UNIVERSITÉ DU QUÉBEC À MONTRÉAL

EFFET DES INHIBITEURS D'ACÉTYLCHOLINESTÉRASE SUR LE FONCTIONNEMENT COGNITIF DANS LA SCHIZOPHRÉNIE

THÈSE
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PAR
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LISTE DES SIGLES ET ABRÉVIATIONS (TEXTE FRANÇAIS)

AChE	Acétylcholinestérase
APA	American Psychiatric Association
BUCHE	Butyrylcholinestérase
CANTAB	Cambridge Neuropsychological Test Automated Battery
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-4ème édition
MCT	Mémoire à court terme
MLT	Mémoire à long terme
PANSS	Positive and Negative Symptoms Scale

LISTE DES SIGLES ET ABRÉVIATIONS (TEXTE ANGLAIS)

ABAB	Counter Balance Design
ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase Inhibitor
AD	Alzheimer Disease
ADAS-GOG	Cognitive Portion of the Alzheimer's Disease Assessment Scale
ALT	Alanine Aminotransferase
APA	American Psychiatric Association
AST	Aspartate Aminotransferase
BuCHE	Butyrylcholinesterase
CANTAB	Cambridge Neuropsychological Test Automated Battery
CIs	Confidence Intervals
CK	Creatinine Kinase
CRH	Corticotropin Hormones
CVLT	California Verbal Learning Test
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EPS	Extrapyramidal Symptoms
ES	Effect Size
FDA	US Food and Drug Administration's
fMRI	Functional Magnetic Resonance Imaging
LTM	Long Term Memory
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
NMDA	N-methyl-d-aspartate
NIMH	National Institute of Mental Health
PAL	Paired Associates Learning

PANSS	Positive and Negative Symptoms Scale
PRE-A	Conflict Reaction Time
PS	Paradoxal Sleep
RAVLT	Rey Auditory Verbal Learning Test
RBANS	Repeatable Battery for the assessment of Neuropsychological Status
REM	Rapid eye Movement
RTI	Reaction Time
RVP	Rapid Visual Processing
SD	Standard Deviation
SOC	Stockings of Cambridge
SSTICS	Subjective Scale to Investigate Cognition in Schizophrenia
STM	Short-term Memory
SWM	Spatial Working Memory
SWS	Slow Wave Sleep
SZ	Schizophrenia

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RÉSUMÉ

La schizophrénie est une psychopathologie caractérisée par une perturbation du fonctionnement cognitif. Malgré l'efficacité de certains traitements antipsychotiques en regard de certains symptômes négatifs et positifs, il n'en demeure pas moins que les troubles cognitifs demeurent présents. Ce travail doctoral a pour but d'examiner l'effet des inhibiteurs d'acétylcholinestérase sur le fonctionnement cognitif dans la schizophrénie, afin d'en vérifier l'efficacité. Il s'agit d'une famille de médicaments utilisés pour d'autres pathologies où des problèmes cognitifs, en particulier mnésiques, apparaissent liés à un neurotransmetteur particulier, l'acétylcholine.

Aprés une introduction sur les troubles cognitifs en tant qu'éléments importants du tableau clinique de la schizophrénie, nous présentons les diverses avenues de recherche en pharmacologie visant l'amélioration du fonctionnement cognitif dans la schizophrénie. Cette présentation, sous la forme d'un article intitulé « On the trail of a cognitive enhancer for the treatment of schizophrenia » met en évidence l'implication du système cholinergique dans les troubles cognitifs de la schizophrénie.

Sur la base de cette littérature, nous avons effectué une étude sur les effets de la rivastigmine, un inhibiteur d'acétylcholinestérase, chez des patients atteints de schizophrénie et présentant des troubles cognitifs. Les résultats de cette étude clinique menée auprès de patients sous médication neuroleptique et rivastigmine de manière concomitante n'ont pas révélé d'effet particulier de la rivastigmine sur le fonctionnement cognitif dans la schizophrénie.

Les données contradictoires entre les études récentes sur l'effet des inhibiteurs d'acétylcholinestérase sur le fonctionnement cognitif dans la schizophrénie, et la notre nous ont incité à effectuer une méta-analyse. Le but de cette méta-analyse était de statuer sur les effets des différents inhibiteurs d'acétylcholinestérase sur le dysfonctionnement cognitif dans la schizophrénie. Les résultats de cette méta-analyse ont montré une faible contribution des inhibiteurs d'acétylcholinestérase dans l'amélioration des fonctions mnésiques chez les patients atteints de schizophrénie.

Nos résultats expérimentaux et méta-analytiques ne permettent pas de confirmer notre hypothèse initiale stipulant que les inhibiteurs d'acétylcholinestérase puissent être efficaces pour le traitement des troubles cognitifs dans la schizophrénie. En fait, les faibles résultats obtenus apparaissent liés à des facteurs méthodologiques et un effet de pratique. En outre, plusieurs études récentes mieux contrôlées ne révèlent pas d'effet du traitement. Il ne semble donc pas prometteur de poursuivre des études dans ce domaine de recherche.

Mots clés : Schizophrénie ; Fonctionnement Cognitif ; Mémoire ; Inhibiteur d'Acétylcholinestérase ; Rivastigmine.

CHAPITRE I

INTRODUCTION

INTRODUCTION

Définition et prévalence

La schizophrénie est considérée comme l'un des troubles psychiatriques les plus graves. Plus de 300 000 personnes en sont atteintes au Canada (Schuchman et Hébert, 2008). Le taux de prévalence est estimé à environ 1% de la population, indépendamment de la culture et de la région. L'état actuel des connaissances sur les causes probables de la schizophrénie suggère la contribution de certains facteurs environnementaux, ainsi qu'une prédisposition génétique possible. L'incidence familiale constitue un important facteur de risque de développer la schizophrénie.

Les premiers symptômes de la schizophrénie surviennent généralement au début de l'âge adulte, entre 17 et 25 ans chez les hommes et entre 25 et 35 ans chez les femmes. La maladie affecte autant les hommes que les femmes. L'apparition de la maladie avant l'âge de 16 ans ou après 50 ans est plutôt rare. La plupart des individus présentent une phase de prodrome où certains symptômes se manifestent, sans remplir toutefois les critères diagnostiques de la maladie. Le premier épisode peut survenir de manière aigüe dans un intervalle de deux à trois semaines.

Les principaux symptômes de la schizophrénie se divisent en deux catégories, soit les symptômes positifs et les symptômes négatifs (Crow, 1980). Les symptômes positifs se traduisent par des excès tels que les hallucinations, le délire et les pensées bizarres, alors que les symptômes négatifs se distinguent par des comportements déficitaires tels que l'apathie, l'alogie (pauvreté du langage), l'anhédonie (incapacité d'éprouver du plaisir) et l'affect plat. La PANSS est une échelle standardisée qui permet d'évaluer les niveaux de sévérité des symptômes positifs et négatifs.

Les troubles cognitifs et de l'humeur s'avèrent également très fréquents dans la schizophrénie. Ces symptômes ont des répercussions dans toutes les sphères du

fonctionnement de l'individu — sur les plans social, occupationnel et psychologique, ainsi que des émotions et de la motivation.

La classification diagnostique la plus utilisée dans la pratique clinique est le DSM-IV qui dresse une liste des symptômes cliniques qui doivent être présents pour établir un diagnostic de schizophrénie (American Psychiatric Association, APA 1994). Selon les critères du DSM-IV, on distingue cinq sous-types dans la schizophrénie, nommés désorganisé, catatonique, paranoïde, indifférencié et résiduel. Malgré les critères diagnostiques proposés par le DSM-IV et d'autres manuels diagnostics comme le ICD-10 (World Classification of Diseases 10th Revision), la schizophrénie est considérée comme une entité hétérogène. Les critères du DSM-IV et du ICD-10 sont axés principalement sur les symptômes positifs et les symptômes négatifs, omettant d'inclure les troubles affectifs et les déficits cognitifs (Lindermayer et khan, 2006).

On observe de nombreuses différences individuelles au niveau de la symptomatologie clinique chez les patients atteints de schizophrénie. On note donc un large éventail de symptômes dans la schizophrénie, qui se trouvent parfois à des pôles opposés. La schizophrénie est un trouble mental complexe. En fait, il s'agit probablement de plusieurs maladies regroupées sous une même terminologie, la schizophrénie. Cette importante variation au niveau des symptômes cliniques rend difficile la recherche d'un remède et expliquerait la nécessité d'une grande diversité au niveau de la médication.

Traitements psychopharmacologiques de la schizophrénie

La chlorpromazine fut le premier agent neuroleptique utilisé pour traiter la schizophrénie en 1952, suivi de l'halopéridol en 1958. Jusqu'au début des années 1980, plusieurs molécules apparentées à la chlorpromazine et à l'halopéridol ont été mises au point, ce qui a généré trois classes d'antipsychotiques classiques pour le

traitement de la schizophrénie soit les phénothiazines, les butyrophénones, les thioxanthènes. Les neuroleptiques sont des médicaments à effet neurobiologique qui visent à réduire les symptômes psychotiques. Les neuroleptiques exercent une action au niveau de la transmission synaptique, notamment pour les neurotransmetteurs comme la dopamine. Les neuroleptiques classiques sont efficaces pour les symptômes positifs, mais n'ont pas d'effet apparent sur les symptômes négatifs et les déficits cognitifs (Beasley et al., 1997; Stip, 2000). De plus, ils induisent des effets secondaires, dont des symptômes extrapyramidaux chez plus de 75% des patients (Olie et al., 1999). Ils se produisent lorsque l'activité dopaminergique s'avère trop réduite par la prise de médication et ils s'illustrent pas une série de manifestations physiques et psychiques. Les symptômes extrapyramidaux associés aux neuroleptiques sont des effets indésirables se traduisant par de l'akinésie, de la dystonie, de la dyskinésie et du parkinsonisme (Stroup et al., 2006).

Au cours des dernières années, le développement des neuroleptiques atypiques, une nouvelle génération de neuroleptiques n'impliquant pas les mêmes récepteurs que les neuroleptiques classiques, a permis d'améliorer la symptomatologie des patients. Des essais cliniques ont révélé que certains neuroleptiques atypiques dont l'olanzapine permettent d'améliorer la mémoire explicite chez les patients atteints de schizophrénie (Meltzer et McGurk, 1999; Stip, 2000). De plus, il a été avancé que certains neuroleptiques atypiques sont plus efficaces que les neuroleptiques classiques dans la réduction des symptômes négatifs (Kane et al., 1988; Beasley et al., 1997). Ce thème sera abordé plus en détail dans l'article présenté au Chapitre I du présent ouvrage.

Cependant, malgré les avancées en psychopharmacologie, certains symptômes cliniques subsistent toujours chez les patients atteints de schizophrénie, dont des troubles du fonctionnement cognitif.

Dysfonctionnement cognitif dans la schizophrénie

L'ampleur du déficit cognitif constitue un facteur primordial à considérer dans le pronostic et la réinsertion sociale des patients atteints de schizophrénie. Les déficits cognitifs sont associés au niveau de fonctionnement dans la schizophrénie (Green, 2006). Au cours de la dernière décennie, un grand nombre de travaux ont montré que les déficits cognitifs font partie intégrante du tableau clinique de la schizophrénie. Les déficits cognitifs persistent tout au long de la maladie, même en période de rémission des symptômes cliniques. La nature de ces déficits, qui sont durables et chroniques, s'étend à l'ensemble du fonctionnement cognitif.

Les déficits d'attention, de mémoire et de fonctions exécutives qui sont associés au pronostic à long terme, s'avèrent les mieux documentés dans la schizophrénie (Green et al., 2000 ; Heinrichs et Zakzanis, 1998 ; Nuechterlein et al., 2004). Toutefois, on note aussi des difficultés aux plans de la perception visuelle, des habiletés langagières (Tugal et al., 2004) et des processus psychomoteurs (Malhotra et al., 2004).

Au niveau de l'attention, les déficits sont bien documentées dans la schizophrénie, particulièrement pour ce qui est de l'attention sélective (Hagh-Shenas et al., 2002; Filbey et al., 2008). De plus, les deux composantes principales de la mémoire, soit la mémoire à court terme (MCT) et la mémoire à long terme (MLT), sont également touchées dans la schizophrénie.

Des déficits ont été rapportés dans les trois sous-systèmes de la mémoire de travail, à savoir la boucle phonologique (verbale), la tablette visuospatiale et l'administrateur central (Aleman et al., 1999 ; Fleming et al., 1997; Kebir et Tabbane, 2008). Cependant, les résultats sont mitigés lorsqu'un test de rappel sériel ou la tâche de « Brown-Peterson » sont employés (Park et al., 1992 ; Stip, 1996). Des différences méthodologiques peuvent possiblement expliquer l'hétérogénéité de ces résultats.

Certains auteurs soutiennent que les déficits d'attention seraient en partie responsables des déficits mnésiques observés dans la schizophrénie (Nuechterlein et Dawson, 1984). En fait, pour que l'information soit emmagasinée, il faut d'abord qu'elle soit encodée, ce qui nécessite un minimum d'attention.

Dans les sous-systèmes de la MLT, la mémoire explicite, qui réfère à l'apprentissage conscient, semble la plus atteinte chez les patients atteints de schizophrénie, tant aux niveaux de l'encodage que de la récupération de l'information (Tamlyn et al., 1992; Cirillo et Seidman, 2003). Par ailleurs, plusieurs études rapportent que le rappel implicite serait préservé dans la schizophrénie (Léger et al., 2001 ; Sponheim et al., 2004; Lecardeur et al., 2007). On remarque donc une dissociation entre rappel explicite et implicite (Perry et al., 2000). Ces résultats suggèrent que des processus neuronaux différents sont impliqués dans les rappels explicite et implicite.

Les résultats d'études sont contradictoires pour certains aspects de la mémoire non-déclarative, dépendamment des tests utilisés (Soler et al., 2007). Certains auteurs notent des performances normales dans des tâches de lecture de mots inversés et d'apprentissage d'une séquence motrice (Clare et al., 1993 ; Schmand et al., 1992), alors que d'autres soutiennent que la mémoire procédurale est limitée (Bédard et al., 1996; Horan et al., 2008). Des différences méthodologiques peuvent expliquer l'hétérogénéité de ces résultats (Aleman et al., 1999).

Les fonctions exécutives, qui regroupent un ensemble de fonctions impliquées dans la résolution de problèmes (i.e. l'initiation, la planification, l'exécution d'une action, le raisonnement et la flexibilité mentale), sont associées aux lobes frontaux. Des déficits exécutifs ont été notés chez les patients atteints de schizophrénie comparés aux individus normaux (Bora et al., 2005; Malhotra, et al., 2004). Les déficits exécutifs chez les patients atteints de schizophrénie seraient même plus importants que ceux de patients avec des lésions frontales. Ces résultats suggèrent

qu'il y aurait d'autres régions cérébrales impliquées dans les déficits exécutifs de la schizophrénie. Une étude récente de Guillem et al. (2008) met en évidence la relation entre les déficits exécutifs et les symptômes positifs de la schizophrénie.

Une étude récente de Brooks et al. (2007) montre d'ailleurs le lien entre les récepteurs dopaminergiques du noyau accumbens et la modulation de l'acétylcholine dans le cortex préfrontal. Le système cholinergique joue un rôle prédominant dans la pathophysiologie de la schizophrénie. Les interactions cholinergiques et dopaminergiques sont pertinentes dans l'expression des symptômes positifs et négatifs (Tandon et al., 1991) et des déficits cognitifs (Brooks et al., 2007). Toutefois, les différents degrés d'implication des systèmes de neurotransmetteurs dans l'expression des symptômes cliniques de la schizophrénie restent à clarifier.

L'acétylcholine dans la pathogenèse de la schizophrénie

Plusieurs études ont montré que la réduction de l'activité cholinergique joue un rôle dans les déficits cognitifs du spectre de la schizophrénie, plus particulièrement dans le dysfonctionnement mnésique (Karson et al., 1996; Kirrane et al., 2001). Il est largement admis qu'une perturbation aux niveaux des récepteurs nicotiniques et muscariniques cérébraux (préfrontaux) (Breese et al., 2000; Crook et al., 2001; Freedman et al., 2000) et des interneurones des structures sous corticales (Holt et al., 1999; German et al., 1999) est observée dans la schizophrénie.

Les récepteurs muscariniques post-synaptiques M1 s'avèrent les plus connus pour leur implication dans la mémoire. Ces récepteurs ont été identifiés comme le site potentiel d'action des inhibiteurs d'acétylcholinestérase en raison de leur localisation post synaptique et leur densité dans l'hippocampe et le cortex cérébral (Flynn et al., 1995). De plus, il été admis que la consommation de nicotine chez les

patients atteints de schizophrénie peut avoir un impact sur leur fonctionnement cognitif (Blaxton et al., 2001).

L'implication du système cholinergique dans la pathogenèse de la schizophrénie nous amène implicitement à la conclusion qu'un traitement exerçant un impact sur ce système pourrait s'avérer efficace dans le traitement des déficits cognitifs. Une augmentation de l'activité cholinergique devrait permettre d'améliorer le fonctionnement cognitif. Certaines études suggèrent que les inhibiteurs d'acétylcholinestérase peuvent permettre d'améliorer les fonctions mnésiques, non seulement dans la maladie d'Alzheimer, mais aussi dans d'autres pathologies, tel que la schizophrénie et le Parkinson.

Le système cholinergique s'avère perturbé dans plusieurs maladies associées à un dysfonctionnement cognitif, tel que la maladie d'Alzheimer. Les perturbations du système mnésique font partie prenante du tableau clinique dans cette maladie. La mémoire implique plusieurs systèmes neuronaux et différents types de neurotransmetteurs. Il est bien établi que le système cholinergique est associé à la mémoire. Parmi les huit voies cholinergiques identifiées, celle principalement impliquée dans les troubles de mémoire dans la maladie d'Alzheimer relie le noyau basal de Meynert au cortex cérébral et aux amygdales.

Étant donné que les troubles de mémoire sont sensibles aux modifications du taux d'acétylcholine cérébrale et vu l'efficacité des médicaments augmentant le taux d'acétylcholine sur les troubles mnésiques, il apparaît pertinent de proposer aux patients ayant des troubles mnésiques une telle approche thérapeutique. Ainsi, on peut présumer que la prise de rivastigmine, un inhibiteur d'acétylcholinestérase, pourrait permettre d'améliorer le fonctionnement cognitif chez les patients atteints de schizophrénie. Les différents inhibiteurs d'acétylcholinestérase visant à rétablir l'équilibre du système cholinergique touchent l'AChE seulement ou ont une double action affectant l'AChE et la BUCHE. La rivastigmine est un inhibiteur

d'acétylcholinestérase qui exerce une double action, ce qui suggère qu'elle pourrait s'avérer plus efficace.

Des études récentes présentent toutefois des résultats contradictoires en ce qui a trait aux effets des inhibiteurs d'acétylcholinestérase sur le fonctionnement cognitif dans la schizophrénie. Certains auteurs notent des améliorations du fonctionnement cognitif (Erickson et al., 2005; Lenzi et al., 2003; Schubert et al., 2006), alors que d'autres ne rapportent pas de changement (Freudenreich et al., 2005; Sharma et al., 2006). La méthodologie employée peut être en cause dans la diversité de ces résultats. Une revue de littérature récente n'a pas permis de statuer sur l'efficacité des inhibiteurs d'acétylcholinestérase dans le traitement des déficits cognitifs dans la schizophrénie (Ferreri et al., 2006).

Objectifs et hypothèses de la recherche

L'objectif principal du présent travail doctoral consiste à vérifier dans un premier temps les effets de la rivastigmine sur le fonctionnement cognitif de patients atteints de schizophrénie. Nous nous attendons à une amélioration aux niveaux de l'attention et de la mémoire. Dans un deuxième temps, nous nous proposons d'analyser les résultats d'études réalisées à ce jour sur l'efficacité des anticholinestérases sur le fonctionnement cognitif dans la schizophrénie à l'aide de méthodes méta-analytiques. La présente thèse ne constitue pas pour autant un travail de biochimie pharmacologique.

Au Chapitre II, qui fera l'objet de l'article intitulé « On the trail of a cognitive enhancer for the treatment of schizophrenia », le lecteur sera sensibilisé aux différentes avenues de recherche pharmacologique en vue d'améliorer le fonctionnement cognitif dans la schizophrénie. Cet article a été publié dans la revue « Progress in Neuro-Psychopharmacology & Biological Psychiatry » en janvier 2005. Nous y soulevons l'hypothèse que les systèmes cholinergiques et glutaminergiques

joueraient un rôle dans le dysfonctionnement cognitif de la schizophrénie, en plus des systèmes dopaminergiques et sérotoninergiques déjà connus. Ces résultats nous amènent au postulat qu'une médication agissant sur le système cholinergique pourrait s'avérer efficace pour traiter les déficits cognitifs dans la schizophrénie.

Sur la base de cette hypothèse, tel que précité, nous avons effectué une étude sur les effets de la rivastigmine, un inhibiteur d'acétylcholinestérase, chez des patients atteints de schizophrénie. Le Chapitre III nous présente un article sur cette étude qui a été publié dans la revue « Current Medical Research and Opinion » en février 2007. Le design « chassé-croisé » inclut des patients prenant des neuroleptiques et de la rivastigmine de manière concomitante dans la condition expérimentale.

Nos hypothèses de départ reposent à priori sur le fait que la prise de rivastigmine devrait induire une amélioration de la performance cognitive aux niveaux de l'attention et de la mémoire. Plusieurs fonctions cognitives, dont l'attention, la mémoire, le langage, la psychomotricité et les fonctions exécutives sont évaluées avec la batterie informatisée CANTAB. CANTAB constitue un outil standardisé qui peut être utilisé indépendamment de la langue (Levaux et al., 2007). Les symptômes cliniques sont également évalués avec la PANSS dans les conditions pré et post traitement cholinergique.

Les résultats contradictoires de certaines études récentes sur les effets des inhibiteurs d'acétylcholinestérase sur le fonctionnement cognitif dans la schizophrénie, nous ont motivé à faire des études méta-analytiques. La méta-analyse se définit comme un ensemble de procédures utilisé pour faire le sommaire statistique de résultats provenant de différentes études qui ont étudié le même phénomène (Fried et Ager, 1998 ; Haccoun, 1999). Le processus méta-analytique permet de donner un sens aux résultats des études accumulées sur un même sujet et d'orienter la direction des recherches futures (Durlak et Lipsey, 1991; Hunter et Schmidt, 1990).

Le Chapitre IV de cette thèse nous propose une première méta-analyse sur les effets des inhibiteurs d'acétylcholinestérase sur l'attention, la motricité, le langage et les fonctions exécutives dans la schizophrénie. Au Chapitre V, une seconde méta-analyse sur les effets des inhibiteurs d'acétylcholinestérase sur la mémoire dans la schizophrénie nous est exposée. Ces deux articles ont été publiés dans la revue Clinical Neuropharmacology dans les numéros de mai-juin et juillet-août 2007 respectivement. Finalement, on retrouve dans la conclusion une discussion sur chacun des articles inclus dans cette thèse, suivie d'une conclusion plus générale.

CHAPITRE II

PREMIER ARTICLE

ON THE TRAIL OF A COGNITIVE ENHANCER FOR THE TREATMENT OF SCHIZOPHRENIA

On the trail of a cognitive enhancer for the treatment of schizophrenia

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Résumé de l'article

La compréhension des mécanismes biochimiques impliqués dans le dysfonctionnement cognitif présent dans la schizophrénie est d'une importance cruciale dans l'élaboration des traitements. L'objectif de la présente revue vise à mettre à jour l'état des connaissances sur les traitements pharmacologiques des déficits cognitifs dans la schizophrénie. Plusieurs études ont montré que les neuroleptiques atypiques permettent une certaine amélioration au niveau cognitif, bien que des difficultés persistent toujours. L'habileté des neuroleptiques atypiques à augmenter l'activité dopaminergique et cholinergique peut expliquer leur efficacité à améliorer les déficits cognitifs. Un mécanisme relié à l'apprentissage est le blocage des récepteurs D2 qui s'avèrent plus balancés avec les neuroleptiques atypiques. Un niveau d'activité dopaminergique optimal est essentiel dans le cortex préfrontal pour un fonctionnement cognitif normal. On rapporte des différences dans l'efficacité des différents neuroleptiques sur le fonctionnement cognitif dans la schizophrénie. De nombreuses études ont montré que la clozapine, la ziprasidone, l'olanzapine, et le rispéridone possèdent des propriétés cholinergiques qui procurent une augmentation de la relache d'acétylcholine dans le cortex préfrontal. Il a été montré que les inhibiteurs d'acétylcholinestérase peuvent permettre d'améliorer les fonctions mnésiques pas seulement dans la maladie d'Alzheimer, mais aussi dans d'autres pathologies. Des études ont révélé une association entre la diminution de l'activité cholinergique et le dysfonctionnement cognitif dans la schizophrénie. Ces résultats suggèrent qu'une augmentation de l'activité cholinergique devrait engendrer une amélioration au niveau des fonctions cognitives. En outre, la perturbation de la neurotransmission glutaminergique peut aussi jouer un rôle dans les déficits cognitifs observés dans la schizophrénie. Des études méta-analytiques sur les différents essais cliniques apparaissent nécessaires dans ce domaine d'étude.

Mots-clés: Cognition ; Système Cholinergique ; Neuroleptique ; Schizophrénie.

Abstract

The aim of this critical review is to address that the study of cognition and antipsychotics is not always driven by logic and that research into real pro-cognitive drug treatments must be guided by a better understanding of the biochemical mechanisms underlying cognitive processes and, by the same token, cognitive deficits. Many studies have established that typical neuroleptic drugs do not improve cognitive impairment. Atypical antipsychotics improve cognition, but the pattern of improvement differs from drug to drug. Diminished cholinergic activity has been associated with memory impairments. Why atypical drugs improve aspects of cognition might lie in their ability to increase dopamine and acetylcholine in the prefrontal cortex. An optimum amount of dopamine activity in the prefrontal cortex is critical for cognitive functioning. Another mechanism is related to procedural learning, and would explain the quality of the practice during repeated evaluations with atypical antipsychotics due to a more balanced blockage of D2 receptors. Laboratory studies have shown that clozapine, ziprasidone, olanzapine and risperidone all selectively increase acetylcholine release in the prefrontal cortex, whereas this is not true for haloperidol and thioridazine. A few studies have suggested that cholinomimetics or AChE inhibitors can improve memory functions not only in Alzheimer's disease but also in other pathologies. Some studies support the role of decreased cholinergic activity in the cognitive deficits of schizophrenia. Some studies demonstrated that decreased choline acetyltransferase activity was related to deterioration in cognitive performance in schizophrenia. Overall, results suggest the hypothesis that the cholinergic system is involved in the cognitive dysfunctions observed in schizophrenia and that increased cholinergic activity may improve these impairments. Furthermore, a dysfunction of glutamatergic neurotransmission could play a key role in cognitive deficits associated with schizophrenia. Further meta-analysis of various clinical trials in this field is required to account for matters on the grounds of evidence-based medicine.

Keywords: Cognition; Cognitive enhancer; Cholinergic system; Neuroleptic; Schizophrenia.

Abbreviations

AChE: Acetylcholinesterase

ABAB: Counter Balance Design

ADAS-GOG cognitive portion of the Alzheimer's Disease Assessment Scale

BuChE: Butyrylcholinesterase

CANTAB: Cambridge Neuropsychological Test Automated Battery

CRH: Corticotropin hormones

EPS: Extrapyramidal Symptoms

FDA:US Food and Drug Administration's

LTM: Long-Term Memory

NMDA: N-methyl-d-aspartate

PRE-A: Conflict Reaction Time

REM: Rapid Eye Movement

RVP: Rapid Visual Processing

PS: Paradoxal Sleep

SOC: Stocking of Cambridge

STM: Short-Term Memory

SWS: Slow Wave Sleep

1. Background

It is very well documented that persons with schizophrenia show neurocognitive impairments across multiple domains (Green 1998). These include impairments in motor functioning (King 1994; Voruganti et al 1997), in various aspects of attentional abilities (Green and Walker 1986; Raine et al, 1997; Addington et al, 1997; Chen et al, 1998), in executive functions (Tollefson 1996; Heinrichs and Zakzanis 1998) and in memory functioning (Goldberg et al, 1993a,b) (Fig. 1). For a more complete review of the cognitive deficits present in schizophrenia, the reader is referred to Sharma and Harvey (2000a,b) and Green (1996).

Cognition can grow increasingly impaired with each episode of schizophrenia, and most patients remain in the fifth percentile below normal in neuropsychological functioning (Green 1998). Furthermore, vocational functioning is impaired in patients with schizophrenia. Approximately 85% of these patients are unemployment irrespective of treatment. Cognitive deficits are thought to account in large part for this poor functional outcome (Green 1996; Green et al. 2000). McGurk and Meltzer (2000), demonstrated that a relationship exists between cognitive deficits and work status among schizophrenic patients. As such, there is recognition that improving cognitive functioning is crucial in this patient population. However, we must determine which cognitive domains should be targeted and which psychopharmacological treatments are promising candidates for improving functioning.

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Insert Figure 1 about here

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Much research has taken place attempting to determine if psychopharmacological interventions can ameliorate cognitive impairments in schizophrenia. However, this area of research requires methodological refinement (Harvey and Keefe, 2001). Recently the NIMH has identified obstacles that are

likely to interfere with the development of pharmacological agents for treating cognition in schizophrenia. These include: a lack of a consensus as to how cognition in schizophrenia should be measured; differing opinions as to the pharmacological approaches that are most promising; challenges in clinical trial design; concerns in the pharmaceutical industry regarding the US Food and Drug Administration's (FDA) approaches to drug approval for this indication; and issues in developing a research infrastructure that can carry out clinical trials of promising drugs. The MATRICS is a new US funded program bringing together representatives of academia, industry and government in a consensus process for addressing all of these obstacles (Green et al, 2004)

The aim of this paper is to examine how an understanding of biochemical mechanisms underlying cognitive processes can lead to pro-cognitive drug treatments in schizophrenia.

2. Antipsychotic medication effects on neurocognition in schizophrenia

Table 1 lists the domains and instruments, which are typically used in research examining the effects of antipsychotic medications on neurocognition in schizophrenia. Knowing that antipsychotic medications influence the positive and negative symptoms of schizophrenia, what effect do they have on cognitive functioning? It is important to remember that neuroleptics were not synthesized and prescribed for the purpose of treating cognitive deficits. From the outset, 50 years ago, the goal of synthesis and prescription has primarily been to attenuate positive symptoms (and with the advent of atypical neuroleptics, negative symptoms as well) and possibly to protect against symptoms of depression (Stip, 2000a). Consequently, their potential to be recognized conceptually as cognitive enhancers is relatively artificial. Empirically, the questions regarding their impact on cognition flowed from the investigation of secondary effects. Above all, it was hoped that these drugs would not bring about deterioration in this area.

Table 2 provides a brief summary of results from trials examining the effects of antipsychotic medications in schizophrenia. Comprehensive reviews examining the effects of atypical medications have been presented elsewhere (Keefe et al., 1999; Purdon, 1999), therefore, a rehashing of this literature is beyond the scope of this paper. It is generally agreed that atypical medications are better for cognition when compared to conventional medications. This conclusion is based on studies that compared haloperidol at elevated doses. However, it must be noted that recent research using lower doses of haloperidol has demonstrated that there is very little difference between atypical and typical medications on cognitive functioning (Keefe et al., 2004).

3. On the trail of a hypothesis based on the psychopharmacologic profile

In terms of psychopharmacology, trials conducted over the past few years have shown that atypical neuroleptics such as olanzapine can improve skills related to explicit memory (Stip, 2000b). These results seemed odd to certain authors, given that olanzapine was supposed to have an anticholinergic psychopharmacological profile. Instead, few clinical anticholinergic effects were noted during the clinical trials, even when olanzapine was compared with drugs without an anticholinergic profile. Though early results were contradictory, recent controlled studies have shown that clozapine has a positive effect on various cognitive areas, especially verbal fluency and attention (Sharma and Mockler, 1998). It has also been suggested that a 5-HT_6 receptor antagonist effect may account for olanzapine's positive impact on memory. In this connection, a relationship has been demonstrated between 5-HT_6 receptors antagonism and both improvement in spatial learning in rats and increased cerebral acetylcholine (Fig. 2).

In addition, it has been suggested that clozapine and olanzapine are more effective than conventional neuroleptics in reducing negative symptoms (Kane et al., 1988; Beasley et al., 1997). Although other pharmacological mechanisms (5-HT_2

antagonism, selective mesolimbic dopamine blockade) have been proposed to explain the efficacy of clozapine and olanzapine against negative symptoms, their pronounced antimuscarinic activity may be one of the mechanisms involved (Tandon, 1997).

3.1 Dopamine

An optimum amount of dopamine activity in the prefrontal cortex is critical for cognitive functioning. From a neurochemical point of view, the "dopaminergic hypothesis" suggests that schizophrenic psychosis results from an increase in central dopaminergic transmission (Van Rossum, 1966). Conventional neuroleptics block postsynaptic dopamine D2 receptors (Farde et al., 1986). To see an improvement in positive symptoms, these receptors must be blocked 60% to 70% (Fitzgerald et al., 1999). When more than 80% blockade occurs, extrapyramidal symptoms appear (Farde et al., 1992). Atypical neuroleptics do not affect the same receptors, as do conventional neuroleptics. According to Meltzer (1990), their effectiveness in treating negative symptoms and their weak propensity for inducing extrapyramidal symptoms may be attributable to their greater affinity to serotonin 5-HT_2 receptors than for D2 receptors. Other authors (Kapur and Seeman, 2000) have suggested it is more a question of differences in the ability to dissociate rapidly from dopaminergic receptors. In this regard, the affinity component that expresses the D2 receptor-unbinding rate (K_{off}) is faster for atypical neuroleptics such as clozapine and quetiapine, which may explain their atypical clinical properties.

Animal studies have demonstrated that clozapine increases dopamine efflux in the prefrontal cortex, with little or no effect on the limbic system. Ziprasidone, an investigational agent, was found to be more potent than clozapine in increasing dopamine efflux in the prefrontal cortex and also to have no effect on the limbic system. Both olanzapine and risperidone increase dopamine efflux in the prefrontal cortex as well. By contrast, haloperidol does not increase dopamine efflux in the

prefrontal cortex, which may be part of the reason why older antipsychotic agents do not improve cognitive impairment.

Insert Table 1 about here

Insert Table 2 about here

Chakos et al. (1995) found that the caudate nuclei of patients treated with classical neuroleptics increased in volume, whereas the caudate nuclei volume of patients treated with clozapine diminished. For the first time, researchers demonstrated that neuroleptics had a direct effect on the brain's structures. Procedural memory requires intact basal ganglia to operate properly. Procedural learning refers to the process of learning either a cognitive or motor procedure in which the strategy of execution cannot be explicitly described (i.e., learning by doing). Procedures are then progressively learned over successive trials until there is an automation of the optimal performance. Studies of neurodegenerative disorders such as Huntington's and Parkinson's diseases show that a striatal dysfunction could affect procedural learning. In patients with schizophrenia treated with neuroleptics, some studies have reported that procedural learning is affected (Scherer et al., 2003). In normal volunteers, acute administration of chlorpromazine induces a deficit in procedural learning, which suggests a direct effect of neuroleptics, presumably via a D2 dopamine blockade in the striatum. Recently, we have shown that patients with schizophrenia who were treated with haloperidol showed deficits in procedural learning tasks, whereas clozapine- or risperidone-treated patients presented no such difficulties (Scherer et al., 2003). Purdon et al. (2003) observed differences between olanzapine, risperidone and haloperidol on procedural learning in patients with schizophrenia. They concluded that risperidone and haloperidol negatively impacted procedural learning to a greater extent relative to olanzapine. Purdon et al. (2003)

state that this difference is most likely due to differential D2 binding profiles in the dorsal striatum between medications. The differential effect of these substances on the striatal D2 receptors, irrespective of their classification as conventional or atypical neuroleptics, may explain these results. Data obtained in Montreal, in patients with schizophrenia treated with Olanzapine and haloperidol using iodine 123- BZM with SPECT have shown that the melody of learning (or smoothness or learning consistency) in a visuomotor procedural task varies inversely with D2 receptor level saturation (Paquet et al., 2004). This line of research suggests that longitudinal studies examining the difference between atypical and typical (blocking a lot D2) agents requiring repeated measures with regard to cognitive performance can only be due a better preservation of the practice effect, i.e. the procedural learning. This is not due per se to the direct effect of the medication on the task but on the implicit learning of a task, which is related to a lower D2 blockade. In conclusion improvement related to new antipsychotics is related to a better side effect profile but not to a direct cognitive enhancing effect.

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Insert Figure 2 about here

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3.2 Cholinergic system

Cholinergic therapy (inhibition of cholinesterase) in Alzheimer's disease initially focused on inhibiting AChE, because AChE was the only enzyme known to be involved in inactivating acetylcholine in the healthy brain. However, it is now largely acknowledged that inhibition of AChE using specific inhibitors (donepezil) can elevate brain ACh levels, as evidenced in pre-clinical studies. AChE inhibitors divide into two main therapeutic classes based on their mode of action. Dual-action AChE inhibitors target both AChE and BuChE, whereas single-action AChE inhibitors target one of the two cholinesterase (AChE or BuChe) more specifically. Rivastigmine, which is CNS selective, is a dual-action AChE inhibitor (Kennedy et

al., 1999). In placebo-controlled clinical trials lasting six months, rivastigmine had significant beneficial effects on the cognitive functions of patients with mild-to-moderate Alzheimer's disease (Giacobini, 2000). The cognitive functions of patients who received placebo deteriorated, while the mean variation in scores measuring the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-GOG) improved significantly among patients who received 3 to 6 mg of rivastigmine twice daily. In addition, the clinical trials demonstrated that rivastigmine provided benefits with respect to ADL, behavior and cognition across the entire disease continuum.

Diminished cholinergic activity has been associated with memory impairment (Karson et al., 1993, 1996). As is the case with dopamine, atypical antipsychotic agents also increase the efflux of acetylcholine in the prefrontal cortex. This is another quality that sets them apart from the typical antipsychotics. Laboratory studies have shown that clozapine, ziprasidone, olanzapine and risperidone all selectively increase acetylcholine release in the prefrontal cortex, whereas this is not true for haloperidol and thioridazine. Atypical antipsychotic drugs are not all the same, however; these have different effects on cognition, which is probably explained by the potency of their relative activity at different receptor sites. Compared with clozapine, olanzapine, quetiapine and risperidone, ziprasidone is more potent at the following key receptor sites: D2, 5-HT2a, 5-HT1a, and 5-HT2c receptors (Schotte et al., 1995).

3.3 Cholinergic system and schizophrenia

Numerous studies have pointed to an anomaly of the cerebral (prefrontal) nicotinic and muscarinic receptors in schizophrenia (Breese et al., 2000; Freedman et al., 2000; George et al., 2000; Crook et al., 2001; Lai et al., 2001) or of the interneurons of the subcortical structures (Holt et al., 1999; German et al., 1999). Tandon et al. (1991) suggested that the cholinergic system played a key role in the pathophysiology of schizophrenia and that cholinergic-dopaminergic interactions

were pertinent in the expression of positive and negative symptoms. More specifically, these authors suggested that muscarinic hyperactivity might be relevant in the production of negative symptoms and that reduced cholinergic activity might be associated with positive symptoms (Tandon and Greden, 1989). Finally, the Tandon group showed that biperiden, a relatively selective anticholinergic muscarinic M1 antagonist, reduced negative symptoms in unmedicated schizophrenic patients (Tandon et al., 1991, 1992a). Consequently, it would appear that the beneficial effects could not be attributed solely to improvement in extrapyramidal symptoms.

Another argument suggesting that cholinergic activity is involved in the negative symptoms of schizophrenia centers on its implication in sleep regulation (Tandon et al., 1992b; Riemann et al., 1994). According to Hobson (1988), PS appears when aminergic neurotransmission is low (REM-off system) and/or when cholinergic neurotransmission is elevated (REM-on system). Given that REM sleep regulation and the phasic and tonic aspects of dreaming are under cholinergic control, several groups have conducted sleep studies with a view to clarifying the role of the cholinergic system in schizophrenia. Increased cholinergic activity is associated with shortened REM latency and a reduction in SWS duration. Studies have shown that presence of negative symptoms correlates significantly with shortened REM latency (Tandon et al., 1991) and increased SWS (Ganguli et al., 1987; Van Kammen et al., 1988; Tandon and Greden, 1989). In studies involving healthy subjects, administration of AChE inhibitors has at times shortened PS latency (Schredl et al., 2000; Holsboer-Trachsler et al., 1993). However, in populations where REM latency is already reduced, as is the case with schizophrenics, no effect was observed—possibly because the cholinergic system is hyperfunctional in this disease (Tandon and Greden, 1989; Keshavan et al., 1992).

Negative symptoms have also been linked to an increase in post-dexamethasone cortisol (Tandon et al., 1991; Saffer et al., 1985), in growth hormone response to TRH (Keshavan et al., 1989), and in pyridostigmine (O'keane et al., 1994), during the acute psychotic phase of schizophrenia. These data indirectly support the role of increased muscarinic activity in the production of negative symptoms, as cholinergic mechanisms are known to play a role in the release of corticotrophin hormones (CRH) and in the regulation of growth hormone response to TRH stimulation.

It seems, then, that cholinergic hyperactivity may be involved in the production of negative symptoms in a subgroup of patients with schizophrenia and that cholinergic interaction with other transmitters may be important in the pathogenesis of negative symptoms during certain phases of the disease.

Atypical antipsychotics increase acetylcholine release in prefrontal cortex and hippocampus (Ichikawa et al., 2001). Olanzapine seems to be the most powerful on this mechanism as suggested by Shirazi-Southall'study (2002) on the acetylcholine efflux in rat hippocampus. Other drugs useful in psychiatry with indications other than schizophrenia could be of potential beneficial effect in schizophrenia.

A few studies have suggested that cholinomimetics or AChE inhibitors can improve memory functions not only in Alzheimer's disease but also in other pathologies. Some studies support the role of decreased cholinergic activity in the cognitive deficits of schizophrenia (Karson et al., 1993, 1996). These studies demonstrated that decreased choline acetyltransferase activity was related to deterioration in cognitive performance in schizophrenia. A recent study indicated that reduced anticholinergic activity played a role in the cognitive deficits of the schizophrenia spectrum (Kirrane et al., 2001). These authors showed that administration of cholinomimetics such as physostigmine improved cognitive performance in a visuospatial working memory task among patients with schizotypical personality disorder.

Similarly, a case study using an ABAB design which is a counterbalanced design to prevent the possibility of carry-over effects from trial to trial with donepezil as an add-on treatment to risperidone showed improvement in verbal fluency (MacEwan et al., 2001). However, a recent report by Friedman et al. (2002) failed to show any beneficial effect on cognition of donepezil added on to risperidone among 36 patients. In their discussion of these unexpected results, the authors raised methodological issues that remain to be analyzed more closely, including the effects of tobacco use on their series of patients (nicotinic tolerance was not evaluated). In this regard, it was recently demonstrated that, when given nicotine, patients with schizophrenia who smoked showed an improvement in episodic memory performance (Blaxton et al., 2001). Overall, these results suggest the hypothesis that the cholinergic system is involved in the cognitive dysfunctions observed in schizophrenia and that increased cholinergic activity may improve these impairments (Hussain et al., 2001).

The presence of abnormal cholinergic function in schizophrenia provides the rationale to test the effectiveness of cholinesterase inhibitors in treating cognitive impairment in cognitively impaired patients with schizophrenia (Chouinard et al., 2004; Stip et al., 2004). Nineteen patients (age 28.6 ± 6.7 years; M=11, F=2) stabilized with atypical neuroleptic underwent neurocognitive evaluations performed with Cambridge Neuropsychological Test Automated Battery (CANTAB) before and after 12 weeks of treatment with rivastigmine. Doses were adjusted depending on the tolerability of patients. Beginning at 3 mg/day reaching 6 mg the first month to progressively increase to 9mg/day. Tasks used were "Stockings of Cambridge" (SOC) which evaluated executive functions and procedural memory and "Rapid Visual Processing" (RVP), which evaluated sustained attention, working memory and visual detection. The results revealed that patients have improvements in executive functions such as planning after treatment with rivastigmine: they resolved more problems in a minimum of moves on the SOC. We also noted improvement in

procedural memory: the patients proceed more rapidly on SOC after initial move. The patients show improvement in sustained attention: they made less error on RVP task in detecting stimuli. The PANSS score did not show a deterioration of the positive symptoms. Another recent study by Lenzi et al. (2003) found that rivastigmine resulted in significant improvements in quality of life, which were paralleled by significant improvements in cognitive function, learning, and memory, and trends for improvement in attention.

3.4 Glutamatergic system and cognitive deficits in schizophrenia

The glutamatergic neurons are the major excitatory pathways linking the cortex, limbic system and thalamus, three regions believed to be involved in schizophrenia. A recent approach in the treatment of persistent negative symptoms and cognitive deficits has centered on the use of N-methyl-d-aspartate (NMDA) receptor agonists, such as glycine, D-serine and D-cycloserine. These drugs, when taken in conjunction with conventional or atypical antipsychotics, have brought about a significant reduction in both negative and cognitive symptoms. The importance of the glutamate NMDA receptor stems from the fact that its blockade can induce behavioral and cognitive deficits in normal subjects which mimic schizophrenia (Krystal et al., 1999). Agents that indirectly enhance NMDA receptor function via the glycine modulatory site reduce negative symptoms and variably improve cognitive functioning in schizophrenic patients treated with typical antipsychotics (Goff and Coyle, 2001). Tsai et al. (1998) reported cognitive improvement in performance on the Wisconsin Card Sorting Test among schizophrenic patients who took D-serine together with antipsychotics. Following a comprehensive review of the literature addressing the role of glutamate in the pathophysiology of schizophrenia, these authors concluded that a dysfunction of glutamatergic neurotransmission could play a key role in the negative symptoms and cognitive deficits associated with schizophrenia.

3.5 Noradrenergic systems

The role of noradrenergic systems in cognition has been well studied. Animal as well as human research demonstrate that norepinephrin has a direct influence on prefrontal cortical functioning via postsynaptic α_{2a}-adrenoceptors (Friedman et al, 2004; Arnsten 2004). Animal research has demonstrated that noradrenergic projections from the locus ceruleus to the prefrontal cortex can influence cognitive functioning, and more specifically, working memory and selective attention abilities. For instance, Coull (1994) demonstrated that agonism of the $\alpha_{1\text{-}2}$ receptors using clonidine and guanfacine can improve aged monkeys ability to attend to a delayed response task. Reducing noradrenergic activity has been shown to impair monkeys' attention abilities (Friedman et al., 2004). Friedman et al. (2004) reviewed the literature on potential noradrenergic targets which could influence cognitive functioning in schizophrenia. They concluded that an alpha 2a agonist such as guanfacine could improve cognitive functioning. Another target proposed was the inhibition of norepinephrin reuptake using atomoxetine.

In summary, the basis for the effectiveness of atypical antipsychotic agents on cognition rests on their ability to promote increased dopaminergic and cholinergic activity in the prefrontal cortex, antagonism at the 5-HT2a, 5-HT1a, 6, and 7 sites, and actions on other neurotransmitter systems. Numerous actions modulating the effects of atypical antipsychotics on DA and Ach release have been suggested: increasing prefrontal cortical dopamine and acetylcholine efflux (Kuroki et al., 1999); Diminish the stimulation of AMPA/kainate glutamate receptors (Moghaddam et al., 1997) by 5-HT2a antagonism (Aghajanan and Marek, 2000) and 5-HT1a agonism (Ichikawa et al., 2001); blockade of neurotoxic effects of glutamate (Olney and Farber, 1995) changing pattern of gene expression in specific brain area (Robertson and Fibiger, 1996) or enhancing neurogenesis and connectivity (Gould, 1999). Some authors showed a contribution of 5-HT2a and D2 receptor antagonism to dopamine efflux in prefrontal cortex and N. Accumbens (Liegeois et al., 2002). In addition the

role of 5-HT1a agonism in dopamine efflux in prefrontal cortex has been demonstrated (Yoshino et al., 2002).

4. New investigational agents

The discovery of atypical neuroleptics for the treatment of schizophrenia made it possible to improve the condition of patients. Meltzer (1990) defined atypical neuroleptics in terms of three characteristics: efficacy in treating negative symptoms and patients refractory to conventional therapies; few extrapyramidal effects; and mild prolactin elevation. There are several families of atypical neuroleptics: dibenzodiazepines (clozapine, olanzapine, quetiapine, zotepine and amoxapine), benzamides (remoxipride and amisulpride), benzisoxazole (risperidone), ziprasidone and sertindole.

Ziprasidone is the latest of the atypical antipsychotic agents. It presents a low incidence of side effects and an interesting and unique receptor profile. In one study, patients with schizophrenia who were stable on conventional antipsychotics, olanzapine, or risperidone were switched to ziprasidone on a flexible dosing schedule of 80 to 160 mg/day in an open-label fashion (Harvey et al., 1997). The switch to ziprasidone resulted in a statistically significant improvement in total learning and long-delay recall for patients originally taking conventional antipsychotics ($P<0.01$), olanzapine ($P<0.001$), or risperidone ($P<0.001$). A statistically significant improvement in the Digital Span Subtraction Test (a measure of attention/motor function) was observed in patients on ziprasidone who were switched from conventional antipsychotics or risperidone ($P<0.05$), but not in patients switched from olanzapine. Scores on the Continuous Performance Test significantly improved among patients switched from olanzapine ($P=0.01$) or risperidone ($P=0.038$), but they worsened among those switched from conventional antipsychotic medication. Significantly fewer errors were noted on the Wisconsin Card Sort Test (a measure of executive functioning) (Heaton, 1981) among patients switched from risperidone to

ziprasidone ($P<0.001$), but not much effect was discerned among those switched from olanzapine to ziprasidone.

Ziprasidone treatment was associated with significant improvement across multiple areas of cognition when patients were switched from conventional antipsychotics, olanzapine, risperidone, or ziprasidone at doses used in the study. Cognitive improvements were noted for learning and memory, attention, and executive functions. The results suggested that ziprasidone had the potential to improve cognitive deficits. It also proposed that after a switch from other compounds to ziprasidone, the practice effect due to repetition of neuropsychological sessions with several tasks was facilitated.

Aripiprazole is a novel antipsychotic drug with a partial affinity to dopamine D2 receptors and a high affinity to 5-HT(1A) receptors. This stabilizing effect on the dopamine-serotonin system may contribute to the overall efficacy of aripiprazole against the anxiety, depression, negative symptoms, and cognitive deficits associated with schizophrenia (Jordan et al., 2002). Cornblatt et al. (2002) demonstrated aripiprazole's superiority over olanzapine in secondary verbal memory, but not in visual memory or executive functioning. Aripiprazole's neurocognitive benefits and the favorable side-effects profile may provide health advantages and facilitate psychosocial rehabilitation.

5. Conclusion

Cognitive impairment is now recognized as a major contributor to poor functional outcome among patients with schizophrenia. It is no longer sufficient to treat positive and negative symptoms; treatment should also be aimed at improving cognition in an attempt to help patients function better in the community. Typical antipsychotic agents do not improve cognition, and they induce a host of adverse effects. Anticholinergic drugs, which are used as adjuncts to antipsychotic agents,

also have adverse effects. The newer antipsychotic agents appear to have a more favorable side-effects profile and to improve cognition. However, these drugs act differently across the cognitive domains (Harvey and Keefe 2001).

Multiple avenues of research in neurotransmission suggest that neurotransmitters other than dopamine and serotonin are implicated in the clinical symptoms of schizophrenia, especially cognitive impairments. Consequently, the administration of drugs modulating cholinergic or glutamatergic neurotransmission holds the potential of a novel treatment for the cognitive deficits associated with schizophrenia. What remains to be clarified is the nature, extent and mechanisms of these cognitive deficits as well as the link between the deficits and the effects of the medication. Also, further meta-analysis of this field is required to account for matters on the grounds of evidence-based medicine. Promising studies in which cognitive tasks involving working memory have been investigated using fMRI (Mendrek et al., 2001) may allow us to gain a better understanding of the mechanisms at play. If, as suggested by the evidenced-based literature, outcome is related to the cognitive spheres, then cognitive psychopharmacology is a discipline that cannot be overlooked. Where schizophrenia is concerned, we have taken but the first few steps on the road that will lead to the discovery of a cognitive enhancer.

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Table 1. Neurocognitive tests and descriptions

Domain	Description	Assessments
Psychomotor speed and dexterity	Psychomotor performance is typically assessed with motor tasks which place minimal demands on 'thinking' or cognition.	Grooved Peg Board; Finger Tapping Test; Pin Test (Lezak, 1983; Spreen & Strauss, 1991).
Visuoperceptual/ motor processing	Visuoperceptual and motor processing tasks require some higher-order cognitive functioning in addition to motor functioning	Trail Making Test Part A (Trails A) (Lezak, 1983) and Digit Symbol Substitution Test (Wechsler, 1981).
Verbal memory	Memory for lists of words and for verbatim recall of short paragraphs.	Rey Auditory-Verbal Learning Test (Spreen and Strauss, 1991); California Verbal Learning Test, (Delis et al., 1987); Hopkins Verbal Learning Test (Brandt, 1991), Logical memory from the WMS-R; Verbal Paired Associates from the WMS-R; Digit Span Forward from WMS-R or WAIS-R.
Visual memory	Memory for nameable and non-nameable objects	Figural Memory (WAIS-III; Kaufman and Lichtenberger, 1998); Rey-Osterrieth Complex Figure Test [Rey-O] (Spreen and Strauss, 1991); (3) Visual Reproduction from the WMS-R; and (4) Visual Paired Associates from the WMS-R.

Domain	Description	Assessments
Attention	Attention can be divided according to types of attention: (1) selective: ability to attend to relevant or target stimuli over irrelevant stimuli; (2) sustained: ability to focus on a task for an extended period of time; (3) divided: ability to attend to two or more attentional tasks at the same time	Selective: Stroop Color Word Test (Golden, 1978); Petersen Consonant Trigram test (PCT) (Spreen and Strauss, 1991); Digit Span Distractibility Test (Oltmanns and Neale 1975; Oltmanns, 1978); Span of Apprehension test (SoA) (Nuechterlein and Dawson, 1984) Sustained : Continuous Performance Test (CPT) Divided: Dichotic Listening
Working memory	Refers to the mental manipulation of either verbal or non-verbal information that is held in Short-Term Memory	Verbal Working Memory: Digit Span Backward; Letter Number Sequencing (WAIS-III; Kaufman and Lichtenberger, 1998) Non-Verbal Working Memory: Visual Memory Span Backward (WAIS-III; Kaufman and Lichtenberger, 1998)

Table 2. Summary of studies examining the effects of atypical antipsychotic medications on neurocognitive functioning in schizophrenia

Author(s)	Design and trial duration	Study medication(s)	Motor	Visual perceptual	Verbal memory	Visual memory	Executive functioning	Reaction time	Attention	Working memory
Classen and Laux, 1988	Open-label 7 days	Cozapine Haloperidol Fluphenazine (*N*=50)	cloz = hal						cloz = hal = fluphen	
Goldberg et al. 1993b	Open-label variable range: 3 to 24 months	Clozapine (*N*=13)		0 cloz	0 cloz	0 cloz - cloz (detected for immediate and delayed recall on visual reproduction)	0 cloz			0 cloz
Hagger et al. 1993	Open-label, 26 weeks	Clozapine (*N*=36)		0 cloz at 6 weeks cloz +at 6 months	+ cloz		0 cloz (on WCST) + cloz (verbal fluency)		- cloz at 6 weeks back to baseline at 6 months	
Buchanan et al. 1994	Double-bline (1st 10 weeks) followed by open-label for 1 year	Clozapine Haloperidol (*N*=38)			0 cloz 0 hal	0 cloz 0 hal	0 cloz 0 hal + cloz (verbal fluency after 1 year)		0 cloz 0 hal	0 cloz 0 hal
Lee et al. 1994	Open-label 1 year	Clozapine various typicals (*N*=47)		cloz > typicals	+ cloz + Typicals		+ cloz (WCST) + cloz (verbal fluency) 0 cloz (Trails B) 0 typicals (WCST) 0 typicals (Trails B) 0 typicals (verbal fluency)		+ cloz 0 typicals cloz = typicals	
Zahn et al., 1994	Single-blind cross-over; 6 weeks on active medications and 20 days on placebo cross-over	Clozapine Fluphenazine Placebo (*N*=25)						cloz = fluphen = placebo		

Author(s)	Design and trial duration	Study medication(s)	Motor	Visual perceptual	Verbal memory	Visual memory	Executive functioning	Reaction time	Attention	Working memory
Daniel et al. 1996	Single-blind cross-over 6 weeks per treatment	Clozapine Risperidone (*N*=20)			cloz = risp	cloz = risp	cloz = risp		cloz = risp	cloz = risp
Grace et al. , 1996	Open-label 3 years	Clozapine (*N*=31)		+ cloz	+ cloz	+ cloz	+ cloz			+ cloz
Stip and Lussier 1996	Open-label average of 26 weeks	Risperidone (*N*=13)			0 risp			+ risp	0 risp (CPT) + risp (Span of Apprehension)	
Fujii et al., 1997	Open-label 1 year	Clozapine (*N*=22)		0 cloz			0 cloz			
Galletly et al., 1997	Open-label 32 weeks	Clozapine (*N*=19)		+ cloz	+ cloz		+ cloz		+ cloz	
Green et al., 1997	Double-blind 12 weeks	Risperidone Haloperidol (*N*=59)							+ risp 0 hal risp > hal	
Rossi et al., 1997	Open-label 4 weeks	Risperidone (*N*=25)		+ risp	0 risp		+ risp			+ risp
Lindenmayer et al., 1998	Open-label 12 weeks	Clozapine Risperidone (*N*=35)		0 cloz 0 risp cloz = risp	0 cloz 0 risp cloz >risp (list learning) cloz =risp (paragraphs)	0 cloz 0 risp cloz = risp	0 cloz 0 risp cloz = risp		0 cloz 0 risp cloz = risp	0 cloz 0 risp cloz = risp
Sax et al., 1998	Open-label 9 weeks	Quetiapine (*N*=10) Normal Controls (*N*=12)							+ Q; Q = NC at f/up	
Kern et al., 1998	Double-blind 12 weeks	Risperidone Haloperidol (*N*=56)	+ risp 0 hal risp > hal		+ risp + hal risp > hal				risp > hal	
Manschreck et al., 1999	Open-label 12 months; comparison of patients who were discharged and inpatients	Clozapine (*N*=54)	+ cloz (discharged patients only)	0 cloz	0 cloz	0 cloz	+ cloz (discharged patients only on verbal fluency only)	0 cloz		

Author(s)	Design and trial duration	Study medication(s)	Motor	Visual perceptual	Verbal memory	Visual memory	Executive functioning	Reaction time	Attention	Working memory
Liu et al.,.2000	Double-blind 12 weeks	Risperidone Haloperidol (*N*=38)							0 risp 0 hal risp = hal	
Purdon et al., 2000	Double-blind 1 year	Olanzapine Risperidone Haloperidol (*N*=65)	+ olan 0 risp 0 hal olan > hal risp = hal	0 olan 0 risp olan = risp olan > risp	0 risp	+ olan + risp + hal olan = risp = hal	+ olan 0 risp 0 hal olan = risp = hal			
Potkin, 2001	Double-blind during active treatment; single-blind during the placebo cross-over period; 6 weeks per treatment arm	Clozapine Haloperidol (*N*=27)		+ cloz + hal	+ cloz + hal cloz > hal (list learning) cloz = hal (WMS-R memory index)		WCST 0 cloz 0 hal cloz = hal Trails B + cloz 0 hal cloz > hal Verbal Fluency 0 cloz 0 hal cloz > hal			
Purdon et al., 2001a	Open-label 6-8 weeks	Clozapine (*N*=18)		+ cloz	+ cloz (list learning; paragraphs; paired associates) 0 cloz (digit span forward)	+ cloz	+ cloz (Trails B and verbal fluency) 0 cloz (WCST)		0 cloz	0 cloz
Purdon et al., 2001b [1]	Double-blind 26 weeks	Quetiapine Haloperidol (*N*=25)	0 quet 0 hal	+ quet + hal	Verbal List Learning 0 quet 0 hal Paragraph Memory (immediate recall) + quet + hal	Visual List Learning + quet 0 hal Complex Figure + quet 0 hal Visual Reproduction 0 quet 0 hal	WCST + quet 0 hal Trails B 0 quet + hal			

Author(s)	Design and trial duration	Study medication(s)	Motor	Visual perceptual	Verbal memory	Visual memory	Executive functioning	Reaction time	Attention	Working memory
Smith, 2001	Double-blind for 8 weeks, then open-label olanzapine for 12 weeks	Olanzapine Haloperidol (*N*=34)			0 olan 0 hal olan = hal + olan during 3 month open label phase (verbal paired associates)	0 olan 0 hal olan = hal + olan during 3 month open label phase (visuospatial memory)	0 olan 0 hal olan = hal	0 olan 0 hal olan = hal		0 olan 0 hal olan = hal
Velligan et al., 2002	Double-blind 24 weeks	Quetiapine Haloperidol (*N*=58)	--	+ quet + hal quet > hal-	0 w/in analyses; quet = hal quet > hal				que > hal at 24 wks	
Stip et al., 2003	Open-label 8 weeks	Olanzapine (*N*=134)			+ olan		+ olan			
Bilder et al., 2002	Double-blind 14 weeks	Clozapine Risperidone Olanzapine Haloperidol (*N*=101)	+ cloz 0 risp 0 olan 0 hal				0 cloz + risp + olan 0 hal			

cloz—clozapine; hal—haloperidol; risp—risperidone; olan—olanzapine: quet—quetiapine; fluphen—fluphenazine; +, indicates improved performance; - indicates reduced performance; >, indicates greater improvement of one medication over the other

Figure 1. Cognitive profile.

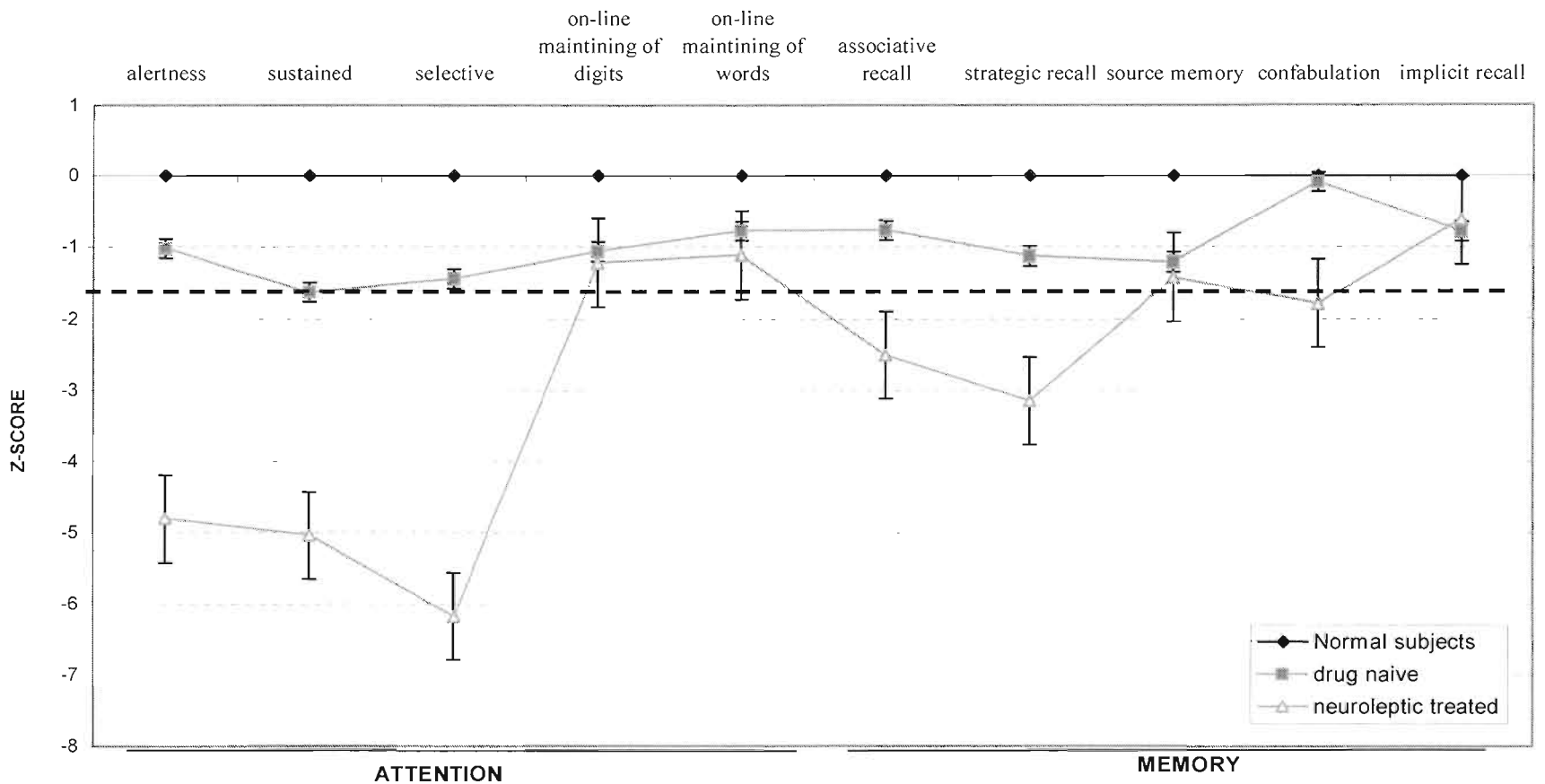
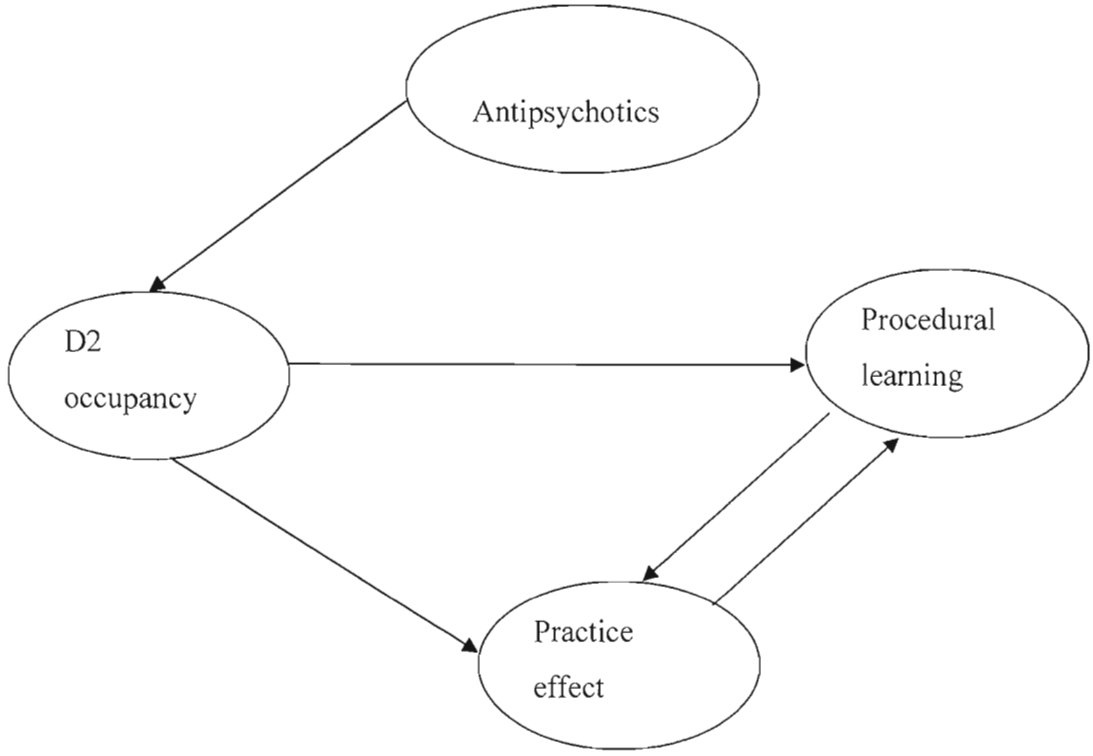


Figure 2. Low and high D2 occupancy.



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CHAPITRE III

DEUXIÈME ARTICLE

RIVASTIGMINE TREATMENT AS AN ADD-ON TO ANTIPSYCHOTICS IN PATIENTS WITH SCHIZOPHRENIA AND COGNITIVE DEFICITS

Rivastigmine treatment as an add-on to antipsychotics in patients with schizophrenia and cognitive deficits

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Running head: Rivastigmine in patients with schizophrenia

Résumé de l'article

Malgré l'avancement dans le domaine psychopharmacologique pour le traitement des symptômes cliniques de la schizophrénie, il n'en demeure pas moins que des déficits cognitifs persistent aux niveaux de l'attention, de la mémoire et des fonctions exécutives. Plusieurs études ont mis en évidence l'implication du système cholinergique dans le fonctionnement cognitif. L'efficacité des inhibiteurs d'acétylcholinestérase comme la rivastigmine pour traiter le dysfonctionnement cognitif a été montrée dans des pathologies, tel que la maladie d'Alzheimer et le Parkinson. On a aussi suggéré qu'une perturbation du système cholinergique, particulièrement dans le cortex préfrontal, soit reliée aux troubles cognitifs observés dans la schizophrénie. Ce qui nous amène à l'hypothèse que la rivastigmine pourrait permettre d'améliorer les déficits cognitifs chez les patients atteints de schizophrénie. À partir d'une étude utilisant un design croisé, nous avons fait le recrutement de 58 patients, qui ont été évalués avec la batterie Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS). De ce nombre, 24 patients qui correspondaient aux critères d'inclusion ont été retenus. Finalement, 20 patients ont participé à l'étude, car quatre d'entre eux ont été retirés de l'étude. Tous les participants rencontraient les critères du DSM-IV pour un diagnostic de schizophrénie. Les patients ont continué leurs traitements antipsychotiques et ont été traités de manière concomitante avec la rivastigmine pour une durée de trois mois. Le dosage était déterminé en fonction de la tolérance, commençant à 3mg/DIE pour augmenter progressivement à 9mg/DIE. Les fonctions cognitives ont été évaluées à trois reprises, soit au début de l'étude, et après trois et six mois. Les résultats n'ont pas révélé de différence significative après le traitement avec la rivastigmine sur les variables neurocognitives évaluant l'attention, la mémoire et les fonctions exécutives. En conclusion, ces résultats suggèrent que la rivastigmine, un inhibiteur d'acétylcholinestérase, ne semble pas exercer d'effet notable sur le fonctionnement cognitif chez les patients atteints de schizophrénie stabilisés avec des neuroleptiques atypiques.

Mots-clés: Inhibiteurs d'Acétylcholinestérase ; Cognition ; Rivastigmine ; Schizophrénie.

ABSTRACT

Objective: Although new atypical antipsychotic agents have been found to improve overall cognitive function in patients with schizophrenia (SZ), some aspects of memory, attention and executive functions still remain impaired. Acetylcholinesterase (AChE) inhibitors, such as rivastigmine, have been shown to improve cognition in other disorders, particularly Alzheimer's disease. Dysfunctions in cholinergic systems, especially in the prefrontal cortex, have been identified in SZ, suggesting that cholinesterase inhibitors may be effective in treating cognitive deficits in this disease. *Research design and methods:* Using a randomized crossover design, we assessed SZ patients with stable symptoms and poor cognitive functioning. Fifty-eight patients with memory deficits, according to subjective complaints or based on clinicians' observations, were assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS). Only 24 of these subjects met the inclusion criteria. Twenty patients took part in the study (four dropped out). All subjects meeting the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM□IV) criteria for SZ were maintained on their current antipsychotic medication (18 atypicals and two typicals) and were randomly assigned to treatment with rivastigmine. Dosage was a function of tolerability, beginning at 3 mg/day and progressively increasing to 9 mg/day. Subjects were given the Cambridge Neuropsychological Test Automated Battery (CANTAB) at baseline and 3 and 6 months. *Results:* The results revealed no significant improvement in any of the cognitive variables investigated following rivastigmine treatment and symptom severity scores remained unchanged over all recorded time periods. *Conclusion:* Rivastigmine treatment did not appear to enhance cognition in SZ patients with important cognitive impairments. This finding needs to be interpreted with care and requires substantiation with larger sample size studies with patients treated with cognitive enhancer for longer periods.

Key words: Acetylcholinesterase inhibitors, Cognition, Rivastigmine, Schizophrenia.

Introduction

It has been suggested that cholinergic agonists, including acetylcholinesterase (AChE) inhibitors, such as rivastigmine, may slow down cognitive decline not only in Alzheimer's disease but also in other pathologies[1,2]. In Alzheimer's disease, the effect of AChE inhibitors may slow down cognitive deficits in patients with mild to moderate deficits but does not improve deficits that already exist[3]. A recent systematic review showed that donepezil, rivastigmine and galantamine can delay cognitive impairment (evaluated with the Alzheimer's Disease Assessment Scale Cognitive Subscale [ADAS-Cog]) in patients with mild-to-moderate Alzheimer's disease, at least for 6 months[4]. Important future studies on AChE inhibitors in Alzheimer's disease would be to evaluate combination therapies or prevention with other agents, such as A-beta or estrogens[3]. Another study investigating the effects of rivastigmine on dementia associated with Parkinson's disease showed an improvement in attention and executive functions[1]. Others authors also investigated the pharmacological treatment of cognitive impairment in dementia with Lewy bodies; AChE inhibitors were shown to be effective[2].

Some studies have also pointed to an abnormal cholinergic system in schizophrenia (SZ) as decreased numbers of muscarinic and nicotinic receptors[5,6]. The presence of abnormal cholinergic function in patients with SZ provides a rationale for testing the effectiveness of cholinesterase inhibitors in treating the cognitive impairments often seen in SZ, such as memory and attention deficits[7,8]. Such impairments are often observed at the onset of the illness and do not appear to be attributable to the antipsychotic treatment[9].

The cognitive impairments that appear in the earliest phases of schizophrenia persist throughout its course[10]. Attention[11–13], memory[14,15], and executive function[16,17] may be affected, usually moderately. Neurocognitive impairments are a major impediment to social and vocational rehabilitation[18]. In addition, patients with

executive deficits have been found to be less functional in their daily living activities, assessed with specific tasks (choosing a menu, shopping the ingredients, cooking a meal)[19]. Thus, improvement in cognitive function in SZ patients should be considered in the search for new treatments.

MATRICS, a new US-funded program that brings together representatives of academia, industry and government, has been set up to investigate cognitive deficits in SZ[20]. This program has identified the main obstacles that are likely to interfere with the development of pharmacological agents for treating cognitive problems in schizophrenia. These include a lack of a consensus as to how cognition in schizophrenia should be measured, differing opinions as to the most promising pharmacological approaches, challenges in clinical trial design, concerns in the pharmaceutical industry regarding the US Food and Drug Administration's (FDA) approaches to drug approval for this indication and issues in developing a research infrastructure that can carry out clinical trials of promising drugs.

A number of studies have shown that various atypical antipsychotic medications result in cognitive benefits in schizophrenia patient[21,22]. A meta-analysis conducted by Woodward *et al.*[23] revealed that atypicals are superior to typicals in improving overall cognitive function. In this study, estimate of effect size was calculated (ES = 0.24). Some improvements were noted in the speed of learning and processing with specific atypical antipsychotics. However, cognitive impairment still persists with atypical neuroleptics and provides a rationale to search for new agents to improve cognition.

Several hypotheses have been advanced concerning the neural systems involved in SZ. Alteration of cholinergic activity may play an important role in the cognitive impairments seen in this disease. Freedman *et al.*[24] showed that there is a lower density of nicotinic receptors in the hippocampus of SZ patients. Reduced numbers of muscarinic and nicotinic receptors may contribute to cognitive impairments[25]. Karson

et al.[26] demonstrated that there is a correlation between cognitive impairments and decreased brain choline acetyltransferase levels in SZ. These results suggest that the abnormality of cholinergic system is correlated with cognitive dysfunction in SZ[27].

Physostigmine showed a trend in improving visuospatial working memory (p = 0.07), but not serial verbal learning among patients with schizotypal personality disorder[28]. A case study by MacEwan *et al.*[29] using donepezil as an add-on treatment (10 mg per day for 12 weeks) to risperidone in patients with schizophrenia (paranoid type) showed an improvement in verbal fluency. Conversely, a report by Friedman *et al.*[30] failed to show any beneficial effect of donepezil add-on therapy (10 mg per day for 12 weeks) on cognition in SZ patients (n = 36). The cognitive battery used evaluated, attention, memory and executive functions. The authors suggested that these unexpected results may be due to the effects of tobacco (nicotinic tolerance was not evaluated). In fact, chronic tobacco use produces desensitization of nicotinic receptors[31]. It is noteworthy that in SZ smokers, nicotine is associated with improved performance on visuospatial memory tasks[32].

More recent studies have produced contradictory results regarding the efficiency of AChE inhibitors in SZ. As highlighted by MATRICs[20], many obstacles may interfere with the development of pharmacological agents for treating cognitive problems in schizophrenia. Some reports suggest that the enhanced cholinergic activity triggered by AChE inhibitors improves cognitive function significantly in SZ[33–35] but others have failed to find any significant improvement[36,37].

A meta-analysis of 10 studies conducted by our group investigated the effects of AChE inhibitors on memory in SZ[38]. The results revealed a mild but significant improvement in short-term (p = 0.07) and long-term (p = 0.01) memory after treatment with cholinergic enhancers. However, additional analyses showed that these patients still performed worse than controls after treatment with cholinergic enhancers. The symptom progression was not affected as observed on the Positive

and Negative Symptoms Scale (PANSS) curve which remained stable through out the trial.

In this perspective, the current study was designed to assess the effects of rivastigmine as an add-on therapy to antipsychotic medication on cognitive function in SZ-spectrum patients who have moderate to severe cognitive impairment. We aimed to determine the extent to which this type of medication may enhance cognition in SZ, taking into account nicotine consumption.

Methods

Setting

This study was carried out at the Fernand-Seguin research center, which is part of Louis–Hippolyte Lafontaine Hospital. As two patients were recruited from Charles LeMoyne Hospital (by Dr J-P. Melun), the study was approved by the ethics committees of both hospitals.

Subjects

The study examined 20 patients (five women and 15 men) assigned to one of two groups (groups 1 or 2). The mean age of the patients was 28.85 ± 7.92 years. Nineteen patients fulfilled the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnosis of SZ and one patient in group 2 presented with schizoaffective disorder (APA)[39]. Fourteen patients reported smoking cigarettes on a daily basis (three women and 11 men, age 27.5 ± 6.1 years) and six were non-smokers (two women and four men, age: 32.5 ± 10.3 years). The clinical characteristics of the two groups are reported in Table 1.

All patients had been on stable antipsychotic medication for at least 2 months prior to the commencement of the study and medication dosage was kept unchanged for the duration of the study. Four patients included in the study received

anticholinergic medication during the study. Eighteen patients were under atypical antipsychotics (nine olanzapine, four clozapine, three quetiapine and two risperidone), one was receiving zuclopenthixol (male, 50 year old) and one was receiving chlorpromazine (male, 37 year old). The mean doses and chlorpromazine equivalence for each group were calculated and presented in Table 1[40].

Eligibility

Patients aged 18 to 50 years participated in the study. The inclusion criteria were a score < 75 on the immediate or delayed memory indices of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). This battery has been previously validated with schizophrenia patients[41]. This criterion was established based on the scores of healthy subjects (range = 90.8 to 102.9 on the memory index). It takes about 30 minutes to complete the test. Patients with current substance abuse (amphetamines, Ecstasy, PCP, cocaine, THC or alcohol), other Axis 1 or 3 diagnoses, or pronounced suicidal potential were excluded.

Recruitment

A total of 58 patients were assessed with the RBANS and the Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS) upon referral by psychiatrists, based on subjective complaints of memory deficits or on doctors' observations. Thirty-five patients were eliminated for various reasons (older age, a diagnosis of drug abuse, failure to meet the diagnosis for SZ spectrum, or possible pregnancy). Ten patients scored higher than the allowed RBANS score in the inclusion criteria and 13 patients refused to participate. All participants received a full explanation of the study before they gave informed written consent.

Twenty-four patients were thus recruited and only twenty completed the study. Four patients dropped out of the study after a few weeks into the trial while they were receiving rivastigmine. Of these four patients, one developed disorganized thought,

another was hospitalized due to pronounced suicidal tendencies and two refused to continue the trial without giving any specific reason.

Clinical assessments

All patients were assessed with classical psychiatric assessments, in addition to the PANSS. These assessments were performed at baseline, 3 and 6 months into the study by the same trained rater[42].

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Insert Table 1 about here

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Cognitive assessment

The Cambridge Neuropsychological Test Automated Battery (CANTAB) was administered to all patients by someone well trained to administer this battery. This battery has been standardized on large populations, including patients with SZ, and can be used repeatedly with the same subject[43–46]. Because all tests in the battery are nonverbal, CANTAB evaluates cognitive performance independently of language and culture. The tasks used were: (1) Paired Associates Learning (PAL) for the assessment of long term memory (LTM); (2) Reaction Time (RTI) for processing speed; (3) Rapid Visual Processing (RVP) for sustained attention; (4) Stockings of Cambridge (SOC) for executive function; and (5) Spatial Working Memory (SWM) for working memory. Subjective complaints of cognitive deficit were evaluated using the SSTICS[47,48].

Nicotine questionnaire

The Fagerström questionnaire, a reliable questionnaire on tobacco smoking habits, was administered to each patient before and after 3 months of treatment with rivastigmine[49]. The maximum score on this questionnaire is 11 and the lowest score is 0; a score greater than 6 represents nicotine dependence.

Titration and administration of rivastigmine

Rivastigmine was administered as a function of patients' tolerance. Patients began rivastigmine treatment at a dose of 1.5 mg twice daily during the first month. This dose was raised to 3 mg twice daily during the second month and then to 4.5 mg twice daily during the third month. The dose was taken with a full meal in the morning and evening.

Tolerability

During rivastigmine treatment, patients were closely followed on a weekly basis by nurses. At each visit, parameters were checked including vital signs (weight and blood pressure). In addition, blood samples were taken before and after rivastigmine treatment (urea, creatine, total bilirubin, triglycerides, creatinine kinase [CK], aspartate aminotransferase [AST], alanine aminotransferase [ALT], phosphate alkaline and cholesterol levels).

Experimental design

This study was a randomized crossover trial. All patients were assessed at baseline (T1). Patients were randomly assigned to one of two groups for 3 months – rivastigmine plus antipsychotics (group 1) or antipsychotics alone (group 2). At the end of 3 months (T2), all patients were evaluated a second time with the same cognitive tests used at baseline. For the next 3 months, the patients in group 1 discontinued rivastigmine while the patients in group 2 received rivastigmine. At the end of this additional 3 months (T3), the cognitive performance of patients in both groups was evaluated for the third time (T3) (see Table 2).

Statistical analysis

Random assignment was used to avoid any confound between the two groups. Baseline differences in cognitive functioning (CANTAB) and clinical symptoms

(PANSS) were assessed using *t*-tests for independent groups. The statistical relationships between SSTICS, RBANS and PANSS were also conducted at baseline.

All CANTAB cognitive variables were assessed separately using a Latin square design. The same analyses were performed with the PANSS measures (negative, positive, general and total scale scores).

Results

Baseline

Despite the random assignment, we found significant age differences between the two groups of patients. The Student *t*-test revealed that patients in group 1 were significantly older than those in group 2 ($p = 0.05$). There was no other difference between the two groups in the duration of illness, CANTAB or PANSS measures at baseline. In addition, there was no significant difference between the two groups with regard to antipsychotic medication, chlorpromazine equivalent or nicotinic dependence. Duration of illness data was missing for two patients in group 2.

There was a significant positive correlation between the RVP (CANTAB) and the PANSS at baseline, suggesting that sustained attention is correlated with positive and general symptoms, and patients with more positive symptoms made more errors ($p = 0.03$). Also, patients who scored high on the Fagerström questionnaire (categorized as smokers) performed better on the total RBANS scale and had more negative symptoms ($p < 0.05$) than patients with lower scores. Seven patients showed nicotine dependence in scoring higher than 6 on the Fagerström questionnaire.

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Insert Table 2 about here

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Cognitive data

Statistical analyses performed with the Latin square design did not reveal any change after rivastigmine treatment on any of the CANTAB variables (all p-values > 0.05) Table 3 shows several variables of each task analyzed. Nor was there any change on the SSTICS after rivastigmine treatment ($p = 0.42$).

Clinical data

Clinical symptoms remained unchanged following rivastigmine treatment in patients, as assessed with PANSS (positive, negative, general and global symptoms) (see Table 3). Effectively, we have not observed any difference in cognitive enhancement outcomes between add-on rivastigmine treatment and placebo.

Tolerability

As mentioned above, two patients were removed from the study because of worsening SZ symptoms. The most frequent side effects reported by patients ($n = 5$) during the study were nausea and vomiting, which disappeared almost entirely after the instruction to take the medication with a meal was emphasized to patients. Follow up for compliance with medication and doses was performed once weekly by nurses.

One patient reported weight loss and three others mentioned more vivid dreams. Ninety-five percent of the patients were compliant with the medication protocol with an exception of one patient that had side effects with a dose of 3 mg BID.

Some slight anomalies were found in blood samples during rivastigmine treatment. Three patients showed transitional CK augmentation with normal troponins (one of these patients also had a familial history of cholecystitis). Two of these patients were on olanzapine and the other on clozapine. The patient with

familial history of cholecystitis was on clozapine. An increase in cholesterol and triglycerides was detected in two patients.

Insert Table 3 about here

Discussion

This randomized crossover study investigated the effect of rivastigmine, an AChE inhibitor, concomitant to antipsychotic medication on cognitive function in patients with SZ. The results did not reveal any effect of this medication on cognitive functioning as assessed with neurocognitive tasks (CANTAB) or on clinical symptoms. Our main concern was that the well-known relationship between rivastigmine and increased cholinergic activity might increase patients' positive symptoms. But our results did not show any worsening of either positive or negative symptoms.

In the study by Friedman *et al.*[30] there was no change in cognitive function after use of donepezil therapy as an adjunctive treatment to risperidone in SZ patients. The dose in two conditions was 5 mg and 10 mg per day for 12 weeks. The authors suggested that this was probably due to a selection confound, as their selected patients had a *z*-core of –3.5 on the California Verbal Learning Test (CVLT). Thus, the patients in their study had severe cognitive deficits, especially in memory. On the other hand, Lenzi *et al.*[35] observed cognitive improvement after only 1 month of treatment with rivastigmine (12 mg per day for 12 months) in patients with SZ. In that study, the patients presented mild cognitive impairment at baseline.

The effects of this type of inhibitor may be parallel to what is found in Alzheimer's disease, where the effect of AChE inhibitors may slow down cognitive deteriorations but will not improve any deficits that already exist[3]. In the present study, it is possible that the cognitive deficits exhibited by subjects were too severe

for any beneficial effect of rivastigmine to be observed. In summary, these data suggest that AChE inhibitors in SZ would serve more effectively as a preventive therapy than for the treatment of schizophrenia patients with severe cognitive deficits.

A meta-analysis investigating the effectiveness of AChE inhibitors in SZ in eight studies revealed a weak but significant improvement in short term memory and LTM[38]. One interesting factor to consider in future efforts is the effect of the different AChE inhibitors used. As in our study, Sharma *et al.*[50] did not find a beneficial cognitive effect with rivastigmine, but Schubert *et al.*[51] reported improvement in cognition (i.e. attention and memory) with galantamine treatment in schizophrenia patients. As proposed by MATRICS, the heterogeneity of the results may be partially explained by the problems concerning the tools and methodology used to investigate cognitive deficits. It is probable that certain tests to detect improvements in cognitive deficits in SZ are more sensitive than others.

It is possible that the lower dosage used in our study may have contributed to rivastigmine's lack of impact on cognitive function. Rivastigmine was administered at doses ranging from 1.5 mg to 4.5 mg twice daily (the last month of the trial 4.5 mg, BID). This was done to avoid nausea, the main side effect reported with this medication. In Alzheimer's disease, rivastigmine is usually administered at a higher dosage of 6 mg twice daily. It is also important to remember that 16 of the patients in this study were cigarette smokers, and this subgroup showed better performance on the RBANS initially. Cholinergic receptors in smokers are desensitized by nicotine and this may reduce the effect of AChE inhibitor treatment. Moreover, cognitive improvements associated with nicotine in smokers are probable and may mask the effect of rivastigmine in these patients. However, there is no drug interaction with rivastigmine, contrary to the possible drug interaction between tobacco products (such as nicotine) and donepezil or galantamine. In any case, the effects of these drugs on improving cognitive function and eventual social adaptation can be

questioned. If any effect is reported, it is of little magnitude, and some studies, including ours, have failed to find any change over time in both cognitive and clinical symptoms.

The main limitation in our trial is that the sample might be too small to detect a relatively little effect size. Moreover, the treatment duration (3 months) on rivastigmine may be too short and the doses may be too low, so that no significant effect could be obtained. This seems to be true even in studies conducted to detect an effect in elderly patients with dementia. Finally, our sample was heterogeneous regarding the basic antipsychotic medication. Chew *et al.*[52] reported that atypical antipsychotics clozapine, olanzapine and quetiapine have significant affinity for the muscarinic receptor and showed dose-dependant increases of anticholinergic activity. However, in our study, the patients were equivalent in the two groups for these three medications and dosage (see Table 1). Sixteen of the twenty-one patients were on these medications, and this could partially explain why no changes were observed after rivastigmine treatment. Also, one possible difficulty concerns the fact that patients were randomly assigned to groups. As a result, the patients in group 1 were significantly older than those in group 2.

A recent functional magnetic resonance imaging (fMRI) study revealed that rivastigmine treatment in SZ increased cerebellar activity and influenced attentional processes[53]. Recent psychopharmacological and fMRI studies tend to show that many neurotransmitters are involved in cognitive functions in SZ. Future research on cognitive enhancers in SZ is necessary, especially using physiological approaches such as fMRI and electrophysiology.

Conclusion

In conclusion, rivastigmine treatment did not appear effective in ameliorating cognitive deficits in SZ patients with important cognitive impairments. One must be careful in making any firm conclusions based on our current data, and our recommendation is that a larger sample should be treated with a cognitive enhancer over a longer time before any definitive conclusion can be drawn.

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Table 1. Characteristics of the two groups at baseline

	Group 1		Group 2	
N	9		11	
Age, years (SD)	32.67 (8.65)		25.73 (5.95)	
Sex, n				
Female	3		2	
Male	6		9	
Disease duration, years (SD)	8.77 (7.79)		4.25 (5.28)	
RBANS (SD)	71.11 (8.45)		67.64 (10.96)	
PANSS Total (SD)	74.00 (0.71)		75.00 (5.66)	
SSTICS (SD)	39.00 (23.79)		32.38 (12.35)	
Fagerström (SD)	3.77 (3.90)		4.78 (3.15)	
Smokers	5		9	
	n	Mean dose, mg	*n*	Mean dose, mg
Olanzapine	4	13.75	5	16.50
Risperidone	0	–	2	3.25
Quetiapine	2	450.00	1	600.00
Clozapine	2	600.00	2	400.00
Chlorpromazine	0	–	1	50.00
Zuclopenthixol	1	15.00	0	–
Chlorpromazine (equiv.)	9	490.00	11	402.30

*From the thioxanthene class, characterized with a high affinity for dopamine D_1, D_2, α_1-adrenergic and serotonin 5-HT_2 receptors and a low affinity for hispamine H_1, muscarinic, cholinergic and α_2-adrenergic receptors

PANSS=Positive and Negative Symptoms Scale; RBANS= Repeatable Battery for the Assessment of Neuropsychological Status; SSTICS= Subjective Scale to Investigate Cognition in Schizophrenia

Table 2. Experimental design

	Group 1			Group 2		
	T1 baseline	T2 3 months	T3 6 months	T1 baseline	T2 3 months	T3 6 months
Treatment						
Rivastigmine	X	X			X	X
Eligibility						
RBANS	X			X		
Experimental measures						
CANTAB	X	X	X	X	X	X
SSTICS	X	X	X	X	X	X
Nicotinic tolerance	X	X	X	X	X	X
Safety, tolerability						
PANSS	X	X	X	X	X	X
Blood sampling	X	X			X	X
Vital signs	X	X			X	X

CANTAB = Cambridge Neuropsychological Test Auto mated Battery; PANSS = Positive and Negative Symptoms Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SSTICS = Subjective Scale to Investigate Cognition in Schizophrenia

Table 3. Latin square analysis on cognitive variables (CANTAB) and clinical symptoms (PANSS) for rivastigmine effects.

	F	*p*-value
Reaction time		
Movement time	0.26	0.62
Reaction time	0.64	0.56
Paired associates learning		
Stage completed	0.06	0.79
Total trials	1.16	0.29
Total errors	0.56	0.53
Stockings of Cambridge		
Initial think time	0.002	0.92
Subsequent time	0.070	0.85
Rapid visual processing		
Total hits	3.17	0.08
Total misses	2.55	0.12
Spatial working memory		
Total errors	0.24	0.63
Strategy	0.78	0.61
PANSS		
Positive symptoms	0.17	0.69
Negative symptoms	0.80	0.62
General symptoms	0.26	0.62
Total score	0.76	0.78

PANSS = Positive and Negative Symptoms Scale

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CHAPITRE IV

TROISIÈME ARTICLE

ORAL CHOLINESTERASE INHIBITOR ADD-ON THERAPY FOR COGNITIVE ENHANCEMENT IN SCHIZOPHRENIA: A QUANTITATIVE SYSTEMATIC REVIEW, PART 1

Oral cholinesterase inhibitor add-on therapy for cognitive enhancement in schizophrenia: a quantitative systematic review, part 1

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Résumé de l'article

Les perturbations cognitives dans la schizophrénie sont associées aux problèmes de fonctionnement social et d'intégration vocationnelle. Dans un tel contexte, la recherche de traitement pharmacologique visant l'amélioration de la performance cognitive s'avère cruciale. Certaines études ont utilisé des inhibiteurs d'acétylcholinestérase dans le but d'améliorer les fonctions cognitives dans la schizophrénie. Cette médication, habituellement prescrite pour la maladie d'Alzheimer, permet une certaine amélioration au plan de la mémoire. L'objectif de la présente étude consiste à faire une revue quantitative systématique sur les effets des inhibiteurs d'acétylcholinestérase dans la schizophrénie sur plusieurs fonctions cognitives (i.e. attention, langage, fonctions motrices et fonctions exécutives). À partir de recherches électroniques exhaustives, de recherches manuelles, de la vérification des listes de références sur les études relevées et de contacts avec les chercheurs nous avons extrait toutes les données pertinentes disponibles. Les études qui ont été retenues pour les analyses méta-analytiques comparaient la performance cognitive de patients atteints de schizophrénie pré et post traitement avec des inhibiteurs d'AChE. Les études sélectionnées consistent en des essais cliniques randomisés et contrôlés à design croisé. Les résultats révèlent un léger effet significatif sur les variables d'attention après le traitement à partir d'inhibiteurs d'AChE. De plus, on note une tendance au plan des fonctions motrices. Toutefois, il n'y a pas de changement significatif après le traitement avec les inhibiteurs d'AChE sur les variables du langage et des fonctions exécutives. En conclusion, malgré des recherches exhaustives de la littérature, peu de données sont disponibles. Les résultats révèlent une légère amélioration au plan de l'attention et une tendance au niveau des habiletés motrices après la prise d'inhibiteurs d'AChE chez des patients atteints de schizophrénie. Nous ne pouvons nous prononcer clairement sur l'efficacité des inhibiteurs d'AChE pour le traitement des troubles cognitifs dans la schizophrénie en raison du nombre limité d'études disponibles à ce jour. Des études comportant des échantillons plus larges s'avèrent nécessaires.

Mots-clés : cognition ; schizophrénie ; inhibiteurs d'acétylcholinestérase ; rivastigmine ; galantamine ; donepezil ; méta-analyse

ABSTRACT

Rationale: Cognitive impairment in schizophrenia is associated with outcomes affecting social function and vocational performance. Cognitive enhancement is thus recognized as fundamental in the treatment of schizophrenia. Some clinical trials have used acetylcholinesterase inhibitors (AChEIs) add-on therapy to test the cognitive-enhancing effects of these kinds of medication, which is usually prescribed for indications other than schizophrenia. *Objective:* To perform a quantitative systematic review of the effects of AChEI on various cognitive domains (attention, language, and motor and executive functions) in schizophrenia. *Data Source:* Exhaustive electronic search engines, hand searches, cross-referencing of studies, and contacts with investigators were carried out. *Data Selection:* The studies included compared neurocognitive performance in patients with schizophrenia before and after AChEI treatment in randomized controlled trials and crossover and open trials of AChEI in people with schizophrenia. *Results:* Our findings reveal a small, but significant, homogeneous effect estimate of AChEI on attention before and after treatment. A small nonsignificant heterogeneous effect estimate was yielded for motor performance after AChEI treatment. However, no significant change appears in language performance or executive functions after AChEI treatment, independently of the type of AChEI. After AChEI treatment, when patients were compared with control groups, no difference appears in attention and executive functions. Nevertheless, the analysis reveals that the control groups performed better on language tasks than patients after AChEI treatment but worse on motor tasks. *Conclusions:* Despite an extensive investigation of the electronic and gray literature, few data appropriate for the meta-analysis were found. The results reveal a small improvement in attention and a trend on motor tasks after AChEI medication in schizophrenia. No clear conclusion can yet be reached concerning the cognitive-enhancing effects of AChEI considering the small number of studies available. This finding needs to be substantiated by larger trials. This systematic review

complements a meta-analysis focusing on memory, which showed a small improvement with a cocktail of antipsychotics and AChEIs.

Key Words: cognition, schizophrenia, acetylcholinesterase inhibitor, rivastigmine, galantamine, donepezil, meta-analysis.

Cognitive impairments in schizophrenia are common and remain difficult to treat.[1] However, some atypical neuroleptics generate cognitive benefits in schizophrenic patients.[2,3] A meta-analysis conducted by Woodward et al[4] showed that atypicals are superior to typicals in improving cognitive deficits in schizophrenia. However, some cognitive deficits remain with atypical neuroleptics; these deficits are important because they affect the social and vocational rehabilitation of patients with schizophrenia.[5,6]

In a recent article "On the Trail of a Cognitive Enhancer," we reviewed the potential operative mechanism and explored drugs that may be efficient in enhancing cognition.[7] This article pointed out that 1 current avenue of research in this domain is the role of cholinesterase inhibitors as potential cognitive enhancers in schizophrenia. This fact provided the rationale for verifying the efficiency of this medication in schizophrenia by a meta-analytic method. Some cognitive impairments in schizophrenia have been potentially associated with diminished cholinergic activity.[8,9]

The 3 cholinesterase inhibitors donepezil, rivastigmine, and galantamine are most widely recommended for clinical use in mild-to-moderate Alzheimer disease (AD),[10,11] although the average benefit seems slight.[12] The rationale for these recommendations is that evidence from randomized controlled trials has shown that all 3 drugs have some beneficial effects on cognitive and global outcome measures.[13] Nevertheless, the latest studies suggest that their effectiveness in AD is debatable.[14,15] In schizophrenia, there is no official recommendation, and some studies have been conducted to test the cognitive enhancing profile of these compounds.[16-18] Evidence-based medicine requires a significant data set in this domain, and there is a consensus that cognition in schizophrenia should be studied with a more rational approach (MATRICS).[6] The general uncertainty prompted us to review all available trials on cholinesterase inhibitors in schizophrenia.

In a more focused meta-analytic study, part 2, we performed a systematic quantitative review of acetylcholinesterase inhibitor (AChEI) effects specifically on memory in schizophrenia. The results of that meta-analysis demonstrate a significant small effect estimate for treatment between the start and end points of the trial on long-term memory (n = 8) and nonsignificant on short-term (n = 9). However, the results should be interpreted with care, given the small number of studies examined.

The objective of this complementary systematic review is to explore the clinical use of 3 types of AChEI (donepezil, rivastigmine, and galantamine) on attention, language, and motor and executive functions in schizophrenia. Specifically, we hypothesized that a quantitative review of the literature would reveal the following: (1) whether any improvement in neurocognitive performance in this population is clinically significant, (2) whether all neurocognitive domains are affected similarly by the treatment regimen, and (3) whether there is a difference between the various AChEIs' impacts on any of the cognitive functions in schizophrenia.

MATERIALS AND METHODS

Search Strategy for Identification of Studies

A structured search of the electronic literature was done via PubMed (all years), PsychINFO on the OVID platform (1967 to third week of February 2006), and EMBASE on the OVID platform (1980–2006, week 8). Conference proceedings abstracts (eg, International Congress on Schizophrenia Research and American Psychiatric Association) were screened via ISI Web of Science (1979–2006). In addition, an exhaustive search of the reference lists of all trials was performed; some authors were then contacted to obtain more information on possible unpublished data. There was no limitation on the language of studies.

The key words used were the following: ''schizophrenia'' and ''rivastigmine or tacrine or pyridostigmine or physostigmine or eserine or neostigmine or galantamine or edrophonium or echothiophate or donepezil or demecarium or ambenonium.''

Review Methodology

With a consensus, the authors (A.A.S., E.S., and S.C.) verified each of the publications that met the inclusion criteria and assessed them independently based on a predefined checklist of criteria for methodological quality. We included all articles that presented original data on randomized, double-blind, placebo-controlled, crossover, and open trials with donepezil, rivastigmine, or galantamine in patients with schizophrenia and excluded trials that did not examine clinical outcomes. The studies were cross-referenced by A.A.S.

Inclusion

Studies were included if they concerned schizophrenia-spectrum disorder (schizophrenia and schizoaffective disorder) patients taking any of the cholinesterase inhibitors (rivastigmine, tacrine, pyridostigmine, physostigmine, eserine, neostigmine, galantamine, edrophonium, echothiophate, donepezil, demecarium, or ambenonium) and being tested for cognitive function. Only validated rating scales were used for cognitive assessment because they tend to report true clinical values.[19] We included only studies assessing cognitive domains: attention, language, motor, or executive functions.

Exclusion

Studies of the following types were excluded: (1) case study/letter/correspondence/review, (2) animal study, (3) monotherapy, (4) molecular/genetic investigation, (5) conference review, or (6) head-to-head comparison of cholinesterase inhibitors. Studies of patients with schizophrenia and comorbid dementia were excluded.

Homogeneity of Effect Size Estimates

It is only reasonable to aggregate effect size (ES) estimates when ESs are homogeneous. Hence, Q statistics were calculated for the ES estimates. To reach homogeneity (nonsignificant distribution at $P < 0.1$), studies introducing variability were excluded. A random-effects model was used. Because of the small sample size, our concern with evaluating heterogeneity was minimal.

Statistical Analysis

The mean, SD, and sample size (N) for each study were used to calculate the effects. In the absence of these valuable first-ranked data, we referred to F values or ESs reported by the authors. Comprehensive Meta-Analysis[20] and D-Stat[21] were used along with Excel to calculate the ES estimates for continuous scale data. All ES estimates are calculated for 95% confidence intervals (CIs).

Data Extraction

Two reviewers (A.A.S. and S.C. or E.S.) independently extracted data; disagreements were resolved by consensus.

For the study by Malhotra et al,[22] the SDs were calculated from reported SE and all the mean changes transformed to standard means to carry out the meta-analysis.

For calculation of the overall mean and SD for the language assessment in Mendelsohn et al,[23] the available data were pooled using D-Stat. This procedure was replicated for the studies of Nahas et al[24] and Malhotra et al.[22]

In case of multiple case reports (eg, Bora et al[16]), an overall mean and SD were calculated for each cognitive measure before and after treatment with a total of 5 participating subjects.

Quality Assessment

To obtain reliable and valid results from clinical trials and thus validate our hypothesis, we had to use the quality check method for the studies.[25] In this vein, we used the Cochrane review checklist as our model for carrying out quality checks. The checklist items are the following: (1) allocation of concealment, (2) blinding of participant, (3) blinding of investigator, (4) blinding of outcome assessment, (5) intention to treat analysis, and (6) completeness of follow-up. We assigned 1 point for each criterion if the study reported it. Moreover, the quality assessment was done in case of a probable heterogeneity effect on the estimate. However, for each primary analysis, an analysis with quality-assessed studies would follow. At this point, a reference to the quality assessment of the studies would be made. This approach would divide the studies into 2 groups, with weaker and stronger designs, where a stronger design refers to a random double-blind study.

Analysis

The meta-analysis has 2 foci: primary and secondary analysis of the cognitive subdomains (eg, attention, language, and motor and executive functions). The primary analysis consists of 2 analyses: (1) ES estimates for the treatment effect in the treatment group before and after administration of the medication, and (2) ES estimates for the end-point trial of treatment (cholinesterase inhibitor) versus control (placebo) groups. The secondary analysis consists of clinical assessment to clean out any heterogeneity effects or masking effects.

RESULTS

Search Result Description

The search progression from PubMed, EMBASE, PsychINFO, and Web of Science led to a total of 366 possible studies. Data obtained from electronic searches, reference lists, gray literature, and communication with trialists were then evaluated

for meta-analytic evaluation (note: the cholinesterase inhibitors echothiophate and demecarium are not indexed in the PsychINFO database).

Studies Meeting Inclusion and Exclusion Criteria

In the first step, 26 studies met our inclusion criteria. We were able to exploit 12 of them for our meta-analytic evaluation. For 11 studies, although the authors were contacted, no further data were retrievable, and 1 study was rejected after contact with the author because it was no longer matches the inclusion criteria. The remaining 2 studies were rejected before the primary meta-analysis took place. The literature only mentions 3 types of cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) as having a direct clinical application for cognitive enhancement in schizophrenia.

Included Studies

Our meta-analysis covers 12 studies, including both posters and peer-reviewed articles (Table 1). The sample size in these studies ranged from 5 to 251, with a mean of 37.1. The add-on medication was donepezil in 6 studies, rivastigmine in 5, and galantamine in 1. The reported donepezil dosage ranged from 5 to 10 mg/d, whereas rivastigmine ranged from 3 to 12 mg/d (the study by Van de Graaff et al[52] and Sharma et al[45] reported a BID dosage), and galantamine from 8 to 16 mg/d. Overall, AChEIs were added to both typical and atypical antipsychotics. Of the 6 studies of donepezil, 5 were double-blind studies. The rivastigmine trials were 3 double- blind, random, placebo-controlled, 1 open-label, 1 crossover, and 1 open trial. The only galantamine study consisted of multiple case reports. The duration of the trials ranged from 6 to 12 weeks, with a mean of 9.8 and a mode of 12 weeks (Table 1).

Authors of the possible studies were contacted to obtain unreported data. Where applicable, such data were aggregated to the overall analysis, and further meta-analytic evaluations were subsequently performed. For studies with missing data, refer to Table 2.

Excluded Studies

The physostigmine study by Kirrane et al[33] involving patients with schizotypal personality disorder, although it met the inclusion and exclusion criteria, was considered as an outlier because of the method of drug administration (intravenous vs oral). The rivastigmine study by Ophir et al[42] was excluded given the concomitant add-on electroconvulsive therapy. The study by Arnold et al[45] matched our criteria but had missing data. The authors were contacted. They reported the incorporation of the poster data in a later study,[46,47] which no longer matched our criteria for inclusion (see Table 2). The study by Kumari et al[34] was excluded because they reported on memory assessment only, which was originally incorporated in our memory meta-analysis. The McEvoy et al[40] poster reported data only in the graph. Schubert et al[43] reported *t* test results with *P* values, comparing the mean change of the treatment arm (galantamine) with that of placebo. Authors were contacted to retrieve mean and SD for each arm of the study, no further data emerged. A very recent Letter to the Editors by Noren et al[41] has been omitted because of exclusion criteria and missing data. Seven additional studies corresponded to our inclusion criteria[37] but lacked extractable data for our meta-analysis. We contacted the authors, but no further data emerged (see Table 2).

Insert Table 1 about here

Composite Effect

Estimate—Description of Studies

Our meta-analysis pertains to specific cognitive domains: attention, language, and motor and executive functions. The authors reached a consensus on classifying the various neuropsychological tests under each cognitive domain (see Table 3). The classification was conducted based on neuropsychological assessment tools.[48,49] Tasks calling on the planning and organization, self-regulation, and initiation aspects of the executive function were pooled to form the composite executive effect estimate. The tests for attention subdomains (eg, sustained attention, etc) were similarly pooled. The scales for assessing language were also pooled to yield an effect estimate for this cognitive subcategory. Finally, the same process was used for pooling motor functions.

Outcome Measures

Our chief interest was in determining the clinical significance of treatment with add-on AChEIs for neurocognitive functions (attention, language, and motor and executive functions) in schizophrenia. Hence, our primary analysis was based on studies reporting cognitive performance before and after AChEI treatment in schizophrenia. Further analysis was based on the double-blind, placebo-controlled arm designs. Data from crossover designs were included when possible.

Insert Table 2 about here

Insert Table 3 about here

In our secondary analysis, schizophrenia patients were compared after treatment with a control group (placebo). Our outcome measures related to possible clinical and methodological masking effects (eg, trial duration and drug type).

Insert Table 4 about here

Moderating Factors

Trial Duration (Short-term Versus Long-term)

A trial of less than 12 weeks is considered to be short term according to the consensus reached by the authors. Furthermore, in the recent literature on AD, rivastigmine has proven to be efficacious in a long-term treatment plan when evaluated with the Mini-Mental State Examination.[50]

Single-action Versus Dual-action AChEI (Donepezil Versus Galantamine Versus Rivastigmine)

Donepezil and galantamine are selective AChEIs, unlike rivastigmine, which inhibits both AChE and butyrylcholinesterase.[51,52] In clinical trials for AD, Stahl[53] reported no improvement at all in any of the cognitive functions after 6 weeks or more of AChEI treatment. Their action tends to increase the AChE in the neocortex.

It is uncertain which of the available cholinesterase inhibitors should be prescribed as initial add-on therapy to augment cognitive performance. Acetylcholinesterase and butyrylcholinesterase have different reported impacts on neurological activity in cognitively associated brain regions (eg, thalamus and hypothalamus).[54] Thus, we further analyzed the effect obtained from single-action versus dual-action drugs.

Study Characteristics

In the secondary analysis, we used studies with double-blind, placebo-controlled designs because this is known to be a robust clinical design (high-quality studies).

Insert Table 5 about here

Antipsychotics (Atypical Versus Typical Versus Mixed)

Lieberman et al[55] report in the CATIE study that there is a difference in add-on treatment with atypical antipsychotics in contrast to typical neuroleptics. In this vein, we pursued our analysis, where applicable, looking into this difference in relation to add-on AChEI.

Results of the Meta-analysis

Attention

The comparison of treatment, from baseline to end of trial, with a random-effects model revealed a small, homogeneous, and significant effect estimate (Table 4). A later analysis was performed to see whether the drug type would alter the effect estimate. The effect estimate was significant for donepezil (n = 5) and nonsignificant for rivastigmine (n = 4), with a low effect estimate (where ES = 0.5 is considered to be medium) has yielded (donepezil, ES = 0.235; rivastigmine, ES = 0.314). Further analysis of single-action AChEIs combining donepezil and galantamine yielded a small, nonsignificant effect estimate (ES = 0.241; P = 0.026; CI, 0.029-0.452). A fixed-effects meta-regression analysis revealed that, overall, as the duration of the treatment increased, the effect estimate tended to increase (slope of the point estimate, –0.002; SEM, 0.026), yet it remained nonsignificant (P = 0.370). A run controlling for the type of antipsychotic yielded small effect estimates (typical, ES = 0.276 [P = 0.318, not significant]; atypical, ES = 0.259 [P = 0.01, significant]).

On a random-effects model, the effect estimate (weighted Hedges' g) obtained was homogeneous, very small (where ES = 0.2 is considered to be small), and nonsignificant for a comparison of patients who received add-on treatment with

cholinesterase inhibitors to patients enrolled in the control arm of the studies at the end of trials (doubleblind, placebo-controlled studies [n = 5]; Table 5).

Language

On language assessment, we had 6 studies (n = 166 at baseline, n = 149 at end point) with 9% attrition. Our data analysis consisted of mean and SD for 5 studies and 2 studies with ESs for aggregation. As we obtained a homogeneous effect estimate, we performed a meta-regression analysis (Table 4). The interpretation remains the same with time, although the effect estimate decreases, albeit nonsignificantly ($P = 0.45$). The classic fail-safe N suggested that the total number of studies needed to bring the P value to higher than $\alpha = 0.05$ is nil. The effect estimate differed for different drugs, with donepezil being used in most studies (3 studies; ES = 0.054; CI, –0.191 to 0.299; $P = 0.667$), followed by rivastigmine (2 studies; ES = 0.391; CI, –0.566 to 1.348; $P = 0.423$).

We performed an effect estimate analysis on 4 studies comparing the end-point data of the experimental and control groups. The effect estimate was significant, favoring the control group (ES = –0.393; CI, –0.644 to –0.141; $P = 0.002$). When we removed the study that was not in the original analysis[24] and used double-blind studies, the effect again favored the control group (ES = –0.420; CI, –0.679 to –0.169; $P = 0.002$). A classical fail-safe N with 2 tail and $\alpha = 0.05$ revealed that a total of 2 missing studies would bring P value to higher than α. The results should be interpreted with extreme caution because of the small sample size.

Motor Functions

On motor assessment, the effect estimate comparing results before and after treatment was border to homogeneous, where $P > 0.1$ is considered as homogeneous. Performing the classic fail-safe N, we obtained the number of studies (11 studies) that

would be needed to raise the *P* value to higher than $\alpha = 0.05$. A funnel plot was produced using SE by Hedges' *g* to detect the confounding study.

By eyeballing the AChEI used in the studies, we found that 1 (Mendelsohn et al[23]) of 5 studies was standing out and matched the confounding study found by the funnel plot.

After removing this rivastigmine study, our data were homogeneous on the randomeffects model in patients treated with add-on AChEI (ES= 0.239; CI, –0.014 to 0.465; $P = 0.038$). It is noteworthy that this evaluation had an overall 9% attrition rate, baseline (n = 171) to end point (n = 154). Meta-regression analysis based on the Hedges' *g* versus duration of treatment on 4 of 5 studies showed a linear decline. The duration of treatment increased when the effect estimate decreased (point estimate slope based on fixed-effects regression = 0.013; SEM, 0.028; intercept = 0.085), yet this effect was nonsignificant ($P = 0.643$). An analysis based on the type of antipsychotic was conducted for the 3 studies with donepezil. The effect estimate for the atypical antipsychotics (2 studies) was significant yet small (ES = 0.229; $P = 0.078$; CI, –0.026 to 0.484).

When controlling for the 3 studies [22,27,29] that made a comparison with a control group, the end-point data comparison showed the results of the random-effects model to be not significant (ES = 0.428; CI, –0.465 to 1.322, $P = 0.347$) and heterogeneous ($Q = 12.994$; $P = 0.002$; Table 5). An attempt at detecting a heterogeneity factor with a funnel plot failed because of the limited number of studies involved in this analysis. It is also noteworthy that the effect tends to favor the experimental group: schizophrenic patients taking AChEI in addition to antipsychotics performed slightly better than controls on the motor coordination tasks/manipulative dexterity tests such as the Grooved Pegboard (Table 5).

Executive Functions

An analysis of performance before and after treatment was performed using the random-effects estimate (n = 7). A very small, nonsignificant, negative, homogeneous effect estimate was yielded (Table 4). This result illustrates no significant change in performance on executive function tasks by schizophrenic patients who take added cholinesterase inhibitors. The result obtained was consistent with donepezil (4 studies) and rivastigmine (2 studies). The type of antipsychotic regimen, although nonsignificant, was seen as the prominent factor: atypical antipsychotics (ES = –0.076; $P = 0.493$; n = 5) versus typical antipsychotics (ES = 0.189; $P = 0.494$; n = 2). Overall, as the duration of treatment increased, the effect estimate decreased, as seen by the fixed-effects meta-regression (slope of the point estimate = –0.0181; SEM, 0.020), but the effect remained nonsignificant ($P = 0.381$).

Table 5 illustrates the results of the analysis comparing schizophrenic patients taking add-on cholinesterase with the control group. The Hedges' g effect estimate was homogeneous, very small, and nonsignificant based on best-quality studies (n = 4). A classic fail-safe N analysis revealed that no study would be required to raise the P value higher than $\alpha = 0.05$. Overall, the fixed-effects meta-regression showed that, as the duration of treatment increased, the effect estimates decreased (slope of the point estimate = –0.057; SEM, 0.033); this effect was close to significant ($P = 0.089$). The analysis was further extended to the type of antipsychotic used as the primary medication; the typical antipsychotic group with 2 studies outperformed the atypical, and this was shown to be an influential factor. Although the effect estimate remained small and nonsignificant, patients taking typical antipsychotics with add-on cholinesterase treatment performed better on tasks of executive function (ES = 0.281; $P = 0.485$).

Post Hoc Sensitivity Analysis

An analysis of the 4 cognitive domains was carried out after excluding the Malhotra et al[22] study because it represents more than 50% of our sample size. For attention, the effect estimate for before versus after AChEI treatment remained in the small range, and it was significant (P = 0.019). In the comparison between treated patients at the end of the trial and a control group, the effect changed from low small to high small (ES = 0.441), but it was significant (P = 0.038).

For motor functions, the effect estimate increased to medium range (ES = 0.597; P = 0.037), and it was significant; effect estimate for the executive function remained in the low range, and it was nonsignificant (ES = 0.036; P = 0.816) when comparing schizophrenia patients before treatment with after treatment. The effect estimate for executive dysfunction, comparing schizophrenia patients with a control group at the end of trials, remained in the small range (ES = –0.015; P = 0.968).

As for language, the effect estimate was small and nonsignificant (ES = –0.146; P = 0.604).

We could not have carried out further analyses with an end-point comparison of treated patients with control patients for language and motor because removing the Malhotra et al[22] study would have reduced the total number of studies to less than required to carry out a meta-analytic interpretation.

DISCUSSION

The overall results of this study reveal a heterogeneous effect estimate on certain variables (eg, motor functions). Consequently, an evidence-based medical approach to managing cognitive disabilities in patients with schizophrenia by taking into account the quality of clinical trials and other demographic factors (eg, age) is necessary to better plan further studies. A limitation concerning our meta-analysis is the paucity of data available to date, especially from well-designed studies involving

random double-blind, placebo-controlled trials of AChEIs added onto antipsychotics for cognitive enhancement in schizophrenia. Many studies on the topics could not be included in our meta-analysis because of unreported data; although the authors were contacted, no further data emerged. Furthermore, our analysis consisted of first within-group comparison so as to evaluate AChEI treatment effect, which suggests a possible treatment effect because any apparent cognitive-enhancing effect is potentially confounded with novelty and practice effects. However, discussion of any significant within-group comparison as evidence for a therapeutic effect if it is not confirmed by the between-group analysis must be done with caution. Thus, in light of significant statistical power, a negative within-group result would suggest a partial or lesser benefit for the particular cognitive domain. Thus, our results must be interpreted carefully at this point.

There is a significant improvement in neurocognitive functions, especially attention. As Rosenthal[56] mentions, in this case, because the total number of subjects involved in these studies is small, we fail to detect the true effect; however, if the true effect is quite small, the costs of this error may not be too great. It is speculated that the attrition rate observed in studies is caused in part by the long duration of trials because patients with schizophrenia find it difficult to comply with the conditions of clinical trials. Moreover, this attrition might also be explained by possible side effects associated with AChEI (eg, nausea, diarrhea, dizziness, and depression). It is important to note that some studies add anticholinergic medication to the antipsychotic medication and cholinesterase inhibitor; because of the limited number of studies,[23] we have not done further meta-analytic evaluation of this confounding variable.

Another possible limitation is that non-specific stimulation of a variety of muscarinic and nicotinic acetylcholine receptors may result in masking or dampening of possible beneficial effects associated with stimulation of selective receptors, such

as the M_1 or M_4 muscarinic receptors or α7 nicotinic receptor. However, our data may not promote the nonselective approaches to the enhancement of cholinergic neurotransmission in schizophrenia.

From a neuropharmaceutical perspective, 1 limitation on the current study is the concomitant treatment with drugs other than antipsychotics, for instance, anticholinergic medications, as their interactions with rivastigmine are problematic. This is the price we pay every time we try to stay close from the real life of clinical practice with patients seen in clinical settings. Many of this subtype of patients (cognitively impaired) receive other concomitant medication.

Moreover, in the context of neurocognitive testing, it remains debatable whether a given test belongs to a specific cognitive domain. In this vein, with minimal available data, our analysis only concerns overall cognitive domains (eg, attention or motor functions), and not subdomains (eg, selective attention under attention or learning strategy under executive functions).

The relatively higher effect estimate for the rivastigmine studies can be explained because they are frequently crossover studies with very small sample sizes. Further studies on add-on galantamine treatment are warranted because of its properties as a tertiary amine, cholinomimetic enhancer, and nicotinic agonist.

A limitation on meta-analysis is that large studies with significant results are more likely to be published than small studies with nonsignificant results;[57,58] however, we brought together a greater number of small studies with nonsignificant results. The small number of studies required to change the *P* value to a higher α than 0.05 for the language domain suggests that further double-blind, placebo-controlled, random-arm design studies are warranted. The greater language deficit or lack of improvement over time observed with an add-on cholinesterase inhibitor may be caused by a major confounding factor in part from the pragmatic memory (long-term

and short-term memory) deficit in this population. Conversely, the small deficiency in the attention effect estimate is probably linked to the memory deficits reported elsewhere.

In conclusion, based on the preliminary data available, a combination of AChEIs with antipsychotics for cognitive enhancement in schizophrenia seems to have some beneficial effects in 2 cognitive domains: attention and memory.

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TABLE 1. Demographic Representation of the Studies Included in the Cholinesterase Inhibitor Quantitative Review (N = 12)

Studies	N	AChEI	Dosage mg/d	Antipsychotic	Design	Duration wk
Aasen et al [26]	20	Rivastigmine	3–12	Atypical	DB-PC-RND	12
Bora et al [16]	5	Galantamine	8–16	Clozapine	CR	8
Buchanan et al [17]	15	Donepezil	5–10	Olanzapine	PS-OL	6
Freudenreich et al [27]	36	Donepezil	up to 10	Typical	DB-PC	8
Friedman et al [28]	36	Donepezil	5–10	Risperidone	DB-PC-RND	12
Mendelsohn et al [23]	13	Rivastigmine	9	Atypical	OL	12
Nahas et al [24]	6	Donepezil	5–10	Olanzapine Risperidone	DB-PC-CO-PS-RND	12
Sharma et al [29]	21	Rivastigmine	3-12	Risperidone Olanzapine Quetiapine	DB-PC-RND	24

Tugal et al [30]	12	Donepezil	5	Fluphenazine Pimozide	DB-PC-CO-RND	6
Van de Graaff et al [31]	8	Rivastigmine	6–12	Clozapine Risperidone Zuclopenthixol	OT-PS	6
Chouinard, et al [32*]	22	Rivastigmine	3–9	Atypical	CO-RND	12
Malhotra et al [22*]	251	Donepezil	5–10	Risperidone Olanzapine Quetiapine Ziprasidone Aripiprazol	DB-PC-RND	12

*Poster

CO indicates crossover; Cr, case report; DB, double-blind; OL, open-label; OT, open-trial; PC, placebo-controlled; PS, pilot study; RND, random.

TABLE 2. Demographic Representation of the Studies With Missing Data.

Studies	N	AChEI	Design	Duration, wk	NP	Result	Reason for exclusion
Erickson et al [18]	15	Donepezil	DB-RND-CO	18	RVLT, Trail A and B	SI	NFD
Kirrane et al [33]	10	Physostigmine	DB-PC	NR	Dot test Serial learning task	NR	Method of administration (intravenous)
Kumari et al [34]	36	Rivastigmine	DB-PC-RND	12	n-back task	NR	Visuospatial memory task
Lenzi et al [35]	16	Rivastigmine	OL	54	CPT, WMS	I	NFD
Tuma et al [36]	30	Donepezil	DB-PC	16	Attention Learning executive function	NS	NFD
Kim et al [37*]	24	Donepezil	DB-PC-RND	12	Digit span-backward executive function	SI	NFD

Lenzi et al [38*]	21	Donepezil	PS	54	Executive function	SI	NFD
Mazeh et al [39]*	20	Donepezil	DB-CO-PC	12	ADAS-COG	NS	NFD
McEvoy et al [40]	24	Galantamine	2 x 3 Factorial	4	CPT, Stemberg memory test, simple reaction time, digit sequence token motor, fluency, symbol coding, Tower of London	I	NFD
Noren et al[41]	12	Galantamine	OL	12	Cognitive performance indicator	I	Letter, missing data
Ophir et al [42*]	30	Rivastigmine	DB-PC-RND	4	ADAS-COG	I	Concurrent ECT Administration

Schubert et al [43]	16	Galantamine	DB-PC-RND	8	RBANS: attention, language, Verbal comprehension, CPT COM	ISAC	NFD
Stryjer et al [44*]	6	Donepezil	SB	4	ADAS-COG	I	Only global cognition reported

*Poster.

ADAS-COG indicates Alzheimer's Disease Assessment Scale Cognitive Subscale; CPT, continuous performance test; CPT COM, Continues Performance Task, error of Commission; DB, double-blind; I, improvement; ISAC, Improved Selected Aspects of Cognition; NFD, no further data; NP, neuropsychological tests; NR, not reported; NS, no significant change; OL, open-label; PC, placebo-controlled; PS, pivotal study; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RND, random; RVLT, Rey Auditory Verbal Learning Test; SI, slight improvement; WMS, Wechsler Memory Scale.

TABLE 3. Neuropsychological Scales Used in Each Study

Studies	Executive Function	Motor	Language	Attention
Aasen et al [26]	—	—	—	Sustained attention test for fMRI: non-zero number and specific number
Bora et al [16]	Trail making B Stroop interference	—	Animal naming	Trail making A, animal naming CPT omission % CPT commission %
Buchanan et al [17]	—	Grooved pegboard	—	GDS-CPT hits/false alarms
Freudenreich et al [27]	Trail making B	Grooved pegboard	—	Digit span forward, Trail making A
Friedman et al [28]	Trail making B WCST (total category)	—	Verbal fluency	CPT d-prime, Trail making A, digit span distraction (nondistraction), digit span distraction (distraction)

Mendelsohn et al [23]	—	ADAS-item 3	ADAS-item 2, ADAS-item 8, ADAS-item 11	—
Nahas et al [24]	—	—	COWAT performance, verbal fluency	—
Sharma et al [29]	Trail making B, WCST-category completed	Finger Tapping	Verbal fluency-categorical verbal fluency-phonological	Trail making A, CPT d'
Tugal et al [30]	WCST-category completed, WCST-perseverative errors, Trail making B	—	Verbal fluency	Trail making A, digit span forward
Van de Graaff et al [31]	—	—	—	CPT-hit rate, CPT-false alarm
Chouinard et al [32]	CANTAB-SOC	—	—	CANTAB-RVP

Malhotra et al [22]	WISC-III-labyrinth, WCST-computerized	Grooved pegboard	Controlled oral word association test, category instances	WAIS-R-digit symbol CPT

ADAG indicates Alzheimer's Disease Assessment Scale; CPT, continuous performance test; COWAT, Controlled Oral Word Association Test; fMRI, functional magnetic resonance imaging; WCST, Wisconsin Card Sorting Test; WISC, Wechsler Intelligence Scale for Children; CANTAB-SOC, Cambridge Neuropsychological Test Automated Battery-Stocking of Cambridge; CANTAB-RVP, Cambridge Neuropsychological Test Automated Battery-Rapid Visual Information Processing.

TABLE 4. Random-Effects Model: Effect Estimate Per cognitive Domain Comparing Before With After Add-on AChEI Treatment

Cognitive domain	No. Studies	Effects (Hedges' *g*)	*P*	CI (Lower/Higher)	*Q*	*P*
Attention	10	0.261	0.006*	0.074-0.448	4.024	0.910
Executive function	7	–0.039	0.704	–0.241 to 0.163	2.202	0.900
Language	6	0.247	0.148	–0.088 to 0.583	7.346	0.196
Motor	5	0.459	0.026	–0.054 to 0.865	8.658	0.034†

*Significant
†Heterogeneous

TABLE 5. Effect Estimate Per Cognitive Domain Comparing Control With Experimental Groups at the End Point (Random Effect)

Cognitive domain	No. Studies	Effects (Hedges' *g*)	*P*	CI (Lower/Higher)	*Q*	*P*
Attention	5	0.175	0.253	–0.125 to 0.475	4.813	0.307
Motor	3	0.428	0.347	–0.465 to 1.322	12.994	0.002†
Executive function	4	0.073	0.737	–0.500 to 0.354	5.275	0.153
Language	4	–0.393	0.002*	–0.644 to –0.141	1.158	0.763

*Significant
†Heterogeneous

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CHAPITRE V

QUATRIÈME ARTICLE

ADD-ON THERAPY WITH ACETYLCHOLINESTERASE INHIBITORS FOR MEMORY DYSFUNCTION IN SCHIZOPHRENIA: A SYSTEMATIC QUANTITATIVE REVIEW, PART 2

Add-on therapy with acetylcholinesterase inhibitors for memory dysfunction in schizophrenia: a systematic quantitative review, part 2

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Running head : AChEI and memory dysfunction in schizophrenia

Résumé de l'article

Les déficits mnésiques font partie intégrante du tableau clinique dans la schizophrénie et ils demeurent difficiles à traiter. Il est montré qu'une amélioration au plan de la mémoire est associée à un meilleur fonctionnement des patients. Certaines études ont voulu vérifier l'efficacité des inhibiteurs d'acétylcholinestérase (AChE) comme traitement pour les troubles cognitifs dans la schizophrénie. Cette médication prescrite habituellement pour la maladie d'Alzheimer s'avère efficace pour stabiliser temporairement les déficits cognitifs dans cette pathologie. L'objectif de la présente étude consiste à faire une revue systématique à partir de la méthode méta-analytique sur les effets des inhibiteurs d'AChE sur la mémoire dans la schizophrénie. La sélection des études pertinentes s'est effectuée à partir de recherches informatiques et manuelles et la revue des listes de références, ainsi que certaines communications avec les auteurs. Les études éligibles devaient comparer la performance cognitive de patients atteints de schizophrénie pré et post traitement avec des inhibiteurs d'AChE. Les études incluses devaient avoir utilisé un design croisé et être des essais cliniques randomisés et contrôlés. Les résultats révèlent une amélioration aux niveaux de la mémoire à court terme (MCT) et de la mémoire à long terme (MLT) de faible à modérée après le traitement avec les inhibiteurs d'AChE. Toutefois, lorsque comparé au groupe contrôle (i.e. placebo), les patients sont moins performants sur les variables de MCT et MLT, sans toutefois être significatif. On note donc un effet du traitement sur la MLT avec les inhibiteurs d'AChE, selon les résultats de huit études (n=209). L'effet estimé s'avère significatif et presque hétérogène. Cet effet augmente légèrement en fonction de la durée du traitement. Des analyses de variables modératrices sur le type d'inhibiteurs d'AChE utilisé (cinq avec donepezil, deux avec rivastigmine et une avec galantamine) et d'antipsychotiques (six avec neuroleptiques atypiques et deux avec neuroleptiques classiques), n'ont révélé aucune particularité. En conclusion, malgré des recherches approfondies, le nombre d'études incluses dans cette méta-analyse s'avère limité (n=10). Cette revue quantitative systématique ne procure pas d'évidence claire à savoir si les inhibiteurs d'AChE devraient être prescrits pour les troubles mnésiques dans la schizophrénie.

Mots-clés : mémoire, schizophrénie ; inhibiteur d'acétylcholinestérase ; rivastigmine ; donepezil ; méta-analyse ; cognition.

ABSTRACT

Rationale: Memory impairment is frequent in schizophrenia and remains difficult to treat. Improved memory function is associated with a better functional outcome. Some clinical trials have used add-on therapy with acetylcholinesterase inhibitors (AChEIs) to test the cognitive enhancement effect of this kind of medication, which is usually prescribed for other indications than schizophrenia. *Objective:* To perform a systematic review with meta-analysis. *Methods:* Studies were identified using electronic search engines, hand searches, cross-referencing of studies, and contacts with investigators. Eligible studies were those comparing cognitive performance in patients with schizophrenia before and after AChEI treatment, randomized controlled trials, and crossover and open trials of AChEI in people with schizophrenia, with trial duration of more than 2 weeks. Validated neurocognitive measures and computerized batteries were used to corroborate the effect. *Results:* Our findings reveal a small to medium improvement in short-term memory and long-term memory (LTM) performance when patients are compared with the baseline performance, but when compared with controls (placebo treatment) at the end of the trial, they performed worse on both short-term memory and on LTM. However, the effects were nonsignificant. The LTM magnitude estimate demonstrating a treatment effect between the start and end points of the trial consisted of 8 studies (before treatment, n = 209; overall attrition rate, 8%). The effect estimate was significant and close to heterogeneous. Duration of trial increases the effect estimate slightly. The analysis was broken down by AChEI: 5 studies of donepezil (effect size [ES], —0.352), 2 studies of rivastigmine (ES, 0.383), and 1 study of galantamine. There were 6 studies of AChEI added to second-generation antipsychotics (ES, 0.424) and 2 studies of first generation antipsychotics (ES, 0.207). *Conclusions:* Notwithstanding an extensive investigation, eligible data for the meta-analysis were nominal. To date, and overall, our quantitative systematic review provides no clear evidence on whether AChEIs should be prescribed for memory enhancement in patients with schizophrenia.

Key Words: memory, schizophrenia, acetylcholinesterase inhibitor, rivastigmine, galantamine, donepezil, meta-analysis, cognition.

Memory deficiencies in schizophrenia are common and remain difficult to treat.[1] In our recent article, ''On the Trail of a Cognitive Enhancer,'' we reviewed the potential mechanisms and drugs that might enhance cognition.[2] Cognitive impairment— primarily memory deficits — in schizophrenia has been potentially associated with low functioning of the cholinergic system.[2-4] Currently, the 3 acetylcholinesterase inhibitors (AChEIs) donepezil, rivastigmine, and galantamine are widely recommended for clinical use in Alzheimer disease (AD). For instance, the American Academy of Neurology recommends AChEIs for AD (and other dementias), although the average benefit seems to be small.[5] The rationale for these recommendations is that evidence from randomized controlled trials has shown that all 3 drugs have beneficial effects on cognitive and global outcome measures. Nevertheless, the latest studies suggest their effectiveness is debatable,[6] and their clinical meaningfulness is still disputed.[7,8] There is no official guideline on using these compounds for schizophrenia, and studies have been conducted to test their cognitive-enhancing profile. Evidence-based medicine requires a significant data set in this domain, and there is a consensus that cognition in schizophrenia should be studied with a more rational approach (Measurement and Treatment Research to Improve Cognition in Schizophrenia).[9] A recent review by Ferreri et al[10] summarized the clinical trials that investigated the cognitive enhancing potential of add-on AChE treatment in schizophrenia, raising several questions. These various questions prompted us to review all the available trials on AChEIs in schizophrenia. The objective of this quantitative review is to explore the scientific evidence for the clinical use of donepezil, rivastigmine, and galantamine to improve memory performance in schizophrenia using meta-analytic techniques.

METHOD

Search Strategy for Identification of Studies

A structured search of the electronic literature was done via PubMed (all years), PsychINFO (1967 to third week of April 2005) and EMBASE (1980 to 2005, week 31), and conference proceeding abstracts (eg, International Congress on Schizophrenia Research and American Psychiatric Association) were screened via ISI Web of Science (1979–2005). In addition, an exhaustive search of the reference lists of all trials was performed; researchers were then contacted to obtain more information on possible unpublished data. There was no limitation on the language used in the publication of the studies. The key words used were the following: ''schizophrenia'' and ''rivastigmine or tacrine or pyridostigmine or physostigmine or eserine or neostigmine or galantamine or edrophonium or echothiophate or donepezil or demecarium or ambenonium.'' An updated search on ''yet to be published'' or ''in-press'' studies at the time of first search was performed on PubMed till the date of submission of this manuscript.

Review Method

Upon consensus, 2 of the authors (A.A.S. and E.S. or S.C.) studied each of the publications that met the inclusion criteria and assessed them independently, following a predefined checklist of criteria for methodological quality. We included all papers that presented original data on randomized, double-blind, placebo-controlled, crossover, and open trials with donepezil, rivastigmine, or galantamine in patients with schizophrenia and excluded trials that did not adequately examine clinical outcomes. The studies were cross-referenced by AAS.

Inclusion

Our criteria included studies of schizophrenia-spectrum disorder patients who were taking any of the AChEIs (rivastigmine or tacrine or pyridostigmine or physostigmine or eserine or neostigmine or galantamine or edrophonium or echothiophate or donepezil or demecarium or ambenonium) and being tested for cognitive function. Only validated published rating scales for schizophrenia were used for cognitive assessment.[11] In this article, only studies reporting memory performances were included in the aggregation of effect estimate.

Exclusion

Studies were excluded if they involved (1) a case study/letter/correspondence review, (2) an animal study, (3) monotherapy, (4) patients who have psychotic disorders other than schizophrenia, (5) a post-mortem study, (6) molecular/genetic investigation, or (7) a conference review.

Homogeneity of Effect Size Estimates

It is only reasonable to aggregate effect size estimates when the effect sizes are homogeneous. Hence, Q-statistics were calculated for the effect size estimates. To achieve homogeneity (nonsignificant distribution at $P < 0.1$), studies introducing variability were excluded. A random-effects model was used. Because of the small sample size, our concern with evaluating heterogeneity was minimal.

Statistical Analysis

When available, means, standard deviations (SDs), and sample sizes (n) for each study were used to calculate the effects. In the absence of this valuable first-ranked data, we referred to F values or effect size as reported by the author. Comprehensive meta-analysis[12] and D-STAT[13] were used along with Excel to calculate the effect size estimates for the continuous scale data. All effect size estimates were calculated for 95% confidence intervals (CIs).

Composite Effect Estimate: Description of Studies

Our meta-analysis pertains to 2 memory domains: (1) long-term memory (LTM) and (2) short-term memory (STM).[1,14,15] Moreover, the memory functions—primary (immediate), secondary (delayed), explicit, implicit, episodic, semantic, priming, and procedural were classified based on the notes by Schacter et al.[16] Explicit and implicit memory tasks were pooled to derive the LTM effect. Tasks relating to visuospatial, auditory input, phonological loop, and central executive of working memory components were pooled to form the STM effect.

Data Extraction

Two reviewers (A.A.S. and S.C. or E.S.) independently extracted data; disagreements were resolved by discussion until consensus was reached. For the study by Malhotra et al,[17] all the reported standard errors (SEs) were translated into SDs, and all the mean changes transformed to standard means then imported into the Excel software for further meta-analytic evaluation. Moreover, for the overall STM measures in means and SDs, the reported means and SDs for the letter-number test of auditory working memory and the computerized test of visuospatial memory were pooled. In multiple case reports,[18] overall mean and SD were calculated for each memory measure with 5 research participants. For the overall measure of STM in this study, means and SDs of the reported scales were pooled using D-STAT. The data were then aggregated with the remaining studies for meta-analytic evaluation. In the study by Friedman et al,[19] the average reported effect sizes for the 5- and 10-mg doses of donepezil were calculated and then used in the meta-analysis. An effect size (Cohen *d*) was calculated from the *F* value for the 2-back part of the n-back task of working memory reported by Kumari et al.[20] The raw *d* was then incorporated into comprehensive meta-analysis for overall STM analysis. For the study by Sharma et al,[21] the California Verbal Learning Test was only used at screening; hence, only 2 reported measures of short-term verbal memory (Digit symbol) and spatial memory (Dot test) that were used during the trial with *F* values were used.

Quality Assessment

To have reliable and valid results from clinical trials and, thus, support our hypothesis, we had to use the quality check method for the studies.[22] In this vein, we used the Cochrane review checklist as our model for carrying out quality checks. The checklist consists of (1) allocation of concealment, (2) blinding of participant, (3) blinding of investigator, (4) blinding of outcome assessment, (5) intention to treat analysis, and (6) completeness of follow-up. Thus, we assigned 1 point to each criterion if the study reported it. Moreover, the quality assessment was done in case of a probable heterogeneity effect on the estimate.

RESULTS

The primary result consisted of 2 analyses: (1) effect size estimates for treatment effects in the treatment group before and after the administration of medication and (2) effect size estimates for end-point treatment trials (AChEI) vs controls. The secondary analysis consisted of clinical assessment to clean up heterogeneity effects and was further explored for masking effects.

Search Result Description

The search progression from PubMed, EMBASE, PsychINFO, and Web of Science led to 366 possible studies. Data were obtained from the electronic search, reference list search, gray literature, and communications with authors.

Studies Meeting the Inclusion and Exclusion Criteria

There were 25 studies that met our inclusion and exclusion criteria, 13 of which were useable for our meta-analytic evaluation. For the remaining 12 studies, although the authors were contacted, we failed to gather the necessary data (Table 1).

Authors of the studies that potentially met the criteria were contacted to acquire the unreported data. When applicable, data were then aggregated into the overall analysis, and further meta-analytic evaluations were performed. The 10 studies included with memory measures (LTM and STM) fell into 2 categories: articles and posters from conference proceedings. The number of subjects enrolled in these studies ranged from 5 to 251. Five of the studies were clinical trials of donepezil (5–10 mg/d), 3 were on rivastigmine (3–12 mg/d), and 1 was a case report on galantamine (8–16 mg/d) as add-on therapy to common typical or atypical antipsychotics. All the rivastigmine studies concerned add-ons to atypical neuroleptics. Four of the donepezil trials were double-blind (investigator and patient) and placebo-controlled, and 3 were random. The rivastigmine studies included 1 open-label, 1 crossover, and 2 random, double-blind, placebo-controlled designs. The duration of the studies ranged from 6 to 24 weeks (both mode and median were at 12 weeks, which demonstrated statistically that we have a normal distribution). Seven studies reported on both LTM and STM, whereas the remaining reported on either LTM or STM (for a total studies in each memory subfunction) (refer to Table 2).

Insert Table 1 about here

The studies that were excluded from the memory meta-analysis were those by Kirrane et al,[28] Ophir et al,[29] Erickson et al,[30] Lenzi et al,[31] McEvoy et al,[32] Stryjer et al,[33] Arnold et al,[34] Schubert et al,[35] and Noren et al.[36]

Insert Table 2 about here

The study of physostigmine by Kirrane et al[28] was considered as an outlier due to the method of drug administration (ie, intravenous vs oral). The rivastigmine study by Ophir et al[29] was ruled out of the meta-analysis because it involved concomitant add-on electroconvulsive therapy. The donepezil trial by Erickson et al[30] matched the

inclusion and exclusion criteria, but was excluded because it did not report the SDs for the RAVLT, a test of LTM. The study by Lenzi et al[31] was also excluded from the meta-analytic evaluation due to lack of data at the end point. The McEvoy et al[32] poster reported data in the graph. The article of Stryjer et al[33] met our criteria, but it reported the overall cognitive change tested with the Alzheimer Disease Assessment Scale-Cognitive Subscale and failed to report results by cognitive function, so it was not included. The poster by Arnold et al[34] matched our criteria but had missing data. The authors were contacted, and it turned out that the subjects from the poster study were incorporated into later studies [37,38] that no longer met our inclusion criteria; thus, the earlier study was excluded from the meta-analysis. The study by Schubert et al[35,39] reported a mean change at the end of the trial for the Repeatable Battery for the Assessment of Neuropsychological Status subscales (immediate and delayed memory). A letter to the editor by Noren et al[36] reported administration of both verbal and learning memory and working memory scales; however, no data were provided. As this study matched 1 of our exclusion criteria (letter), no attempt has been done to collect these data. All other authors of the excluded studies were contacted, but no further data emerged overall.

Outcome Measures

Our primary interest was in determining the clinical significance of treatment with add-on AChEIs for memory function (LTM and STM) in schizophrenia. Along these lines, an end-point comparison with the control group was calculated. Our secondary outcome measures consisted of possible clinical and methodological masking effects (eg, trial duration, drug type, etc). Our primary analysis was based on all studies reporting preclinical and postclinical (end-point) trial data. The secondary analysis was based on double-blind, placebo-controlled, two-arm designs. Data from crossover designs were included where possible.

Moderating Factors

Trial Duration (Short Term vs Long Term)

According to Measurement and Treatment Research to Improve Cognition in Schizophrenia,[40] the trials need to be of adequate duration to show an enduring effect on cognition (ie, minimum of 6 months). Moreover, Stahl[41] notes that small memory improvements can be observed after 6 weeks. In addition, Harvey and Keefe[42] report on cognitive-enhancing studies ranging between 6 and 12 weeks in length on average. In this vein, we considered trials lasting less than 12 weeks to be short term. Furthermore, in the recent literature on AD, rivastigmine has proven to be efficacious in a long-term treatment plan when evaluated with the Mini-Mental State Examination.[43]

Single-action vs Dual-Action AChEI (Donepezil vs Galantamine vs Rivastigmine)

As it is not certain which of the available AChEIs should be prescribed as initial add-on therapy by virtue of augmenting cognitive performance, and as there is a reported difference between butyrylcholinesterase and acetylcholinesterase of neurological activity in brain regions associated with memory (eg, thalamus and hypothalamus),[44] in our study, we did further analyses to compare the effect obtained from drugs with dual- vs single-action properties.

Study Characteristics (Double-Blind vs Non–Double-Blind)

In our secondary analysis, we used studies with double-blind placebo-controlled designs because this clinical design is known to be robust.

Before- and After-Treatment Comparison (Experimental Group)

At the beginning of our meta-analysis, we first verified whether there is any difference from the baseline for subjects receiving add-on treatment with AChEIs. We then compared these subjects to the control groups at the end of the studies.

Insert Table 3 about here

Results of the Meta-Analytic Procedures

For the STM assessment, we had 9 studies (n = 208 at baseline and 191 at end point) with an approximately 9% attrition rate. Our data analysis pertained to reported means and SDs and effect sizes for 2 studies (Friedman et al[19] and Kumari et al[20]) and reported *F* values for 1 study.[21] The effect estimate (Hedge *g*) obtained ranged from small to medium; it was homogeneous and nonsignificant (refer to Table 3). There was a difference between effect estimates in random and fixed-effects models. At this point, a metaregression analysis of the duration of treatment vs Hedge *g* was done (fixed-effects regression and point estimate slope, –0.031; SEM, 0.011), which revealed a decrease in effect estimates when the duration of the trial increases. Further analysis was performed to differentiate between AChEIs. There was a difference in effect between AChEIs: 4 studies with donepezil (ES = 0.246; *P* value = 0.034; CI = 0.019–0.473), 4 studies with rivastigmine (ES, 0.299; *P* value = 0.223, NS; CI = –0.182 to 0.780), and 1 study with galantamine. Because of the limited number of studies, the effect of galantamine could not be accurately determined. More differences were observed when we divided the studies by type of antipsychotic: 7 studies of atypical (ES = 0.279; *P* value = 0.048; CI = 0.002–0.555) and 2 studies of typical antipsychotics (ES = 0.055; *P* value = 0.841; CI = –0.485 to 0.596).

Although Hedge *g* takes sample size into consideration, and we had a homogeneous effect estimate for the overall STM assessment on a random-effects model, we performed an analysis removing the largest study, which contributed for more than 50% of the sample size in our overall analysis. The analysis yielded a nonsignificant homogeneous effect estimate (ES = 0.241; CI = –0.046 to 0.528).

After considering studies with an end-point control comparison, a nonsignificant nonheterogeneous small-effect estimate based on a random-effects model yielded results for 4 double-blind studies (ES = –0.236; n experimental subjects, 134; n for the control, 129). Three with donepezil (n for the experimental subjects, 123; n for the controls, 119) (ES = 0.293; CI = 0.041–0.546; *P* value = 0.023; *Q* value = 1.832; *P* value = 0.400) (refer to Table 4). The above ES reveals that the chance that the experimental group will perform better than the control group is close to 42%. These findings demonstrate that there is a small to medium improvement in STM performance when patients are compared with the baseline and to the controls at the end of the trial with donepezil. However, the overall negative-effect estimate obtained is due to the significant improvement of patients on Dot test from the study of Sharma et al.[21] Most clinical trials have similar findings. An analysis was performed without the study of Malhotra et al.[17] The effect estimate was found to be nonsignificant (ES = –0.216; *P* value = 0.556; CI = –0.936 to 0.504).

The LTM effect estimate demonstrating a treatment effect based on the results before the trial and after the end point consisted of 8 studies (n = 209 before treatment and n = 192 at the end of trial; overall attrition rate of slightly more than 8%). The effect estimate was significant and close to heterogeneous (refer to Table 3). There was a difference between the random- and fixed-effects models. The fixed-effects model was smaller yet very significant (Fig. 1).

Insert Table 4 about here

A fixed-effects regression analysis based on 8 original studies showed that as the duration of the trial increases, the effect estimate slightly increases (point estimate slope = –0.019; SEM = 0.051). The analysis was broken down by AChEI: 5 studies of donepezil (ES = –0.352; *P* value = 0.094; CI = –0.060 to 0.765), only 2 studies of rivastigmine (ES = 0.383; *P* value = 0.294; CI = –0.333 to 1.099), and 1 study of

galantamine. Because of the minimal number of available studies, the effect of add-on galantamine was inconclusive. A further analysis was performed on the type of antipsychotic. There was a difference in the effect estimate for the type of antipsychotic: 6 studies of second-generation antipsychotics (ES = 0.424; *P* value = 0.035; CI = 0.031 to 0.818) and 2 studies of first-generation antipsychotics (ES = 0.207; *P* value = 0.455; CI = –0.335 to 0.749). All studies in the rivastigmine group involved add-on treatment on top of atypical antipsychotics. As for the donepezil studies, an effect estimate was done to compare atypical (3 studies) to typical (2 studies) antipsychotics (atypical ES = 0.446; *P* value = 0.194; CI = –0.227 to 1.120 vs typical ES = –0.207; *P* value = 0.455; CI = –0.335 to 0.749). At this point, we referred to the quality assessment of the studies. We divided the studies into 2 groups with weaker and stronger designs, where stronger designs referred to double-blind and random studies. This division separated the effect into 2 groups, 1 with 3 studies with random double-blind trials.

We then calculated an effect estimate without the study by Malhotra et al.[17] The effect estimate for the AChEIs (baseline and end point), with 7 studies in the analysis, yielded a significant homogeneous magnitude (ES = 0.453; CI = 0.093–0.813).

Insert Figure 1 about here

The effect estimate for the comparison of the control and experimental groups is homogeneous yet nonsignificant, favoring the control group (refer to Table 4). Further analysis was done to control for the kind of antipsychotic, the AChEI used as add-on therapy, and the trial design. All studies included in this analysis were clinical trials of donepezil, double-blind and placebo-controlled. After controlling for the effect of the antipsychotic, the effect was different in atypical (1 study) and typical antipsychotics (2 studies). Although a slight LTM improvement was noted when

AChEIs are given in conjunction with typical antipsychotics, the effect estimate remained nonsignificant (ES = –0.073; *P* value = 0.803; CI = –0.645 to 0.499].

DISCUSSION

Our quantitative review attempts to address and surmise the relatively small and discrepant findings of studies examining cholinesterase inhibitors in schizophrenia. First, we used the within-group comparison as our primary approach to evaluate AChEI treatment effect. However, this type of analysis can only suggest a possible treatment effect because any apparent memory-enhancement effect is potentially confounded with novelty and practice effects. In light of this consideration, we should be prudent in discussing any significant within-group comparison as evidence for a therapeutic effect if it is not confirmed by the between-group analysis. The effect size of AChEI as an add-on to antipsychotic medication in schizophrenia is relatively mild. In a sense, our results confirm what was documented by Kumari et al[20] for unchanged brain activation with this medication and is in line with recent review findings of Ferreri et al.[10] In neuropsychiatric illnesses other than AD, it is speculated that AChEIs would benefit normal, healthy, naturally aging individuals based on the assumption that an increase in cholinergic activity after the use of AChEI agents may be the cause. The same reasoning has been applied to schizophrenia. Overall, our quantitative systematic review provides no clear evidence on whether AChEIs should be prescribed for memory enhancement in patients with schizophrenia. However, it has implications for methodological considerations affecting future research and pharmacological advancement and consequences for treatment and therapeutic decisions in practice. The studies included had methodological weaknesses, including small sample sizes (from 5 to 36 subjects), except for 1 study with 251 research participants.[17] The selection of patients was not always based on a previous assessment, showing that they had a well-documented cognitive-memory deficit except in 3 studies, Chouinard et al,[26] Sharma et al,[21] and Friedman et al[19]. However, it is noteworthy that the dosage of the AChEI prescribed as a concomitant treatment

for schizophrenia in these studies matches the recommended dosage for other pathologies (eg, AD).[41] In addition, we evaluated 3 AChEIs: donepezil, rivastigmine, and galantamine. We were forced to combine the results of these 3 agents because of the limited number of studies with any 1 drug, except perhaps for donepezil. However, the drugs have different mechanisms of action. In particular, galantamine is an allosteric modulator of the nicotinic receptors. Because the only galantamine study is a case series, this is a limitation.

Moreover, our results show that the fixed- and random-effects models' assessment of LTM in the before/after comparison differs. The difference in effect estimates between AChEIs, which is particularly noticeable for rivastigmine, can be explained by the fact that they are crossover studies and by the small sample size. This difference can also be explained by the observable discrepancies related to the lack of specificity of the tests used to assess STM and LTM; a meta-analysis cannot fully take this diversity into consideration. A recent study of schizophrenia patients by our group showed that the effects of rivastigmine on memory are not unitary but stem from its action at different time points within the information processing cascade.[45] Using event-related potentials, we showed that rivastigmine affects various components of the cognitive process in different ways, whereas some components are not affected at all. Our results suggested that AChEIs may favor the quantitative aspects of retrieval, that is, easier discrimination between old and new items, but not the accessibility of the information in memory. Thus, an AChEI such as rivastigmine does not have a homogeneous action on memory.

One limitation on this study is the paucity of available data—especially from random, double-blind, placebo-controlled trials—on the use of AChEIs as add-ons to antipsychotics for treating cognitive-memory impairment in schizophrenia; thus, our results must be interpreted with caution. Several studies (n = 9) matched our inclusion and exclusion criteria, yet the data from these studies are unavailable, which made the

interpretation of our results inconclusive. We consider our systematic review to be a first attempt to assess this kind of treatment; as yet, it seems that there are far too few studies to engage in a more meaningful meta-analysis. There are several methodological problems with conducting a meta-analysis on a very few studies. Moreover, 1 of the studies accounts for more than 50% of the total number of patients in the analysis. It is also important to note that the use of anticholinergic medication concomitant to the existing antipsychotic and the AChEI has also been reported in a few studies; however, due to the small number of studies,[27] we did not do any further meta-analytic evaluation of this confounding variable. In addition, although we might conclude that these medications are mildly efficacious for memory, the likely placebo effect in these types of studies has never been adequately determined. In fact, the study by Malhotra et al[17] suggested that the placebo effect in these studies is substantial. In this systematic review, we focused solely on memory function for AChEIs. This is the first step because these drugs have been found to have other effects in AD, and it is certainly possible that they may have effects on other cognitive functions such as attention in patients with schizophrenia.

CONCLUSION

The literature on cognitive enhancement and schizophrenia is burgeoning. Our systematic review constituted a meta-analysis of 10 studies looking at the cognitive benefits of AChEIs in patients with schizophrenia. The results suggest that there is a small improvement in STM and LTM with these medications. Nonspecific stimulation of a variety of muscarinic and nicotinic acetylcholine receptors may result in masking or dampening of possible beneficial effects associated with stimulation of selective receptors such as the M1 or M4 muscarinic receptors or $\alpha 7$ nicotinic receptor. The eligible data for the meta-analysis were nominal, and no result reached clinical significance. We still need more studies to establish a more significant conclusion such as the ideal design, duration, and outcomes in future studies of AChEI use in schizophrenia.

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TABLE 1. Demographic Representation of the Studies (n = 10) Included in the Current Quantitative Review

Studies	N	AChEI	Dosage (mg/d)	Antipsychotic	Design	Duration (wk)
Malhotra, et al[17*]	251	Donepezil	5–10	Risperidone Olanzapine Quetiapine Ziprasidone Aripiprazole	DB-PC-RND	12
Freudenreich, et al[23]	36	Donepezil	5–10	Typical	DB-PC	8
Tugal, et al[24]	12	Donepezil	5	Fluphenazine Pimozide	DB-PC-CO-RND	6
Buchanan, et al[25]	15	Donepezil	5–10	Olanzapine	PS-OL	6
Friedman, et al[19]	36	Donepezil	5–10	Risperidone	DB-PC-RND	12
Bora, et al[18]	5	Galantamine	8–16	Clozapine	CR	8
Kumari, et al[20]	36	Rivastigmine	3–12	Risperidone Quetiapine Olanzapine	DB-PC-RND	12
Chouinard, et al[26]	22	Rivastigmine	3–9	Atypical	CO-RND	12
Mendelson, et al[27]	13	Rivastigmine	9	Mostly atypical	OL	12
Sharma, et al[21]	21	Rivastigmine	3-9	Risperidone Olanzapine Quetiapine	DB-PC-RND	24

*Poster.

CO indicates crossover; CR, case report; DB, double-blind; PC, placebo-controlled; PS, pilot study; OL, open-label; RND, random; SB, single-blind.

TABLE 2. Memory Scales Used in Each Study

Studies	STM	LTM
Kumari et al [20]	n-Back (2-back)	—
Fredenreich et al [23]	Digit span backward	Hopkins Verbal Learning Test Benton Oral Word Association Test
Tugal et al [24]	Digit span backward	Visual reproduction 1 Visual paired associates 1 Visual reproduction 2 Visual paired associates 2 Logical memory 2 Logical memory 1 Verbal paired associates 1 Verbal paired associates 2 Figural memory
Buchanan et al [25]	—	Benton visual retention test number correct RAVLT (trials 1–5 total)
Freidman et al [19]	SWM (15-s delay)	RAVLT (delayed recall)
Malhotra et al [17]	Auditory working memory (letter–number) Visuospatial memory	Hopkins verbal learning test
Bora et al [18]	AC2T total	RAVLT (recall)
Chouinard et al[26]*	CANTAB-SWM	CANTAB-PAL
Mendelson et al [27]	ADAS-cog, item 5	ADAS-cog, item 7
Sharma et al [21]	Digit symbol scaled score Dot test	—

*Poster

ACT indicates auditory consonant trigram; ADAS-cog, Alzheimer's Disease Assessment Scale—cognitive subscale; PAL, paired associated learning; RAVLT, Rey Auditory Verbal Learning Test; SWM, spatial working memory.

TABLE 3. Effect Estimate for Each Memory Domain Comparing Results Before Treatment to the End Point of AChEI Cotreatment

Effect Model	Memory Domain	No. Studies	Effects (Hedge *g*)	*P*	CI(Lower/ Higher)	Cochrane *Q*	*P**
Random	LTM	8	0.362	0.019†	0.061 – 0.663	11.984	0.101
	STM	9	0.226	0.117	–0.003 to 0.454	12.927	0.114
Fixed	LTM	8	0.263	0.008†	0.068 – 0.459	11.984	0.101
	STM	9	0.124	0.074	–0.012 to 0.270	12.927	0.114

* Homogeneous; †Significant.

TABLE 4. Effect Estimate for Each Memory Domain Comparing Control and Experimental Groups at the End Point (Random Effect)

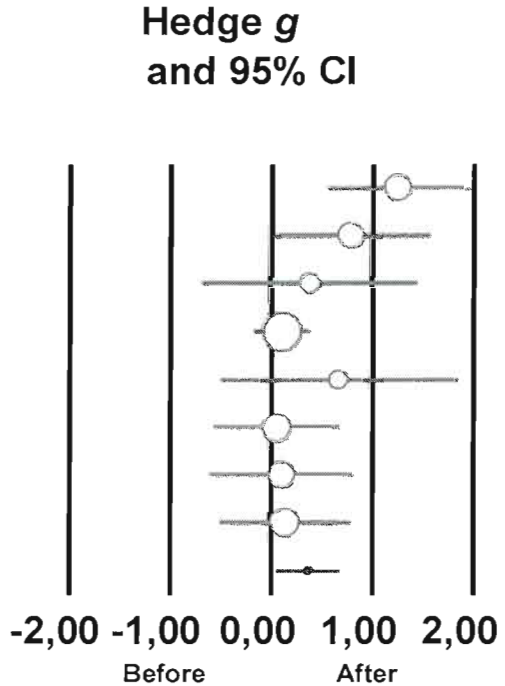
Cognitive Domain	No. Studies	Effects (Hedge *g*)	*P*	CI (Lower/Higher)	*Q*	*P**
LTM	3	–0.240	0.061	–0.492 to 0.011	0.769	0.681
STM	4	–0.236	0.208	–0.604 to 0.132	4.214	0.239

* Homogeneous.

FIGURE 1. Blobbogram representation of studies on LTM before and after AChEI cotreatment.

Study name	Hedge *g*	*P*	Lower limit	Upper limit
Friedman et al (2002)	1,252	0,000	0,550	1,953
Mendelsohn et al (2004)	0,792	0,045	0,017	1,567
Tugal et al (2004)	0,385	0,475	-0,671	1,441
Malhotra et al (2005)	0,108	0,433	-0,162	0,379
Bora et al (2005)	0,672	0,255	-0,486	1,829
Chouinard et al (2005)	0,057	0,855	-0,551	0,664
Buchanan et al (2002)	0,108	0,761	-0,589	0,805
Freudenreich et al (2005)	0,143	0,657	-0,488	0,775
	0,362	0,019	0,061	0,663

Statistics for each study



Random-effects model (n=8 Studies)

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CHAPITRE VI

CONCLUSION

Discussion

Le présent projet de thèse avait deux objectifs principaux, d'une part d'évaluer les effets de la rivastigmine, un inhibiteur d'acétylcholinestérase sur le fonctionnement cognitif dans la schizophrénie et d'autre part d'utiliser les approches méta-analytiques pour juger de l'efficacité des inhibiteurs d'acétylcholinestérase sur le fonctionnement cognitif dans la schizophrénie.

Revue sur les traitements des troubles cognitifs dans la schizophrénie

L'article intitulé "On the trail of cognitive enhancer for the treatment of schizophrenia" nous a permis de constater l'orientation des recherches dans le traitement des troubles cognitifs dans la schizophrénie. L'étude des différents mécanismes d'action des neuroleptiques atypiques et leur propension à améliorer le fonctionnement cognitif constitue une source d'information cruciale dans le développement de traitements pour les troubles cognitifs dans la schizophrénie. En plus, de la sérotonine et de la dopamine, d'autres neurotransmetteurs comme l'acétylcholine et le glutamate jouent un rôle dans la symptomatologie de la schizophrénie.

Des études récentes d'envergure commanditées par des gouvernements ont été menées sur l'efficience des antipsychotiques, comparant les neuroleptiques atypiques aux neuroleptiques typiques. L'étude "Clinical antipsychotic trials of intervention effectiveness" (CATIE) menée par le NIMH, qui a été réalisée aux États-Unis, conclut qu'il n'y a pas de différence entre l'efficacité des neuroleptiques atypiques et typiques au niveau de la cognition (Keefe et al., 2007). Deux autres études réalisées au Royaume-Uni avec l'étude CUtLASS (Jones et al., 2006) et en Europe avec l'étude EUFEST (Davidson et al., 2009) arrivent à la même conclusion sur l'équivalence des neuroleptiques atypiques et typiques au plan de la cognition.

La supériorité des neuroleptiques atypiques comparés aux neuroleptiques typiques pour traiter les déficits cognitifs dans la schizophrénie ne semble donc pas fondée. Pour plus de détails sur ces résultats, on peut se référer à une revue critique récente des études CATIE et CUtLASS (Stip et al., 2008).

L'implication de l'acétylcholine dans les troubles cognitifs de la schizophrénie semble maintenant établie. Par ailleurs, il reste à en déterminer la nature et l'étendue. Plusieurs circuits neuronaux différents peuvent être impliqués dans une même fonction cognitive et, à l'inverse une même région cérébrale peut être impliquée dans plusieurs fonctions cognitives.

Plusieurs études se sont intéressées aux effets d'un traitement cholinergique dans la schizophrénie. Les résultats montrent l'implication des récepteurs nicotiniques et muscariniques dans le dysfonctionnement cognitif. Il n'est pas surprenant de constater qu'environ deux tiers des patients atteints de schizophrénie fument la cigarette. La nicotine exerce un effet thérapeutique pour eux. Ces résultats nous ont amené à réaliser une étude sur les effets de la rivastigmine sur les déficits cognitifs dans la schizophrénie.

Étude sur la rivastigmine

L'étude que nous avons effectuée sur les effets de la rivastigmine dans la schizophrénie ne révèle pas de changement significatif au plan du fonctionnement cognitif, tel qu'évalué avec les tâches neurocognitives de CANTAB. Notre principale préoccupation initialement dans cette étude concernait la relation bien connue entre l'augmentation de l'activité cholinergique et l'aggravation possible des symptômes positifs. Il appert qu'elle n'était pas fondée puisque le traitement avec la rivastigmine n'a pas engendré de changement au niveau des symptômes cliniques, tant pour les symptômes positifs que négatifs évalués avec le PANSS.

Au cours des dernières années, les études ont révélé des résultats contradictoires sur l'efficacité des inhibiteurs d'acétylcholinestérase dans la schizophrénie. L'un des facteurs à considérer dans l'hétérogénéité des ces résultats représente les caractéristiques de l'échantillon de patients atteints de schizophrénie sélectionnés. Dans une étude de Friedman et al. (2002), le traitement cholinergique donepezil concomitant au traitement neuroleptique n'a pas montré de résultat significatif sur le fonctionnement cognitif. Ces auteurs soutiennent que leurs résultats négatifs pourraient être reliés au fait que les patients avaient un rendement inférieur à plus de 3.5 écart-type de la norme au CVLT. Les patients inclus dans leur étude présentaient des déficits cognitifs importants au plan de la mémoire. Dans cette étude les résultats négatifs seraient en lien avec l'intensité des troubles mnésiques, selon les auteurs.

Toutefois, Lenzi et al. (2003) rapportent une amélioration du fonctionnement cognitif après un mois de traitement avec la rivastigmine chez des patients atteints de schizophrénie. Fait notable, les patients présentaient un faible niveau de troubles cognitifs au départ dans cette étude. Sur la base de ces résultats et ceux de notre étude, il apparaît possible qu'un traitement avec des inhibiteurs d'acétylcholinestérase soit plus efficace chez des patients présentant des troubles cognitifs légers. Nous pouvons établir un parallèle avec ces résultats et ce que l'on observe dans la maladie d'Alzheimer où la médication s'avère plus efficace à stabiliser la détérioration cognitive dans les premiers stades de la maladie qu'à améliorer les déficits sévères déjà installés (Ibach and Haen, 2004). La diminution des récepteurs cholinergiques post-synaptiques avec l'évolution de la maladie peut expliquer le fait que la médication soit plus efficace en début de maladie.

Dans cette optique, il est possible que les déficits cognitifs préalables s'avèrent trop cristallisés chez les patients inclus dans notre étude pour qu'ils puissent bénéficier d'un traitement cholinergique. En somme, ces données suggèrent

l'hypothèse qu'un traitement avec les inhibiteurs d'acétylcholinestérase dans la schizophrénie pourrait davantage constituer une thérapie préventive que curative.

C'est dans ce contexte que nous suggérons que dans les perspectives de recherches ultérieures, on puisse s'adresser à un nouveau type de population qui fait l'objet d'essais pharmacologiques, mais à notre connaissance sans utilisation des inhibiteurs d'acétylcholinestérase : les patients à haut risque de schizophrénie.

D'autres facteurs expérimentaux pourraient s'avérer questionnables dans notre étude, tel que la taille réduite de l'échantillon (i.e. 20 patients) et la brève durée du traitement (i.e. trois mois). Notons toutefois, qu'une étude récente de Keefe et al. (2007), constituée d'un échantillon de plus de 250 patients, n'a pas montré de résultat significatif et qu'une autre étude où la rivastigmine a été administrée sur une période de six mois n'a pas révélé d'amélioration (Sharma et al., 2006). Soulignons aussi que nous n'avions pas de groupe placebo dans notre étude avec la rivastigmine.

L'interaction de la rivastigmine avec les neuroleptiques constitue un facteur qu'il aurait été préférable de contrôler dans notre étude. Par exemple, l'affinité pour les récepteurs muscariniques de certains neuroleptiques atypiques, tel que la clozapine, l'olanzapine et la quétiapine est reconnue. En fait, une désensibilisation des récepteurs muscariniques ou nicotiniques peut expliquer que la rivastigmine ne soit pas efficace dans le traitement des troubles cognitifs de la schizophrénie. S'il y avait d'éventuelles études, celles-ci devraient tenir compte de la consommation de nicotine et du type de neuroleptiques administrés aux patients. La prise de médication anti-cholinergique, parfois administrée pour atténuer les symptômes extrapyramidaux, aurait aussi avantage à être contrôlée.

Compte tenu de nos résultats, il apparaît probable que la rivastigmine ne soit pas efficace pour le traitement des troubles cognitifs dans la schizophrénie indépendamment du contrôle de toutes les variables expérimentales.

Études méta-analytiques

Nos études méta-analytiques investiguant l'efficacité des inhibiteurs d'acétylcholinestérase dans la schizophrénie ne permettent pas de tirer de conclusion claire. Bien que nous ayons couvert toute la littérature, seulement huit études ont été retenues pour les analyses méta-analytiques.

Les résultats montrent une légère amélioration aux niveaux de l'attention et de la mémoire à long terme lorsqu'on compare le même groupe de patients avant et après traitement avec ACHeI. La taille de l'effet est faible, mais significative, ce qui signifierait que les inhibiteurs d'acétylcholinestérase puissent exercer un certain effet sur le fonctionnement cognitif. Néanmoins, il est possible que les effets bénéfiques constatés puissent être attribuables à un effet de pratique, puisque nos résultats méta-analytiques ne montrent pas de différence entre les groupes contrôles et les patients traités avec ACHeI. Cette notion a été introduite de façon générale par Goldberg et al. (2007), lorsqu'il a pu mettre en évidence, grâce à un design approprié, utilisant un groupe contrôle que les effets bénéfiques des antipsychotiques atypiques sur la cognition étaient liés à un effet de pratique. Une récente étude publiée après notre méta-analyse par Buchanan et al. (2008), suggère un effet de pratique avec un inhibiteur de l'acétylcholinestérase, la galantamine.

Des analyses statistiques plus poussées montrent que lorsqu'on regroupe les études ayant employé le donepezil (i.e. cinq études) on note un effet du traitement au niveau de l'attention, alors que les études ayant utilisées la rivastigmine (i.e. quatre études) ne montrent pas d'effet du traitement. En fait, les trois types d'inhibiteur d'acétylcholinestérase employés dans les études soit le donepezil, la rivastigmine et la galantamine ont des mécanismes d'action différents au niveau du système cholinergique. Le donepezil et la galantamine interviennent au niveau de l'Ache seulement, alors que la rivastigmine exerce une double action aux niveaux de l'Ache et de la Buche. Rappelons que l'Ache et la Buche sont deux types de cholinestérase.

Les médicaments exerçant une action sur la BUCHE peuvent affecter certaines autres voies cholinergiques, puisqu'il y en a huit en tout. La principale voie cholinergique impliquée dans la mémoire relie le noyau basal de Meynert au cortex cérébral et aux amygdales. On note aussi des différences en ce qui a trait aux récepteurs nicotiniques et muscariniques. La plupart des inhibiteurs d'acétylcholinestérase exerce une action au niveau des récepteurs muscariniques M1. Une étude sur les effets de la galantamine qui agit principalement sur les récepteurs nicotiniques révèle des améliorations aux niveaux de l'attention et de la mémoire dans la schizophrénie (Schubert et al., 2006).

Les résultats de la méta-analyse ne révèlent pas d'effet du traitement sur les autres fonctions cognitives, soit aux plans du langage, de la psychomotricité ou des fonctions exécutives. À ce stade, des analyses de variables modératrices seraient nécessaires, mais difficiles à réaliser en raison du nombre limité d'études disponibles. Ces analyses permettraient de comprendre pourquoi certaines études révèlent des effets bénéfiques des inhibiteurs d'acétylcholinestérase sur le fonctionnement cognitif dans la schizophrénie (Buchanan et al., 2003; Lenzi et al., 2003), alors que d'autres études ne montrent pas d'amélioration (Freudenreich et al., 2005; Friedman et al., 2002; Tugal et al., 2004).

Discussion générale

D'autres articles ont été publiés récemment sur l'effet des inhibiteurs d'acétylcholinestérase dans la schizophrénie (Fagerlund et al., 2007; Keefe et al., 2007, Buchanan et al., 2008). Les résultats de ces études ne sont pas significatifs. Notons que les études de Keefe et al. (2007) et de Malhotra et al. (2004) qui a été incluse dans nos méta-analyses semblent provenir du même échantillon de sujets (N=250). L'étude de Buchanan mérite d'être nuancée puisqu'il explique ses résultats en rapport avec un effet de pratique.

Dans une revue de littérature sur l'effet des inhibiteurs d'acétylcholinestérase dans la schizophrénie, Risch (2008) en arrive à la conclusion que ce type de médication n'est pas une option de choix pour le traitement des troubles cognitifs dans la schizophrénie. Il se base sur les résultats des études récentes qui ne montrent pas d'amélioration au plan de la cognition. Cet avis est confirmé par Voss et al. (2008), qui soulignent que l'espoir des premiers résultats lors des essais ouverts ne s'est pas maintenu lors des essais randomisés, placébo-contrôlés.

L'hétérogénéité des résultats des études suggèrent qu'un sous-groupe de patients puisse bénéficier d'un traitement cholinergique. La question consiste à se demander s'il s'avère nécessaire de poursuivre des études cliniques afin d'identifier quels sous-groupes de patients pourraient profiter d'un traitement cholinergique. Il est probable que les études qui ont révélé des résultats significatifs soient attribuables à des facteurs expérimentaux mal contrôlés. Cela nous ramène par ailleurs aux problèmes de classification du spectre de la schizophrénie. Il manque aussi dans ce domaine, des données claires et probantes sur les phénotypes de schizophrénie reliés à de tels déficits cognitifs. Nous n'avons pas non plus à notre disposition des données suffisamment probantes sur les typages génétiques en lien avec les neurotransmetteurs impliqués dans la schizophrénie.

Il est également important de rappeler que les deux tiers des patients inclus dans notre étude étaient des fumeurs et que ce sous-groupe a obtenu une meilleure performance cognitive au RBANS lors du recrutement. Il est possible que les récepteurs nicotiniques des fumeurs soient désensibilisés ce qui peut s'avérer en lien avec l'inefficacité du traitement. Une autre variable qui aurait eu avantage a être contrôlée dans les recherches est l'homogénéité du traitement neuroleptique administré avec les inhibiteurs d'acétylcholinestérase.

Les neuroleptiques typiques comme l'halopéridol exercent une action principalement sur le système dopaminergique D2 et ils ont aussi certaines propriétés de blocage cholinergique. Par contre, les neuroleptiques atypiques affectent plusieurs systèmes de neurotransmetteurs dont la dopamine, la sérotonine et le système cholinergique. Si l'on tient compte du fait que chaque neuroleptique atypique a un profil pharmacologique différent, il est possible qu'un traitement cholinergique soit efficace dépendamment du type de neuroleptique administré de manière concomitante.

Tel que proposé par MATRICS, l'hétérogénéité des résultats peut être partiellement en lien avec les problèmes concernant les outils et la méthodologie employés pour l'évaluation du fonctionnement cognitif. Il est probable que certains tests soient plus sensibles pour détecter les changements au plan des fonctions cognitives. Notre choix d'utiliser CANTAB qui est une batterie informatisée d'évaluation neuropsychologique, standardisée auprès d'une population de patients atteints de schizophrénie, vient du fait que sa passation est très appréciée et qu'elle permet de tester des populations d'origines linguistiques diverses, tel que la situation se présente au Québec. Bien que CANTAB ne fasse pas partie des tests sélectionnés par les américains du groupe MATRICS, son utilisation dans la schizophrénie est bien documentée (Levaux et al., 2007) et il est fréquemment utilisé dans les essais cliniques. Il n'y a pas de donnée qui montre que CANTAB est non fiable au niveau de la sensibilité. Par ailleurs, il serait préférable que les prochains essais cliniques évaluant les fonctions cognitives dans la schizophrénie soient effectués à partir de la batterie de tests neuropsychologiques sélectionnées par MATRICS.

Perspectives d'avenir

Ce travail doctoral a consisté à explorer l'effet d'une intervention pharmacologique sur le système cholinergique dans le but d'améliorer le fonctionnement cognitif de patients atteints de schizophrénie. Cet effet a été étudié indirectement avec la famille des inhibiteurs d'acétylcholinestérase. Qu'en est-il des agonistes muscariniques? Les interventions pharmacologiques dans la schizophrénie sont concentrées principalement sur la dopamine et dans une moindre mesure, sur la sérotonine et le glutamate. Cependant, nous l'avons vu, ces traitements sont imparfaits particulièrement pour traiter les symptômes négatifs.

La dopamine est modulée à travers le système muscarinique central, un réseau complexe avec au moins huit voies cholinergiques muscariniques majeures et largement distribuées par ses terminaisons par les récepteurs post synaptiques. On a montré chez les patients atteints de schizophrénie un faible « binding » des récepteurs muscariniques dans le cortex préfrontal, dans la formation hippocampique et dans le striatum (Dean et al., 2008). Des études récentes ont lié les différences dans les sous types des récepteurs muscariniques M4 et M5 avec les phénomènes « psychotic like » dans les modèles animaux (Chan et al., 2008; Maehara et al., 2008).

Dans une étude avec des patients déments, la xanoméline, un agoniste muscarinique M1 et M4, était associée à une amélioration de la cognition, des délires, des hallucinations et de la méfiance. Une étude de quatre semaines, à répartition aléatoire et contrôlée de la xanoméline, a été réalisée avec 20 patients atteints de schizophrénie. Ces patients étaient malades depuis environ 15 ans et ils ne montraient pas d'amélioration ou ils se détérioraient avec la médication antérieure (Shekhar et al., 2008). La médication a été stoppée de trois à sept jours avant le début d'une phase d'une semaine où ils recevaient un placebo. Ensuite, les patients étaient répartis aléatoirement à la xanoméline (inférieure ou égale à 225 mg par jour) ou au placebo.

Lorsqu'on compare la condition placebo au traitement avec la xanoméline, on observe une aggravation de la sévérité de la maladie avec le placebo. Au total, les symptômes positifs et négatifs et les mesures de la cognition, comme la mémoire explicite et la mémoire à court terme s'étaient améliorés.

Cette étude a suggéré que les actions sur les récepteurs muscariniques pouvaient encore avoir leur place dans les approches thérapeutiques de la schizophrénie. Des études plus larges sont quand même nécessaires pour mieux délimiter la nature et le degré d'amélioration des symptômes négatifs et cognitifs mais aussi pour déterminer la tolérance à ce type de médicament. Il reste à déterminer si ces agents muscariniques agissent directement à travers les voies dopaminergiques ou par d'autres mécanismes qui nécessitent d'être précisés (Shekhar et al., 2008). Ce champ de recherche est à confronter à celui des inhibiteurs d'acétylcholinestérase et demeure une perspective intéressante comme en témoigne l'éditorial de Lieberman et al. (2008).

Dans une revue de littérature récente, l'efficacité d'un autre type de médication, le modafinil, qui agit sur la noradrénaline et le glutamate, n'est pas clair pour le traitement des déficits cognitifs dans la schizophrénie (Saavedra-Velez et al., 2009).

Conclusion

Les résultats de notre étude montrent que les objectifs initiaux visant l'amélioration du fonctionnement cognitif chez des patients atteints de schizophrénie avec un agent cholinergique ne sont pas rencontrés. Les données que nous avons recueillies dans cette étude montrent que la rivastigmine n'est pas efficace pour le traitement des dysfonctions cognitives dans la schizophrénie. Ces résultats vont dans le même sens que ceux de Sharma et al. (2006).

Une étude récente rapporte des améliorations aux niveaux de la reconnaissance en modalité verbale et du rappel en modalité visuelle avec un traitement de donepezil chez des patients atteints de schizophrénie traités avec l'halopéridol (Lee et al., 2007). Par contre, toutes les autres études récentes ayant utilisé le donepezil chez des patients atteints de schizophrénie ne montrent pas de résultats concluants au niveau de la cognition (Akhondzadeh et al., 2008; Fagerlund et al., 2007; Keefe et al., 2007; Kohler et al., 2007). On observe les mêmes résultats non-significatifs avec les études récentes ayant utilisé la rivastigmine pour le traitement des troubles cognitifs dans la schizophrénie (Sharma et al., 2006). Toutefois, les résultats demeurent contradictoires lorsque la galantamine est employée comme traitement des déficits cognitifs dans la schizophrénie. Deux études récentes révèlent des résultats significatifs (Buchanan et al., 2008; Schubert et al., 2006), alors qu'une autre étude ne montre pas d'effet du traitement (Dyer et al., 2008). L'efficacité de la galantamine dans le traitement des déficits cognitifs dans la schizophrénie reste donc à clarifier.

Les méta-analyses que nous avons réalisées sur l'impact des inhibiteurs d'acétylcholinestérase sur les déficits cognitifs dans la schizophrénie révèlent à peine une légère amélioration aux niveaux de l'attention et de la mémoire à long terme. Et pas de différence après traitement en comparaison d'un groupe contrôle placebo. Il ne semble donc pas nécessaire de poursuivre d'autres travaux sur l'efficacité des inhibiteurs d'acétylcholinestérase dans le traitement des troubles cognitifs de la schizophrénie. Ce type de médication ne s'est pas avéré efficace pour pallier les troubles cognitifs dans la schizophrénie du moins en ce qui a trait à la rivastigmine et au donepezil. Tel que précité, il semble y avoir encore des études qui montrent que la galantamine pourrait être efficace. Des études supplémentaires permettraient d'établir s'il s'agit encore de facteurs expérimentaux en cause ou si cette molécule est vraiment efficace pour le traitement des déficits cogntifs dans la schizophrénie.

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ANNEXE A

CRITÈRES DIAGNOSTIQUES DE LA SCHIZOPHRÉNIE SELON LE DSM-IV (1994)

A. Symptômes caractéristiques: deux (ou plus) des manifestations suivantes sont présentes, chacune pendant une partie significative du temps pendant une période d'un mois.

(1) idées délirantes
(2) hallucinations
(3) discours désorganisé
(4) comportement grossièrement désorganisé ou catatonique
(5) symptômes négatifs, p. ex., émoussement affectif ou perte de volonté.

N.B. Un seul symptôme du Critère A est requis si les idées délirantes sont bizarres ou si les hallucinations consistent en une voix commentant en permanence le comportement ou les pensées du sujet, ou si, dans les hallucinations, plusieurs voix conversent entre elles.

B. Dysfonctionnement social ou dans les activités: Pendant une partie significative du temps depuis la survenue de la perturbation, un ou plusieurs domaines majeurs du fonctionnement tels que le travail, les relations interpersonnelles, ou les soins personnels sont nettement inférieurs au niveau atteint avant la survenue de la perturbation.

C. Durée: Des signes permanents de la perturbation persistent pendant au moins 6 mois.

D. Exclusion d'un trouble schizo-affectif et d'un trouble de l'humeur.

E. Exclusion d'une affection médicale générale due à une substance.

F. Relation avec un trouble envahissant du développement: en cas d'antécédent de trouble autistique ou d'un autre trouble envahissant du développement, le diagnostic additionnel de schizophrénie n'est fait que si des idées délirantes ou des hallucinations prononcées sont également présentes pendant au moins un mois.

ANNEXE B

FORMULAIRE DE CONSENTEMENT

RENSEIGNEMENTS DESTINÉS AU PATIENT ET FORMULAIRE DE CONSENTEMENT

Titre de l'étude : Effets de la rivastigmine sur le fonctionnement cognitif et le sommeil des patients atteints de schizophrénie avec déficits cognitifs

Investigateurs : Dr Emmanuel Stip – Centre de recherche Fernand-Seguin
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CANADA

Numéro de téléphone : (514) 251-4015

INTRODUCTION

Vous êtes invité à participer à un projet de recherche qui consiste à vous administrer un médicament qui devrait améliorer votre fonctionnement cognitif. La rivastigmine améliore le fonctionnement cognitif chez certaines populations et il y a lieu de croire qu'elle pourrait être efficace pour les symptômes de la schizophrénie. C'est donc un *médicament expérimental* dans la schizophrénie bien que son efficacité soit reconnue pour d'autres maladies.

Dans cette étude, vos fonctions cognitives c'est-à-dire votre attention et votre mémoire seront évalués à trois reprises, soit au début de l'expérience, ainsi qu'à la douzième et la vingt-quatrième semaine.

Les évaluations de la performance cognitive auront lieu au laboratoire de sommeil du centre de recherche Fernand-Seguin. Chaque évaluation de la performance cognitive, d'une durée d'une heure et demie, se fera à partir d'une batterie de tests informatisés de mémoire et d'attention. De plus, vous aurez aussi à remplir un questionnaire sur les déficits cognitifs.

Lors des trois évaluations vous aurez également un enregistrement de votre activité cérébrale au cours d'une tâche de mémoire. Chacun de ces enregistrements durera environ une heure et demi

CRITÈRES D'ADMISSION

Afin de déterminer si vous pouvez participer à l'étude :

- on vous posera des questions sur votre fonctionnement cognitif;
- on vous soumettra à une courte évaluation d'habiletés cognitives;
- on vous interrogera sur la qualité de votre sommeil et de votre vie en général;
- on recueillera vos antécédents médicaux et psychiatriques et on vous soumettra à un examen physique;
- on déterminera si vous consommez des drogues illicites ou de l'alcool;
- si vous êtes une femme en âge de procréer, on vous soumettra à un test de grossesse. Les résultats de ce test doivent être négatifs pour que vous participiez à l'étude.

Si le médecin juge que vous êtes un bon candidat, vous recevrez le médicament à l'étude. Si vous ne pouvez tolérer le traitement, on vous retirera de l'étude.

PARTICIPATION EN CONSULTATION EXTERNE

Vous devrez voir le médecin chargé de l'étude en consultation externe. Le médecin ou le personnel chargé de l'étude vous interrogeront sur vos symptômes de schizophrénie, et votre santé physique en général. Il pourrait s'avérer nécessaire de prélever des échantillons additionnels de votre sang ou de votre urine s'il faut répéter certaines épreuves de laboratoire pour votre sécurité. Si vous êtes une femme en âge de procréer, vous vous soumettrez à un test de grossesse une fois par mois.

Vous devrez prendre le médicament tel que prescrit par le médecin. Si vous êtes confus ou si vous oubliez quels comprimés vous devez prendre, vous devez téléphoner immédiatement à l'infirmière ou au médecin chargé de l'étude pour qu'ils puissent vous aider. Vous devrez garder le médicament hors de la portée des enfants.

Afin de pouvoir mesurer adéquatement les effets du médicament à l'étude, il vous est interdit de consommer de l'alcool ou des drogues illicites pendant votre participation.

AUTRES MÉDICAMENTS OU INTERVENTIONS

Pendant votre participation à cette étude, vous continuerez votre traitement habituel. Certains médicaments vous seront interdits, le médecin chargé de l'étude vous les indiquera. Si un traitement avec un des médicaments interdits s'impose, vous devez en informer le médecin ou le personnel chargé de l'étude.

On ne vous interdira pas de prendre ce médicament, mais on pourrait vous demander d'arrêter de prendre le médicament à l'étude pour votre propre sécurité, car certains médicaments pourraient ne pas être adaptés au traitement à l'étude, et vous pourriez subir des problèmes physiques. Par conséquent, si vous devez prendre un nouveau médicament en vente libre ou si vous devez changer votre médication habituelle durant votre participation à cette étude, il vous faut d'abord consulter le médecin qui en est chargé.

Nous vous prions d'informer le médecin chargé de l'étude de tous les traitements médicaux que vous recevrez durant l'étude (p. ex., une chirurgie élective). Par ailleurs, vous ne devriez pas faire de don de sang durant votre participation à l'étude ni pendant le mois qui suit l'arrêt de traitement du médicament à l'étude.

RISQUES ET INCONVÉNIENTS

Les études cliniques sur la rivastigmine ont révélé quelques effets secondaires potentiels rapportés principalement durant la phase d'adaptation posologique. Les plus fréquemment observés sont : les nausées, les vomissements et les étourdissements. Habituellement, ces effets secondaires sont légers et s'estompent durant un traitement prolongé.

Vous devez informer le médecin ou l'infirmière de tous les médicaments que vous prenez, car certains agents vous sont défendus pendant votre participation à l'étude.

FEMMES EN ÂGE DE PROCRÉER

Les femmes qui prévoient une grossesse durant cette étude ne peuvent pas y participer. Si vous êtes enceinte ou si vous allaitez, vous ne pouvez pas y participer non plus. Il est important que vous ne preniez pas le médicament à l'étude si vous devenez enceinte. Si vos règles sont en retard ou si vous constatez un changement dans votre cycle menstruel habituel, vous devriez contacter immédiatement le médecin chargé de l'étude.

Si vous êtes une femme en âge de procréer, vous devez accepter de prévenir la grossesse durant votre participation à cette étude en utilisant une méthode de contraception efficace. Avant que vous commenciez à prendre le médicament à l'étude, le médecin ou le personnel chargé de l'étude examineront avec vous la méthode de contraception que vous utilisez et les mesures de prévention de la grossesse, et ils surveilleront cette donnée tout au long de votre participation à l'étude. Aucune méthode de contraception n'est efficace à 100 %. Il est donc important que vous utilisiez votre méthode de contraception correctement.

Vous devez discuter de tout changement de méthode de contraception avec le médecin chargé de l'étude. Il y va de votre sécurité, puisque l'exposition au médicament à l'étude pourrait comporter des risques imprévus pour vous ou pour le fœtus, si vous devenez enceinte.

Si vous devenez enceinte pendant votre participation à l'étude, on vous en retirera immédiatement et on vous adressera à un spécialiste en soins obstétriques. Vous serez entièrement responsable de tous les aspects des soins obstétriques et pédiatriques.

AVANTAGES POSSIBLES

Si vous participez à cette étude, vous recevrez la rivastigmine. Elle est commercialisée aux États-Unis et au Canada et dans de nombreux autres pays. Elle constitue un traitement potentiel des déficits cognitifs de la schizophrénie. Toutefois, aucun avantage ne peut vous être garanti, mais vous aurez la possibilité de contribuer au progrès de la recherche scientifique.

NOUVEAUX RÉSULTATS

On vous communiquera tout nouveau renseignement concernant les risques, qui pourrait influencer votre désir de participer à cette étude.

TRAITEMENT ET INDEMNISATION

En acceptant de participer à cette étude, vous ne renoncez à aucun de vos droits ni ne libérez nommément les chercheurs, les organismes, les entreprises ou les institutions impliqués de leurs responsabilités légales et professionnelles.

CONFIDENTIALITÉ ET ACCÈS À VOS DOSSIERS

Vos dossiers médicaux liés à l'étude sont confidentiels dans la mesure où les lois en vigueur le permettent. Les résultats de cette recherche peuvent être présentés lors de réunions ou peuvent être publiés, mais sans que votre identité ne soit dévoilée.

En signant le présent consentement, vous autorisez l'accès à vos dossiers médicaux.

FRAIS

Vous n'aurez rien à débourser pendant votre participation à l'étude. Les médicaments à l'étude, les interventions, et les consultations externes seront gratuites.

INDEMNISATION

Vous recevrez une compensation monétaire pour votre participation à cette étude, et dans certain cas les frais de transport de votre lieu de résidence ou de travail jusqu'au Centre de recherche seront aussi payés.

PERSONNE-RESSOURCE EN CAS D'URGENCE/COMITÉ DE DÉONTOLOGIE

En tout temps, vous pouvez poser des questions concernant les risques possibles ou inconnus reliés à cette étude. Si vous avez des questions au sujet de l'étude ou si vous manifestez des effets secondaires ou des troubles médicaux, veuillez contacter le médecin chargé de l'étude, D[r] Emmanuel Stip, au (514) 251-4015 poste 2345 ou l'un des membres du personnel chargé de l'étude, Sylvie Chouinard, au (514) 251-4015 poste 3514.

Pour toute question sur vos droits à titre de sujet de recherche, vous pouvez contacter un membre du comité de déontologie de l'établissement : Direction des Services professionnels – Hôpital Louis-H. Lafontaine – 7401, rue Hochelaga, Montréal (Québec) H1N 3M5 – tél. : (514) 251-4000

PARTICIPATION VOLONTAIRE ET ABANDON DE L'ÉTUDE

Votre participation à cette étude est volontaire. Vous pouvez refuser d'y participer ou vous pouvez décider de vous en retirer en tout temps, sans aucune pénalité et sans perte des avantages auxquels vous avez droit. Votre décision n'affectera en rien les soins médicaux dispensés dans ce centre. Si vous désirez retirer votre consentement, veuillez en informer immédiatement le médecin chargé de l'étude et prendre rendez-vous pour la visite finale.

Le médecin chargé de l'étude peut également mettre fin à votre participation sans votre consentement, pour les raisons suivantes :

- le médicament semble vous nuire sur le plan médical;
- vous ne tolérez pas le médicament à l'étude;
- vos symptômes de schizophrénie s'aggravent;
- vous ne suivez pas les recommandations du médecin et les directives de l'étude;
- on a découvert que vous ne répondez pas aux exigences de l'étude;
- raisons administratives.

CONSENTEMENT

En signant cette formule de consentement, vous acceptez de participer à cette étude de recherche de votre propre gré. Votre signature indique que vous avez lu et compris les renseignements qui vous ont été présentés. Vous ne devriez pas signer la formule si on ne vous a pas donné l'occasion de poser des questions et si on n'y a pas répondu de façon satisfaisante. Vous recevrez une copie de ce formulaire pour la garder dans vos dossiers.

_____
Signature du patient Date

_____
Nom du patient en caractères d'imprimerie

_____
Signature de la personne qui mène l'entrevue et fait signer le consentement Date

_____
Nom en caractères d'imprimerie de la personne qui mène l'entrevue et fait signer le consentement

_____
Signature du témoin ou du tuteur, le cas échéant Date

_____
Nom en caractères d'imprimerie du témoin ou du tuteur