. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 10.

Results

Patients in the two groups (DD and SCZ) did not differ in age, sex, diagnosis subtype, ethnicity, education level, and duration of illness. Overall, patients in the DD group had a better cognitive performance (Table 2). On the PAL task, the DD patients had a better « first trial memory score » ($F(1, 74)= 4.167$, $p= 0.045$). They also completed a greater number of stages on the first trial ($F(1, 74)= 5.682$, $p= 0.020$). However, the groups did not differ in the other PAL scores. DD patients also showed a better performance on the MOT task. The mean time required to attain the target on the screen was smaller in the DD group ($F(1, 74)= 4.849$, $p=0.031$). On the SSTICS, a non-significant trend was observed, where DD patients seemed to report greater cognitive complaints than patients in the SCZ group.

Table 2. Cognitive performance in DD and SCZ patients.

	DD patients		SCZ patients			
	Mean	SD	Mean	SD	F	p-value
PAL						
- First trial memory score	17.1	4.9	14.8	4.9	4.167	0.045
- Stages completed (SC)	7.7	0.6	7.5	1.3	1.506	0.224
- SC on first trial	5.5	1.1	4.9	1.1	5.682	0.020
- Total errors	24.8	21.6	26.6	22.4	0.123	0.727
- Total trials	14.4	5.5	15.2	4.4	0.436	0.436
MOT [1]	1102.1	419.8	1308.9	381.9	4.849	0.031
SSTICS [2]	31.4	10.8	26.2	15.1	2.990	0.088

[1] *Score expressed in milliseconds; a higher score means a slower speed processing.*

[2] *Data was missing for two patients in the DD group.*

- *A posteriori analysis: DD sub-groups*

Considering the negative cognitive impact of cocaine in schizophrenia (see discussion), we carried an a posteriori analysis. Patients in the DD group were divided into two subgroups: with (n= 13) and without (n= 31) cocaine abuse/dependence. The cocaine (COC) and the non-cocaine (NCC) groups were compared with each other on the PAL task, before being compared to the SCZ group. This procedure lead to three general observations: (i) patients in the NCC group displayed less errors than patients in the COC group (NCC= 20.4 ±18.5; COC= 35.5 ±25.2; F (1, 42)=4.961, p= 0.031); (ii) patients in the NCC group had a better « First

trial memory score » than patients in the SCZ group (NCC= 17.7 ±5.4; SCZ= 14.8 ±4.9; F (1, 61)=5.142, p= 0.027), and they completed more stages on first trial (NCC= 5.7 ±1.2; SCZ= 4.9 ±1.1; F (1, 61)= 7.838, p=0.007) (iii) however, patients in the COC group did not perform better than patients in the SCZ group.

- *A posteriori analysis: subjective and objective performance*

Since the DD group showed a non-significant trend towards greater cognitive complaints, we investigated the interactions between objective and subjective cognition. Pearson's correlation analyses were performed between the SSTICS and PAL scores, for each groups. In the DD group, negative correlations were observed between the SSTICS and two PAL scores: « first trial memory score » (r= -0.372; p 0.017) and « number of stages completed on first trial » (r= -0.361; p= 0.02). Also, a positive correlation was found between the SSTICS and PAL « total errors » (r= 0.342; p= 0.029). In the SCZ group, negative correlations were observed between the SSTICS and two PAL scores: « number of stages completed » (r= -0.419; p= 0.017) and « number of SC on first trial » (r= -0.416; p= 0.018). Thus, in both groups, patients reported greater cognitive complaints when their objective performance was worse.

Discussion

The main finding of the study regards the cognitive performance of DD patients on the CANTAB PAL task, which was better than the performance of SCZ patients. Our results suggest that DD patients are less impaired in visuo-spatial explicit memory, a fronto-temporal function, and psychomotor processing. Paradoxically, patients in the DD group tended to report greater cognitive complaints than SCZ patients. As such,

our results suggest that DD patients could be more conscious of their cognitive deficits, even if they objectively perform better than SCZ patients. However, in both groups, there was a relation between subjective complaints and the actual performance: the worse the objective performance, the greater the cognitive complaints.

Our results replicate the findings of two recent studies showing that DD patients are less impaired in their cognitive functioning than SCZ patients (Carey et al., 2003; Joyal et al., 2003). To date, only a few studies have assessed the cognitive performance of DD patients, with results being far from conclusive. Some studies have failed to demonstrate any differences between DD and SCZ patients (Pencer & Addington, 2003; Addington & Addington, 1997; Cleghorn et al., 1991), while other studies have shown greater cognitive impairments among DD patients (Liraud & Verdoux, 2002; Allen et al., 2000) – mainly those abusing cocaine (Serper et al., 2000a, 2000b). Future studies will need to explain the contradictory nature of the results published so far. In our opinion, the type of substances abused, the length of the addiction history and compliance with medication could be key confounding factors to control in greater detail. In that regard, it is noteworthy that cocaine consumption has affected our results. Indeed, only the DD patients not addicted to cocaine showed a better cognitive performance on the PAL task, compared to SCZ patients.

The principal strength of the study lies in the use of CANTAB to assess cognition in dual diagnosis schizophrenia. CANTAB comprises a series of computerised tasks well validated and precise enough to detect subtle differences between groups of patients with neuropsychiatric disorders (Fray et al., 1996). To our

knowledge, this is the first study to investigate cognition in addicted schizophrenia patients with CANTAB.

The current study has limitations. Only one cognitive function (PAL) has been assessed in the study, because it was the only function common to all participants. In addition, intelligence was not controlled. Lastly, we were not able to provide chlorpromazine equivalents for the two groups. But we established that the DD patients were more frequently treated with typical antipsychotics, which can impair cognitive performance. In the same vein, DD patients presented a more florid symptomatology, which is associated with more, not less, cognitive deficits.

The current cross-sectional study has shown DD patients to be less impaired in their cognitive functioning, compared to SCZ patients. As such, our results suggest either that substance abuse relieves the cognitive deficits of schizophrenia (self-medication hypothesis) or that the patients with less cognitive deficits would be more prone to substance abuse. However, two series observations can be objected against the self-medication hypothesis: (i) acutely, no psychoactive substance has a positive impact on explicit memory; (ii) in their chronic effects, alcohol, cannabis and cocaine impair visual explicit memory. In the future, longitudinal data would be required to discriminate between these two interpretations.

Addendum

Group matching being sub-optimal, an analysis of covariance was performed with group as the independent variable, and age, length of disease, PANSS total score and antipsychotic type (1^{st} versus 2^{nd} generation). This ANCOVA revealed significant differences between patient groups, where dual diagnosis patients showed better cognitive performances (and better subjective insight) on the following scores: (i) PAL first trial memory score [F (5,70)= 6.257; p= 0.0001]; (ii) PAL stages completed [F (5,70)= 5.674; p= 0.0001]; (iii) PAL stages completed on first trial [F (5,70)= 7.587; p= 0.0001]; (iv) PAL total errors [F (5,70)= 3.142; p= 0.013]; (v) PAL adjusted total errors* [F (5,70)= 6.886; p= 0.0001]; motor screening score [F (5,70)= 4.632; p= 0.001]); and (vi) SSTICS total score [F (5,68)= 4.755; p= 0.001]). Only "PAL total trials" did not emerged as significant, after adjustment for age, length of disease, PANSS total score and antipsychotic type [F (5,70)= 1.425; p= 0.226].

* Total errors adjusted for trials completed.

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4e article

Increased extrapyramidal symptoms in schizophrenia patients with a comorbid substance use disorder.

Stéphane Potvin (PhD candidate) [1,2]; Tania Pampoulova (MD, MSc) [1,2]; Adham Mancini-Marië (MD) [1,2]; Olivier Lipp (MD) [2]; Roch-Hugo Bouchard (MD) [3]; Emmanuel Stip (MD, MSc) [1,2].

[1] Centre de recherche Fernand-Seguin, Hôpital Louis-H Lafontaine

[2] Hôpital Louis-H Lafontaine, University of Montreal

[3] Centre de recherche Université Laval Robert-Giffard

Running title

EPS in dual diagnosis schizophrenia

Key words

Comorbidity – schizophrenia – substance use disorders – cocaine – extrapyramidal symptoms

Corresponding author

Emmanuel Stip, MD, M.Sc, CSPQ; Centre de recherche Fernand-Seguin; 7331, rue Hochelaga; Montreal, Quebec, Canada; H1N 3V2; Tel: (514) 251-4015; Fax: (514) 251-2617; E-mail address: emmanuel.stip@umontreal.ca

Abstract

A paucity of data has been gathered about the impact of psychoactive substances on extrapyramidal symptoms (EPS) in schizophrenia. So far, inconsistent results have been reported. Forty-one schizophrenia outpatients (n=41) (DSM-IV criteria) were divided into two groups: with (n=17) and without (n=24) a substance use disorder (alcohol, cannabis and/or cocaine). Both groups were matched for socio-demographic data and psychiatric symptoms (PANSS). EPS were evaluated with the ESRS and the BAS and all patients were stabilized either on quetiapine or clozapine. Patients receiving anticholinergic drugs were excluded. Analyses of variance were conducted on both groups and showed that schizophrenia patients with a comorbid substance use disorder (especially cocaine) displayed more EPS, compared to non-abusing patients.

1. Introduction

The lifetime prevalence of substance used disorders (SUD) in schizophrenia is close to 50%. In decreasing order, patients abuse alcohol, cannabis and cocaine. Psychoactive substances (PAS) have negative consequences on the course of the pathology, which translate into a higher incidence of psychotic relapses, depressive episodes, homelessness, unemployment, as well as legal and health problems[1].

Antipsychotic medications have been the mainstay of schizophrenia treatment since the early 1950s. Efficacious for positive symptoms, antipsychotic treatment can lead to disabling extrapyramidal symptoms (EPS), such as parkinsonian signs, dystonia and dyskinesia. These antipsychotic-induced EPS (especially parkinsonism) are most probably related to striatal dopaminergic blockade[2].

PAS may interact with antipsychotics in the development of EPS. Indeed, most PAS exert an impact on the basal ganglia[3], despite heterogeneous mechanisms of action. Although not systematically studied, most PAS have been associated with extrapyramidal side effects[4]. Cocaine has been associated with signs of parkinsonism, dystonia, dyskinesia and akathisia[5]. Cocaine blocks dopamine transporters localized in the nigrostriatal system, whose dopaminergic neurons project from the substantia nigra pars compacta to the dorsolateral striatum. In its acute effects, cocaine increases striatal dopamine release in humans[5]. However, its chronic effects are associated with striatal dopaminergic down-regulation[6], similar to the striatal dopamine deficit observed in Parkinson's disease. In the case of alcohol, the withdrawal from this PAS is associated with signs of autonomic hyperactivity, including tremors. Whether chronic alcohol consumption is a risk factor for movement disorders remains controversial. As for cannabis, its effects on movement in humans are not well documented but animal studies show that it induces catalepsy

and potentiates neuroleptic-induced hypokinesia. The main psychoactive agent of cannabis (Δ^9-tetrahydrocannabinol) binds to the CB_1 cannabinoid receptor localized in the substantia nigra pars reticulata and globus pallidus. CB_1 receptor was shown to be involved in movement inhibition in animals[7].

A paucity of data has been gathered about the effects of PAS on EPS in schizophrenia and inconsistent results have been reported. Whereas some studies have shown increased EPS[8,9], others have shown no differences[10], or even less EPS in dual diagnosis patients[11]. The most consistent finding has been the increased risk for tardive dyskinesia in dual diagnosis patients[9,12].

The study of EPS in dual diagnosis is a difficult topic, since numerous confounding factors may affect results. Noticeably, most published studies have not systematically controlled variables like psychiatric symptoms, antipsychotic dosage and anticholinergic drugs. The current study sought to investigate the effects of PAS on EPS in dual diagnosis schizophrenia, while controlling these factors.

2. Methods

2.1. Participants

Forty-one outpatients with a schizophrenia spectrum disorder diagnosed using the Structured Clinical Interview for DSM-IV (SCID-IV) participated in the study. The scientific research program was approved by the local ethics committee and all subjects gave written informed consent.

Participants were divided into two groups: with and without a SUD (abuse/dependence) (last three months). A cross-sectional study design produced 24 patients in the dual diagnosis (DD) group and 17 patients in the schizophrenia only (SCZ) group. Patients from the DD group suffered from one or more of the following

SUD: alcohol only (n=5); cannabis only (n=12), cocaine plus alcohol or cannabis (n=7). SUD diagnoses were complemented with urine drug screenings. Only patients treated for more than a month either with clozapine or quetiapine -associated with the lowest EPS liability[13]- were included in study. Only five patients were treated with clozapine, all in the SCZ group. The potential effects of antipsychotics on EPS were considered through dose equivalency estimation to 100mg/d of chlorpromazine[14]. Medication adherence was verified using pill count. Patients receiving anticholinergics were excluded from the study.

2.2. Assessments

The Positive and Negative Syndrome Scale (PANSS)[15] was administered to measure severity of schizophrenia symptoms. EPS were evaluated with the Extrapyramidal Symptoms Rating Scale (ESRS)[16]. The ESRS provides a score for the patients' subjective appraisal of his symptoms, objective scores for parkinsonism, dystonia and dyskinesia, and a global evaluation of EPS. Akathisia was evaluated with the Barnes Akathisia Scale[17]. EPS were assessed by three well-trained physicians (TP, AMM & RHB), who were not blind to drug abuse status but were blind to the objective of the study. Quantities of PAS (any PAS) used in the last week by patients in the DD group were also registered. Money spent on PAS was calculated based on the value market in Quebec province (Canada).

2.3. Statistical analyses

Differences in EPS between the DD and SCZ groups were analysed using one-way analyses of variance (ANOVA) with group as the independent variable. Independent t-tests were used to analyse potential differences in socio-demographic data and psychiatric symptoms between groups. Dichotomous variables were evaluated using

Pearson's chi-square test. Correlation analyses were performed using Pearson's test. Statistical analyses were performed using the Statistical Package for Social Sciences, version 10.

3. Results

Both groups of patients did not differ in terms of age (SCZ: 31.8 years±10.9; DD:31.4 years±10.5; t=0.096; p=0.924), sex (SCZ: 5F & 12 M; DD:3F & 21 M; χ^2=1.812; p=0.178), ethnicity (SCZ: 15/17 caucasian; DD: 23/24 caucasian), education level (SCZ: 11.9 years±2.5; DD:11.1 years±2.1; t=0.994; p=0.329) and duration of illness (SCZ: 107.4 months ±103.8; DD: 101.6 months ±105.3; t=0.176; p=0.861). No differences emerged between the two groups for antipsychotic dosage (SCZ:870.7mg ±347.7; DD:761.2 ±327.8; t=1.018; p=0.316). There were also no differences between the two groups in psychiatric symptoms, assessed with the PANSS ([total score] SCZ:86.5±15.5; DD:80.2±10.3; t=1.477; p=0.152). Affective symptoms were controlled with the PANSS "affective factor" (e.g. "somatic concern", "anxiety", "guilt", "tension", and "depression" items). Again, no differences were noticed between the two groups (SCZ:12.8± 2.7; DD:13.7 ±2.7; t=-1.040; p=0.305).

DD patients reported more subjective EPS complaints. The total ESRS score was higher in the DD group than the SCZ group. More specifically, DD patients had more parkinsonian signs than SCZ patients. Similarly, DD patients were more frequently diagnosed with Parkinsonism (Table 1). Consistent with these results, PAS use (any PAS, last week, in dollars) was positively correlated with subjective EPS (r=0.573; p=0.003), total EPS (r=0.496; p=0.014), parkinsonian signs (r=0.449; p=0.028) and global EPS (r=0.472; p=0.020) in the DD group.

A sub-analysis was performed on cocaine (n=7), since it has the worst consequences in schizophrenia[8]. Relative to the SCZ group, patients with abusing cocaine had greater EPS complaints, more total and global EPS, and increased parkinsonian signs, Parkinson diagnoses and signs of akathisia.

Table 1: Extrapyramidal symptoms in dual diagnosis schizophrenia

	Subjective		Total		**Parkinsonism**			Dystonia			**Dyskinesia**			**Global**		**Akathisia**		
	Mean	SEM	Mean	SEM	Mean	SEM	Dx	Mean	SEM	Dx	Mean	SEM	Dx	Mean	SEM	Mean	SEM	Dx
(1) SCZ group (n=17)	1.6	0.3	2.9	0.6	1.9	0.6	4	0.2	0.1	0	0.8	0.3	0	4	0.2	0.3	0.2	0
(2) DD group (n=24)	3.2	0.5	9.3	2.2	8.7	1.9	17	0.3	0.3	1	0.3	0.2	1	4.2	0.4	0.7	0.2	1
(2a) Cocaine (n=7)	3.9	1.4	16.9	6.3	14.7	5.1	6	0.4	0.3	1	1.0	1.0	1	5.6	1.0	1.3	0.5	1
F-value (p-value)																		
1 vs 2	4.687 (0.037)		5.513 (0.024)		8.657 (0.005)			0.071 (0.791)			2.417 (0.128)			0.123 (0.727)		2.050 (0.160)		
1 vs 2a	4.567 (0.044)		11.79 (0.002)		14.88 (0.001)			0.464 (0.503)			0.056 (0.815)			4.835 (0.039)		6.325 (0.020)		
χ^2 (p-value)																		
1 vs 2					8.912 (0.003)			0.726 (0.394)			0.726 (0.394)					0.726 (0.394)		
1 vs 2a					7.889 (0.005)			2.534 (0.111)			2.534 (0.111)					2.534 (0.111)		

DD= dual diagnosis group; Dx= number of patients diagnosed with an EPS; ESRS= Extrapyramidal Symptoms Rating Scale; SCZ= schizophrenia only group; SEM= standard error of the mean

4. Discussion

The current cross-sectional study sought to investigate the effects of PAS on EPS in schizophrenia. DD patients subjectively complained of more EPS. Objectively, the total ESRS score was higher in the DD group relative to the SCZ group. More specifically, DD patients displayed more parkinsonian signs and more Parkinsonism diagnoses than SCZ patients. Noteworthy, PAS use (any PAS) was positively correlated with subjective EPS, parkinsonian signs, total and global EPS in the DD group. Also of interest, no patients in either group suffered from tardive dystonia or tardive dyskinesia. Dystonic and dyskinetic reactions were all acute. This result contrasts with the previous literature on the topic[9,12].

Compared to abstinent patients, DD patients displayed greater EPS (especially parkinsonian signs). As such, this result suggests that PAS may exert a detrimental impact on parkinsonian signs in schizophrenia patients. However, the cross-sectional design of study does not allow to rule out the reverse explanation, namely that schizophrenia patients could use PAS to get a relief from their parkinsonian signs (self-medication hypothesis)[18]. Distinctively, more signs of akathisia were observed in cocaine abusers. Thus, cocaine may worsen akathisia in schizophrenia. This result is consistent with the pharmacology of cocaine, which blocks the dopamine and norepinephrine transporters in the motor pathways[5]. However, it must be considered that cocaine abusers were also abusing either alcohol or cannabis. Thus, the increased signs of akathisia in this group of abusers could be related to poly-substance abuse, not cocaine abuse per se.

Studies conducted on EPS in dual diagnosis schizophrenia have not been conclusive. Noticeably, most studies have not properly controlled variables such as

psychiatric symptoms, antipsychotic dosage and anticholinergics. To overcome these limitations, we controlled confounding effects by matching groups for age, sex, ethnicity, education level, duration of illness, antipsychotic dosage, psychiatric symptoms, and anticholinergic drugs. Nevertheless, uncontrolled factors may have contributed to our results. For instance, affective symptoms were not assessed with a specific scale in the current study, but were controlled with the PANSS "affective factor". Another study limitation was the small sample size. Also, we cannot rule out the potential confounding effects of antipsychotic medication (even after controlling for chlorpromazine equivalency) and of PAS withdrawal or PAS intoxication, which may have mimicked iatrogenic EPS, since patients in the DD group were active abusers at the time of assessment. As mentioned in the introduction, tremors are associated with alcohol withdrawal; dystonia and akathisia with cocaine intoxication; and psychomotor retardation with cannabis intoxication and with cocaine withdrawal.

Future longitudinal studies involving larger samples will be required to discriminate between the self-medication hypothesis and the notion of deleterious effects of PAS on EPS in schizophrenia. Greater attention to cocaine and its consequences in schizophrenia is needed.

Our findings show significant relations between substance abuse and EPS in dual diagnosis schizophrenia patients, but cannot determine in which direction the relation may be, whether SUD lead to higher EPS or vice versa.

Acknowledgments

The study program was supported by AstraZeneca Pharmaceuticals. ES is chairman of the Eli Lilly Chair of Schizophrenia from University of Montreal. SP is holder of a doctoral scholarship from the Canadian Institute in Health Research (CIHR). The authors would like to thank Julie Villeneuve for her comments on the article.

Competing interest

None to disclose

Copyright

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5e article

- BRIEF REPORT -

Quetiapine in patients with comorbid schizophrenia-spectrum and substance use disorders: an open-label trial.

(Short title: Quetiapine in patients with schizophrenia and SUD)

Stéphane Potvin [1,2]; Emmanuel Stip, [1,2]; Olivier Lipp [1,2]; Robert Élie [1,3]; Adham Mancini-Marië [1,2]; Marie-France Demers [4,5]; Marc-André Roy [4,5]; Roch-Hugo Bouchard [4,5]; Alain Gendron [6].

[1] Centre de recherche Fernand-Seguin; Hôpital Louis-H Lafontaine

[2] Department of psychiatry; University of Montreal

[3] Department of pharmacology; University of Montreal

[4] Department of psychiatry, Laval University

[5] Centre de recherche Université Laval Robert-Giffard

[6] AstraZeneca Pharmaceuticals; Montreal, Quebec, Canada

3 475 words

Corresponding author

Emmanuel Stip, MD, MSc, CSPQ; Centre de recherche Fernand-Seguin; 7331 Hochelaga; Montreal, Quebec, Canada H1N 3V2; Tel: (514) 251-4015; Fax: (514) 251-2617; Email: [redacted]

Abstract

Background Preliminary evidence suggests that clozapine relieves craving for psychoactive substances in schizophrenia patients. Quetiapine shares crucial pharmacological properties with clozapine. Promising results have been described with quetiapine therapy in patients with psychosis and substance use disorder. **Methods** Based on DSM-IV criteria, patients were diagnosed with comorbid schizophrenia-spectrum and substance use disorders. Patients were switched to quetiapine for a 12-week open-label trial. Craving, quantities used, days of consumption, severity of substance abuse were assessed every 3 weeks. Alcohol and Drug Use Scales were administered on baseline and end-point. Psychiatric symptoms, depressive symptoms, extrapyramidal symptoms and cognition were also assessed on baseline, week 6 and week 12. **Results** Twenty-four schizophrenia-spectrum patients were included in the LOCF analyses, responding to one or more of the following substance use disorder: cannabis (15 patients); alcohol (10 patients); and other psychoactive substances (9 patients). Overall, severity of substance abuse improved during the study. Less weekly days were spent on drugs of abuse. A decrease in the weekly Canadian dollars spent on psychoactive substances was also observed. Cognition, psychiatric, depressive and extrapyramidal symptoms also significantly improved ($p<0.05$). **Conclusions** In this open-label, uncontrolled trial, significant improvements were noted in substance abuse, psychiatric symptoms, extrapyramidal symptoms and cognition during quetiapine therapy. The study suffered from three main limitations: (i) the open-label design of the study (ii) the patients' poor compliance; and (iii) the small sample size involved. Controlled studies on the use of quetiapine in dual diagnosis schizophrenia are warranted to confirm that the effects are drug-related.

Key words

Schizophrenia – substance use disorders – atypical antipsychotics – quetiapine – positive and negative symptoms – extrapyramidal symptoms – cognition

Introduction

Epidemiological studies report that the lifetime prevalence of substance use disorders (SUD) is close to 50 % among patients with schizophrenia[1]. Schizophrenia patients consume, in decreasing order, alcohol, cannabis and cocaine, if we exclude here tobacco. Psychoactive substances (PAS) exert a negative impact on the course of the pathology. Compared to abstinent patients, schizophrenia patients with SUD relapse more frequently, they are more depressed and suicidal, they engage more frequently in criminal activities, and they are more frequently homeless and unemployed[2].

Because of their anti-dopaminergic activity, conventional antipsychotic medications have been repetitively shown to decrease cocaine self-administration in rodents[3,4]. However, available clinical data suggest that conventional antipsychotics lack efficacy against SUD in schizophrenia[5].

Preliminary evidence from case reports, retrospective and open studies suggests that clozapine relieves craving for psychoactive substances in schizophrenia patients[6,7]. Quetiapine shares crucial pharmacological properties with clozapine. Indeed, both medications show rapid dissociation from D_2-dopamine receptors; they possess a similar 5-HT_{2A}/D_2 affinity ratio; and they act as partial agonists at the 5-HT_{1A} serotonin receptors[8,9]. A 12-week open label trial has shown that add-on quetiapine therapy diminished cocaine intake in 17 patients with bipolar disorder[10]. The same group has also studied 24 psychiatric patients initially treated with

conventional antipsychotic medications. Twelve patients were maintained while 12 were discontinued from their medication. Of them, 8 patients were switched to quetiapine (for clinical purposes) and showed improvements in psychostimulant cravings ($p<0.05$)[11]. Similarly, we have reported a series of eight psychosis patients dependent on cannabis who significantly decreased their consumption after (mean) six months of treatment with quetiapine[12].

Currently, the main explanation for the schizophrenia – SUD comorbidity is the self-medication hypothesis[13]. According to this perspective, schizophrenia patients use PAS to get a relief either from their negative symptoms, their anxio-depressive affects, their extrapyramidal symptoms (EPS) and/or their cognitive deficits. Interestingly, second-generation antipsychotics (including quetiapine) have shown some efficacy in the treatment of these symptoms[14-17]. Also, meta-analyses have shown a lower EPS propensity with some second-generation antipsychotics (including quetiapine), compared to conventional antipsychotic medications[18,19].

The current open-label trial was carried out in order to explore if quetiapine relieves SUD in schizophrenia; and if it retains its antipsychotic properties in dual diagnosis patients.

Methods

Participants

Patients were diagnosed with a schizophrenia spectrum disorder and a comorbid SUD (last 3 months), using the Structured Clinical Interview for DSM-IV (Note: Data about other axis-I and axis-II disorders were not systematically gathered. The SCID was applied by a trained student and trained psychiatrists.). All patients signed

a detailed informed consent form. The study was approved by the local scientific and ethics committee.

Exclusion criteria were the following: (i) patients already on quetiapine or clozapine; (ii) patients hospitalized or acutely ill; (iii) total score lower than 65 on the Positive and Negative Syndrome Scale (PANSS)[20]; (iv) pregnancy; (v) female subjects of childbearing potential without adequate contraception; (vi) abnormal liver function (hepatic enzymes more than 3 times the upper normal limits); (vii) any clinically meaningful unstable renal, hepatic, cardiovascular, respiratory, cerebrovascular disease or other serious, progressive physical disease.

Patients were screened two weeks prior to baseline, where they were switched to quetiapine for a 12-week open-label trial. Before being switched to quetiapine, patients were treated with one or more antipsychotics, which were discontinued within a two-week period (Note: There was no wash-out period). Quetiapine dosage (between 200 and 800 mg) and titration followed the guidelines specified in the Product Monograph (2000). Compliance to quetiapine was assessed via pill count, except for 3 non-collaborative patients. For practical reasons, pill count was complemented with information from the family, pharmacy and/or social worker. Concomitant medications were allowed.

Along with their participation in the study, usual treatment opportunities (e.g. psychosocial intervention, drug counselling, etc.) were allowed. Four patients received such treatment. However, patients in need of a formal addiction treatment program (e.g. therapeutic community) were not included in the study.

Assessments

To measure SUD (all psychoactive substances) in schizophrenia, numerous instruments were administered on weeks 0 (baseline), 3, 6, 9 and 12 (end-point). The cravings of patients for their drug of choice in the last week were assessed using a visual analog scale (from 0 to 100 %), and a modified version of the Penn Alcohol Craving Scale (PACS)[21]. The PACS is a reliable and valid craving scale for alcohol, simple to administer. In the two sites where the study was conducted (Montreal & Quebec City, Canada), schizophrenia patients mostly use alcohol and cannabis. To measure cannabis craving, we replaced in the PACS the word « alcohol » by « drug of choice ». Quantities of PAS used in the last week were also registered, using the TimeLine Follow-Back (TLFB) procedure[22]. Quantities used were noted for all PAS, not only the patient's drug of choice. Amount spent on PAS was calculated based on the value market in Quebec province (Canada). Days of consumption (last week) were also registered. Apart from cravings and PAS use, SUD severity was measured with the Alcohol Use and the Drug Use Scales (AUS & DUS) on baseline and end-point (applied for the last 3 months)[23]. The AUS and DUS are 5-point scales based on DSM criteria for severity of disorder: 1= abstinence; 2= use without impairment; 3= abuse; 4= dependence; and 5= severe dependence. SUD severity (all PAS) was also evaluated with an adapted 8-item scale, based on DSM-IV criteria of substance dependence. A trained student and a trained nurse scored [from 0 (no problem) to 5 (severe problem)] the patient's SUD severity on the following items: (i) loss of control; (ii) time spent on PAS; (iii) impact of SUD on social life; (iv) impact of SUD on daily occupations; (v) physical impact of SUD; (vi) psychiatric impact of SUD; (vii) impact of SUD on compliance; and (viii) ability to enjoy pleasures other than substance use. To complement our evaluation of SUD, urine screenings were

performed on weeks 0 and 12, in search for benzodiazepines, cannabinoids, opiates, phencyclidine and psychostimulants. Patients were informed beforehand of urine screenings. In the case of alcohol, plasmatic GGT (gamma-glutamyltransferase) levels were assessed on weeks 0 and 12. Breath analyses were also performed but did not prove to be useful (all scores= 0).

The psychiatric and depressive symptoms of schizophrenia were evaluated, respectively with the PANSS and the Calgary Depression Scale for Schizophrenia (CDSS)[24], on weeks 0, 6 and 12, by psychiatrists and a trained doctoral student. Extrapyramidal symptoms were evaluated on weeks 0, 6 and 12, using the Extrapyramidal Symptoms Rating Scale[25] and the Barnes Akathisia Scale[26], by psychiatrists and a trained post-doctoral fellow.

Cognition was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB)[27], a series of computerised tasks. The tests were run on computers with touch-sensitive colour monitors. Patients first completed a « motor screening task » (MOT), an index of psychomotor speed, where patients are asked to place a finger on a flashing cross. Then, patients completed the « paired associates learning » (PAL) and "spatial working memory" (SWM) tasks (random order).

During the SWM, participants are successively shown an array of 3, 4, 6 and 8 boxes hiding blue tokens that need to be discovered one by one. The following variables were measured: (i) *Total errors*: the number of times the subject revisits a box in which a token has already been found or a box already found to be empty during the same search; (ii) *Strategy*: a measure of strategy was calculated based on the observation that an efficient strategy is to follow a predetermined search

sequence beginning with the same box (Note: Higher scores denote poorer use of this strategy).

The PAL task is designed to assess visuo-spatial explicit memory. During the PAL task, white boxes are presented on the screen, which open up one by one (random order) to reveal coloured patterns. The patients' task is to remember which pattern belongs in which box (pattern-location association). The task progresses from the first stage, where only one box contains a coloured pattern, to the last stage, where 8 boxes contain a coloured pattern. For each stage, patients are allowed up to nine reminding trials to locate all the patterns. Performance on PAL was scored using 3 indices: (i) Total errors: the total number of incorrect placements, summed across the eight stages; (ii) Total trials (maximum= 10 trials by stage); (iii) First trial memory score: the total number of patterns correctly located, on the first trial, summed across the eight stages (range: 0 – 26) (Note: Higher scores denote better performances).

The patients' cognitive complaints were assessed with the Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS)[28]. The scale comprises 21 Likert-type questions covering four cognitive areas: attention, executive functions, memory and praxis.

Statistical analyses

Symptomatic evolution of the patients during quetiapine treatment was assessed for significance using an analysis of variance (ANOVA) for repeated measures in time, for SUD, psychiatric, neurological and cognitive variables. Quetiapine-related changes from baseline and kinetic changes in study variables were evaluated as *a*

priori contrasts. The critical level of significance for rejecting the null hypothesis was set at 5%. Q-test for heterogeneity (outlier data) was applied when necessary.

Results

Study participants

Thirty-three dual diagnosis outpatients were screened two weeks prior to the baseline. 4 patients did not meet our inclusion criteria. On baseline, 29 patients were thus switched to quetiapine. 5 patients were drop-outs. Unrelated to an increase in PAS use, the 5 drop-outs were related to the following reasons: lost-to-follow-up (2 patients), dissociative experience (1 patient), heightened hostility (1 patient) and tachycardia (1 patient). 23 patients completed the whole trial and another patient abandoned the study after 9 weeks. These 24 patients were included in the last observation carried forward (LOCF) analyses. Socio-demographic data, diagnostic data and data about medication for these patients are presented in Table 1.

The mean *prescribed* dose of quetiapine (week 12) was 545.8 mg ± 258.2, whereas the mean *taken* dose was 466.6 mg ± 227.3 (after pill count).

Table 1: Study participants (n=24)

Data	*Result*
Age	30.7 years ± 10.6
Sex	22 males; 2 females
Ethnicity	22 Caucasian
Duration of illness	95.6 months ± 106.3
Education level	11.4 years ± 2.0
Psychiatric diagnosis	Schizophrenia (14 patients) Schizoaffective disorder (8 patients) Schizophreniform disorder (2 patients)
SUD diagnoses	Alcohol abuse (1 patient) Alcohol dependence (9 patients) Amphetamine abuse (1 patient) Cannabis abuse (1 patient) Cannabis dependence (14 patients) Cocaine abuse (3 patients) Cocaine dependence (4 patients) Phencyclidine abuse (1 patient) Poly-substance use disorder (9 patients)
Previous antipsychotic medication(s) *	Chlorpromazine (1 patient) Flupenthixol (1 patient) Haloperidol (1 patient) Olanzapine (15 patient) Perphenazine (1 patient) Risperidone (5 patients) Thioridazine (1 patient) Ziprasidone (1 patient)
Adjuvant medications	Anticonvulsants (1 patient) Antidepressants (8 patients) Benzodiazepines (3 patients) Mood stabilizers (5 patients)

* Two patients were receiving two antipsychotic medications before being switched to quetiapine

Substance use disorders

Of the 24 patients included in the LOCF analyses, alcohol was the drug of choice for 8 patients; cannabis for 14 patients; cocaine for 1 patient; and PCP for 1 patient. 22 patients used alcohol during the study; 19 patients used cannabis; and 10 patients other PAS (amphetamine, cocaine & PCP).

Overall, SUD severity improved during the study, as assessed via the DSM-IV adapted scale. Fewer days per week were spent on SUD. A decrease in the weekly dollars spent on PAS (all PAS) was also observed (Table 2).

Cravings for alcohol (VAS & PACS) did not improve significantly over time, but weekly money spent on alcohol significantly diminished ($p<0.05$) (Table 2). However, after exclusion of outlier data (Q-test), the decrease in money spent on alcohol was no longer significant ($F(1,80)= 2.716$; NS) (Note: One patient spending 120 weekly canadian dollars on alcohol spontaneously became abstinent). In addition, the decrease in money spent on alcohol was not paralleled by a decrease in plasmatic GGT levels (baseline GGT= 30.3 UI/L ± 5.1 (SEM); end-point GGT= 32.5 UI/L ± 5.6; $F(1,20)= 1.429$; NS) (outlier excluded). Also, the AUS score did not improve over time.

Cravings for cannabis significantly diminished during quetiapine therapy (VAS & PACS) ($p<0.01$ & $p<0.05$), but not weekly money spent on cannabis or other PAS (e.g. amphetamine, cocaine & PCP) (Table 2). In addition, there was a decrease in the number of positive PAS urine screenings. Before quetiapine, 21 positive urine screenings were detected: amphetamine (1 patient), cannabis (15 patients), cocaine (4 patients) and phencyclidine (1 patient). After quetiapine (LOCF), 16 positive screenings were noted: cannabis (13 patients) and cocaine (3

patients). In addition, the DUS score significantly diminished from baseline ($p < 0.05$).

Table 2: Substance use data (ANOVA for repeated measures)

	Week 0 (baseline)		**Week 3**		**Week 6**		**Week 9**		**Week 12 * (LOCF)**		**Baseline vs quetiapine**		
Measures	Means	SEM	Means	SEM	Means	SEM	Means	SEM	Means	SEM	F	Df	P
Cravings (VAS)													
Alcohol (n=8)	55.8	6.2	35.9	6.1	39.6	8.1	55.1	11.5	38.8	8.5	3.009	1,28	NS
Cannabis (n=14)	65.7	5.5	58.6	6.4	44.6	6.6	47.1	6.6	46.4	6.8	15.740	1,52	<0.01
Cravings (PACS)													
Alcohol (n=8)	16.0	1.4	12.0	1.4	12.3	2.3	14.6	2.8	11.3	2.1	3.102	1,28	NS
Cannabis (n=14)	17.4	1.4	16.5	1.8	15.4	1.7	15.4	2.0	14.4	1.8	4.820	1,52	<0.05
$ per week (all PAS)	93.2	13.2	73.2	18.7	60.2	13.6	53.9	9.1	62.4	12.2	7.367	1,92	<0.01
Alcohol (n=22)	30.7	7.4	18.5	4.8	20.0	5.6	18.5	5.7	23.5	6.4	5.532	1,84	<0.05
Cannabis (n=19)	53.2	13.4	39.5	10.1	38.1	10.0	40.3	9.7	47.3	13.3	3.200	1,72	NS
Other PAS (n=10)	55.0	23.5	60.0	35.5	28.0	25.9	12.0	6.8	8.0	4.4	1.562	1,36	NS
Days of consumption	5.4	0.4	4.4	0.5	5.4	0.5	4.4	0.5	4.8	0.5	5.944	1,92	<0.05
AUS	2.5	0.2	---	---	---	---	---	---	2.3	0.2	1.683	1,23	NS
DUS	3.4	0.3	---	---	---	---	---	---	3.0	0.3	4.832	1,23	<0.05
SUD severity**	22.1	0.9	18.0	1.5	18.1	1.1	17.2	1.5	17.3	1.6	20.390	1,92	<0.01

AUS = Alcohol Use Scale; DUS = Drug Use Scale; PACS = Penn Alcohol Craving Scale (modified); PAS= psychoactive substance; SUD= substance use disorder; VAS = Visual Analog Scale; * Twenty-three out of 24 patients completed the whole trial, while one patient completed the study on week 9; ** DSM-IV adapted scale: scores range from 0 to 40

Psychiatric symptoms

There were significant improvements from baseline in positive ($p<0.01$), negative ($p<0.01$), general ($p<0.01$) and total ($p<0.01$) PANSS scores during quetiapine therapy. A significant improvement in depressive symptoms was also observed ($p<0.01$) (Table 3). In the case of EPS, no significant changes in time were noticed. However, the linear trend (baseline vs end-point) emerged as significant for total [$F(1,46)= 5.856$; $p<0.05$] and global [$F(1,46)= 5.719$; $p<0.05$] ESRS scores. Similarly, no significant changes in time in parkinsonian signs were noticed, but the linear trend was significant [$F(1,46)= 4.695$; $p<0.05$] (Table 3).

Table 3: Psychiatric symptoms & EPS (ANOVA for repeated measures)

	Week 0 (baseline)		Week 6		Week 12 (LOCF)		Baseline vs quetiapine		
Measures	Means	SEM	Means	SEM	Means	SEM	F	Df	P
PANSS									
Positive	18.5	0.9	17.1	0.7	15.9	0.9	10.460	1,46	<0.01
Negative	19.4	1.0	18	1.0	15.8	0.9	8.259	1,46	<0.01
General	41.8	1.2	39.8	1.3	36.3	1.4	8.766	1,46	<0.01
Total	79.8	2.2	75.1	2.4	68	2.7	12.33	1,46	<0.01
Depression	7.3	1.0	6.8	1.1	4.1	0.8	8.628	1,46	<0.01
ESRS									
Subjective	4.2	0.6	3.2	0.5	2.8	0.6	3.556	1,46	NS
Total	10.8	3.2	8.9	2.3	4.5	1.2	3.483	1,46	NS
Parkin.	9.9	2.9	8.3	1.9	5.0	1.2	2.759	1,46	NS
Dystonia	0.4	0.3	0.3	0.3	0.0	0.0	0.940	1,46	NS
Dyskinesia	0.6	0.4	0.3	0.2	0.1	0.1	1.520	1,46	NS
Global	4.5	0.4	4.2	0.4	3.5	0.2	3.463	1,46	NS
BAS									
Akathisia	0.6	0.2	0.7	0.2	0.3	0.1	0.234	1,46	NS

BAS= Barnes Akathisia Scale; EPS= extrapyramidal symptoms; ESRS= Extrapyramidal Symptoms Rating Scale; Parkin.= parkinsonian signs

Cognition

There was an overall improvement from baseline in cognition during the study. On the SWM task (n=23), patients also made significantly fewer total errors ($p<0.01$)

during the study. But there was no improvement in their strategy score. On the PAL task, patients made significantly fewer errors ($p<0.05$) and required less trials ($p<0.05$) to complete the task, although their "1st trial memory score" did not improve. There was also no improvement in psychomotor speed, as assessed by the MOT task (Table 4). Paralleling the objective results, patients reported significantly less subjective cognitive complaints on the SSTICS at the end of study, compared to baseline (n=21) (baseline: 30.6 ± 2.1 (SEM); end-point: 27 ± 2.6; F (1,20)=4.666; $p<0.05$).

Table 4: CANTAB (repeated measures ANOVA)

	Week 0 (baseline)		**Week 6**		**Week 12 (LOCF)**		**Baseline vs quetiapine**		
Measures	Means	SEM	Means	SEM	Means	SEM	F	Df	P
Motor screening									
(milliseconds)	1086.3	83.6	996	78.9	921.3	45.9	2.968	1,46	NS
PAL									
1st trial memory score	18.1	1.0	18.3	1.0	19	1.0	0.358	1,46	NS
Total errors	20.3	4.5	14.2	2.7	15.1	4.2	4.616	1,46	<0.05
Total trials	13.5	1.1	12.3	0.7	11.5	0.6	7.281	1,46	<0.05
SWM (n= 23)									
Strategy score	34.1	1.2	31.4	1.6	32.5	1.5	3.295	1,44	NS
Total errors	34.7	5.0	26.4	4.6	27.3	4.1	8.256	1,44	<0.01

CANTAB= Cambridge Neuropsychological Test Automated Battery; PAL= paired associates learning; SWM= spatial working memory

Tolerability

In general, quetiapine was well tolerated. Since schizophrenia is associated with a hyper-dopaminergic state[29] and PAS increase dopamine release[30,31], a high ratio of psychotic relapses could have been expected. However, in the current trial, there was only one psychotic relapse, which occurred two weeks after study end-point and required a change in antipsychotic medication. As it could have been predicted, based on pharmacological interactions between PAS and antipsychotics, numerous adverse events were noted during the study: somnolence (n=14), dizziness (n=8), acute pain (n=7), dry mouth (n=6), cold (n=6), headaches (n=5), cough (n=4), diarrhea (n=4), fatigue (n=4), hypersalivation (n=4), insomnia (n=4), loss of appetite (n=4), palpitations (n=4), sedation (n=4), nausea (n=3) and suicidal ideas (n=3)

Prolactin levels decreased during quetiapine therapy (n=19) (baseline: 9.8 µg/L ± 1.2 (SEM); end-point: 6.1 µg/L ± 1.1; $F(1,18)= 7.140$; $p< 0.05$). This result is consistent with the prevailing literature on quetiapine in single diagnosis schizophrenia[32]. Conversely, an increase in heart rate was observed (baseline: 73.1 beats/minute ± 2.3 (SEM); 80.6 beats/min ± 2; $F(1,23)= 10.28$; $p< 0.01$). Again, this result is consistent with the current knowledge about quetiapine[33], but it could also be the product of a pharmacological interaction between quetiapine and PAS. No weight gain was noticed (baseline: 79.3 kilograms [kg] ± 3.7 (SEM); end-point: 79.1 kg ± 3.6; $F(1,23)= 0.024$; NS). In the literature, quetiapine has been associated with low to moderate weight gain[34].

Methodological note

It has been regularly reported that schizophrenia patients are sensitive to PAS, as patients may develop a SUD even when PAS are used in small quantities. For this

reason, most substance abuse scales (e.g. Addiction Severity Index) under-estimate the severity of SUD in schizophrenia patients[35,36]. Also worth mentioning, poly-substance use is frequent in dual diagnosis schizophrenia[37]. In the current trial, numerous instruments were used to measure SUD in schizophrenia, including instruments used in a different context. For instance, a modified version of the PACS was administered to patients, whether alcohol was their drug of choice or not. In addition, an adapted scale based on DSM-IV criteria was used to evaluate SUD severity. Supporting the use of these procedures, significant positive Pearson correlations were observed between the craving VAS and the PACS on weeks 0 ($r= 0.746$; $p< 0.005$), 6 ($r= 0.883$; $p< 0.005$), 9 ($r= 0.833$; $p< 0.005$; and 12 ($r= 0.778$; $p< 0.005$), but not week 3 ($r= 0.284$; NS). We also noticed significant positive Pearson correlations between SUD severity, as assessed by the DSM-IV adapted scale, and the AUS score on baseline ($r= 0.427$; $p< 0.005$), and between SUD severity and the DUS score on week 12 ($r= 0.656$; $p< 0.005$).

Discussion

The current open-label trial was carried out in order to pursue two objectives: (i) to investigate the evolution of schizophrenia patients with SUD during a homogenous treatment with an atypical antipsychotic medication (e.g. quetiapine); and (ii) to explore whether quetiapine retains its antipsychotic properties in dual diagnosis patients. Overall, the results of the current open-label trial offer partial support for these two hypotheses.

During quetiapine therapy, SUD severity improved (DSM-IV adapted scale & DUS, but not AUS). Fewer days per week were spent by schizophrenia patients on substance use. As for drug cravings, no changes were observed with alcohol, but

cravings for cannabis diminished during treatment, yet money spent on cannabis did not decrease significantly. A decrease in the weekly dollars spent on PAS (all PAS) was also observed, but it did not seem to be related to the decrease in the money spent on a specific PAS. Less money was spent on alcohol by the end of the study. However, after exclusion of outlier data, the decrease in money spent on alcohol was no longer significant. In addition, the decrease in money spent on alcohol was not paralleled by a decrease in plasmatic GGT levels. There was a decrease in positive PAS urine screenings during the study. Before quetiapine, 21 positive urine screenings were detected. After quetiapine (LOCF), 16 positive screenings were registered. However, money spent on cannabis or other PAS (e.g. amphetamine, cocaine & PCP) did not change significantly.

Under quetiapine therapy, there was an improvement in positive, negative, general and total PANSS scores. An improvement in depressive symptoms was also observed. In addition, there was an overall improvement in cognition during the study. On the PAL task (visuo-spatial explicit memory), patients made fewer errors and required less trials to complete the task, although their "1st trial memory score" did not improve. On the SWM task, patients also made fewer total errors during the study. But there was no improvement in their strategy score, which measures the "central executive" component of working memory. There was also no significant improvement in psychomotor speed, as assessed by the MOT task. In accordance with these objective results, schizophrenia patients reported less subjective cognitive complaints at the end of study, compared to baseline. These results are consistent with the literature on quetiapine and its impacts in non-abusing schizophrenia patients[17,38,39]. EPS (especially parkinsonian signs) also improved significantly, but only when the linear trend (baseline vs end-point) was considered. This result is

consistent with the very low EPS propensity of quetiapine[8], whereas olanzapine (the most frequently prescribed antipsychotic medication at baseline) is associated with a low EPS liability[19].

To our knowledge, this is the first study investigating the impact of quetiapine on the substance use profiles of schizophrenia patients with SUD. One of the strengths of the study was the systematic assessment of poly-substance abuse, instead of specific PAS. Lending support to our decision, poly-susbtance use was frequent in the patient sample (21/24 patients), as expected. Also of value, the study comprised a systematic evaluation of the key symptoms identified by the self-medication hypothesis, namely negative symptoms, depression, EPS & cognition. In addition, cognition was measured with CANTAB, a battery of automated cognitive tests highly sensitive to detect subtle cognitive deficits in neuropsychiatric disorders[40].

Overall, our results cannot be attributed *per se* to the pharmacological effects of quetiapine, for three main reasons: (i) the open-label design of the study which does not control the placebo effect; (ii) the patients' poor compliance; and (iii) the small sample size involved. In the specific case of cognition, a practice effect cannot be excluded. However, the preliminary results reported here may encourage other research groups to investigate with greater methodological care the impact of antipsychotics on cognition in dual diagnosis schizophrenia. Another limitation of the study was SUD assessment. By evaluating poly-substance abuse, the study intended to reflect more closely the daily reality of patients. But this strategy has limited the statistical power of the analyses performed on specific PAS. Finally, it must be acknowledged that 15 patients at baseline were treated with olanzapine, which has shown an efficacy in dual diagnosis schizophrenia in preliminary reports[6].

Conclusion

During quetiapine therapy, improvements in SUD severity were observed among schizophrenia patients. As for substance cravings, no significant changes were observed with alcohol, but cravings for cannabis diminished during treatment. A decrease in the weekly canadian dollars spent on PAS (all PAS) was also observed, but it could not be attributed to a decrease in the money spent on a specific PAS. Due to the study design, it cannot be inferred that the improvements in SUD were actually related to the pharmacological effects of quetiapine. Regarding symptomatology, there was an improvement in positive, negative and depressive symptoms. In addition, there was an overall improvement in cognition during the study. However, no significant changes in time in EPS were noticed. Improvements in SUD were related in time with changes in psychiatric symptoms and spatial working memory. This finding may suggest that improvements in schizophrenia symptoms rendered PAS use less necessary or less detrimental, as predicted by the self-medication hypothesis. However, the reverse explanation cannot be excluded, namely that the patients' psychiatric/cognitive symptoms improved secondary to improvements in SUD. Future studies will need to assess the impact of first- and second-generation antipsychotics on specific PAS use in schizophrenia, in double-blind placebo controlled trials.

Acknowledgments

The authors wish to dedicate this work to Dr Jean-Yves Roy, a pioneer psychiatrist in Quebec who passed way before the completion of this trial. The study was supported by AstraZeneca Pharmaceuticals. ES is holder of the Eli Lilly Chair of Schizophrenia from the University of Montreal. SP is holder of a doctoral scholarship from the Canadian Institute in Health Research (CIHR). The authors would like to thank the doctors, students and staff who helped in recruitment (Pierre Léouffre, Christo Todorov), patient follow-up (Patrick Barabé, Richard Cloutier, Mimi Dumont, Lise Fournier, Marc-André Sirois) and study assessments (Nancy Légaré, Tania Pampoulova).

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Article VI

- BRIEF REPORT -

Anhedonia and social adaptation predict substance abuse evolution in dual diagnosis schizophrenia

(Running title: Predictors in schizophrenia with SUD)

Stéphane Potvin *(PhD)*[1,2]; Emmanuel Stip *(MD,MSc)*[1,2]; Olivier Lipp *(MD)*[1,2]; Marc-André Roy *(MD)*[3]; Marie-France Demers *(MSc)*[3]; Roch-Hugo Bouchard *(MD)*[3]; Alain Gendron *(PhD)* [4].

[1] Centre de recherche Fernand-Seguin; Hôpital Louis-H Lafontaine; Montreal, Canada

[2] Department of psychiatry; University of Montreal; Montreal, Canada

[3] Centre de recherche Université Laval Robert-Giffard; Quebec, Canada

[4] AstraZeneca Pharmaceuticals; Montreal, Canada

Words 1662

Corresponding author

Emmanuel Stip, MD, MSc, CSPQ; Centre de recherche Fernand-Seguin; 7331 Hochelaga; Montreal, Quebec, Canada H1N 3V2; Tel: (514) 251-4015; Fax: (514) 251-2617; Email: [redacted]

Abstract

Background The current study sought to identify the variables, derived from the self-medication hypothesis, which predicted SUD evolution during a homogeneous 3-month antipsychotic treatment (quetiapine). **Methods** Twenty-four patients were diagnosed with schizophrenia and SUD (mainly cannabis and alcohol). SUD, psychiatric symptoms, anhedonia and social adjustment were assessed at baseline and study endpoint. Linear regression analyses were performed. **Results** Regression analyses showed that better social adaptation and worse anhedonia predicted SUD improvements. Conversely, greater PAS use predicted endpoint positive and depressive symptoms. **Conclusions** These results suggest that: (i) substance abuse may interfere with psychiatric prognosis in schizophrenia; and (ii) dual diagnosis treatments leading patients to engage in alternative social activities may render the social lifestyle of substance abuse less appealing. Large-scale longitudinal studies are warranted to dissociate the causes and consequences of substance abuse in schizophrenia.

Key words

Schizophrenia – substance use disorders – anhedonia – social adaptation

1. Introduction

Epidemiological studies report that the lifetime prevalence of substance use disorders (SUD) is close to 50 % among schizophrenia patients (Kavanagh et al., 2002; Regier et al., 1990). In decreasing order, schizophrenia patients consume alcohol, cannabis and cocaine. To account for the high prevalence of SUD in schizophrenia, the main model is Khantzian's self-medication hypothesis (Khantzian, 1997,1985). According to this hypothesis, schizophrenia patients use PAS as a means to alleviate distress and painful affect, and negative-type symptoms such as blunted affect, anhedonia and social isolation/maladjustment (Mueser et al., 2000). Consistent with the hypothesis, some studies show that schizophrenia patients who abuse cannabis or cocaine have less severe negative symptoms, compared to abstinent patients, a result confirmed by 2 recent meta-analyses (Potvin et al., 2006a; Talamo et al., 2006).

In contrast with the self-medication hypothesis, which suggests that schizophrenia leads to substance abuse, the "vulnerability model" states the reverse, namely that substance abuse actually "causes", precipitates or exacerbates schizophrenia (Tien and Anthony, 1990). Coherent with this view, there is evidence that psychoactive substances (PAS) exert a negative impact on the course of the pathology. Compared to abstinent patients, addicted schizophrenia patients experience more frequently psychotic relapses and depressive episodes (Mueser et al., 1998). In addition, substance abuse is associated with an earlier age of psychosis onset in schizophrenia, which suggests that PAS act as triggers of first-episode (Veen et al., 2004). Although controversial, the best evidence in favour of the vulnerability model comes from longitudinal studies reporting a two-fold increased risk to develop psychotic symptoms in cannabis smokers, relative to non-smokers (Arseneault et al., 2002; Fergusson et al., 2005; Henquet et al., 2005).

Most studies of SUD in schizophrenia have a cross-sectional design and involve patients treated with heterogeneous antipsychotic medications (Addington and Addington, 1997; Bersani et al., 2002; Serper et al., 1999). The current study is a 3-month follow-up of dual diagnosis patients treated with a homogeneous antipsychotic treatment, namely quetiapine (for more details, see Potvin et al., 2006b). A second-generation antipsychotic, quetiapine has an efficacy for the treatment of the key symptoms (e.g. negative symptoms) that patients theoretically try to self-medicate (Srisurapanont et al., 2004). The prospective study sought to identify the variables, derived from the self-medication hypothesis, which predict SUD evolution in schizophrenia, and sought to determine if substance abuse is a predictor of symptomatic evolution, as it can be inferred from the vulnerability model.

2. Methods

2.1 Participants

Based on DSM-IV criteria, patients were diagnosed with a schizophrenia spectrum disorder and comorbid SUD (abuse or dependence) (last 3 months). All patients signed a detailed informed consent form. The study was approved by the local scientific and ethics committee.

Exclusion criteria were the following: (i) patients already on quetiapine or clozapine; (ii) patients hospitalized or acutely ill; (iii) total score lower than 65 on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987); (iv) pregnancy; (v) female subjects without adequate contraception; (vi) any clinically meaningful unstable physical disease.

On baseline, 29 dual diagnosis outpatients were switched to quetiapine for a 12-week open-label trial. Five patients were drop-outs, related to the following reasons: lost-to-follow-up (n=2), dissociation (n=1), hostility (n=1) and tachycardia (n=1). Twenty-three patients completed the whole trial and another patient abandoned the study after 9 weeks. These 24 patients (22 males; 2 females; mean age: 30.7 years ± 10.6; 22 Caucasian) were included in the last observation carried forward (LOCF) analysis.

Patients suffered from schizophrenia (n=14), schizoaffective disorder (n=8) and schizophreniform disorder (n=2). Mean duration of illness was 95.6 months ± 106.3. Mean education level was 11.4 years ± 2. Patients were diagnosed with the following SUD: cannabis (n=15); alcohol (n=10); cocaine (n=7); amphetamine (n=1); and phencyclidine (n=1); including 10 cases of poly-substance abuse. The mean *taken* dose of quetiapine (week 12) for trial completers (n=24) was 466.6 mg ± 227.3 (pill count).

2.2 Assessments

To measure SUD in schizophrenia, various instruments were administered on weeks 0 (baseline) and 12 (end-point). Quantities used in the last week – all PAS – were registered, according to the TimeLine Follow-Back procedure (Sobell and Sobell, 1992). Amount spent on drugs of abuse was calculated based on the value market in Quebec province (Canada). SUD severity was measured with the Alcohol Use and Drug Use Scales (AUS & DUS, composite score) (Drake et al., 1990). SUD severity (all PAS) was also evaluated with an 8-item adapted scale, based on DSM-IV criteria of SUD [22]. A trained doctoral student and a trained nurse scored [from 0 (no problem) to 5 (severe problem)] the patients' SUD severity on the following items:

(i) loss of control; (ii) time spent on PAS; (iii) impact of SUD on social life; (iv) impact of SUD on daily occupations; (v) physical impact of SUD; (vi) psychiatric impact of SUD; (vii) impact of SUD on compliance; and (viii) ability to enjoy pleasures other than substance use.

Psychiatric variables were assessed with the PANSS, the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990), the Chapman Physical and Social Anhedonia Scales (a 101-item self report) (Chapman et al., 1976), and the Social Adjustment Scale (a 42-item self-report) (Weissman et al., 1981).

2.3 Statistical analyses

After adjustment for antipsychotic dosage, stepwise linear regression analyses were performed, using baseline negative symptoms, anhedonia and social adjustment as regressors and endpoint SUD scores as dependent variables; and conversely, using baseline SUD scores as regressors and endpoint positive and depressive symptoms as dependent variables. Stepwise regression generates consecutive models in which significant predictors are sorted according to the amount of variance they account for a given dependent variable. Stepwise regression analyses were applied separately on the end-point data and the difference (Δ) between end-point and baseline. The Kolmogorov-Smirnov one-sample test for normality and Q-test for heterogeneity (outlier data) were applied and emerged as non-significant for all variables. Statistical analyses were conducted with the Statistical Package for Social Sciences, version 10. The critical level of significance for rejecting the null hypothesis was set at 5%.

3. Results

3.1 Psychiatric variables as predictors of SUD

For end-point PAS use, the stepwise regression produced a model including two significant predictors (e.g. baseline social adaptation & physical anhedonia) which accounted for 55.3% (adjusted R^2) of the variance [F(3,20)=10.486; p=0.0001]. Baseline social adaptation was a significant predictor which accounted for: 31.5% of the variance of the end-point AUS-DUS composite score [F(2,21)=5.387; p=0.030]; 40.3% of the variance of the end-point DSM-IV adapted scale score [F(2,21)=13.257; p=0.002]; 18.9% of the variance of the ΔPAS use [F(2,21)=5.059; p=0.038]; and 24.5% of the variance of the ΔDSM-IV adapted scale score [F(2,21)=6.255; p=0.021] (Table 1).

3.2 SUD variables as predictors of psychiatric symptoms

Baseline PAS use was a significant predictor which accounted for: 32.1% of the variance of end-point depressive symptoms (CDSS) [F(2,21)=8.225; p=0.009]; and 22.2% of the variance of Δpositive symptoms (PANSS) [F(2,21)=6.003; p=0.023] (Table 1).

Table 1: Stepwise linear regression analyses

Regressors	R^2	β	t	p-value
Clinical predictors of substance abuse evolution				
Dependent variable: Δ PAS use (in dollars)				
Social adaptation	0.189	0.443	2.209	0.038
Dependent variable: Δ DSM-IV adapted scale				
Social adaptation	0.245	0.483	2.501	0.021
Dependent variable: Endpoint AUS – DUS composite score				
Social adaptation	0.204	0.460	2.321	0.030
Dependent variable: Endpoint PAS use (in dollars)				
Model	0.611 (0.553)*		F(3,20)=10.486	0.0001
- social adaptation		0.651	4.534	0.0001
- physical anhedonia		-0.533	-3.679	0.001
Dependent variable: Endpoint DSM-IV adapted scale				
Social adaptation	0.403	0.625	3.641	0.002
Substance abuse predictors of clinical evolution				
Dependent variable: Δ PANSS-positive symptoms				
PAS use (in dollars)	0.222	0.465	2.450	0.023
Dependent variable: Endpoint depressive symptoms (CDSS)				
PAS use (in dollars)	0.321	0.516	2.868	0.009

CDSS= Calgary Depression Scale for Schizophrenia; PANSS= Positive and Negative Syndrome Scale; PAS= psychoactive substance; β= standardized regression coefficient; R^2= % of variance of the dependent variable explained by the model; Δ: % of change from baseline to end-point; * adjusted R^2

Discussion

The prospective study sought to identify the variables, derived from the self-medication hypothesis, which predict SUD evolution in schizophrenia, and sought to determine if substance abuse is a predictor of symptomatic evolution, as it can be inferred from the vulnerability model.

In par with the vulnerability model, substance abuse was a predictor of symptomatic evolution. More precisely, greater baseline PAS use predicted more severe end-point depressive symptoms and worse evolution in positive symptoms. These results are consistent with the psychotic relapses and depressive episodes frequently observed in dual diagnosis patients (Hunt et al., 2002; Margolese et al., 2006; Mueser et al., 1998).

Social adaptation emerged as a significant predictor of all substance abuse scores (end-point and Δ). That is, worse social functioning (e.g. higher social adaptation scores) predicted worse SUD outcomes. This result is consistent with previous studies showing increased social problems in dual diagnosis schizophrenia (Mueser et al., 1998; Negrete, 2003). Stepwise regression analyses also produced a model where (physical) anhedonia emerged with social adaptation as significant predictors of PAS use (endpoint), whereas negative symptoms did not emerge as significant predictors. The more patients suffered from anhedonia, the less they used PAS at the end of the study [regression coefficient (β)= –0.533], a result in par with a recent meta-analysis showing that schizophrenia patients with SUD suffer from less anhedonia symptoms, relative to non-abusing patients (Potvin et al., 2006b).

Consistent with the self-medication hypothesis, our results suggest that substance abuse may be related to specific negative symptoms in schizophrenia, not to negative symptoms *per se*. They also suggest that there may be no direct

relationship between anhedonia and substance use in schizophrenia, but instead, a relation between anhedonia, social adaptation and substance use. In the current study, the greatest SUD improvements occurred in patients with the most severe anhedonia symptoms and the greatest social adaptation in terms of job, school, family, hobbies and intimate relationships. Thus, we would like to hypothesize that dual diagnosis treatments (pharmacological and/or psychosocial) may produce their greatest SUD benefits in the patients corresponding to the social and symptomatic profile described here. In dual diagnosis patients, treatments leading patients to engage in alternative social activities may render the social lifestyle of substance abuse less necessary and less appealing.

The regression analyses performed in the current prospective study provide results consistent with both the self-medication hypothesis and the vulnerability model. As such, our results show that these comorbidity models are not necessarily contradictory with one another, but may be in fact complementary. For instance, our results do not support a direct relationship between negative symptoms and substance use, but highlight instead a relationship between substance use, anhedonia and social adaptation. Noteworthy, our data may help identify the characteristics of dual diagnosis patients (e.g. anhedonia & social adaptation) which are the most likely to benefit from dual diagnosis treatments. However, our results must be considered cautiously, since the clinical the trial involved a small sample.

Controlled studies of treatments (pharmacological and/or psychosocial) rewarding social leisure other than the substance abuse lifestyle are required in dual diagnosis schizophrenia. Large-scale longitudinal studies are also warranted to dissociate the causes and consequences of substance abuse in schizophrenia.

Acknowledgments

The authors wish to dedicate this work to Dr Jean-Yves Roy, a pioneer psychiatrist in Quebec who passed way before the completion of this trial. The study – an Investigator Initiated Trial (IIT) – was supported by AstraZeneca Pharmaceuticals. ES is holder of the Eli Lilly Chair of Schizophrenia from the University of Montreal. SP is holder of a doctoral scholarship from the Canadian Institute in Health Research (CIHR). The authors would like to thank the doctors and staff who helped in recruitment (Pierre Léouffre), patient follow-up (Patrick Barabé, Richard Cloutier) and study assessments (Lise Fournier).

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7e article

Endogenous cannabinoids in patients with schizophrenia and substance use disorder during quetiapine therapy

Stéphane Potvin (PhD cand)[1,2], *Édouard Kouassi* (PhD)[4], *Olivier Lipp* (MD)[1,3], *Roch-Hugo Bouchard* (MD)[5], *Marc-André Roy* (MD)[5], *Marie-France Demers* (MSc)[5], *Alain Gendron* (PhD)[6], *Giuseppe Astarita* (PhD)[7], *Daniele Piomelli* (PhD)[7], *Emmanuel Stip* (MD, MSc)[1,3].

[1] Fernand-Seguin Research Center, Louis-H Lafontaine Hospital; Montreal, Canada

[2] Biomedical Sciences Program, Faculty of medicine, University of Montreal; Montreal, Canada

[3] Department of psychiatry, Faculty of medicine, University of Montreal; Montreal, Canada

[4] Department of pharmacology; Faculty of medicine; University of Montreal

[5] Centre de recherche Université Laval Robert-Giffard; Quebec, Canada

[6] AstraZeneca Pharmaceuticals; Montreal, Canada

[7] ***Departments of Pharmacology and Biological Chemistry, University of California, Irvine; California, USA***

Corresponding author

Emmanuel Stip, MD, MSc, CSPQ; Centre de recherche Fernand-Seguin; 7331 Hochelaga; Montreal, Quebec, Canada; H1N 3V2; Tel: (514) 251-4015; Fax: (514) 251-2617; Email: emmanuel.stip@umontreal.ca

Acknowledgments

The authors wish to dedicate this work to Dr Jean-Yves Roy, a pioneer psychiatrist in Quebec who passed away before the completion of this trial. The study – an Investigator Initiated Trial – was supported by AstraZeneca Pharmaceuticals. The experiments complied with the current laws of Canada. ES is holder of the Eli Lilly Chair of Schizophrenia from the University of Montreal. SP is holder of a doctoral scholarship from the Canadian Institute in Health Research (CIHR). The authors would like to thank the doctors, students and staff who helped in recruitment (Pierre Léouffre, Christo Todorov), patient follow-up (Patrick Barabé, Richard Cloutier, Mimi Dumont, Lise Fournier, Marc-André Sirois) and study assessments (Nancy Légaré, Tania Pampoulova).

Abstract

Background Recently, it has been proposed that disturbances in the endogenous cannabinoid (ECB) system in schizophrenia may contribute to their enhanced sensitivity to psychoactives substances (PAS), and that the beneficial effects of second-generation antipsychotics for substance abuse in schizophrenia may involve modulatory effects on the ECB system. In the current open-label trial of quetiapine in dual diagnosis schizophrenia, we sought to determine: (i) whether ECB predict substance abuse evolution in patients during treatment; and (ii) whether quetiapine modulates plasmatic ECB. **Methods** Twenty-nine patients with schizophrenia and substance use disorders (SUD) were switched to quetiapine for a 12-week period. Twenty-four patients were study completers (>9 weeks). Peripheral ECB were measured, using high-performance liquid chromatography/mass spectrometry, in patients (at weeks 0,6,12) and 17 healthy volunteers. **Results** Baseline anandamide (AEA) levels were significantly higher in patients, relative to controls. No significant changes in AEA occurred during quetiapine treatment. Baseline AEA predicted endpoint SUD scores (alcohol & cannabis). **Discussion** AEA was elevated in dual diagnosis patients. The observed elevations in AEA levels at baseline are in keeping with growing literature describing ECB dysfunctions in the pathophysiology of schizophrenia. SUD parameters improved during quetiapine therapy, but no changes in ECB occurred over time. It is thus unlikely that improvements in substance abuse were mediated by modulatory effects of quetiapine on plasmatic ECB. In addition, baseline AEA predicted endpoint SUD scores, which makes it a potential target for pharmacological agents aimed at relieving substance abuse in schizophrenia.

Key words *Schizophrenia – substance use disorders – cannabis – endogenous cannabinoids – anandamide – quetiapine*

Abbreviations

2-AG = 2-arachidolyglycerol

AEA = anandamide

AUS = Alcohol Use Scale

CB_1 receptor = cannabinoid-1 receptor

CB_2 receptor = cannabinoids-2 receptor

CDSS = Calgary Depression Scale for Schizophrenia

CNS = central nervous system

CSF = cerebrospinal fluid

DUS = Drug Use Scale

ECB = endogenous cannabinoids

FAEA = bioactive fatty-acid ethanolamides

OEA = oleylethanolamide

PANSS = Positive and Negative Syndrome Scale

PAS = psychoactive substances

PEA = palmitylethanolamide

PET = positron emission tomography

PPAR-α = peroxisome-proliferator-activated receptor-alpha

SUD = substance use disorders

1. Introduction

There is growing interest for the link between schizophrenia and substance abuse. The discovery of the endogenous cannabinoid (ECB) system may help to understand the nature of this link. For decades, cannabis has been reported to induce a transient psychotic disorder, which mimics the positive symptoms of schizophrenia (Nunez & Gurpegui, 2002). Cannabis also seems to provoke an amotivational syndrome mimicking the negative symptoms of the disorder (Solowij & Grenyer, 2002). In addition, cannabis disrupts cognitive functions (e.g. selective attention) recognized as being impaired in schizophrenia (Pope et al., 2001; Emrich et al., 1997). Moreover, recent well-controlled studies suggest that cannabis smoking is associated with a two- to three-fold increase in psychotic symptoms, but not necessarily in psychosis diagnoses (Semple et al., 2005; Arsenault et al., 2002). In light of these observations, cannabis has recently emerged as a reliable "model psychosis" (D'Souza et al., 2004).

Discovered in the last decade, the ECB system is composed of at least two natural ligands, anandamide [AEA] and 2-arachidonoylglycerol [2-AG], and at least two cannabinoid receptors (CB_1 & CB_2) (Ameri, 1999). Preliminary data suggest that the ECB system is dysfunctional in schizophrenia. CB_1 receptors are distributed in high densities in brain regions known to be impaired in schizophrenia, such as the prefrontal cortex, hippocampus and basal ganglia (Ameri, 1999). Moreover, AEA levels are abnormally elevated in the cerebrospinal fluid (CSF) of schizophrenia patients (Giuffrida et al., 2004; Leweke et al., 1999). Also, *post mortem* studies have shown altered CB_1 receptor densities in schizophrenia (Dean et al., 2001). Lastly, an association between the CB_1 receptor gene polymorphism and schizophrenia may exist (Leroy et al., 2001).

The heightened vulnerability of schizophrenia patients to psychoactive substances (PAS), including cannabis, is largely acknowledged. The odds ratio of lifetime substance abuse in patients with schizophrenia is two or three times higher than in the general population – for cannabis, it is 5 or 6 times higher (Regier et al., 1990). Also, the frequency of psychotic relapses and hospitalizations is increased in schizophrenia patients who abuse PAS, including cannabis (Linszen et al., 1994). However, the reasons for this heightened vulnerability remain unclear. One explanation may lie in biological disturbances common to both schizophrenia and substance abuse. For instance, some authors have proposed that dopamine sensitization, a well-characterized pathophysiological feature of schizophrenia (Moghaddam & Krystal, 2003), may render patients more sensitive to the rewarding effects of PAS (Tsapakis et al., 2003; Chambers & Self, 2002). Similarly, we recently proposed that disturbances in the ECB system may provide a mechanistic explanation for the high prevalence of substance use disorders (SUD) in schizophrenia patients (Potvin et al., 2005), considering the implication of the ECB system in both psychotic and addictive processes (Arnold et al., 2005; Giuffrida et al., 2004; Ameri, 1999).

The pharmacological treatment of substance abuse in schizophrenia has not attracted systematic interest until recently. So far, the most promising results have been obtained with clozapine (Green et al., 2002). Based on current knowledge, no antipsychotic drugs have affinities for CB_1 receptors. However, Sundram et al (2005) have recently shown that chronic administration of clozapine, but not haloperidol nor chlorpromazine, decreases [^{3}H]CP55940 binding to the CB_1 receptor in the rat nucleus accumbens. This brain region receives dopaminergic projections from the ventral tegmental area, and mediates the rewarding effects of most PAS, including

cannabis (Wise, 2002). This finding has led this group to hypothesize that the beneficial effects of clozapine for SUD in schizophrenia may involve modulatory effects on the ECB system (Sundram et al (2005).

Quetiapine shares crucial pharmacological properties with clozapine: fast dissociation from D_2-dopamine receptors; similar 5-HT_{2A}/D_2 affinity ratio; and partial agonism at 5-HT_{1A} serotonin receptors (Meltzer et al., 2003). The modulatory effects of quetiapine on CB_1 receptors are unknown. But benefits similar to those of clozapine have been reported with quetiapine in schizophrenia patients abusing amphetamines, cocaine or cannabis (for a review, see Potvin et al., 2005). Based on these preliminary results, we conducted an open-label trial investigating the impact of quetiapine in dual diagnosis schizophrenia. During the trial, we sought to determine: (i) whether baseline ECB predict substance abuse evolution in patients during treatment; and (ii) whether quetiapine modulates plasmatic ECB, as these modulatory effects may provide mechanistic explanations for the reported benefits of second-generation antipsychotics in dual diagnosis patients.

2. Methods

2.1 Participants

Patients were diagnosed with a schizophrenia spectrum disorder and a comorbid SUD (abuse or dependence) (last 3 months), using the Structured Clinical Interview for DSM-IV. All patients signed a detailed informed consent form. The study was approved by the local scientific and ethics committee, and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Exclusion criteria were the following: (i) patients already on quetiapine or clozapine; (ii) patients hospitalized or acutely ill; (iii) patients in need of an inpatient

addiction treatment program; (iv) total score lower than 65 on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987); (v) pregnancy; (vi) female subjects of childbearing potential without adequate contraception; (vii) abnormal liver function (hepatic enzymes more than 3 times the upper normal limits); and (viii) any clinically meaningful unstable renal, hepatic, cardiovascular, respiratory, cerebrovascular disease or other serious, progressive physical disease.

Thirty-three dual diagnosis outpatients were screened. Four patients did not meet our inclusion criteria. At baseline, 29 patients were switched from their previous antipsychotic medication(s) to quetiapine for a 12-week open-label trial. Twenty-three patients completed the whole trial, and another one completed 9 weeks of the study. There were 5 cases of drop-outs for the following reasons: lost-to-follow-up (2 patients), dissociative experience (1 patient), heightened hostility (1 patient) and tachycardia (1 patient).

The 29 patients assessed on baseline suffered from schizophrenia (n=16), schizoaffective disorder (n=11) and schizophreniform disorder (n=2). Mean duration of illness was 91.3 months ±97.4. Mean education level was 11.0 years ±2.1. Patients responded to one or more of the following SUD: cannabis (18 patients); alcohol (13 patients); cocaine (7 patients); amphetamine (1 patient); hallucinogens (1 patient) and phencyclidine (PCP) (1 patient). SUD diagnoses were complemented with drug urine screenings.

Controls consisted of 17 healthy volunteers. Patients and controls were similar in terms of age [patients: 30.1 years (mean) ±10.1 (SD) vs controls: 26.9 years ±6.0; t=1.218; p=0.230], sex [patients: 25 males & 4 females vs controls: 14 males & 3 females; χ^2=0.123; p=0.725] and ethnicity [patients: 27 Caucasian vs controls: 15 Caucasian; χ^2=0.320; p=0.572]. There were no significant differences of

weight between patients and controls (patients: 82.4 kg ± 24.5 vs controls: 74.1 kg ± 15.4; t=1.259; p=0.215).

Before being switched to quetiapine, study completers (n=24) were treated with one or more of the following antipsychotics: olanzapine (15 patients); risperidone (5 patients); ziprasidone (1 patient); haloperidol (3 patients) and other conventional antipsychotics (4 patients). Dosage of quetiapine (between 200 and 800 mg) and titration followed the guidelines specified in the Canadian Product Monograph, 2000 (Note: There was no wash-out period). Compliance to quetiapine was assessed via pill count, complemented with information from the family, pharmacy and/or social worker. Mean prescribed dose of quetiapine (week 12) for trial completers (n=24) was 545.8 mg ± 258.2, whereas the mean taken dose was 466.6 mg ± 227.3 (pill count). Concomitant drugs were allowed.

2.2 Assessments

To measure SUD in patients with schizophrenia, several instruments were administered on weeks 0 (baseline) and 12 (end-point) (for more information, see Potvin et al., 2006). Quantities used (last week) were registered, according to the TimeLine Follow-Back procedure (Sobell & Sobell, 1992). Quantities taken were registered for all PAS, not only the patient's drug of choice. Amount spent on drugs of abuse was calculated based on the market value in Quebec province (Canada). SUD severity was measured with the Alcohol and Drug Use Scales (AUS and DUS) (Drake et al., 1990). The AUS and DUS are 5-point scales based on DSM-IV criteria for severity of SUD: 1= abstinence; 2= use without impairment; 3= abuse; 4=dependence; and 5=severe dependence. SUD severity (all PAS) was also evaluated with an 8-item adapted scale, based on DSM-IV criteria of substance

dependence. The patients' SUD severity was scored [from 0 (no problem) to 5 (severe problem)] on the following items: (i) loss of control; (ii) time spent on PAS; (iii) impact of SUD on social life; (iv) impact of SUD on daily occupations; (v) physical impact of SUD; (vi) psychiatric impact of SUD; (vii) impact of SUD on compliance; and (viii) ability to enjoy pleasures other than substance use.

Psychiatric variables were assessed with the PANSS (Kay et al., 1987) and the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990).

2.3 ECB / bioactive fatty-acid ethanolamides

Peripheral AEA and 2-AG were measured in dual diagnosis patients and healthy volunteers. As exploratory analyses, palimitylethanolamide (PEA) and oleylethanolamide (OEA) were also measured. Although structurally related to AEA, PEA and oleoylethanolamide OEA are two noncannabinoid bioactive fatty-acid ethanolamides (FAEA), as theses lipids do not bind to cannabinoids receptors, but bind with high affinity to the peroxisome-proliferator-activated receptor-alpha (PPAR-α) (LoVerme et al., 2005; Fu et al., 2003).

We collected blood samples (2ml) between 13:00 and 16:00 pm, using heparinized tubes. Within one hour, blood samples were centrifuged (3200 rpm for 15 minutes), and plasma (1ml) was stored at –80°C in glass vials. Plasma samples were spiked with internal standards (100pmol of $[^2H_4]$-OEA and $[^2H_4]$-PEA, 10 pmol of $[^2H_4]$-AEA and 250 pmol of $[^2H_8]$-2-AG) and proteins were precipitated by adding cold acetone. Lipids were extracted with chloroform/methanol/water and quantified by isotope-dilution (Giuffrida et al., 2000) using a 1100-liquid chromatography system coupled to a 1946A-mass spectrometer detector (Agilent Technologies, Inc., Palo Alto, CA) equipped with an electrospray ionization chamber. Lowest limits of

quantification were 0.1 pmol for AEA, 1.2 pmol for OEA and PEA, 1.8 pmol for 2-AG.

2.4 Statistical analyses

Differences in ECB/FAEA plasmatic levels between patients and controls were assessed with analyses of variance (ANOVA) with group as the independent variable. Evolution of psychiatric symptoms, substance abuse and ECB/FAEA during quetiapine treatment was assessed for significance using ANOVA for repeated measures. The Kolmogorov-Smirnov one-sample test for normality was applied. Among FAEA, OEA displayed a non-normal distribution ($Z= 1.589$; $p= 0.013$). For OEA, non-parametric tests were thus used (e.g. Mann-Whitney and Wilcoxon tests). Simple linear regression analyses were also performed, using baseline AEA as a predictor and endpoint psychiatric and substance use scores as dependent variables. Outlier data (Q-test for heterogeneity) were replaced by mean scores. Statistical analyses were conducted with the Statistical Package for Social Sciences, version 10. The critical level of significance for rejecting the null hypothesis was set at 5%.

3. Results

3.1 Clinical evolution (psychiatric symptoms & SUD)

Overall, among patient completers, SUD severity scores (composite AUS-DUS, DSM-IV adapted scale) improved during the study. A decrease in dollars spent weekly on PAS (all PAS) was observed (for more information, see Potvin et al., 2006). Improvements in positive, negative and depressive symptoms were also observed (Table 1).

Table 1: Symptomatic and substance abuse evolution in time (ANOVA for repeated measures)

	Week 0		Week 6		Week 12		Baseline vs quetiapine		
Measures	Means	SEM	Means	SEM	Means	SEM	F	Df	p
PAS use (in dollars)	93.2	13.2	60.2	13.6	62.4	12.2	6.927	1,46	<0.05
Alcohol ($)	30.7	7.4	20.0	5.6	23.5	6.4	2.274	1,42	NS
Cannabis ($)	53.2	13.4	38.1	10.0	47.3	13.3	1.886	1,36	NS
DSM-IV adapted scale *	22.1	0.9	18.1	1.1	17.3	1.6	11.738	1,46	<0.01
AUS	2.5	0.2	---	---	2.3	0.2	1.683	1,23	NS
DUS	3.4	0.3	---	---	3.0	0.3	4.832	1,23	<0.05
PANSS-Positive	18.5	0.9	17.1	0.7	15.9	0.9	10.46	1,46	<0.01
PANSS-Negative	19.4	1.0	18	1.0	15.8	0.9	8.259	1,46	<0.01
PANSS-General	41.8	1.2	39.8	1.3	36.3	1.4	8.766	1,46	<0.01
PANSS-Total	79.8	2.2	75.1	2.4	68	2.7	12.33	1,46	<0.01
CDSS	7.3	1.0	6.8	1.1	4.1	0.8	8.628	1,46	<0.01

AUS= Alcohol Use Scale; CDSS= Calgary Depression Scale for Schizophrenia; DUS= Drug Use Scale; PANSS= Positive and Negative Syndrome Scale; PAS= psychoactive substance; SEM= standard error of the mean; SUD= substance use disorder; * Scores range from 0 to 40

3.2 ECB in patients and controls

At baseline, AEA was detectable in 28 patients (out of 29); and 2-AG in 23 patients. AEA was detectable in 17 healthy volunteers (out of 17); and 2-AG in 8 controls. At baseline, AEA levels were significantly elevated in dual diagnosis patients, compared to healthy volunteers, but not 2-AG levels (Table 2). Despite improvements in substance abuse, AEA levels remained significantly elevated in patients, relative to controls, after treatment with quetiapine [AEA: F (1,39)= 6.29; p= 0.017] [2-AG: F (1,26)= 2.31; p= 0.141].

Table 2: Baseline endogenous cannabinoids in patients with patients with schizophrenia and substance use disorder, relative to controls

ECB	**Patients (baseline)**		***Controls***				
	Mean *	SEM	Mean	SEM	**F**	**Df**	**p**
AEA	6.3	1.2	2.1	0.3	7.130	1,44	0.011
2-AG	39.4	6.1	22.5	3.2	2.150	1,30	0.153
FAEA							
PEA	13.0	1.7	5.7	1.7	6.163	1,23	0.021
					U **		**p**
OEA	22.1	5.5	4.5	0.4	63.000		0.0001

AEA= anandamide; 2-AG= 2-arachidonylgycerol; ECB = endogenous cannabinoids; FAEA = bioactive fatty-acid ethanolamides; PEA= palmitylethanolamide; OEA= oleylethanolamide; SEM= standard error of the mean; * p/mol; ** Mann-Whitney U

3.3 Evolution of ECB in time

Among patient completers, no significant changes in AEA and 2-AG plasmatic levels were observed during quetiapine therapy (Table 3).

Table 3: Endogenous cannabinoids during quetiapine therapy

	Baseline		*Week 6*		**Week 12**				
ECB	Mean *	SEM	Mean	SEM	Mean	SEM	**F**	**Df**	**p**
AEA	5.8	1.1	6.6	1.6	5.7	1.2	0.126	2,44	0.882
2-AG	40.9	7.1	32.2	5.6	34.8	4.6	0.708	2,38	0.499
FAEA									
PEA	13.2	1.8	11.9	1.0	11.7	1.7	0.335	2,26	0.718
							Weeks	**Z ****	**p**
OEA	22.0	6.3	34.7	9.5	20.5	4.1	0 to 6	-0.900	0.368
							0 to 12	-0.400	0.689

2-AG= 2-arachidonylgycerol; AEA= anandamide; ECB = endogenous cannabinoids; FAEA = bioactive fatty acid ethanolamides; PEA= palmitylethanolamide; OEA= oleylethanolamide; SEM= standard error of the mean; * p/mol; ** Wilcoxon Z

3.4 Simple linear regression analyses

Simple linear regression analyses were performed using AEA and 2-AG as predictors, and substance use scores and psychiatric symptoms as dependent variables. To increase statistical power, these analyses involved study completers

(n=24) and drop-outs (n=5). As shown in Table 4, baseline peripheral AEA of patient completers was a significant predictor of endpoint PAS use (in dollars) [F (1,26)= 13.50; p= 0.001], , alcohol drinks [F (1,26)= 4.41; p= 0.046], AUS scores [F (1,26)= 5.39; p= 0.028], cannabis joints [F (1,26)= 7.97; p= 0.009] and DSM-IV adapted scale score [F (1,26)= 6.53; p= 0.017]. Baseline 2-AG did not predict endpoint substance abuse scores, baseline AEA and 2-AG did not predict endpoint psychiatric symptoms, and baseline psychiatric and substance use scores did not predict endpoint AEA and 2-AG values.

Table 4: Baseline endogenous cannabinoids as predictors of substance abuse evolution in dual diagnosis schizophrenia (simple linear regression analyses)

Dependent variable	Predictor	R^2	β	t	p
Endpoint PAS use (in dollars)	AEA *	0.342	0.585	3.674	0.001
Endpoint alcohol drinks	AEA	0.145	0.381	2.101	0.046
Endpoint AUS	AEA	0.172	0.414	2.322	0.028
Endpoint cannabis joints	AEA	0.235	0.484	2.822	0.009
Endpoint DSM-IV adapted scale	AEA	0.201	0.448	2.554	0.017

AEA = anandamide; AUS = Alcohol Use Scale; PAS = psychoactive substance; β = standardized regression coefficient; R^2 = % of the variance of the dependent variable explained by the predictor; * n=28

3.5 Exploratory analyses

At baseline, PEA was detectable in 16 patients; and OEA in 29 patients. PEA was detectable in 8 controls and OEA in 17 controls. At baseline, PEA and OEA plasmatic levels were significantly elevated in dual diagnosis patients, compared to healthy volunteers (Table 2). Despite improvements in substance abuse, PEA and OEA levels remained significantly elevated in patients, relative to controls, after treatment with quetiapine [PEA: $F(1,20)= 4.91$; $p= 0.039$] [OEA: $U= 60.50$; $p= 0.0001$].

Among patient completers, no significant changes in PEA and OEA plasmatic levels occurred during quetiapine therapy (Table 3).

4. Discussion

Table 1 summarizes the results for psychiatric symptoms and substance abuse (for more information, see Potvin et al., 2006). Overall, the improvements in substance abuse observed during the trial are consistent with preliminary results showing benefits of second-generation antipsychotics in dual diagnosis patients (Brown et al., 2003; Green et al., 2002). During the trial, we sought to determine: (i) whether baseline ECB predict substance abuse evolution in patients during treatment; and (ii) whether quetiapine modulates plasmatic ECB, as these modulatory effects may provide mechanistic explanations for the reported benefits of second-generation antipsychotics in dual diagnosis patients.

4.1 ECB

At baseline, peripheral levels of AEA were increased in dual diagnosis patients, compared to healthy volunteers. This result is consistent with the study of De Marchi et al (2003), who found elevated plasmatic AEA levels in schizophrenia patients. It is

also consistent with the findings of Giuffrida et al (2004) and Leweke et al (1999) in the CSF of patients, but discrepant with the results from the same group, who did not find increased plasmatic AEA levels in schizophrenia patients (Giuffrida et al., 2004). The most studied ECB, AEA is a full CB_1 agonist and a partial agonist at CB_2 receptors (Gonsoriek et al., 2000). AEA has multiple functions in the central nervous system (CNS), including processing of natural and drug rewards, memory, stress and pain relief (Ameri, 1999). In the current study, the increased peripheral AEA levels may reflect a state of arousal, produced by an activation of the peripheral sympathetic system. Consistent with this interpretation, physical exercise has been recently shown to produce an elevation in plasmatic AEA levels (Sparling et al., 2003).

To our knowledge, this is the first study to measure 2-AG in patients with schizophrenia. There was no significant difference in baseline 2-AG in patients as compared to controls. This result does not support the hypothesis of Pryor (2000), who proposed an excess in 2-AG platelet release as a mediator of cognitive deficits in schizophrenia.

In par with one of our hypotheses, we discovered that baseline AEA levels were significant predictors of endpoint substance abuse scores. Higher AEA levels on baseline predicted worse substance abuse outcomes (cannabis and alcohol) at study endpoint. This result is consistent with pre-clinical studies showing a role for AEA in drug addiction (Arnold et al., 2005; Basavarajappa & Hungund, 2002; Ameri, 1999), and it may suggest that disturbances in the ECB system in schizophrenia contribute to their enhanced sensitivity to cannabis and alcohol.

Contrary to our expectation, no changes in ECB levels were observed during quetiapine therapy. Therefore, it is unlikely that the presumed benefits of quetiapine

in dual diagnosis patients depend on modulatory effects on ECB. This lack of effect of quetiapine contrasts with the pre-clinical findings from Dean et al. (2005) using clozapine; with the results of De Marchi et al. (2003), who showed a decrease in peripheral AEA levels in schizophrenia patients responding to olanzapine treatment; and with the finding from Giuffrida et al. (2004), who showed cross-sectional differences in cerebrospinal AEA levels in schizophrenia patients treated with first- and second-generation antipsychotics. This lack of effect of quetiapine on ECB levels might suggest that the elevated ECB in dual diagnosis patients are trait- rather than state-dependent. However, this lack of effect of quetiapine must be interpreted cautiously, since schizophrenia patients in our study were also substance abusers, they were mostly on second-generation antipsychotics at study entry, and they were stable in terms of psychiatric symptoms at baseline, whereas patients in the trial from De Marchi et al. (2003) were acutely ill.

4.2 Exploratory analyses

At baseline, peripheral levels of PEA and OEA were increased in patients, compared to healthy volunteers. PEA and OEA levels remained elevated in patients at study endpoint, as no significant changes in PEA and OEA levels occurred during quetiapine therapy.

PEA has well-documented anti-inflammatory actions (Lo Verme et al., 2005). Therefore, the increased PEA levels found in patients may be related to inflammatory processes associated with schizophrenia (Garver et al., 2003) and/or drug abuse (Szabo, 1999).

OEA is an anorexic lipid which produces satiety and reduces weight gain in rodents (Fu et al., 2003). Here, we found increased plasmatic OEA levels in patients,

relative to controls. This result is counter-intuitive, since patients with schizophrenia tend to be over-weighted (Müller et al., 2004), not the reverse. However, patients in our sample did not significantly differ in weight compared to controls. This paradoxical result may be due to substance abuse, which is often associated with loss of appetite (Budney et al., 2004; Falck-Ytter & McCullough, 2000). Further studies are required about the potential role of OEA in appetite/weight disturbances in schizophrenia patients and/or substance abusers.

4.3 Scope and summary

The observed elevations in AEA levels at baseline are in keeping with growing literature describing ECB dysfunctions in schizophrenia. Schizophrenia is thought to involve impairments in dopamine, glutamate and acetylcholine (Moghaddam & Krystal, 2003). Interestingly, these neurotransmitters stimulate AEA synthesis/release in rodents (Stella & Piomelli, 2001; Giuffrida et al., 1999). The fact that baseline AEA levels predicted substance abuse outcomes is of direct interest for future biological studies on dual diagnosis schizophrenia. This finding may suggest that disturbances in the ECB system in schizophrenia contribute to their enhanced sensitivity to cannabis and alcohol. Also, the predictive value of AEA makes it a potential target for new pharmacological probes aimed at relieving substance abuse in patients with or without schizophrenia. Three pharmacological strategies have been examined in pre-clinical studies to modulate AEA activity: (i) the blockade of CB_1 receptors; (ii) the inhibition of AEA transport; and (iii) the inhibition of fatty acid amid hydrolase (FAAH), an enzyme that catalyzes AEA (Cravatt & Lichtman, 2003). In humans, rimonabant (a CB_1 antagonist) reduced the acute effects of cannabis (Huestis et al., 2001) and it is currently under investigation for tobacco

smoking in a phase-III clinical trial. In rodents, rimonabant has been shown to reduce alcohol preference (Lallemand et al., 2001), heroin self-administration (De Vries et al., 2003) and cocaine reinstatement (De Vries et al., 2001). As for AM404 (AEA transport inhibitor), it seems to relieve the signs of withdrawal of morphine in rodents (Del Arco et al., 2002).

Our study had some limitations. First, the size of the sample may explain the negative result for 2-AG. This result may reflect a type-II error, as 2-AG was detectable in 23 patients and 8 controls. Moreover, drugs of abuse were heterogeneous (mostly alcohol, cannabis and cocaine). However, increasing pre-clinical studies show a modulatory role of the ECB system in alcohol-related behaviors (Colombo et al., 2005; Basavarajappa & Hungund, 2002). In addition, the peripheral measurement of ECB makes it difficult to draw conclusions about CNS functioning. Lastly, our study lacked a comparison group of non-abusing schizophrenia patients, which precluded from determining whether elevations in AEA at baseline were related to schizophrenia, substance abuse or an interaction between the two conditions. This problem will be addressed by our group in the near future. However, it must be considered that AEA remained elevated in patients relative to controls at study endpoint, despite significant reductions in PAS consumption during the trial. This makes it unlikely that AEA elevations were merely the result of the acute effects of PAS.

In summary, an increase of baseline AEA levels was observed in patients with schizophrenia and SUD, compared to controls. The result of increased peripheral AEA levels in patients are in keeping with a growing amount of evidence linking disturbances in the ECB system to the pathophysiology of schizophrenia. Contrary to our expectation, no significant changes in ECB levels were observed

during quetiapine treatment. It is thus unlikely that improvements in substance abuse were mediated by modulatory effects of quetiapine on ECB. Lastly, baseline AEA predicted substance abuse outcomes, which makes it a potential target for pharmacological agents aimed at relieving substance abuse in schizophrenia.

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Discussion

1. L'automédication

La prévalence à vie d'une toxicomanie (abus ou dépendance) est près de 50% chez les patients souffrant de la schizophrénie. Dans l'ordre décroissant, ceux-ci consomment de l'alcool, du cannabis, des psychostimulants et des autres substances psychoactives (SPA). La toxicomanie chez les schizophrènes interfère défavorablement avec le cours de la psychopathologie, ce qui se traduit en des rechutes psychotiques, des épisodes dépressifs, des actes de violence, des conduites criminelles, ainsi que des problèmes de logement, d'emploi et de santé (Potvin et al., 2003a; Mueser et al., 1998).

Alors que les conséquences de la toxicomanie chez les schizophrènes sont relativement bien documentées, les raisons qui incitent ces patients à consommer demeurent largement inconnues. De tous les modèles étiologiques formulés jusqu'ici, l'hypothèse de l'automédication est le modèle qui a retenu le plus l'attention des cliniciens et chercheurs. Selon Khantzian (1997, 1985), le schizophrène aurait recours aux SPA en vue d'obtenir un soulagement de certains symptômes clés, incluant les symptômes négatifs et cognitifs de la psychopathologie. Pour qu'une telle construction soit véridique, il importe de démontrer que les schizophrènes toxicomanes présentent moins de symptômes négatifs/cognitifs, comparés aux schizophrènes sans toxicomanie. À cette fin, nous avons entrepris trois études : une méta-analyse, une étude en imagerie par résonance magnétique fonctionnelle, et une étude neuropsychologique transversale.

1.1 Les symptômes négatifs chez les schizophrènes toxicomanes

Afin d'évaluer la validité de l'hypothèse de l'automédication, un certain nombre d'études cliniques transversales ont été réalisées, mesurant l'intensité des symptômes négatifs chez les schizophrènes avec ou sans toxicomanie. Les résultats de ces études n'étant pas uniformes, il nous est apparu opportun d'entreprendre une méta-analyse des études publiées jusqu'ici, en portant une attention particulière à deux facteurs potentiellement confondants, à savoir le type de SPA et l'échelle utilisée pour mesurer les symptômes négatifs. Nous avons identifié 18 études transversales, comparant la symptomatologie négative des schizophrènes avec ou sans toxicomanie, où les symptômes négatifs étaient évalués avec la SANS (Scale for the Assessment of Negative Symptoms). De ces 18 études, 13 études comprenaient des données suffisantes pour faire l'objet d'un traitement statistique (après contact par courriel des auteurs). De plus, 2 des études ont dû être exclues de la méta-analyse pour des raisons méthodologiques. 11 études ont donc été incluses dans le calcul méta-analytique final (Potvin et al., 2006b). Pour chaque étude, nous avons calculé une taille de l'effet (« effect size ») à l'aide des scores moyens (et de l'écart-type) sur le SANS pour chacun des 2 groupes. Utilisant un modèle à effets aléatoires (« random-effect model »), une taille de l'effet composée (« composite effect size ») a été calculée, ajustée en fonction de la taille des échantillons compris dans chacune de ces études. Ainsi, nous avons obtenu une taille de l'effet modérée négative et significative, suggérant que la symptomatologie des schizophrènes toxicomanes serait effectivement moins sévère que celle des schizophrènes sans toxicomanie.

Dans des analyses secondaires, nous avons également pu contrôler une série de facteurs potentiellement confondants, tels que l'âge, le sexe, les symptômes

positifs, la nature de la toxicomanie (présente ou passée), le statut des patients (interne ou externe), etc. Par ailleurs, nous avons pu démontrer que l'anhédonie est le symptôme négatif où les plus grandes différences entre les deux groupes émergent, un résultat compatible avec l'hypothèse de l'automédication de Khantzian. Enfin, une dernière sous-analyse a révélé que l'observation d'une symptomatologie négative moins sévère chez les schizophrènes toxicomanes est valable pour l'abus ou la dépendance au cannabis ou à la cocaïne, mais pas pour l'abus ou la dépendance d'alcool.

1.2 Étude en IRMf

Dans le prolongement de cette méta-analyse, nous avons cherché à démontrer si les différences de symptomatologie négative pouvaient avoir un corollaire sur le plan du fonctionnement cérébral. Selon une hypothèse physiopathologique bien connue, la symptomatologie négative de la schizophrénie serait associée à un fonctionnement déficitaire du cortex préfrontal (Stip et al., 2005b; Fahim et al., 2004; Grace, 1993; Weinberger et al., 1987). Dans la mesure où les schizophrènes toxicomanes ont moins de symptômes négatifs, notre attente était que les schizophrènes avec toxicomanie auraient une réponse émotionnelle accrue lorsque soumis à des stimuli de nature émotionnelle, laquelle se traduirait par une activité accrue du cortex préfrontal.

Des extraits de film de nature émotionnelle furent présentés à 12 schizophrènes avec toxicomanie (cannabis et/ou alcool) et 11 schizophrènes sans toxicomanie alors qu'étaient enregistrées leurs réponses hémodynamiques à l'aide de l'imagerie par résonance magnétique fonctionnelle (IRMf) (appareil 1.5 Tesla). Des extraits de film furent choisis en raison de leur caractère dynamique, qui reflètent

davantage la réalité de tous les jours. Par un procédé de soustraction, des extraits émotionnels (exemple: un fils apprenant la mort imminente de son père) et des extraits neutres (exemple: jardinage) furent présentés aux sujets, selon le protocole « bloc » (« block design ») suivant: (i) extrait émotionnel (3 minutes); (ii) pause (18 secondes); (iii) extrait de film neutre (3 minutes). Après avoir analysé les réponses individuelles à l'aide du logiciel SPM99 (« Statistical Parametric Mapping,99 »), selon un modèle à effets fixes (« fixed-effect model »), un modèle à effets aléatoires (« random-effect model ») fut ensuite implanté pour l'analyse de groupe, permettant de produire des tests t à 1 et 2 échantillon(s). Après l'examen d'IRMf, les sujets étaient invités à évaluer l'intensité de l'expérience émotionnelle induite par les extraits de film sur une échelle visuelle analogue de 0 (pas d'émotion) à 8 (émotion la plus intense jamais vécue).

Conformément à notre hypothèse, les schizophrènes toxicomanes ont rapporté une réponse émotionnelle plus intense que les schizophrènes sans toxicomanie, sur l'échelle visuelle analogue. Sur le plan cérébral, un test t à 1 échantillon a révélé des loci d'activation dans le CPFm (aire 10 de Brodmann) droit et le gyrus supramarginal (aire 40 de Brodmann) dans le groupe avec un double diagnostic, et dans la protubérance du tronc cérébral dans la groupe des schizophrènes sans toxicomanie. Un test t à 2 échantillons a par ailleurs mis en lumière des activations accrues du cortex pariétal supérieur droit (aire 7) et le CPFm gauche (aire 10) chez les schizophrènes toxicomanes, comparés au groupe non-toxicomane (Potvin et al., Sous presse). Ces résultats montrent que les différences de symptomatologie négative entre les schizophrènes avec ou sans toxicomanie ont un corollaire cérébral.

Fait important: nos résultats ne semblent pas dépendre du de substances consommées par les patients. Parmi le groupe toxicomane, 5 patients présentaient un

trouble de consommation d'alcool, alors que 5 patients abusaient à la fois de l'alcool et du cannabis. De façon exploratoire, nous avons réalisé un test t à 2 échantillons, comparant les patrons d'activation cérébrale de chacun de ces sous-groupes. Les activations détectées dans les deux groupes se sont avérées similaires, suggérant que les activations du CPFm et du cortex temporopariétal dans le groupe toxicomane est valable à la fois pour l'abus d'alcool et l'abus de cannabis.

Par ailleurs, nous avons réalisé une seconde étude en IRMf auprès des mêmes patients, mais soumis cette fois à une série d'image statiques conçues et validées pour susciter des réactions aversives spontanées. Soumis à cette seconde série de stimuli émotionnels, le groupe toxicomane a rapporté, ici encore, une réponse émotionnelle plus intense, se traduisant par des activations cérébrale accrues du CPFm, du cortex orbitofrontal, du gyrus parahippocampique et de l'amygdale chez les schizophrènes toxicomanes (voir Annexe I) (Potvin et al., 2006c). Ainsi, les réponses émotionnelles et cérébrales accrues détectées dans le groupe toxicomane ne semblent pas dépendre du type de stimuli utilisés.

1.3 Étude neuropsychologique

Dans son sens usuel, l'hypothèse de l'automédication renvoie à l'idée d'un soulagement des symptômes négatifs par les SPA. De façon analogue, il a été proposé que le schizophrène pourrait recourir aux SPA en vue d'obtenir un soulagement de ces déficits cognitifs. Ici comme dans le cas des symptômes négatifs, il importe tout d'abord de démontrer, de façon contre intuitive, que les schizophrènes toxicomanes ont moins de déficits cognitifs que les schizophrènes sans toxicomanie.

Afin de mettre à l'épreuve cette hypothèse, nous avons comparé le fonctionnement cognitif de 44 schizophrènes toxicomanes (cannabis et alcool,

surtout) et de 32 schizophrènes sans toxicomanie (Potvin et al., 2005a). Ces patients étaient comparés sur deux tâches cognitives choisies parmi la batterie informatisée CANTAB (Cambridge Neuropsychological Tests Automated Battery) (Fray et al., 1996), à savoir le « motor screening task », un test qui mesure la vitesse psychomotrice, et le « paired associates learning task », un test qui mesure la mémoire explicite visuospatiale. L'appréciation subjective des patients de leur propre fonctionnement cognitif était évalué à l'aide du SSTICS (Subjective Scale To Investigate Cognition in Schizophrenia) (Stip et al., 2003). Dans cette étude transversale, nous avons démontré que les schizophrènes toxicomanes présentaient une plus grande vitesse psychomotrice, une meilleure mémoire explicite, et qu'ils avaient tendance à être davantage conscients de leurs déficits cognitifs. Malheureusement, l'appariement des patients dans cette étude n'était pas optimal. Nous avons donc repris les analyses de variance de cette étude, mais en contrôlant cette fois, à titre de co-variables, l'âge, la durée de la pathologie, la sévérité des symptômes (score total au PANSS) et le type d'antipsychotique (« atypique » ou « typique »). Après ajustement en fonction de ces variables, les différences entre les groupes sont apparues davantage significatives (voir Addendum du 3^{e} article de la thèse). Ainsi, conformément à notre attente, nos résultats suggèrent une relative préservation du fonctionnement cognitif des schizophrènes toxicomanes.

1.4 Problème d'interprétation

Que les schizophrènes toxicomanes aient moins de symptômes négatifs, une relative préservation du fonctionnement du CPFm et un fonctionnement cognitif mois altéré est certainement cohérent avec l'hypothèse de l'automédication. Ces résultats posent toutefois un problème d'interprétation. Selon l'hypothèse de l'automédication, les

SPA procureraient au schizophrène un soulagement de certains symptômes clés, comme les symptômes négatifs/cognitifs. Mais rien n'interdit que ce soit l'inverse qui soit vrai, c'est-à-dire que les schizophrènes présentant moins de symptômes négatifs/cognitifs sont davantage prédisposés à développer une toxicomanie. Comme l'ont fait valoir Mueser et al. (2000) et Joyal et al. (2003), la mode de vie de la toxicomanie, aussi dysfonctionnel soit-il, requiert un minimum d'habiletés sociales et de capacités d'organisation, qui font précisément défaut aux schizophrènes présentant les plus sévères symptômes négatif et déficits cognitifs.

En raison de la nature transversale des études décrites dans la présente thèse, il nous est impossible, pour des raisons méthodologiques, de déterminer si la relative préservation affective, cognitive et cérébrale des schizophrènes est primaire ou secondaire à la consommation de SPA.

2. Les conséquences négatives de la toxicomanie chez les schizophrènes

Dans la série d'études réalisées sur la comorbidité schizophrénie – toxicomanie, nous avons mis en relief une série de résultats qui ont une pertinence dans l'élucidation de la complexe étiologie de cette double condition, comme nous venons de le voir. Nous avons également montré des différences entre les schizophrènes avec et sans toxicomanie qui s'ajoutent à la liste des nombreuses conséquences négatives de la toxicomanie chez les schizophrènes (exemples: rechutes, épisodes dépressifs, etc.). En outre, nous avons réalisé une étude transversale comparant les symptômes extrapyramidaux (SEP: signes parkinsoniens, dystonie, dyskinésie et akathisie) de 24 schizophrènes toxicomanes (cannabis, alcool et cocaïne) et de 17 schizophrènes sans toxicomanie (Potvin et al., 2006a). Dans cette étude, le groupe toxicomane présentait davantage de SEP, plus particulièrement les signes parkinsoniens. Une sous-analyse

a également révélé que la consommation de cocaïne était associée à davantage d'akathisie. Ces résultats suggèrent que la consommation de SPA pourrait aggraver les SEP associés à la prise de médicaments antipsychotiques.

3. Traitement pharmacologique

En dépit des conséquences néfastes associées à la toxicomanie chez les schizophrènes, peu d'études pharmacologiques ont été réalisées auprès des patients porteurs d'un double diagnostic, principalement pour des raisons méthodologiques. Récemment, des données préliminaires ont soulevé la possibilité que la clozapine puisse soulager les craving des patients schizophrènes (Drake et al., 2000; Zimmet et al., 2000). Toutefois, en raison de dangers d'agranulocytose, une approche thérapeutique fondée sur la clozapine semble peu pratique. La quétiapine est un analogue pharmacologique de la clozapine, qui partage certaines propriétés clés avec cette molécule (Potvin et al., 2003b). En effet, ces deux antipsychotiques ont un ratio d'affinités similaires pour les récepteurs D_2 de la dopamine et 5-HT_{2A} de la sérotonine; ces molécules se dissocient rapidement des récepteurs dopaminergiques D_2; ce sont des agonistes partiels des récepteurs 5-HT_{1A}; enfin, ces molécules possèdent une affinité modérée pour les récepteurs 5-HT_3 -qui relaient incidemment les effets anti-*craving* de l'ondansetron.

Comme le suggèrent la littérature méta-analytique, la clozapine a une efficacité supérieure aux antipsychotiques de première génération, tels que l'halopéridol, ce qui n'est pas le cas de la quétiapine. Néanmoins, la quétiapine a des propriétés cliniques similaires à la clozapine, qui ont leur importance dans le cadre d'un traitement offert à des patients souffrant de schizohrénie et de toxicomanie. Dans la mesure où les schizophrènes consomment en SPA en guise

d'automédication, il est pertinent d'observer que la clozapine et la quétiapine induisent peu ou pas de dysphorie, peu ou pas de SEP; ces antipsychotiques ont des effets sédatifs, thymorégulateurs et anxiolytiques, et ils présentent une certaine efficacité dans le traitement des symptômes négatifs et des déficits cognitifs (Potvin et al., 2003b).

Pour ce qui est de la toxicomanie, des résultats préliminaires suggèrent que la quétiapine, tout comme la clozapine, pourrait soulager les *craving* de schizophrènes (Potvin et al., 2004; Brown et al., 2003, 2002; voir l'Annexe II).

Partant de ce rationnel pharmacologique et clinique, nous avons réalisé une étude ouverte d'une durée de 12 semaines auprès de patients à la fois schizophrènes et toxicomanes, diagnostiqués à l'aide du SCID-IV. À intervalles réguliers, une évaluation exhaustive de la toxicomanie était effectuée, comprenant les variables suivantes : (i) l'intensité des *craving* pour la substance de choix; (ii) les quantités de toutes les SPA consommées au cours de la dernière semaine; (iii) une évaluation psychiatrique de la sévérité de la toxicomanie; (iv) des dépistages urinaires; et (v) une mesure sanguine des taux hépatiques de GGT (gamma-glutamyl transferase).

L'étude comprenait également une évaluation clinique exhaustive, répétée à intervalles réguliers, comprenant les variables clés dérivées de l'hypothèse de l'automédication, à savoir : (i) les symptômes positifs et négatifs de la schizophrénie, mesurés à l'aide du PANSS; (ii) les symptômes dépressifs, mesurée à l'aide de la CDSS (Calgary Depression Scale for Schizophrenia; (iii) les SEP, mesurés à l'aide de l'ESRS (Extrapyramidal Symptoms Rating Scale) et l'échelle d'akathisie de Barnes; et (iv) le fonctionnement cognitif, mesuré à l'aide de deux tâches cognitives (mémoire de travail, mémoire explicite et vitesse psychomotrice) choisies parmi la batterie de test informatisés CANTAB.

Sur le plan de la toxicomanie, nous avons observé une diminution de l'argent dépensé à la consommation, une diminution des appétences pour le cannabis, de même qu'une amélioration de la sévérité de la toxicomanie. En fin d'étude, les conséquences de la toxicomanie semblaient moins néfastes qu'elles ne l'étaient en début d'étude. Sur le plan clinique, nous avons noté une amélioration de la symptomatologie positive, négative et dépressive. À la fin d'étude, les patients avaient également moins de signes extrapyramidaux. Fait intrigant: les patients se sont améliorés sur le plan de la cognition, que ce soit la mémoire de travail ou la mémoire explicite (Potvin et al., 2006d). Dans l'ensemble, ces résultats suggèrent que la quétiapine pourrait soulager la toxicomanie des schizophrènes, tout en conservant ses habituelles propriétés cliniques. Ils justifient de mieux tester cette hypothèse, à l'occasion d'études bien contrôlées impliquant un plus grand échantillon de patients.

Par ailleurs, nous étions intéressés à déterminer si les variables cliniques à l'entrée de l'étude permettaient de prédire l'évolution de la toxicomanie dans le temps, et inversement, si les variables de la toxicomanie pouvaient prédire l'évolution clinique des patients. Pour cette analyse de régression linéaire multiple, nous avons ajouté comme variables cliniques l'adaptation sociale ainsi que certains traits de personnalité (recherche de sensations fortes et impulsivité), soit des variables inspirés de modèles autres que le traditionnel modèle d'automédication (Potvin et al., Soumis). Cette analyse de régression multiple a mis en relief l'adaptation sociale et l'anhédonie comme variables prédictives de l'évolution de la toxicomanie. En retour, les quantités initiales de SPA consommées se sont avérées prédictives de l'évolution des symptômes positifs et dépressifs (Note: Même si cela n'est pas décrit dans l'article 6 de la thèse, aucune relation ne fut détectée entre la

toxicomanie d'une part, et la cognition et les SEP d'autre part). Ces résultats suggèrent que la sévérité de la toxicomanie constitue un obstacle à une évolution favorable sur le plan symptomatique. Inversement, l'évolution de la toxicomanie semble dépendre de l'anhédonie et de l'adaptation sociale des patients. Ces derniers résultats cadrent bien avec l'hypothèse de l'automédication, et ils suggèrent un lien complexe entre les symptômes négatifs, l'adaptation sociale et la toxicomanie dans la schizophrénie.

4. Les cannabinoïdes endogènes

Parmi les facteurs communs à la psychose et la toxicomanie, il y aurait des perturbations de certains systèmes de neurotransmission, telles que la sensibilisation dopaminergique. Dans cette optique, nous avons formulé une hypothèse impliquant le système des cannabinoïdes endogènes (CBE). Découvert au cours de la dernière décennie, le système des CBE relaie dans le cerveau les effets du cannabis, et il semble dysfonctionnel dans la schizophrénie (Giuffrida et al., 2004). Notre attente générale était que le fonctionnement anormal de ce système pourrait rendre compte, du moins en partie, de la sensibilité particulière des schizophrènes aux SPA. Au cours du projet pharmacologique avec la quétiapine, nous avons effectué un dosage plasmatique des CBE (anandamide et 2-arachidonylglycérol) chez les patients aux semaines 0, 6 et 12 de l'étude, et chez des volontaires sains (dosage à une seule reprise) (Potvin et al., Soumis). Nous avons découvert une élévation de l'anandamide chez les patients, comparés aux volontaires sains. Ces résultats sont compatibles avec la littérature préliminaire qui suggère une implication des CBE dans la pathophysiologie de la schizophrénie. Par ailleurs, la quétiapine n'a eu aucun effet sur les CBE plasmatiques dans le temps. Ces résulats suggèrent que les effets

potentiellement bénéfiques de la quétiapine chez les schizophrènes toxicomanes ne dépendent pas d'un effet modulateur sur les CBE plasmatiques. À la fin du traitement, l'élévation de l'anandamide est demeurée significative chez les patients, malgré une diminution significative de leur consommation de SPA dans le temps. Aussi, il est improbable que les élévations observées en début d'étude aient uniquement été le produit des effets aigus des SPA. Enfin, nous avons observé que les taux d'anandamide en début d'étude étaient de prédicteurs significatifs des scores de toxicomanie des patients en fin d'étude. Ce dernier résultat est compatible avec notre hypothèse de départ, voulant que la sensibilité des schizophrènes aux SPA soit en lien avec des perturbations du système des CBE. De plus, ce résultat laisse présager que des médicaments modulant l'activité de l'anandamide pourraient soulager la toxicomanie de patients souffrant ou non de schizophrénie.

5. Limites méthodologiques

Certaines faiblesses méthodologiques limitent la portée des observations faites au cours des diverses études qui composent la présente thèse. Voici les principales faiblesses méthodologiques de chacune d'entre elles.

5.1 Méta-analyse

- La principale faiblesse méthodologique de la méta-analyse sur les symptômes négatifs réside dans le choix d'inclure uniquement les études transversales ayant évalué les symptômes négatifs à l'aide du SANS. Bien que cette échelle soit la plus exhaustive des échelles d'évaluation des symptômes négatifs, bien que son utilisation signale l'intention des chercheurs de faire de l'évaluation des symptômes négatifs une priorité de leur étude, bien que cette échelle soit

moins « contaminée » que le PANSS (Positive and Negative Syndrome Scale) par des items cognitifs, il aurait été pertinent de savoir si les différences observées dans la méta-analyse auraient également émergé en incluant des études évaluant les symptômes négatifs à l'aide du PANSS. Incidemment, un autre groupe a récemment réalisé cette méta-analyse, et ils ont démontré, à l'aide du PANSS, que les schizophrènes toxicomanes ont significativement moins de symptômes négatifs, relativement aux patients non-toxicomanes (Talamo et al., 2006).

5.2 Études en IRMf

- La faiblesse méthodologique la plus notable des études en IRMf réside dans l'évaluation de la toxicomanie, qui a été effectué à partir d'une fouille rétrospective des archives médicales. Il aurait été préférable d'établir les diagnostics de toxicomanie à l'aide du SCID-IV (Structured Clinical Interview for DSM-IV) et de déterminer la sévérité de la toxicomanie des patients à l'aide d'une échelle validée.
- Même si nos sous-analyses n'ont pas révélé de différences notables entre les consommateurs de cannabis et d'alcool, il aurait été préférable d'étudier une substance spécifique, plutôt qu'une hétérogénéité de SPA.
- En plus de contrôler l'effet potentiel des antipsychotiques par un calcul des équivalents chlorpromazine, il aurait fallu obtenir des informations quant à l'observance médicamenteuse, de même que l'histoire médicamenteuse des patients.

- Une évaluation directe des signes d'intoxication ou de sevrage aurait été souhaitable, afin d'exclure la possibilité que les activations cérébrales observées soient attribuables à ces effets pharmacologiques.

5.3 Étude neuropsychologique

- Même si nous avons contrôlé cette lacune en procédant à une analyse de covariance (voir Appendum du 3^{e} article), l'appariement clinique et socio-démographique des groupes avec et sans toxicomanie aurait pu être davantage optimal.
- Seulement deux fonctions cognitives ont été évaluées, à savoir la vitesse psychomotrice et la mémoire explicite visuospatiale. Il aurait été intéressant d'évaluer certaines fonctions cognitives frontale, telles que les fonctions exécutives.

5.4 Étude sur les symptômes extrapyramidaux

- Cette étude portait sur un petit échantillon (n=41) de patients.
- L'étude ne comprenait pas d'évaluation spécifique des affects dépressifs, qui peuvent jouer un rôle dans l'émergence de certains signes extrapyramidaux.

5.5 Étude pharmacologique

- Étant donné qu'il s'agissait d'une étude ouverte, et non pas d'une étude randomisée à double insu avec placebo, il ne nous est pas permis de déterminer si les effets bénéfiques observés au cours de l'étude sont attribuables à la quétiapine, à un effet placebo ou encore la prise en charge des patients au cours de l'étude.

- L'étude incluait un petit échantillon de patients (n=24).
- L'étude incluait des patients présentant un trouble de consommation à une hétérogénéité de SPA (alcool, cannabis, stimulants et phencyclidine).

5.6 Étude sur les prédicteurs de la toxicomanie chez les patients schizophrènes

- En raison du faible échantillon de patients (n=24), l'analyse de régression multiple avait une valeur exploratoire seulement. Afin de corroborer ces résultats, une analyse confirmatoire effectuée auprès d'un échantillon plus nombreux de patients serait requise.

5.7 Étude sur les cannabinoïdes endogènes

- En plus d'inclure un petit échantillon, l'étude comprenait seulement un groupe de patients présentant un double diagnostic de schizophrénie et de toxicomanie. En comprenant également un groupe de schizophrènes sans toxicomanie, il aurait été possible de déterminer si l'élévation des taux d'anandamide observée dans l'étude sont liées à la schizophrénie, à la toxicomanie ou à la combinaison des deux troubles.
- L'étude incluait des patients abusant de substances diverses (alcool, cannabis, stimulants et phencyclidine). Étant donné que les CBE relaient directement dans le cerveau les effets du cannabis, il aurait été pertinent d'inclure dans le groupe comorbide seulement des schizophrènes présentant un abus ou une dépendance au cannabis. Des études animales suggèrent certes un rôle modulateur des CBE dans les effets chroniques de l'alcool, des opiacés et des stimulants (Basavarajappa & Hunglund, 2002; De Vries et al., 2001; Mas-

Nieto et al., 2001), il n'en demeure pas moins que le lien entre CBE et cannabis est plus direct.

6. Orientations futures

Au terme de la présente thèse, il est possible d'élaborer un certain nombre de pistes de réflexion en vue de poursuivre la recherche sur les liens complexes entre la schizophrénie et la toxicomanie.

6.1 Méta-analyse

- Il y aurait lieu d'utiliser la méthode méta-analytique afin d'identifier les facteurs expliquant la nature contradictoire des résultats des études transversales mesurant le cognition et les SEP chez les schizophrènes avec et sans toxicomanie. Le type de SPA consommées, l'observance au traitement, l'âge des patients et le type de fonction cognitive (ou de SEP) seraient des facteurs potentiels à considérer.

6.2 Imagerie fonctionnelle & symptômes négatifs

- Il serait intéressant de refaire les études en imagerie fonctionnelle, suivant le même devis expérimental, mais après avoir évalué la toxicomanie à l'aide d'instruments validés et reconnus, et non pas une fouille d'archives médicales.
- Dans les études en IRMf, nous avons utilisé des stimuli visant à provoquer des émotions négatives (tristesse et aversion). Dans l'esprit de l'hypothèse de l'automédication de l'anhédonie, il serait intrigant de reprendre la même

étude, mais en utilisant cette fois des stimuli provoquant des émotions et affects positifs (exemple: plaisir et joie).

- Les futures études dans le domaine devraient cibler des substances spécifiques, et non pas un amalgame de SPA.

6.2 La neurotoxicité des SPA

- Il serait pertinent d'étudier la neurotoxicité potentielle des SPA (surtout la cocaïne) chez les patients souffrant de schizophrénie, à l'aide de l'IRM anatomique (volumétrique ou morphométrique), par le biais d'études transversales comparant des schizophrènes avec et sans toxicomanie co-occurrente (pour un exemple, voir Potvin et al., Sous presse). Chez des toxicomanes non-psychotiques, des indices de neurotoxicité ont été rapportés avec l'alcool dans le CPF, le thalamus, l'hippocampe, les noyaux gris centraux et le cervelet (Sullivan & Pfefferbaum, 2005); dans le cas de la cocaïne, ses effets néfastes semblent surtout se manifester au niveau du CPF, du cortex temporal et des noyaux gris centraux (Franklin et al., 2002; Jacobsen et al., 2001).

6.3 Cognition & SEP

- Comme nous l'avons noté en introduction, les études transversales visant à évaluer la cognition et les SEP des schizophrènes toxicomanes ont produit des résultats paradoxaux, démontrant à la fois plus et moins de déficits cognitifs et de SEP chez les patients comorbides. Davantage d'études sont requises, tenant compte des facteurs potentiellement confondants identifiés précédemment (voir 6.1).

6.4 Cannabinoïdes endogènes

- Afin de mieux départager les effets respectifs de la schizophrénie et de la toxicomanie sur l'augmentation des taux de CBE observée chez les patients comorbides, il serait nécessaire de mesurer les CBE chez des schizophrènes non-toxicomanes et des toxicomanes non-schizophrènes.

6.3 Traitement pharmacologique

- Les résultats obtenus dans l'étude ouverte avec la quétiapine justifient de réaliser une étude randomisée, à double insu, avec un antipsychotique de comparaison, préférablement un antipsychotique de première génération comme l'halopéridol. Afin d'avoir la puissance statistique requise, une telle étude devrait comprendre 150 patients par bras.
- Dans cette étude, il serait important de mesurer l'adaptation sociale et l'anhédonie des patients à l'entrée, car ces variables semblent prédire l'évolution de la toxicomanie des patients dans le temps.
- Il serait important de vérifier l'efficacité des médicaments anti-addictifs dans le traitement de la toxicomanie des schizophrènes. Récemment, de telles études ont été réalisées avec la naltrexone, un antagoniste opioïdergique, chez des schizophrènes alcooliques (Petrakis et al., 2004), et le bupropion, un antidépresseur dopaminergique, chez des schizophrènes souffrant de tabagisme (George et al., 2004). D'autres molécules pourraient être mises à l'essai, telles que l'ondansetron (alcool), la méthadone (héroïne) ou encore le topiramate (alcool).

- Dans la mesure où les perturbations du système des CBE rendent les schizophrènes davantage vulnérables aux SPA en général et au cannabis en particulier (ce qui demeure à démontrer), il serait intéressant de mettre à l'épreuve des médicaments agissant sur le système des CBE en vue de soulager la toxicomanie des schizophrènes. Si l'on se fie à la littérature, trois stratégies pharmacologiques peuvent être envisagées, soit: (i) un antagoniste des récepteurs cannabinoïdes CB_1 (d'autant plus que des études de phase III sont en cours dans le traitement du tabagisme); (ii) un inhibiteur du transporteur de l'anandamide (qui soulage, chez l'animal, les signes de sevrage aux opiacés) (Del Arco et al., 2002); ou encore (iii) un inhibiteur de l'amidohydrolase des acides gras (FAAH: «fatty acid amid hydrolase »), l'enzyme de dégradation de l'anandamide (Kathuria et al., 2003).

6.4 Intervention psychosociale

- Étant donnée que le degré d'adaptation sociale semble prédire l'évolution de la toxicomanie chez les schizophrènes, il serait pertinent de réaliser une étude mesurant l'efficacité d'un programme de réhabilitant ciblant une action dans l'environnement immédiat des patients souffrant à la fois de schizophrénie et de toxicomanie.

6.5 Le trouble bipolaire

- De tous les troubles psychiatriques à l'axe I du DSM-IV, c'est chez le trouble bipolaire que l'on rencontre la plus haute prévalence à vie –soit 60%– d'une toxicomanie (Regier et al., 1990), et pourtant, la comorbidité trouble bipolaire – toxicomanie a fait l'objet de moins d'études que la comorbidité

schizophrénie – toxicomanie. Des études similaires à celles réalisées chez les schizophrènes seraient de mise chez les patients souffrant d'un trouble bipolaire et d'une toxicomanie co-occurente.

7. Modèle longitudinal de la comorbidité « schizophrénie – toxicomanie »

Depuis la découverte de la haute prévalence à vie de la toxicomanie chez les patients souffrant de schizophrénie, de nombreux travaux cliniques ont été entrepris, démontrant un effet additif de la schizophrénie et de la toxicomanie. S'inspirant d'une philosophie de réduction des méfaits, ces travaux ont mis en évidence toute une série de conséquences néfastes de la toxicomanie chez les schizophrènes, incluant des rechutes psychotiques, des hospitalisations, des épisodes dépressifs, des idées suicidaires, des problèmes de criminalité, de logement d'emploi, de logement et des problèmes de santé.

Intégrant les apports de la neuropsychologie, de la pharmacologie et de la biologie, des travaux plus récents (incluant les travaux de la présente thèse) démontrent qu'en dépit de ces conséquences, les patients souffrant à la fois de schizophrénie et de toxicomanie auraient des symptômes négatifs moins sévères, de meilleures aptitudes relationnelles et possiblement moins de déficits cognitifs.

Cette contradiction dans les résultats expérimentaux a été nommée le « paradoxe de la comorbidité schizophrénie – toxicomanie » par Penk et al. (2000), et elle n'a pas reçu – à notre connaissance – d'explication satisfaisante à ce jour. En guise de conclusion aux travaux de cette thèse, nous souhaitons proposer un modèle général de la comorbidité « schizophrénie – toxicomanie », permettant de réconcilier les résultats apparemment paradoxaux publiés jusqu'ici dans la littérature.

Comme nous l'avons mentionné en introduction de cette thèse, trois modèles généraux tentent de rendre compte de la haute prévalence de la toxicomanie chez les schizophrènes, à savoir l'hypothèse de l'automédication [schizophrénie → toxicomanie] (Khantzian, 1997,1985), le modèle de vulnérabilité [toxicomanie → schizophrénie] (Andreasson et al., 1989,1987; Arsenault et al., 2002), et le modèle des facteurs communs [facteurs communs → schizophrénie et toxicomanie] (Chambers et al., 2001; Tsapakis et al., 2003). Or, il existe des données probantes supportant chacun de ces modèles (surtout le modèle de vulnérabilité). Selon le modèle que nous voulons ici proposer, il serait possible de réconcilier ces trois grands modèles, en les situant dans un axe longitudinal (Figure 1), où la durée de la toxicomanie et l'âge des patients seraient les variables clés.

Selon le modèle longitudinal proposé ici, les schizophrènes consommateurs de SPA auraient des symptômes négatifs, des déficits cognitifs et des déficits relationnels moins sévères que les patients non-consommateurs, surtout lorsqu'ils sont jeunes et qu'ils sont dans les premières phases d'expérimentation avec la substance. Les évidences présentées dans les articles I, II, III et VI de notre thèse corroborent ces hypothèses. Dans un même ordre d'idées, il a été démontré que les schizophrènes toxicomanes ont un meilleur ajustement prémorbide que les patients non-toxicomanes (Arndt et al., 1992), et que les troubles de consommation sont moins fréquents chez les schizophrènes avec le syndrome déficitaire (lequel se caractérise par des symptômes négatifs proéminents (Kirkpatrick, 2003,1996).

Comme nous l'avons mentionné à quelques reprises au cours de la thèse, il y a deux façons d'interpréter ces résultats. Conformément à l'***hypothèse de l'automédication***, on pourrait penser que la consommation de SPA soulage les symptômes négatifs, les déficits relationnels et cognitifs de la schizophrénie.

Inversement, on pourrait penser que ce sont les patients les schizophrènes ayant les symptômes négatifs les moins sévères qui sont le plus susceptibles de développer une toxicomanie, car le mode de vie de la toxicomanie – aussi dysfonctionnel soit-il – requiert un minimum d'aptitudes relationnelles et organisationnelles. Peu importe l'interprétation à laquelle on souscrit, l'observation importante ici est que dans les premières phases d'***expérimentation*** avec la substance, les schizophrènes consommateurs auraient moins de symptômes négatifs, moins de déficits cognitifs et de meilleures aptitudes relationnelles, que les patients non-consommateurs.

Comparativement à la population générale, la toxicomanie se développe plus rapidement dans la schizophrénie (Drake et Noordsy., 1994) et une plus grande proportion de patients schizophrènes est à risque de développer un trouble de consommation (abus ou dépendance). En effet, le risque relatif de développer une toxicomanie (abus ou dépendance) est plus élevé dans la schizophrénie que dans la population générale (pour l'alcool, le risque est de 2 à 3 fois plus élevé; pour le cannabis, 4 à 5 fois; et pour la cocaïne, environ 10 fois) (Regier et al., 1990). De plus, des évidences préliminaires suggèrent que les patients schizophrènes sont plus sensibles aux effets renforçateurs des SPA (Smelson et al., 2002c; Spring et al., 2003). Par ailleurs, il existe des preuves à l'effet que les schizophrènes peuvent développer une toxicomanie en consommation des quantités inférieures à celles habituellement consommées par les toxicomanes non-psychotiques. Enfin, des travaux cliniques démontrent qu'il est plus difficile de traiter la toxicomanie des patients souffrant de schizophrénie que la toxicomanie des patients qui ne sont pas porteurs d'une psychopathologie co-occurrente (Ziedonis et al., 2003).

Selon le modèle longitudinal élaboré ici, cette sensibilité particulière des patients schizophrènes aux effets des SPA, laquelle concoure au ***développement de la***

dépendance aux SPA chez ces patients, pourrait s'expliquer à l'aide du ***modèle des facteurs communs***. Plus spécifiquement, cette sensibilité des schizophrènes aux effets des SPA pourrait être le reflet de perturbations neurobiologiques communes à la schizophrénie et la toxicomanie, impliquant le système de récompense. Dans la littérature, des perturbations de la neurotransmission dopaminergique, des hormones du stress et des cannabinoïdes endogènes ont été proposées comme dénominateurs communs à la schizophrénie et la toxicomanie. Pour des raisons pratiques, nous n'avons pas pu évaluer directement le rôle de la dopamine et des glucocorticoïdes chez des patients présentant un double diagnostic. Par contre, dans l'article VII de la thèse, nous avons pu démontrer que les schizophrènes avec les taux d'anandamide les plus élevés en début de traitement étaient ceux dont la consommation et la sévérité de la toxicomanie ont suivi l'évolution la plus défavorable au cours d'un traitement avec un antipsychotique de seconde génération. Même si le modèle des facteurs communs a généré peu d'études jusqu'ici, ces résultats justifient que de plus amples travaux soient entrepris en ce sens, en investiguant le fonctionnement de la dopamine chez des patients avec un double diagnostic, et d'autres neurotransmetteurs ou hormones potentiellement impliqués dans les deux conditions.

Étant donné que les patients souffrant de schizophrénie ont plus de difficultés que les toxicomanes non-psychotiques à reprendre le contrôle sur leur consommation une fois que celle-ci devient compulsive, la toxicomanie se chronicise chez un nombre significatif de ces patients. Selon le modèle longitudinal que nous esquissons ici, c'est dans ce contexte qu'apparaît l'ensemble des ***conséquences négatives*** associées à la toxicomanie chez les schizophrènes, lesquelles corroborent le ***modèle de vulnérabilité***. Aussi, ***à long terme***, la toxicomanie finirait par se traduire, chez les patients schizophrènes, par des rechutes psychotiques, des hospitalisations, des

problèmes de logement, des épisodes dépressifs, des problèmes d'emploi, de la criminalité, des problèmes de santé, et davantage de symptômes extrapyramidaux (Mueser et al., 1998; Negrete, 2003; voir également les articles IV et VI de la thèse).

L'une des implications de ce modèle longitudinal, c'est qu'il y aurait une complémentarité des trois principaux de la comorbidité « schizophrénie – toxicomanie », dans la mesure où l'on entrevoit les causes et les conséquences de la toxicomanie chez les schizophrènes en fonction d'un axe temporel (Figure I). Présentement, nous sommes en train de réaliser une méta-analyse visant à évaluer la validité du modèle longitudinal dans le cas spécifique du fonctionnement cognitif des schizophrènes avec et sans toxicomanie co-occurente. La cognition constitue une bonne façon de mettre à l'épreuve le modèle longitudinal, car c'est dans ce domaine que le caractère paradoxal des résultats est le plus frappant. En effet, parmi les études publiées jusqu'ici, certaines d'entre elles ont démontré une détérioration cognitive chez les schizophrènes toxicomanes, comparés à des patients non-toxicomanes, alors que d'autres études ont démontré précisément le contraire (incluant l'article III de la présente thèse). Dans cette méta-analyse, nous avons émis l'hypothèse que l'âge des patients (considéré ici comme une approximation de la durée de leur toxicomanie) permet de prédire la direction (positive ou négative) de la taille des effets (*effect size estimates*) calculés pour chacune des études incluses (voir Tableau I de l'Introduction). Les résultats de nos analyses corroborent cette hypothèse et démontrent que les jeunes patients (< 30 ans) souffrant de schizophrénie et de toxicomanie ont une meilleure performance cognitive globale que les patients non-toxicomanes, alors qu'on observe l'inverse chez les patients plus âgés (> 40 ans) (Potvin et al., En préparation).

À l'évidence, des études longitudinales sont requises afin d'évaluer la validité du modèle ici esquissé. Dans la mesure où ce modèle devait être corroboré, il aurait des implications pour le traitement de cette double condition. Sur le plan de la réadaptation, il pourrait justifier la mise sur pieds de programmes thérapeutiques ciblant la toxicomanie dès son apparition chez les patients schizophrènes. Sur le plan pharmacologique, il pourrait inciter à développer des médicaments agissant sur des systèmes de neurotransmission communs à la schizophrénie et la toxicomanie. La sélectivité mésolimbique des antipsychotiques de seconde génération constitue un premier pas en sens, mais on peut entrevoir un futur pour les études pharmacologiques mettant davantage à contribution la diversité des neurotransmetteurs et des hormones impliqués dans les deux conditions.

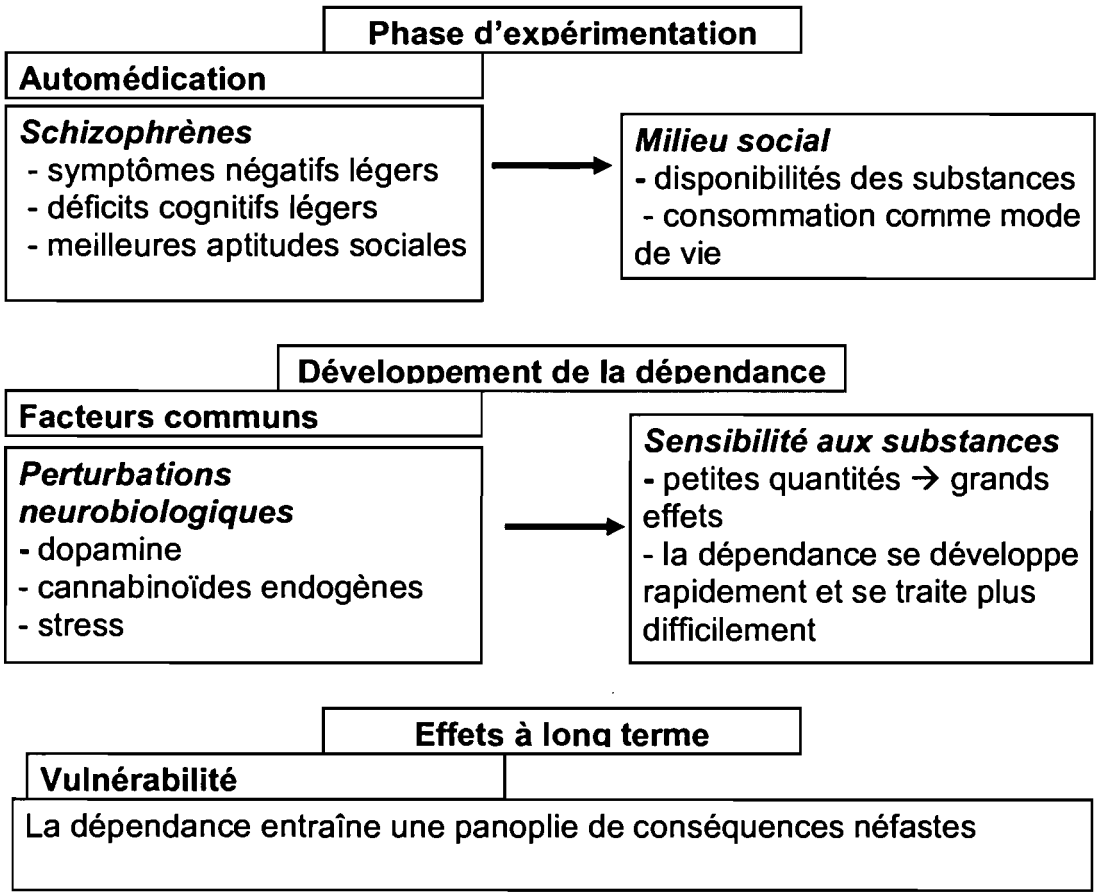
Tableau 1 : Récapitulation de la thèse sous forme schématique

Modèles	**Modèle de la vulnérabilité**	**Hypothèse de l'automédication**	**Modèles des facteurs communs**
Lien postulé	Toxicomanie → Psychose	Psychose → Toxicomanie	Facteurs communs → psychose & toxicomanie
Facteurs clés	Incidence de la psychose Pronostic psychiatrique	Symptômes négatifs Affects anxio-dépressifs Cognition	Traits de personnalité Environnement social Dopamine
État de la connaissance	• Le cannabis accroît de 2 à 3 fois l'incidence de la psychose • Les schizophrènes toxicomanes ont un pronostic défavorable: - plus de rechutes psychotiques - plus d'épisodes dépressifs et d'idées suicidaires - plus de problèmes d'observance - plus de violence et de criminalité - plus de problèmes de logement, d'emploi et de santé • Les études transversales sur les symptômes extrapyramidaux des schizophrènes toxicomanes ont produit des résultats contradictoires	• Des études transversales ont comparé les symptômes négatifs des schizophrènes avec ou sans toxicomanie. Les résultats de ces études ne font pas consensus • Les substrats neurophysiologiques de cette différence potentielle sont inconnus • Les études transversales sur la cognition des schizophrènes toxicomanes ont produit des résultats contradictoires • En soulageant les symptômes négatifs, anxio-dépressifs et cognitifs, les antipsychotiques de seconde génération pourraient soulager la toxicomanie des schizophrènes	• Ce modèle a suscité très peu d'études empiriques

Tableau 1 (suite): Récapitulation de la thèse sous forme schématique

Modèles	Modèle de la vulnérabilité	Hypothèse de l'automédication	Modèles des facteurs communs
Contributions de la thèse	• Les schizophrènes toxicomanes ont des symptômes extrapyramidaux plus sévères (article 4) • La sévérité de la toxicomanie prédit une évolution défavorable sur le plan des symptômes positifs et dépressifs (article 6)	• Les schizophrènes toxicomanes ont des symptômes négatifs moins sévères que les patients non-toxicomanes (article 1) • Cette différence symptomatique s'accompagne d'un traitement cortical plus élaboré (article 2) • L'anhédonie prédit l'évolution de la toxicomanie dans le temps chez les schizophrènes (article 6) • Il y a une relative préservation de la mémoire explicite chez les schizophrènes toxicomanes (article 3) • Apport théorique: la préservation des symptômes négatifs/cognitifs pourrait être primaire et non pas secondaire à la toxicomanie (articles 1,2 & 3) • La quétiapine semblerait soulager la toxicomanie des schizophrènes (article 5)	• L'évolution de la toxicomanie chez les schizophrènes est liée à l'environnement social (article 6) • Formulation d'une nouvelle hypothèse: la sensibilité des schizophrènes aux substances psychoactives pourrait dépendre des perturbations du système des cannabinoïdes endogènes, associées à la pathologie (article 7) • Les taux d'anandamide prédisent l'évolution de la toxicomanie dans le temps chez les schizophrènes (article 7)

Figure 1: Modèle théorique longitudinal



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ANNEXE I

Neural correlates of the affect regulation model in schizophrenia patients with drug use history: an fMRI study *

Stéphane Potvin, Adham Mancini-Marië, Cherine Fahim, Mario Beauregard, Boualem Mensour, Ph.D[5], Emmanuel Stip M.D., M.Sc.[1,3]

* Résumé publié dans *Schizophrenia Bulletin* 2005; 31 (2): 431.

Background The lifetime prevalence of substance use disorders among schizophrenia patients is close to 50%. The negative consequences of substance abuse in schizophrenia are well documented, but the aetiology of this comorbid condition remains unknown. According to the "affect regulation model", schizophrenia patients would abuse drugs in order to cope with their negative affects. Supporting the model, clinical studies have shown that dual diagnosis patients have less blunting of affect, and that they experience more negative affect.

Rationale We hypothesized that patients with a history of addiction would have increased cerebral activations in response to aversive stimuli, when compared to abstinent ones.

Methods Schizophrenia patients were divided into two groups: patients with (n = 12) (SCZ-SUD group) and without (n = 11) (SCZ group) an addiction history (alcohol and/or cannabis). Using functional magnetic resonance imaging (fMRI), patients

were scanned during passive viewing of emotionally negative pictures (International Affective Picture System).

Results Subjectively, the emotional experience induced by viewing the negative pictures was significantly higher in the SCZ-SU group than in the SCZ group. Neurally, in the SCZ-SU group, significant loci of activation were identified in the right medial prefrontal cortex (Brodmann area –BA10), left medial prefrontal cortex (BA10), right orbitofrontal cortex (BA47), and left amygdala. No significant loci of activation were observed in the SCZ group.

Conclusions These results suggest that the functioning of the medial prefrontal cortex, thought to be impaired in patients with prominent negative symptoms, would be more preserved in dual diagnosis schizophrenia.

Key words schizophrenia – substance use disorders – aversion – negative symptoms – prefrontal cortex – parahippocampal gyrus – functional magnetic resonance imaging

ANNEXE II

The effect of quetiapine on cannabis use in eight psychosis patients with drug dependency *.

Stéphane Potvin, Emmanuel Stip, Jean-Yves Roy

* Rapport de cas ("case report") publié dans *Canadian Journal of Psychiatry* 2004; 49 (10): 711.

Potvin, Stéphane; MA, doctoral candidate, biomedical sciences, University of Montreal; intern at Centre de recherche Fernand-Seguin and Clinique Cormier-Lafontaine, 110 rue Prince-Arthur ouest, Montréal, Québec, Canada, H2X 1S7
Email: [redacted]

Stip, Emmanuel; MD, M Sc, CSPQ; clinical professor, University of Montreal; psychiatrist, Hôpital Louis-H. Lafontaine; researcher, Centre de recherche Fernand-Seguin.

Roy, Jean-Yves; MD, FRCP, CSAM; clinical professor, University of Montreal; associate researcher, Centre de recherche Fernand-Seguin; medical director, Clinique Cormier-Lafontaine.

Word count: 454 words (text)

TO THE EDITOR: Approximately one-half of all patients with schizophrenia abuse or depend on psychoactive substances at some point during their lives (1), but few studies to date a strict basis for an integrated pharmacological treatment for this schizophrenia – addiction comorbidity. Because of their strong dopamine D_2-receptor antagonism, conventional antipsychotics such as haloperidol should in theory be the treatment of choice for comorbid schizophrenia and substance abuse. In practice, however, such treatment has not been demonstrated to be consistently effective and has only controlled drug abuse in special cases (2). A few pilot studies suggest that, among the conventional antipsychotics, flupenthixol may reduce cravings in schizophrenia patients with cocaine addiction (3). To date, the most promising results have been obtained with clozapine, a prototype of the atypical antipsychotics (4). Sharing certain key properties with clozapine (for example, $5HT_2$-D_2 ratio) (5), quetiapine may also reduce drug cravings in psychosis patients with addictions. A pilot study of 12 patients suffering from bipolar disorder (BD) and cocaine addiction appears to support this hypothesis (6). To expand on this promising result, we report case histories for eight psychosis patients whose cannabis use habits significantly improved after treatment with quetiapine.

Case report

The group of patients (5 men and 3 women) included 4 patients with schizophrenia and 4 with affective BD. All patients had cannabis dependency, and 2 also had a cocaine use disorder, according to DSM-IV criteria. Their mean age was 38.5 years (range: 25 and 46 years). Before quetiapine was initiated, they received antipsychotics (5 patients), antidepressants (2 patients), lithium (2 patients),

clonazepam (2 patients) and procyclidine (1 procyclidine). All 8 patients were given quetiapine for an average of 5.8 months, at dosages ranging between 100 and 1200 mg daily. Concomitantly, 4 patients received antidepressants, 2 received gabapentin, and 1 was on methadone maintenance treatment. Overall, an average 97.3 % reduction in their weekly cannabis use was observed with an average quetiapine dosage of 388 mg daily. When interviewed, patients reported consuming an average of 35.6 joints weekly of cannabis (range: 18 to 56 joints) before quetiapine introduction. After quetiapine treatment, patients reported an average cannabis consumption of 1.1 joint weekly.

Like clozapine, quetiapine has proven benefits when compared with conventional antipsychotics (7,8). First, clozapine and quetiapine have a beneficial effect on mood. Showing mesolimbic selectivity, these agents do not appear to cause extrapyramidal symptoms. Further, these medications produce no or little neuroleptic-induced dysphoria. Last, it is possible that these atypical antipsychotics (mainly clozapine) alleviate the negative and cognitive symptoms of schizophrenia more than do conventional antipsychotics. To the extent that some patients with schizophrenia may take substances as a form of self-medication, the clinical data presented here suggest that quetiapine, like clozapine, could form the basis of integrated pharmacological treatment for the psychosis–addiction comorbidity. Further controlled research is needed to validate the preliminary data collected to date.

Acknowledgment:

The authors would like to pay tribute to Jean-Yves Roy, a pioneer psychiatrist in dual diagnosis in Montreal, who passed away in April 2004.

Funding and support:

We received no financial support, either from pharmaceutical companies or from public research institutions, to gather the data described in this letter.

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