Contrasting the Effects of Haloperidol and Olanzapine on Attention and Working Memory
in Schizophrenia: A Double-Blind Flexible Dose Study

in partial fulfillment of the requirements
for the degree of Doctor of Philosophy

Carleton University, Department of Psychology

by

Luc Boulay, B.A. (Hon), M.A.

National Library
of Canada

Bibliothèque nationale
du Canada

Acquisitions and
Bibliographic Services

Acquisisitons et
services bibliographiques

395 Wellington Street
Ottawa ON K1A 0N4
Canada

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

ISBN: 0-612-83513-8

Our file Notre référence

ISBN: 0-612-83513-8

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

Canada

The undersigned recommend to the
Faculty of Graduate Studies and Research
Acceptance of the thesis:

"Contrasting the Effects of Haloperidol and Olanzapine on Attention and Working
Memory in Schizophrenia: A Double-blind Flexible Dose Study"

submitted by

Luc Boulay

in Partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Chair

External Examiner

Thesis Supervisor

Carleton University
April, 2003

ABSTRACT

Persons suffering with schizophrenia have impairments in several neurocognitive domains. Research on the effects of atypical antipsychotic medications in schizophrenia showed that these agents have the potential to improve neurocognitive functioning. As a result of poor designs in many of these studies, it has been difficult to isolate the contribution of atypical medications in the putative improvements.

The purpose of this study was to contrast the effect of an older antipsychotic (haloperidol) and a newer antipsychotic (olanzapine) on neurocognitive functioning in schizophrenia. Three groups of participants were recruited: (a) 27 male and female patients diagnosed with schizophrenia in their first 5 years of illness, (b) 9 first-degree family members, and (c) 13 normal controls. Prior to double-blind randomization, all subjects were assessed on four occasions within 5 days (pre-randomization period) on the same neurocognitive battery. The battery consisted of 13 measures focusing on attention and working memory abilities. Repeated assessments prior to randomization was chosen as a method to control for learning and practice effects. Patients were then randomized to 56 days of treatment with haloperidol or olanzapine (post-randomization). All subjects were assessed on neurocognitive measures at Days 28 and 56.

Results revealed the presence of learning and practice effects during the pre-randomization period on motor tasks (Grooved Peg Board and Finger Tapping), verbal short-term memory (Digit Span Forward), attention (D2 Test of Attention, Stroop, and Digit Span Distractability), and on a measure of verbal working memory (Letter-Number Sequencing). Reaction time (Simple and Choice Reaction Time), short-term visuospatial memory (Circles

Away Test and Visual Memory Span), visual working memory (Visual Memory Span Backward), and verbal working memory (Digit Span Backward) were resistant to learning and practice effects.

There were no changes in performance for any of the four groups during the two month post-randomization period. Therefore, it can be concluded that olanzapine and haloperidol did not affect performance on measures of motor functioning, verbal short-term memory, attention, verbal working memory, reaction time, visuospatial short-term memory, and visual working memory.

ACKNOWLEDGMENTS

I would like to thank all who participated as subjects in this study. At times, I found myself losing sight of why I wanted to conduct this project. My interaction with patients and family members always brought me back to the real purpose.

Sincere thanks to my advisor, Dr. Tom Tombaugh. The training he has provided will undoubtedly serve me well throughout my research career. His candor and honesty has always been appreciated. I thank him for showing me that I am capable of accomplishing more than I thought.

To the members of my examining committee. I realize that committing to this process is time consuming. Thank you all for giving me your time. Particular thanks to my external examiner, Dr. Garry Remington from Toronto.

To my colleagues. This dissertation project would not have been possible without their commitment. Particular thanks goes to Dr. Alain Labelle. I fully recognize that he has been a driving force in this project. His unwavering support and patience have been pivotal and have been very much appreciated. I would also like to thank Dr. Dominique Bourget, Dr. Sharman Robertson, Dr. Pierre Tessier, Dr. Rami Habib, Dr. Helen Ward and Dr. Robert Milin for recruiting patients into this study. I am very fortunate to work in an environment where research is viewed as an important component in the treatment of schizophrenia. I would also like to thank Dr. Scot Purdon who introduced me to neuropsychological research.

To the clinical trials research staff. Their hard work in clinical trials has provided much of the funding for this project. Their role has not gone unnoticed. Thank you Sandhya, Karen, Hilda, Cathy, Allison and Colleen.

To my friends, too numerous to mention. I am a very lucky person when I can make such a statement. I thank them for listening during the ups and downs. Their support will never be forgotten. Particular thanks to Julie and Hans for being available to read drafts of this dissertation.

To my father and Ginette. My father has served as a model to follow. My decision to complete doctoral work was largely based on witnessing his successes and accomplishments. Even in “retirement”, he has an unabating passion for his work. As far back as I can remember, he told me to find something to do in life that is like a hobby and get paid for doing it. I think I’m there. I know mom would have been proud.

Ginette, knowing that my father has found someone has been a great comfort to me. Thank you for taking care of our father.

To my in-laws, Pat and Don. Their words and acts of encouragement throughout the years have been invaluable. Just being there and my knowing that they were there in times of need has always been a comfort to me, Shannon, Liam and Avery. Thank you.

To my sisters. I am so pleased that they have both come to live in Ottawa with their families. In the end, it’s all about family.

To Shannon, Liam and Avery. The three people who define who I am. This accomplishment is as much Shannon’s as it is mine. We completed it as a team. Her patience, support and love have never faltered. These are the things I love most about her. I know that with her, we can do anything. We’ll always find a way. To my sons, Liam and Avery. When I think of them I smile, I’ve never known such joy. This work has taken me away from them on numerous occasions, I hope they know I’ll always be there. As I have

experienced with my father, I hope that this accomplishment will serve as a model for the two
them in their endeavors through life.

TABLE OF CONTENTS

ACCEPTANCE FORM	ii
ABSTRACT	iii
ACKNOWLEDGMENTS	v
LIST OF TABLES	xi
LIST OF FIGURES	xii
LIST OF APPENDICES	xiv
PURPOSE	1
INTRODUCTION	3
Background on Schizophrenia	3
The Symptoms of Schizophrenia	3
Neurocognitive Function in Schizophrenia	5
The Psychopharmacological Treatment of Schizophrenia	11
Typical Neuroleptic Medications: Haloperidol	11
Atypical Neuroleptic Medications: Olanzapine	13
Mechanisms of Action	14
The Effect of Typical Neuroleptics on Neurocognition in Schizophrenia	18
The Effects of Atypical Antipsychotics on Neurocognition in Schizophrenia ...	19
Psychomotor Functioning	24
Visuoperceptual/Motor Processing	30
Memory	41
Executive Functioning	56
Attention: Arousal	68
Sustained Attention	74
Selective Attention	79
Divided Attention	89
Working Memory	90
Summary: The Effects of Atypical Antipsychotic Medications on Neurocognitive Functioning in Schizophrenia	94

EXPERIMENT: EFFECTS OF HALOPERIDOL AND OLANZAPINE ON ATTENTION AND WORKING MEMORY IN SCHIZOPHRENIA: A DOUBLE-BLIND FLEXIBLE DOSE STUDY	97
Purpose and Rationale	97
Hypothesis	98
Methodological Issues	98
METHOD	106
Participants	106
Measures	109
Procedures	116
Statistical Analyses	117
RESULTS	120
Clinical Scales	120
Motor Functioning	123
Grooved Peg Board	123
Finger Tapping	125
Reaction Time	130
Simple	130
Choice	132
Verbal Short-Term Memory	136
Digit Span Forward	136
Visuospatial Short-Term Memory	139
Circles Away 10 Second Delay	139
Visual Memory Span	141
Attention	144
Selective (D2 Test of Attention)	144
Stroop	146
Digit Span Distractability Test	148
Visual Working Memory	155

Visual Memory Span Backward	155
Verbal Working Memory	158
Digit Span Backward	158
Letter Number Sequencing	160
DISCUSSION	166
Strengths and Limitations of this Study	180
Future Directions	184
Implications	185
REFERENCES	187

LIST OF TABLES

Table 1 Demographic Information	109
Table 2 Patient Group Characteristics	109
Table 3 Means and Standard Deviations on the Clinical Scales in the Post-randomization Period (Days 0 and 56)	121

LIST OF FIGURES

Figure 1. Trial design summary	117
Figure 2. Grooved Peg Board pre-randomization	123
Figure 3. Grooved Peg Board post-randomization	124
Figure 4. Finger Tapping pre-randomization	125
Figure 5. Finger Tapping post-randomization	126
Figure 6. Simple Reaction Time pre-randomization	131
Figure 7. Simple Reaction Time post-randomization	132
Figure 8. Choice Reaction Time pre-randomization	133
Figure 9. Choice Reaction Time post-randomization	134
Figure 10. Digit Span Forward pre-randomization	136
Figure 11. Digit Span Forward post-randomization	137
Figure 12. Circles Away Visuospatial Memory Test pre-randomization	139
Figure 13. Circles Away Visuospatial Memory Test post-randomization	140
Figure 14. Visual Memory Span Forward pre-randomization	141
Figure 15. Visual Memory Span Forward post-randomization	142
Figure 16. D2 Test of Attention pre-randomization	144
Figure 17. D2 Test of Attention post-randomization	145
Figure 18. Stroop pre-randomization	146
Figure 19. Stroop post-randomization	147
Figure 20. Digit Span Distractability Test pre-randomization	148
Figure 21. Digit Span Distractability Test post-randomization	149
Figure 22. Visual Memory Span Backward pre-randomization	155
Figure 23. Visual Memory Span Backward post-randomization.	156
Figure 24. Digit Span Backward pre-randomization	158
Figure 25. Digit Span Backward post-randomization	159
Figure 26. Letter Number Sequencing in the pre-randomization	160
Figure 27. Letter Number Sequencing post-randomization	161

Figure 28. Performance at baseline (Time 1) and endpoint (Time 2, 4 to 6 weeks later) on the delayed component of the WMS-R Logical Memory.	168
Figure 29. Changes in performance from baseline (Time 1) to endpoint (Time 2, 4 to 6 weeks later) in a group of normal controls in the absence of interventions. . . .	169

LIST OF APPENDICES

Appendix A	Baseline Antipsychotic Medications	211
Appendix B	Patient Consent Form	213
Appendix C	Family Consent Form	226
Appendix D	Normal Control Consent Form	233
Appendix E	Patient Characteristics	240
Appendix F	Neurocognitive Battery	242
Appendix G	Demographic Sheet	271
Appendix H	Means and Standard Deviations for Each Test in the Pre-randomization Period (Days -4a, -4b, -3 and 0)	272
Appendix I	Mean Percent Change Scores from Day -4a to -4b; -4a to -3; and from -4a to 0	279
Appendix J	Means and Standard Deviations for Each Test in the Post-randomization Period (Days 0, 28 and 56)	286
Appendix K	Mean Percent Change Scores from Day 0 to 28 and from Day 0 to 56 .	293
Appendix L	Concomitant Medications	300

Purpose

The purpose of this study is to contrast the effects of a new antipsychotic medication called olanzapine to that of an older medication called haloperidol on attention and working memory in persons with schizophrenia. Older antipsychotic medications used in the treatment of schizophrenia are effective in alleviating the psychotic features of the illness and have little effect on affective or cognitive symptoms. Consequently, it was thought that both these deficits were unyielding and unamenable to pharmacological treatments. However, this view has changed with the advent of a new class of antipsychotic medications that was developed with the aim of reducing the unpleasant side-effects that often characterize older neuroleptics. This new class of antipsychotics was found to improve the psychotic as well as the affective features of the illness. It has been known for some time that the severity of affective symptoms tends to coincide with cognitive impairments, therefore, several researchers have postulated that these the newer medications may also improve cognitive abilities in schizophrenia.

Indeed, preliminary reports suggest that the newer medications used to treat schizophrenia appear to have positive effects on neurocognition. As this literature is in its infancy and is based on several poorly designed studies, it is unclear as to which cognitive domain(s) is (are) specifically enhanced as a result of treatment with the newer agents. More recent studies with improved experimental design suggest that there may not be a substantial divide between newer and older medications to treat schizophrenia.

A determination that atypical medications can enhance cognitive functioning in schizophrenia would have tremendous implications. For instance, it is well known that

persons with schizophrenia have difficulty working or retaining a job, establishing and fostering significant relationships, completing school, and living independently. Such functional outcomes are related to the cognitive deficits inherent in the disorder and not the psychosis as one may assume. Therefore, improving patients' cognitive functioning may improve their functional outcome. However, before making a link between enhanced cognition and enhanced functional outcome, a firmer grasp on how these medications affect cognition is necessary.

Introduction

Background on Schizophrenia

Schizophrenia is regarded as the most devastating of the mental illnesses, usually gripping persons in early adulthood and remaining with them throughout their lives (Black & Andreasen, 1999). The World Health Organization (1996) reports that 0.5% of the global population suffers from schizophrenia at any given time (prevalence); a number which ranges from 0.3% to 0.9% going from the least developed to the most developed countries respectively. Additionally, 1 in 100 persons will be affected by schizophrenia in their lifetime (incidence). According to the Schizophrenia Society of Canada (1999), the current cost of schizophrenia to Canadians is in excess of 4 billion dollars annually – a figure derived by calculating direct costs (inpatient and outpatient costs, medication costs, lodging costs, and supportive living costs) and indirect costs (lost productivity, compensation, costs to the family). In the United States in 1991, this figure was estimated at 64 billion dollars (Williams & Dickson, 1995).

In addition to the economic costs, the human costs are great; suicide is among the leading causes of death in persons diagnosed with schizophrenia (Caldwell & Gottesman, 1990). Their rate of attempted suicide is between 30 and 40% with 10% successfully ending their lives (Addington & Addington, 1992; Cohen, Test, & Brown, 1990; Labelle & Boulay, 1999).

The Symptoms of Schizophrenia

The symptoms attributed to schizophrenia are multifaceted and are typically categorized into two dimensions: the positive and the negative (Andreasen, Arndt, Alliger,

Miller, & Flaum, 1995; Carpenter, Strauss, & Bartko, 1973; Silver et al., 1993; Strauss, Carpenter, & Bartko, 1974). The positive symptom category (also sometimes called productive symptoms) refers to those symptoms which are added to normal mental functioning. These are symptoms produced by the illness. They tend to vary with clinical state (Andreasen et al., 1995; Carpenter, Heinrichs, & Wagman, 1988; Kay & Opler, 1987) and are typically responsive to neuroleptic treatment (Roy & DeVriendt, 1994). Symptoms classified as positive include hallucinations, delusions, conceptual disorganization, excitement (accelerated motor behavior, heightened responsivity to stimuli, hypervigilance, or excessive mood lability), grandiosity, suspiciousness and/or feelings of persecution, and hostility.

The negative symptom category represents aspects of mental functioning which are lost as a result of the schizophrenic process and are the more enduring and stable components of the illness (negative symptoms are also sometimes referred to as deficit symptoms) (Andreasen et al., 1995; Carpenter et al., 1988; Kay & Opler, 1987; Kay, Opler, & Fiszbein, 1986). Like the positive symptoms, the negative symptoms are also responsive to neuroleptic therapy (Beasley et al., 1996; Chouinard & Arnott, 1993; Schooler, 1994). Examples of negative symptoms are blunted affect, anhedonia, emotional withdrawal, poor rapport, passive and/or apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking.

No single pathognomic factor has been identified in schizophrenia. Consequently, the diagnosis of this illness relies heavily on the symptoms mentioned above. Physicians diagnose schizophrenia according to the most current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994). A person must

have at least two of the following five symptoms present most of the time for a period of at least 1 month. These include positive symptoms such as (a) delusions, (b) hallucinations, (c) disorganized speech, (d) grossly disorganized or catatonic (ranging from stupor to mutism) behavior and (e) negative symptoms such as affective flattening, alogia or avolition. Additionally, evidence that these symptoms have resulted in social and/or occupational dysfunction must also be present. The DSM-IV also allows for the classification of patients into different subtypes of schizophrenia. These include the paranoid type (preoccupation with delusions or frequent auditory hallucinations); the disorganized type (marked by disorganized speech and behavior, and flat or inappropriate affect); the catatonic type (relating to either a lack of, excessive, or inappropriate voluntary motoric movements); the undifferentiated type (these patients have the core symptoms of schizophrenia but do not meeting the criteria for any of the subtypes mentioned above); and finally the residual type (while these patients do not have any of the psychotic features of the illness, they have some of the negative features).

Neurocognitive Function in Schizophrenia

There is very little doubt that the clinical phenomenological features of schizophrenia, such as the positive and negative symptoms mentioned above, result from some form of brain dysfunction. In fact, many researchers have postulated that schizophrenia may be a neurocognitive disorder “with the various signs and symptoms reflecting the downstream effects of a cognitive deficit” (Black & Andreasen, 1999, p. 436). Indeed, it is very well documented that persons with schizophrenia show neurocognitive impairments across multiple domains (Green, 1998). For instance, these individuals perform between 1 and 2 standard deviations lower on tests of general intelligence relative to the general population

(such as on the Wechsler Adult Intelligence Scale - Revised [WAIS-R], Wechsler, 1981) (Frith, 1995; Hawkins, Sullivan, & Choi, 1997). Cross-sectional studies suggest that intellectual functioning is in the average range premorbidly, declines in the first decade after the onset of psychotic symptoms and then stabilizes in the more chronic phase of the illness. Subsequent deteriorations are no more pronounced than those attributable to normal aging (Frith, 1995; Green, 1998; Mockler, Riordan, & Sharma, 1997).

Impairments in motor functioning have also been consistently reported. Schizophrenia patients take more time to complete fine motor tasks (e.g., grooved pegboard), produce fewer finger taps than normal controls in an allotted time and are impaired on measures of eye movements (King, 1994; Voruganti, Heslegrave, & Awad, 1997).

Schizophrenia patients are also impaired on various aspect of attentional abilities. These include arousal (Raine, Benishay, Lencz, & Scarpa, 1997), sustained attention (Chen et al., 1998), selective attention (Addington, Addington, & Gasbarre, 1997), and divided attention (Green & Walker, 1986).

Impairments in various domains of memory functioning are also often reported. For instance, persons with schizophrenia show deficits in learning lists of words over repeated trials (Schwartz, Rosse, & Deutsch, 1992; Wexler, Stevens, Bowers, Sernyak, & Goldman, 1998). They recall less verbatim information about a story immediately after it has been presented as well as over delay periods (Goldberg et al., 1990; Hawkins et al., 1997; Seidman et al., 1994). Similar findings are reported when they are required to remember visual information (Goldberg et al., 1990; Hawkins et al., 1997; Schwartz et al., 1992). Additionally, they are impaired in recalling unrelated word pairs (e.g., cabbage/pen)

(Goldberg et al., 1990). Despite these deficits, persons with schizophrenia typically perform within normal limits on tasks of recognition memory (Goldberg et al., 1993a), short-term memory (such as the digit forward task of the WAIS-R), non-declarative procedural memory (such as the pursuit rotor task) (Goldberg et al., 1993a; Goldberg & Weinberger, 1988) and they are able to correctly recall related word pairs (e.g., metal/iron) (Goldberg et al., 1990). Finally, although these individuals are unable to learn as much information as normal controls, they are able to retain comparable proportions of information over time, indicating that they show similar rates of forgetting to normal controls (Goldberg et al., 1993a).

Maintaining that schizophrenia may be a neurocognitive disorder, a link between the key symptoms of schizophrenia and neurocognitive functioning has been made in the literature. For instance, according to the DSM-IV:

“Disorganized thinking (“formal thought disorder,” “loosening of associations”) has been argued by some (Bleuler, in particular) to be the single most important feature of schizophrenia. . . . The speech of individuals with Schizophrenia may be disorganized in a variety of ways. The person may “slip off the track” from one topic to another (“derailment” or “loose associations”); answers may be obliquely related or completely unrelated (“tangentiality”).” (p. 276)

Several researchers have argued that an impaired working memory system may represent the neurocognitive analogue to disordered thought processes (Goldman-Rakic, 1994; Goldman-Rakic & Selemon, 1997; Spindler, Sullivan, Menon, Lim, & Pfefferbaum, 1997; Spitzer, 1997). This hypothesis is plausible given the vast amount of literature which consistently reports impaired working memory abilities in individuals suffering from schizophrenia (e.g.,

Carter et al., 1996; Carter et al., 1998; Fleming et al., 1997; Fleming, Goldberg, Gold, & Weinberger, 1995; Keefe et al., 1995; Keefe, Lees, & DuPre, 1997; Park & Holzman, 1992; Park & Holzman, 1993; Park, Holzman, & Goldman, 1995; Spindler et al., 1997).

Working memory is defined as a “brain system that provides temporary storage and manipulation of the information necessary for such complex tasks as language comprehension, learning and reasoning” (Baddeley, 1986, p. 556). Additionally, this “information is updated on a moment-to-moment basis or retrieved from long-term stores, held in mind, and used to guide behavior by ideas, concepts, and stored knowledge” (Goldman-Rakic & Selemon, 1997, p. 437). Andreasen (1997) describes how impairments in working memory could result in several of the positive and negative symptoms of schizophrenia. She states:

“an inability to hold a discourse plan in mind and monitor speech output leads to disorganized speech and thought disorder; the inability to maintain a plan for behavioral activities could lead to negative symptoms such as avolition or alogia; and the inability to reference a specific external or internal experience against associative memories ... could lead to an altered consciousness of sensory experience that would be expressed as delusions or hallucinations.” (p. 1589)

Recognizing that working memory may be implicated in the disordered thought processes in schizophrenia, what is known about the brain areas which subserve this function? Evidence from the monkey and human literature convincingly demonstrates that the prefrontal cortex is crucial to intact working memory abilities (Boulay, 1998; Goldman-Rakic, 1996; Rao, Rainer, & Miller, 1997; Sawaguchi & Goldman-Rakic, 1991). Patients with schizophrenia often have difficulty with neurocognitive tasks which rely on the integrity of

the prefrontal cortex. For example, they frequently show impairments on tasks of executive functioning which require planning (the Tower of London) (Andreasen et al., 1992), set shifting (the Wisconsin Card Sorting Test) (Berman, Torrey, Daniel, & Weinberger, 1992), word generation (Verbal Fluency) (Brekke, Raine, Ansel, Lencz, & Bird, 1997; Dolan, Grasby, Fletcher, & Friston, 1997; Frith, 1995; Goldberg et al., 1998), and response inhibition (the Stroop Color-Word Test) (Buchanan, Holstein, & Breier, 1994; Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997; Grön, 1998). Further, parallels have been made between the cognitive dysfunctions observed in persons with schizophrenia and in persons with damage to their frontal lobes (e.g., Goldberg et al., 1993a; Goldberg et al., 1988; Park & Holzman, 1992).

Functional brain imaging studies reinforce the above findings by relating the poor performance on many of these tasks to hypoactivity of the prefrontal cortex (Andreasen et al., 1992; Berman et al., 1992; Callicott et al., 1998; Carter et al., 1998; Dolan et al., 1993; Stevens, Goldman, Gore, Fulbright, & Wexler, 1998; Yurgelun et al., 1996). For example, Andreasen et al. (1992) studied regional cerebral blood flow (rCBF) using positron emission tomography (PET) in persons with schizophrenia while they were performing a visual executive function task called the Tower of London. This task has been shown to activate the left mesial prefrontal cortex as well as the right parietal cortex in normal controls. Andreasen et al. reported a lack of activation in both of these cortical areas in their patient group. Furthermore, using functional magnetic resonance imaging (fMRI), Yungelun-Todd and colleagues (1996) studied blood oxygen utilization in patients while they performed a verbal task (Verbal Fluency). This task is typically characterized by an increase in activity in

the left prefrontal cortex and a decrease in activity in the left temporal cortex in normal controls. Interestingly, the schizophrenia group showed the reverse pattern; there was reduced activity in the left prefrontal cortex and increased activity in the left temporal lobe. Similarly, in measuring rCBF while performing the Wisconsin Card Sorting Test, a task which requires a person to maintain information in mind and shift mental sets when required, Berman et al. (1992) observed a significant decrease in metabolic activity in the prefrontal cortex. Parenthetically, findings from functional neuroimaging studies such as the those cited do not appear to be an artifact of chronic antipsychotic medication use. According to Buchsbaum et al. (1992) and Andreasen et al. (1992), hypofrontality is also present in never-medicated patients.

In addition to the neurobehavioral evidence implicating the prefrontal cortex in schizophrenia, neuroanatomical findings suggest the presence of structural abnormalities in this cortical area. Post mortem studies have revealed greater neuronal cell densities as well as reduced cortical thickness in the prefrontal cortex (Goldman-Rakic & Selemon, 1997; Weinberger, Aloia, Goldberg, & Berman, 1994). According to Goldman-Rakic and Selemon (1997), "this denser cell packing indicates that the meshwork of connectivity in which cortical neurons are embedded may be under represented in the brain of schizophrenia subjects" (p. 441). However, it must be noted that many brain structures investigated in schizophrenia have been found to be aberrant in some way or other (Weinberger et al., 1994). Several review papers on the neuropathology of schizophrenia agree that, as a result of conflicting findings, it is impossible to convincingly isolate a particular brain region or a combined series of brain regions as being implicated in the disorder (for a review of the neuroanatomy of

schizophrenia see Chua & McKenna, 1995; Dwork, 1997; Heckers, 1997; Stevens, 1997; Weinberger et al., 1994).

In summary, persons with schizophrenia are impaired in numerous neurocognitive domains. Perhaps most notable among these impairments is working memory. Several authors have hypothesized that deficits in working memory abilities may underlie some of the symptoms of the illness. Therefore, working memory itself could be a target for psychopharmacological interventions. The sections which follow will describe the two main classes of antipsychotic medications used in the treatment of schizophrenia. Their potential for influencing neurocognitive functioning will also be examined.

The Psychopharmacological Treatment of Schizophrenia

Currently, two main classes of antipsychotic medications predominate in the treatment of schizophrenia (MacEwan, 1993). The first class, called typical neuroleptics, refers to the older conventional antipsychotics. The medications which make up the second more recent class are called atypical antipsychotics. The section which follows will highlight the fundamental pharmacological differences which distinguish haloperidol (a typical antipsychotic) from olanzapine (an atypical antipsychotic). Also, the hypothesized mechanisms behind their clinical efficacy and potential effects on neurocognition in schizophrenia will be presented.

Typical Neuroleptic Medications: Haloperidol

The development of dopamine blocking agents to treat the symptoms of schizophrenia is largely based on the dopamine hypothesis in schizophrenia which states that “certain dopamine pathways are overactive” (Seeman, 1993). This hypothesis was founded on the

observation that dopamine blocking agents can alleviate some of the symptoms of schizophrenia. At present, several subtypes of dopamine receptors have been identified in the human brain and include the dopamine-1 like (dopamine-1 and dopamine-5) and the dopamine-2 like (dopamine-2,3,4) receptors. Research on the role of dopamine in schizophrenia has primarily focused on the dopamine-2 receptor subtype (Seeman, 1993). This is as a result of findings which demonstrate that the antagonism of dopamine-2 receptors appears to be the most effective method for alleviating positive symptoms (Nyberg, Farde, Eriksson, Halldin, & Eriksson, 1993). For example, a selective dopamine-1 antagonists (SCH39166) has been shown to have very little antipsychotic effects in schizophrenia (de Beaufort, Labelle, Naber, Jones, & Barnes, 1995) whereas a dopamine-2 blocking agent such as haloperidol is effective at reducing psychotic symptoms (Cassens, Inglis, Appelbaum, & Gutheil, 1990; Johnstone, Crow, Frith, & Owens, 1988). Older conventional antipsychotic agents like haloperidol, whose principle mode of action is the antagonism of the dopamine-2 receptor subtype, are referred to as typical neuroleptics (Meltzer & McGurk, 1999). While effective in controlling the positive symptoms of schizophrenia, this class of antipsychotics is limited in its efficacy to alleviate the negative symptoms of the illness (Beasley et al., 1996; Marder & Meibach, 1994).

Unfortunately, typical antipsychotics have a propensity to cause unpleasant side-effects. These include sedation and blurred vision “which are often attributed to [their] antihistaminic and anticholinergic effects” (Spohn & Strauss, 1989, p. 368). Furthermore, because dopamine blocking agents not only affect the mesolimbic dopamine pathway but the nigrostriatal pathway as well (the principal pathway implicated in Parkinson’s disease), drug

induced parkinsonism often develops (Casey, 1993; Casey, 1997). Parkinsonism presents with extrapyramidal symptom (EPS) characterized by muscle rigidity, uncontrollable tremors and restlessness (Spohn & Strauss, 1989). According to Casey (1997), EPS is observed in up to 75% of patients treated with conventional antipsychotics. As a result, anticholinergic drugs such as benztropine and artane are often used to counteract these side-effects (Spohn & Strauss, 1989). Additionally, long-term treatment with typical agents has been associated with tardive dyskinesia (TD) (Labelle, 1997).

Atypical Neuroleptic Medications: Olanzapine

The limited efficacy and poor side-effect profiles associated with typical agents provided an impetus to develop better drugs for the treatment of schizophrenia. Recent drug development strategies have examined the combined activity of both dopamine and serotonin rather than primarily focusing on the role of dopamine. This new strategy is founded on the observation that clozapine (considered the prototypical atypical) (Beasley et al., 1996) is effective at reducing both the positive as well as the negative symptoms of schizophrenia without inducing EPS (Gerlach, 1991). In examining the mechanisms by which clozapine functions, receptor binding studies have demonstrated that clozapine has a much greater affinity for serotonin receptors relative to dopamine receptors – similar to dopamine receptors, several subtypes of serotonin receptors have also been identified (e.g., serotonin 1A-1E, 2A - 2C, 3A - 3C) (Meltzer & McGurk, 1999; Ohuoha, Hyde, & Kleinman, 1993). Using this pharmacological profile, a new breed of antipsychotic medications has been developed and is referred to as atypical antipsychotics. By definition, atypical antipsychotics such as olanzapine, risperidone, and clozapine are characterized by their ability to potently

block serotonin receptors relative to dopamine receptors and do not induce EPS at clinically appropriate doses (Beasley et al., 1996; Meert, de Haes, & Janssen, 1989; Meltzer & McGurk, 1999).

Mechanisms of Action

The mechanisms by which typical and atypical antipsychotic medications function to relieve the symptoms of schizophrenia are not well understood (Keefe, Silva, Perkins, & Lieberman, 1999). Given that blocking dopamine is effective in reducing psychotic symptoms, one would think that these symptoms result from an abundance of the dopamine neurotransmitter being present in the brain. However, this is not the case. Dopamine content is within normal limits in persons with schizophrenia (Seeman, 1995). Therefore, two hypotheses have been put forth to explain the prominent role of dopamine in schizophrenia. The first posits that there may be a dysregulation of the communication between dopamine-1 and dopamine-2 receptors. The dopamine-1 receptor has been found to regulate the activity of the dopamine-2 receptor and “with the ‘brakes’ removed on dopamine-2, the dopamine-2 receptor may then become overactive, leading to hallucinations and delusions” (Seeman, 1995). The second hypothesis proposes that there may be an abnormal elevation in the number of dopamine-2 and dopamine-4 receptors in the brains of persons with schizophrenia (Seeman, 1995). Dopamine-4 has also been implicated in the psychotic dimension of the illness (Lahti, Evans, Stratman, & Figur, 1993). This latter situation would also result in an over activity of dopamine in the brain (Seeman, 1995). There is support for both theories in the literature (Chua & McKenna, 1995; Dolan et al., 1997; Seeman, Guan, & Van Tol, 1993).

There are two major dopamine pathways in the brain. Dopamine neurons in the nigrostriatal pathway originate from the substantia nigra and project to the striatum, the thalamus and to the frontal cortex (Mega & Cummings, 1994; Snell, 1992). In the second dopamine pathway, the mesolimbic pathway, dopamine cells originate in the ventral tegmentum and project to the limbic system. Although found throughout the brain, the main areas of dopamine neuron concentrations are located in the frontal cortex (the dopamine-1 more so than the dopamine-2 type) (Nyberg et al., 1993; Sawaguchi & Goldman-Rakic, 1991), the cingulate gyrus, the striatum as well as in the entorhinal cortex (part of the medial temporal lobe) (Cohen & Servan-Schreiber, 1993).

While the positive symptoms of schizophrenia are hypothesized to result from a dysfunction of the mesolimbic system (Bogerts, 1997), several researchers have posited that the negative symptoms and the neurocognitive symptoms are related to a prefrontal cortical dysfunction (Goldman-Rakic & Selemon, 1997) (the differential effects of typical and atypical medications on neurocognition will be reviewed in the following section). Therefore, it is thought that the therapeutic effect that the typical antipsychotics have on positive symptoms results from the blockade of dopamine-2 receptors in the mesolimbic pathway (Gerlach, 1991; Kapur et al., 1996). Although typical antipsychotic medications have very little effect on negative symptoms and cognition (Keefe et al., 1999), animal studies provide evidence that dopamine does influence prefrontal cortical functioning. Cohen and Servan-Schreiber (1993) posit that “dopamine plays a modulatory role in the brain, by enhancing the ability of the neurons to transmit signals and reduce their distortion by noise” (p. 86). Indeed, minor changes in prefrontal cortical dopamine activity can result in impairments on frontal tasks

(Diamond, 1996). For example, Sawaguchi and Goldman-Rakic (1991) injected a dopamine-1 antagonist directly into the prefrontal cortex of monkeys while they performed a visuospatial delayed matching-to-sample task. They reported dose dependent declines in performance with higher doses. To determine if this effect was specific to reduced dopamine-1 receptor activity or if this effect could be observed by antagonizing other receptor types, they separately injected a selective dopamine-2 as well as a selective serotonin-2 antagonist in the prefrontal cortex. Both of these antagonists failed to produce the same impairments as observed with the dopamine-1 antagonist. A follow-up report by these same researchers (Sawaguchi & Goldman-Rakic, 1994) reported that haloperidol had similar effects on a visuospatial delayed matching-to-sample task as did the selective dopamine-1 antagonist. They explain this finding by indicating that, in addition to being a potent dopamine-2 antagonist, haloperidol also has a weak affinity for dopamine-1 receptors.

Receptor binding studies have revealed that the atypical agent olanzapine has a high affinity for serotonin-2A and serotonin-2C receptors and a relatively weaker affinity for dopamine-2 receptors (Moore, 1997). Serotonin-2 receptors have been found in the highest concentrations in the frontal cortex, nucleus accumbens, olfactory tubercle and the striatum; areas which coincide with brain regions rich in dopamine receptors (Oluoha et al., 1993). Keefe et al. (1999) state that it is extremely difficult to predict how atypical neuroleptics may exert their beneficial effects on cognition since medications such as olanzapine not only have affinities to serotonin-2A-2C and dopamine-2, they also influence many other neurotransmitter systems. Ellis and Nathan (2001) support this view. Their review of the literature implies that agonizing or antagonizing one neurotransmitter system can have effects

on other systems either directly or indirectly. For instance, GABA, the muscarinic cholinergic system and serotonin all influence dopamine activity in the prefrontal cortex. In addition, as mentioned above, dosing is important in that many systems have an inverted U dose-response function. Nevertheless, speculation on how atypical antipsychotics may exert their beneficial influence on both the positive and the negative symptoms as well as cognitive improvements continues to be anchored on the dopamine hypothesis. More specifically, it is thought that serotonin may modulate dopamine activity (Kahn & Davidson, 1993). For instance, Ohuoha and colleagues (1993) posit that the prefrontal cortex may be impaired in its ability to inhibit dopamine in the basal ganglia resulting in an overactivity of dopamine in the brain. The regulatory effect that atypical neuroleptics have on serotonin in the prefrontal cortex may result in the regulated inhibition of dopamine in the basal ganglia. Indirect evidence to this effect comes from an animal study which reported that the antagonism of serotonin-2 in the prefrontal cortex affected dopamine neuronal activity in the ventral tegmentum (origin of dopamine neurons involved in the mesolimbic pathway) (Palfreyman et al., 1993). “The ability of [atypical medications] to spare dopaminergic neurons in the striatum and to enhance dopaminergic output in the cortex may account for its ability to improve cognitive function compared with typical neuroleptics” (Sharma & Mockler, 1998, p.16S).

In summary, typical neuroleptics, such as haloperidol, are characterized by their ability to potently block dopamine-2 receptors while having almost no affinity for serotonin receptors. From a clinical perspective, these medications are effective at reducing the positive symptoms of schizophrenia but demonstrate little beneficial effects on the negative symptoms. Because this class of antipsychotics blocks dopamine in the nigrostriatal pathway, it has a

propensity to induce motor side-effects. Atypical medications are characterized by their ability to potently block both dopamine and serotonin receptors. They improve both the positive and negative symptoms of schizophrenia and do not induce motor side-effects at clinically appropriate doses.

Knowing that antipsychotic medications influence the positive and negative symptoms of schizophrenia, what effect do they have on cognitive functioning? The following sections will examine the effects of typical and atypical antipsychotic medications on neurocognitive functioning.

The Effect of Typical Neuroleptics on Neurocognition in Schizophrenia

Several review articles addressing the effect of typical antipsychotic medications such as chlorpromazine and haloperidol on neurocognition in schizophrenia have been published (Cassens et al., 1990; Hagger et al., 1993; King, 1990; Meltzer & McGurk, 1999; Sharma & Mockler, 1998, Spohn & Strauss, 1989). A summary of these reviews is provided below.

Researchers have examined the effects of typical neuroleptics on neurocognition in schizophrenia since the 1950's and articles reviewing this literature report several consistent findings. To begin, typical antipsychotics can produce decrements and improvements in attentional processes. Whereas the acute administration of typical neuroleptics results in poorer sustained and selective attention, their chronic administration can improve this cognitive domain (i.e., selective and sustained attention) (Oltmanns, Ohayon, & Neale, 1978). However, improvements never reach that of normal functioning and do not appear to enhance higher-order cognitive functions such as executive functioning or working memory (Cassens et al., 1990; King, 1990; Sharma & Mockler, 1998). Additionally, this class of antipsychotics

can negatively affect visuospatial abilities and verbal and non-verbal learning (Buchanan et al., 1994; King, 1990). Another consistent finding relates to a dose dependent relationship between impairments on motor tasks with elevated doses of typical agents causing greater impairment (Cassens et al., 1990; King, 1990). For example, Cassens et al. (1990) report that low doses of chlorpromazine (up to 150 mg/day) do not affect performance on Finger Tapping whereas doses between 200 and 300 mg/day will significantly reduce tapping performance. In addition to motor speed, Cassens et al. state that tasks involving fine motor movements are susceptible to elevated doses of chlorpromazine (e.g., line tracing).

To summarize, other than improving some aspects of attention (sustained and selective) with chronic administration, typical neuroleptic medications have little beneficial effect on neurocognition.

The Effects of Atypical Antipsychotics on Neurocognition in Schizophrenia

Until very recently, it was thought that the negative and neurocognitive deficits of schizophrenia were not amenable to pharmacological treatment. However, this notion has been challenged with the introduction of atypical antipsychotic medications. As previously discussed, this class of medications is effective in the alleviation of the positive and some negative symptoms of schizophrenia. According to Voruganti et al. (1997), increased negative symptoms tend to coincide with more severe neurocognitive deficits. Given this relationship, there is reason to believe that atypical medications may also improve neurocognitive functioning (Andreasen, 1985).

At present, there are 28 published reports on the effects of atypical medications on neurocognition in schizophrenia. Twelve of these studies examined the effects of clozapine:

two are double-blind (Buchanan et al., 1994; Potkin, 2001), one used a cross-over design (Daniel et al., 1996), and the remainder were open-label (Classen & Laux, 1988; Fujii, Ahmed, Jokumsen, & Compton, 1997; Galletly, Clark, McFarlane, & Weber, 1997; Goldberg et al., 1993a; Grace et al., 1996; Hagger et al., 1993; Lee, Thompson, & Meltzer, 1994; Lindenmayer et al., 1998; Meyer-Lindenberg et al., 1997; Purdon, Labelle, & Boulay, 2001; Zahn, Pickar, & Haier, 1994). Seven studies examined the effects of risperidone on neurocognition in schizophrenia: five were double-blind (Green et al., 1997; Green et al., 2002; Kern et al., 1998; Kern et al., 1999; Liu, Chen, Chang, & Lin, 2000; McGurk et al., 1997) and two were open label (Rossi et al., 1997; Stip & Lussier, 1996). There are only three reports on the effects of olanzapine on neurocognition. Two were double-blind (Purdon et al., 2000; Smith, 2001) and the other was open-label (Stip et al., 2002). Three studies examined the effect of quetiapine; two were double-blind randomized trials (Purdon, Malla, Labelle, & Lit, 2001; Velligan et al., 2002) and the third was an open label study (Sax, Strakowski, & Keck, Jr., 1998). In addition, one study examined clozapine, olanzapine, risperidone and haloperidol over a 2 year period (Bilder et al., 2002).

These studies will be discussed within the context of specific cognitive domains: (1) psychomotor functions, (2) visuoperceptual/motor processing, (3) memory, (4) executive functions, and (5) attention.

Before proceeding, six points about study design are warranted. First, across studies, baseline assessments were conducted under various medication conditions. One study did not specify baseline medications (Grace et al., 1996; Potkin, 2001). Some studies assessed patients while they were receiving typical antipsychotic medications (Buchanan et al., 1994;

Fujii et al., 1997; Goldberg et al., 1993a; Purdon, Labelle, & Boulay, 2001; Stip & Lussier, 1996; Velligan et al., 2002), atypical antipsychotics (Daniel et al., 1996) or a mix of typical and atypical medications at baseline (Galletly et al., 1997; Smith, 2001; Stip et al., 2002; Zahn et al., 1994). Other studies assessed patients after they had been washed-out from typical neuroleptics (Green et al., 1997; Hagger et al., 1993; Kern et al., 1998; Kern et al., 1999; Lee et al., 1994; Lindenmayer et al., 1998; Meyer-Lindenberg et al., 1997) or a mix of typical and atypical antipsychotics (Liu et al., 2000; Meyer-Lindenberg et al., 1997; Purdon et al., 2001; Rossi et al., 1997; Sax et al., 1998) for periods ranging from 4 to 9 days. One study assessed patients when they were tapered down from their typical or atypical medications and subsequently washed-out for a 2 to 9 day period (Purdon et al., 2000).

Second, antiparkinsonism medications such as benztropine and artane were often prescribed to control motor side-effects. Antiparkinsonism drugs are known to negatively impact new learning, long-term memory, procedural learning, and working memory (Frith, 1997; Spohn & Strauss, 1989; Rusted, 1988; Rusted & Warburton, 1988). In fact, only one (Hagger et al., 1993) of the 21 studies examining the effects of atypical medications on neurocognition prohibited the use of any psychotropic concomitant medications. Another study covaried anticholinergic medication use or non-use with neurocognitive results (Velligan et al., 2002) and Liu et al. (2000) did not allow adjunctive medications within 24 hours of cognitive testing.

Third, control groups within studies differed significantly. Fourteen studies contrasted the effects of atypical antipsychotics with typical neuroleptics (Buchanan et al., 1994; Classen & Laux, 1988; Green et al., 1997; Green et al., 2002; Kern et al., 1998; Kern et al., 1999; Lee

et al., 1994; Liu et al., 2000; Potkin, 2001; Purdon et al., 2000; Purdon et al., 2001; Smith, 2001; Velligan et al., 2002; Zahn et al., 1994), four contrasted different atypical medications (Bilder et al., 2002c; Daniel et al., 1996; Lindenmayer et al., 1998; Purdon et al., 2000), two incorporated normal controls (Meyer-Lindenberg et al., 1997; Sax et al., 1998) and nine did not have any control groups (Fujii et al., 1997; Galletly et al., 1997; Goldberg et al., 1993a; Grace et al., 1996; Hagger et al., 1993; Purdon et al., 2001; Rossi et al., 1997; Stip et al., 2002; Stip & Lussier, 1996).

Fourth, the time of the first reassessment after baseline assessments was vastly different across studies. One study did not conduct any baseline neurocognitive assessments and reassessed patients once after 7 days of treatment (Classen & Laux, 1988), another assessed patients weekly on seven occasions beginning at day 2 (Meyer-Lindenberg et al., 1997) and another after 1 week (Liu et al., 2000). Four studies reassessed patients after 1 month of treatment (Green et al., 1997; Kern et al., 1998; Kern et al., 1999; Rossi et al., 1997), seven after 6 weeks of treatment (Daniel et al., 1996; Hagger et al., 1993; Lee et al., 1994; Potkin, 2001; Purdon et al., 2000; Stip et al., 2002; Zahn et al., 1994), three after 8 weeks (Purdon et al., 2001; Smith, 2001; Stip et al., 2002), one after 10 weeks of treatment (Buchanan et al., 1994), one after 3 months of treatment (Lindenmayer et al., 1998), two after 6 months (Purdon et al., 2001; Velligan et al., 2002), and two after 1 year of treatment (Grace et al., 1996; Purdon et al., 2000). Due to the variability in the time of reassessment in four studies, a strict reassessment time tag cannot be determined (Fujii et al., 1997; Galletly et al., 1997; Goldberg et al., 1993a; Stip & Lussier, 1996). In addition, the number of reassessments after baseline assessments differed across studies. Ten investigations only

reassessed patients once after baseline assessments (Daniel et al., 1996; Fujii et al., 1997; Galletly et al., 1997; Goldberg et al., 1993a; Lindenmayer et al., 1998; Liu et al., 2000; Purdon et al., 2001; Rossi et al., 1997; Velligan et al., 2002; Zahn et al., 1994). Nine reassessed patients twice after baseline assessments (Buchanan et al., 1994; Goldberg et al., 1993a; Kern et al., 1998; Kern et al., 1999; Potkin, 2001; Purdon et al., 2001; Sax et al., 1998; Smith, 2001; Stip & Lussier, 1996), three studies reassessed patients on three occasions after baseline assessments (Grace et al., 1996; Lee et al., 1994; Purdon et al., 2000) and one study assessed patients seven times after baseline (Meyer-Lindenberg et al., 1997).

Fifth, a heterogeneity with respect to the duration of illness within and between studies exists. For instance, only one study included patients whose duration of illness was less than 5 years (Purdon et al., 2000). One study examined patients who had an average duration of illness of 6 years, one of 8 years (Liu et al., 2000), one of 10 years (Galletly et al., 1997), one of 11 years (Daniel et al., 1996), 3 of 12 years (Goldberg et al., 1993a; Purdon et al., 2001; Velligan et al., 2002), one of 13 years (Zahn et al., 1994), two of 14 years (Buchanan et al., 1994; Hagger et al., 1993), and two of 16 years (Potkin, 2001; Purdon et al., 2001). Five studies included patients who were ill for an average of more than 18 years (Green et al., 1997; Kern et al., 1998; Kern et al., 1999; Lindenmayer et al., 1998; Smith, 2001) while eight studies did not provide any information about duration of illness (Classen & Laux, 1988; Fujii et al., 1997; Grace et al., 1996; Lee et al., 1994; Rossi et al., 1997; Sax et al., 1998; Stip et al., 2002; Stip & Lussier, 1996). Finally, one study included patients with an extraordinarily large range in duration of illness (3 to 21 years) (Goldberg et al., 1993a).

Sixth, while the majority of studies included patients who were treatment resistant (Daniel et al., 1996; Fujii et al., 1997; Goldberg et al., 1993a; Grace et al., 1996; Green et al., 1997; Hagger et al., 1993; Kern et al., 1998; Kern et al., 1999; Lindenmayer et al., 1998; Meyer-Lindenberg et al., 1997; Potkin, 2001; Purdon et al., 2001; Smith, 2001), only a handful included patients who were treatment responsive (Buchanan et al., 1994; Lee et al., 1994).

Psychomotor Functioning

Given the preponderance of evidence which clearly shows that atypical medications are superior to traditional antipsychotics for reducing EPS (Beasley et al., 1996; Chouinard & Arnott, 1993), it is surprising to note that only four studies have examined the influence of atypical medications on psychomotor functions. One examined the effects of clozapine (Classen & Laux, 1988), one the effects of risperidone (Kern et al., 1998), another the effects of both risperidone and olanzapine (Purdon et al., 2000) and finally, one on the effects of quetiapine (Purdon et al., 2001).

Psychomotor performance is typically assessed with tasks which place minimal demands on 'thinking' or cognition. The Grooved Peg Board and Finger Tapping tests are among the most widely used instruments to assess fine motor movements and motor speed. Both of these tasks do not require any kind of higher-order cognitive processing (Lezak, 1983; Spreen & Strauss, 1991). The Grooved Peg Board requires subjects to place several pegs with grooves into holes which have matching grooves. The dependent variable for this task is the time to completion. Similar to the Grooved Peg Board is a task called the Pin Test (Kern et al., 1998). This test requires subjects to push a pin through several holes as quickly

as possible in a thirty second period. The dependent variable for this test is the number of holes punched.

Motor speed is measured with the Finger Tapping test. This test requires subjects to tap with their index finger as many times as possible within 10 seconds. This procedure is repeated several times for each hand and the mean number of taps serves as the dependent variable. In addition to these well known motor instruments, a lesser known task called the Line-tracing Task has been used by Classen and Laux (1988) to examine the effects of clozapine on motor precision in schizophrenia. This task measures the ability to accurately trace over a line as quickly as possible. The number of deviations from the line as well as the time to completion are the two dependent variables.

Clozapine. The influence of clozapine on psychomotor performance was investigated using a between group design which compared it to haloperidol and fluphenazine; both typical neuroleptics (Classen & Laux, 1988). Patients in this study were assessed after 7 days of treatment. Results demonstrated no differences between clozapine and typical antipsychotics on the Line-tracing Task or the Grooved Peg Board. The significance of these findings is difficult to interpret given that patients were assessed once and that exposure to treatment lasted only 7 days. As will be illustrated in subsequent sections, clozapine's effects on other neurocognitive parameters only occur after several weeks of therapy. Therefore, a longer treatment duration may have yielded different results. Additionally, EPS was not assessed using a standard instrument such as the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard, Ross-Chouinard, Annable, & Jones, 1980). Therefore, it is impossible to determine if the lack of improvement on psychomotor tasks was related to a lack of

improvement on EPS. Finally, there were only 10 cases in the clozapine group compared to 25 in the haloperidol group and 15 in the fluphenazine group. Therefore, the power to detect significant findings was most likely inadequate. Given these limitations, this study yields little useful information about the effect of clozapine on psychomotor functioning.

Risperidone. A double-blind study by Kern et al. (1998) examined risperidone and haloperidol over 8 weeks of treatment on the Pin Test. Within group analyses, comparing baseline assessments after a 3 to 7 day washout from haloperidol to performance after 8 weeks of risperidone treatment, revealed that the total number of holes punched was significantly higher with risperidone treatment and that there was no change in performance with haloperidol treatment. A between group comparison of percent improvement over 8 weeks of treatment demonstrated that the risperidone group improved to a greater degree than the haloperidol group. Unlike Classen and Laux's (1988) investigation, this study did evaluate EPS using the ESRS and determined that both the risperidone and haloperidol groups did not differ on motor side-effect symptoms after 8 weeks of treatment. The authors attribute this finding to the use of antiparkinsonism medications throughout the study by both groups. An analysis of covariance revealed that improved performance on the Pin Test by the risperidone group was not related to EPS.

Despite these positive findings, risperidone's effect on the Pin Test is difficult to determine due to several methodological limitations inherent in Kern et al.'s (1998) study. Prior to baseline assessments and treatment randomization, all patients were treated with haloperidol for 3 weeks and then washed-out for 3 to 7 days. As a result, the positive findings associated with risperidone and not haloperidol on psychomotor functioning may

reflect the discontinuation of haloperidol rather than actual improvements related to risperidone. Additionally, the absence of a normal control group makes it difficult to rule out practice and learning effects in the risperidone group. As such, the only conclusion which can be drawn from this study is that risperidone may improve psychomotor performance on the Pin Test.

Although Purdon et al. (2000) did not use the Pin Test, their findings suggest that fine manual dexterity is not enhanced with risperidone treatment. Purdon et al.'s analyses are based on data from the Last Observation Carried Forward (LOCF). Patients who were not able to complete the 54 week trial had their data from their last assessment carried forward to the end-point visit. Using the Grooved Peg Board as their measure of fine manual dexterity, a within-group analysis revealed that there was no significant improvement from baseline assessments to end-point. The same was observed for those treated with haloperidol. Although there was a decrement in performance in this group, it was not statistically significant. In addition, comparisons in change scores (the magnitude of change from baseline to end-point) between those treated with risperidone and those treated with haloperidol showed that both groups did not differ on the Grooved Peg Board.

Purdon et al.'s (2000) study also investigated psychomotor speed using the Finger Tapping test. Within group analyses revealed no improvements in performance for either the risperidone or haloperidol treated groups from baseline to end-point. Similar to the finding for the Grooved Peg Board, a non-statistically significant decrement in performance was observed for the haloperidol treated group. Additionally, there was no difference in change scores from baseline to end-point between the risperidone and haloperidol groups.

The contrast between Purdon et al.'s study and Kern et al.'s study in manual dexterity may be related to baseline antipsychotic medication. Unlike Kern et al.'s design, Purdon et al.'s study slowly withdrew patients from their antipsychotic medications over a 1 month period. Purdon et al. did not specify the types of antipsychotic medications received by patients during this phase. When patients reached the lowest possible therapeutic dose, they were completely withdrawn from their medications for a 2 to 9 day period after which baseline assessments were conducted. Given this lead-in phase, it can be assumed that the influence of previous antipsychotic treatment on baseline neurocognitive assessments was less in this study compared to Kern et al.'s study. This supports the notion that withdrawing patients from haloperidol rather than risperidone treatment may have been responsible for the positive effects reported by Kern and colleagues.

Olanzapine. Purdon et al.'s (2000) study is the only published report examining the effect of olanzapine on psychomotor functioning. Within group LOCF analyses demonstrated that treatment with olanzapine was associated with improved performance on the Grooved Peg Board and the Finger Tapping Test from baseline to endpoint. Pairwise analyses contrasting the change scores between olanzapine and haloperidol revealed that olanzapine was superior to haloperidol on the Finger Tapping test as well as on the Grooved Peg Board. Purdon et al. examined the influence of EPS within the context of a general index of cognitive functioning (one score reflecting several neurocognitive domains). Therefore, it is not possible to isolate the influence of EPS associated with risperidone, haloperidol or olanzapine on psychomotor performance.

Quetiapine. The only study to investigate the effect of quetiapine on psychomotor functioning in schizophrenia was conducted by Purdon and colleagues (2001). Their 6 month trial was double-blind and all patients were washed out from their previous medications for a minimum of 48 hours. At the end of the washout period, patients were randomly assigned to treatment with either quetiapine (300 to 600 mg/day) or haloperidol (10 to 20 mg/day). Dosing was flexible and the duration of treatment was 6 months with very little variability in test-retest intervals between patients.

Neurocognitive assessments were repeated 8 weeks after the initiation of treatment and again 6 months later. Because of the small sample size and high attrition rates, particularly among the group randomized to haloperidol, between group analyses were not performed. Both the Grooved Peg Board and the Finger Tapping test were administered. Overall, there were absolutely no within group differences in performance for either the quetiapine or the haloperidol groups on both motor tasks. A lack of significant findings may be as a result of the baseline medication. Because a mix of patients entered the trial on typical or atypical medications, any potential changes associated with either medication may have been negated.

Atypicals versus atypical. The only report contrasting atypical agents was published by Purdon et al. (2000). As already mentioned, olanzapine was compared to risperidone in a 12 month double-blind trial. Pairwise analyses contrasting the change scores between olanzapine and risperidone revealed that olanzapine was superior on the Finger Tapping test as well as the Grooved Peg Board.

Summary. Too little information is currently available to comment on clozapine's effectiveness on psychomotor functioning. The two studies addressing the effect of risperidone on fine motor movement are contradictory. The same is true for differences between risperidone and haloperidol. While Kern et al.'s (1998) study reports a superiority of risperidone over haloperidol, Purdon et al.'s (2000) study does not. Nevertheless, in considering both studies, Purdon et al.'s was better designed and suggests that risperidone has little influence on psychomotor performance. However, to clarify this issue, future investigations will have to properly control for baseline antipsychotic medications and incorporate appropriate control groups (such as placebo). Finally, the only study to investigate olanzapine on psychomotor tasks showed that this compound may positively influence performance on fine manual dexterity and psychomotor speed. These preliminary data also suggest that olanzapine is superior to both risperidone and haloperidol on psychomotor tasks. However, this finding will have to be replicated before it can be determined with any degree of certainty that olanzapine does have beneficial effects on psychomotor performance. In considering quetiapine, a single report indicates that this medication does not influence, either positively or negatively, performance on either the Grooved Peg Board or Finger Tapping.

Visuoperceptual/Motor Processing

Visuoperceptual and motor processing tasks are somewhat different than tasks of psychomotor functioning. As already mentioned, psychomotor tasks isolate motor functioning from higher-order cognitive processing. However, visuoperceptual and motor processing tasks require some higher-order cognitive functioning in addition to motor

functioning. According to Meltzer and McGurk (1999), the two most frequently used tasks for examining visuoperceptual and motor processing abilities in schizophrenia research are the Trail Making Test Part A (Trails A) (Lezak, 1983) and Digit Symbol Substitution Test (Wechsler, 1981). The Trails A test requires subjects to connect a series of randomly placed numbers on a page in ascending sequence as quickly as possible. The time required to complete this task is the dependent variable. The Digit Symbol Substitution Test requires subjects to match numbers with unique corresponding symbols as quickly as possible in 90 seconds. The procedures for this task are as follows: a sheet of paper with several squares is placed in front of the subject. Each of these squares contains a number and a blank square directly below. A key at the top of the page provides the subject with the number and symbol combinations. Their task is to draw the corresponding symbol for each number in the blank square. The dependent variable for this task is the number of correctly placed symbols in a 90 second period. Because the successful completion of the Digit Symbol Substitution Test relies on several cognitive abilities, it should be noted that this test also measures psychomotor speed, memory, sustained attention, and executive functioning.

Clozapine. A total of seven studies have examined the effects of clozapine on the Digit Symbol Substitution Test. However, Potkin et al. (2001) only reported results for WAIS-R indices without examining individual subscale tasks. Therefore, their study provided no information on the effect of clozapine on the Digit Symbol Substitution Test. Of the remaining studies, two reported negative findings. Goldberg et al.'s (1993) open-label flexible dose study failed to detect improvements on the Digit Symbol Substitution Test in a group of chronic treatment-resistant patients. Considering this study's design, this negative

finding is not surprising. The heterogeneity across reassessment intervals ranged from 3 months to 2 years. Therefore, the inclusion of patients exposed to clozapine for short periods with those who received the drug for extended periods may have negated any positive results. Along the same line, the mean duration of illness in this study was 12 years and ranged from 3 to 21 years. As mentioned in the introduction, neurocognitive declines occur over the first 10 years of illness and then stabilize. Because the Digit Symbol Substitution Test is a sensitive non-specific measure of cognitive compromise, it could be expected that patients in the early phase of their disease (within first 10 years) may perform better on this task than those in a later phase. A second study examining the influence of clozapine on the Digit Symbol Substitution Test by Lindenmayer and colleagues (1998) also failed to observe changes over 3 months of treatment. The authors attribute this finding to the short duration of the trial.

Hagger et al. (1993) reported no improvement on the Digit Symbol Substitution Test after 6 weeks of clozapine treatment whereas significant gains were apparent at 6 months. Although the negative finding at 6 weeks supports the notion that exposure to clozapine for short periods may not influence neurocognition, the lack of any control groups in this study makes it impossible to conclude that 6 months of clozapine therapy was responsible for improvements on the Digit Symbol Substitution Test. Given that subjects were exposed to the Digit Symbol Substitution Test on three occasions, improvements in this task may simply reflect practice effects. In fact, this test can also be used clinically as an indicator of incidental learning (Lezak, 1995). To their credit, Hagger et al. attempted to address the issue of practice effects. They reported on a pilot study wherein they examined the performance of

a separate group of 9 patients stabilized with clozapine treatment for at least 1 year. Patients in the pilot study were assessed twice over a 3 week period. Result revealed that there was no difference on the Digit Symbol Substitution Test from baseline to 3 weeks. However, this result cannot be generalized to that of the central study for several reasons. First, the treatment durations are completely incompatible. Second, patients in the central study were being withdrawn from typical agents whereas subjects in the pilot study had been receiving clozapine for over a year. Finally, patients in the central study were exposed to the Digit Symbol Substitution Test three times, not twice as in the pilot study. In summary, the possibility of practice effects on the Digit Symbol Substitution Test at 6 months remains.

Every other study reporting positive findings with respect to improved performance on the Digit Symbol Substitution Test as a result of clozapine therapy do so in the absence of control groups. For instance, Galletly and colleagues (1997) also reported an improvement on the Digit Symbol Substitution Test when contrasting performance at baseline with performance after an average of 6 months of clozapine therapy. Similar to Hagger et al.'s (1993) study, Galletly et al.'s study lacked control groups. Therefore the possibility of practice effects in this study cannot be ruled-out. In addition, Fujii et al. (1997) also observed improvements on the Digit Symbol Substitution Test after 12 to 16 months of clozapine therapy. However, this observation is based only on subjects who completed the study (10 of 22), thus biasing the sample. Moreover, this open-label within group study did not have any control groups; leaving the possibility that enhanced performance on the Digit Symbol Substitution Test reflects practice effects. Another study examining the effect of clozapine on the Digit Symbol Substitution Test was conducted by Grace et al. (1996). They too

observed significant gains over 3 years of clozapine therapy. However, similar to the studies just reviewed, the present study did not incorporate any control groups in the design. In fact, subjects in this study were exposed to the same assessment instruments four times over 3 years. Grace et al.'s conclusion, based on a repeated-measures analysis, that the Digit Symbol Substitution Test improved over time as a result of clozapine therapy is ill-conceived. More recently, Purdon et al. (2001) also examined psychomotor functioning using the Digit Symbol Substitution Test. This was an open label, 8 week trial of treatment resistant patients who had been ill for an average of 16 years. All 18 patients, with the exception of 1 who was unmedicated at the time of baseline assessments, were receiving a mixture of psychotropic and concomitant medications throughout the study. Purdon and colleagues determined that there was a significant improvement in performance on the Digit Symbol Substitution Test. However several issues prevent conclusions regarding clozapine's role in this finding. First, practice effects cannot be ruled-out since control groups were not used. Second, because the vast majority of patients were receiving typical as well as other concomitant medications at baseline assessments, any improvement may have been as a result of medication changes over the 8 week trial. Finally, significant reduction in parkinsonism symptoms were observed using the ESRS at end point. Since performance on the Digit Symbol Substitution Test is reliant on psychomotor abilities, improvement on this measure may have been related to improved motor side-effects.

In considering the differential effect of clozapine with typical neuroleptics, Lee et al. (1994) reported that 1 year of clozapine treatment was associated with better performance on the Digit Symbol Substitution Test. Although this study was a parallel group study where

patients were randomly assigned to clozapine or typical neuroleptic treatment, it must be noted that treatment was not blinded. Additionally, since patients were assessed on the same measures four times over 1 year, a normal control group should have been included to determine if the improvement on the Digit Symbol Substitution Test was related to practice effects. The only two studies which report on the effect of clozapine on the Trails A test report contradictory findings. Fujii et al. (1997) reported no improvement in time to completion over 1 year of treatment. In fact, there was a non-significant decline in performance. However, it is not possible to determine if clozapine was responsible for this decline given the lack of control groups. A study with a longer treatment duration conducted by Grace et al. (1996) observed gains on this task over a 3 year period. Grace et al.'s significant finding can be explained by the fact that their group of patients were very slow in completing this task at baseline (77 seconds) in contrast to Fujii et al.'s group (32 seconds). Therefore, Grace's group of patients had more opportunity to improve on this task. Despite this positive finding, concluding that clozapine could be responsible for enhanced performance on the Finger Tapping test cannot be made for two reasons: (a) faster performance in Grace's study may simply be attributable to switching subjects from older typical neuroleptics to clozapine and (b) subjects were exposed to the Trails A task four times over a 3 year period, leaving the possibility that enhanced performance may be attributable to practice and learning effects. Because there were no control groups in this study, this latter point cannot be commented on further.

At present, there are no studies which have contrasted the effects of clozapine with typical neuroleptics on the Trails A test.

Risperidone. Three studies examined the effect of risperidone on the Digit Symbol Substitution Test. The only study to report an improvement on the Digit Symbol Substitution Test was conducted by Rossi et al. (1997). This observation is based on a comparison between baseline performance with performance after 4 weeks of risperidone therapy in a single group of subjects. Although statistically significant, it must be noted that the actual gains on this task were modest. Nevertheless, the authors conclude that “even though risperidone was used in a short-term treatment, its efficacy in reducing cognitive abnormalities has been demonstrated” (p. 42). On the contrary, risperidone’s efficacy has not been demonstrated for two reasons. To begin, all but 3 of the 25 subjects in this study were receiving typical antipsychotic medications at baseline neurocognitive assessments. Therefore, the withdrawal of typical neuroleptic treatment, and not risperidone, may have been the determining factor in the observed improvements on the Digit Symbol Substitution Test. In addition, once again, the possibility that improvements may be related to learning and practice effects must be considered given an absence of control groups.

Lindenmayer and colleagues (1998) also investigated the effect of risperidone on the Digit Symbol Substitution Test and reported a non-significant decline in performance over 12 weeks of treatment. Much like the other studies reviewed, this study is methodologically flawed and only provides information about the effect of elevated doses of risperidone on visuomotor and motor processing tasks. By the end of the 12 week treatment period, the mean daily dose of risperidone was greater than 9 mg/day, a dose higher than the recommended amount of 4 to 6 mg/day. The literature has demonstrated that there is a dose dependent relationship between EPS and risperidone dosage. As a result, EPS induced by

higher doses of risperidone require treatment with anticholinergic medications which can negatively affect neurocognitive performance (Marder & Meibach, 1994).

Using more clinically appropriate doses of risperidone (mean daily dose was 6 mg/day) Purdon and his group (2000) observed absolutely no difference in performance on the Digit Symbol Substitution Test from baseline to end point (LOCF). Furthermore, there was no difference between risperidone and haloperidol. However, it must be noted that Purdon's sample consisted of early psychosis patients (within their first 5 years of illness) whereas the study by Lindenmayer et al. (1998) examined patients who were treatment-resistant and who had a mean duration of illness of 18 years. As such, the effect of appropriate doses of risperidone on the Digit Symbol Substitution Test in a more chronic schizophrenia population remains to be determined.

At present, there are no reports with regard to the effect of risperidone on the Trails A test.

Olanzapine. Although not significant, a trend toward improvement on the Digit Symbol Substitution Test with olanzapine treatment was reported by Purdon et al. (2000) when contrasting baseline assessments with LOCF data. Also, there was no difference between olanzapine and haloperidol on this task. Stip et al.'s (2002) open-label trial found that the time required to complete the Trails A test significantly declined over 8 weeks of treatment with olanzapine. However, because there were no control groups in this study, it is difficult to determine if improvements were due to the medication or practice and learning effects.

Quetiapine. Two studies have reported on the effect of quetiapine on the Digit Symbol Substitution Test (Purdon et al., 2001; Velligan et al., 2002). Both were double-blind randomized trials using haloperidol as the comparison medication. Purdon et al's (2001) flexible dose study contrasted the effect of quetiapine (300 to 600 mg/day) and haloperidol (10 to 20 mg day) in a group of schizophrenia patients who had a mean duration of illness of 12 years. Due to a high attrition rate (56% overall), between treatment contrasts were not possible. Within group analyses on the Digit Symbol Substitution Test were conducted between baseline performance and LOCF data. Without alpha being corrected for multiple comparisons, a significant within group difference on the Digit Symbol Substitution Test was observed for quetiapine as well as for haloperidol ($p = .049$). The statistical significance for both was negated when Bonferroni corrections were applied. One of the main issues making the interpretation of these results difficult is the high attrition rate in the haloperidol group. Of the 25 patients entered into this study, 13 were randomized to quetiapine and 12 to haloperidol. Of the 13 in the quetiapine group, 9 completed the 6 month trial. Of the 12 patients randomized to haloperidol treatment, only 3 were able to complete the 6 month trial. Therefore, when examining LOCF data, it is clear that the data set for the quetiapine group is comprised of more patients having had three exposures to the Digit Symbol Substitution Test in contrast to the haloperidol group. Therefore, the within group differences observed may reflect practice and learning effects.

The second study to contrast quetiapine with haloperidol was conducted by Velligan and colleagues (2002). Data analysis for this study is based on completer data only, meaning that 58 patients of 116 completed the full 24 week trial. Baseline assessments were

conducted while all patients were receiving an average of 9.2 mg/ day of haloperidol. Follow-up assessments were completed after 24 weeks of double-blind randomized treatment with either 600 mg/day of quetiapine or 12 mg/day of haloperidol. Rather than using the traditional Digit Symbol Substitution Test, Velligan et al. used the Symbol-Digit Substitution test. In this task, subjects are required to write the numbers which correspond to the symbols. They found no between group differences on this task over the 24 week trial. Within group analyses were not conducted.

At the present time, there is no published report on the effect of quetiapine on the Trails A test.

Atypicals versus atypicals. Two studies which have examined the differential effects of atypical antipsychotic agents on the Digit Symbol Substitution Test have reported no difference between treatments. Lindenmayer et al. (1998) contrasted the effects of clozapine and risperidone on the Digit Symbol Substitution Test over 12 weeks of treatment and failed to observe significant differences between these two atypical medications. The only other study to contrast the effects of atypical medications on the Digit Symbol Substitution Test was conducted by Purdon et al. (2000). These researchers compared the effects of olanzapine and risperidone and also reported no beneficial effect of one atypical over the other. No study has contrasted quetiapine with another atypical agent on either the Digit Symbol Substitution Test or the Trails A test.

Summary. Four of seven studies examining the contribution of clozapine on visuoperceptual and motor processing tasks reported positive effects. Despite these positive results, methodological flaws inherent in each of these studies prohibit the conclusion that

clozapine definitely enhances performance in this neurocognitive domain. At most, it can be concluded that inadequately controlled preliminary clinical studies suggest that clozapine may enhance performance on visuoperceptual and motor processing abilities.

Limited data with regard to risperidone as well as olanzapine suggest that these atypical medications have few effects on visuoperceptual/motor processing. With regard to quetiapine, one report found a significant improvement whereas the other did not. As such, the potential influence of quetiapine on visuoperceptual/motor processing is undetermined.

Two studies examined the effect of quetiapine versus haloperidol on the Digit Symbol Substitution Test. One provided within group information and the other between group information. There does not appear to be any advantage of quetiapine over haloperidol on visuoperceptual/motor processing tasks. Within groups, it is difficult to determine from the Purdon et al. (2001) study if those randomized to quetiapine actually performed better over time on this task relative to the haloperidol group, or if this result is due to one additional exposure to the task in the quetiapine group.

Studies which have contrasted atypical medications with typical medications have revealed that both clozapine and olanzapine significantly improve these measures relative to typical medications. No benefit of risperidone over haloperidol has been reported and incomplete information regarding quetiapine prohibits making concrete conclusions. Lastly, contrasts between atypical medications have shown that these agents impact this neurocognitive domain equally.

Memory

Tests which examine memory functioning are typically classified into those which assess verbal and visual memory. The most commonly used tests in research investigating the effects of atypical medications on verbal memory in schizophrenia are: (1) verbal list learning (Rey Auditory-Verbal Learning Test) (Spreen & Strauss, 1991); the California Verbal Learning Test, (Delis, Kramer, Kaplan, & Ober, 1987); the Hopkins Verbal Learning Test (Brandt, 1991), (2) memory for paragraphs (Logical memory from the WMS-R); (3) Verbal Paired Associates from the WMS-R; and (4) and Digit Span Forward from WMS-R or WAIS-R. It should be noted that the digit forward task is sometimes considered as a task of attention span (Purdon et al., 2000).

As the name suggests, verbal list learning refers to a subject's ability to remember a list of words over several trials. Immediately after the presentation of each trial and after a 20 to 30 minute delay period, the subjects are required to recall as many words as they can in any order. Performance on this type of test is measured by the number of correctly recalled words on the first trial (immediate recall), the final learning trial (learning), and after a delay period (delayed recall). Memory for paragraphs (stories) requires the subject to listen to and recall a short paragraph verbatim. This type of test also assesses immediate and delayed recall. Verbal Paired Associates requires subjects to remember easy (related) words pairs over repeated trials and as well as difficult (unrelated) word pairs. An example of an easy word pair is 'metal - iron' and a difficult word pair is 'cabbage - pen'. When asked for the word which goes with 'metal', 'iron' is more easily recalled than is 'pen' as the word that goes with 'cabbage'. The two studies which examined Verbal Paired Associates used the

total number of correctly recalled easy and difficult word pairs over three learning trials as their dependent variable. The Digit Span Forward test simply requires subjects to immediately recall increasingly longer sequences of digits in the correct order. The dependent variable for this test is the total number of correctly recalled sequences.

The most commonly used visual memory tests are: (1) Figural Memory from the WMS-R; (2) memory for complex figures (such as the Rey-Osterrieth Complex Figure Test [Rey-O]; Spreen & Strauss, 1991); (3) Visual Reproduction from the WMS-R; and (4) Visual Paired Associates from the WMS-R. Figural Memory simply requires subjects to identify previously seen non-nameable figures among several foils. The dependent variable for this task is the total number of correctly identified figures. The Rey-O is a complex non-nameable figure. With the figure present, subjects are instructed to copy it as carefully as they can without having been told that they will have to recall it from memory immediately after they have finished. The dependent variables for the Rey-O are the total number of items correctly remembered in the immediate and delayed free-recall conditions. Visual Reproduction consists of four non-nameable figures. Each figure is presented individually to the subject for a 10 second learning period. After each presentation, the subject is instructed to reproduce the figure from memory. The dependent variables for this memory test are the total number of correctly recalled items from the four figures immediately after presentation and after a 30 minute delay. The Visual Paired Associates test is similar to the Verbal Paired Associates test with the exception that there is no easy/difficult distinction. Subjects are required to learn color and design pairs over trials. The two studies which examined Visual Paired Associates used the total number of correctly identified color - design pairs over three learning trials.

Clozapine. Eight studies have examined the effects of clozapine on memory. Findings with respect to verbal memory will be presented first. Goldberg and colleagues (1993), Purdon et al. (2001), as well as Potkin et al. (2001) administered the full WMS-R (Wechsler, 1987) to determine the effects of clozapine on memory. Goldberg et al.'s study was an open-label trial which assessed subjects at baseline while they were receiving typical neuroleptics and again after 3 to 24 months of clozapine therapy. These investigators reported that there were no within group differences on any of the verbal WMS-R subtests. This finding was not surprising given the significant methodological flaws inherent in this study. As previously mentioned, the heterogeneity in reassessment time (from 3 to 24 months) and in the duration of illness in their patient population (from 3 to 21 years) most likely hindered the possibility of observing significant findings.

Conversely, Purdon et al. (2001) did find significant within group improvements on certain measures of immediate as well as delayed free recall. These included verbal list learning as measured with the California Verbal Learning Test, WMS-R logical memory for paragraphs, and for the WMS-R Verbal Paired Associates. However, these gains may be related to a reduction in anticholinergic medications since there was a significant reduction in parkinsonism symptoms or to an exposure to the same material on two occasions.

Although Potkin et al. (2001) did not examine individual subtests from the WMS-R, they did report that clozapine was associated with improved performance on all global learning indices. They also stated that patients randomized to haloperidol improved and that there was no significant difference between groups. As such, it would seem that improvements in both groups could have been as a result of practice and learning effects.

Buchanan et al. (1994) conducted a double-blind 10 week trial examining the effect of clozapine and haloperidol on several neurocognitive parameters. Similar to Goldberg et al.'s (1993) study, this investigation failed to detect any significant improvements on verbal WMS-R subtests when comparing baseline assessments with those obtained after 10 weeks of clozapine or haloperidol treatment. Moreover, no between treatment difference on WMS-R measures were reported. The authors hypothesized that the relatively short duration of this trial may in part account for these negative findings. Buchanan et al. reexamined performance in a 1 year open-label clozapine extension study. Those originally assigned to clozapine therapy continued on this regimen and those assigned to haloperidol were treated with clozapine after the end of the 10 week double-blind phase. This open-label extension trial also failed to demonstrate any beneficial effects of clozapine on memory functioning. Buchanan and colleagues posit, and correctly so, that clozapine's anticholinergic effects may limit its ability to improve memory functioning. In keeping with these negative results, Lindenmayer et al. (1998) also found that clozapine had no positive effects on memory for paragraphs over 12 weeks of open-label clozapine treatment.

Despite these negative findings, improvements on learning lists of words with clozapine therapy have been reported by several authors (Hagger et al. 1993; Lee et al. 1994; Galletly et al. 1997; Grace et al. 1996; Potkin, 2001; Purdon et al., 2001). However, Hagger et al. (1993), Galletly et al. (1997), Grace et al. (1996) as well as Purdon et al. (2001) did not include comparison groups in their studies and alternative test forms were not used. Obviously, learning and practice effects must be considered given that subjects were exposed to the same list of words two (Galletly et al., 1997; Purdon et al., 2001), three (Hagger et al.,

1993), and four times (Grace et al., 1996). Supporting this notion is a study by Lee et al. (1994). They compared clozapine to various typical agents in a group of treatment resistant patients on verbal list learning over four periods. The same list of words was used at each assessment and within group improvements for both clozapine and typical neuroleptics were reported. There was no difference between treatment regimes. Potkin et al. (2001) found similar results in their study comparing clozapine and haloperidol. Therefore, the conclusion that clozapine (and typical neuroleptics in Lee's study) improves verbal list learning is premature. Rather, these findings merely demonstrate that patients with schizophrenia are able to learn the same list of words (not different lists of words) over testing sessions (not within testing sessions). Using alternative lists of words, Lindenmayer and colleagues (1998) did not observe improvements on list learning when performance at baseline was compared to performance after 12 weeks of clozapine therapy. Considered together, the results of these studies do not appear to warrant the conclusion that clozapine enhances verbal list learning.

With respect to memory for visual material, Goldberg et al. (1993) and Buchanan et al. (1994) reported no significant improvements on Figural Memory or Visual Paired Associates with clozapine therapy. As previously mentioned, the possibility of observing significant effects of clozapine on any neurocognitive parameters in Goldberg et al.'s study is hampered by the extreme variability in reassessment periods (ranging from 3 to 24 months) as well as the heterogeneity in the duration of illness in their patient sample. All the same, the likelihood that clozapine has no effect on Figural Memory or Visual Paired Associates is strengthened by Buchanan et al.'s study. In addition to examining performance in a group of clozapine treated subjects, they also assessed performance in a group of haloperidol

subjects. Within group analyses comparing performance at baseline with that after 10 weeks of treatment revealed that both clozapine and haloperidol did not enhance functioning on these visual memory tasks. Therefore, this study suggests that clozapine, as well as haloperidol, fails to improve visual memory abilities. To determine if the short duration of the trial may have accounted for these results, all patients were reassessed after 1 year. Results from the 1 year follow-up are based on all patients receiving clozapine. Patients randomized to the haloperidol arm of the study during the 10 week double-blind phase were switched to clozapine for a 1 year period. Results after 1 year revealed that clozapine continued to have little beneficial effect on Figural Memory and Visual Paired Associates. Purdon et al.'s (2001) open label trial also failed to observe any significant gains on immediate recall of non-Verbal Paired Associates. However, these researchers did observe significant gains on the immediate recall of novel figures. No improvements in delayed recall of non-verbal stimuli was detected. In considering memory for Visual Reproduction and memory for complex figures, it appears that clozapine does not benefit this cognitive domain. While Goldberg et al. (1993) observed decrements on immediate and delayed Visual Reproduction, Buchanan et al. (1994) as well as Lindenmayer et al. (1998) did not observe such decrements. Since Goldberg et al. did not include control groups in their study, it is difficult to determine the significance of the observed decrement in Visual Reproduction. It is interesting to note that, despite using the same stimuli over assessments, both Buchanan et al. as well as Lindenmayer et al. failed to observe enhanced performance which could be related to practice effects. In fact, Buchanan et al. included a haloperidol comparison group in their study and observed that they too failed to improve over two exposures to the same stimuli over 10

weeks. In addition, Lindenmayer et al. included a risperidone control group in their study. Like the clozapine group, the risperidone treated subjects were tested twice on the same visual material and failed to improve when performance at baseline was compared to performance after 12 weeks of therapy.

Unlike the two studies above, Grace and colleagues (1996) observed positive effects on the immediate recall of a complex figure over 3 years of clozapine treatment. It is understood that this positive result cannot legitimately be attributable to the effect of clozapine given that there were no control groups and that the same complex visual figure was used at each of the four assessment periods. Nonetheless, this result does provide some information about practice and learning effects for visual material. Schizophrenia patients may require several exposures over testing session to the same stimuli before they begin to benefit from practice effects.

Risperidone. While none of the six studies investigating the effects of risperidone on memory administered a complete memory battery, findings suggest that risperidone has little beneficial influence on verbal memory. Stip and Lussier's (1996) open-label flexible dose study contrasted the performance of one group of patients who were receiving various typical neuroleptics at baseline with their performance after an average of 58 days (range from 42 to 90 days) and again after an average of 171 days (range from 138 to 212) of risperidone treatment. These investigators reported that there was no beneficial effect of risperidone on list learning over time. However, several methodological issues negate drawing any conclusions about risperidone's role on verbal list learning. To begin, the small sample size ($N = 13$) as well as the variability in test-retest intervals may have contributed to a Type II

error. Also, control groups were not included in the design and alternative forms for the list learning test were not used. The only conclusion which can be drawn from this study is that there was no improvement for learning the same list of words over repeated – but variable – time intervals.

Lindenmayer et al.'s (1998) open-label study as well as Purdon et al.'s (2000) double-blind study did use alternative test versions to examine the effect of risperidone on list learning. Lindenmayer and colleagues reported that there were no improvements when baseline measures were compared to those after 12 weeks of risperidone treatment. Likewise, Purdon et al. observed that there were no changes in performance when baseline measures were compared to those with LOCF data. The only contradictory finding comes from Kern et al. (1999) who observed improvements on list learning over 8 weeks of treatment with risperidone. Their double-blind trial contrasted the effects of risperidone and haloperidol at baseline, 4 weeks and 8 weeks after the initiation of antipsychotic therapy on verbal list learning; alternative lists of words were not used. Within group analyses revealed that both risperidone as well as haloperidol improved retention. The authors note "this improvement is most likely due to practice effects from repeated administration of the same version of the [verbal list learning test]" (p. 227). However, between group analyses demonstrated that the risperidone treated group was able to learn more words at 8 weeks compared to the haloperidol group. Because alternative lists of words were not used and because both groups showed an effect of practice, it cannot be assumed that risperidone enhances a patient's ability to acquire words over time. As with the other studies reviewed thus far, the concept of learning is confused with that of memory. Learning refers to a person's ability to acquire

information over repeated trials. Patients in the current study were exposed to the same list of words five times at each testing interval. This means that by the end of the third testing session, patients were exposed to the same list of words 15 times. This design reflects learning abilities for one list of words over the whole study. To assess learning and memory for individual testing sessions, snap shots of performance are required at each testing interval. One list with five exposures should be used at baseline, a new list with five exposures at time two and a new list with five exposures at time three. With respect to learning, this study demonstrates that risperidone enhances a patient's ability to benefit from practice and learning effects beyond that of those treated with haloperidol for learning the same list of words over 8 weeks of repeated cumulative exposures, not three individual snap shots. To say anything about the effects of these two medications on memory for lists of words, (i.e., retention after the first time the list is presented or after it has been presented for the fifth time), the use of alternative lists is imperative.

Risperidone appears to have no effect on short-term memory as assessed by the Digit Span Forward test (Rossi et al., 1997; Stip & Lussier, 1996). Additionally, memory for paragraphs does not appear to improve with risperidone treatment. Lindenmayer et al. (1998) conducted a 12 week study examining the effect of risperidone on memory for paragraphs. It is not clear from this study if alternative paragraphs were used. Nevertheless, when comparing within group performance at baseline with that after 12 weeks of risperidone therapy, there were no differences in the amount of information recalled. The mean daily dose of risperidone after 12 weeks was 9 mg/day, a dose which is considered somewhat elevated in contrast to the mean daily recommended dosage range of 4 to 6 mg/day. A dose of 9

mg/day can produce EPS which may require management with anticholinergic medications. Lindenmayer et al. reported that, in contrast to a clozapine control group, the risperidone group required more anticholinergic medications to control EPS. Knowing that anticholinergics can negatively affect memory performance, it is difficult to determine if dosage was a confounding factor in the negative results observed in this study.

Purdon et al.'s (2000) study addresses the above issue. They too examined the effect of risperidone on memory for paragraphs. The mean daily dose of risperidone in this study was 6 mg/day and alternative forms of the memory test were used. Despite these methodological improvements, there was no significant improvement on memory for paragraphs from baseline assessments to LOCF observations and performance did not differ in contrast to a group of patients treated with haloperidol. As a result, preliminary information suggests that risperidone may not influence memory for paragraphs.

The influence of risperidone on visual memory is equivocal. While Lindenmayer et al. (1998) have not observed improvements in this domain, Purdon et al. (2000) reported an improvement in the immediate recall of a complex figure. As previously mentioned, it is unclear if Lindenmayer et al.'s study used alternative forms of visual stimuli. Factors which may have contributed to a Type II error in their study included an elevated average daily dose of risperidone which necessitated the use of anticholinergic medications to control EPS and a small sample size ($n = 13$). In their sample of 20 subjects treated with risperidone, Purdon et al. (2000) did observe significant improvements in an ability to immediately recall a complex figure when baseline performance was compared to performance with LOCF data. This study did use alternative forms of visual stimuli, therefore it can be assumed that learning

effects related to the repeated exposure to the same stimuli was not an issue in the present study. Tempering the notion that risperidone alone may positively affect memory for complex figures is the fact that the other two comparison groups included in Purdon's study, those treated with olanzapine and those treated with haloperidol, also improved in this cognitive domain and that there was no difference between groups. Consequently, from this study, it appears as though immediate memory for complex figures is related to improved performance by typical as well as atypical antipsychotic medications and that there is no superiority of one medication over the other.

Olanzapine. Stip and colleagues (2002) studied memory for list learning in an open-label 8 week trial of olanzapine. They observed significant improvements in immediate as well as delayed recall at 4 and 8 weeks. Despite using alternate forms of the Rey Auditory Verbal Learning Test, the significance of these findings is difficult to determine since control groups were not included.

Purdon et al.'s (2000) 1 year double-blind study revealed that olanzapine has equivocal effects on verbal and visual memory. With respect to verbal memory, positive effects on verbal list learning were observed when baseline performance was compared to LOCF data. This finding can be considered as robust given that (a) alternative lists of words were used in this study, and (b) both the risperidone and haloperidol control groups did not improve on this task. However, improvements on memory for paragraphs in relation to olanzapine treatment was not detected. In considering memory for visual material, treatment with olanzapine did improve the subjects' ability to recall different versions of complex figures when baseline assessments were compared to those at end-point (LOCF data). However, as

mentioned previously, both risperidone as well as haloperidol were associated with significant improvements on this cognitive function and between group pairwise contrasts did not reveal any superiority of one treatment over the other.

A study conducted by Smith et al. (2001) examined memory in a group of chronic patients in a long-term hospital setting. Their study contrasted olanzapine and haloperidol in a double-blind 8 week trial. In considering memory for lists of words, paragraphs, Verbal Paired Associates, and Digit Span Forward, they did not find any effect of olanzapine or haloperidol on memory functioning. Additionally, there was no difference between treatments. These investigators also examined treatment with open label olanzapine after 3 months and determined that memory for Verbal Paired Associates improved. Overall, these findings are in contrast to those reported by Purdon et al. (2000). However, it must be noted that Smith's trial was of shorter duration and that, perhaps most importantly, they studied patients who's average illness duration was 25 years in contrast to patients in Purdon's study who had been ill less than 5 years.

Quetiapine. Two studies have investigated the effect of quetiapine on memory (Purdon et al., 2001; Velligan et al., 2002). Velligan and colleagues (2002) examined immediate recall for verbal list learning using the Hopkins Verbal Learning Test. These authors did not conduct within group analyses. In contrasting performance at 24 weeks (ANCOVA using baseline values as covariates) between quetiapine and haloperidol, they did not observe any statistically significant difference in recall over the 24 week trial. Although there are six equivalent alternate forms of the Hopkins Verbal Learning Test, the authors did not indicate if alternate forms were used in both testing sessions. A significant between group

difference in favor of those treated with quetiapine was detected on a paragraph recall test after a 15 minute delay. In fact, performance for those treated with haloperidol actually declined slightly over the 24 week trial. The direct influence of quetiapine on this result is difficult to interpret since 50% of those treated with haloperidol required anticholinergic treatment compared to only 8% in the quetiapine group. When Velligan and colleagues covaried anticholinergic use with performance on the Hopkins Verbal Learning Test, the significant between group difference was negated. Therefore, this may be an artifact of differential anticholinergic use and not differential antipsychotic efficacy. Tests examining visual memory were not administered and within group comparisons were not conducted.

While using alternate forms of the Rey Auditory Verbal Learning Test, Purdon et al's (2001) 6 month study found that quetiapine and haloperidol had no effect on immediate recall using LOCF data. As will be recalled, between group comparisons were not possible due to the overall high attrition rate. In considering immediate recall for paragraphs, within group analyses using LOCF data revealed that both the quetiapine as well as the haloperidol groups improved over time. Purdon et al. also examined immediate visual memory using the design learning test, WMS-R Visual Reproduction subtest and the Rey-O complex figure. A significant within group difference was observed for the design learning test as well as the Rey-O complex figure test for patients treated with quetiapine only. The lack of significance for those randomized to haloperidol is difficult to interpret for the following reason. As previously mentioned, the use of LOCF data in this study biases results in favor of those randomized to quetiapine because of the very high attrition rate in the haloperidol group. As such, many more quetiapine patients had a full three exposures to the tests compared to those

randomized to haloperidol. The validity of this argument could be challenged on the basis that alternate test forms were used. The issue of material specific learning effects is certainly addressed with the use of alternate forms, however, the quetiapine group had a least one more opportunity to practice or develop a strategy for remembering new material. With respect to immediate recall of the WMS-R Visual Reproduction material, no within group differences were noted for either treatment group.

Atypical versus atypical. Daniel et al. (1996) examined memory functioning using the WMS-R as well as the Rey-O. Using a double-blind randomized cross-over design, they determined that there was no difference on any memory measure after 6 weeks of therapy with either clozapine or risperidone. Lindenmayer and colleagues (1998) observed that patients treated with clozapine improved in their performance on a verbal list learning test compared to patients treated with risperidone after 12 weeks of treatment. However, between group differences were not observed on a paragraph memory test or on a test for pattern memory. Purdon et al. (2000) contrasted olanzapine to risperidone on several memory measures and determined that there were no statistically significant differences between the two treatments.

Summary. Design issues inherent in every study conducted thus far concerning clozapine's influence on memory functioning in schizophrenia prevents drawing definitive conclusions. For instance, of nine studies, seven lacked appropriate blinding (Galletly et al., 1997; Goldberg et al., 1993a; Grace et al., 1996; Hagger et al., 1993; Lee et al., 1994; Lindenmayer et al., 1998; Purdon et al., 2001), six either had no control groups or lacked appropriate control groups (Galletly et al., 1997; Goldberg et al., 1993a; Grace et al., 1996;

Hagger et al., 1993; Purdon et al., 2001), and seven did not use alternative stimuli over repeated assessment intervals for the purpose of reducing learning and practice effects (Buchanan et al., 1994; Goldberg et al., 1993a; Grace et al., 1996; Hagger et al., 1993; Lee et al., 1994; Purdon et al., 2001). Based on the current literature, there is no evidence to suggest that clozapine influences, either positively or negatively, verbal or visual memory in schizophrenia.

Similarly, the majority of studies examining the effect of risperidone on memory functioning in schizophrenia are flawed. Of six studies, three lacked appropriate blinding (Lindenmayer et al., 1998; Rossi et al., 1997; Stip & Lussier, 1996), four either had no control groups or lacked appropriate control groups (Kern et al., 1999; Lindenmayer et al., 1998; Rossi et al., 1997; Stip & Lussier, 1996), three failed to use alternative forms of memory tests (Kern et al., 1999; Rossi et al., 1997; Stip & Lussier, 1996), and one study used elevated doses of risperidone which necessitated the use of anticholinergic medications (Lindenmayer et al., 1998). In considering these studies together along with Purdon et al.'s (2000) double-blind study, risperidone appears to have very little effect on verbal or visual memory abilities in persons with schizophrenia.

The only studies on the effect of olanzapine on memory functioning were conducted by Purdon et al. (2000), Stip et al. (2002) and Smith et al. (2001). Despite preliminary results which reveal that this atypical agent may have some beneficial effects on both verbal and non-verbal memory functioning in less chronic populations, there does not appear to be any difference between its effects and haloperidol.

Only two studies have investigated the effect of quetiapine on verbal and visual memory. From these two studies, it appears that quetiapine does not influence memory for learning lists of words. However, evidence from these two reports suggest that quetiapine may have an effect on immediate as well as delayed recall for paragraphs. Also, there may be some beneficial influence of quetiapine on immediate memory for design list learning as well as for immediate recall of a complex figure. This result warrants further investigation since Purdon and colleagues (2001) are the only investigators to this point to have examined the effect of quetiapine on visual memory,

Too few studies exist to comment on the potential differential effects of clozapine and risperidone or olanzapine and risperidone on memory functioning in schizophrenia.

Executive Functioning

Executive functioning refers to higher-order cognitive operations which require the concurrent processing of four principle elements: (1) motivation, (2) planning, (3) execution, and (4) the evaluation of performance. Motivation refers to a person's ability to initiate and sustain their attention. Planning involves the evaluation of possible solutions to a problem. Once planning is complete, the plan must then be initiated and executed. The final component involves the evaluation of performance during the execution of a plan. An ongoing evaluation of performance and appropriate shifting of responses requires that the person be able to monitor relevant information and events (see Lezak, 1983; Luria, 1973; Stuss & Benson, 1986).

Four measures to assess executive functioning within the context of atypical medication effects in schizophrenia predominate. They are: (1) the Wisconsin Card Sorting

Test (Heaton, 1981); (2) the Trail Making Test Part B (Trails B) (Spreeen & Strauss, 1991); (3) Verbal Fluency; (Lezak, 1983) and (4) the Mazes test. In addition, one study (Purdon et al., 2000) examined Design Fluency (the non-verbal counterpart to Verbal Fluency).

Using feedback after each response, the Wisconsin Card Sorting Test requires a person to discover the rules which govern the test by matching several cards to one of four key cards. After ten correct responses, the sorting rule changes and the person must again determine the new sorting principle. Although the Wisconsin Card Sorting Test yields several dependent variables, two outcome measures are typically reported in the literature evaluating the effects of atypical medications in schizophrenia: (1) the number of perseverative responses given; (2) the number of categories completed. Verbal Fluency is measured by a task called the Controlled Oral Word Association test (Spreeen & Strauss, 1991). A person is required to produce as many words as possible which begin with certain letters (F, A, S) or which belong to specific categories (animals, fruit, vegetables) in 60 seconds. The dependent variables are the number of words produced for each letter and the number of words produced for each category. Trails B requires a person to connect a series of randomly placed circles (each containing a letter or a number) located on a page in sequence while alternating between letters and numbers. For example, they are required to draw a line from 1 to A, from A to 2, from 2 to B, from B to 3 and so forth. The dependent variable is the time to completion. Design Fluency requires a person to draw as many different non-nameable drawings as possible in 5 minutes. The Mazes test requires persons to navigate through several mazes which range in difficulty from easy to challenging. The dependent variables for this test are the time required to complete each maze and the number of mistakes

encountered while navigating through the maze (wrong turns). A computerized version of this task allows investigators to measure the route taken by the subject, with shorter routes indicating better performance.

Clozapine. Five investigations examining the performance of chronic schizophrenia patients using the Wisconsin Card Sorting Test found no significant improvement on either the numbers of categories achieved or reductions in perseverative errors over 8 weeks to 1 year of clozapine treatment (Buchanan et al., 1994; Goldberg et al., 1993a; Hagger et al., 1993; Potkin, 2001; Purdon et al., 2001). However, one other study found a trend toward improvement and another found a significant improvement. Fujii et al.'s (1997) open-label trial assessed patients at baseline while they were receiving various typical neuroleptics. A comparison between baseline performance with that after 12 months of clozapine treatment revealed that there was a trend toward a significant decrease in the number of perseverative errors and an increase in the number of cards correctly sorted. However, it must be remarked that of the 22 patients originally assessed at baseline, only 10 were reassessed at the 1 year follow-up. In addition, "on average, subjects were taking more other [concomitant] medications that were likely to affect cognition during the typical neuroleptic [baseline] phase than during the clozapine phase. . . . These other [concomitant] medications were anticholinergics, benzodiazepines, lithium, and anticonvulsants" (p. 242). Because there was no control group in this study, it is impossible to determine if the positive findings reported were due to (1) clozapine treatment, (2) a reduction of concomitant medications, or (3) an end-point sample bias. As a result, this study provides limited insight into the effect of clozapine on executive functioning in schizophrenia.

The only study to find statistically significant improvements on the Wisconsin Card Sorting Test was conducted by Lee and colleagues (1994). They studied patients who were treatment-responders and in their first 5 years of illness. They observed reductions on perseverative errors after 6 months of treatment with clozapine compared to baseline assessments and reported that these improvements were maintained over 1 year. The control group treated with typical agents only showed improvements when perseverative errors at baseline were compared to those at 6 weeks. The element which distinguishes this study from the others which report negative findings is the duration of illness in the patient samples. For instance, the mean duration of illness in Goldberg et al.'s (1993) study was 12 years, and 14 years for Hagger et al.'s (1993) and Buchanan et al.'s (1994) studies. Information about illness duration was not provided by Fujii et al. (1997). Consequently, the effect of clozapine on the Wisconsin Card Sorting Test may somehow be related to illness duration.

With respect to performance on Verbal Fluency, all but two studies (Lindenmayer et al., 1998; Potkin, 2001) examining the effect of clozapine reported improved performance. Hagger et al. (1993), Galletly et al. (1997), Grace and colleagues (1996) and Purdon et al. (2001) reported significant improvements in their open-label studies which did not include comparison groups. As a result, it is difficult to determine the influence of clozapine on Verbal Fluency. Lee's group (1994) conducted an open-label investigation which compared the performance of subjects receiving various typical antipsychotic agents and clozapine. Within group analyses demonstrated that there was no improvement on Verbal Fluency in the group receiving typical agents when baseline assessments were compared to performance after 6 weeks, 6 months and 12 months of treatment. Significant improvements were noted

for the clozapine group at all three reassessment periods. In addition, clozapine was found to be superior to typical medications on this task. Buchanan et al. (1994) contrasted the effect of clozapine with haloperidol in a 10 week double-blind study. They determined that the haloperidol group's performance significantly declined when baseline assessments were compared to those after 10 weeks of treatment. The clozapine group did not show any difference in performance. However, an open-label extension phase, where all patients were receiving clozapine, revealed that there were significant gains made on this task after 1 year of treatment. Although these latter two studies are more methodologically sound in comparison to the others and suggest that clozapine may enhance performance on Verbal Fluency, normal control groups could have provided information about potential practice effects. Subjects in Buchanan et al.'s study repeated the same Verbal Fluency task on three different occasions. Likewise, Lee et al.'s subjects were exposed to the same task on four occasions.

Lindenmayer et al. (1998) conducted an open-label study contrasting the effect of clozapine and risperidone on Verbal Fluency. Within group comparisons failed to detect differences on this task for both clozapine and risperidone. With respect to the effect of clozapine on Verbal Fluency, the authors hypothesized that their negative findings may be due to the relatively short duration of their study (12 weeks). Although plausible, others have found improvements in Verbal Fluency after 6 to 8 weeks of clozapine therapy (Hagger et al., 1993; Lee et al., 1994; Purdon et al., 2001).

With two exceptions (Potkin, 2001; Purdon et al., 2001), a consensus as to the effect of clozapine on the Trails B and the Mazes tests exists in the literature. It seems that

clozapine has no beneficial effect on the Trails B test over 10 weeks to 1 year of therapy (Fujii et al., 1997; Goldberg et al., 1993a; Lee et al., 1994; Lindenmayer et al., 1998). However, Purdon et al. (2001) observed a significant decrease in the time required to complete this executive functioning task. Both Purdon's (2001) and Potkin's (2001) groups examined chronic treatment resistant patients over 6 to 8 weeks and found improvements on the Trails B test. Therefore, it may be that short term treatment with clozapine may improve performance on this task. Alternatively, because the time interval was shorter in these two studies, patients may have benefitted from sustained practice and learning effects.

Several authors have reported that clozapine significantly enhances performance on the Mazes test. As with the other cognitive domains reviewed thus far, a closer inspection of these studies' design methodology prohibits making this statement. Hagger et al.'s (1993) open-label within group study did not have any control groups and failed to observe enhanced performance on the Mazes test after 6 weeks of clozapine treatment whereas significant gains were reported after 6 months. Given that the same mazes were administered for a third time at the 6 month reassessment period, this finding may simply reflect a practice effect and not improvements in executive functioning. Similarly, another open-label within study design which did not incorporate any control groups reported improvements on the same mazes when performance at baseline was compared to performance after 4 to 8 months of clozapine therapy (Galletly et al., 1997).

The only study to include a control group of healthy normal volunteers demonstrated that clozapine was associated with enhanced performance on Mazes test (Meyer-Lindenberg et al., 1997). The inclusion of a group of normal controls aids in determining if this

improvement was as a result of practice effects or an actual effect of clozapine treatment. Practice effects in this study are of significance since subjects were assessed at baseline, days 2, 7, 14, 21, 28, 35 and 42. Put simply, subjects were exposed to the same mazes on eight different occasions. Results demonstrated that the normal control group's performance steadily improved over repeated exposures. Even though the clozapine group's performance never approached that of normal functioning, the authors conclude that "the improvement of patients treated with clozapine was similar to that of normal controls" (p. 40). Given that the normal control group improved over time, it is reasonable to conclude that the clozapine group's performance is most likely attributable to a practice and learning effect and not to improvements in executive functioning. Despite this obvious interpretation, Meyer-Linderberg et al. conclude that "the study provides evidence for a beneficial effect on cognitive functions (visuomotor integration, planning, looking-ahead) in the maze paradigm" (p. 41) with clozapine treatment.

Several studies have contrasted the effects of atypical and typical antipsychotics on executive functioning. A short 10 week study conducted by Buchanan et al. (1994) failed to show any significant differences between clozapine and haloperidol on measures of executive functioning. These measures included the Wisconsin Card Sorting Test, Verbal Fluency and Trails B. A 12 week study by Lindenmayer and colleagues (1998) support these findings. They also failed to observe significant differences on either Verbal Fluency or Trails B. However, a 1 year trial by Lee et al. (1994) revealed that clozapine was superior to haloperidol on Verbal Fluency and that there were no between group differences on the Wisconsin Card Sorting Test or Mazes test.

Risperidone. With respect to the effects of risperidone on the Wisconsin Card Sorting Test, Rossi et al. (1997) reported improvements in the number of categories attained and reductions in the number of error responses after 4 weeks of treatment. However, because this study was open-label and did not have any control groups, it is difficult to determine the significance of this result. The possibility of a learning effect or having been withdrawn from previous typical neuroleptics and then washed out for 1 week prior to baseline assessments may have contributed to this positive finding. The only other study to investigate the Wisconsin Card Sorting Test in relation to risperidone treatment was conducted by Purdon and colleagues (2000). Purdon's investigation was a double-blind randomized trial which compared performance between risperidone, olanzapine and haloperidol. Their dependent variable was more specific than that of Rossi et al. Rather than simply considering the total number of error responses, Purdon et al. examined perseverative errors. Using this measure, they did not observe any positive effects of risperidone when baseline measures were compared to LOCF data. The same effect was true for those assigned to haloperidol and between group analysis revealed that performance by the risperidone and haloperidol groups did not differ. However, the olanzapine group did produce significantly less perseverative errors at end-point. Because these results are based on a sample of early phase subjects, it is not known if this finding will generalize to more chronic populations.

The only two studies to report on the effects of risperidone on Verbal Fluency and Trails B did not find any improvements on these tasks over a 1 year period (Lindenmayer et al., 1998; Purdon et al., 2000). However, Purdon et al. did observe improvements in design

fluency over 1 year. At present, there are no investigations on the effects of risperidone on the Mazes test.

Although several studies have contrasted the effects of risperidone and typical antipsychotics, namely haloperidol, on cognitive functioning in schizophrenia (Stip & Lussier, 1996; Green et al., 1997; Kern et al., 1998; Kern et al., 1999), it is surprising to note that only one trial has assessed executive functioning (Purdon et al., 2000). The tasks assessed by Purdon et al. were the Wisconsin Card Sorting Test, Verbal Fluency, design fluency and Trails B. They observed that none of these tasks were differentially affected by either treatment. Olanzapine and haloperidol were contrasted on the same tasks and Purdon et al. observed that olanzapine was superior to haloperidol on Verbal Fluency only.

Olanzapine. An open-label trial of the effect of olanzapine on verbal and category fluency by Stip et al. (2002) revealed that patients were able to produce more words after 8 weeks of treatment. They also reported an improvement in the time required to complete the Trails B test. However, the lack of control groups in this study makes it difficult to determine if these results are an artifact of practice and learning effects. Supporting the notion that practice and learning effects may have been implicated in improved Verbal Fluency is a trial by Purdon et al. (2000). While their 1 year double-blind random assignment trial contrasting the effect of olanzapine, risperidone and haloperidol reported within group improvements on Verbal Fluency, between group analyses did not reveal any difference in treatments. With respect to the Wisconsin Card Sorting Test, Purdon and colleagues also reported significant improvements for the olanzapine group. However, as already mentioned, the risperidone and haloperidol groups did not change from baseline to endpoint and there were no significant

differences between the three treatments. In addition, they reported significant within group improvements over baseline assessments on the Wisconsin Card Sorting Test. The authors also noted that performance on the Trails B test was not preferentially affected.

Finally, Smith et al. (2001) examined performance on the Wisconsin Card Sorting Test as well as Verbal Fluency in a group of chronic patients in a long-term care setting. Their study contrasted olanzapine to haloperidol in an 8 week double-blind trial and after 3 months of open-label treatment with olanzapine. They concluded that neither 8 weeks or 3 months of olanzapine treatment altered performance on these tasks. Additionally, there was no change associated with haloperidol. These results are discrepant with those of Purdon et al. (2000). This may be due to the difference in the duration of illness between the two samples; less than 5 years in Purdon's study versus 25 years in Smith's study. Furthermore, while Smith et al. assessed patients at 3 months, Purdon's group assessed patients over 1 year.

Quetiapine. A total of two studies have investigated the effect of quetiapine on executive functioning in schizophrenia. Both were double-blind, randomized trials contrasting quetiapine with haloperidol. Velligan et al. (2002) assessed the effect of quetiapine on Trails B only. No significant between group difference were observed after 24 days of treatment. Within group analyses were not provided by the authors. However, upon inspection of the baseline and the day 24 data, it is clear that those randomized to haloperidol improved (from 91 to 67 seconds) in their performance to a greater extent than those randomized to quetiapine (from 75 to 65). This highlights the importance of including control groups in repeated measures designs. Purdon et al. (2001) used the Trails B as well as the Wisconsin Card Sorting Test (perseverative errors) in their 6 month study. Patients were assessed at

baseline, 8 weeks and at 6 months. Interestingly, within group analyses revealed that the haloperidol group's time to complete Trails B became slower whereas there was no change in performance for the quetiapine group. It must be noted that this finding may simply reflect a ceiling effect in the quetiapine group since they performed this task faster at baseline relative to the haloperidol group. Using LOCF data, the authors found a significant decrease in perseverative errors on the Wisconsin Card Sorting Test for the quetiapine group only. As previously stated, the main caveat in this study is the use of LOCF data within the context of very high attrition rates in the haloperidol group. Many more patients randomized to quetiapine complete the 6 month trial relative to those randomized to haloperidol, meaning that many more patients in the quetiapine group were exposed to the assessments on three occasions.

Atypicals versus atypicals. Studies contrasting atypical antipsychotic medications on several executive functioning tasks have failed to uncover the superiority of one medication over the others. Daniel et al.'s (1996) cross-over study, where each treatment lasted 6 weeks, revealed no difference between clozapine and risperidone on Verbal Fluency or the Wisconsin Card Sorting Test. A 12 week study by Lindenmayer et al. (1998), which also compared clozapine and risperidone, reported no between group differences on Verbal Fluency or the Trails B test. Similarly, Purdon et al.'s (2000) 1 year investigation found no group differences between olanzapine and risperidone on any of their executive functions measures (Verbal Fluency; design fluency; Trails B; Wisconsin Card Sorting Test).

Summary. Other than the suggestion of an improvement in early phase patients, there is very little evidence that clozapine improves performance on the Wisconsin Card Sorting

Test in patients who are chronically ill and treatment-resistant. In addition, methodological limitations make any concrete conclusions about clozapine's influence on Verbal Fluency difficult. Stated conservatively, five studies suggest that clozapine may improve performance on this task. With two exceptions, it seems that clozapine has limited influence on the Trails B test or on the Mazes test. Nevertheless, considered together, these studies suggest that clozapine may have beneficial effects on some measures of executive functioning.

Commenting on the effects of risperidone on measures of executive functioning is difficult due to the limited number of investigations and contradictory findings. At present, the only well controlled study demonstrated that performance on the Wisconsin Card Sorting Test was not affected by risperidone therapy. The only two studies to examine the influence of risperidone on Verbal Fluency and the Trails B test failed to detect any improvements in performance. Considered together, evidence thus far does not indicate that risperidone positively influences executive functioning.

Olanzapine's effect on executive functioning in schizophrenia is undetermined. Whereas one report on early phase patients observed significant improvements, another study examining chronic treatment resistant hospitalized patients reported no effect of olanzapine.

Determining quetiapine's effect on executive functioning is not possible. One report concluded that there was no difference between quetiapine and haloperidol on the Trails B test. The other ascertained that the haloperidol group improved significantly on this test whereas the quetiapine group's performance did not change. However, the superiority of one over the other could not be determined since between group analyses were not possible. With respect to the Wisconsin Card Sorting Test, Purdon et al. (2001) found that perseverative

errors significantly declined in the quetiapine group only. Once again, the influence of more exposures to this test in the quetiapine group relative to the haloperidol group confounds the interpretation of results.

In considering the differential effect of atypical and typical antipsychotic medications on executive functions, only olanzapine was shown to be superior to haloperidol on one measure of executive functioning (Verbal Fluency). With respect to the differential effects of atypical medications on executive functioning, two studies contrasting clozapine and risperidone in addition to one study comparing olanzapine and risperidone did not provide any evidence for the superiority of one of these compounds over the others.

Attention: Arousal

Attentional deficits have always been regarded as a hallmark feature of schizophrenia (Cornblatt & Keilp, 1994; Erlenmeyer & Cornblatt, 1978; Granholm II, 1992; Green & Walker, 1986; Kenny & Meltzer, 1991). However, the literature examining atypical medication effects on attention in schizophrenia is exceedingly difficult to interpret. This difficulty is due to researchers' tendency to conceptualize attention as one entity and to measure it using various methods (Kenny & Meltzer, 1991). For example, in Purdon et al.'s (2000) study, "attention span" was measured using simple span tests while Buchanan et al. (1994) used the Stroop Color-Word test as a measure of "executive functioning/attention" and Lee et al. (1994) categorized the Digit Symbol Substitution Test as a measure of "attention". These three examples highlight the fact that the concept of attention differs qualitatively and quantitatively across studies. Referring to similar discrepancies in the

literature, van Zomeren and Brouwer (1994) state: "This should not be considered wrong or inconsistent, but it does illustrate that there are no pure tests of attention" (p. 159).

To clarify some of these discrepancies, several authors have proposed that attention may best be understood if it is conceptualized as consisting of several components. According to Mirsky, Fantie and Tatman s (1995):

When necessary, one must also be able to select the appropriate stimulus on which to act from all the information that bombards the sensorium. Having selected, one must then be able to maintain fixation on the target, thereby resisting the tendency to be attracted by competing, but irrelevant or redundant, stimuli. When required, one must be able to terminate one's fixation and switch one's focus to another target. Sometimes one must carry out two functions simultaneously, splitting one's attention between a main target while monitoring what is happening in the periphery. (p. 18)

Although attention has been conceptualized in numerous ways (see Mesulam, 1990; Posner, Inhoff, & Friedrich, 1987; Posner & Presti, 1987), the components of attention as delineated by the literature in rehabilitation psychology and neuropsychology will be applied here (see Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991; Posner & Rafal, 1985). These disciplines subdivide attention into four basic components: (1) arousal; (2) sustained attention; (3) selective attention (also referred to as focused attention); and (4) divided attention.

Numerous authors have proposed that selective as well as divided attention could belong to a category called 'strategic attentional control' (also sometimes referred to as 'supervisory attentional control') (Posner et al., 1987; Van Zomeren & Brouwer, 1994). This concept refers to the conscious guiding of attention which places demands on cognition

beyond that of arousal and sustained attention. Additionally, strategic attentional control blends with the notion of working memory, both conceptually and neuroanatomically.

To better understand and make sense of the literature as it pertains to the influence of atypical medications on attention, the following strategy will be adopted: (1) each attentional component will be operationally defined; (2) the neuroanatomical substrates for each will be discussed; (3) the most widely accepted tasks used to measure each component will be identified; and (4) studies which have used such tasks will then be discussed within the context of individual attentional components.

The most basic – and necessary – component which can affect all aspects of attention as well as higher-order cognitive functions is arousal (Posner & Rafal, 1985). Arousal refers to a person's alertness and preparedness for responding to information processing demands. According to the Yerkes-Dodson Law, too much or too little arousal can negatively impact performance on attentional tasks (Van Zomeren et al., 1994; Whyte, 1992). Arousal itself can be subdivided into two types. The first is tonic arousal and refers to a person's natural fluctuation in arousal levels throughout the day independent of tasks a person may be performing. The second type of arousal is called phasic arousal and refers to changes in level of arousal in response to environmental demands. According to Posner and Rafal (1985), changes in phasic arousal can be induced by tasks which incorporate warning signals which alert the organism to an impending requirement to react. Warning signals have been found to result in "speeding of reaction times to any subsequent stimulus; cardiac deceleration; changes in organic skin resistance (GSR; also referred to as skin conductance); and dilatation of the pupil" (Posner & Rafal, 1985, p. 184).

From a neuroanatomical standpoint, the ascending reticular activating system (ARAS), a meshwork of neuronal fibers located in the brainstem, is responsible for maintaining levels of arousal necessary to meet the demands of environmental stimuli. Via specific reciprocal projections with the thalamus and non-specific projections to the whole of the neocortex, the ARAS is also implicated in bringing the cortex 'on-line' when necessary. Conversely, the cortex – the frontal cortex in particular – regulates levels of activity in the ARAS. Posner and Rafal (1985) make the point that medications which negatively alter tonic arousal (medications with antipsychotic properties which make a person's sleepy for example) can negatively impact that person's ability to sustain his or her attention over extended periods of time. Within the context of the present study, this is a very important point since haloperidol and olanzapine are known to cause sedation (Beasley et al., 1996).

Several methods have been used to assess arousal in schizophrenia, the majority involve electrophysiological methods. These include the orienting response as measured by skin conductance (Raine et al., 1997), changes in contingent negative variation (CNV) in relation to the presence of a warning signal (Van Zomeren et al., 1994), and smooth pursuit eye movements (Park & Holzman, 1993). A review of the literature by Szymanski, Kane and Lieberman (1991) reveals that all of these parameters are consistently found as being impaired in persons with schizophrenia. In addition to electrophysiological methods, Van Zomeren and Brouwer (1994) state that a behavioral method such as speed of reaction time (RT) can also provide information about a person's phasic arousal. In its simplest form, a RT task requires a person to respond as rapidly as possible when a target stimulus appears. In order to use RT as an estimate of phasic arousal, two simple RT tasks must be used; while one has a warning

signal before the stimulus onset, the other does not. A subtraction of the mean RT for each of these two tasks provides an estimate of a person's preparedness to respond. According to several reviews of the RT literature, persons with schizophrenia are significantly slower on all types of RT paradigms compared to normal controls (Nuechterlein & Dawson, 1984; Spohn & Strauss, 1989). Considering that reduced RT in schizophrenia was reported prior to the advent of neuroleptic therapy, it would appear that slower RT is not an artifact of neuroleptic treatment.

Clozapine. At present, there are only three studies which have assessed the effects of atypical medications on RT. Using a cross-over single-blind design (experimenters were unblinded), Zahn, Pickar and Haier (1994) contrasted the effects of clozapine, fluphenazine (a typical neuroleptic), and placebo on two RT tasks in persons with chronic schizophrenia. The order of drug administration was the same for all patients. Fluphenazine was administered first, placebo second and clozapine third. Fluphenazine and clozapine were administered for a 6 week period and the mean duration of time spent on placebo was 20 days. Patients were receiving a mixture of typical and atypical antipsychotic agents at baseline assessments.

The simple RT (SRT) condition required patients to respond by lifting their finger from a telegraph key whenever they heard a tone (imperative stimulus, S2). A warning signal (S1) was given in this condition and the S2 was randomly presented 4 or 8 seconds later. Despite clozapine's superiority over fluphenazine and placebo in alleviating clinical symptoms, and its better motor side-effect profile relative to fluphenazine, no differences between the

three treatments emerged on the SRT. This study demonstrated that, in the presence of improved motor side-effects, performance on a SRT is not enhanced.

Risperidone. Two studies have examined risperidone's effect on SRT. An open-label within group investigation reported that SRT was enhanced with risperidone treatment (Stip & Lussier, 1996). Baseline assessments were conducted when all patients were receiving typical medications (haloperidol or fluphenazine) in combination with antiparkinsonian medications (benztropine or procyclidine). These patients were then treated with risperidone and reassessed on clinical and neurocognitive measures at 2 and 6 months intervals. The simple RT task was unwarned and required subjects to respond when an apple appeared on a computer monitor at random intervals (either 2, 4, 6, or 8 seconds). Similar to Zahn et al.'s (1994d) study, significant improvements in clinical symptoms and motor side-effects were associated with atypical (risperidone) treatment. Stip and Lussier reported that treatment with risperidone resulted in faster SRT speed when compared to baseline measures. This improvement was most pronounced in the period from baseline to 2 months. It must be noted that there were significant improvements in EPS. Therefore, the confounding effect of motor side-effects on enhanced performance cannot be ruled out. Additionally, since there were no control groups, practice effects cannot be ruled out. Consequently, it cannot be stated with certainty that risperidone was the determining factor in the improved performance on SRT.

Olanzapine. There is only one published report on the effect of olanzapine on SRT in persons diagnosed with schizophrenia. Smith et al. (2001) evaluated the effect of olanzapine and haloperidol on SRT in chronic treatment resistant patients residing in a long-term hospital facility. These researchers reported no affect of either medication and that there

was no difference between medications. These results did not change with a 3 month open-label extension of treatment with olanzapine only.

Quetiapine. There is no information on the effect of olanzapine on SRT.

Summary. The only study to examine clozapine's influence on RT reported that it had no effect. Serious methodological flaws attributed to the only study to examine risperidone's effect on SRT prohibit making any conclusions. The only study to examine the effect of olanzapine on SRT reported negative findings in a group of chronic treatment resistant hospitalized patients. Considering these studies together, very little can be said about the influence of atypical agents on SRT.

Sustained Attention

Sustained attention, also called vigilance, refers to a person's ability to maintain his/her focus on a task over an extended period of time in a quiet environment (Van Zomeren et al., 1994). The ability to do so necessarily implicates the concept of arousal. Therefore, the integrity of the reticular formation as well as the tectum, both located in the mid-brain, and the reticular nucleus of the thalamus are associated with sustained attention (Mirsky, 1987).

The benchmark test for assessing sustained attention is the Continuous Performance Test (CPT). Of all the published studies reporting on the effects of atypical antipsychotics on neurocognition in schizophrenia, four have used the CPT (Daniel et al., 1996; Liu et al., 2000; Sax et al., 1998; Stip & Lussier, 1996).

The CPT requires subjects to continually sustain their attention over a period of several minutes. Although several versions of the CPT have been employed in research, a

typical version will pseudo-randomly display individual uppercase letters in the center of a monitor for 250 milliseconds with an inter-stimulus intervals (ITI) of 1 second. Subjects are instructed to respond as quickly as possible (by lifting their index finger off a mouse button) only when the target letter 'X' appears. Twenty-five percent of all the letters are targets. The CPT typically yields five measures: number of hits, errors of commission, errors of omission, reaction time, and discriminability (d'). Discriminability is a measure of "a subject's ability to discriminate a signal from background noise" which incorporates both hits and errors of commission. Higher values for d' indicate better discriminability. Generally, persons with schizophrenia tend to have lower d' values compared to normal controls (Nuechterlein, Dawson, & Green, 1994).

Cornblatt and Keilp (1994) state that poor performance on the CPT by patients with schizophrenia appears to be independent of clinical status (acutely ill or remitted), chronicity of illness (early phase [first 5 years] versus chronic), and clinical symptoms. They report that treatment with conventional neuroleptics, such as haloperidol, have some beneficial effects on performance. Cassens et al. (1990) reviewed the literature on attention in schizophrenia dating from the 1950's to 1990. They concluded that the acute administration (within 1 to 3 days) of typical neuroleptics can impair sustained attention when contrasted with medication-free performance. However, a longer duration of treatment (beyond 4 weeks) with these neuroleptic agents can improve performance on the CPT.

Clozapine. The only study to examine the effect of clozapine on sustained attention was conducted by Daniel et al. (1996). Unfortunately, within group analyses were not

reported. It is therefore not possible to comment on clozapine's effect on sustained attention performance.

Risperidone. Stip and Lussier (1996) studied the effect of risperidone in patients previously treated with typical antipsychotics. Baseline assessments were conducted while they were receiving these medications. Patients were treated with open-label risperidone for a 16 week period. Their version of the CPT used pictures of fruit as stimuli. As in their RT task, the target stimulus was an apple and distractor stimuli were other fruit. The total duration of the sustained attention task was 15 minutes (3 blocks of 5 minutes each). No differences were reported at either 8 or 16 weeks of treatment. Liu et al. (2000) contrasted risperidone and haloperidol on two versions of the CPT; the degraded and non-degraded versions. Their double-blind 12 week trial revealed that neither risperidone nor haloperidol affected performance on either version of the CPT and that there was no difference between treatments. Therefore, it appears that risperidone does not differentially affect performance on the CPT.

Olanzapine. There are no reports on the effect of olanzapine on sustained attention.

Quetiapine. The only study examining the effect of quetiapine on sustained attention was conducted by Sax et al. (1998). They used the CPT (degraded version). A total of 10 patients (n = 2 inpatients; n = 8 outpatients) receiving either no medications, typical or atypical medications prior to pre-seroquel baseline assessments were evaluated. Time 2 reassessments were conducted an average of 24 ($\pm$ 22 days) days after the pre-medication baseline assessment and time 3 was conducted an average of 40 ($\pm$ 23) days later. No

information regarding the sample's duration of illness was provided. A control group of 12 normal controls matched for age, sex, race and education was tested on the CPT.

Time 2 reassessments were conducted on only 5 of these subjects an average of 61 (± 16 days) days later. A between group analysis of performance at baseline revealed that the patient group performed significantly worse than the normal control group whereas there was no difference between groups at time 3. Within group repeated measures analyses revealed that the patient group improved significantly from time 1 to time 3, even in the absence of change on the BPRS. Normal control group differences between time 1 and time 3 were not statistically significant. The latter result may be due to the small sample size and/or a ceiling effect as indicated by the fact that the control group performed at near perfect levels at baseline.

Although not stated by the authors, these results suggest that quetiapine treatment may 'normalize' performance on a task of sustained attention in persons with schizophrenia. However, several issues prohibit this conclusion. Several review articles have reported that typical neuroleptics can also enhance performance on the CPT (Cassens et al., 1990; Cornblatt et al., 1994). Given that 7 of the 10 patients were assessed when they were medication free at baseline, the question remains: Would treatment with any antipsychotic have improved performance on this task of sustained attention? Also, if both types of medications enhance performance on the CPT, is quetiapine superior to a typical neuroleptic? A control group of patients randomized to treatment with a typical neuroleptic could have elucidated these questions. Although the inclusion of a group of matched normal controls is commendable, only 5 of these 12 subjects were reassessed. They were reassessed once after

the initial testing whereas the patient group was subjected to three separate assessment sessions. Also, test-retest intervals for each group were extremely variable. Given this variability, time becomes a potentially confounding variable. Finally, there was a wide variation in the dosages prescribed to the patients. The range for quetiapine was from 75 mg/day to 600 mg/day and, because of the small sample size, very little can be said about the optimal dosage range for maximized cognitive benefit.

Atypical versus atypical. The primary purpose of Daniel et al.'s (1996) cross-over study was to contrast the side-effect profiles of clozapine and risperidone. In doing so, they also examined sustained attention using the CPT in 20 chronic treatment-resistant patients. Curiously, the authors did not note which variable they used as an outcome measure for the CPT. At the time of screening, all patients were stable and received clozapine. This was a single-blind, flexible-dose cross-over study wherein 10 of the 20 patients received clozapine first and risperidone second. Conversely, the remaining 10 patients received risperidone first and clozapine second. Exposure to each medication lasted 6 weeks and the cross-over period lasted 1 week; during which time patients were tapered from their first medication and began treatment with the second medication. At no time were patients receiving both clozapine and risperidone concurrently. Continuation of concomitant medications throughout the study was allowed. Between group comparisons on the CPT at the end of 6 weeks with each treatment revealed no advantage of one medication over the other. The lack of significant positive results may stem from the relatively short treatment duration, the short cross-over period, and a carry-over effect of both medications into the second phase of treatment. Furthermore, drawing any conclusions about the effects of risperidone or clozapine on sustained attention

is difficult due to a lack of appropriate control groups (normal controls and/or a group receiving typical neuroleptics) and limited information about which variable was used as the outcome measure for the CPT.

Summary. One study reported on the effect of both clozapine and risperidone on sustained attention and another on the effect of risperidone only. Both studies failed to observe any affect of treatment on the CPT. As stated in the introduction to this section, chronic treatment with typical agents can improve performance on this task. Therefore, these negative reports may not be surprising given that patients were treated with medications (both typical and atypical) at baseline assessments thus possibly leaving little room for improvement. With respect to quetiapine, conclusions as to the effect of this drug on sustained attention are not possible given the methodological flaws present in the only study to examine this attentional domain.

In order to determine if atypical medications have beneficial effects on sustained attention, a study would have to include patients who were medication free for a sufficient period (or be neuroleptic naive) at baseline. They would then have to be randomized to treatment with typical or atypical medications or placebo and assessed over several weeks. The inclusion of a normal control group, examined in the same manner as the patients group(s), would provide information about practice effects.

Selective Attention

Selective attention is defined as the “selective biasing of neural function which facilitates the processing of specific information for special treatment, while tuning out the other [perhaps irrelevant and distracting] signals” (Posner & Rafal, 1985, p. 184). Thus,

selective attention allows individuals to filter-out irrelevant stimuli in favor of relevant stimuli for subsequent processing (Paulesu, Frackowiak, & Bottini, 1997).

To identify the neuroanatomical substrates which may be implicated in selective attention, Posner and colleagues (1987a; 1987b) subdivided selective attention into three process components: (1) disengage, (2) move, and (3) engage. For a person to change their visual focus, they must first disengage from the current focus, move to the new focus and finally, before being able to determine what the new focus is, it must first be engaged. According to Posner and Presti (1987b), each of these three subprocesses are subserved by different neuroanatomical substrates. The engage process is subserved by the posterior parietal cortex (more so by the right hemisphere); the move process is subserved by the mid-brain; and the disengage process is subserved by the posterior parietal cortex in addition to the lateral pulvinar (posterior nucleus of the thalamus). When stimuli are verbal, thus minimizing or even negating the possibility of visual mediation, the thalamus appears to play a role in selectively attending to this type of information. More specifically, the reticular nucleus of the thalamus (located in the most anterior portion of the thalamus) receives inputs from the mediodorsal frontal system. According to Whyte (1992), the reticular nucleus of the thalamus is capable of detecting “neural regions that are currently active (whether from external stimulation or internal thought) and amplify their activity” (p. 946).

Although several instruments have been developed to assess selective attention, research on the effects of atypical medication has used the Stroop Color-Word Test (Stroop) (Golden, 1978), the Span of Apprehension test (SoA) (Nuechterlein & Dawson, 1984), choice reaction time paradigms (CRT) (Kern et al., 1998; Zahn et al., 1994), the Digit Span

Distractibility Test (Oltmanns & Neale J.M., 1975; Oltmanns et al., 1978), and the Petersen Consonant Trigram test (PCT) (Spreen & Strauss, 1991).

The Stroop consists of three conditions, each lasting 45 seconds. First, subjects are required to read aloud down several columns which consist of words referring to colors (red, green, blue). Second, they are required to name the color of the ink in which a series of X's are printed. Third, color-words are printed in incongruent colored ink (e.g., the word red printed in blue ink). Subjects are required to ignore the word and report the ink color. The Stroop yields three dependent variables: (1) the total number of words (W) correctly read, (2) the total number of colors (C) correctly identified, and (3) the total number of correctly named colors from the incongruent color-word condition (C-W). An interference index score can be calculated using the above information. Scores above 0 indicate that the subject is not susceptible to interference effects whereas score falling below zero indicated that the subject is vulnerable to interference effects (Golden, 1978).

Several studies have reported that persons with schizophrenia perform more poorly relative to normal controls on the Stroop test (Mahurin, Velligan, & Miller, 1998; Schooler, Neumann, Caplan, & Roberts, 1997) and that these impairments are not amenable to typical neuroleptic therapy (Cassens et al., 1990). Few studies have investigated the effect of atypical medications on the Stroop test.

Clozapine. Buchanan et al.'s (1994) double-blind trial examined the influence of clozapine and haloperidol on the Stroop. A comparison of baseline performance, where all patients were receiving fluphenazine, with that after 10 weeks of treatment revealed that neither clozapine nor haloperidol significantly enhanced performance on the Stroop. A 1 year

open-label clozapine follow-up examination also failed to detect any benefit of either clozapine or haloperidol. Likewise, Purdon et al's (2001) 8 week open label study did not find any improvements in the Stroop interference scores. Classen and Laux (1988) failed to observe any within and between group effects on Stroop performance in groups of patients treated with clozapine, haloperidol or flupenthixol (a typical agent) for 7 days. The short duration of this trial may have been a factor contributing to the negative finding. A 12 week study by Lindenmayer et al. (1998) failed to report any improvements on the Stroop in two groups of subjects treated with either clozapine or risperidone. These results are based on a comparison of performance at baseline, when patients were receiving antipsychotic medications (unspecified), to that after 12 weeks of clozapine or risperidone therapy.

Risperidone. Lindenmayer (1998) has conducted the only study examining the effect of risperidone on the Stroop. As already mentioned, it was observed that risperidone had no effect on this selective attention task.

Risperidone's effect on the SoA was investigated by Stip and Lussier (1996). Typically, the SoA requires subjects to focus on a computer monitor where a row consisting of different letters flash for brief periods. Each presentation can range in length from 1, 4, 7 or 10 letters. Subjects are required to respond as quickly as possible whenever the letter 'X' appears in the array. A review of studies on the effects of typical neuroleptics on the SoA by Spohn and Strauss (1989) indicates that medications such as haloperidol can improvement performance.

Stip and Lussier (1996) studied a single group of patients who were receiving various typical neuroleptics at baseline. Subsequent to baseline assessments, patients were treated

with risperidone over a 16 week period. Results revealed that there were improvements on the SoA. In particular, the authors noted better detection of target stimuli. However, risperidone's causative role is difficult to ascertain for several reasons. First, the lack of comparison groups makes it difficult to determine if this positive finding was related to treatment with risperidone or if performance was enhanced because participants were withdrawn from their traditional antipsychotics. Additionally, substantial reductions in concomitant medications were noted over the course of open-label treatment with risperidone. This may have been a factor since anticholinergic medications can negatively impact tasks which require sustained and selective attentional resources (Spohn & Strauss, 1989). Finally, as previously mentioned, typical neuroleptics such as haloperidol can improve performance on this task.

Choice reaction time (CRT) paradigms were used by Zahn et al. (1994) and Kern et al. (1998) to assess the effect of atypical medications on selective attention. The CRT condition in Zahn et al.'s study required subjects to respond by lifting their right finger from a key whenever they heard a tone or by lifting their left finger if the stimulus was a light. Although this trial was open-label, they examined the performance of subjects randomly assigned to treatment with clozapine, fluphenazine or placebo after 6 weeks, 6 months and 12 months. Despite clozapine's superiority over fluphenazine and placebo in alleviating clinical symptoms, and its better motor side-effect profile relative to fluphenazine, no differences between the three treatments emerged on the CRT test. This study lends support to previous findings in that clozapine does not positively influence selective attentional abilities.

Kern et al. (1998) contrasted the effects of risperidone and haloperidol in two groups of treatment-resistant schizophrenia patients on a CRT task. Prior to randomization, all patients were treated with open-label haloperidol for a 3 week duration. Baseline assessments were conducted at the end of this period. Patients were then randomized to a double-blind fixed-dose trial of risperidone or haloperidol for a 4 week period. A subsequent 4 week double-blind flexible-dose period allowed the physician to adjusted the patient's dose either up or down.

The serial RT task required subjects to respond when an asterisk appeared in one of four locations (on a horizontal plane) by touching one of four corresponding keys on a computer keyboard. Although the order of the locations where the asterisk appeared may have seemed random, it actually appeared in a fixed sequence. As a result, the serial RT task also assessed the subject's ability to profit from incidentally learning where the asterisk would appear next; and should result in faster RT. At baseline, when all patients received haloperidol, there were no between group differences. When baseline performance was compared to that after 4 weeks of treatment with risperidone and haloperidol, the risperidone group had significantly faster RT. The haloperidol group's RT remained relatively unchanged throughout the duration of the study. According to the authors, it is difficult to determine the impact of motor side-effects on RT because there were no between group differences at any time on an EPS scale. They attribute the similarities in EPS to the use of antiparkinsonism medications in both the risperidone and haloperidol groups. Although the authors do not explicitly state that there were improvements in clinical symptoms with risperidone treatment, this is implied by their covarying the effects of clinical status on RT which did not affect

risperidone's superiority on RT. Therefore, RT appears to be independent of improvements in psychopathology. In addition, this faster RT was not attributable to incidental learning since both groups did not differ at any time point on a measure of motor learning on this task. However, although subjects were washed-out for a period of 3 to 7 days from antipsychotic medications prior to baseline assessments, they were all stabilized with haloperidol for 3 weeks before the washout period. Therefore, it is possible that this positive finding is attributable to being withdrawn from haloperidol and not risperidone treatment. This caveat could have been addressed in Kern et al.'s study if they had assessed patients after the 3 week haloperidol lead-in phase. A comparison of performance at this time point with that at the end of the washout phase may have shown that CRT was faster after the withdrawal of haloperidol and that its reintroduction may have caused poor CRT performance.

A study by Green et al. (1997) examined selective attention with the use of the Digit Span Distractibility Test. It must be noted, however, that they refer to the Digit Span Distractibility Test as a test of verbal working memory. Because this task does not require the manipulation of the information held in short-term stores, it is classified here as a test of selective attention (see Addington et al., 1997). Tests of selective attention involve two conditions: One with and one without a distractor. Typically, normal controls as well as patients with schizophrenia will perform more poorly in the distractor condition. However, it is not clear if poor performance is as a result of the distractor condition being more difficult or the distractor itself. To differentiate between task difficulty and the effect of a distractor condition, Oltmanns and colleagues (1975; 1978) developed the Digit Span Distractibility Test. This test equates the performance of normal control subjects on both the distractor and

no-distractor conditions, meaning that the level of difficulty is the same for both. In the non-distractor condition, subjects are required to listen to a series of six digits presented in a female voice; each digit is presented at the rate of 1 every 2 seconds. At the end of each six digit string, subjects are required to write down as many of the digits in the correct order as possible. In the distractor condition, subjects are required to listen to and remember five target digits presented by the female voice while ignoring four distractor digits read by a male voice. The four distractor digits are interjected between each of the five target digits. Similar to the non-distractor condition, the rate of target digit presentation in the distractor condition is also 2 seconds. Given that normal controls perform equally well in both conditions, decrements observed in the distractor condition are most likely attributable to the condition itself and not the level of difficulty.

Green et al.'s (1997) double-blind parallel group study examined the effects of risperidone and haloperidol on the Digit Span Distractibility Test over 8 weeks. Participants in this study were treatment-resistant chronic schizophrenia patients. Prior to baseline assessments, patients were stabilized with haloperidol over a 3 week period. Patients were then washed-out for 3 to 7 days, at the end of which baseline assessments were conducted. Patients were randomly assigned to blinded fixed dose treatment with risperidone or haloperidol for 4 weeks and the remainder of the 8 week trial allowed flexible dosing and remained double-blind. Compared to baseline assessments, Green et al. reported that patients treated with risperidone improved significantly on both the distractor and non-distractor conditions at 4 and 8 week reassessments. The group treated with haloperidol did not show any gains. In fact, Green et al. observed a non-significant decline in performance on the

distractor condition from 4 to 8 weeks. In addition, between group comparisons revealed that the risperidone treated group performed better than the haloperidol group on both conditions at 4 and 8 weeks. However, concluding that risperidone was instrumental in beneficially altering performance on a selective attentional task may not be accurate. These findings may simply represent an improvement in attention span (remembering more numbers) because better performance on both the distractor and non-distractor conditions were observed. A case for an improvement in selective attention could have been made if performance had been enhanced on the distractor condition only.

Three studies (Galletly et al., 1997; Hagger et al., 1993; Lee et al., 1994) have examined selective attention with the use of the Petersen Consonant Trigram (Spreen & Strauss, 1991). This test consists of two conditions. The first condition requires subjects to repeat three letters which, taken together, do not form a word. The second condition requires them to recall the letters after a 3, 9 or 18 second delay period, during which time they are instructed to count backward by 3's from a given number. The dependent variable derived from this test is the number of total letters correctly recalled.

Hagger et al. (1993) assessed performance on the Petersen Consonant Trigram in a group of treatment-resistant schizophrenia patients. At baseline, these patients were washed-out from various typical agents for a mean period of 9 days and were reassessed after 6 months of clozapine therapy. There were no comparison groups. Significant decline in performance occurred after 6 weeks of clozapine treatment. However, a recovery to baseline performance levels was observed at 6 months. Another within subject study with no control groups (Galletly et al., 1997) reported a finding contrary to that of Hagger's group. They

observed that performance on the Petersen Consonant Trigram improved over 8 months of clozapine treatment. Conclusions from both these studies are limited due to the lack of control groups. Lee and colleagues (1994) conducted a parallel group study which contrasted the effects of clozapine and various typical agents on the Petersen Consonant Trigram over 1 year. They reported improvements on this task after 6 weeks of clozapine therapy. However, gains beyond those at 6 weeks were not detected at 6 or 12 months. The group assigned to haloperidol treatment did not improve on this task. Additionally, there were no differences between the clozapine and haloperidol groups.

Olanzapine. The only study to report on the effect of olanzapine on CRT was conducted by Smith and colleagues (2001). These investigators compared olanzapine to haloperidol in a group of chronic treatment resistant patients in a long-term facility. This study was conducted in two phases. The first phase was a double-blind trial of olanzapine and haloperidol whereas the second phase was a 3 month open-label extension trial of olanzapine only. Results revealed that olanzapine had no effect on CRT at either 8 weeks or 3 months. Haloperidol did not change performance over 8 weeks of treatment and did not significantly differ from olanzapine.

Quetiapine. One study contrasted quetiapine and haloperidol on the Stroop (Velligan et al., 2002). This double-blind randomized fixed-dose study examined performance at baseline and again 24 weeks later. Between group analyses revealed that patients randomized to quetiapine performed better than those randomized to haloperidol at end-point when baseline scores were used as a covariate. In examining change scores from baseline to end-point, it is clear that the quetiapine group improved in their performance to a greater extent

relative to those randomized to haloperidol (+11 versus 4 respectively on the color-word condition). However, 50% of those randomized to haloperidol received anticholinergic medication compared to 8% of patients randomized to quetiapine. As such, psychomotor side-effects cannot be ruled-out in explaining the smaller improvement in performance in the haloperidol group. It can be concluded that quetiapine does not seem to impair selective attention.

Summary. There is little evidence to suggest that clozapine enhances performance on several tasks of selective attention. There is some preliminary evidence which suggests that risperidone may benefit certain selective attention tasks (SoA, Digit Span Distractibility Test). Also, whereas there appears to be no difference between clozapine and typical antipsychotics on selective attention, risperidone was demonstrated as being superior to haloperidol. The only trial to investigate the effect of olanzapine on CRT was negative. It can be concluded from the only study to examine quetiapine that it does not seem to impair performance on the Stroop. However, any superiority over haloperidol has yet to be established.

Divided Attention

According to Morse and Montgomery (1992), “Divided attention takes [the concepts of sustained and selective attention] one step further and requires the patient to monitor and respond simultaneously to multiple pieces/channels of information” (p. 122). Divided attention is subserved by neuroanatomical substrates similar to those of working memory. As such, these will be discussed in the section on working memory.

Very few tests have been developed to assess divided attention. The best known assessment instruments are those which use dichotic listening paradigms (Van Zomeren et al.,

1994). Unfortunately, there are no studies reporting the effects of atypical medications on divided attention using a dichotic listening task.

Working Memory

Working memory is defined as a “brain system that provides temporary storage and manipulation of the information necessary for such complex tasks as language comprehension, learning and reasoning” (Baddeley, 1986, p. 556). The most widely accepted model of working memory is that proposed by Baddeley and Hitch (1996), which suggests that working memory functions as an integrated system composed of three components. The central component, called the central executive, is responsible for the “attentional control of working memory”. It coordinates the information it receives from two other components called the slave systems: (1) the phonological loop and (2) the visuospatial sketchpad. The phonological loop is dedicated to the processing of non-spatial information whereas the visuospatial sketchpad is dedicated to the processing of spatial information. In addition to receiving information from these two systems, the central executive continuously summons and uses information or knowledge stored in long-term memory (Boulay, 1998; Fuster, 1997).

The use of working memory tasks which distinguish between stimuli types (spatial, non-spatial, or verbal) is of neuroanatomical importance. Monkey as well as human studies investigating various stimuli modalities in working memory tasks have demonstrated that each is subserved by different neuroanatomical circuits, all of which are reciprocally connected with the prefrontal cortex. For example, spatial working memory tasks principally recruit the occipito-parietal visual pathway which provides the prefrontal cortex with spatial information

(Courtney, Ungerleider, Keil, & Haxby, 1996; Owen, Evans, & Petrides, 1996; Sweeney et al., 1996). Tasks which use non-spatial stimuli will activate the occipito-temporal visual pathway which provides the prefrontal cortex with information about the physical qualities of objects (ie., shape, size, or color) (Jiang et al., 1998; Salmon et al., 1996). Finally, verbal working memory tasks have been found to be subserved by Broca's area as well as the supramarginal gyrus. Both of these areas operate with the prefrontal cortex to hold verbal information on-line over delay periods (Cohen et al., 1997; Fiez et al., 1996; Petrides, Alivisatos, Meyer, & Evans, 1993). Regardless of the stimulus modality used, each will recruit the dorsolateral prefrontal cortex for the maintenance, and if necessary, the manipulation of information held in working memory (Boulay, 1998; Owen, 1997; Rao et al., 1997).

Spatial and non-spatial (Carter et al., 1996; Fleming et al., 1997; Keefe et al., 1995; Keefe et al., 1997; Park & Holzman, 1992; Park & Holzman, 1993; Park, Holzman, & Goldman, 1995; Spindler et al., 1997), as well as verbal working memory (Carter et al., 1998; Fleming et al., 1995; Purdon, 1996) are consistently found to be impaired in persons with schizophrenia. However, very few studies have assessed the influence of atypical medications in working memory.

The use of the Digit Span Backward from the WAIS-R and the WMS-R has been used as a measure of verbal working memory. Upon hearing a series of numbers, subjects are required to repeat the numbers in the reverse order. This test becomes more difficult as the number of digits in each series increases. Two groups of investigators have assessed verbal working memory using Digit Span Backward (Grace et al., 1996; Rossi et al., 1997).

Although several others have used the Digit Span Forward and backward tests in their research, they report on combined scores without providing information about the individual tests (Fujii et al., 1997; Goldberg et al., 1993a; Purdon et al., 2000).

Using the Digit Span Backward test, Grace et al. (1996) observed that patients were able to recall significantly more digits after 3 years of clozapine therapy. However, these authors did not include comparison groups. Therefore their conclusion that clozapine was responsible for enhancing performance on this measure of verbal working memory is tenuous.

A 4 week study conducted by Rossi and colleagues (1997) examined the effect of risperidone on the digit-span backward test. They observed significant gains on this measure. Similar to Grace et al.'s. (1996) study, a lack of appropriate control groups makes inferences about risperidone's effect on working memory difficult.

Although the Paced Auditory Serial Attention Test (PASAT) is considered a test of speed of information processing that taps into several cognitive processes, its successful completion places heavy demands on working memory abilities. As such, the PASAT will be discussed within the context of working memory. The PASAT requires subjects to listen to digits which are presented at a fixed rate. Subjects are instructed to add pairs of digits as they are presented, report the sum aloud, and concentrate on adding the next pair while discarding their previous response. For example, if the following digits are presented: 4, 1, 6, 3; the subject is required to add the first pair $[4 + 1]$, report the result $[=5]$, discard the result, add the next pair $[1 + 6]$, report the result $[=7]$, discard the result, add the next pair $[6 + 3]$, report the result $[=9]$, discard the result and so on. Lindenmayer et al.'s. (1998) study assessed performance on this task by examining the number of incorrect additions. The

rate at which digits were presented was not reported in their study. Within group comparisons of baseline performance with that of 12 weeks of antipsychotic treatment revealed that neither clozapine nor risperidone enhanced performance on this task.

Smith et al. (2001) have conducted the only study to date which reports on verbal working memory using the Digit Span Backward test. They report on an 8 week double-blind trial comparing olanzapine to haloperidol in a group of treatment resistant chronic patients residing in a long-term facility. These investigators found no within or between group differences, indicating that neither olanzapine or haloperidol had an effect on verbal working memory. A 3 month open-label study using olanzapine only also failed to show any improvements.

Summary. Two studies have reported beneficial effects of clozapine and risperidone on verbal working memory using the Digit Span Backward test. However, a lack of control groups in both prohibits concluding that either atypical agent directly enhanced performance. One study contrasting the effect of clozapine and risperidone on the PASAT did not report any within or between group benefits of either medication on performance. It is difficult to determine olanzapine's effect on verbal working memory since the only study to examine this cognitive function did so in a group of severely ill patients. These three studies make it difficult to determine what effect atypical agents may have on verbal or spatial working memory.

No studies to date have examined the effect of atypical medications on spatial working memory performance in schizophrenia.

Summary: The Effects of Atypical Antipsychotic Medications on Neurocognitive Functioning in Schizophrenia

Without considering the literature critically, one may conclude that atypical antipsychotic medications have beneficial effects across several cognitive domains in schizophrenia. The present review challenges this general conclusion. A critical evaluation of the literature has demonstrated that the vast majority of positive findings reported are at best tenuous. The primary reasons why clear conclusions cannot be drawn is because poor experimental methodology was used in the majority of studies. Nevertheless, within the context of these methodological shortcomings, several preliminary observations can be extracted.

The present review discerned that clozapine: (a) does not appear to enhance psychomotor functioning; (b) may enhance visuospatial and motor processing; (c) does not have a beneficial effect on verbal or visual memory; (d) may have some beneficial effects on executive functioning; (e) may or may not have an effect on arousal – the findings thus far are inconclusive; (f) does not influence sustained attention; (g) does not enhance performance on several tasks of selective attention; and (h) may or may not influence performance on tasks of verbal or visual working memory, a lack of data thus far prohibits making any conclusions. There are no published reports concerning the effect of clozapine on divided attention. With respect to risperidone, it was illustrated that: (a) the findings regarding psychomotor functioning are inconclusive; (b) it has few beneficial effects on visuoperceptual and motor processing tasks; (c) it has very little effect on visual or verbal memory; (d) it does not enhance performance on tasks of executive functioning; (e) no conclusions with respect to

arousal can be extended due to a lack of well controlled studies; (f) it does not influence performance on sustained attention; (g) it may have some beneficial influence on certain selective attentional tasks; and (h) two reports suggests that it has little influence on verbal working memory. There are no published reports concerning the effect of risperidone on divided attention.

Considering the effect of olanzapine on neurocognition in schizophrenia, the literature suggests that: (a) it may improve psychomotor functioning; (b) it has few beneficial effects on visuoperceptual and motor processing tasks; (c) it may have some beneficial influence on specific tests of verbal and visual memory; (d) there is conflicting evidence with respect to executive functioning and (e) one report suggests that it has very little influence on verbal working memory. At the present time, it is impossible to comment on olanzapine's influence on (a) arousal, (b) sustained attention, (c) selective attention, (d) divided attention, and (e) visual working memory.

Finally, with respect to quetiapine, three studies suggest that: (a) it may not affect psychomotor functioning; (b) there is conflicting evidence regarding its effect on visuoperceptual and motor processing tasks; (c) it does not have an effect on memory for lists of words whereas it may be related to improved memory for visual material; (d) it may have some beneficial influence on executive functioning; (e) it may be related to improved performance on sustained attention; and (f) it does not have an effect on selective attention. There is no information on the effect of quetiapine on: (a) arousal; (b) divided attention or (c) verbal and visual working memory.

In considering the literature as a whole, it is not clear which cognitive domains may be improved by atypical agents or if these newer medications are superior to the older neuroleptics. Additionally, because the pharmacological profile of each atypical agent differs significantly, the effect of each on neurocognition remains uncertain (Meltzer & McGurk, 1999). A critical review of the literature only allows us to reason that several poorly controlled preliminary clinical studies suggest that atypical agents in general may have beneficial effects on neurocognition in schizophrenia. It must be underscored that these results should be considered as preliminary. As such, properly controlled prospective double-blind trials are required for the delineation of the effects of atypical medications on cognition in schizophrenia.

Experiment: Contrasting the Effects of Haloperidol and Olanzapine on Attention and Working Memory in Schizophrenia: A Double-Blind Flexible Dose Study

Purpose and Rationale

Patients diagnosed with schizophrenia almost invariably suffer from severe deficits across several neurocognitive domains. Half a century ago, when neuroleptic medications were first introduced, it was found that they were efficacious in alleviating the positive symptoms of the illness. However, both the negative symptoms as well as cognitive deficits remained unchanged. The unpleasant motor side-effects associated with older typical neuroleptics necessitated the development of newer compounds with a more favorable side-effect profile. As expected, these newer compounds, called atypical antipsychotics, were found to beneficially affect the positive symptoms of the illness and had a better motor side-effect profile. Additionally, it was observed that atypical medications alleviated some of the negative symptoms of schizophrenia. Because research has demonstrated that more severe negative symptoms tend to correspond to more severe neurocognitive deficits, several investigators hypothesized that atypical medications may have some beneficial influence on cognition. This line of reasoning has resulted in several published research papers on the effects of clozapine, risperidone, olanzapine, and quetiapine on neurocognitive functioning in schizophrenia. Overall, these preliminary clinical studies suggest that atypical medications may have a positive effect on several cognitive domains.

It will be recalled that attentional impairments in schizophrenia have always been regarded as a hallmark feature of the disorder. Also, several authors have hypothesized that working memory may represent the neurocognitive analogue to disordered thought processes

in schizophrenia. Therefore, it is reasonable to assume that improvements in these cognitive domains could have significant implications. Indeed, research has demonstrated that cognition, and not positive symptoms, is related to functional outcome. For instance, Green's (Green, 1996) review of the literature suggests that impairments in attention and working memory abilities may be a rate limiting factor in overall functional outcome; relating to social problem solving, skill acquisition, and community outcome. Curiously, however, both attention and working memory have been under investigated among studies examining the effects of atypical medications on neurocognition. In fact, only eight studies have investigated attentional processes and only three have examined verbal working memory abilities. To date, there is no information on the effect of olanzapine on attentional or working memory abilities in schizophrenia. The purpose of this study is to contrast the influence of olanzapine and haloperidol on attention and working memory functioning in a group of early phase schizophrenia patients.

Hypothesis

Atypical antipsychotic medications, including olanzapine, show a trend toward improving cognitive functioning in schizophrenia whereas conventional typical neuroleptics do not. Therefore, it is hypothesized that olanzapine will be superior to haloperidol in enhancing performance on several attentional and working memory processes in individuals suffering from schizophrenia.

Methodological Issues

The current study attempted to remedy several methodological issues common to many of the studies discussed in this prospectus. More specifically, eight common

methodological flaws have been identified: (a) a lack of control over baseline medication status, (b) blinding, (c) a lack of appropriate control groups, (d) the influence of learning and practice effects, (e) test/retest interval variability, (f) illness duration, (g) inappropriate experimental medication doses, and (h) the use of concomitant medications.

Baseline Medication Status

It will be recalled that carry-over effects from antipsychotic, as well as concomitant medications, at baseline pose a significant challenge in the interpretation of the effects of experimental drug treatments. The most effective method for controlling this confound is by studying patients who are neuroleptic naive or who have not received any antipsychotic agents for several months. However, the recruitment of such patients is difficult and would require an extended period of time (Kane, Schooler, Marder, Simpson, & Casey, 1994; Keefe et al., 1999). For instance, in the schizophrenia program at the Royal Ottawa Hospital, 5 years is the estimated time required to recruit 30 never medicated patients (A. Labelle, personal communication, May 1, 2000).

As such, what are the guidelines for controlling the confounding effect of baseline medication status? At the present time, the only published suggested guideline is that proposed by Keefe and colleagues (1999). They state that “given the limited research previously conducted in this area [examining the effect of atypical medications on cognition in schizophrenia], the only requirement regarding the pharmacological status at baseline is that the baseline medication be determined” (p. 202). The majority of published studies examining the effect of atypical agents on neurocognitive functioning did not provide this information and the interpretation of results continues to be ambiguous.

To date, the most stringent design attempting to control for baseline medication effects was conceived by Purdon et al. (2000). Their study included patients receiving typical or atypical medications prior to study entry. Purdon and colleagues titrated antipsychotic medications downward over a 1 month period which was followed by a 2 to 9 day washout period. Using this approach, the superiority of two atypical medications (including olanzapine) over haloperidol was delineated.

All patients entering this study were assessed on three occasions within a 2 day period while they were receiving regular antipsychotic medications as well as concomitant medications. Antidepressant medications were discontinued prior to enrolment. Appendix A outlines the antipsychotic as well as concomitant medications received by patients during baseline assessments. The fourth neurocognitive baseline assessment was conducted after patients were washed-out from all medications for a 72 hour period. Patients were not allowed to receive any benzodiazapine medications at any time during the study. However, they were allowed to receive zopiclone on a regular or on an as needed basis. Furthermore, each treatment consisted of equal numbers of patients having received typical and atypical medications at entry into this study. This randomized block procedure ensured that any baseline medication carry-over effects remaining after the 3 day washout period were balanced within each experimental treatment.

Blinking

Several studies reviewed in the introduction were open-label (e.g., Galletly et al., 1997; Grace et al., 1996; Hagger et al., 1993; Kenny & Meltzer, 1991; Lindenmayer et al.,

1998; Meyer-Lindenberg et al., 1997; Rossi et al., 1997; Stip & Lussier, 1996; Zahn et al., 1994). Patients in the current study were randomized to double-blind treatment.

Control Groups

While it is common practice in psychological research to include control groups, only three studies reviewed included a sample of normal controls (Hagger et al., 1993; Meyer-Lindenberg et al., 1997; Sax et al. 1998). Several either lacked appropriate control groups or did not employ control groups whatsoever (e.g., Fujii et al., 1997; Galletly et al., 1997; Goldberg et al., 1993a; Grace et al., 1996; Hagger et al., 1993; Purdon et al., 2001; Rossi et al., 1997; Stip et al., 2002; Stip & Lussier, 1996).

In addition to the 2 treatment groups (olanzapine and haloperidol), a group of age matched healthy normal controls were included in the current study. These subjects provided information about normal performance on each cognitive test as well as information regarding learning and practice effects over repeated exposures to the same material.

A group of first degree family members were also included in the current study. Their inclusion was appropriate for two reasons: (a) there is little doubt that schizophrenia is, to a certain extent, genetically mediated (McGuffin & Sturt, 1986; Prescott & Gottesman, 1993), and (b) several studies have demonstrated that never diagnosed family members of persons with schizophrenia perform more poorly on certain cognitive tasks (e.g., tasks of sustained attention as well as working memory) compared to normal controls but better than their ill relative (Chen et al., 1998; Goldberg et al., 1993b; Park et al., 1995; Szmanski, Kane, & Lieberman, 1991). Therefore, a control group of never diagnosed family members with a putatively subtle neurocognitive compromise similar to, but not as extreme as, the

experimental group provided valuable information with regard to practice effects in the absence of psychotropic medications.

Learning and Practice Effects

Several studies did not use alternative forms of test materials for which practice effects would be expected over repeated trials (e.g., Buchanan et al., 1994; Galletly et al., 1997; Goldberg et al., 1993a; Grace et al., 1996; Hagger et al., 1993; Kern et al., 1999; Lee et al., 1994; Meyer-Lindenberg et al., 1997; Stip & Lussier, 1996). Because this study focused on attentional as well as working memory functioning, practice effects based on remembering specific stimuli previously presented was expected to be minimal. Therefore, alternative test forms were not used. However, the repeated exposure to the same material could have some non-specific effects on enhanced performance over time (e.g., less anxiety on the second and subsequent testing sessions; the development of strategies in the completion of certain tasks). As a result, all patients were assessed on the same neurocognitive battery on four occasions prior to randomization to double-blind treatment. By using data obtained from the fourth assessment as the baseline measures for treatment, the likelihood of attributing any cognitive gains observed in the double-blind treatment phase to learning and practice effects is minimal.

Test/Retest Time Intervals

Although the majority of investigations were consistent in their test/retest time intervals, four studies were extraordinarily variable in their reassessment periods (Fujii et al., 1997; Galletly et al., 1997; Goldberg et al., 1993a; Stip & Lussier, 1996). This is an important issue since antipsychotic medications may require some time before changes in cognitive functioning emerge. Therefore, the pooling of subjects who were reassessed over

a short exposure to treatment with those who were exposed for longer periods may result in a type II error (e.g., Goldberg et al., 1993a). Time of exposure to treatment is a nuisance factor which can easily be controlled. This study reassessed all subjects over six specific time intervals ensuring a homogeneity of exposure to treatment.

Illness Duration

As will be recalled, neurocognitive decrements tend to occur in the first 10 years of illness. The majority of studies examined medication effects in pooled samples of patients with different illness durations (e.g., Galletly et al., 1997; Goldberg et al., 1993a; Hagger et al., 1993; Lindenmayer et al., 1998). For instance, as already mentioned, Goldberg et al. grouped patients whose illness duration ranged from 3 to 21 years. Such between patient heterogeneity could potentially negate the ability to detect the positive or negative influence of antipsychotic medications on cognitive functioning (type II error). The current study only included patients whose duration of illness was 5 years or less.

Inappropriate Experimental Medication Doses

Although the majority of studies used clinically appropriate doses of study medications, two investigations used overly elevated doses (Kern et al., 1999; Lindenmayer et al., 1998). Recent literature has clearly demonstrated that higher doses of antipsychotic medications do not necessarily result in a better response; rather they are likely to result in increased side-effects and poorer neurocognitive performance (e.g., Lindenmayer et al., 1992). Therefore, dosing in the current study was flexible, at the discretion of the treating physician and allowed for the use of low therapeutic doses.

Use of Concomitant Medications

The use of concomitant medications was not adequately controlled for or accounted for in several studies (e.g., Buchanan et al., 1994; Classen & Laux, 1988; Daniel et al., 1996; Fujii et al., 1997; Galletly et al., 1997; Goldberg et al., 1993a; Grace et al., 1996; Kern et al., 1998; Kern et al., 1999; Lee et al., 1994; Lindenmayer et al., 1998; Rossi et al., 1997; Stip & Lussier, 1996; Zahn et al., 1994). Medications such as antidepressants, benzodiazepines and anticholinergics are known to have negative effects on neurocognitive functioning. Therefore, when taken in conjunction with experimental antipsychotic treatments, an absence of improvements or decrements in cognitive performance may be incorrectly attributed to the antipsychotic medication of interest.

Extrapyramidal symptoms are a common side-effect mainly associated with typical neuroleptic treatment. Therefore, the use of anticholinergic concomitant medications was allowed throughout the current study. It was anticipated that the use of lower doses of haloperidol in this relatively young sample would result in less anticholinergic use. Because olanzapine is not associated with EPS at clinically appropriate doses, the use of anticholinergics in this sample was expected to be minimal. When required, the use of anticholinergic medications was closely monitored and documented. We also intended to determine if differential effects on cognitive performance might have been as a result of anticholinergic use (sample stratification based on high versus low anticholinergic doses). However, since there was no effect of treatment on neurocognitive functioning, this analysis was not performed.

The use of benzodiazepine medications was not permitted at anytime during the current study. Generally, several days of washout from these medications are required before their detrimental impact on cognition is alleviated. As an alternative, zopiclone was used on an as needed basis in order to control anxiety throughout the study. Zopiclone is a hypnotic which acts as a benzodiazepine. It has less adverse and less prolonged effects on cognitive functioning. Several reports have demonstrated that cognitive functioning returns to pre-medication baseline levels 8 hours after the last ingestion of zopiclone (Moon, Hindmarch, & Holland, 1990; Musch & Maillard, 1990). Therefore, a minimum of 8 hours since the last dose of zopiclone had to have elapsed before a patient was assessed on neuropsychological tests.

Method

Participants

Four groups of subjects were recruited in the current study: (a) a patient group randomly assigned to olanzapine, (b) a patient group randomly assigned to haloperidol, (c) a group of first degree family members related to the schizophrenia patient group, and (d) a group of normal controls. All subjects provided voluntary signed informed consent prior to participation (see Appendixes B, C, and D for consent forms).

The patient group consisted of in- or outpatients recruited from the Schizophrenia Program at the Royal Ottawa Hospital. Both male and female patients between the ages of 18 to 65 years were eligible. Prior to enrollment, each of the following inclusion and none of the exclusion criteria were met: (a) patients were in the early phase of their illness (within 5 years of diagnosis), (b) they met DSM-IV criteria for schizophrenia (either disorganized type [295.10]; paranoid [295.30]; undifferentiated type [295.90]; or schizoaffective disorder [295.70]), (c) they were in a medication transition phase – meaning that they and their psychiatrist had decided to discontinue their current antipsychotic therapy for whatever reason, and (d) they had a total score between 60 and 100 on the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1986).

Exclusion criteria included: (a) a history of seizure disorder, (b) a history of traumatic brain injury resulting in loss of consciousness, (c) current alcohol or drug abuse, (d) having received depot neuroleptic treatment within the past 6 months; and (e) developmentally delayed.

A total of 30 patients participated in the consenting process and signed an informed consent form (Appendix B). Patient characteristics are presented in Appendix E. Of these, 2 were unable to complete the four assessments during the pre-randomization period and 1 was lost to follow up after having completed the first pre-randomization baseline assessment. The remaining 27 patients completed all four pre-randomization assessments. Of these, 14 were randomized to treatment with olanzapine and 13 to haloperidol. It must be noted that 9 patients were receiving olanzapine at study entry. Therefore, 5 were pseudo-randomly assigned to treatment with olanzapine and 4 to treatment with haloperidol. A total of 5 patients, all randomized to haloperidol, terminated the study prior to the end of the 56 day post-randomization period. Reasons for early termination included a lack of efficacy in 1 case (AR23), persistent extrapyramidal symptoms despite anticholinergic treatment in 3 cases (AS26, SB36 and RA42) and a dystonic reaction in 1 case (EL20). Patients AR23 and AS26 completed 28 days of double blind treatment and patient RA42 completed 49 days. Data from the last observation for these 3 cases were carried forward and included in the post-randomization analyses. However, patient EL20 was only able to complete 3 days of double-blind therapy and SB36 8 days. Due to the short exposure to blinded treatment, it was decided that these 2 cases would not be included in the analyses. Therefore, a total of 25 patients were included in the pre- and post-randomization analyses. Fourteen were randomized to olanzapine and 11 to haloperidol.

A total of 9 first degree family members were recruited. Their participation was contingent on the following inclusion criteria: (a) male or female between the ages of 18 - 65 years; (b) must be a biologically related first degree family member of one of the patients

participating in the study; and (c) must be willing to undergo neuropsychological testing on six different occasions. The exclusion criteria were: (a) a documented history of mental illness, (b) meeting the criteria for schizophrenia or schizophrenia spectrum disorders as determined from the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992), (c) a history of seizure disorder; (d) a history of traumatic brain injury resulting in the loss of consciousness; (e) current alcohol or drug abuse; and (f) developmentally delayed.

A control group consisting of 13 normal healthy volunteers was recruited from the community. Their participation was contingent on the following inclusion criteria: (a) male or female between the ages of 18 - 65 years, and (b) were willing to undergo neuropsychological testing on six different occasions. The exclusion criteria were: (a) a history of personal or familial (among first degree relatives) mental illness, (b) meeting criteria for schizophrenia or schizophrenia spectrum disorders as determined from the FIGS; (c) a history of seizure disorder; (d) history of traumatic brain injury resulting in the loss of consciousness; (e) current alcohol or drug abuse; and (f) developmentally delayed.

Demographic data for all participants are presented in Table 1. The groups did not differ in age ($F [3,43] = 1.46, p = n.s.$), gender ($\chi^2 [3] = 3.36, p = n.s.$), education ($F [3,43] = 1.57, p = n.s.$), or on an estimate of general intelligence ($F[3,43] = 2.73, p = n.s.$). Comparisons between pairs of groups on each demographic measure were also non-statistically significant.

Furthermore, there were no differences between patients randomized to olanzapine or haloperidol in age of illness onset ($t [23] = -0.13, p = n.s.$), duration of illness

($t [23] = -1.59, p = n.s.$), patient disposition throughout the study ($\chi^2 [2] = 0.05, p = n.s.$) or in number of hospitalizations, $t (23) = -0.48, p = n.s.$ (see Table 2).

Table 1

Demographic Information

Group	Age (M,SD)	Gender (Males / Females)	Education (M,SD)	Estimated General Intelligence (M,SD)
Ol (n=14)	32.86 (12.08)	10 / 4	12.29 (2.67)	100.91 (8.66)
Hal (n=11)	34.73 (10.62)	8 / 3	13.00 (2.93)	104.46 (8.66)
FM (n=9)	43.33 (15.30)	4 / 5	14.67 (2.12)	109.38 (6.12)
NC (n=13)	33.31 (13.06)	6 / 7	14.00 (3.34)	108.54 (8.40)

Note. General intelligence was estimated based on a method developed by Barrona.

Table 2

Patient Group Characteristics

Group	Age of illness onset Mean years (S.D.)	Duration of Illness Mean years (S.D.)	Patient Disposition In / Out / In+Out	Total Number of Hospitalizations
Ol (n=14)	31.29 (12.26)	1.68 (1.03)	3 / 5 / 6	1.14 (0.95)
Hal (n=11)	31.91 (12.09)	2.64 (1.94)	3 / 4 / 4	1.36 (1.36)

Note. In = inpatient, Out = outpatient, In+Out = had both an inpatient and outpatient status during the study.

MeasuresClinical Scales

The PANSS (Kay et al., 1986) was used to assess psychopathology in the schizophrenia patients only. The PANSS is a validated 7 point (1 = absent to 7 = extreme)

30 item scale specifically developed to assess the symptoms of schizophrenia. It consists of three subscales which rate patients on positive symptoms (7 items), negative symptoms (7 items) and on general psychopathology (16 items). A total score is obtained by adding the three subscales. The Calgary Depression Scale for Schizophrenia (CDSS; Addington & Addington, 1990) was used to measure depressive symptoms in patients. The CDSS is a validated 9 item scale capable of reliably dissociating between negative and depressive symptoms.

Extrapyramidal motor side-effects were assessed using the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard et al., 1980). The ESRS is a validated instrument specifically developed for rating patients on the severity of parkinsonism, dystonia, and dyskinesia. The PANSS, CDSS and ESRS were completed by psychiatrists who had met interrater reliability criteria in previous clinical trials conducted in the Schizophrenia Program at the Royal Ottawa Hospital.

Family History

The Family Interview for Genetic Studies (FIGS; Maxwell, 1992) is a validated semi-structured interview schedule capable of reliably identifying 12 potential psychiatric diagnoses in family members of probands. It was conducted by one individual (Luc Boulay) for rating consistency.

Neurocognitive Battery

The neurocognitive battery focused on attention and working memory. Detailed descriptions of administration procedures as well as recording sheets for each test are presented in Appendix F. Each assessment was conducted by one individual (Luc Boulay).

Estimate of general intellectual functioning. General intellectual functioning was estimated using a method derived by Barona as described in (Gregory, 1987). Using different weightings, this method combines education, age, gender, race and occupation to estimate general intellectual functioning.

Motor functioning. Fine motor movement was evaluated using the Grooved Peg Board (Lafayette Instrument, 1989). This task required subjects to place pegs into a 5 x 5 matrix of holes as quickly as possible. Dominant hand and non-dominant hand performance were assessed. The dependent variable for this task was the mean time to completion for both hands combined.

Motor speed was measured using the Finger Tapping test (Psychological Assessment Resources, Inc. [PAR], 1992). This test required subjects to press a lever with their index finger as many times as possible within 10 seconds. This procedure was repeated several times for each hand. The mean number of taps for both hands combined served as the dependent variable.

Reaction time. Simple Reaction Time (SRT) was measured using a computerized task developed by Tombaugh and Francis (1999a). Subjects were required to respond as rapidly as possible by pressing the spacebar on a computer keyboard when they saw an 'X' appear on a monitor. The median time to respond in milliseconds over four blocks of ten trials was the dependent variable.

Choice Reaction Time (CRT) was assessed using a computerized test developed by Tombaugh and Francis (1999b). This task required subjects to respond as rapidly as possible by pressing a computer key with their right index finger when two identical numbers appeared

on a computer monitor (9 and 9; 4 and 4). If the numbers were different (9 and 4; 4 and 9), subjects were required respond by pressing a computer key with their left index finger. The dependent variable for this task was the median reaction time in milliseconds over 3 blocks of 12 trial for both conditions.

Verbal short-term memory. Verbal short-term memory was assessed with the Digit Span Forward subtest from the WMS-R (Wechsler, 1987). Subjects were required to listen to a series of digits of increasing span length ranging from three to eight. At the end of each digit string, subjects verbally reported as many digits they could remember in the correct order. Raw scores were used as the dependent variable.

Visuospatial short-term memory. Visuospatial short-term memory was evaluated with the Circles Away Test (Boulay, 2000). This test consists of three conditions: (a) an immediate condition, (b) a 3 second delay condition, and (c) a 10 second delay condition. Using a computer monitor, subjects were required to focus on a centrally located cross on a white background for a period of 2 seconds. The cross then disappears and an open circle (the target location) appeared in 1 of 68 possible positions to for a duration of 1 second (together, these 68 locations form a circle). Immediately following the target presentation, the 68 reference circles appear on the monitor. In the response phase, the subjects were required to indicate where the target circle appeared by touching one of the reference circles. The same procedures were used in the 3 s and 10 s delay conditions. To ensure that subjects shifted their gaze away from the target location and to reduce the potential for the verbal mediation of stimulus location during the 3 and 10 second delay periods, individual white uppercase letters appeared on a black background in the center of the monitor at the rate of

one every second. Subjects were instructed to name each letter aloud as they appeared. The 68 possible locations appeared at the end of the delay and the subjects were required to indicate where the target was located. The sum of the number of circles away from target locations over the 16 trials in each condition served as the dependent variable.

The Visual Memory Span Forward subtest of the WMS-R (Wechsler, 1987) was also used to assess visuospatial short-term memory. This test was computerized for presentation and scoring consistency. Subjects saw an array of eight red squares displayed on a computer monitor. Some squares flash from red to white and back to red again at the rate of one every second forming a pattern. Sequence lengths ranged from two to eight squares. Immediately after each sequence, subjects were required to repeat the patterns from memory. Raw scores were used as the dependent variable.

Attention. The D-2 Test of Attention is a test of visual selective and sustained attention (Brickenkamp & Zillmer, 1998; Spreen & Strauss, 1991). This pencil and paper cancellation test required subjects to cross out all letters 'd' only if they had any combination of two dashes (one on top and one on the bottom; two on top or two on the bottom). Subjects were given 20 seconds per line (total of 14 lines) to cross-out as many targets as possible. The dependent variable was the concentration performance index. This was calculated by subtracting the number of correctly crossed out targets from errors of commission and omission.

The Stroop was used as a measure of selective attention (Golden, 1978; Spreen & Strauss, 1991). The Stroop has three conditions, each lasting 45 seconds. First, subjects were required to read aloud down several columns which consist of words referring to colors

(red, green, blue). Second, they were required to name the color of the ink in which a series of X's are printed. Third, color-words are printed in incongruent colored ink (e.g., the word red printed in blue ink). Subjects were required to ignore the word and report the ink color. Interference scores were calculated based on the total number of words correctly read, the total number of colors correctly identified, and the total number of correctly named colors from the incongruent color-word condition. These scores were then converted to T-scores for analyses.

The Digit Span Distractability test was used as a measure of selective attention. This test consists of two conditions; no-distractor and distractor conditions. In the no-distractor condition, subjects listened to a string of six digits recorded in a female voice presented at the rate of one every 2 seconds. At the end of the string, subjects had to recall as many of these digits as possible in the correct order. In the distractor condition, target digits were presented by a female voice at the rate of one every 2 seconds; however, distractor digits were interjected between each of the target digits by a male voice. Subjects were required to listen to and remember target digits presented by the female voice while ignoring distractor digits from the male voice. The proportion of correctly recalled digits in the distractor condition was the dependent variable in the current study. This was calculated by dividing the total number of correctly recalled digits by the maximum possible score (35) (Addington et al., 1997; Green & Walker, 1986; Green et al., 1997; Oltmanns, 1978; Oltmanns & Neale, 1975; Spring, 1985).

Visual working memory. The backward condition of the visual memory span from the WMS-R (Wechsler, 1987) assessed visuospatial working memory. Similar to the tapping

forward condition, subjects were instructed to watch green squares on a computer monitor flash from green to white and back to green again at the rate of 1 every second in sequences of increasing length (range from two to seven). They were required to repeat the pattern in reverse order. Raw scores were the dependent variable.

Verbal working memory. The Digit Span Backward condition of the WMS-R (Wechsler, 1987) assessed verbal working memory. Rather than repeating numbers in the same order as in the Digit Span Forward condition, subjects were required to give the numbers in reverse order from last to first. Raw scores were used as the dependent measures.

The Letter-Number Sequencing subtest of the WAIS-III (Wechsler, 1997) required subjects to listen to a series of intermixed numbers and letters. At the end of the presentation, they were asked to repeat the series by recalling the numbers first in ascending order followed by the letters in alphabetical order. Raw scores were used as the dependent measures.

Order of Test Administration

The order of test administration was the same for all six assessments: (a) Circles Away Test; (b) Digit Span Distractibility Test; (c) Digit Span Forward; (d) Finger Tapping; (e) Digit Span Backward; (f) Grooved Peg Board; (g) Simple RT; (h) Choice RT; (i) Stroop; (j) the D2 Test of Attention; (k) Visual Memory Span Forward; (l) Visual Memory Span Backward; and (m) Letter Number Sequencing. This order was established to ensure the interspersal of easy and difficult tasks, tasks with different modalities (verbal and visual), and tasks which are completed quickly with those of longer duration (Lezak, 1983).

It should be noted that the A-X Continuous Performance Test was also administered to all subjects. However, technical difficulties prohibited the analysis of these data.

Procedures

Screening

Subjects who met all of the inclusion and none of the exclusion criteria were asked to participate in this study. Signed informed consent was obtained. Demographic data were collected from each participant (see Appendix G). The FIGS was completed for all candidates. For patient safety reasons, a physical examination was conducted by a study physician with the patients only.

Pre-Randomization

Refer to Figure 1 for a summary of the trial design. All subjects underwent neurocognitive testing twice on Day -4, once in the morning (Day -4a) and once in the afternoon (Day -4b). Day -3 marked the first day of the medication washout period which lasted 72 hours ($\pm$ 6 hours). A psychiatrist completed clinical efficacy (PANSS and CDSS) and safety (ESRS) assessments on Days -3 and 0 for the patient subjects only. Day 0 was defined as the end of the 72 hour medication washout period. All subject groups completed neurocognitive assessments at Days -3 and 0.

Post-Randomization

Day 0 marked the beginning of 56 days of randomized double-blind treatment with either olanzapine or haloperidol for patient subjects only. Clinical efficacy (PANSS and CDSS) as well as safety (ESRS) assessments were conducted by study psychiatrists at Days 28 and 56. Because this was a flexible dose study, patients were able to see their own psychiatrists outside of scheduled study visits. Any changes in medication dosing or in concomitant medication status (adding or removing a concomitant medication or any changes

in experimental medication dosing) were documented. All subject groups completed neurocognitive assessments at Days 28 and 56.

Figure 1. Trial design summary. All subject groups underwent four neurocognitive assessments during the pre-randomization period (Days -4a, -4b, -3 and 0). Patients were washed out from their antipsychotic medications for a 72 hour period between Days -3 and 0. Once assessments at Day 0 were complete, patients were randomized to 56 days of double-blind treatment with either olanzapine or haloperidol. Family member and normal control groups did not receive any medications. All subject groups were reassessed on neurocognitive measures at Days 28 and 56.

Statistical Analyses

Results for each cognitive test will be divided into two sections. The first section addresses the question of practice effects during the pre-randomization period. The second section seeks to determine the manner in which olanzapine and haloperidol affected cognition during the post-randomization period. As described previously, all subjects underwent neurocognitive testing on four occasions during the pre-randomization phase (Days -4a, -4b, -3 and 0). Since randomization to olanzapine or haloperidol had not taken place during this

time, any changes in performance that might occur during the pre-randomization period would be primarily due to the effects that repeated administration of the cognitive tests had on behaviour (i.e., practice effects). However, cognitive changes occurring after the randomization of olanzapine and haloperidol (post-randomization Days 0, 28 and 56) would be attributable to the effects of the medications.

All dependent variables from the pre- and post-randomization periods were screened for violations related to repeated measures ANOVA. However, attempts at normalizing data using various transformations were not effective. Therefore the original data were analyzed.

The data from the pre- and post randomized periods were analyzed in two ways. First, repeated measures analysis of variance (RMA) were used. A three groups (patients, family members, normal controls) by four times (Days -4a, -4b, -3 and 0) mixed split plot design was used in the pre-randomization period. Because the literature has consistently demonstrated that patients perform more poorly on neurocognitive measure when compared to family members and normal controls, main effects of group were anticipated. Main effects of time were also anticipated reflecting practice and learning effects. However, since repeated exposures to the cognitive tests were not expected to produce differential effects on patients, family members and normal controls, group by time interactions were not anticipated. That is, any differences in the level of cognitive functioning that occurred on the first day of testing were expected to remain throughout the pre-randomization period. A slightly different picture was expected to emerge in the post-randomization period. Here, the differential

effects of the two drug regimes were expected to produce significant main effects which progressively increase over the two test periods resulting in a significant group by time interaction.

The second type of analysis used change scores. These scores were employed to evaluate the degree to which the initially lower performance of the patient group was reflected on subsequent trials, particularly those following the randomization of medication. That is, it was important to determine if performance at Days -4b, -3 and 0 in the pre-randomization phase was influenced by baseline performance at Day -4a. Perhaps even more critical, differences in performance at Day 0 had to be considered when examining performance at Days 28 and 56 in the post-randomization phase. To equate groups on baseline performance in the pre-randomization phase, mean percent change scores for each group on each variable were calculated between Day -4a and the three subsequent testing sessions. The same procedure was used in the post-randomization phase between Day 0 and the following two sessions. These scores were calculated using the following formula: $((\text{score at time X} - \text{score at baseline}) / \text{score at baseline}) \times 100\%$. Two ANOVAs using these percent change scores for each dependent variable were conducted; one examining pre-randomization performance and the other post-randomization performance. Group effects were expected to disappear once performance was equated for differences in baseline performance in the pre-randomization phase. However, equating performance at the beginning of the post-randomization periods was not expected to overshadow medication effects.

Results

The results section will be presented in a bipartite manner. Statistical analyses for each section will be presented first and will be followed by a summary paragraph.

Clinical Scales

Both patient groups were similar at baseline (Day 0) in psychopathology, depressive symptoms and extrapyramidal symptom severity (see Table 3). A comparison of clinical scores at baseline revealed there was no difference between the groups on any of the PANSS subscale scores; positive: $t(25) = 0.12$, $p = \text{n.s.}$, negative: $t(25) = 0.71$, $p = \text{n.s.}$, general psychopathology: $t(25) = 0.59$, $p = \text{n.s.}$ Furthermore, the groups did not differ on the PANSS total score, $t(25) = 0.84$, $p = \text{n.s.}$ and on depressive symptoms as measured with the Calgary Depression Scale, $t(25) = -1.23$, $p = \text{n.s.}$ In addition, patients in both groups did not differ on motor symptoms as assessed with the ESRS; parkinsonism: $t(25) = 0.49$, $p = \text{n.s.}$, dystonia: $t(25) = 0.59$, $p = \text{n.s.}$, and dyskinesia: $t(25) = -0.47$, $p = \text{n.s.}$

There were no differences between patients treated with olanzapine or haloperidol at the end of the 2 month trial on any of the clinical scales (see Table 3). More specifically, there was no difference between patients on the PANSS positive ($t[22] = 1.48$, $p = \text{n.s.}$), negative ($t[22] = 0.49$, $p = \text{n.s.}$), and general psychopathology ($t[22] = 1.58$, $p = \text{n.s.}$) subscale scores, or on the PANSS total score ($t[22] = 1.52$, $p = \text{n.s.}$). Moreover, treatments did not differentially affect depressive symptoms as measured with the CDS-S ($t[22] = -1.89$, $p = \text{n.s.}$) or on motor functioning as measured with the ESRS; Parkinsonism: $t(22) = 0.10$, $p = \text{n.s.}$; dystonia: $t(22) = 1.25$, $p = \text{n.s.}$; dyskinesia: $t(22) = 0.94$, $p = \text{n.s.}$

Table 3

Means and Standard Deviations on the Clinical Scales in the Post-randomization Period (Days 0 and 56)

Measure	Group	Post-Randomization	
		0 ^a	56 ^b
		<u>M</u> (<u>SD</u>)	<u>M</u> (<u>SD</u>)
PANSS			
Positive	OI	18.14 (5.84)	15.43 (6.07)
	Hal	17.85 (6.95)	12.00 (3.74)
Negative	OI	22.50 (4.67)	17.79 (6.89)
	Hal	20.77 (7.76)	17.90 (7.84)
Gen. Psych.	OI	35.50 (44)	28.79 (5.07)
	Hal	33.77 (69)	26.20 (4.96)
Total	OI	76.14 (10.07)	62.00 (12.84)
	Hal	72.38 (13.76)	56.10 (12.97)
CDS-S	OI	2.79 (3.96)	1.36 (1.28)
	Hal	4.85 (4.76)	4.10 (5.07)
ESRS			
Parkinsonism	OI	6.93 (7.03)	7.79 (7.75)
	Hal	5.69 (6.03)	6.80 (6.73)
Dystonia	OI	0.21 (0.80)	0.57 (1.50)
	Hal	0.08 (0.28)	0.00 (0.00)
Dyskinesia	OI	0.64 (1.50)	1.36 (2.02)
	Hal	1.00 (2.38)	0.10 (0.32)

Note. ^a Olanzapine N=14 and Haloperidol N = 13; ^b Missing data for AR23 and two subjects, EL20 and SB36, were excluded from the analyses. Therefore the total n for the haloperidol group at Day 56 is 10. Within group analyses from Day 0 to Day 56 for the haloperidol group are based on these 10 cases.

Comparative Literature

There was no overall difference between olanzapine and haloperidol on any of the clinical measures after 2 months of treatment. Clinical trials contrasting olanzapine and haloperidol on psychopathology have demonstrated that olanzapine and haloperidol alleviate positive symptoms to a similar degree (Tollefson et al., 1997). Our results are consistent with this finding in that there was no difference between groups on positive symptoms. With respect to the negative symptoms, the literature has demonstrated that olanzapine is superior to haloperidol on this symptom domain (Tollefson et al., 1997). Our between group findings do not support this observation. A link between negative symptoms and dosage of haloperidol has been debated in the literature (Allan, Sison, Alpert, Connolly, & Crichton, 1998). Lower doses of haloperidol in conjunction with more use of anticholinergic medications in this group may have influenced scores on the negative subscale of the PANSS. In considering depressive symptoms, olanzapine has been shown to be superior to haloperidol on this symptom domain (Tollefson et al., 1997). However, our results do not support this observation. A larger sample size would be necessary to delineate this finding further. There were no differences between groups on the ESRS parkinsonism, dystonia or dyskinesia subscales. However, those randomized to haloperidol required more anticholinergic medications relative to those randomized to olanzapine. Several clinical trials have reliably demonstrated that haloperidol has a propensity to cause motor side-effects to a greater extent than does olanzapine. The relatively lower average dose of haloperidol prescribed (< 10 mg/day) in this study may have accounted for this result.

Motor FunctioningGrooved Peg Board

Pre-randomization. Figure 2 (left panel) depicts the time required by the Pt, FM and NC groups to complete the Grooved Peg Board test over the four pre-randomization assessments. A visual inspection of this figure clearly indicates that the Pt group required more time to complete the Grooved Peg Board relative to the FM and the NC groups. This observation was supported with a significant main effect of group, $F(2,44) = 10.44$, $p < .0001$ (see Appendix H). This figure also shows that the time to complete this fine motor

Figure 2. Grooved Peg Board pre-randomization. Left Panel: Time required by the Pt, FM and NC groups to complete the grooved-peg board task in the pre-randomization period. Right Panel: Mean percent change scores on the grooved-peg board task for the Pt, FM and NC groups from Day -4a to Day -4b, Day -4a to Day -3 and from Day -4a to Day 0.

movement task decreased over successive trials, $F(3,42) = 18.52$, $p < .0001$. A group by time interaction was not observed indicating that the initial differences between the groups were maintained throughout the pre-randomization period, $F(6,84) = 0.75$, $p = \text{n.s.}$ An examination of mean percent change scores supports this observation and shows that practice

and learning effects were equivalent across groups, $F(6,84) = 0.42$, $p = ns$ (see Figure 2 right panel and Appendix I).

Post-randomization. From Figure 3 (left panel and Appendix J) it is evident that the Ol as well as the Hal groups required more time to complete the Grooved Peg Board compared to the FM and NC groups, $F(3,43) = 7.12$, $p = .001$. It should also be noted that the superiority of the FM and NC groups was essentially unchanged from baseline (Day 0).

Figure 3. Grooved Peg Board post-randomization. Left Panel: Time required by the Ol, Hal, FM and NC groups to complete the grooved-peg board task in the post-randomization period. Right Panel: Mean percent change scores on the grooved-peg board task for the Pt, FM and NC groups from Day 0 to Day 28 and from Day 0 to Day 56.

Moreover, in examining performance over time, the flat nature of all four curves indicates that performance did not appreciably change over the 2 month trial, $F(2,42) = 0.98$, $p = ns$. The lack of a significant group by time interaction ($F[6,84] = 0.65$, $p = ns$) coupled with a lack of differences in mean percent change scores ($F[6,84] = 0.61$, $p = ns$) (see Figure 3 right panel, and Appendix K) highlights the fact that performance on the Grooved Peg Board did not change for any of the groups over the 2 month post-randomization phase. It can be

concluded that randomization to treatment with olanzapine or haloperidol in the patient group had no effect on Grooved Peg Board performance in the post-randomization phase.

Finger Tapping

Pre-randomization. Figure 4 (left panel and Appendix H) shows the average number of finger taps produced (right and left hands combined) over the four pre-randomization assessments. As can be observed by the overlapping nature of the three curves, there is virtually no difference in the number of taps produced between groups during the pre-randomization period, $F(2,42) = 0.29$, $p = ns$. The increase in the number of taps over the

Figure 4. Finger Tapping pre-randomization. Left Panel: Mean number of taps produced by the Pt, FM and NC groups (right and left hands) on the Finger Tapping test in the pre-randomization period. Right Panel: Mean percent change scores test for the Pt, FM and NC groups from Day -4a to Day -4b, Day -4a to Day -3 and from Day -4a to Day 0.

course of the four assessments ($F[3,40] = 16.27$, $p < .0001$) suggests the presence of a practice effect. The lack of a group by time interaction indicates that each group performed similarly over the four pre-randomization sessions, $F(6,80) = 0.77$, $p = ns$. The lack of a between group difference in mean percent change scores indicates comparable levels of

practice effects across groups, $F(6,80) = 0.85$, $p = ns$ (see Figure 4 right panel and Appendix I).

Post-randomization. Figure 5 (left panel, and Appendix J) demonstrates that none of the four groups significantly differed from one another on the Finger Tapping test during the post-randomization period ($F [3,41] = 0.47$, $p = ns$) and that there was no change in performance over time, $F (2,40) = 0.01$, $p = ns$. In addition, there was no group by time interaction, $F(6,80) = 0.67$, $p = ns$. Figure 5 (right panel, and Appendix K) highlights the finding that performance for all four groups remained unchanged over the 2 month post-randomization period, $F (6,80) = 0.70$, $p = ns$. Considered together, these results indicate that peak performance on the finger tapping test was achieved by Day 0 for all groups and that randomization to olanzapine or haloperidol had absolutely no influence on performance in the patient groups.

Figure 5. Finger Tapping post-randomization. Left Panel: Mean number of taps produced by the Ol, Hal, FM and NC groups (right and left hands) on the Finger Tapping test in the post-randomization period. Right Panel: Mean percent change scores for the Ol, Hal, FM and NC groups from Day 0 to Day 28 and from Day 0 to Day 56.

Comparative Literature

Both the Grooved Peg Board and the Finger Tapping tests were used as measures of psychomotor functioning. Consistent with the literature contrasting performance between patients and normal controls, the patient group was slower at completing the Grooved Peg Board task relative to normal controls in the pre-randomization period (King, 1994). Performance by patients on the Finger Tapping test was virtually identical to that of the normal and family member control groups; both in the pre- and post-randomization phases. This latter result may have been due to the fact that all patients entering this trial were receiving atypical medications and were washed-out for 3 days or were medication free throughout the 5 day pre-randomization period. This is an important point since typical neuroleptics have been found to negatively affect motor tasks (Cassens et al., 1990; King, 1990). Therefore, potential decrements related to typical medication use was not an issue for this sample. Also, the composition of our sample may have influenced performance on the Finger Taping test. According to Lezak (1995b), young males tend to perform better on this motor task and our sample was predominantly comprised of younger males.

Learning and practice effects were detected for both the Grooved Peg Board and the Finger Tapping test in the pre-randomization period. Improved performance in normal controls has been documented over repeated administrations for the Grooved Peg Board (Feinstein, Brown, & Ron, 1994). However, the Finger Tapping test is usually resistant to learning and practice effects when normal control subjects are assessed over several weeks (Salinsky, Storzbach, Dodrill, & Binder, 2001). McCaffrey et al. (2000) also report very little improvement over two assessments. An examination of mean percent change scores revealed

that all three groups improved at the same rate and that differences at baseline were maintained throughout the pre-randomization trial. Similar to McCaffrey et al.'s review, our subjects do not show very much change on the second assessment. Change in our sample appear after the fourth assessment. Therefore, the Finger Tapping test may be resistant to change for two assessments. However, improvements may become apparent after four sessions.

In considering the 2 month post-randomization period for both the Grooved Peg Board and the Finger Tapping test, there was no change beyond that seen at Day 0 for any of the four groups. Mean percent change scores remained virtually nil for all four groups on the two motor tasks. This finding indicates that treatment with olanzapine or haloperidol in the patient group had little effect on the Grooved Peg Board or the Finger Tapping tests. One may have expected a decrement in performance on these tasks for the haloperidol group. A possible reason why this decrement was not observed may be related to the average daily dose of haloperidol used in this study. On average, patients received 9.32 mg/day ($n = 11$, LOCF) which is substantially lower than doses used historically. In fact, the mean daily dose for the eight patients randomized to haloperidol who completed the study was 7.5 mg/day. Furthermore, there were no differences between the olanzapine and haloperidol groups on the ESRS at the end of the 2 month trial. Nevertheless, it must be noted that benztropine was prescribed for 3 of 14 (21%) patients randomized to olanzapine and 8 of 13 (62%) patients randomized to haloperidol to counteract motor side-effects.

These results conflict with those reported by Purdon and colleagues (2000). They too examined the influence of olanzapine and haloperidol on the Grooved Peg Board as well

as the Finger Tapping test in a similar group of patients. When not corrected for multiple comparisons, they reported that olanzapine was superior to haloperidol on both tasks after 1 year of treatment. The discrepancy between their results and our own could be due to several factors. First is the difference in duration between our trial and Purdon et al.'s trial. Their trial was 1 year whereas ours was 2 months. Therefore, it is possible that any beneficial influence of olanzapine on fine motor functioning may not be evident at 8 weeks. Alternatively, it may be that subjects randomized to olanzapine in Purdon's trial had more exposures to the Grooved Peg Board relative to those randomized to haloperidol. This is a critical point considering attrition rates in their study. Many more patients randomized to haloperidol in the Purdon investigation were prematurely withdrawn before the end of the 1 year study. For those who completed the study, they were exposed to the Grooved Peg Board on four occasions. A caveat to this position is that the saliency of practice and learning effects can vary as a function of test-retest intervals with shorter intervals favoring larger practice effects (Dikmen, Heaton, Grant, & Temkin, 1999). Therefore, it could be argued that any learning or practice effects on the Grooved Peg Board and the Finger Tapping test in Purdon's study may have decayed after 6, 30 and 54 weeks thereby making learning and practice effects less of an issue. A lack of any improvement in the two other groups in their study, risperidone and haloperidol, and the fact that each treatment was dosed appropriately strengthens this statement. Finally, Purdon et al. observed that patients randomized to haloperidol had significantly more Parkinsonism relative to those in the olanzapine group when examining LOCF data. Patients in both groups in our trial were not different on EPS at baseline nor at the end of the trial.

More recently, Bilder et al. (2002) also reported that olanzapine had no effect on Finger Tapping over 14 weeks of treatment. This was true of risperidone as well as haloperidol whereas clozapine was found to significantly improve simple motor speed. However, this finding is relevant to treatment resistant hospitalized patients who were receiving 20 mg of olanzapine, 8 mg of risperidone, 20 mg of haloperidol and 450 mg of clozapine.

Two other investigations have examined the effect of atypical medications on the Grooved Peg Board and report discrepant findings. While Kern et al. (1998) reported that risperidone was superior to haloperidol on a similar motor task over 12 weeks (Pin test), Purdon et al. (2001) did not observe any within group changes on the Grooved Peg Board or the Finger Tapping test with quetiapine or haloperidol over 3 months of treatment. Differences in sample composition, test-retest intervals and variability in haloperidol dosage between these studies and ours could account for these discrepant findings.

Reaction Time

Simple

Pre-randomization. Figure 6 (left panel and Appendix H) shows the time required to press the space bar on a computer keyboard when an 'X' appeared on a monitor. The Pt group required significantly more time to respond on the simple reaction time task than did the FM and NC groups, $F(2,44) = 8.65, p < .002$. Response times over the four pre-randomization assessments did not change significantly, ($F[3,42] = 1.20, p = ns$) indicating that there were no practice or learning effects on this task. The differential performance by the groups at Day -4a was maintained during the pre-randomization period as shown by a

non-significant group by time interaction, $F(6,84) = 1.41$, $p = ns$. An examination of mean percent change scores revealed that changes in performance over time did not significantly differ between groups showing that baseline performance at Day -4a did not significantly influence performance on subsequent trials, $F(6,84) = 1.43$, $p = ns$ (see Figure 6 right panel and Appendix I). These results indicate that the patient group consistently required more time to respond relative to the two control groups. Furthermore, there were no significant practice or learning effects on the simple reaction time task and the magnitude in change in performance for each group over the four assessments was comparable.

Figure 6. Simple Reaction Time pre-randomization. Left Panel: Mean response times in msec for the Pt, FM and NC groups on a simple reaction time task in the pre-randomization period. Right Panel: Mean percent change scores in performance on the simple reaction time task by the Pt, FM and NC groups between Day -4a and Day -4b, Day -4a and Day -3, and Day -4a and Day 0.

Post-randomization. Figure 7 (left panel and Appendix J) depicts how randomization to either olanzapine or haloperidol affected performance on the simple reaction time task over the 2 month post-randomization phase. Results reveal that both patient groups required more time to respond in comparison to both control groups, $F(3,43) = 6.33$, $p < .005$. No

significant change in performance over time ($F [2,42] = 1.75$, $p = ns$), no group by time interaction ($F [6,84] = 0.76$, $p = ns$), and no between group difference in mean percent change score ($F [6,84] = 0.77$, $p = ns$) (see Figure 7 right panel and Appendix K) indicate that there was no change in performance for any group in the post-randomization period. It can be concluded that randomization to olanzapine or haloperidol in the patient group did not significantly alter performance on this simple reaction time task.

Figure 7. Simple Reaction Time post-randomization. Left Panel: Mean response times in msec for the Ol, Hal, FM and NC groups on a simple reaction time task in the post-randomization period. Right Panel: Mean percent change scores in performance on the simple reaction time task by the Ol, Hal, FM and NC groups between Day 0 and Day 28 and from Day 0 and Day 56.

Choice

Pre-randomization. Figure 8 (left panel and Appendix H) shows response times for determining if two numbers appearing simultaneously on a computer monitor were the same or different. It is apparent from this figure that the Pt group was significantly slower to respond than were the FM and NC groups. This observation was supported statistically, $F (2,42) = 5.23$, $p < .01$. No overall change in performance was observed from Day -4a to Day

0 indicating that there were no learning or practice effects, $F(3,40) = 1.82$, $p = ns$. In addition, there was no interaction ($F[6,80] = 0.38$, $p = ns$) and mean percent change scores were almost identical for each group, $F(6,80) = 0.29$, $p = ns$ (see Figure 8 right panel and Appendix I). These results indicate that the patients were consistently slower to respond than both control groups and that there is no evidence of learning or practice effects on this choice reaction time task. Furthermore, when equated for differences at baseline (Day -4a), there is virtually no difference between groups in mean percent change scores indicating that existing differences at baseline did not influence performance over the other three assessments.

Figure 8. Choice Reaction Time pre-randomization. Left Panel: Mean response times in msec for the Pt, FM and NC groups on a choice reaction time task in the pre-randomization period. Right Panel: Mean percent change scores in performance on the choice reaction time task by the Pt, FM and NC groups between Day -4a and Day -4b, Day -4a and Day -3, and Day -4a and Day 0.

Post-randomization. From Figure 9 (left panel and Appendix J), it is apparent that both patient groups differ from both control groups on the choice reaction time task; an observation supported by a significant main effect of group, $F(3,41) = 4.91$, $p < .01$. The

absence of a main effect of time ($F [2,40] = 1.23$, $p = ns$), the lack of an interaction ($F [6,80] = 0.51$, $p = ns$) and no significant difference between groups on mean percent change scores ($F [6,80] = 0.64$, $p = ns$) indicate that there was no change in performance over time for any of the groups and that the differences observed between groups at Day 0 were carried over from the pre-randomization period and sustained throughout the 2 month post-randomization period (see Figure 9 right panel and Appendix K). In short, it can be concluded that neither olanzapine nor haloperidol had any significant influence on choice reaction time.

Figure 9. Choice Reaction Time post-randomization. Left Panel: Mean response times in msec for the OI, Hal, FM and NC groups on a choice reaction time task in the post-randomization period. Right Panel: Mean percent change scores in performance on the choice reaction time task by the OI, Hal, FM and NC groups between Day 0 and Day 28 and from Day 0 and Day 56.

Comparative Literature

There is very little evidence in the literature to suggest that atypical medications will enhance performance on reaction time tasks. Our study supports this view. Performance on both the simple as well as choice reaction time tasks was slower for patients compared to performance by both the normal and family member control groups during the pre-

randomization period. This finding is consistent with the literature which addresses differences in speed of information processing between normal control subjects and patients with schizophrenia (King, 1991; Voruganti et al., 1997). Practice and learning effects were not observed for either task in the pre-randomization period. This finding is not surprising since performance on SRT or CRT tasks are usually stable across repeated measures, even when test-retest periods are short. For example, Wilson et al. (2000) assessed brain injured as well as normal controls on twenty occasions over a 4 week period and found that there were no learning or practice effects on a SRT task in either group. Also, Tombaugh (personal communication, January 31, 2003) has not found practice effects over four assessments on either the SRT or CRT.

Treatment with olanzapine or haloperidol did not influenced performance on either the SRT or CRT tests in this study. The level of performance seen at Day 0 was maintained throughout the 2 month post-randomization period. This was true of all groups. This observation is in keeping with another report by Smith et al. (2001) who contrasted olanzapine and haloperidol after 8 weeks of treatment in a group of chronic treatment resistant patients in a long-term setting. With respect to clozapine, another atypical antipsychotic medication, Zahn et al. (1994) observed that 6 weeks of treatment with clozapine or fluphenazine did not significantly improve performance on a simple or choice reaction time task despite significant improvements in EPS for the clozapine group.

Verbal Short-Term MemoryDigit Span Forward

Pre-randomization. Figure 10 (left panel and Appendix H) shows performance on the WMS-R Digit Span Forward test. As can be seen in this figure, there is a significant difference in performance between the three groups, $F(2,44) = 12.73$, $p < .0001$. Post-hoc analyses revealed that the patient group remembered fewer series of numbers in comparison to the NC group only, Tukey, a , $p < .0001$. In addition, the Pt, FM and NC groups combined improved over time indicating the presence of practice and learning effects, $F(3,42) = 5.46$, $p < .005$. The lack of an interaction ($F[6,84] = 0.78$, $p = ns$), in addition to no difference between groups on mean percent change scores ($F[6,84] = 0.79$, $p = ns$), indicate that the

Figure 10. Digit Span Forward pre-randomization. Left Panel: Performance by the Pt, FM and NC groups on the Digit Span Forward subtest of the WMS-R (raw scores) in the pre-randomization period. Right Panel: Mean percent change scores on the Digit Span Forward subtest for the Pt, FM and NC groups from Day -4a to Day -4b, Day -4a to Day -3 and from Day -4a to Day 0.

initial differences between groups at Day -4a were maintained throughout the three subsequent testing sessions and that practice and learning effects were similar for each group

(see Figure 10 right panel and Appendix I). From these results it can be concluded that there were practice and learning effects on the Digit Span Forward test and that these effects were equivalent over groups. Additionally, initial differences between groups at baseline (Day 0) were maintained during the pre-randomization period.

Post-randomization. As can be seen in Figure 11 (left panel and Appendix J), the Ol, Hal, FM and NC groups differed significantly from one another on the Digit Span Test in the post-randomization period ($F [3,43] = 9.12, p < .0001$). Both the Ol and Hal groups correctly recalled fewer series of digits when compared to the NC group, Tukey $a, p < .0001$.

Figure 11. Digit Span Forward post-randomization. Left Panel: Performance by the Ol, Hal, FM and NC groups on the Digit Span Forward subtest of the WMS-R (raw scores) in the post-randomization period. Higher scores mean better performance. Right Panel: Mean percent change scores on the Digit Span Forward subtest for the Ol, Hal, FM and NC groups from Day 0 to Day 28 and from Day 0 to Day 56.

Differences observed at Day 0 were maintained during the 2 month post-randomization period. This latter finding is supported by a non-statistically significant main effect of time ($F [2,42] = 0.30, p = ns$) and a non-statistically significant group by time interaction ($F[6,84] = 2.09, p = ns$). Although not completely evident from Figure 11 (right panel), mean percent

change scores were not statistically significant between groups suggesting that performance at Day 0 did not influence performance at Days 28 and 56, $F(6,84) = 1.99$, $p = ns$ (also see Appendix K). Two outliers, one in each patient group, account for the non-significant visible interaction on mean percent change scores. These results indicate that there was no effect of 56 days of treatment with either olanzapine or haloperidol on the Digit Span Forward subtest of the WMS-R.

Comparative Literature

Short-term verbal memory was assessed using the Digit Span Forward subtest of the WMS-R. Patients were unable to correctly recall series of digits as well as the normal control group. This finding is in keeping with other studies which have examined performance on the Digit Span Forward subtest of the WMS-R for patients with schizophrenia, first-degree family members and normal controls (Conklin, Curtis, Katsanis, & Iacono, 2000; Green & Walker, 1986). A lack of significant differences in the present study between the Pt and FM groups may reflect insufficient power to detect such a difference. Practice and learning effects were observed during the pre-randomization period. Learning and practice effects are negligible when the Digit Span Forward and Backward are considered together (Dikmen et al., 1999). Lezak (1995) suggests that alternate digit sequences be used if subjects are to be repeatedly assessed, implying that there may be some level of learning and practice effects. Wilson et al. (2000) were able to demonstrate that subjects who suffered a brain injury could improve their performance when exposed to this task more than 10 times whereas performance for normal controls remained stable over 20 administrations. An examination of the effect of time for each group in our study reveals a similar pattern. The Pt group was the only group to

show significant improvement ($F[3,12] = 3.77, p < .05$) whereas the FM and NC did not improve over repeated exposures.

There was no effect of olanzapine or haloperidol on this short-term verbal memory task in the post-randomization period. This result is entirely consistent with several studies which examined olanzapine (Smith, 2001), clozapine (Buchanan et al., 1994; Daniel et al., 1996; Goldberg et al., 1993; Purdon et al., 2001) and risperidone (Rossi et al., 1997; Stip & Lussier, 1996). From these studies, and our own, it can be postulated that atypical, and typical, neuroleptics have very little influence on the Digit Span Forward test.

Visuospatial Short-Term Memory

Circles Away 10 Second Delay

Pre-randomization. Figure 12 (left panel and Appendix H) shows that the Pt group made more errors identifying a target location on a computer monitor after a 10 second delay relative to both the FM and NC groups, $F(2,44) = 11.10, p < .0001$. The absence of a main

Figure 12. Circles Away pre-randomization. Left Panel: Accuracy on a visuospatial memory task by the Pt, FM and NC groups in the pre-randomization period. Higher scores indicate poorer performance. Right Panel: Mean percent difference scores for the Pt, FM and NC groups from Day -4a to Day -4b, Day -4a to Day -3 and from Day -4a to Day 0.

effect of time suggests that there were no significant practice or learning effects, $F(3,42) = 0.98$, $p = ns$. The non-significant interaction ($F[6,84] = 1.17$, $p = ns$), coupled with no significant differences in mean percent change scores, suggest that differences in performance between the Pt, FM and NC groups at Day -4a were sustained over the three subsequent trials, $F(6,84) = 0.90$, $p = ns$ (see Figure 12 right panel and Appendix I).

Post-randomization. Once randomized to treatment with either olanzapine or haloperidol, it can be seen in Figure 13 (left panel and Appendix J) that the two patient groups differ from the two control groups on the Circles Away visuospatial memory test. This

Figure 13. Circles Away post-randomization. Left Panel: Accuracy on a visuospatial memory task by the Ol, Hal, FM and NC groups in the post-randomization period. Higher scores indicate poorer performance. Right Panel: Mean percent difference scores for the Ol, Hal, FM and NC groups from Day 0 to Day 28 and from Day 0 to Day 56.

observation was supported by an overall main effect of time, $F(3,43) = 6.79$, $p < .002$. The Ol group performed more poorly than both the FM and NC groups (Tukey a , $p < .005$ and $.0001$, respectively). This may reflect a sample bias since the Ol and Hal groups differed (although non-significantly) in their performance at Day 0. Performance on this test did not change for any of the groups over the 2 month post-randomization period. Differences seen

at baseline (Day 0) were maintained throughout the post-randomization period. A non-significant main effect of time ($F[2,42] = 0.94$, $p = ns$), a non-significant interaction ($F[6,84] = 0.62$, $p = ns$), as well as no difference in mean percent change scores support the latter statement, $F(6,84) = 0.55$, $p = ns$ (see Figure 13 right panel and Appendix K). As such, randomization to treatment with either olanzapine or haloperidol did not alter performance on a visuospatial memory task.

Visual Memory Span

Pre-randomization. Figure 14 (left panel see Appendix H) outlines how the Pt, FM and NC groups performed on the Visual Memory Span Forward subtest of the WMS-R. A main effect of group was detected indicating that the three groups differed in their ability to

Figure 14. Visual Memory Span pre-randomization. Left Panel: Performance on the Visual Memory Span Forward subtest from the WMS-R by the Pt, FM and NC groups in the pre-randomization period. Higher scores indicated better performance. Right Panel: Mean percent change scores on the Visual Memory Span Forward by the Pt, FM and NC groups from Day -4a to Day -4b, Day -4a to Day -3 and from Day -4a to Day 0.

correctly remember increasingly difficult sequences of spatial patterns, $F(2,44) = 9.74$, $p < .0001$. Performance on this visual task was stable across the four pre-randomization

assessments since no main effect of time ($F [3,42] = 2.59, p = ns$) and no significant interaction, ($F [6,84] = 1.36, p = ns$) occurred. Also, mean percent change scores were not significantly different, $F(6,84) = 1.42, p = ns$ (see Figure 14 right panel and Appendix I).

Post-randomization. The Ol, Hal, FM and NC groups differed in their performance on the Visual Memory Span Forward subtest of the WMS-R in the post-randomization period, $F (3,43) = 6.08, p < .005$ (see Figure 15 and Appendix J). Performance by all four groups at Days 28 and 56 merely reflect performance at Day 0. This can be seen in Figure 15 (left and right panels) and is supported statistically with no significant main effect of time ($F [2,42] = 0.92, p = ns$), no significant group by time interaction ($F[6,84] = 0.39, p = ns$), and no difference in mean percent change scores, $F(6,84) = 0.35, p = ns$ (see Appendix K). Therefore, 2 months of treatment with either olanzapine or haloperidol did not significantly impact performance on the Visual Memory Span Forward subtest of the WMS-R.

Figure 15. Visual Memory Span post-randomization. Left Panel: Performance on the Visual Memory Span Forward subtest from the WMS-R by the Ol, Hal, FM and NC groups in the post-randomization period. Higher scores indicated better performance. Right Panel: Mean percent change scores on the Visual Memory Span Forward by the Pt, FM and NC groups from Day 0 to Day 28 and from Day 0 to Day 56.

Comparative Literature

Two assessments were used in this study to assess visuospatial memory. The first was the Circles Away Test and the other the visual memory span subtest of the WMS-R. Patients' performance on both was poorer relative to the normal and family member control groups during the pre-randomization period. No effects of learning or practice were observed on either test. From the WMS-R manual (Wechsler, 1987), learning and practice effects are minimal for the visual memory span forward subtest from 4 to 6 week test-retest intervals. However, there is no information on repeated assessments during shorter time intervals. The Circles Away test was developed by the author (Luc Boulay) and normative data on a large group of normal control has not been gathered. Nevertheless, the data obtained in 13 healthy normal controls suggest that performance on this test is stable over short test-retest intervals (reliability coefficient $\alpha = 0.71$) and over 1 and 2 month intervals (reliability coefficient $\alpha = 0.84$).

Performance at the end of the pre-randomization period, Day 0, did not appreciably change for any of the four groups in the post-randomization period. Between group differences at Day 0 did not account for level of performance at Days 28 and 56. As such, it appears that olanzapine and haloperidol exerted little influence on visuospatial memory. Using a paper and pencil test (see Keefe et al., 1995) similar to the Circles Away computerized test, Smith et al. (2001) also observed that olanzapine was no different than haloperidol. However, their performance did improve after 3 months of open label therapy with olanzapine. Patients in our study may have also shown an improvement if the duration of the trial was longer. Improvement reported in Smith's trial was observed during the open

label phase in the absence of control groups making it difficult to delineate olanzapine's contribution. Consistent with our observations, other atypical medications do not appear to enhance performance on visuospatial abilities (Daniel et al., 1996; Goldberg et al., 1993).

Attention

Selective (D2 Test of Attention)

Pre-randomization. Overall, as can be seen in Figure 16 (left panel and Appendix H), the Pt, FM and NC groups significantly differed in the pre-randomization phase on the D2 Test of attention, $F(2,44) = 17.84$, $p < .0001$. Significant practice and learning effects for subsequent trials were observed showing that all groups were able to correctly identify and cross-out more targets over successive testing sessions, $F(3,42) = 69.26$, $p < .0001$. Initial

Figure 16. D2 Test of Attention pre-randomization. Left panel: Concentration Performance index scores of the D2 Test of Attention for the Pt, FM and NC groups in the pre-randomization period. These scores are comprised of the total number of targets crossed-out minus errors of omission and errors of commission. Higher scores mean better performance. Right Panel: Mean percent change scores for the Pt, FM and NC groups on the Concentration Performance index of the D2 Test of Attention from Day -4a to Day -4b, Day -4a to Day -3, Day -4a to Day 0.

differences in performance by the groups were maintained over the pre-randomization period as indicated by the lack of a significant group by time interaction, $F(6,84) = 1.14$, $p = ns$. Finally, an ANOVA of mean percent change scores revealed that practice and learning effects were equivalent for all groups, $F(6,84) = 1.73$, $p = ns$ (see Figure 16 right panel and Appendix I). B

Post-randomization. From Figure 17 (left panel and Appendix J) it is clear that the Ol and Hal groups differed from the FM and NC groups during the post-randomization period on the D2 Test of Attention. This observation is supported statistically by a significant main

Figure 17. D2 Test of Attention post-randomization. Left panel: Concentration Performance index scores of the D2 Test of Attention for the Ol, Hal, FM and NC groups in the post-randomization period. These scores are comprised of the total number of targets crossed-out minus errors of omission and errors of commission. Higher scores mean better performance. Right Panel: Mean percent change scores for the Ol, Hal, FM and NC groups on the Concentration Performance index of the D2 Test of Attention from Day 0 to Day 28 and from Day 0 to Day 56.

effect of group, $F(3,43) = 10.75$, $p < .0001$. The parallel curves in Figure 17 (left and right panels) show that performance did not change over time ($F[2,42] = 0.27$, $p = ns$) and that differences in performance at Day 0 remained virtually unchanged at Days 28 and 56, $F[6,84]$

= 0.99, $p = \text{ns}$. Also, differences in performance observed at Day 0 had no influence on performance at Days 28 or 56, $F(6,84) = 0.70$, $p = \text{ns}$ (see Appendix K). These results suggest that 2 months of treatment with either olanzapine or haloperidol had no effect on attention as assessed with the D2 Test of Attention.

Stroop

Pre-randomization. Figure 18 (left panel and Appendix H) depicts performance on the Stroop for the Pt, FM and NC groups in the pre-randomization period. As revealed by a main effect of group, the Pts, FM and NCs differed in their ability to suppress interfering information, $F(2,44) = 9.64$, $p < .0001$. Post-hoc analyses revealed that the NC and Pt groups differed significantly, Tukey a , $p < .0001$. Although not completely obvious from

Figure 18. Stroop pre-randomization. Left Panel: T-Scores for the Pt, FM and NC groups on the Stroop in the pre-randomization period. Higher scores signify less susceptibility to interference. Right Panel: Mean percent change scores (calculated using T-Scores) for the Pt, FM and NC groups on the Stroop from Day -4a to Day -4b, Day -4a to Day -3, and from Day -4a to Day 0.

Figure 18 (left panel), a significant main effect of time indicates that there were practice and learning effects on this selective attention task, $F(3,42) = 5.09$, $p < .005$. A group by time

interaction was not observed indicating that the initial differences between the groups were maintained throughout the pre-randomization period, $F(6,84) = 0.58$, $p = ns$. An examination of mean percent change scores supports this observation and shows that practice and learning effects were equivalent across groups, $F(6,84) = 0.51$, $p = ns$ (see Figure 18 right panel and Appendix I).

Post-randomization. Figure 19 (left panel and Appendix J) depicts the effect of 2 months of treatment with either olanzapine or haloperidol in patients compared to the FM and NC groups on the Stroop. It was observed that there was a significant main effect of group

Figure 19. Stroop post-randomization. Left Panel: T-Scores for the Ol, Hal, FM and NC groups on the Stroop in the post-randomization period. Higher scores signify less susceptibility to interference. Right Panel: Mean percent change scores (calculated using T-Scores) for the Ol, Hal, FM and NC groups on the Stroop from Day 0 to Day 28 and from Day 0 to Day 56.

in the post-randomization phase, $F(3,43) = 5.01$, $p = .005$. Differences between all four groups at Days 28 and 56 did not appreciably differ from baseline performance (Day 0). This statement is supported by the lack of a main effect of time ($F[2,42] = 1.89$, $p = ns$) and a non-significant group by time interaction, $F(6,84) = 0.36$, $p = ns$. Performance by each group

was related to performance at Day 0 given the non-significant difference in mean percent change scores, $F(6,84) = 0.48$, $p = ns$ (see Figure 19 right panel and Appendix K). In summary, performance on the Stroop test by each group in the post-randomization period is simply carried forward from the pre-randomization period. As such, 2 months of treatment with either olanzapine or haloperidol did not alter performance in patients on the Stroop test.

Digit Span Distractability Test

Pre-randomization. Figure 20 (left panel and Appendix H) shows the proportion of correctly recalled digits by the Pt, FM and NC groups on the Digit Span Distractability Test during the pre-randomization period. Analyses revealed that the three groups differed

Figure 20. Digit Span Distractability pre-randomization. Left Panel: Proportion of correctly recalled digits by the Pt, FM and NC groups on the Digit Span Distractability Test in the pre-randomization period. Higher scores mean better performance. Right Panel: Mean percent change scores of the proportion of correctly recalled digits from the Digit Span Distractability Test for the Pt, FM and NC groups from Day -4a to Day -4a, Day -4a to Day -3 and from Day -4a to Day 0.

in their ability to recall numbers in the correct sequence within the context of interference, $F(2,44) = 10.29$, $p < .0001$. A significant main effect of time signifies a progressive increase

in performance over time, $F(3,42) = 4.43$, $p < .01$. The lack of a significant group by time interaction indicates that the differences observed between the three groups changed in the same direction over the four pre-randomization assessments, $F(6,84) = 0.80$, $p = ns$. Despite differences at baseline, there was no difference between the Pt, FM or NC groups in practice and learning effects, $F(6,84) = 0.73$, $p = ns$ (see Figure 20 right panel and Appendix I).

Post-randomization. Performance on the Digit Span Distractability Test by the Ol, Hal, FM and NC groups during the post-randomization phase is shown in Figure 21 (left panel and Appendix J).

Figure 21. Digit Span Distractability post-randomization. Left Panel: Proportion of correctly recalled digits by the Ol, Hal, FM and NC groups on the Digit Span Distractability Test in the post-randomization period. Higher scores mean better performance. Right Panel: Mean percent change scores of the proportion of correctly recalled digits from the Digit Span Distractability Test for the Ol, Hal, FM and NC groups from Day 0 to 28 and from Day 0 to Day 56.

Analyses revealed that the four groups differed from one another on this test of selective attention, $F(3,43) = 6.63$, $p < .002$. The Ol group differed significantly from both the FM and NC groups (Tukey a , $p < .008$ and $.0001$, respectively). The sharp rise in performance by the Hal group is as a result of 5 subjects achieving a maximum score followed

by a decline in performance by 3 of these subjects on Day 56. A non-significant main effect of time ($F [2,42] = 0.37, p = ns$) as well as a non-significant group by time interaction ($F [6,84] = 1.71$) indicate that there was no appreciable change in performance for any group over the three post-randomization assessments. Also, an analysis of mean percent change scores showed that, when adjusted for performance at Day 0, there were no statistically significant differences between groups, $F (6,84) = 1.69, p = ns$ (see Figure 21 right panel and Appendix K).

Comparative Literature

Attention in the present study was assessed using three tests. These were the D2 Test of Attention, the Stroop and the Digit Span Distractability Test. Results during the pre-randomization period revealed that each of these attentional tests were susceptible to learning and practice effects and that patients consistently performed more poorly than the control groups. Differences between the groups at baseline did not differentially influence practice and learning effects since there was no difference in mean percent change scores for the three groups. Differences between patients and normal controls have been reported on the D2 Test of Attention (Brickenkamp & Zillmer, 1998), the Stroop (Schooler et al., 1997) and on the Digit Span Distractability Test (Oltmanns & Neale, 1975). Other than documented differences between patients and family members on the Stroop (Laurent et al., 2000), there is no information on differences between these two groups on the D2 Test of Attention or the Digit Span Distractability Test.

Evidence of learning and practice effects on these types of tests is not surprising since “tests that require an unfamiliar or infrequent practiced response. . . are likely to show

significant practice effects” (p. 469, Wilson, Watson, Baddeley, Emslie, & Evans, 2000). This statement applies to two of the three attention tests used in this study; the D2 Test of Attention and the Stroop. Practice effects in normal controls have been documented for the D2 Test of Attention (Spreen & Strauss, 1991) as well as other similar pencil and paper cancellation tests (e.g., the Digit Cancellation Task, Salinsky et al., 2001). Furthermore, practice and learning effects have been observed for the Stroop (Dikmen et al., 1999; Feinstein et al., 1994; Lezak, 1995; Salinsky et al., 2001).

Distractability as measured with the Digit Span Distractibility Test appears to be stable in medicated schizophrenia patients over two (Addington et al., 1997) and three assessments (Serper, Davidson, & Harvey, 1994). Other research has suggested that unmedicated schizophrenia patients will improve on this distractibility task once they are treated with antipsychotic medications, namely haloperidol (Oltmanns, Ohayon, & Neale, 1979; Serper et al., 1994). Despite a 3 day washout between Day -3 and Day 0, it is highly probable that traces of antipsychotic medications remained in our sample of patients which may explain why we did not observe decrements in performance at the end of the washout period.

Results from the post-randomization period revealed that there was no change in performance for any of the four groups on the D2 Test of Attention, the Stroop or on the Digit Span Distractibility Test. Initial differences between the two control groups and the patient group at the beginning of the post-randomization period remained once patients were randomized throughout the 2 month trial. This result suggests that olanzapine and haloperidol have no effect on attentional tasks sensitive to selective and sustained attention. At the present time, no study has specifically examined the effect of olanzapine and

haloperidol on any of these three measures. However, our findings can be discussed within the context of trials which have examined other atypical agents.

Only two other studies have examined the effect of atypical medications on the Stroop. Similar to our own results with olanzapine and haloperidol, there appears to be no within or between group advantages of clozapine over haloperidol on the Stroop (Buchanan et al., 1994; Purdon et al., 2001). As such, it appears that atypical or typical medications may have very little influence on the Stroop.

The only study to specifically examine the effect of an atypical agent in relation to haloperidol on the Digit Span Distractibility Test reports that risperidone is superior to haloperidol on this test of distractibility (Green et al., 1997). Findings from our study contrast with those of Green and colleagues. This may be as a result of several factors, the most obvious being the different atypical medications used in the two studies. There is the possibility that risperidone and olanzapine differentially affect performance on the Digit Span Distractibility Test. This could only be verified with a trial examining both medications. Moreover, our trial observed the presence of practice and learning effects during the pre-randomization period. Therefore, the positive effect seen with risperidone may be as a result of practice and learning effects. To their credit, Green and colleagues included haloperidol in their study and showed a slight decline in performance in this group. Dosing for those receiving haloperidol was set at 15 mg/day, which is twice the dosage observed in our study. Nevertheless, the elevated doses of haloperidol may have prohibited patients from benefitting from practice and learning effects on the Digit Span Distractibility Test.

Other investigators have examined the effect of atypical medications on a test with properties similar to the Digit Span Distractibility Test. This test is called the Petersen Consonant Trigram. Results on the effect of clozapine on the Petersen Consonant Trigram are mixed. Hagger et al. (1993) observed that 6 weeks of clozapine therapy actually resulted in decrements in performance on the Petersen Consonant Trigram and that performance returned to baseline levels after 6 months. In their open label trial with no control groups, Galletly et al. (1997) reported that clozapine was related to improved performance after 8 months of treatment. Lee et al. (1994) contrasted clozapine to haloperidol in their open label trial and stated that improvements in performance were observed after 6 weeks of treatment whereas treatment with haloperidol resulted in no change. Despite improved performance in the clozapine group, there was no difference between the two treatments. Finally, with respect to quetiapine, Velligan and colleagues (2002) reported that quetiapine was superior to haloperidol on the Petersen Consonant Trigram after 24 weeks of treatment. Although these studies examined different atypical agents on a task which was different from our own, it is difficult to conclude that atypical medications improve performance on tasks of distractibility. From our results on the Digit Span Distractibility Test, we observed that such tasks are susceptible to learning and practice effects. It could be argued that the atypical medications were responsible for the improved performance since Lee et al. (1994) and Velligan et al. (2002) included control groups receiving typical agents and found that they did not improve in their performance. On the other hand, all patients entering both these trials were receiving older agents. Therefore, the improvement seen with clozapine and quetiapine

may have been as a result of the treatment or, alternatively, it could have been due to being withdrawn from the older medications.

To our knowledge, ours is the only study to have examined the effect of olanzapine, or any atypical medication for that matter, on the D2 Test of Attention. Because the D2 Test of Attention is a test of selective as well as sustained attention, our results will be examined within the context of studies which investigated the effect of atypical medications on a similar task, the Continuous Performance Test (CPT). Two studies have investigated the effect of risperidone on the CPT and demonstrated that risperidone does not improve performance (King, 1994; Liu et al., 2000; Stip & Lussier, 1996). Liu et al. (2000) also included a control group of patients randomized to haloperidol and observed no change in performance over 12 weeks. Furthermore, there were no differences between those treated with risperidone or haloperidol. These results are in keeping with ours in that we did not observe any benefit of olanzapine or haloperidol on the D2 Test of Attention in the post-randomization period. Unlike our results and those with respect to risperidone, Sax et al. (1998) reported that quetiapine positively affected performance on the CPT degraded version. Their study was an open label trial which included a group of healthy normal control subjects. A lack of improvement for the control subjects may have been as a result of a ceiling effect. It is possible that quetiapine may differentially affect performance on the CPT relative to risperidone or perhaps olanzapine. A trial contrasting all three agents would be required for such a determination.

Visual Working MemoryVisual Memory Span Backward

Pre-randomization. From Figure 22 (left panel and Appendix H), it appears that the Pt group had greater difficulty reproducing visual patterns in reverse compared to the FM and NC groups, an observation which was supported statistically, $F(2,44) = 5.83$, $p < .01$. There were no practice and learning effects during the pre-randomization period ($F[3,42] = 2.02$, $p = ns$), and performance was relatively stable for all three groups as indicated by the lack of a significant group by time interaction, $F(6,84) = 1.82$, $p = ns$. Finally, differential performance on the Visual Memory Span Backward Test at Day -4a did not influence results at Day -4b, -3 or 0, $F(6,84) = 1.70$, $p = ns$ (see Figure 22 right panel and Appendix I).

Figure 22. Visual Memory Span Backward pre-randomization. Left Panel: Performance on the Visual Memory Span Backward subtest of the WMS-R by the Pt, FM and NC groups in the pre-randomization period. Higher scores mean better performance. Right Panel: Mean percent change scores for the Pt, FM and NC groups on the Visual Memory Span Backward from Day -4a to Day -4b, Day -4a to Day -3 and from Day -4a to Day 0.

Post-randomization. As can be observed from Figure 23 (left panel and Appendix J), the Ol, Hal, FM and NC differed significantly in their performance on the Visual Memory

Span Backward subtest in the post-randomization period, $F(3,43) = 4.24$, $p < .02$. However, none of the groups appreciably changed from their baseline performance at Day 0. This is supported by a non-significant main effect of time ($F[2,42] = 0.26$, $p = ns$), as well as by a non-significant group by time interaction, $F(6,84) = 1.06$, $p = ns$. In addition, there was no difference between groups on mean percent change scores, $F(6,84) = 1.47$, $p = ns$ (see Figure 23 right panel and Appendix K). As such, it can be concluded that randomization to treatment with olanzapine or haloperidol did not affect performance on the Visual Memory Span Backward subtest.

Figure 23. Visual Memory Span Backward post-randomization. Left Panel: Performance on the Visual Memory Span Backward subtest of the WMS-R by the OI, Hal, FM and NC groups in the post-randomization period. Right Panel: Mean percent change scores for the OI, Hal, FM and NC groups on the Visual Memory Span Backward from Day 0 to Day 28 and from Day 0 to Day 56.

Comparative Literature

Visual working memory in this study was examined with the Visual Memory Span Backward subtest. The patient, family member and normal control groups differed significantly from one another in the pre-randomization period. Results from the normal

control group in our study are consistent with published norms for the WMS-R suggesting that patients with schizophrenia perform more poorly on this task (Wechsler, 1987). This visual working memory test was not susceptible to practice and learning effects. Consistent with our findings, practice and learning effects on this test and similar tests (e.g., Corsi blocks) tend to be minimal in normal control subjects (McCaffrey, Duff, & Westervelt, 2002).

Two months of treatment with olanzapine or haloperidol did not differentially affect performance in the patient group. Differences in performance between the four groups were still present in the post-randomization period. In addition, performance attained at Day 0 was maintained throughout the 2 month post-randomization period. An examination of mean percent change scores confirmed that initial differences between the groups at baseline were not responsible for performance throughout the post-randomization period.

At the present time, there are no reports of the differential effect of olanzapine and haloperidol on the Visual Memory Span Backward subtest. However, information on the effect of other atypical medications on this task have been published. Goldberg et al. (1993) and Buchanan et al. (1994) have reported that clozapine has no effect on the Visual Memory Span Backward test in chronic schizophrenia patients over three assessments occurring between 10 weeks and 2 years. Furthermore, Buchanan and colleagues included a control group of patients randomized to treatment with haloperidol. They found that haloperidol did not influence performance on this visual working memory task and that clozapine and haloperidol did not differ from one another. Daniel et al. (1996) contrasted the effect of clozapine with haloperidol and found that neither drug influenced performance on the Visual

Memory Span Backward test. Our results are in keeping with these reports. As such, it may be concluded that treatment with various atypical medications (olanzapine, clozapine or risperidone) may have little beneficial effect on this task of visuospatial working memory.

Verbal Working Memory

Digit Span Backward

Pre-randomization. A significant main effect of group was noted on the Digit Span Backward subtest of the WMS-R indicating that the PT group was not as successful in correctly reversing increasingly longer sequences of numbers in comparison to both the FM and NC groups, $F(2,44) = 11.12$, $p < .0001$ (see Figure 24 left panel and Appendix H).

Figure 24. Digit Span Backward pre-randomization. Left Panel: Raw scores on the Digit Span Backward subtest of the WMS-R for the Pt, FM and NC groups in the pre-randomization period. Right Panel: Mean percent change scores in performance on the Digit Span Backward Test by the Pt, FM and NC groups between Day -4a and Day -4b, Day -4a and Day -3 and Day -4a and Day 0.

Performance for the groups did not change over time as revealed by a non-significant main effect of time ($F[3,42] = 1.78$, $p = ns$) and a non-significant interaction, $F(6,84) = 0.28$, $p = ns$. An examination of mean percent change scores revealed that changes in performance

over time did not significantly differ between groups suggesting that baseline performance at Day -4a did not influence performance on subsequent trials, $F(6,84) = 0.34$, $p = ns$ (see Figure 24 right panel and Appendix I).

Post-randomization. As can be seen in Figure 25 (left panel and Appendix J), the Ol, Hal, FM and NC groups differed significantly from one another on the Digit Span Backward test in the post-randomization period, $F(3,43) = 10.36$, $p < .0001$. Post-hoc analyses revealed that the Ol group performed worse than the FM and NC groups (Tukey a , $p < .002$ and $p < .0001$, respectively). The patients randomized to Hal performed more poorly than

Figure 25. Digit Span Backward post-randomization. Left Panel: Performance by the Ol, Hal, Fm, and NC groups on the Digit Span Backward test (raw scores) in the post-randomization period. Higher scores mean better performance. Right Panel: Mean percent change scores for the Digit Span Backward test for the Ol, Hal, FM and NC groups from Day 0 to Day 28 and from Day 0 to Day 56.

the NC group only (Tukey a , $p < .002$). Differences observed at Day 0 were maintained during the 2 month post-randomization period. This latter finding is supported by a non-statistically significant main effect of time ($F[2,42] = 2.57$, $p = ns$) and a non-statistically significant group by time interaction, $F[6,84] = 1.23$, $p = ns$. Mean percent change scores

were not statistically significantly different between groups suggesting that performance at Day 0 did not influence performance at Days 28 and 56, $F(6,84) = 1.11$, $p = ns$ (see Figure 25 right panel and Appendix K). These results indicate that there was no effect of 56 days of treatment with either olanzapine or haloperidol on the Digit Span Backward test.

Letter Number Sequencing

Pre-randomization. The Pt, FM and NC groups differed from one another on the Letter Number Sequencing test, $F(2,43) = 12.27$, $p < .0001$ (see Figure 26 left panel and Appendix H). A main effect of time indicated that learning and practice effects occurred

Figure 26. Letter-Number Sequencing pre-randomization. Left Panel: Raw scores on the Letter Number Sequencing test for the Pt, FM and NC groups in the pre-randomization period. Right Panel: Mean percent change scores in performance on the Letter Number Sequencing test by the Ol, Hal, FM and NC groups between Day -4a and Day -4b, Day -4a and Day -3 and Day -4a and Day 0.

during the pre-randomization period, $F(3,41) = 4.29$, $p < .02$. The differential performance by the groups at Day -4a was maintained during the pre-randomization period as shown by a non-significant group by time interaction, $F(6,82) = 1.09$, $p = ns$. An examination of mean percent change scores revealed that changes in performance over time did not significantly

differ between groups showing that baseline performance at Day -4a did not significantly influence performance on subsequent trials, $F(6,82) = 0.78$, $p = ns$ (see Figure 26 right panel and Appendix I).

Post-randomization. Once randomized to treatment with either olanzapine or haloperidol, it can be seen in Figure 27 (left panel and Appendix J) that the two patient groups differ from the two control groups on the Letter Number Sequencing test. This observation

Figure 27. Letter-Number Sequencing post-randomization. Left Panel: Performance by the OI, Hal, Fm, and NC groups on the Letter Number Sequencing test (raw scores) in the post-randomization period. Higher scores mean better performance. Right Panel: Mean percent change scores for the Letter Number Sequencing test for the OI, Hal, FM and NC groups from Day 0 to Day 28 and from Day 0 to Day 56.

was supported by an overall main effect of group, $F(3,42) = 10.11$, $p < .0001$. Performance for this test did not change over the 2 month post-randomization period. Differences seen at baseline (Day 0) were maintained throughout the post-randomization period. A non-significant main effect of time ($F[2,41] = 1.88$, $p = ns$), a non-significant group by time interaction ($F[6,82] = 0.75$, $p = ns$), and no difference in mean percent change scores support the latter statement, $F(6,82) = 0.73$, $p = ns$ (see Figure 27 right panel and Appendix K).

Therefore, randomization to treatment with olanzapine or haloperidol did not alter performance on the Letter Number Sequencing test.

Comparative Literature

Verbal working memory was assessed using two measures. These were the Digit Span Backward subtest from the WMS-R and the Letter Number Sequencing subtest from the WAIS-III. Group differences were found between the patient group and the two control groups on both tests. Differences between normal controls and patients on the Digit Span Backward test have been observed by others (Conklin et al., 2000; Stratta et al., 1997) and differences between patients and family members have also been observed (Conklin et al., 2000). With respect to the Letter Number Sequencing test, there are no reports which have specifically compared performance on the Letter Number Sequencing task between patients with schizophrenia and normal controls or between family members of patients with schizophrenia and patients. However, performance on this test by normal controls in our study are in keeping with those which have been published in the WAIS-III manual (Wechsler, 1997). Therefore, as our results suggest, it can be assumed that patients with schizophrenia tend to perform more poorly on this verbal working memory task compared to normal controls. Practice and learning effects were evident for the Letter Number Sequencing test but not the Digit Span Backward test. There is very little information on the effect of repeated assessments on the Letter Number Sequencing test. From the WAIS-III manual, it appears that this test is not susceptible to practice and learning effects in normal control subject. However, this information is based on a test-retest interval of an average of 35 days. The improved performance seen in our subjects may have been as a result of

repeated assessments in a very short period of time, four assessments within 5 days. Tests which require practiced responses are susceptible to learning and practice effects. The properties of the Letter Number Sequencing test, whereby a person may become more efficient by way of developing strategies for sorting and ordering letters and numbers, makes it vulnerable to learning and practice effects. With respect to the Digit Span Backward test, it appears that performance over two repeated assessments across different test-retest time frames is relatively stable and not susceptible to practice and learning effects. A lack of improvement over the four assessments in the pre-randomization period when examining patients with schizophrenia, family members and normal controls supports this notion.

There was no evidence of change for any of the four groups on either the Digit Span Backward test or the Letter Number Sequencing test during the post-randomization period. Differences in performance between the family members and normal control groups with the patient groups remained throughout the post-randomization period. In addition, performance at Day 0, when patients were randomized to olanzapine or haloperidol, did not influence performance over the 2 month trial. Mean percent change scores indicated that all groups did not significantly differ from one another in their pattern of performance over the 2 month blinded trial.

The only report specifically contrasting the effect of olanzapine and haloperidol on the Digit Span Backward test was published by Smith et al. (2001). They observed that olanzapine and haloperidol did not enhance performance on this test over 8 weeks of double-blind treatment. In addition, there was no difference between the two treatments on this task of verbal working memory. Our results support Smith et al.'s findings, although patients in

their study were chronic treatment resistant patients living in a long-term care facility. Other atypical medications do not seem to enhance performance on the Digit Span Backward test. For instance, Goldberg et al. (1993), Lee et al. (1994), Buchanan et al. (1994) and Purdon et al. (Purdon et al., 2001) have all reported that clozapine does not positively influence performance on the Digit Span Backward test. Moreover, there does not appear to be any difference between clozapine and haloperidol on this measure (Buchanan et al., 1994) or between clozapine and risperidone (1996). The only study to report discrepant findings was published by Grace et al. (1996). These investigators found that clozapine improved performance on the Digit Span Backward test. The main difference between this study and the other with respect to clozapine is the duration of treatment. For instance, the trial duration for studies finding no influence of clozapine on the Digit Span Backward test ranged between 6 weeks and 1 year whereas Grace's trial was 3 years in duration. Nevertheless, the consistency between our trial contrasting the influence of olanzapine and haloperidol and others with clozapine suggest that atypical medications have very little influence on verbal working memory as assessed with the Digit Span Backward test.

The only study to examine the effect of atypical medications on the Letter Number Sequencing test in patients with schizophrenia was conducted by Bilder and colleagues (2002). Their 14 week study contrasted the effect of olanzapine, clozapine, risperidone and haloperidol in a group of treatment resistant schizophrenia inpatients. Results with respect to the Letter Number Sequencing test specifically are somewhat difficult to interpret since these authors conducted a principal-components analysis in order to reduce the number of dependent variables examined. As a result, each individual variable was not evaluated

independently. The Letter Number Sequencing test loaded on a factor named the “general executive and perceptual organization” domain. It was observed that 14 weeks of treatment with both olanzapine and risperidone was associated with an improvement in this domain. Therefore, it could be ventured that there may have been an improvement on the Letter Number Sequencing alone. Fortunately, the authors presented a table listing pre- and post means for each of the assessments used in their study. Indeed, improvements in raw scores were noted for both the olanzapine (6.8 to 8.1) and risperidone (8.1 to 9.0) treated groups. However, it must be noted that the clozapine and haloperidol groups showed improvements in raw scores as well (8.1 to 9.5 and 7.9 to 8.4 respectively). Since our study demonstrated the presence of practice and learning effects during the pre-randomization period and no change during the post-randomization period, it could be argued that there may have been a significant practice and learning component to the improved performance seen in the olanzapine and risperidone groups in Bilder et al.’s study. As such, olanzapine’s influence on the Letter Number Sequencing test in Bilder et al.’s study remains uncertain.

Discussion

Three key findings were observed in this study. First, patients almost invariably performed more poorly than did both the family member and normal control groups on neurocognitive measures. Second, any changes in performance on neurocognitive measures occurred in the pre-randomization phase indicating the presence of learning and practice effects. Third, when patients were randomized to treatment with olanzapine or haloperidol, performance remained stable throughout the 2 month post-randomization period. As such, it can be concluded that these two medications did not produce any change on measures of motor functioning, verbal and visual short-term memory, attention, reaction time and verbal and visual working memory in early phase patients diagnosed with schizophrenia. The discussion which follows will address each of these three findings. The major implications as well as limitations of this study will also be addressed.

Differential Cognitive Performance Between Patients and Control Groups

Findings from our study are consistent with other reports that patients with schizophrenia tend to perform more poorly compared to normal controls and family members on tasks which rely on the integrity of the frontal cortex. Several reasons could account for this finding. For instance, histological studies have demonstrated that patients with schizophrenia have greater cell densities as well as reduced cortical thickness in the prefrontal cortex. Structural evidence suggests that this region is smaller in size. Subcortical structures such as the thalamus and basal ganglia with connections to the prefrontal cortex have also been shown to be smaller compared to normal controls. Neurochemical abnormalities have also been reported. A dysregulation of dopaminergic activity in the prefrontal cortex has been

observed in persons with schizophrenia. Finally, functional neuroimaging studies suggest that persons with schizophrenia have reduced activity in the prefrontal cortex when presented with cognitive tasks known to recruit this cortical region (for reviews see Chua & McKenna, 1995; Csernansky & Newcomer, 1994; Goldman-Rakic & Selemon, 1997; Heckers, 1997). Given these findings, it would be expected that persons with schizophrenia would perform more poorly on neurobehavioural measures.

Learning and Practice Effects

Several factors may contribute to learning and practice effects. Individuals may become less anxious in subsequent testing sessions. They may develop strategies for completing certain tests or they may simply memorize stimuli. Whatever the cause, learning and practice effects pose a significant challenge to neuropsychologists who assess patients repeatedly over time. Neuropsychologists need to interpret results within the context of learning and practice in order to determine the effectiveness of an intervention or to gauge disease progression. This has spawned research which examines what changes in cognitive performance may be expected from learning and practice effects in several patient populations (e.g., Bruggemans, Van de Vijver, & Huysmans, 1997; Chelune, Neugle, Lüders, Sedlak, & Awad, 1993). In fact, McCaffrey, Duff and Westervelt (2002) have published a comprehensive text which details the effects of repeated assessments on many of the neuropsychological tests currently in use.

With this in mind, one of the greatest problems with research on medication effects on neurocognition in schizophrenia is the lack of attention paid to possible learning and practice effects. An example using a single memory test will be used to illustrate the

confounding effect of learning and practice on the interpretation of results. Purdon et al. (2001) published a study examining the effect of 6 weeks of clozapine on a comprehensive neuropsychological battery. This was an open label trial with no control groups. They reported a significant improvement on the delayed component of the WMS-R logical memory subtest. As Figure 28 shows, patients' performance on this test did improve after 6 weeks of clozapine therapy. However, in the absence of control groups, it may be erroneous to conclude that this improvement was due to the effect of medication.

Figure 28. Performance at baseline (Time 1) and endpoint (Time 2, 4 to 6 weeks later) on the delayed component of the WMS-R Logical Memory.

From the WMS-R manual and McCaffrey et al's (2002) review, there is evidence that normal control subjects perform better on this task after it is readministered 4 to 6 weeks later. This information makes it impossible to attribute improved performance in the patient group solely to clozapine (see Figure 29). In addition to demonstrating how learning and practice effects can confound the interpretation of results, this example also highlights the importance of including control groups in research which repeatedly administers tests. These groups allow investigators to assess how subjects may naturally perform over time in the

absence of interventions. Figure 29 highlights the importance of considering learning and practice effects in the interpretation of results.

Figure 29. Changes in performance from baseline (Time 1) to endpoint (Time 2, 4 to 6 weeks later) in a group of normal controls in the absence of interventions.

Some investigators have indicated that a normal control group in research examining medication effects in schizophrenia is unnecessary if robust normative data are available. The caveat with this approach stems from the fact that normative data are often generated from a single testing session. Therefore, comparing scores from patients who have been exposed to tests on more than one occasion to normative data obtained from a single testing session is highly problematic. Comparison between normative data and data obtained from repeated measures can occur under two circumstances. First, data obtained at baseline for patients can be compared to normative data. However, comparing data obtained at sessions two, three, four and so forth to baseline should be avoided. Second, a normal control group is unnecessary and normative data can be utilized only if it has been demonstrated that performance on a certain test does not change as a function of repeated exposures.

Investigators who have attempted to account for learning and practice effects have done so by using alternate parallel forms for tests with salient stimuli, such as lists of words. Although this method negates the potential for the recall of specific stimuli, it does not account for changes which may occur as a result of subjects being less anxious or as a result of their developing a strategy to help them recall more words.

To account for learning and practice effects in this study, all subjects were exposed to the same neurocognitive battery on four occasions within 5 days prior to the randomization of patients to olanzapine or haloperidol. The notion was that subjects would most likely perform to the best of their ability after completing the battery on the fourth occasion. Performance attained on the fourth assessment served as the baseline for the post-randomization period. During the post-randomization period, we did not observe any changes on any of the measures in control groups or when patients were randomized to treatment. Based on these results, changes seen in our study reflected learning and practice effects and once peak performance was achieved, atypical and typical medications did not further alter performance.

Using a repeated baseline approach for separating learning and practice effects from medication effects has been criticized by investigators in the field. For instance, S. E. Purdon (personal communication, January 6, 2003) indicated that the repeated exposure of patients to the same neurocognitive assessments may produce ceiling effects thereby reducing a test's sensitivity to detect medication effects. This scenario is possible if atypical medications do not enhance performance beyond that of learning and practice effects. Nevertheless, the inclusion of a normal control group can shed some light on where ceiling effects may appear.

In our study, the normal control and family member groups were assessed the same number of times over the same time period. It was demonstrated that these groups of subjects performed better than patients on the majority of measures in both the pre- and post randomization periods. Therefore, patients in our study did not reach a ceiling level of performance since there was room for further improvement relative to the normal control group. If atypical neuroleptics enhance cognitive performance, patients randomized to olanzapine should have shown some improvement beyond their peak performance at day 0, after their fourth exposure to the neurocognitive battery. It could also be argued that ceiling effects may differ for normal controls and patients with schizophrenia and that ceiling effects observed in normal controls are not applicable to patients. This is most likely correct since patients rarely perform as well as normal controls on many neurocognitive tasks. However, if atypical antipsychotic medications have the potential for cognitive enhancement beyond learning and practice effects, then improvements beyond the ceiling effect established with typical medications should be observed. It may be that atypical medications exert their beneficial effect by accelerating the rate at which patients exhibit learning and practice effects.

Discrepancy Between the Current Results and those of other Studies

No difference between olanzapine or haloperidol occurred on any of the measures administered in this study. We also showed that patients are capable of profiting from learning and practice. However, other studies have reported improved neurocognitive performance with atypical medications and no improvements with typical medications. How can we reconcile these observations with results from this study? One possible explanation may reside in the potentially detrimental effects typical neuroleptics may have on learning and

practice effects. Also, the use of composite scores may have impacted the interpretation of results in some studies.

Effect of antipsychotic medications on learning and practice effects. Support for the view that typical agents are not associated with improved performance over repeated assessments emerges from several sources. Review papers describing the effects of typical neuroleptics on neurocognitive functioning in schizophrenia have concluded that this class of antipsychotic does not generally affect neurocognition either positively or negatively (e.g., Cassens et al., 1990; Spohn & Strauss, 1989). Further, in trials contrasting atypical to typical medications, several authors report that typical agents have no beneficial influence on neurocognitive functioning (e.g., Buchanan et al., 1994; Green et al., 1997; Kern et al., 1998; Purdon et al., 2000; Purdon et al., 2001; Smith, 2001). This neutral effect may in fact be of central importance in that typical neuroleptics may suppress learning and practice effects.

The neurocircuitry and neurochemistry implicated in learning and practice effects may shed some light on how typical and atypical agents differ in their effects. The striatum which makes up part of the basal ganglia has been identified as a key component in the neuronal circuitry responsible for different types of learning. In their review of the role of the striatum in neuropsychological functioning, Rauch and Savage (1997) write:

the striatum can be viewed as mediating rule-based learning, which can wholly support types of nonconscious information processing (such as procedural learning) that lead to the acquisition of behaviors that are performed automatically. In addition, this type of operation plays an ancillary role in enhancing the efficiency of higher-order processes, such as those involved in working memory. (pp. 756-746).

The striatum functions within a corticostriatothalamic circuit which has reciprocal connections to the prefrontal cortex (Mega & Cummings, 1994; Snell, 1992) and dopamine is a key neurotransmitter in this circuit (Palermoro-Neto, 1997). Conventional medications such as haloperidol have been differentiated from atypical medications on the basis of their dopamine relative to serotonin binding profile as well as on their potential for producing extrapyramidal symptoms at clinically appropriate doses (Beasley et al., 1996; Meert et al., 1989; Meltzer & McGurk, 1999). The mechanism by which drug induced extrapyramidal symptoms emerge is well understood. Dopamine neurons in the nigrostriatal pathway originate from the substantia nigra and project to the striatum, the thalamus and the frontal cortex (Mega & Cummings, 1994; Snell, 1992). Medications with a high affinity for blocking dopamine-2 receptors in the striatum have been shown to induce extrapyramidal side effects. It is well documented that haloperidol is a potent dopamine-2 antagonist and that higher doses produce extrapyramidal symptoms (e.g., Nordstrom et al., 1993). Such symptoms are much less common with atypical medications such as olanzapine (Beasley et al., 1996). This evidence suggests that drugs which potently block dopaminergic activity in the striatum could have profound effects on cognition.

Two studies conducted by Bédard et al. (2000; 1996) support this notion. Patients with schizophrenia receiving clozapine, risperidone or haloperidol were evaluated on two tasks that are highly susceptible to learning and practice effects. The first was a mirror drawing task and the other was the Tower of Toronto. A group of normal control subjects were also investigated to detect normal learning patterns on these tasks. Two principal findings emerged. First, both groups of patients performed more poorly than the normal

control group. Second, patients treated with different medications differed in their pattern of performance over time. More specifically, patients treated with haloperidol fluctuated in their performance on the mirror drawing task more than those treated with clozapine or risperidone. Normal controls, as well as those treated with clozapine or risperidone, showed a much smoother learning curve. Also, patients treated with haloperidol or risperidone had a flatter learning curve on the Tower of Toronto than normal controls or those treated with clozapine. This finding is interesting in that the completion of initial trials heavily rely on the integrity of frontal cortical functioning. In fact, the first few administrations of the Tower of Toronto are considered to assess executive functions. If this task has been 'figured out' by subjects, then successive trials of this task require much less effortful processing. The authors posit that dopamine antagonism in the striatum, resulting in disruptions of the striato-frontal circuit, may have been responsible for slower acquisition on the Tower of Toronto. That is, patients were unable to learn this initially difficult task which affected their ability to subsequently improve in their performance. Although considered to be an atypical agent, risperidone has also been shown to be a potent dopamine-2 antagonist and can induce extrapyramidal symptoms at higher, yet still clinically appropriate, doses (Remington & Kapur, 1999). This may explain why persons receiving risperidone and haloperidol performed similarly on the Tower of Toronto.

Bédard et al. (1996) have also examined the differential effect of haloperidol, clozapine and neuroleptic naive patients on the mirror drawing task. Results from this investigation were similar to their Tower of Toronto study. They demonstrated that patients treated with haloperidol displayed more fluctuation in learning compared to the clozapine

treated group and the neuroleptic naive group. The authors concluded that drugs with a high affinity for dopamine-2 blockade in the striatum may impair patients' ability to acquire skills over repeated assessments more than drugs with a lower affinity for dopamine-2 blockade.

Perhaps the doses of conventional medications were too high in previous studies to allow for learning and practice effects. Research conducted by Kapur et al. (1996) has demonstrated that doses as low as 2-4 mg of haloperidol per day can result in the dopamine-2 blockade necessary to achieve clinical efficacy in persons with schizophrenia. Furthermore, these investigators reported that this low dose was not associated with the extrapyramidal motor side-effects typically seen at higher doses. If, as postulated, typical medications are associated with cognitive suppression, would lowering the dose have an effect on neurocognitive functioning? Preliminary investigations suggest that this may, in fact, be the case. A recent study by Green et al. (2002) indicates there is no difference on neurocognitive functioning between risperidone and low doses of haloperidol (5 mg/day) over a 2 year period. This study suffers from an incomplete analysis in that only composite scores were analyzed. Individual variables were not analyzed separately. Nevertheless, this is the first study in a trend to examining the effects of low doses of haloperidol on cognitive functioning in schizophrenia. It could be argued that these improvements merely reflect learning and practice effects in both groups since they were exposed to the same battery three times. Evidence from this study suggests that higher doses of conventional medications may actually prohibit expected practice and learning effects whereas the newer medications may not have this suppressive cognitive 'side-effect'. This hypothesis may explain why some trials

comparing atypical medications to conventional medications report a superiority of atypical treatment.

At the other end of the dosing spectrum, there is some evidence to suggest that elevated doses of atypical medications may impair neurocognitive performance. A study by Smith et al. (2001) contrasting olanzapine to haloperidol failed to observe any between treatment differences on neurocognitive functioning. Patients in this study were chronic treatment resistant patients. The final mean daily dose of haloperidol was 37.9 mg/day and 20 mg/day for olanzapine. Although this dosage is well within the prescription guidelines, this is the only study to report the effects of olanzapine on neurocognitive functioning at this dose. The lack of improvement observed in the olanzapine treated group is contrary to the literature and reflects the fact that elevated doses of atypical medications are associated with cognitive suppression. Seeman (2002) reports that olanzapine can cause extrapyramidal symptoms at higher doses. It could be postulated that elevated doses result in the suppression of learning and practice effects.

Although attributing drug effects on neurocognitive functioning to dopaminergic blockade in the striatum is an attractive model, it is most likely overly simplistic. In reality, the neurochemical correlates responsible for neurocognitive effects of antipsychotic medications are not well understood (Ellis & Nathan, 2001). Because of their different binding profiles, various medications will have differing effects. For instance, olanzapine principally antagonizes serotonergic-2A/2C, muscarinic-1 and to a lesser extent dopamine-2/1 receptors (Keefe et al., 1999). On the basis of this binding profile, it could be predicted that olanzapine may have detrimental effects on new learning and memory as a result of serotonin-

2A/2C antagonism. Spatial and verbal working memory tasks which require greater processing demands may be impaired due to olanzapine's muscarinic cholinergic receptor antagonism. Furthermore, dopamine-2/1 antagonism could result in executive function deficits. Typical agents such as haloperidol mainly antagonize dopamine-2/4/1 receptors and have very little affinity for serotonergic receptors. Therefore, they may negatively affect executive functioning as well as non-verbal working memory performance (Ellis & Nathan, 2001; Keefe et al., 1999; Meltzer & McGurk, 1999). While information about the effects that individual neurotransmitters have on cognition is helpful, the effects of the interaction between different neurotransmitter systems is unclear. Researchers in this area agree that the influence of different medications on cognition in schizophrenia most likely results from their combined binding profiles (Ellis & Nathan, 2001; Keefe et al., 1999).

The use of composite scores. Authors sometimes emphasize composite neurocognitive domain scores more than individual test scores. We did not use this approach to the interpretation of our results. Composite scores are derived by logically grouping tests with similar properties or statistically using principal components analysis (PCA). The chief reason for utilizing composite scores is to reduce to total number of dependent variables in a study which in turn increases statistical power and reduces the total number of participants required. In addition, some investigators argue that the interpretation and generalization of results to clinical practice is made easier. From a research perspective, we would argue that combining scores is more confusing than helpful. The impact composite scores may have on the interpretation of results is described below.

Purdon et al.'s (2000) study utilized 17 individual measures collapsed into six cognitive domains. A general cognitive index was also generated using the average of the six cognitive domain scores. In their abstract, the authors state that "The general cognitive index derived from the 6 domain scores revealed a significantly greater benefit from treatment with olanzapine relative to haloperidol and olanzapine relative to risperidone" (p. 249). Fortunately, the authors also presented a complete analysis of all individual measures. There were no between group differences on any of the six cognitive domain scores or on any of the 17 individual tests when Bonferroni corrections for multiple comparisons were used. As such, does the general cognitive index score truly reflect the findings of this study? When Bonferroni corrections are not used (i.e., $p < .05$), within groups analyses show improvements for olanzapine on five of six cognitive domain scores. They are attention span, motor skills, Nonverbal Fluency and construction, executive functioning and immediate recall. The greatest difference between olanzapine and haloperidol was on the immediate recall domain ($p = .005$). However, when individual tests are examined to determine which contribute to the significance of this domain score, two (design and verbal list learning) of five differ between groups. Therefore, while there is a statistically significant difference between olanzapine and haloperidol on the immediate memory domain, an examination of individual tests does not convincingly demonstrate olanzapine's overall superiority on immediate memory.

At times, the derivation of domain scores using a PCA lacks clinical logic. For instance, Green et al. (2002) subjected 13 independent variables to a PCA which yielded a three factor solution for 10 of these tests. The remaining three were examined individually.

The first factor was named the perceptual discrimination factor and consisted of the CPT, span of apprehension, the spatial associative test and a spatial working memory test. The second cluster was named the 'memory and fluency factor' and consisted of a verbal fluency test, the California Verbal Learning Test, the Digit Span Distractibility Test, and a motor test called the pin test. The clustering of these four tests does not make intuitive clinical sense. While the California Verbal Learning Test is a test of verbal list learning, verbal fluency is traditionally linked to executive functioning. Also, the Digit Span Distractibility Test assesses selective attention and the pin test is a test of fine motor movement. The final cluster was named the executive functioning factor and consisted of the number of categories achieved on the Wisconsin Card Sorting Test as well as the number of perseverative errors on this test. Both these measures have been linked to executive functioning. The three independent variables which did not make it into a factor structure were the Block Design subtest of the WAIS-R, the Trail Making test and the California Verbal Learning Test recognition error score. The Trail Making Test should have been included with other executive functioning tests. Green et al. (2002) reported that there were no differences between risperidone and haloperidol on any of the three clusters. Because the factor structures are questionable and individual variables were not analyzed, there was an increased risk of a Type II error in this study. Alternatively, as the authors report, there may have been no difference between risperidone and low-dose haloperidol on neurocognitive functioning in persons with schizophrenia.

Strengths and Limitations of this Study

As concluded in the introduction, eight major limitations were identified in studies examining the effects of various antipsychotics on neurocognitive functioning in schizophrenia. These included (a) a lack of control over baseline medication status, (b) blinding, (c) a lack of appropriate control groups, (d) the influence of practice effects, (e) test/retest interval variability, (f) illness duration, (g) inappropriate experimental medication doses, and (h) the use of concomitant medications. Several remedies addressing each limitation were included in the design of the current study. The relevance of each of these eight factors to our results is discussed.

Baseline Medication Status

Carry-over effects from antipsychotic as well as concomitant medications at baseline pose a significant challenge in the interpretation of the effects of experimental drug treatments. We attempted to control for baseline medication status by pseudo-randomly balancing the olanzapine and the haloperidol arms of this study with the number of patients receiving typical medications at baseline. Appendix A shows that there were no patients receiving typical antipsychotic monotherapy. However, three patients randomized to olanzapine and two to haloperidol were receiving a typical agent in combination with an atypical agent. Two neuroleptic naive patients were randomized into each medication arm. Therefore, both medication groups were balanced at baseline for antipsychotic medication.

It was originally proposed that washout durations would be based on the half-life of antipsychotic medications received at baseline. However, due to clinical limitations, the washout period was limited to 72 hours. Despite the washout period, it is difficult to

determine the nature of potential carry-over effects of baseline medications into the post-randomization phase. Therefore, baseline medication status in our study remains a potentially confounding element in the interpretation of results in the post-randomization period.

Blinding

This study was double-blinded.

Control Groups

Control groups in our study significantly improved the interpretability of the results. The use of normal control and family member groups allowed us to establish normal performance and patterns of learning and practice. By contrasting patterns of performance over time between groups, we were able to determine that patients show similar trends in learning and practice despite being consistently and significantly impaired on neurocognitive measures.

Influence of Learning and Practice Effects

The inclusion of a pre-randomization period prior to double-blind treatment significantly impacted the interpretation of results. We clearly observed learning and practice effects on several measures during the pre-randomization period. Once randomized to treatment, there were no subsequent changes for any groups beyond those at Day 0. By controlling for learning and practice effects, we were able to confidently conclude that there was no effect of olanzapine or haloperidol on neurocognitive functioning after 2 months of treatment with either medication.

Test/Retest Time Intervals

Another strength of this study was the consistency in test/retest time intervals. This allowed for a direct comparison of performance between groups without assessment time intervals confounding the interpretation of results.

Illness Duration

All patients were within 5 years of their initial diagnosis of schizophrenia indicating that patients were at about the same stage in their illness. There was no difference between patients randomized to olanzapine and haloperidol on illness duration.

Inappropriate Medication Doses

Patients in our study received doses well within clinically accepted guidelines. Patients randomized to olanzapine received an average of 12 mg/day (median = 10) and patients randomized to haloperidol received an average of 9.32 mg/day (median = 5.00). Although the final dosage of haloperidol is much lower than doses used historically (e.g., > 20 mg/day), clinicians may argue that this dose may still be somewhat elevated in patients in the early phase of their illness.

Use of Concomitant Medications

One of the strengths of the study was the monitoring of concomitant medications (see Appendix L). Benzodiazapines and antidepressant medications were not allowed throughout the pre- and post-randomization periods. Zopiclone, a hypnotic with a very short half-life, was used for patients who required a sleep agent.

Many more patients in the haloperidol group ($n = 7$) required antiparkinsonism side-effect treatment relative to those randomized to olanzapine ($n = 3$). Anticholinergic

medications have been shown to produce neurocognitive impairments, namely in the memory domain. Since our study focused on attention and working memory processes, it could be argued that the predominant use of anticholinergic medications in the haloperidol group did not influence performance on our neurocognitive battery.

Other Limitations of this Study

In addition to the limitations discussed above, three others can be included. These include: sample size, the use of a restricted neurocognitive battery, and the potential influence of time on learning and practice effects. This study may have been underpowered statistically. A power analysis indicates that a total of 180 subjects would have been required to achieve a power of 0.80 in the post-randomization period for four groups (Faul & Erdfelder, 1992). Our neurocognitive battery primarily focused attentional as well as working memory functioning. Therefore, it is impossible to generalize the results of this study to those with differing neurocognitive domains. Further, some tests (e.g., visual memory span backward) may have been insensitive to change, either from learning and practice effects or medication effects. Finally, learning and practice effects are sensitive to the time interval in which subjects are repeatedly exposed to cognitive testing. On certain measures, the longer the time interval between exposures, the less salient the learning and practice effect. Therefore, a direct comparison of our findings with respect to learning and practice effects in a short time span to trials where test-retest intervals were substantially longer may be problematic.

Future Directions

The notion that atypical antipsychotic agents may suppress learning and practice effects relative to atypical agents should be examined empirically. One possible design to evaluate this idea would be to repeat the same experiment, but with two additional groups of patients. These two new groups would also be randomized to double-blind treatment with olanzapine or haloperidol. However, they would not undergo the four pre-randomization assessments. Rather, they would enter the trial at Day 0 which marks their first assessment. Data from the post-randomization period would allow us to contrast performance between patients who were exposed to the four pre-randomization assessments relative to patients who were not. On the basis of results obtained in the current study, it would be predicted that patients who underwent the pre-randomization assessments would achieve their best performance at Day 0 and that this performance would not change after randomization to either medication. However, patients who enter the trial at Day 0 may have a different profile. If haloperidol causes a suppression of learning and practice effects, it would be anticipated that they would not show improvements during the double-blind phase whereas performance would improve for those receiving olanzapine. As previously mentioned, olanzapine's advantage may reside on the rate at which improvement based on learning and practice effects occurs.

Another approach to examining learning and practice effects would involve assessing patients on measures highly sensitive to such effects randomized to double-blind treatment with haloperidol or olanzapine only after they have been stabilized on the medication for at least 3 to 6 months. They could then be evaluated on their ability to profit from repeated

exposures to neurocognitive testing. On the basis of the results obtained in the current study, it would be hypothesized that patients randomized to olanzapine would show learning and practice effects beyond those of the haloperidol group. This evidence would support the notion that the benefit of atypical agents may not reside in their ability to enhance neurocognition, but in their absence of a neurocognitive suppression side-effect.

Implications

This study highlights the importance of a proper design when evaluating the effects of various antipsychotic medications on neurocognitive functioning in schizophrenia. Control groups allowed us to examine performance on neurocognitive functioning in the absence of clinical psychopathology and medication. Repeated assessments prior to randomization to treatment demonstrated that changes in performance in all groups were attributable to learning and practice effects during the pre-randomization period. No changes were observed in the post-randomization period for any group. This indicates that olanzapine and haloperidol had no effect in patients on neurocognitive tasks over a 2 month period.

Perhaps one of the most important implications of this study is that it may have touched on the mechanisms by which improved cognitive performance with atypical medications in persons with schizophrenia may occur. As already stated, it can be speculated that newer atypical medications may merely allow persons with schizophrenia to benefit from learning and practice effects more so than conventional medications. The mechanisms by which atypical agents benefit neurocognitive performance in persons with schizophrenia is of significance for several reasons. Functional outcomes in this patient population is heavily reliant on the integrity of neurocognitive functioning. Therefore, improvements in

neurocognitive functioning could lead to better functional outcomes and hence better quality of life. Also, it may be possible to better identify patients who are the best candidates for rehabilitation services. Finally, future drug development strategies may be aided with the identification of mechanisms by which neurocognition is ameliorated with atypical agents. If, as postulated from this research, atypical medications do not have a neurocognitive suppression side-effect whereas typical agents may, it will be important to capitalize on this information to avoid drugs which could interfere with this process.

From a clinical perspective, it was demonstrated that patients receiving olanzapine and haloperidol did not significantly differ on clinical and side-effect measures. However, patients who terminated the study early were all randomized to haloperidol. Furthermore, a greater proportion of patients randomized to haloperidol required anticholinergic medications to control drug-induced extrapyramidal side-effects. As a result, olanzapine was better tolerated by patients in the early phase of their illness. As such, atypical medications appear to be a better choice than typical medications when treating patients with schizophrenia in the early phase of their illness.

References

- Addington,D., Addington,J., & Schissel,B. (1990). A depression rating scale for schizophrenics. Schizophrenia Research, 3(4), 247-251.
- Addington,D.E., & Addington,J.M. (1992). Attempted suicide and depression in schizophrenia. Acta Psychiatrica Scandinavica, 85, 288-291.
- Addington,J., Addington,D., & Gasbarre,L. (1997). Distractibility and symptoms in schizophrenia. Journal of Psychiatry & Neuroscience, 22(3), 180-184.
- Allan,E.R., Sison,C.E., Alpert,M., Connolly,B., & Crichton,J. (1998). The relationship between negative symptoms of schizophrenia and extrapyramidal side effects with haloperidol and olanzapine. Psychopharmacology Bulletin, 34(1), 71-74.
- American Psychiatric Association. (1994). DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. (4th ed.). Washington, DC: Author.
- Andreasen,N.C. (1997). Linking Mind and Brain in the Study of Mental Illness: A Project for a Scientific Psychopathology. Science, 275, 1586-1587.
- Andreasen,N.C., Arndt,S., Alliger,R., Miller,D., & Flaum,M. (1995). Symptoms of schizophrenia. Methods, meanings, and mechanisms. Archives of General Psychiatry, 52(5), 341-351.
- Andreasen,N.C., Rezai,K., Alliger,R., Swayze,V.W., Flaum,M., Kirchner,P., Cohen,G., & O'Leary,D.S. (1992). Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Assessment with xenon 133 single-photon emission computed tomography and the Tower of London. Archives of General Psychiatry, 49(12), 943-958.
- Bachneff,S.A. (1991). Positron emission tomography and magnetic resonance imaging: a review and a local circuit neurons hypo(dys)function hypothesis of schizophrenia. Biological Psychiatry, 30(9), 857-886.

Baddeley, A.D., & Della Sala, S. (1996). Working memory and executive control. Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences, 351(1397), 1404

Beasley, C.M.J., Tollefson, G., Tran, P., Satterlee, W., Sanger, T., & Hamilton, S. (1996). Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology, 14(2), 111-123.

Berman, K.F., Torrey, E.F., Daniel, D.G., & Weinberger, D.R. (1992). Regional cerebral blood flow in monozygotic twins discordant and concordant for schizophrenia. Archives of General Psychiatry, 49 (12), 927-934.

Bédard, M.A., Scherer, H., Delorimier, J., Stip, E., & Lalonde, P. (1996). Differential effects of D2- and D4-blocking neuroleptics on the procedural learning of schizophrenic patients. Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie, 41(Suppl. 1), S21-S24

Bédard, M.A., Scherer, H., Stip, E., Cohen, H., Rodriguez, J.P., & Richer, F. (2000). Procedural learning in schizophrenia: further consideration on the deleterious effect of neuroleptics. Brain & Cognition, 43(1-3), 31-39.

Bilder, R.M., Goldman, R.S., Volavka, J., Czobor, P., Hoptman, M., Sheitman, B., Lindenmayer, J.P., Citrome, L., McEvoy, J., Kunz, M., Chakos, M., Cooper, T.B., Horowitz, T.L., & Lieberman, J.A. (2002). Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. American Journal of Psychiatry, 159(6), 1018-1028.

Black, D.W., & Andreasen, N.C. (1999). Schizophrenia, Schizophreniform Disorder, and Delusional (Paranoid) Disorders. In R. E. Hales, S. C. Yudofsky, & J. A. Talbot (Eds.), The American Psychiatric Press Textbook of Psychiatry. (pp. 425-473). Washington, DC: American Psychiatric Press, Inc.

Bogerts, B. (1997). The temporolimbic system theory of positive schizophrenic symptoms. Schizophrenia Bulletin, 23(3), 423-435.

Boulay, L.J. (1998). Working memory and the prefrontal cortex. Carleton University. Unpublished Manuscript, Carleton University, Ottawa.

Brandt, J. (1991). The Hopkins Verbal Learning Test: Development of a new verbal memory test with six equivalent forms. The Clinical Neuropsychologist, 5, 125-142.

Brekke, J.S., Raine, A., Ansel, M., Lencz, T., & Bird, L. (1997). Neuropsychological and psychophysiological correlates of psychosocial functioning in schizophrenia. Schizophrenia Bulletin, 23(1), 19-28.

Brickenkamp, R., & Zillmer, E. (1998). The d2 test of attention. Seattle: Hogrefe & Huber Publishers.

Bruggemans, E.F., Van de Vijver, F.J.R., & Huysmans, H.A. (1997). Assessment of cognitive deterioration in individual patients following cardiac surgery: correcting for measurement error and practice effects. Journal of Clinical & Experimental Neuropsychology, 19(4), 543-559.

Buchanan, R.W., Holstein, C., & Breier, A. (1994). The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance. Biological Psychiatry, 36(11), 717-725.

Buchsbaum, M.S., Haier, R.J., Potkin, S.G., Nuechterlein, K., Bracha, H.S., Katz, M., Lohr, J., Wu, J., Lottenberg, S., & Jerabek, P.A. (1992). Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics. Archives of General Psychiatry, 49(12), 935-942.

Caldwell, C.B., & Gottesman, I.I. (1990). Schizophrenics kill themselves too: a review of risk factors for suicide. Schizophrenia Bulletin, 16(4), 571-589.

Callicott, J.H., Ramsey, N.F., Tallent, K., Bertolino, A., Knable, M.B., Coppola, R., Goldberg, T., van Gelderen, P., Mattay, V.S., Frank, J.A., Moonen, C.T., & Weinberger, D.R. (1998). Functional magnetic resonance imaging brain mapping in psychiatry: methodological issues illustrated in a study of working memory in schizophrenia. Neuropsychopharmacology, 18(3), 186-196.

Carpenter, W.T.J., Heinrichs, D.W., & Wagman, A.M. (1988). Deficit and nondeficit forms of schizophrenia: the concept. American Journal of Psychiatry, 145(5), 578-583.

Carpenter, W.T.J., Strauss, J.S., & Bartko, J.J. (1973). Flexible system for the diagnosis of schizophrenia: Report from the WHO international pilot study of schizophrenia. Science, 182(1275), 1278

Carter, C., Robertson, L., Nordahl, T., Chaderjian, M., Kraft, L., & OShora, C.L. (1996). Spatial working memory deficits and their relationship to negative symptoms in unmedicated schizophrenia patients. Biological Psychiatry, 40(9), 930-932.

Carter, C.S., Perlstein, W., Ganguli, R., Brar, J., Mintun, M., & Cohen, J.D. (1998). Functional hypofrontality and working memory dysfunction in schizophrenia. American Journal of Psychiatry, 155(9), 1285-1287.

Casey, D.E. (1993). Serotonergic and dopaminergic aspects of neuroleptic-induced extrapyramidal syndromes in nonhuman primates. Psychopharmacology (Berl), 112 (Suppl. 1), 55-59.

Casey, D.E. (1997). The relationship of pharmacology to side effects. Journal of Clinical Psychiatry, 58 (Suppl. 10), 55-62.

Cassens, G., Inglis, A.K., Appelbaum, P.S., & Gutheil, T.G. (1990). Neuroleptics: effects on neuropsychological function in chronic schizophrenic patients. Schizophrenia Bulletin, 16(3), 477-499.

Chelune, G.J., Neugle, R.I., Lüders, H., Sedlak, J., & Awad, I.A. (1993). Individual change after Epilepsy Surgery: Practice effects and base-rate information. Neuropsychology, 7(1), 41-52.

Chen, W.J., Liu, S.K., Chang, C.J., Lien, Y.J., Chang, Y.H., & Hwu, H.G. (1998). Sustained attention deficit and schizotypal personality features in nonpsychotic relatives of schizophrenic patients. American Journal of Psychiatry, 155(9), 1214-1220.

Chouinard, G., & Arnott, W. (1993). Clinical review of risperidone. Canadian Journal of Psychiatry, 38 (Suppl. 3), 89-95.

Chouinard,G., Jones,B., Remington,G., Bloom,D., Addington,D., MacEwan,G.W., Labelle,A., Beauclair,L., & Arnott,W. (1993). A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. Journal of Clinical Psychopharmacology, 13(1), 25-40.

Chouinard,G., Ross-Chouinard,A., Annable,L., & Jones,B.D. (1980). The extrapyramidal symptom rating scale. Can J Neurol Sci, 7(233)

Chua,S.E., & McKenna,P.J. (1995). Schizophrenia--a brain disease? A critical review of structural and functional cerebral abnormality in the disorder. British Journal of Psychiatry, 166 (5), 563-582.

Classen,W., & Laux,G. (1988). Sensorimotor and cognitive performance of schizophrenic inpatients treated with haloperidol, flupenthixol, or clozapine. Pharmacopsychiatry, 21, 295-297.

Cohen,J.D., Perlstein,W.M., Braver,T.S., Nystrom,L.E., Noll,D.C., Jonides,J., & Smith,E.E. (1997). Temporal dynamics of brain activation during a working memory task. Nature, 386(6625), 604-608.

Cohen,J.D., & Servan-Schreiber,D. (1993). A theory of dopamine function and its role in cognitive deficits in schizophrenia. Schizophrenia Bulletin, 19(1), 85-104.

Cohen,L.J., Test,M.A., & Brown,R.L. (1990). Suicide and schizophrenia: data from a prospective community treatment study. American Journal of Psychiatry, 147(5), 602-607.

Conklin,H.M., Curtis,C.E., Katsanis,J., & Iacono,W.G. (2000). Verbal working memory impairment in schizophrenia patients and their first-degree relatives: evidence from the digit span task. American Journal of Psychiatry, 157(2), 275-277.

Cornblatt,B.A., & Keilp,J.G. (1994). Impaired attention, genetics, and the pathophysiology of schizophrenia [published erratum appears in Schizophr Bull 1994;20(2):248]. Schizophrenia Bulletin, 20(1), 31-46.

Courtney, S.M., Ungerleider, L.G., Keil, K., & Haxby, J.V. (1996). Object and spatial visual working memory activate separate neural systems in human cortex. Cerebral Cortex, 6(1), 39-49.

Csernansky, J.G., & Newcomer, J.W. (1994). Are there neurochemical indicators of risk for schizophrenia? Schizophrenia Bulletin, 20(1), 75-88.

Daniel, D.G., Goldberg, T.E., Weinberger, D.R., Kleinman, J.E., Pickar, D., Lubick, L.J., & Williams, T.S. (1996). Different side-effect profiles of risperidone and clozapine in 20 outpatients with schizophrenia or schizoaffective disorder: a pilot study. American Journal of Psychiatry, 153(3), 417-419.

de Beaulieu, R., Labelle, A., Naber, D., Jones, B.D., & Barnes, T.R.E. (1995). An open trial of the D1 antagonist SCH 39166 in 6 cases of acute psychotic states. Psychopharmacology, 121, 323-327.

Delis, D.C., Kramer, J.H., Kaplan, E., & Ober, B.A. (1987). The California Verbal Learning Test (CVLT). San Antonio, TX: Psychological Corporation.

Diamond, A. (1996). Evidence for the importance of dopamine for prefrontal cortex functions early in life. Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences, 351(1346), 1483-1493.

Dikmen, S.S., Heaton, R.K., Grant, I., & Temkin, N.R. (1999). Test-retest reliability and practice effects of Expanded Halsted-Reitan Neuropsychological Test Battery. Journal of the International Neuropsychological Society, 5, 346-356.

Dolan, R.J., Bench, C.J., Liddle, P.F., Friston, K.J., Frith, C.D., Grasby, P.M., & Frackowiak, R.S. (1993). Dorsolateral prefrontal cortex dysfunction in the major psychoses; symptom or disease specificity? Journal of Neurology, Neurosurgery & Psychiatry, 56(12), 1290-1294.

Dolan, R.J., Grasby, P., Fletcher, P., & Friston, K. (1997). Measuring Neuromodulation with functional imaging. In R. Frackowiak, K. Friston, C. Frith, R. J. Dolan, & J. C. Mazziotta (Eds.), Human Brain Function. (pp. 405-425). San Diego, CA: Academic Press.

- Dwork, A.J. (1997). Postmortem studies of the hippocampal formation in schizophrenia. Schizophrenia Bulletin, 23(3), 385-402.
- Ellis, K.A., & Nathan, P.J. (2001). The pharmacology of human working memory. International Journal of Neuropsychopharmacology, 4, 299-313.
- Erlenmeyer, K.L., & Cornblatt, B.A. (1978). Attentional measures in a study of children at high-risk for schizophrenia. Journal of Psychiatric Research, 14, 93-98.
- GPOWER: a priori, post-hoc, and compromise power analysis for MS-DOS [Computer Software]. (1992). Bonn, FRG: Bonn University, Dept. of Psychology: Faul, F., & Erdfelder, E.
- Feinstein, A., Brown, R., & Ron, M. (1994). Effects of practice of serial tests of attention in healthy subjects. Journal of Clinical & Experimental Neuropsychology, 16(3), 436-447.
- Fiez, J.A., Raife, E.A., Balota, D.A., Schwarz, J.P., Raichle, M.E., & Petersen, S.E. (1996). A positron emission tomography study of the short-term maintenance of verbal information. Journal of Neuroscience, 16(2), 808-822.
- Fleming, K., Goldberg, T.E., Binks, S., Randolph, C., Gold, J.M., & Weinberger, D.R. (1997). Visuospatial working memory in patients with schizophrenia. Biological Psychiatry, 41(1), 43-49.
- Fleming, K., Goldberg, T.E., Gold, J.M., & Weinberger, D.R. (1995). Verbal working memory dysfunction in schizophrenia: use of a Brown-Peterson paradigm. Psychiatry Research, 56(2), 155-161.
- Frith, C. (1995). Functional imaging and cognitive abnormalities. Lancet, 346(8975), 615-620.
- Frith, C.D. (1997). Linking brain and behaviour. In R. S. J. Frackowiak, K. J. Friston, C. D. Frith, R. J. Dolan, & J. C. Mazziotta (Eds.), Human Brain Functioning. (pp. 3-23). London: Academic Press.

Frith, C.D., Friston, K.J., Herold, S., Silbersweig, D., Fletcher, P., Cahill, C., Dolan, R.J., Frackowiak, R.S., & Liddle, P.F. (1995). Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. British Journal of Psychiatry, 167(3), 343-349.

Fujii, D.E.M., Ahmed, I., Jokumsen, M., & Compton, J.M. (1997). The effects of clozapine on cognitive functioning in treatment-resistant schizophrenic patients. Journal of Neuropsychiatry & Clinical Neurosciences, 9, 240-245.

Fuster, J.M. (1997). Network memory. Trends in Neurosciences, 20(10), 451-459.

Galletly, C.A., Clark, R., McFarlane, A.C., & Weber, D.L. (1997). Relationship between changes in symptom ratings, neuropsychological test performance and quality of life in schizophrenic patients treated with clozapine. Psychiatry Research, 72(3), 161-166.

Gerlach, J. (1991). New antipsychotics: classification, efficacy, and adverse effects. Schizophrenia Bulletin, 17(2), 289-309.

Gold, J.M., Carpenter, C., Randolph, C., Goldberg, T.E., & Weinberger, D.R. (1997). Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. Archives of General Psychiatry, 54(2), 159-165.

Goldberg, T.E., Aloia, M.S., Gourovitch, M.L., Missar, D., Pickar, D., & Weinberger, D.R. (1998). Cognitive substrates of thought disorder, I: the semantic system. American Journal of Psychiatry, 155(12), 1671-1676.

Goldberg, T.E., Greenberg, R.D., Griffin, S.J., Gold, J.M., Kleinman, J.E., Pickar, D., Schulz, S.C., & Weinberger, D.R. (1993c). The effects of clozapine on cognition and psychiatric symptoms in patients with schizophrenia. British Journal of Psychiatry, 162, 43-48.

Goldberg, T.E., Ragland, J.D., Torrey, E.F., Gold, J.M., Bigelow, L.B., & Weinberger, D.R. (1990). Neuropsychological assessment of monozygotic twins discordant for schizophrenia. Archives of General Psychiatry, 47(11), 1066-1072.

Goldberg, T.E., Torrey, E.F., Gold, J.M., Ragland, J.D., Bigelow, L.B., & Weinberger, D.R. (1993b). Learning and memory in monozygotic twins discordant for schizophrenia. Psychological Medicine, 23(1), 71-85.

Goldberg, T.E., & Weinberger, D.R. (1988). Probing prefrontal function in schizophrenia with neuropsychological paradigms. Schizophrenia Bulletin, 14(2), 179-183.

Golden, C.J. (1978). Stroop Color and Word Test: Manual for Clinical and Experimental Uses. Chicago: Stoelting Company.

Goldman-Rakic, P.S. (1990). Cortical Localization of Working Memory. In J. L. McGaugh, N. M. Weinberger, & G. Lynch (Eds.), Brain Organization and Memory: Cells, Systems, and Circuits. (pp. 285-298). New York: Oxford University Press.

Goldman-Rakic, P.S. (1994). Working memory dysfunction in schizophrenia. Journal of Neuropsychiatry & Clinical Neurosciences, 6(4), 348-357.

Goldman-Rakic, P.S. (1996). Regional and cellular fractionation of working memory. Proceedings of the National Academy of Sciences of the United States of America, 93(24), 13473-13480.

Goldman-Rakic, P.S., & Selemon, L.D. (1997). Functional and anatomical aspects of prefrontal pathology in schizophrenia. Schizophrenia Bulletin, 23(3), 437-458.

Grace, J., Bellus, S.B., Raulin, M.L., Herz, M.I., Priest, B.L., Brenner, V., Donnelly, K., Smith, P., & Gunn, S. (1996). Long-term impact of clozapine and psychosocial treatment on psychiatric symptoms and cognitive functioning. Psychiatric Services, 47(1), 41-45.

Granholm II, E. (1992). Processing Resource Limitations in Schizophrenia: Implications for Predicting Medication Response and Planning Attentional Training. In D. I. Mangolem (Ed.), Cognitive Neuropsychology in Clinical Practice. (pp. 43-69).

Green, M., & Walker, E. (1986). Attentional performance in positive- and negative-symptom schizophrenia. Journal of Nervous & Mental Disease, 174(4), 208-213.

Green,M.F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? American Journal of Psychiatry, 153(3), 321-330.

Green,M.F. (1998). Schizophrenia from a Neurocognitive Perspective. Probing the Impenetrable Darkness. Boston: Allyn and Bacon.

Green,M.F., Marder,S.R., Glynn,S.M., McGurk,S.R., Wirshing,W.C., Wirshing,D.A., Liberman,R.P., & Mintz,J. (2002). The neurocognitive effects of low-dose haloperidol: a two-year comparison with risperidone. Biological Psychiatry, 51(12), 972-978.

Green,M.F., Marshall,B.D.J., Wirshing,W.C., Ames,D., Marder, SR, McGurk,S., Kern,R.S., & Mintz,J. (1997). Does risperidone improve verbal working memory in treatment-resistant schizophrenia? American Journal of Psychiatry, 154(6), 799-804.

Gregory,R.J. (1987). Adult Intellectual Assessment. Boston: Allyn and Bacon, Inc.

Grön,G. (1998). Auditory and visual working memory performance in patients with frontal lobe damage and in schizophrenic patients with low scores on the Wisconsin Card Sorting Test. Psychiatry Research, 80(1), 83-96.

Hagger,C., Buckley,P., Kenny,J.T., Friedman,L., Ubogy,D., & Meltzer,H. (1993). Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. Biological Psychiatry, 34(10), 702-712.

Hawkins,K.A., Sullivan,T.E., & Choi,E.J. (1997). Memory deficits in schizophrenia: inadequate assimilation or true amnesia? Findings from the Wechsler Memory Scale- - revised. Journal of Psychiatry & Neuroscience, 22(3), 169-179.

Heaton,R.K. (1981). Wisconsin Card Sorting Test Manual. Odessa, Florida: Psychological Assessment Resources, Inc.

Heckers,S. (1997). Neuropathology of schizophrenia: cortex, thalamus, basal ganglia, and neurotransmitter-specific projection systems. Schizophrenia Bulletin, 23(3), 403-421.

Jiang, Y., Haxby, J. V., Martin, A., Maisog, J. M., Ungerleider, L. G., & Parasuraman, R. (1998). Event-related fMRI reveals two human cortical mechanisms during a working memory task. Neuroimage, 7, S10.

Johnstone, E. C., Crow, T. J., Frith, C. D., & Owens, D. G. (1988). The Northwick Park "functional" psychosis study: diagnosis and treatment response. Lancet, 2(8603), 119-125.

Kahn, R. S., & Davidson, M. (1993). Serotonin, dopamine and their interactions in schizophrenia. Psychopharmacology (Berl), 112(Suppl. 1), 1-4.

Kane, J. M., Schooler, N. R., Marder, S. R., Simpson, G. M., & Casey, D. E. (1994). Methods for clinical evaluation of pharmacologic treatments of schizophrenia. In R. F. Prien & D. S. Robinson (Eds.), Clinical evaluation of psychotropic drugs: Principles and guidelines. (pp. 345-372). New York: Raven Press, Ltd.

Kapur, S., Remington, G., Jones, C., Wilson, A., DaSilva, J., Houle, S., & Zipursky, R. (1996). High levels of dopamine D2 receptor occupancy with low- dose haloperidol treatment: a PET study. American Journal of Psychiatry, 153(7), 948-950.

Kay, S. R., & Opler, L. A. (1987). The positive-negative dimension in schizophrenia: its validity and significance. Psychiatric Developments, 2, 79-103.

Kay, S. R., Opler, L. A., & Fiszbein (1986). A Positive and Negative Syndrome Scale (PANSS) Rating Manual.

Keefe, R. S., Lees, R. S., & DuPre, R. L. (1997). Performance of patients with schizophrenia on a pen and paper visuospatial working memory task with short delay. Schizophrenia Research, 26(1), 9-14.

Keefe, R. S., Roitman, S. E., Harvey, P. D., Blum, C. S., DuPre, R. L., Prieto, D. M., Davidson, M., & Davis, K. L. (1995). A pen-and-paper human analogue of a monkey prefrontal cortex activation task: spatial working memory in patients with schizophrenia. Schizophrenia Research, 17(1), 25-33.

Keefe, R.S., Silva, S.G., Perkins, D.O., & Lieberman, J.A. (1999). The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. Schizophrenia Bulletin, 25(2), 201-222.

Kenny, J.T., & Meltzer, H.Y. (1991). Attention and higher cortical functions in schizophrenia. Journal of Neuropsychiatry, 3, 269-275.

Kern, R.S., Green, M.F., Marshall, B.D., Jr., Wirshing, W.C., Wirshing, D., McGurk, S., Marder, S.R., & Mintz, J. (1998). Risperidone vs. haloperidol on reaction time, manual dexterity, and motor learning in treatment-resistant schizophrenia patients. Biological Psychiatry, 44(8), 726-732.

Kern, R.S., Green, M.F., Marshall, B.D., Jr., Wirshing, W.C., Wirshing, D., McGurk, S.R., Marder, S.R., & Mintz, J. (1999). Risperidone versus haloperidol on secondary memory: can newer medications aid learning? Schizophrenia Bulletin, 25(2), 223-232.

King, D.J. (1990). The effect of neuroleptics on cognitive and psychomotor function. British Journal of Psychiatry, 157(799), 799-811.

King, D.J. (1994). Psychomotor impairment and cognitive disturbances induced by neuroleptics. Acta Psychiatrica Scandinavica, 380, 53-58.

King, H.E. (1991). Psychomotor dysfunction in schizophrenia. Amsterdam: Elsevier Science Publishers.

Labelle, A. (1999). Nonneuroleptic drug induced dyskinesias. Unpublished manuscript.

Labelle, A., & Boulay, L.J. (1999). An attempted suicide using transdermal nicotine patches. Canadian Journal of Psychiatry, 44(2), 190.

Lafayette Instrument Manual. (1989). Grooved Peg Board. Instructions / Owner's Manual.

Lahti,R.A., Evans,D.L., Stratman,N.C., & Figur,L.M. (1993). Dopamine D4 versus D2 receptor selectivity of dopamine receptor antagonists: possible therapeutic implications. European Journal of Pharmacology, 236(3), 483-486.

Laurent,A., Biloa-Tang,M., Bougerol,T., Duly,D., Anchisi,A.M., Bosson,J.L., Pellat,J., d'Amato,T., & Dalery,J. (2000). Executive/attentional performance and measures of schizotypy in patients with schizophrenia and in their nonpsychotic first-degree relatives. Schizophrenia Research, 46(2-3), 269-283.

Lee,M.A., Thompson,P.A., & Meltzer,H.Y. (1994). Effects of clozapine on cognitive function in schizophrenia. Journal of Clinical Psychiatry, 55, (Suppl. B), 82-7.

Lezak,M.D. (1983). Neuropsychological Assessment. (2nd ed.). New York: Oxford University Press.

Lezak,M.D. (1995). Neuropsychological Assessment. (3rd ed.). New York: Oxford University Press.

Lindenmayer,J.P., Iskander,A., Park,M., Apergi,F.S., Czobor,P., Smith,R., & Allen,D. (1998). Clinical and neurocognitive effects of clozapine and risperidone in treatment-refractory schizophrenic patients: a prospective study. Journal of Clinical Psychiatry, 59(10), 521-527.

Liu,S.K., Chen,W.J., Chang,C.J., & Lin,H.N. (2000). Effects of atypical neuroleptics on sustained attention deficits in schizophrenia: a trial of risperidone versus haloperidol. Neuropsychopharmacology, 22(3), 311-319.

Luria,A.R. (1973). The Working Brain. New York: Basic Books.

MacEwan,G.W. (1993). New antipsychotic medications: do research results relate to clinical practice? Canadian Journal of Psychiatry, 38, (Suppl. 3), 75-79.

Mahurin,R.K., Velligan,D.I., & Miller,A.L. (1998). Executive-frontal lobe cognitive dysfunction in schizophrenia: a symptom subtype analysis. Psychiatry Research, 79(2), 139-149.

Marder, S.R., & Meibach, R.C. (1994). Risperidone in the treatment of schizophrenia. American Journal of Psychiatry, 151(6), 825-835.

Maxwell, M. E. Manual for the FIGS. Clinical Neurogenetics Branch, Intramural Research Program, National Institute of Mental Health. 8-3-1992.

McCaffrey, R.J., Duff, K., & Westervelt, H.J. (2002). Practitioner's guide to evaluating change with neuropsychological assessment instruments. New York: Kluwer Academic / Plenum Publishers.

McGuffin, P., & Sturt, E. (1986). Genetic markers in schizophrenia. Human Heredity, 36, 65-88.

McGurk, S., Green, M.F., Wirshing, W.C., Ames, D., Marshall, B.D., Jr., Marder, M.D., & Mintz, J. (1997). The effects of risperidone vs. haloperidol on cognitive functioning in treatment-resistant schizophrenia: the trail making test. CNS Spectrums, 2, 60-64.

Meert, T.F., de Haes, P., & Janssen, P.A. (1989). Risperidone (R 64 766), a potent and complete LSD antagonist in drug discrimination by rats. Psychopharmacology (Berl), 97(2), 206-212.

Mega, M.S., & Cummings, J.L. (1994). Frontal-subcortical circuits and neuropsychiatric disorders. The Journal of Neuropsychiatry & Clinical Neurosciences, 6, 358-370.

Meltzer, H.Y., & McGurk, S.R. (1999). The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophrenia Bulletin, 25(2), 233-255.

Mesulam, M.M. (1990). Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Annals of Neurology, 28, 597-613.

Meyer-Lindenberg, A., Gruppe, H., Bauer, U., Lis, S., Krieger, S., & Gallhofer, B. (1997). Improvements of cognitive function in schizophrenic patients receiving clozapine or zotepine: results from a double-blind study. Pharmacopsychiatry, 30(2), 35-42.

Mirsky,A.F. (1987). Behavioral and psychophysiological markers of disordered attention. Environmental Health Perspectives, 74, 191-199.

Mirsky,A.F., Anthony,B.J., Duncan,C.C., Ahearn,M.B., & Kellam,S.G. (1991). Analysis of the Elements of Attention: A Neuropsychological Approach. Neuropsychological Review, 2(2), 109-145.

Mirsky,A.F., Fantie,B.D., & Tatman,J.E. (1995). Assessment of Attention Across the Lifespan. In R. L. Mapou & J. Spector (Eds.), Clinical Neuropsychological Assessment: A Cognitive Approach. (pp. 17-48). New York: Plenum Press.

Mockler,D., Riordan,J., & Sharma,T. (1997). Memory and intellectual deficits do not decline with age in schizophrenia. Schizophrenia Research, 26(1), 1-7.

Moon,C.A., Hindmarch,I., & Holland,R.L. (1990). The effect of zopiclone 7.5 mg on the sleep, mood and performance of shift workers. International Clinical Psychopharmacology, 5, (Suppl. 2), 79-83.

Moore,N.A. (1997). Behavioral pharmacology of Olanzapine. Journal of Clinical Psychiatry, 15(2), 13-15.

Morse,P.A., & Montgomery,C.E. (1992). Clinical syndromes in adult neuropsychology: the paractitioner's handbook. (pp. 120-122). New York: Elsevier.

Musch,B., & Maillard,F. (1990). Zopiclone, the third generation hypnotic: a clinical overview. International Clinical Psychopharmacology, 5, (Suppl. 2), 147-158.

Nordstrom,A.L., Farde,L., Wiesel,F.A., Forslund,K., Pauli,S., Halldin,C., & Uppfeldt,G. (1993). Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. Biological Psychiatry, 33(4), 227-235.

Nuechterlein,K.H., & Dawson,M.E. (1984). Information processing and attentional functioning in the developmental course of schizophrenic disorders. Schizophrenia Bulletin, 10(2), 160-203.

Nuechterlein, K.H., Dawson, M.E., & Green, M.F. (1994). Information-processing abnormalities as neuropsychological vulnerability indicators for schizophrenia. Acta Psychiatrica Scandinavica, 384, 71-79.

Nyberg, S., Farde, L., Eriksson, L., Halldin, C., & Eriksson, B. (1993). 5-HT₂ and D₂ dopamine receptor occupancy in the living human brain. A PET study with risperidone. Psychopharmacology, 110(3), 265-272.

Ohuoha, D.C., Hyde, T.M., & Kleinman, J.E. (1993). The role of serotonin in schizophrenia: an overview of the nomenclature, distribution and alterations of serotonin receptors in the central nervous system. Psychopharmacology (Berl), 112(Suppl. 1), 5-15.

Oltmanns, T.F. (1978). Selective attention in schizophrenic and manic psychoses: the effect of distraction in information processing. Journal of Abnormal Psychology, 87(2), 212-225.

Oltmanns, T.F., & Neale, J.M. (1975). Schizophrenic performance when distractors are present: attentional deficit or differential task difficulty. Journal of Abnormal Psychology, 84(3), 205-209.

Oltmanns, T.F., Ohayon, J., & Neale, J.M. (1978). The effect of anti-psychotic medication and diagnostic criteria on distractibility in schizophrenia. Journal of Psychiatric Research, 14, 81-91.

Oltmanns, T.F., Ohayon, J., & Neale, J.M. (1979). The effect of medication and diagnostic criteria on distractibility in schizophrenia. Journal of Psychiatric Research, 14, 81-91.

Owen, A.M. (1997). The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. European Journal of Neuroscience, 9(7), 1329-1339.

Owen, A.M., Evans, A.C., & Petrides, M. (1996). Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. Cerebral Cortex, 6(1), 31-38.

Palmerero-Neto, J. (1997). Dopaminergic systems: dopamine receptors. The Psychiatric Clinics of North America, 20(4), 705-721.

Palfreyman, M.G., Schmidt, C.J., Sorensen, S.M., Dudley, M.W., Kehne, J.H., Moser, P., Gittos, M.W., & Carr, A.A. (1993). Electrophysiological, biochemical and behavioral evidence for 5-HT₂ and 5-HT₃ mediated control of dopaminergic function. Psychopharmacology (Berl), 112 (Suppl. 1), 60-S67.

Park, S., & Holzman, P.S. (1992). Schizophrenics show spatial working memory deficits. Archives of General Psychiatry, 49(12), 975-982.

Park, S., & Holzman, P.S. (1993). Association of working memory deficit and eye tracking dysfunction in schizophrenia. Schizophrenia Research, 11(1), 55-61.

Park, S., Holzman, P.S., & Goldman, R.P. (1995). Spatial working memory deficits in the relatives of schizophrenic patients. Archives of General Psychiatry, 52(10), 821-828.

Paulesu, E., Frackowiak, R.S.J., & Bottini, G. (1997). Maps of the somatosensory systems. In R. S. J. Frackowiak, K. J. Friston, C. D. Frith, R. J. Dolan, & J. C. Mazziotta (Eds.), Human Brain Function. (pp. 183-242). San Diego: Academic Press.

Petrides, M., Alivisatos, B., Meyer, E., & Evans, A.C. (1993). Functional activation of the human frontal cortex during the performance of verbal working memory tasks. Proceedings of the National Academy of Sciences of the United States of America, 90(3), 878-882.

Posner, M.I., Inhoff, A.W., & Friedrich, F.J. (1987a). Isolating attentional systems: A cognitive-anatomical analysis. Psychobiology, 15(2), 107-121.

Posner, M.I., & Presti, D.E. (1987b). Selective attention and cognitive control. Trends in Neurosciences, 10(1), 13-17.

Posner, M.I., & Rafal, R.D. (1985). Cognitive Theories of Attention and the Rehabilitation of Attentional Deficits. In Meier, M.J., A. L. Benton, & L. Diller (Eds.), Neuropsychological Rehabilitation. (pp. 182-201). New York: The Guilford Press.

- Potkin, S.G.F. (2001). Clozapine enhances neurocognition and clinical symptomatology more than standard neuroleptics. Journal of Clinical Psychopharmacology, 21(5), 479-483.
- Prescott, C.A., & Gottesman, I.I. (1993). Genetically mediated vulnerability to schizophrenia. Psychiatric Clinics of North America, 16(2), 245-267.
- Psychological Assessment Resources, Inc [PAR]. (1992). Finger Tapping User's Guide. [Manual]. PAR Staff: Author.
- Purdon, S.E., Jones, B.D., Stip, E., Labelle, A., Addington, D., David, S.R., Breier, A., & Tollefson, G. (2000). Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. Archives of General Psychiatry, 57, 249-258.
- Purdon, S.E., Labelle, A., & Boulay, L. (2001). Neuropsychological change in schizophrenia after 6 weeks of clozapine. Schizophrenia Research, 48(1), 57-67.
- Purdon, S.E., Malla, A., Labelle, A., & Lit, W. (2001). Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. Journal of Psychiatry & Neuroscience, 26(2), 137-149.
- Raine, A., Benishay, D., Lencz, T., & Scarpa, A. (1997). Abnormal orienting in schizotypal personality disorder. Schizophrenia Bulletin, 23(1), 75-82.
- Rao, S.C., Rainer, G., & Miller, E.K. (1997). Integration of what and where in the primate prefrontal cortex. Science, 276(5313), 821-824.
- Rauch, S.L. (1997). Neuroimaging and neuropsychology of the striatum: Bridging basic science and clinical practice. Psychiatric Clinics of North America, 20(4), 768.
- Remington, G., & Kapur, S. (1999). D2 and 5-HT2 receptor effects of antipsychotics: bridging basic and clinical findings using PET. Journal of Clinical Psychiatry, 60 (Suppl. 10), 15-19.

Rossi,A., Mancini,F., Stratta,P., Mattei,P., Gismondi,R., Pozzi,F., & Casacchia,M. (1997). Risperidone, negative symptoms and cognitive deficit in schizophrenia: an open study. Acta Psychiatrica Scandinavica, 95(1), 40-43.

Roy,M.A., & DeVriendt,X. (1994). Positive and negative symptoms in schizophrenia: a current overview. Canadian Journal of Psychiatry, 39(7), 407-414.

Rusted,J.M. (1988). Dissociative effects of scopolamine on working memory in healthy young volunteers. Psychopharmacology (Berl), 96(4), 487-492.

Rusted,J.M., & Warburton,D.M. (1988). The effects of scopolamine on working memory in healthy young volunteers. Psychopharmacology (Berl), 96(2), 145-152.

Salinsky,M.C., Storzbach,D., Dodrill,C.B., & Binder,L.M. (2001). Test-retest bias, reliability, and regression equations for neuropsychological measures repeated over a 12 - 16 week period. Journal of the International Neuropsychological Society, 7, 597-605.

Salmon,E., Van der Linden,M., Collette,F., Delfiore,G., Maquet,P., Degueldre, Luxen,A., & Franck,G. (1996). Regional brain activity during working memory tasks. Brain, 119(5), 1617-1625.

Sawaguchi,T., & Goldman-Rakic,P.S. (1991). D1 dopamine receptors in prefrontal cortex: involvement in working memory. Science, 251(4996), 947-950.

Sawaguchi,T., & Goldman-Rakic,P.S. (1994). The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. Journal of Neurophysiology, 71(2), 515-528.

Sax,K.W., Strakowski,S.M., & Keck,P.E., Jr. (1998). Attentional improvement following quetiapine fumarate treatment in schizophrenia. Schizophrenia Research, 33(3), 151-155.

Schizophrenia Society of Canada. (1999). What is Schizophrenia. [Internet].

Schooler, C., Neumann, E., Caplan, L.J., & Roberts, B.R. (1997). A time course analysis of Stroop interference and facilitation: comparing normal individuals and individuals with schizophrenia. Journal of Experimental Psychology, 126(1), 19-36.

Schooler, N.R. (1994). Negative symptoms in schizophrenia: assessment of the effect of risperidone. Journal of Clinical Psychiatry, 55 (Suppl. 2), 2-8.

Schwartz, B.L., Rosse, R.B., & Deutsch, S.I. (1992). Toward a neuropsychology of memory in schizophrenia. Psychopharmacology Bulletin, 28(4), 341-351.

Seeman, P. (1993). Schizophrenia as a brain disease. The dopamine receptor story. Archives of Neurology, 50(10), 1093-1095.

Seeman, P. (1995). Dopamine receptors and psychosis. Scientific American, September/October, 2-11.

Seeman, P. (2002). Atypical antipsychotics: mechanism of action. Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie, 47(1), 27-38.

Seeman, P., Guan, H.C., & Van Tol, H.H. (1993). Dopamine D4 receptors elevated in schizophrenia. Nature, 365(6445), 441-445.

Seidman, L.J., Yurgelun-Todd, D., Kremen, W.S., Woods, B.T., Goldstein, J.M., Faraone, S.V., & Tsuang, M.T. (1994). Relationship of prefrontal and temporal lobe MRI measures to neuropsychological performance in chronic schizophrenia. Biological Psychiatry, 35(4), 235-246.

Serper, M.R., Davidson, M., & Harvey, P.D. (1994). Attentional predictors of clinical change during neuroleptic treatment in schizophrenia. Schizophrenia Research, 13(1), 65-71.

Sharma, T., & Mockler, D. (1998). The cognitive efficacy of atypical antipsychotics in schizophrenia. Journal of Clinical Psychopharmacology, 18 (Suppl. 1), 12-19.

Silver,H., David,D., Kaplan,M., Hadjez,J., Tubi,N., Darnel,A., Calev,A., & Lerer,B. (1993). Factor analysis of schizophrenic symptoms and comparison of different rating scales. Schizophrenia Research, 10(1), 67-75.

Smith,R.C., I. (2001). The effects of olanzapine on neurocognitive functioning in medication-refractory schizophrenia. International Journal of Neuropsychopharmacology, 4(3), 239-250.

Snell,R.S. (1992). Neuroanatomy: A Review with Questions and Explantions. Boston: Little, Brown and Company.

Sohlberg,M.M., & Mateer,C.A. (1987). Theory and Remediation of Attention Disorders. New York: The Guilford Press.

Spindler,K. A., Sullivan,E.V., Menon,V., Lim,K.O., & Pfefferbaum,A. (1997). Deficits in multiple systems of working memory in schizophrenia. Schizophrenia Research, 27(1), 1-10.

Spitzer,M. (1997). A cognitive neuroscience view of schizophrenic thought disorder. Schizophrenia Bulletin, 23(1), 29-50.

Spohn,H.E., & Strauss,M.E. (1989). Relation of neuroleptic and anticholinergic medication to cognitive functions in schizophrenia. Journal of Abnormal Psychology, 98(4), 367-380.

Spreen,O., & Strauss,E. (1991). A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. New York: Oxford University Press.

Spring,B. (1985). Distractibility as a marker of vulnerability to schizophrenia. Psychopharmacology Bulletin, 21(3), 509-512.

Stevens,A.A., Goldman,R.P., Gore,J.C., Fulbright,R.K., & Wexler,B.E. (1998). Cortical dysfunction in schizophrenia during auditory word and tone working memory demonstrated by functional magnetic resonance imaging. Archives of General Psychiatry, 55(12), 1097-1103.

Stevens, J.R. (1997). Anatomy of schizophrenia revisited. Schizophrenia Bulletin, 23(3), 373-383.

Stip, E., & Lussier, I. (1996). The effect of risperidone on cognition in patients with schizophrenia. Canadian Journal of Psychiatry, 41(Suppl. 2), 35-40.

Stip, E., Remington, G., Dursun, S.M., Reiss, J.P., Rotstein, E., MacEwan, G.W., Chokka, P.R., Jones, B., Dickson, R.A., & the Canadian switch study group. (in press). A Canadian multi-center trial assessing memory and executive functions in patients with schizophrenia spectrum disorders treated with olanzapine. Journal of Psychiatry & Neuroscience.

Stratta, P., Daneluzzo, E., Prosperini, P., Bustini, M., Mattei, P., & Rossi, A. (1997). Is Wisconsin Card Sorting Test performance related to 'working memory' capacity? Schizophrenia Research, 27(1), 11-19.

Strauss, J.S., Carpenter, W.T.J., & Bartko, J.J. (1974). The diagnosis and understanding of schizophrenia part III. Speculations on the processes that underlie schizophrenic symptoms and signs. Schizophrenia Bulletin, 11, 61-75.

Stuss, D.T., & Benson, D.F. (1986). The Frontal Lobes. New York: Raven Press.

Sweeney, J.A., Mintun, M.A., Kwee, S., Wiseman, M.B., Brown, D.L., Rosenberg, D.R., Carl, & JR. (1996). Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. Journal of Neurophysiology, 75(1), 454-468.

Szmanski, S., Kane, J.M., & Lieberman, J.A. (1991). A selective review of biological markers in schizophrenia. Schizophrenia Bulletin, 17(1), 99-111.

Szymanski, S., Kane, J.M., & Lieberman, J.A. (1991). A selective review of biological markers in schizophrenia. Schizophrenia Bulletin, 17(1), 99-111.

Tollefson, G.D., Beasley, C.M., Jr., Tran, P.V., Street, J.S., Krueger, J.A., Tamura, R.N., Graffeo, K.A., & Thieme, M.E. (1997). Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial [see comments]. American Journal of Psychiatry, 154(4), 457-465.

Tombaugh, T.N., & Francis, M.A. (1999). Simple Reaction Time Test [Computer software].

Tombaugh, T.N., & Francis, M.A. (1999). Choice Reaction Time Test [Computer software].

Treichler, F.R., Hamilton, D.M., & Halay, M.A. (1971). The influence of delay interval on severity of the spatial alternation deficit in frontal monkeys. Cortex, 7, 143-151.

Van Zomeren, A.H., & Brouwer, W.H. (1994). Clinical neuropsychology of attention. New York: Oxford University Press.

Velligan, D.I., Newcomer, J., Pultz, J., Csernansky, J., Hoff, A.L., Mahurin, R., & Miller, A.L. (2002). Does cognitive function improve with quetiapine in comparison to haloperidol? Schizophrenia Research, 53(3), 239-248.

Voruganti, L.N., Heslegrave, R.J., & Awad, A.G. (1997). Neurocognitive correlates of positive and negative syndromes in schizophrenia. Canadian Journal of Psychiatry, 42(10), 1066-1071.

Wechsler, D. (1981). WAIS-R Manual. San Antonio, Tx.: Psychological Corporation.

Wechsler, D. (1987). Wechsler Memory Scale - Revised manual. San Antonio, Tx.: Psychological Corporation.

Wechsler, D. (1997). WAIS-III administration and scoring manual. (3rd ed.). San Antonio: Harcourt Brace & Company.

Weinberger, D.R., Aloia, M.S., Goldberg, T.E., & Berman, K.F. (1994). The frontal lobes and schizophrenia. Journal of Neuropsychiatry & Clinical Neurosciences, 6(4), 419-427.

Wexler, B.E., Stevens, A.A., Bowers, A.A., Sernyak, M.J., & Goldman, R.P. (1998). Word and tone working memory deficits in schizophrenia. Archives of General Psychiatry, 55(12), 1093-1096.

Whyte, J. (1992). Attention and arousal: basic science aspects. Archives of Physical Medicine and Rehabilitation, 73, 940-949.

Williams, R., & Dickson, R. A. (1995). Economics of schizophrenia. Canadian Journal of Psychiatry, 40 (Suppl. 2), 60-67.

Wilson, B. A., Watson, P., Baddeley, A. D., Emslie, H., & Evans, J. J. (2000c). Improvement or simply practice? The effects of twenty repeated assessments on people with and without brain injury. Journal of the International Neuropsychological Society, 6, 469-479.

World Health Organization. (1996). WHO Programme on mental health. [On-line].

Yurgelun, T. D., Wateraux, C. M., Cohen, B. M., Gruber, S. A., English, C. D., & Renshaw, P. F. (1996). Functional magnetic resonance imaging of schizophrenic patients and comparison subjects during word production. American Journal of Psychiatry, 153(2), 200-205.

Zahn, T. P., Pickar, D., & Haier, R. J. (1994). Effects of clozapine, fluphenazine, and placebo on reaction time measures of attention and sensory dominance in schizophrenia. Schizophrenia Research, 13(2), 133-144.

Appendix A

Baseline Antipsychotic Medications: Olanzapine Group

Patient code	Baseline antipsychotic medication(s) / dose(s)	Concomitant medications / dose(s)
MSJ16	olanzapine 20 mg; haloperidol 10mg PRN	citalopram 40mg; risperidone 2mg; lorazepam 2mg PRN; benztropine 1mg PRN
SB17	risperidone 6 mg	benztropine 2 mg PRN; methotrimeprazine 100 mg/day
BH21	clozapine 250 mg	methotrimeprazine 75mg
LL22	olanzapine 7.5 mg	pimozide 6mg; glyburide 5mg; clonazepam 1.5mg; benztropine 2mg
JR25	olanzapine	none
MK27	risperidone 4mg; haloperidol 15 mg	lorazepam 6mg
TSC30	neuroleptic naive	none
DS32	off medications > 1 month	none
NX33	olanzapine 10 mg	lorazepam 4 mg
EL35	neuroleptic naive	venlafaxine 150mg
TB37	risperidone 3 mg	paroxetine 30mg; lorazepam 6mg; zopiclone 7.5mg
VC38	olanzapine 10 mg	citalopram 20mg
AG38	risperidone 4 mg	citalopram 20mg; lorazepam 1mg
LP40	risperidone 6 mg; loxapac 125 mg	procyclidine 15mg

table continues

Baseline Antipsychotic Medications: Haloperidol Group

Patient code	Baseline antipsychotic medication(s) / dose(s)	Concomitant medication(s) / dose(s)
NL18	neuroleptic naive	none
AP19	neuroleptic naive	none
EL20	quetiapine 800 mg	benztropine 2mg; clonazepam 0.5mg; ranitidine 300mg
AR23	olanzapine 20 mg	lorazepam 1mg; sertraline 50mg; benztropine 2mg
KB24	risperidone 4 mg; haloperidol 5mg PRN	acetaminophen 650mg; lorazepam 1mg
AS26	quetiapine 800 mg	benztropine 1mg PRN; trazodone 50mg PRN; clonazepam 0.5mg
VS29	risperidone 4mg	benztropine 1mg
LL31	olanzapine 5 mg	venlafaxine 37.5mg
MLL34	risperidone 2 mg	none
SB36	quetiapine 400mg	paroxetine 7.5 mg PRN
DF41	olanzapine 20mg; haloperidol 3 mg	none
RA42	olanzapine 20 mg; haloperidol 10 mg	lorazepam 1mg; divalproex 1000mg
CG43	quetiapine 400 mg	divalproex 500 mg

Note. PRN = as needed.

Appendix B

Patient Consent Form

PATIENT INFORMATION & INFORMED CONSENT FORM

TITLE: The Relationship Between Treatment Response to Olanzapine (Zyprexa) or Haloperidol (Haldol) and Family History of Schizophrenia and Schizophrenia Spectrum Disorders: A Randomized, Double-blind, Flexible Dose Study [FID-CA-0045]

SPONSOR: Zyprexa Research Fund

Patient Name: _____ Investigator: Dr. Alain Labelle

INTRODUCTION:

THE FOLLOWING INFORMATION DESCRIBES A CLINICAL RESEARCH STUDY AND YOUR ROLE IN IT SHOULD YOU DECIDE TO PARTICIPATE. PLEASE READ CAREFULLY AND DO NOT HESITATE TO ASK ANY QUESTION NOW OR AT ANY TIME DURING THE STUDY.

DESCRIPTION AND PURPOSE OF THE STUDY:

You are being invited to participate in a research study for which there are three purposes. The first is to determine if a presence or absence of a family history of psychiatric illnesses affects a person's response to either olanzapine [Zyprexa] or haloperidol [Haldol]. The second purpose is to compare the effectiveness of olanzapine [Zyprexa] and haloperidol [Haldol]. This will be accomplished by measuring changes at the start of the study and during

the study. The changes being looked at will be changes in symptoms, side-effects and cognitive abilities – such as attention, memory and reasoning for example. The third purpose of this study is to compare cognitive abilities between a group of persons diagnosed with schizophrenia, a group of non-ill relatives (mother, father, brother, sister or offspring), and a control group (comprised of persons never diagnosed with a mental illness and who do not have a family history mental illness). Please note, your relative will not be given any medications.

Both olanzapine and haloperidol are approved in Canada by the Health Protection Branch (HPB) as standard therapies for the treatment of schizophrenia. Past clinical trials have established their safety, effectiveness and tolerability and they can be prescribed to you without participating in this study.

If you decide to take part in this trial, your participation in the trial will last a total of 61 days (9 weeks). A total of 75 subjects will participate in this study here at the Royal Ottawa Hospital.

PROCEDURES TO BE FOLLOWED:

If you decide to participate in this study, you will be required to return to your psychiatrist's office on 9 and possibly 10 occasions.

- Before you can be enrolled in this study, you must have at least one non-ill biological family member (mother, father, brother or sister) who is also willing to participate in this study. They too will be required to sign an informed consent form.
- To determine which family member will be invited to participate, you will be asked about your family history of mental illness. Depending on the number of family

members you have, gathering this information may require one or two interviews of one to two hours in duration. These questions will have to do with medical as well as psychiatric symptoms and diseases that you or your family members may or may not have experienced. If, for whatever reason, you are unable to provide reliable information about your family history, you will be asked permission to contact one of your relatives in order to have them provide this information.

- Before the start of treatment and at the end of the trial (56 days after you start medication), you will undergo a physical examination.
- On five occasions (before entering the study, 3 days before the start of treatment, the day before you are to begin and then 28 days later and then at the end of the study [day56]), you will see your doctor. He/she will conduct a psychiatric evaluation which will assess symptoms associated with schizophrenia as well as depression.
- On 6 of these occasions (twice the day before you are to stop taking your medication, once the day you stop you medication, once the day before you are to begin taking the study medication, and then again 28 days later and then at the end of the study 56 days later), you will also undergo a series of cognitive assessments which will last approximately two hours each. A research associate (member of the study personnel) will assess your attention, memory, and reasoning abilities. As this is a research study, results from the cognitive assessments you complete will not be reported to you.

Any time you notice a return of psychotic symptoms or side effects, contact your study coordinator.

If you choose to leave this study early, it will not affect your medical care in any way.

However, you will be asked to come in for a final visit and assessment.

At the end of this study or if you drop out early, you and your doctor can discuss other treatment options.

MEDICATION:

If you decide to participate in this study, you must agree to cooperate fully with taking the medication as instructed, comply with the study visit schedule, and you must follow the study doctor's instructions.

Once you are enrolled in the study, your current antipsychotic medication(s) will be discontinued for three full days (72 hours). Following this antipsychotic free period, you will then be randomly assigned (like the toss of a coin) to either olanzapine (Zyprexa) OR haloperidol (Haldol) for a two month period (56 days) . Both olanzapine and haloperidol are oral medications. Please understand that you will not be receiving both drugs at any time, you will get olanzapine only OR haloperidol only. You will be required to take between 1 to 4 capsules every evening.

Both you and your doctor will not know which drug you are taking. However, throughout the study, your doctor will be able to adjust the medication you are receiving to a dose which is suitable for you.

If you miss a dose of oral tablets, you may take it a few hours late. Then take your next dose on schedule. Do not double up on doses. Report the missed dose and the date to the study coordinator at the next visit.

You are asked not to take any other prescribed drug, over-the-counter medicine, including vitamins, or alternative therapy (herbal remedy) available at your pharmacy or supermarket unless it has been approved by the study doctor.

All unused oral study medication and empty medication containers are to be returned to the study coordinator.

During the trial, the study doctor will let you know if any additional information is discovered about the study medication that may affect your willingness to participate in this trial.

RISKS AND BENEFITS:

During your participation in this research study, your doctor will closely follow your overall condition. You may get no benefit from your participation in this study. However, possible benefits of participating in this study may include improvement of your condition and relief of symptoms. It is also possible that the results of this trial may be helpful in advancing what is currently known about schizophrenia.

Olanzapine:

Over 3 million patients have been treated with olanzapine world-wide. Common side-effects reported by those taking olanzapine include sleepiness, dizziness, restlessness, weight gain, and a small increase in prolactin which returns toward normal in many patients; meaning that a hormone in the blood might cause decreased interest in sex, breast enlargement or abnormal menstrual periods in women.

Less common side-effects reported by those taking olanzapine include increased appetite, fall in blood pressure upon standing, constipation, dry mouth and increase in

chemicals in the blood that are made by the liver and an increase in a type of white blood cell measured in the blood. Tremors and involuntary movements have also been noted.

In addition to the side-effects named above, olanzapine or the study procedures may have other unknown risks. There may also be unknown risks to your embryo, fetus or unborn child.

Haloperidol is a drug marketed for the treatment of schizophrenia. Some common side effects of haloperidol include: neuromuscular reactions, including involuntary muscle twitches which could be irreversible, insomnia, restlessness, anxiety, agitation, depression, drowsiness, headache, confusion, dizziness, rapid heart beat, impaired liver function, constipation, diarrhea, dry mouth, blurred vision and inability to urinate.

You may also suffer from some fatigue as a result of the cognitive assessments.

As with other antipsychotic drugs, you should be aware of possible sleepiness or dizziness while operating a motor vehicle or machinery while taking the study medications.

COMPENSATION:

You will not be compensated for participation in this study. It is understood that the health care required by you as a result of early withdrawal from the study or an adverse event experienced during the study period will be provided in accordance with Provincial Health Insurance Plans. However, this does not constitute a waiver of any rights you have under Federal or Provincial laws and regulations.

ALTERNATIVE TREATMENTS:

You do not have to take part in this study to be treated for your illness or condition. Other treatments and therapies for your condition are available and you can discuss these with your doctor.

COSTS:

Other than your time, there are no costs to you to participate in this study. All costs for the required doctor visits, examinations, drug supplies, transportation (to and from appointments related to this study only / by bus only), and parking (related to this study only / on the Royal Ottawa Hospital grounds only / parking receipts will be required for compensation) are covered by Eli Lilly Canada Inc., the sponsor of this study.

VOLUNTARY PARTICIPATION & TERMINATION:

Participation in this study is entirely voluntary. If you decide not to participate, this will not affect the care you will receive from your doctor in any way. If you decide to stop being part of this study,

Dr. _____ or one of the staff members (Luc Boulay, M.A.) will talk to you about your choice.

Your participation in this study may be terminated without your consent by Dr. _____, or Eli Lilly Canada Inc. (the sponsor of the study) or the regulatory authorities. If this happens, it might be as a result of a bad reaction that you have to the medication to which you were assigned. Additionally, new information that your doctor or the sponsor learns about olanzapine [Zyprexa] or haloperidol's [Haldol] safety or effectiveness may lead to you being withdrawn from the study.

Also, you are free to withdraw your consent to participate in this research at any time during the study.

If you do discontinue your participation in the study for any of the reasons above, you will be asked to complete a final evaluation consisting of all tests and procedures performed at the beginning of the study.

MEDICAL RECORDS/CONFIDENTIALITY:

Only the doctor and the members of his/her team will know that you are participating in this study. All records and documents relating to your participation in this study will be held strictly confidential and your name will not be reported in any publications. All documents will be identified by your initials and a code number. Access to your Royal Ottawa Hospital clinical records is not permitted without your written consent, i.e. you will be asked to sign a "Form 14 Consent to Disclosure, Transmittal or Examination of a Clinical Record". By signing the "Form 14", you are consenting to inspection and disclosure of your clinical records to Eli Lilly Canada Inc. (sponsor), the Health Protection Branch (HPB) in Canada and the Food and Drug Administration (FDA) in the United States. Please note that no records bearing your name will leave the Royal Ottawa Hospital

QUESTIONS REGARDING PARTICIPATION:

Before signing this consent form, and at any time thereafter, you are free to ask your doctor about any aspect of this study that is not clear to you.

If you have any questions regarding:

- your rights as a research subject, please contact the hospital patient representative at (613) 722-6521

- your participation in this trial, please contact Dr. _____ at (613) 722-6521 ext. 6502 or Luc Boulay, M.A. at (613) 722-6521 ext. 7029 or (613) 593-4907 (pager; when asked to leave your numeric message, just enter your telephone number and Mr. Boulay will contact you as soon as he can).

The Ethics Committee of the Royal Ottawa Hospital has approved the contents and use of this Patient Information and Informed Consent Form.

PARTICIPANT'S ACKNOWLEDGMENT:

Do not sign this form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

I, _____ (print name) have fully reviewed, understand and accept the contents and nature of the information contained in this Patient Information document.

By signing this page, you are confirming the following:

- I have had an opportunity to ask my doctor and/or study personnel questions about this study. These questions have been answered to my satisfaction in terms I can understand.
- I am aware of and understand the possible risks and benefits which have been described to me.
- I agree to follow the study procedures and to provide necessary information to the doctor or other staff members as requested.
- I understand that I can withdraw from the study at any time and that this will not affect my subsequent medical treatment.
- I understand that by signing the "Form 14", that I am agreeing that relevant parts of my medical records may be disclosed to Eli Lilly Canada Inc. (sponsor) or its representatives, the Health Protection Branch (HPB) in Canada and the Food and Drug Administration (FDA) in the United States.
- I have received a copy of this Patient Information document and a signed and dated copy of the Informed Consent Form for my records.

- By signing this form I have not waived any of the legal rights which I otherwise would have as a participant in a research study.
- Based on this information, I voluntarily consent to participate in this study.

_____	_____	_____
Patient's Name (print)	Patient's Signature	Date

_____	_____	_____
Investigator's Name (print)	Investigator's Signature	Date

_____	_____	_____
Witness' Name (print)	Witness' Signature	Date

If the patient is unable to give informed consent:

PATIENT ASSENT:

I have read the explanation and I will participate in this research project.

Patient Name (print)	Patient Signature	Date
----------------------	-------------------	------

LEGAL REPRESENTATIVE CONSENT:

I, (*name of legal representative*) _____ have read the above information and fully understand the nature and purpose of the study in which (*patient's name*) _____ has been asked to take part. The explanation I have been given has described the possible risks and benefits of the study and alternative treatments available for his/her illness. I understand that participation in the trial is voluntary and that the patient may withdraw from the trial at any time and that this will not affect his/her subsequent medical treatment which he/she will receive from his/her own doctor. I agree to the patient's participation in this study.

By signing the Form 14, Consent to Disclosure, Transmittal or Examination of Clinical Record, I am agreeing that the relevant parts of his/her medical records may be disclosed to Eli Lilly or it's representatives, HPB and FDA provided they agree not to disclose the patient's name.

I hereby assent to _____ (*patient's name*) to take part in this clinical trial. I understand this assent may be withdrawn by me or the patient at any time.

_____	_____
Name of Legal Representative (print)	Signature of Legal Representative

_____	_____	_____
Address of Legal Representative (print)	Relationship to Patient	Date

I confirm that I have explained the nature of the trial to the patient's legal representative of the above named patient and assent was obtained for the patient to take part in the study.

_____	_____	_____
Name of Investigator (print)	Signature of Investigator	Date

_____	_____	_____
Name of Witness (print)	Signature of Witness	Date

Appendix C

Family Consent Form

FAMILY MEMBER INFORMATION & INFORMED CONSENT FORM

TITLE: The Relationship Between Treatment Response to Olanzapine (Zyprexa) or Haloperidol (Haldol) and Family History of Schizophrenia and Schizophrenia Spectrum Disorders: A Randomized, Double-blind, Flexible Dose Study [FID-CA-0045]

SPONSOR: Zyprexa Research Fund

Family Member Name: _____ Investigator: Dr. Alain Labelle

INTRODUCTION:

THE FOLLOWING INFORMATION DESCRIBES A CLINICAL RESEARCH STUDY AND YOUR ROLE IN IT SHOULD YOU DECIDE TO PARTICIPATE. PLEASE READ CAREFULLY AND DO NOT HESITATE TO ASK ANY QUESTION NOW OR AT ANY TIME DURING THE STUDY.

DESCRIPTION AND PURPOSE OF THE STUDY:

Your family member, _____ (patient's name) has given us permission to contact you regarding a study being conducted here at the Royal Ottawa Hospital.

You are being invited to participate in a research study for which there are three purposes. The first is to determine if a presence or absence of a family history of psychiatric

illnesses affects schizophrenia patients' response to either olanzapine [Zyprexa] or haloperidol [Haldol]. The second purpose is to compare the effectiveness of olanzapine [Zyprexa] and haloperidol [Haldol] in persons diagnosed with schizophrenia. This will be accomplished by measuring changes at the start of the study and during the study. The changes being looked at will be changes in symptoms, side-effects and cognitive abilities – such as attention, memory and reasoning for example. The third purpose of this study is to compare cognitive abilities between a group of persons diagnosed with schizophrenia, a group of non-ill relatives (mother, father, brother or sister), and a control group (comprised of persons never diagnosed with a mental illness and who do not have a family history mental illness). Please note, you will not be given any medications in this study.

If you decide to take part in this trial, your participation in the trial will last a total of 61 days (about 9 weeks).

PROCEDURES TO BE FOLLOWED:

If you decide to participate in this study, you will be required to return to the Royal Ottawa Hospital on five and possibly six occasions.

- On 6 occasions, you will undergo a series of cognitive assessments which will last approximately two hours each (twice on the day you are enrolled in the study; once the day after, and again 3 days later, and one month and two months later). A Research Associate (member of the study personnel) will assess your attention, memory, and reasoning abilities. As this is a research study, results from the cognitive assessments you complete will not be reported to you.

If you choose to leave this study early, it will not affect your family member's medical care or any future care you may require in any way. However, you will be asked to come in for a final visit and assessment.

If you decide to participate in this study, you must agree to comply fully with the study visit schedule.

You are asked to inform the doctor or research personnel about any medications you have recently taken. These included any prescribed drugs, over-the-counter medicine, vitamins, or alternative therapy (herbal remedy).

RISKS AND BENEFITS:

You may get no direct benefit from your participation in this study. However, it is also possible that the results of this trial may be helpful in advancing what is currently known about schizophrenia.

It is anticipated that there should not be any significant risks to you if you decide to participate in this study. However, you may experience some fatigue associated with the cognitive assessments.

COMPENSATION:

You will not be compensated for participation in this study.

COSTS:

Other than your time, there are no costs to you to participate in this study. However, you will be reimbursed for transportation (to and from appointments related to this study only / by bus only) and parking costs (related to this study / on the Royal Ottawa Hospital grounds only / parking receipts will be required for compensation).

VOLUNTARY PARTICIPATION & TERMINATION:

Participation in this study is entirely voluntary. If you decide not to participate, this will not affect the care that your family member will receive from his/her doctor in any way or any future care you may require. If you decide to stop being part of this study, Dr. _____ or one of the staff members (Luc Boulay, M.A.) will talk to you about your choice.

Your participation in this study may be terminated without your consent by Dr. _____, or Eli Lilly Canada Inc. (the sponsor of the study) or the regulatory authorities. Also, you are free to withdraw your consent to participate in this study at any time.

If you do discontinue your participation in the study for any of the reasons above, you will be asked to complete a final evaluation consisting of all tests and procedures performed at the beginning of the study.

MEDICAL RECORDS/CONFIDENTIALITY:

Only the doctor and the members of his/her team will know that you are participating in this study. All records and documents relating to your participation in this study will be held strictly confidential and your name will not be reported in any publications. All documents will be identified by your initials and a code number. However, the files related to your participation in this study may be examined by external sources. By signing this informed consent, you are consenting to inspection and disclosure of your research files by Eli Lilly Canada Inc. (sponsor).

QUESTIONS REGARDING PARTICIPATION:

Before signing this consent form, and at any time thereafter, you are free to ask the study doctor about any aspect of this study that is not clear to you.

If you have any questions regarding:

- your rights as a research subject, please contact the hospital patient representative at (613) 722-6521
- your participation in this trial, please contact Dr. _____ at (613) 722-6521 ext. 6502 or Luc Boulay, M.A. at (613) 722-6521 ext. 7029 or (613) 593-4907 (pager; when asked to leave your numeric message, just enter your telephone number and Mr. Boulay will contact you as soon as he can).

The Ethics Committee of the Royal Ottawa Hospital has approved the contents and use of this Patient Information and Informed Consent Form.

PARTICIPANT'S ACKNOWLEDGMENT:

Do not sign this form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

I, _____ (print name) have fully reviewed, understand and accept the contents and nature of the information contained in this Family Member Information document.

By signing this page, you are confirming the following:

- I have had an opportunity to ask the study doctor and/or study personnel questions about this study. These questions have been answered to my satisfaction in terms I can understand.
- I am aware of and understand the possible risks and benefits which have been described to me.
- I agree to follow the study procedures and to provide the necessary information to the doctor, nurses or other staff members as requested.
- I understand that I can withdraw from the study at any time and that this will not affect my family member's subsequent medical treatment or any future care I may require.
- I understand that by signing this Informed Consent, that I am agreeing that relevant parts of my study files may be disclosed to Eli Lilly Canada Inc. (sponsor) or its representatives, the Health Protection Branch (HPB) in Canada and the Food and Drug Administration (FDA) in the United States.

- I have received a copy of this Family Member Information document and a signed and dated copy of the Informed Consent Form for my records.
- By signing this form I have not waived any of the legal rights which I otherwise would have as a participant in a research study.
- Based on this information, I voluntarily consent to participate in this study.

_____	_____	_____
Participant's Name (print)	Participant's Signature	Date
_____	_____	_____
Investigator's Name (print)	Investigator's Signature	Date
_____	_____	_____
Witness' Name (print)	Witness' Signature	Date

Appendix D

Normal Control Consent Form

**NORMAL CONTROL GROUP INFORMATION & INFORMED CONSENT
FORM**

TITLE: The Relationship Between Treatment Response to Olanzapine (Zyprexa) or Haloperidol (Haldol) and Family History of Schizophrenia and Schizophrenia Spectrum Disorders: A Randomized, Double-blind, Flexible Dose Study [FID-CA-0045]

SPONSOR: Zyprexa Research Fund

Participant's Name: _____ Investigator: Dr. Alain Labelle

INTRODUCTION:

THE FOLLOWING INFORMATION DESCRIBES A CLINICAL RESEARCH STUDY AND YOUR ROLE IN IT SHOULD YOU DECIDE TO PARTICIPATE. PLEASE READ CAREFULLY AND DO NOT HESITATE TO ASK ANY QUESTION NOW OR AT ANY TIME DURING THE STUDY.

DESCRIPTION AND PURPOSE OF THE STUDY:

You are being invited to be part of a control group in a research study focusing on schizophrenia. There are three purposes in this study. The first is to determine if a presence or absence of a family history of psychiatric illnesses affects schizophrenia patients' response to either olanzapine [Zyprexa] or haloperidol [Haldol]. The second purpose is to compare

the effectiveness of olanzapine [Zyprexa] and haloperidol [Haldol] in persons diagnosed with schizophrenia. This will be accomplished by measuring changes at the start of the study and during the study. The changes being looked at will be changes in symptoms, side-effects and cognitive abilities – such as attention, memory and reasoning for example. The third purpose of this study is to compare cognitive abilities between a group of persons diagnosed with schizophrenia, a group of non-ill relatives (mother, father, brother or sister), and a control group (comprised of persons never diagnosed with a mental illness and who do not have a family history mental illness). Please note, you will not be given any medications in this study. If you decide to take part in this trial, your participation in the trial will last a total of 61 days (about 9 weeks). A total of 75 subjects will participate in this study here at the Royal Ottawa Hospital.

PROCEDURES TO BE FOLLOWED:

If you decide to participate in this study, you will be required to return to the Royal Ottawa Hospital on five and possibly six occasions.

- Before you can be enrolled in this study, it must be established that you have not suffered from a mental disorder and that you do not have a family history of mental illness. Therefore, depending on the number of family members you have, you will be asked to participate in one or two interviews of one to two hours in duration in which you will be asked questions about yourself and your family members. These questions will have to do with medical as well as psychiatric symptoms and diseases that you or your family members may or may not have experienced.

- On 6 occasions, you will undergo a series of cognitive assessments which will last approximately two hours each (twice on the day you are enrolled in the study; once the day after, and again 3 days later, and one month and two months later). A Research Associate (member of the study personnel) will assess your attention, memory, and reasoning abilities. As this is a research study, results from the cognitive assessments you complete will not be reported to you.

If you choose to leave this study early, it will not affect any future care at this institution that you may require in any way. However, you will be asked to come in for a final visit and assessment.

If you decide to participate in this study, you must agree to comply fully with the study visit schedule.

You are asked to inform the doctor or research personnel about any medications you have recently taken. These included any prescribed drugs, over-the-counter medicine, vitamins, or alternative therapy (herbal remedy).

RISKS AND BENEFITS:

You may get no direct benefit from your participation in this study. However, it is also possible that the results of this trial may be helpful in advancing what is currently known about schizophrenia.

It is anticipated that there should not be any significant risks to you if you decide to participate in this study. However, you may experience some fatigue associated with the cognitive assessments.

COMPENSATION:

You will receive a nominal sum of \$20.00 per cognitive testing session (6 sessions x \$20.00 each = \$120.00) to compensate you for any costs incurred while participating in this study.

COSTS:

Other than your time, there are no costs to you to participate in this study.

VOLUNTARY PARTICIPATION & TERMINATION:

Participation in this study is entirely voluntary. If you decide not to participate, this will not affect any future care that you may require at this institution in any way. If you decide to stop being part of this study, Dr. _____ or one of the staff members will talk to you about your choice.

Your participation in this study may be terminated without your consent by Dr. _____, or Eli Lilly Canada Inc. (the sponsor of the study) or the regulatory authorities. Also, you are free to withdraw your consent at any time during the study.

If you do discontinue your participation in the study for any of the reasons above, you will be asked to complete a final evaluation consisting of all tests and procedures performed at the beginning of the study.

MEDICAL RECORDS / CONFIDENTIALITY:

Only the doctor and the members of his / her team will know that you are participating in this study. All records and documents relating to your participation in this study will be held strictly confidential and your name will not be reported in any publications. All documents will be identified by your initials and a code number. However, the files related

to your participation in this study may be examined by external sources. By signing this informed consent, you are consenting to inspection and disclosure of your research files by Eli Lilly Canada Inc. (sponsor).

QUESTIONS REGARDING PARTICIPATION:

Before signing this consent form, and at any time thereafter, you are free to ask the study doctor about any aspect of this study that is not clear to you.

If you have any questions regarding:

- your rights as a research subject, please contact the hospital patient representative at (613) 722-6521
- your participation in this trial, please contact Dr. _____ at (613) 722-6521 ext. 6502 or Luc Boulay, M.A. at (613) 722-6521 ext. 7029 or (613) 593-4907 (pager; when asked to leave your numeric message, just enter your telephone number and Mr. Boulay will contact you as soon as he can).

The Ethics Committee of the Royal Ottawa Hospital has approved the contents and use of this Patient Information and Informed Consent Form.

PARTICIPANT'S ACKNOWLEDGMENTS:

Do not sign this form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

I, _____ (print name) have fully reviewed, understand and accept the contents and nature of the information contained in this Control Group Information document.

By signing this page, you are confirming the following:

- I have had an opportunity to ask the study doctor and /or study personnel questions about this study. These questions have been answered to my satisfaction in terms I can understand.
- I am aware of and understand the possible risks and benefits which have been described to me.
- I agree to follow the study procedures and to provide the necessary information to the doctor, nurses or other staff members as requested.
- I understand that I can withdraw from the study at any time and that this will not affect any future care that I may require at this institution.
- I understand that by signing this Informed Consent, that I am agreeing that relevant parts of my study files may be disclosed to Eli Lilly Canada Inc. (sponsor) or it's representatives, the Health Protection Branch (HPB) in Canada and the Food and Drug Administration (FDA) in the United States.
- I have received a copy of this Control Group Information document and a signed and dated copy of the Informed Consent Form for my records.

- By signing this form I have not waived any of the legal rights which I otherwise would have as a participant in a research study.
- Based on this information, I voluntarily consent to participate in this study.

_____	_____	_____
Participant's Name (print)	Participant's Signature	Date

_____	_____	_____
Investigator's Name (print)	Investigator's Signature	Date

_____	_____	_____
Witness' Name (print)	Witness' Signature	Date

Appendix E

Patient Characteristics: Olanzapine Group

Pt.			Ill.	No.		Employ.	Living	Marital
code	Age	Gender	dur.	hosp.	Educ.	status	arrange.	status
MSJ16	51	Male	1	3	9	Disability	Family	Div.
SB17	42	Fem.	1	1	10	Disability	Indep	Div.
BH21	22	Male	1	2	8	Disability	Family	Single
LL22	22	Male	1	1	12	Disability	Family	Single
JR25	18	Male	0.5	1	10	Disability	Family	Single
MK27	51	Fem.	2	1	15	Disability	Supp. liv.	Div.
TSC30	42	Fem.	0.5	0	13	Disability	Indep.	Div.
DS32	21	Male	1	0	14	PT employ.	Family	Single
NX33	29	Fem.	3	2	10	Disability	Family	Div.
EL35	28	Male	1	0	17	FT student	Family	Single
TB37	46	Male	2	1	15	Disability	Indep.	Div.
VC38	18	Male	2	2	12	PT student	Family	Single
AG38	39	Male	1	0	15	PT employ.	Indep.	Single
LP40	31	Male	3	2	12	Disability	Family	Single

table continues

Patient Characteristics: Haloperidol Group

Pt.			Ill.	No.		Employ.	Living	Marital
code	Age	Gender	dur.	hosp.	Educ.	status	arrange.	status
NL18	32	Male	0.5	0	18	FT employ.	Spouse	Married
AP19	59	Male	0.5	0	18	Disability	Indep.	Priest
EL20	23	Male	1	2	14	Disability	Family	Single
AR23	22	Fem.	5	1	12	Disability	Family	Single
KB24	31	Fem.	5	4	13	Disability	Supp. liv.	Single
AS26	22	Male	1	2	12	Disability	Indep.	Single
VS29	29	Male	4	1	9	Disability	Family	Married
LL31	37	Male	1.5	2	14	Disability	Family	Married
MLL34	48	Male	5	0	13	PT employ.	Indep.	Single
SB36	32	Fem.	5	0	14	Disability	Family	Sep.
DF41	37	Fem.	1	3	12	Disability	Partner	C-law
RA42	27	Male	4	2	9	Unemploy.	Family	Single
CG43	38	Male	1.5	0	13	Disability	Family	Single

Note. Pt. code = patient code; Ill. dur. = duration of illness in years; No. hosp. = number of in-patient hospitalizations; Educ. = years of education; Employ. status = employment status; Living arrange. = living arrangement; Fem. = female; PT employ. = part time employment; FT student = full time student; PT student = part time student; FT employ. = full time employment; Unemploy. = unemployed; Family = living with family; Indep. = living independently; Supp. liv. = supportive living arrangement; Div. = divorced; Sep. = separated; C-law = common law

Appendix F

Neurocognitive Battery

Description of the Neurocognitive Battery to the Patient

Prior to the administration of the following tasks, brief the patient about what they will be asked to do. Say: **The following tests will evaluate your ability to focus your attention and concentration. Some of the tests will assess your memory for numbers and letters for example. You will notice that some of these tests will be easier at the start and will get more and more difficult as you go along. Just try your best. If you need to take a break at any point, just let me know. Do you have any questions?** Answer any question the patient may have. If there are no questions, then proceed to the first task.

Circles Away

Description

The Circles Away task assesses visuospatial short-term memory and consists of three conditions: an immediate condition, a 3 s delay condition, and a 10 s delay condition. Each condition has 16 trials and is presented individually beginning with the immediate condition. Using a computer monitor, subjects are required to focus on a centrally located cross on a white background for a period of 2 seconds. The cross then disappears and an open circle (the target location) appears in one of 68 possible positions to for a duration of 1 s (together, these 68 locations form a circle) (see Figure F1). Immediately following the target presentation, the 68 reference circles appear on the monitor. Subjects are required to indicate where the target circle appeared by touching one of the reference circles. The same procedures are used in 3 s and 10 s delay conditions. To reduce the potential for verbal mediation of stimulus location, individual white uppercase letters appear on a black background in the center of the monitor at the rate of one every second during the 3 s and 10 s delay periods. Subjects are instructed to call out each letter as they appear.

Figure F1. Once subjects are focused on the 'Ready' screen (panel 1), the central cross appears for a 2 seconds duration (panel 2) after which a target location appears (panel 3). Sixty-eight possible locations then appear immediately after, three seconds after, or ten seconds after the target presentation (panel 4).

Dependent Measure

The sum of the number of circles away (total over 16 trials) from the target location for each of the three conditions is used to assess overall accuracy.

Administration Procedures and Directions

Immediate Condition

Sit the subject squarely in front of the computer monitor. Simultaneously demonstrate these instructions using the first computer sample trial for the immediate condition. Say: **This is a test to see how well you can remember where circles appear on this monitor. To begin, you will see a screen with the word “Ready” on it. Following, you will see a white screen with a cross at the center appear for a two second duration. The cross will then disappear and an open circle, called the target, will appear for one second somewhere on the monitor. Immediately after the circle disappears, you will see a screen with many circles on it. Your task is to remember where the target appeared by pointing to one of these circles.**

Any questions? If the subject demonstrates that they understand, proceed with the second example without providing further instructions.

If the subject was able to complete the second example without difficulty, proceed with the test trials. Otherwise, repeat the above instructions as necessary until the subject understands the task.

3 s Delay Condition

Simultaneously demonstrate these instructions using the first computer sample trial for the 3 s delay condition. Say to the subject: **This time, after you see the target location,**

the screen will become black and letters will appear. I want you to say the letter out loud as you see them. After a certain period, the reference circles will appear and you must show me where you think the target location was. Any questions? If the subject does not have any questions, proceed to the second sample trial, otherwise repeat the instructions as often as necessary to insure that the subject understands the task. Say: **Okay, now we will do one just for practice.** Run the second practice trial. At the end of the letter sequences, when the blank white screen appears, say: **Now show me where the target circle appeared.** Regardless of the accuracy of this practice trial, proceed with the actual trials. Say: **Good, you seem to understand how to do this test. Do you have any questions before we do some actual trials?** Answer any questions the subject may have and proceed to the actual trials.

10 s Delay Condition

Say: **This time, the delay period between the time you see the target circle appear and the time you have to respond will be longer. Like the test we just finished, you will have to call out the letters as they appear on the computer screen. Any questions?** If there are no questions, proceed with the actual trials. *Note:* there are no practice trials for this condition.

Circles Away (Score Sheet)

Subject Name: _____ Subject I.D.: _____ Date: _____

Group: NC Pt FM Study Day: -4a -4b -3 0 28 56 ET (Circle One)

Immediate Condition		3 s Delay Condition		10 s Delay Condition	
	#of Circles Away		#of Circles Away		#of Circles Away
1		1		1	
2		2		2	
3		3		3	
4		4		4	
5		5		5	
6		6		6	
7		7		7	
8		8		8	
9		9		9	
10		10		10	
11		11		11	
12		12		12	
13		13		13	
14		14		14	
15		15		15	
16		16		16	
	Total = _____		Total = _____		Total = _____

Digit Span Forward and Digit Span Distractibility Test

Description

Due to the similarity of both tasks, the Digit Span Forward condition is intermixed with the Digits Span Distractibility Test.

Digit Span Forward

The Digit Span Forward condition is used to assess verbal short-term memory (Stratta et al., 1997; Sohlberg & Mateer, 1987). This test requires subjects to listen to a series of digits presented at the rate of one every 2 seconds. At the end of each string, they are required to repeat the digits in the correct order. Sequence lengths begin with three digits and progress to eight. In order to obtain the data required for the Digit Span Distractability Test, discontinuation rules as per the WMS-R manual are modified (Wechsler, 1987). All items from 1 - 6 must be completed. If the subject fails any WMS-R group (two spans of the same length) up to and including group 4, discontinue after the administration of group 6.

Dependent Measures

The Digits Span Forward is scored according to the WMS-R guidelines (Wechsler, 1987). Raw scores are used as the dependent measures.

Digit Span Distractability Test

As mentioned in the introduction, most tests of selective attention involve two conditions: one with and one without a distractor. Normal controls and patients with schizophrenia will typically perform more poorly in a distractor condition. However, it is not clear if poor performance is as a result of the distractor condition being more difficult or the distractor itself. To differentiate between task difficulty and the effect of a distractor

condition, Oltmanns and colleagues (1975; 1978) developed the Digit Span Distractibility Test. This test equates the performance of normal control subjects on both the distractor and no-distractor conditions. In the non-distractor condition of the Digit Span Distractibility Test, subjects are required to listen to a series of six digits presented in a female voice. Each digit is presented at the rate of one every 2 seconds. At the end of each six digit string, subjects are required to repeat as many of the digits in the correct order as possible. In the distractor condition, subjects are required to listen to and remember five target digits presented by the female voice while ignoring four distractor digits read by a male voice. The four distractor digits are interjected between each of the five target digits. Similar to the non-distractor condition, the rate of target digit presentation in the distractor condition is also 2 seconds. In all, there are two practice trials and seven test trials for each condition.

Dependent measures

The total proportion of correctly recalled target digits in the distractor condition is used as the dependent measure. This is calculated by dividing the total number of correctly recalled digits from the total number of possible target digits (49 for the distractor condition) (Addington & Addington, 1997; Green & Walker, 1986; Green et al., 1997; Oltmanns & Neale, 1975; Oltmanns, 1978; Spring, 1985).

Administration Procedures and Directions

The stimuli have been digitally recorded and are presented using a computer (IBM ThinkPad, i Series). Distractor and no-distractor trials are randomly intermixed.

Say: **This is a test to see how well you can remember numbers. You will hear a female voice say ‘listen carefully’ and then say a series of numbers. Your task is remember these numbers in the correct order to the best of your ability. Let’s go through a couple of these for practice.** Give the subject the headphones. Present the first no-distractor practice trial. After the end of the trial, say: **Ok, now tell me the numbers you heard in the same order.** If the subject answers correctly, say: **Good, now let’s do another practice trial.** Otherwise, repeat the first practice trial until it is clear that the subject understands the task.

Present the second No-distractor practice trial then say: **Now, tell me the numbers you heard in the same order.** If the subject answered correctly, say: **Good.** If the subject’s response was incorrect, repeat the second practice trial until it is clear that the subject understands the task.

After the successful completion of the second practice trial, say: **The second part of this test is similar to the first, except that in addition to the female voice reading a series of digits, you will also hear a male voice reading some digits. Your task is to ignore the digits read by the male voice. Just try to remember the digits read by the female voice in the same order. Let’s go through a couple of these for practice.** Present the first distractor practice trial. At the end of the trial say: **Ok, tell me the numbers you heard the female voice say in the same order.** If the subject answered correctly, say: **Good, now let’s do another practice trial.** Otherwise, repeat the first practice trial until it is clear that the subject understands the task. Present the second distractor practice trial. At the end of the trial say: **Ok, tell me the numbers you heard the female voice say in the**

same order. If the subject answered correctly, say: **Good, now we will do some actual trials. Some of these will only have the female voice while others will have both the female and the male voice. Also, the amount of numbers you will have to remember will get progressively longer as we go on. So listen carefully and remember to only pay attention to the female voice and ignore the male voice. Any questions? Otherwise,** repeat the second practice trial until it is clear that the subject understands the task. Present the first trial. Repeat the above instructions as needed.

Digits Span Forward and Digits Span Distractibility Test (p.1)

Subject Name: _____ Subject I.D.: _____ Date: _____

Group: Pilot NC Pt FM Study Day: -4a -4b -3 0 28 56 ET (Circle One)

	WMS-R Digits Forward		WMS-R Pass- Fail	WMS-R Score, 2,1 or 0	DSDT Score			
	No-distractor	Distractor			# correctly recalled digits		# Intrusion	
					N-Distr Cond	Distr Cond	N-Distr Cond	Distr Cond
S A M P L E	37741							
	37687							
		38418						
		38169						
1	39965							
	38417							
		2-8-7-5-4						
		6-4-8-1-5						
2	5-4-1-7							
		8-4-1-6-2-7-3						
	8-3-9-6							
		5-2-4-1-8-6-3						
3	3-6-9-2-5							
	6-9-4-7-1							
		6-4-2-1-8-5-7-9-3						
		7-8-1-2-9-5-6-3-4						
4		7-2-4-3-5-8-9-6-1						
	9-1-8-4-2-7							
		9-6-3-1-8-5-7-4-2						
	6-3-5-4-8-2							
5	2-8-5-3-4-6							
		1-3-7-4-2-8-6-5-9						
		3-6-7-9-4-5-2-1-8						
	8-1-4-9-7-5							

Digits Span Forward and Digits Span Distractibility Test (p.2)

Subject Name: _____ Subject I.D.: _____ Date: _____

Group: Pilot NC Pt FM Study Day: -4a -4b -3 0 28 56 ET (Circle One)

	WMS-R Digits Forward		WMS-R Pass-Fail	WMS-R Score, 2,1 or 0	DSDT Score			
	No-distractor	Distractor			# correctly recalled digits		# Intrusion	
					N-Distr Cond	Distr Cond	N-Distr Cond	Distr Cond
6	9-1-8-2-6-4							
	8-2-9-5-1-7							
		5-1-4-3-9-8-7-6-2						
	5-1-8-3-9-6							
7	1-2-8-5-3-4-6							
	2-8-1-4-9-7-5							
8	3-8-2-9-5-1-7-4							
	5-9-1-8-2-6-4-7							
Total Forward, Max = 12								
Total # of Correctly Recalled Digits in the N-Distractor Condition (Max = 66)								
Total # of Correctly Recalled Digits in the Distractor Condition (Max = 49)								
Total # of Intrusion in the N-Distractor Condition								
Total # of Intrusions in the Distractor Condition								
Proportion of Correctly Recalled Digits in N-Distractor Condition				= () / 66 =				
Proportion of Correctly Recalled Digits in Distractor Condition				= () / 49 =				
Longest Span Correctly Recalled in the N-Distractor Condition								
Longest Span Correctly Recalled in the Distractor Condition								

Digit Span Backward

Description

The Digit Span Backward is a test of verbal working memory. It requires subjects to correctly recall digits in reverse order. Progressive sequence lengths range from two to seven digits. Discontinuation rules as per the WMS-R manual are applied in the backward condition (Wechsler, 1987).

Dependent Measure

Raw scores are used as the dependent measure.

Administration Procedures and Directions

Say: This test is similar to the one you just completed. The only difference is that you will be required to repeat the numbers in reverse order. For example, if she says "9-2", what would you say? If the subject answers correctly, proceed to the second example. Otherwise, repeat the above instructions until it is clear that the subject understands how to complete the task. **Great, let's try another example. Let's say the female voice says "1-4", what would you say?** If the subject answers correctly continue with the instructions. Otherwise, repeat the above instructions until it is clear that the subject understands how to complete the task.

Digits Span Backward

Subject Name: _____ Subject I.D.: _____ Date: _____

Group: Pilot NC Pt FM Study Day: -4a -4b -3 0 28 56 ET (Circle One)

		WMS-R Pass-Fail	WMS-R Score 2,1 or 0
1	37741		
	37687		
2	39570		
	37353		
3	3-8-1-4		
	1-7-9-5		
4	6-2-9-7-2		
	4-8-5-2-7		
	7-1-5-2-8-6		
	8-3-1-9-6-4		
6	4-7-3-9-1-2-8		
	8-1-2-9-3-6-5		
Total (max = 12)			
Longest Span Correctly Recalled			

Simple Reaction Time

Description

The Simple Reaction Time task requires a person to press the space-bar on a computer keyboard as quickly as possible when a cross appears in the center of the computer monitor. In all, there are 10 practice trials and 40 actual trials (four blocks of 10 trials). Each trial is preceded by the word "Ready". The appearance of the cross will vary quasi-randomly from 1 to 5 s.

Dependent Measure

The dependent measure for this task was the median reaction time over the four blocks of 10 trials.

Administration Procedures and Directions

Say to the subjects: **I want to see how quickly you can press the space-bar when an X appears in the center of the computer monitor. You will do several practice trials before doing the actual trials. Any question?** If the patient demonstrates that they understand the task, continue with the practice trials. At the end of the practice trials, say: **Good, now will do some actual trials.**

When this test is completed, make certain to print the data.

Choice Reaction Time

Description

This reaction time test is very similar to the simple reaction time task except that the subject must determine if two numbers which appear simultaneously are the same or different. If the numbers are the same (e.g., 44) the subject must respond by pressing the “?” key. If the numbers are different (e.g., 49) then the subject must respond by pressing to be “Z” key. There will be 12 practice trials and 48 actual trials (four blocks of 12 trials). The timing parameters will be exactly the same as those described in the simple reaction task.

Dependent Measure

The dependent measure for the Choice Reaction Time test will be the median reaction time over the four blocks of 12 trials.

Administration Procedures and Directions

Say to the subjects: **This test is very similar to the one that you just completed. The only difference will be that you must determine if two numbers which appear on the monitor are the same or different. If they are the same, you will respond by pressing the “?” key. If they are different, you’ll respond by pressing the “Z” key. Do you have any questions?** If the subject does not have any questions proceed with the practice trials.

At the end of the practice trials, say to the subject: **Good, now we will do some actual trials. Ready?**

When this test is completed, make sure to print the data.

Stroop

Description

The Stroop is a test of selective attention and consists of three conditions (Golden, 1978; Spreen, O. & Strauss, E., 1991). In the first condition, subjects are required to read words aloud which refer to different colors (red, green, blue). The second condition requires subjects to name the color of the ink in which a series of X's is presented. In the third condition, words are printed in colored ink which does not correspond to the word (e.g., the word red printed in blue ink). Subjects are required to suppress their tendency to read the word and report the incongruent ink color (Spreen & Strauss, 1991).

Administration Procedures and Directions

The instructions as per Golden (Golden, 1978) are utilized.

Dependent Variables:

Four dependent variables are obtainable from the Stroop Color-Word Test. The first is the total number of words (W) correctly read in 45 seconds. The second is the total number of colors (C) correctly identified in a 45 second period. The third is the total number of correctly named colors from the incongruent color-word condition (C-W). The fourth measure is the interference index which is derived from the following formula: The calculation of the predicted C-W performance (C-W') is calculated by $W \times C / W + C$. This predicted score is then subtracted from the actual C-W raw score; therefore, the interference index = (raw C-W) - (C-W'). Interference scores converted to T-scores are used in the data analyses.

Stroop (Score Sheet Page 1; Word Condition)

Subject Name: _____ Subject I.D.: _____ Date: _____

Group: NC Pt FM Study Day: -4a -4b -3 0 28 56 ET (Circle One)

1	RED	21	BLUE	41	GREEN	61	RED	81	BLUE
2	GREEN	22	GREEN	42	RED	62	BLUE	82	GREEN
3	BLUE	23	RED	43	BLUE	63	GREEN	83	RED
4	GREEN	24	BLUE	44	RED	64	RED	84	BLUE
5	RED	25	RED	45	GREEN	65	BLUE	85	GREEN
6	BLUE	26	GREEN	46	BLUE	66	GREEN	86	RED
7	RED	27	BLUE	47	GREEN	67	BLUE	87	GREEN
8	BLUE	28	GREEN	48	RED	68	GREEN	88	RED
9	GREEN	29	RED	49	BLUE	69	RED	89	BLUE
10	BLUE	30	GREEN	50	GREEN	70	BLUE	90	GREEN
11	GREEN	31	RED	51	BLUE	71	RED	91	RED
12	RED	32	BLUE	52	RED	72	GREEN	92	BLUE
13	GREEN	33	RED	53	BLUE	73	RED	93	GREEN
14	BLUE	34	BLUE	54	RED	74	GREEN	94	RED
15	RED	35	GREEN	55	GREEN	75	BLUE	95	BLUE
16	BLUE	36	BLUE	56	RED	76	GREEN	96	RED
17	RED	37	GREEN	57	BLUE	77	RED	97	GREEN
18	GREEN	38	RED	58	GREEN	78	BLUE	98	BLUE
19	RED	39	BLUE	59	RED	79	GREEN	99	RED
20	GREEN	40	RED	60	GREEN	80	BLUE	100	GREEN

Stroop (Score Sheet Page 2; Color Condition)

Subject Name: _____ Subject I.D.: _____ Date: _____

Group: NC Pt FM Study Day: -4a -4b -3 0 28 56 ET (Circle One)

1	BLUE	21	RED	41	BLUE	61	GREEN	81	RED
2	RED	22	BLUE	42	GREEN	62	RED	82	BLUE
3	GREEN	23	GREEN	43	RED	63	BLUE	83	GREEN
4	BLUE	24	RED	44	BLUE	64	GREEN	84	RED
5	GREEN	25	GREEN	45	RED	65	RED	85	BLUE
6	RED	26	BLUE	46	GREEN	66	BLUE	86	GREEN
7	GREEN	27	GREEN	47	RED	67	GREEN	87	RED
8	RED	28	RED	48	BLUE	68	RED	88	BLUE
9	BLUE	29	BLUE	49	GREEN	69	BLUE	89	GREEN
10	RED	30	RED	50	RED	70	GREEN	90	BLUE
11	BLUE	31	BLUE	51	GREEN	71	BLUE	91	GREEN
12	GREEN	32	GREEN	52	BLUE	72	RED	92	RED
13	RED	33	BLUE	53	RED	73	BLUE	93	BLUE
14	GREEN	34	GREEN	54	GREEN	74	RED	94	GREEN
15	BLUE	35	RED	55	BLUE	75	GREEN	95	RED
16	GREEN	36	GREEN	56	GREEN	76	BLUE	96	BLUE
17	BLUE	37	RED	57	RED	77	GREEN	97	RED
18	RED	38	BLUE	58	BLUE	78	RED	98	GREEN
19	GREEN	39	RED	59	GREEN	79	BLUE	99	BLUE
20	BLUE	40	GREEN	60	BLUE	80	RED	100	RED

Stroop (Score Sheet Page 3: Color-Word Condition)

Subject Name: _____ Subject I.D.: _____ Date: _____

Group: NC Pt FM Study Day: -4a -4b -3 0 28 56 ET (Circle One)

1	BLUE	21	RED	41	BLUE	61	GREEN	81	RED
2	RED	22	BLUE	42	GREEN	62	RED	82	BLUE
3	GREEN	23	GREEN	43	RED	63	BLUE	83	GREEN
4	BLUE	24	RED	44	BLUE	64	GREEN	84	RED
5	GREEN	25	GREEN	45	RED	65	RED	85	BLUE
6	RED	26	BLUE	46	GREEN	66	BLUE	86	GREEN
7	GREEN	27	GREEN	47	RED	67	GREEN	87	RED
8	RED	28	RED	48	BLUE	68	RED	88	BLUE
9	BLUE	29	BLUE	49	GREEN	69	BLUE	89	GREEN
10	RED	30	RED	50	RED	70	GREEN	90	BLUE
11	BLUE	31	BLUE	51	GREEN	71	BLUE	91	GREEN
12	GREEN	32	GREEN	52	BLUE	72	RED	92	RED
13	RED	33	BLUE	53	RED	73	BLUE	93	BLUE
14	GREEN	34	GREEN	54	GREEN	74	RED	94	GREEN
15	BLUE	35	RED	55	BLUE	75	GREEN	95	RED
16	GREEN	36	GREEN	56	GREEN	76	BLUE	96	BLUE
17	BLUE	37	RED	57	RED	77	GREEN	97	RED
18	RED	38	BLUE	58	BLUE	78	RED	98	GREEN
19	GREEN	39	RED	59	GREEN	79	BLUE	99	BLUE
20	BLUE	40	GREEN	60	BLUE	80	RED	100	RED

Visual Memory Span

Description

The Visual Memory Span forward condition is used as a measure of visuospatial short term memory and the backward condition is a measure of visual working memory. The following description of the WMS-R Visual Memory Span test has been modified from Wechsler (1987; p. 32):

The two parts of the visual memory span test, tapping forward and tapping backward, are administered separately. On tapping forward the examinee watches the red squares on the computer monitor flash from red to white and back to red again at the rate of one every second in sequences of increasing length, and after each sequence is asked to repeat the performance from memory. On tapping backward the examinee watched the green squares on the computer monitor flash from green to white and back to green again at the rate of one every second in sequences of increasing length, and is asked to repeat the performance in reverse. Administer Tapping Backward even if the examinee does poorly on Tapping Forward.

Dependent Measures

Raw scores for the Forward and Backward conditions are used.

Administration Procedures and Directions

Note, the following instructions are adapted from Wechsler (1987), p. 33-35.

Visual Memory Span Forward

On this computer monitor, there are a number of red squares. One after another, you will see some of these squares go from a red color to a white color and then

back to red. Watch the monitor carefully, because as soon as the squares have finished turning colors, I will ask you to touch those squares in the same order. Do you have any questions? If the subject does not have any questions, proceed to the first trial. At the end of the trial say: **Now, with this pen, touch the same squares that went from red to white and back to red again in the same order.** Regardless of whether the examinee passes or fails trial 1 of item 1, say: **Now we'll do another one. Watch the screen carefully then touch the same squares which went from red to white then back to red again in the same order.** Administer the second trial.

If either trial of item 1 is passed, say: **Let's try one that's a little harder,** and proceed as before with both trials of item 2. Thereafter administer both trials of each succeeding item, regardless of whether the examinee passes the first trial.

Discontinue after failure on both trials of any item.

Visual Memory Span Backward

This screen contains a number of squares like those of the on the screen that we just used, except that the squares are green. In this test some of the squares will turn colors from green to white and back to green again, but this time when the squares have finished turning colors, I want you to touch the squares in reverse order. Watch the screen carefully. At the end the presentation, say: **Now, touch the same squares that change colors but in reverse order.** If the examinee responds by tapping the squares in the same order, say: **Remember, on this part of the test you have to repeat them backward.**

If the examinee responds correctly, say: **That's right,** and proceed to trial 1 of item 1. If the examinee fails the example, say: **No, this square (tap square 2) and then this**

square (tap square 7) are the ones which turned colors. You were to touch them backwards like this. Demonstrate by tapping first square 7 then square 2. Give the examinee a second practice trial, tapping square 8 and then square 1, and then asked to the examinee to touch them in reverse order.

Given no help on the second example or any of the items that follow. Whether the examinee passes or fails the second practice example, proceed to trial 1 of item 1 of the tapping backward series.

If the examinee passes either trial 1 of item 1, proceed to give both trials of item 2. Thereafter administer both trials of each succeeding item, regardless of whether the examinee passes the first trial.

Discontinue after failure on both trials of any item.

Visual Memory Span Test

Subject Name: _____ Subject I.D.: _____ Date: _____

Group: NC Pt FM Study Day: -4a -4b -3 0 28 56 ET (Circle One)

Forward Condition		Pass-Fail	Score 2, 1, 0		Backward Condition		Pass-Fail	Score 2, 1, 0
1	37657			1	37685			
	37836				37805			
2	38389			2	38510			
	38929				39507			
3	3-2-8-4			3	8-4-1-6			
	2-6-1-5				5-2-4-1			
4	5-3-4-6-1			4	4-6-8-5-2			
	3-5-1-7-2				8-1-6-3-7			
5	1-7-2-8-5-4			5	7-1-8-3-6-2			
	7-3-6-1-4-8				3-8-1-7-5-4			
6	8-2-5-3-4-1-6			6	1-5-2-7-4-3-8			
	4-2-6-8-3-7-5				6-7-4-3-1-5-2			
7	7-5-6-3-8-7-4-2							
	1-6-7-4-2-8-5-3							
Total Forward (max=14)				Total Backward (max=12)				
Highest Forward Span				Highest Backward Span				
Achieved				Achieved				

D2 Test of Attention

Description

The D2 Test of Attention is a test of visual selective and sustained attention (Brickenkamp & Zillmer, 1998; Spreen & Strauss 1991). This cancellation test requires subjects to cross out all letters 'd' which have any combination of two dashes (one on top and one on the bottom; two on top or two on the bottom). According to Spreen and Strauss (1991), the D2 Test of Attention is not susceptible to practice effects in patient groups, does not correlate with general intellectual abilities, does correlate with other tests of attention, consistently loads on attentional factors in several factor analytic studies while not loading on motor speed, motor coordination or visual discrimination. This test is also sensitive to medication effects in both normal control as well as psychiatric groups (Brickenkamp & Zillmer, 1998).

Dependent Measures

The concentration performance index is used as the dependent measure. Concentration performance is the number of correctly crossed out targets minus errors of omission and commission.

Administration Procedures and Directions

Administrations procedures according to the D2 Test of Attention manual were utilized (Brickenkamp & Zillmer, 1998). Each subject receives a reporting blank with the front page on top and to soft pencils without erasers; the second pencil to be held in the reserve in case the first one becomes broken. Briefly explain the general purpose of the test in words such as:

With the help of the following task, I would like to see how well you can concentrate on a particular assignment.

Please pay attention. After the word 'Examples' on your recording blank you see three small letters marked with dashes. These are the letter 'd' as in dog, and each is marked with two dashes. The first 'd' has two dashes on the top, and the second has two on the bottom, and the third 'd' has one dash on the top and one the bottom, still making two dashes all together. I would like you to cross out every letter 'd' that has two dashes by making a single line through the letter. Try doing this first with the three examples, then try the practice line. You are not supposed to cross out the other letters. Thus, a 'd' which has more than two or fewer than two dashes should not be crossed out, no matter how many dashes it has. Do you have the questions right now?

These instructions can be repeated, abbreviated or expanded, as long as the meaning is kept basically the same.

Check to determine that the example was properly completed. The subject should have crossed out the letters which correspond to the numbers 1, 3, 5, 6, 9, 12, 13, 17, 19, and 22. If the subject understands the task and has no questions, give the following instructions:

On this side of your recording blank you will see 14 lines with the same letters you have worked on in the practice line. For each one of a the 14 lines you should start on the left side, work to the right and cross out each 'd' with two dashes. This is exactly the same task you did in the practice line. After 20 seconds I will say: 'Stop, next line' you will stop working on that line and immediately start working on the next line.

After another 20 seconds I'll say 'Stop, next line' and you will immediately start working on the next line. Work as *quickly as you can without making mistakes*.

This last sentence should be given verbatim, with equal emphasis on '*as quickly as you can*' and on '*without making mistakes*' so that speed of work (and thus the quantity of performance) and degree of the carefulness (avoiding errors) are equally highlighted. If there are no questions at this point, turn of the page over and give the following instructions:

In the upper left hand corner you can see an arrow pointing to where you should start working on the first line. When I say go, begin working on the first line. Ready! Set! Go!

The stop watch is started at 'Go!' And after 20 seconds the examiner calls '**Stop, next line**' which is repeated every 20 seconds until the test is completed, at which point timing is stopped. The timer should not be stopped at the end of every line, since this would extend the complete working time by the time needed for stopping, resting and then restarting, introducing experimenter effect or bias and a serious error in measurement.

Letter-Number Sequencing

Description

The following modified information regarding the Letter-number Sequencing task is taken from Wechsler (Wechsler, 1997; p. 169 - 171).

The examinee is read a combination of numbers and letters and is asked to recall the numbers first in ascending order and then the letters in alphabetical order. Each item consists of three trials, and each trial is a different combination of numbers and letters.

Administer all practice trials. For each practice item and item trial, say each combination at a rate of one number or letter per second. Allow the examinee ample time to respond (correct responses are in parenthesis).

Dependent Measure

Raw scores are used as the dependent measure.

Administration Procedures and Directions

I am going to say a group of numbers and letters. After I say them, I want you to tell me the numbers first, in order, starting with the lowest number. Then tell me the letters in alphabetical order. For example, if I say B-7, your answer should be 7-B. The number goes first, then the letter. If I say 9-C-3, then your answer should be 3-9-C, the numbers in order first, then the letters in alphabetical order. Let's practice.

Administer all Practice Items:

6-F	(6-F)
G-4	(4-G)
3-W-5	(3-5-W)
T-7-L	(7-L-T)
1-J-A	(1-A-J)

If the examinee makes an error on any practice item, correct her or him and repeat the instructions as necessary. Even if the examinee fails all practice items, continue with the subtest. Record the examinee's response to each trial verbatim, the trial score, the item score, and the total subtest raw score.

Letter-Number Sequencing (Score Sheet)

Subject Name: _____ Subject I.D.: _____ Date: _____

Group: NC Pt FM Study Day: -4a -4b -3 0 28 56 ET (Circle One)

Item	Trial	Item (Response)	Pass / Fail	Score 0,1, 2, 3
1	1	L-2 (2-L)		
	2	6-P (6-P)		
	3	B-5 (5-B)		
2	1	F-7-L (7-F-L)		
	2	R-4-D (4-D-R)		
	3	H-1-8 (1-8-H)		
3	1	T-9-A-3 (3-9-A-T)		
	2	V-1-J-5 (1-5-J-V)		
	3	7-N-4-L (4-7-L-N)		
4	1	8-D-6-G-1 (1-6-8-D-G)		
	2	K-2-C-7-S (2-7-C-K-S)		
	3	5-P-3-Y-9 (3-5-9-P-Y)		
5	1	M-4-E-7-Q-2 (2-4-7-E-M-Q)		
	2	W-8-H-5-F-3 (3-5-8-F-H-W)		
	3	6-G-9-A-2-S (2-6-9-A-G-S)		
6	1	R-3-B-4-Z-1-C (1-3-4-B-C-R-Z)		
	2	5-T-9-J-2-X-7 (2-5-7-9-J-T-X)		
	3	E-1-H-8-R-4-D (1-4-8-D-E-H-R)		
7	1	5-H-9-S-2-N-6-A (2-5-6-9-A-H-N-S)		
	2	D-1-R-9-B-4-K-3 (1-3-4-9-B-D-K-R)		
	3	7-M-2-T-6-F-1-Z (1-2-6-7-F-M-T-Z)		
Total (max = 21)				
Longest Span Correctly Recalled				

Appendix G

Demographic Sheet

Subject Name: _____ Subject I.D.: _____ Date: _____

Group: NC Pt FM

Gender: M F Date of Birth: _____ Age: _____

First Language: _____

Profession: _____

Handedness: R L

Education in Years: Grade school 0 1 2 3 4 5 6 7 8

High school 9 10 11 12

Trade/college 13 14

University/undergraduate 13 14 15

Master's level 17 18

Ph.D. level 19 20 21

Current Medications:

Medical History: ___ Diabetes ___ MVA (date, description)

___ Seizures/Epilepsy ___ Falls: unconsciousness

___ Heart Condition ___ Prev. H.I.

___ History of Depression ___ ECT

___ Other Psychiatric Diagnosis

Current Cognitive Complaints (attention, concentration, memory)

Appendix H

Means and Standard Deviations for Each Test in the Pre-randomization Period
(Days -4a, -4b, -3 and 0)

		Pre-Randomization				
		-4a	-4b	-3	0	Total
Measure	Group	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Motor functioning ^a						
Grooved Peg Board	Pt (n=25)	82.80	77.64	76.66	72.48	77.40
		(17.00)	(18.14)	(15.35)	(13.21)	(15.04)
	FM (n=9)	66.22	62.72	60.17	59.28	62.10
		(6.85)	(6.68)	(6.15)	(6.92)	(5.96)
	NC (n=13)	64.08	59.88	59.38	58.12	60.37
		(9.23)	(8.38)	(9.45)	(8.44)	(8.62)
	Total (N=47)	71.03	66.75	65.40	63.29	
		(2.19)	(2.29)	(2.01)	(1.77)	
Finger Tapping	Pt ^b (n=24)	43.56	46.20	47.37	47.40	46.13
		(7.99)	(7.74)	(6.96)	(7.43)	(7.20)
	FM (n=9)	43.49	47.65	48.88	49.68	47.42
		(9.32)	(5.88)	(4.68)	(4.96)	(5.90)
	NC ^b (n=12)	45.77	47.26	47.97	49.55	47.64
		(4.78)	(3.91)	(5.44)	(4.41)	(4.05)
	Total (N=45)	44.13	46.77	47.83	48.43	
		(7.48)	(6.47)	(6.09)	(6.28)	

table continues

		Pre-Randomization				
		-4a	-4b	-3	0	Total
Measure	Group	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Reaction time ^c						
Simple	Pt (n=25)	338.40	371.35	377.52	372.98	365.06
		(49.98)	(84.12)	(87.50)	(68.74)	(66.57)
	FM (n=9)	314.44	302.94	307.78	299.56	306.18
		(44.63)	(29.62)	(31.73)	(35.54)	(31.14)
	NC (n=13)	289.38	297.35	302.23	296.62	296.39
		(28.79)	(37.94)	(28.44)	(37.90)	(30.07)
	Total (N=47)	324.03	337.50	345.99	349.79	
		(55.48)	(73.23)	(78.03)	(109.61)	
Choice	Pt ^d (n=23)	766.59	709.04	716.89	728.50	730.26
		(219.28)	(127.48)	(165.57)	(137.32)	(150.09)
	FM (n=9)	636.89	620.33	596.89	596.89	612.75
		(77.67)	(68.79)	(71.29)	(57.82)	(52.36)
	NC (n=13)	628.27	608.96	607.15	612.38	614.19
		(91.18)	(103.37)	(107.08)	(90.27)	(88.86)
	Total (N=45)	700.69	662.39	661.19	668.63	
		(179.05)	(119.34)	(145.22)	(126.97)	

table continues

		Pre-Randomization				
		-4a	-4b	-3	0	Total
Measure	Group	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Verbal STM						
Digit Span	Pt (n=25)	6.16	7.04	6.76	6.96	6.73
Forward		(1.99)	(2.37)	(1.88)	(1.93)	(1.83)
	FM (n=9)	7.44	8.11	7.89	8.67	8.03
		(1.74)	(2.15)	(2.32)	(2.29)	(1.99)
	NC (n=13)	9.23	9.85	10.15	9.85	9.77
		(1.74)	(1.77)	(1.68)	(1.57)	(1.47)
	Total (N=47)	7.26	8.02	7.91	8.09	
		(2.27)	(2.45)	(2.38)	(2.26)	
Visuospatial STM						
Circles Away	Pt (n=25)	26.56	27.32	25.12	24.48	25.87
10 second delay		(7.51)	(9.18)	(10.30)	(9.71)	(8.23)
	FM (n=9)	19.56	16.11	16.89	16.78	17.33
		(6.75)	(6.88)	(7.10)	(6.67)	(6.05)
	NC (n=13)	15.69	15.15	14.38	16.85	15.52
		(4.85)	(4.06)	(5.44)	(9.45)	(4.62)
	Total (N=47)	22.21	21.81	20.57	20.89	
		(8.20)	(9.58)	(9.82)	(9.76)	

table continues

Measure	Group	Pre-Randomization				
		-4a	-4b	-3	0	Total
		<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Visual Memory Span Forward	Pt (n=25)	7.56	8.28	8.36	8.88	8.27
		(1.73)	(1.95)	(2.40)	(2.01)	(1.76)
	FM (n=9)	9.78	9.22	9.89	9.56	9.61
		(1.64)	(1.72)	(1.54)	(1.51)	(1.43)
	NC (n=13)	10.23	10.69	11.15	11.15	10.81
		(1.74)	(2.02)	(2.03)	(2.23)	(1.77)
Total (N=47)		8.72	9.13	9.43	9.64	
		(2.10)	(2.15)	(2.45)	(2.18)	
Attention						
D2 Test of Attention	Pt (n=25)	111.96	137.48	146.36	159.40	138.80
		(38.62)	(38.43)	(48.05)	(42.97)	(40.16)
	FM (n=9)	169.11	190.89	209.33	222.89	198.06
		(40.50)	(46.40)	(47.69)	(46.03)	(44.36)
	NC (n=13)	196.08	223.15	242.62	251.31	228.29
		(59.25)	(58.71)	(55.20)	(52.61)	(55.80)
Total (N=47)		146.17	171.40	185.04	196.98	
		(58.50)	(59.17)	(65.27)	(61.54)	

table continues

Measure	Group	Pre-Randomization				
		-4a	-4b	-3	0	Total
		<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Stroop	Pt (n=25)	47.56	47.55	50.51	50.03	48.91
		(5.85)	(8.19)	(5.73)	(7.18)	(5.76)
	FM (n=9)	51.30	51.46	54.37	54.76	52.97
		(4.53)	(4.08)	(5.76)	(7.90)	(4.41)
	NC (n=13)	56.55	55.58	57.30	60.54	57.49
		(7.18)	(7.72)	(6.93)	(9.08)	(6.50)
Digit Span Distractability Test	Total (N=47)	50.76	50.52	53.13	53.84	
		(7.07)	(8.10)	(6.66)	(8.95)	
	Pt (n=25)	53.94	55.20	59.77	59.20	57.03
		(24.12)	(29.97)	(26.78)	(29.12)	(25.03)
	FM (n=9)	72.06	83.81	79.05	86.67	80.40
		(27.17)	(27.18)	(26.84)	(22.90)	(24.88)
	NC (n=13)	85.49	91.65	90.99	94.07	90.55
		(17.04)	(20.05)	(12.39)	(15.84)	(15.20)
	Total (N=47)	66.14	70.76	72.10	74.10	
		(26.48)	(31.47)	(27.06)	(29.38)	

table continues

Measure	Group	Pre-Randomization				Total
		-4a	-4b	-3	0	
		<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Visual working memory						
Visual Memory	Pt (n=25)	6.64	6.88	7.48	7.04	7.01
Span Backward		(1.96)	(1.92)	(2.02)	(2.32)	(1.89)
	FM (n=9)	8.22	8.22	8.56	8.33	8.33
		(1.64)	(1.56)	(1.59)	(2.18)	(1.58)
	NC (n=13)	8.31	9.00	8.85	9.46	8.90
		(1.55)	(1.22)	(1.95)	(1.61)	(1.38)
	Total (N=47)	7.40	7.72	8.06	7.96	
		(1.94)	(1.91)	(1.99)	(2.33)	
Verbal working memory						
Digit Span	Pt (n=25)	5.40	5.72	6.04	5.88	5.76
Backward		(2.10)	(1.93)	(2.11)	(2.01)	(1.77)
	FM (n=9)	7.56	7.89	8.33	8.56	8.08
		(2.51)	(2.15)	(2.55)	(2.51)	(2.18)
	NC (n=13)	8.31	8.54	8.92	8.62	8.60
		(2.18)	(2.54)	(2.40)	(1.85)	(2.02)
	Total (N=47)	6.62	6.91	7.28	7.15	
		(2.53)	(2.47)	(2.60)	(2.44)	

table continues

Measure	Group	Pre-Randomization				
		-4a	-4b	-3	0	Total
		<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Letter Number	Pt (n=25)	9.68	10.00	9.96	10.32	9.99
Sequencing		(2.41)	(2.35)	(2.67)	(3.05)	(2.23)
	FM (n=9)	11.78	12.78	13.56	13.11	12.81
		(3.42)	(3.23)	(3.21)	(3.98)	(3.21)
	NC ^e (n=12)	12.75	14.33	14.08	14.83	14.00
		(2.49)	(2.67)	(2.75)	(2.08)	(2.15)
	Total (N=46)	10.89	11.67	11.74	12.04	
		(2.93)	(3.20)	(3.37)	(3.58)	

Note. Pt = patients; FM = family members; NC = normal controls; STM = Short term memory.

^aAverage of right and left hand performance. ^bOne subject had carpal tunnel syndrome and could not complete the task. ^cMedian reaction times in ms. ^dTwo subjects (KB24 and JR25) were extreme outliers and were therefore not included in this analysis. ^eOne subject from the normal control group, VB10, was schooled in Italy and was not adequately familiar with the English alphabet to complete this task.

Appendix I

Mean Percent Change Scores from Day -4a to -4b; -4a to -3; and from -4a to 0

Measure	Group	Pre-Randomization			Total
		-4a to -4b	-4a to -3	-4a to 0	
		M (SD)	M (SD)	M (SD)	M(SD)
Motor functioning ^a					
Grooved Peg Board	Pt (n=25)	-6.10	-7.02	-11.53	-8.22
		(10.46)	(7.57)	(9.64)	(6.79)
	FM (n=9)	-4.98	-8.94	-10.30	-8.07
		(7.98)	(6.03)	(7.53)	(6.11)
	NC (n=13)	-6.34	-7.33	-9.23	-7.63
		(6.11)	(6.57)	(4.25)	(4.87)
Total (N=47)		-5.95	-7.47	-10.65	
		(8.84)	(6.93)	(8.01)	
Finger Tapping	Pt ^b (n=24)	6.72	9.91	9.75	8.79
		(9.42)	(10.79)	(9.14)	(8.21)
	FM (n=9)	12.81	16.51	18.60	15.98
		(18.99)	(23.02)	(24.68)	(22.15)
	NC ^b (n=12)	3.54	5.32	8.53	5.80
		(5.23)	(11.67)	(6.02)	(6.64)
Total (N=45)		7.09	10.01	11.20	
		(11.36)	(14.35)	(13.33)	

table continues

		Pre-Randomization			
		-4a to -4b	-4a to -3	-4a to 0	Total
Measure	Group	M (SD)	<u>M</u> (SD)	<u>M</u> (SD)	<u>M</u> (SD)
Reaction time ^c					
Simple	Pt (n=25)	9.20	11.10	10.79	10.36
		(15.57)	(16.80)	(16.52)	(14.35)
	FM (n=9)	-2.61	-1.30	-4.05	-2.65
		(10.93)	(9.70)	(9.26)	(9.21)
	NC (n=13)	2.69	4.87	2.66	3.40
		(6.17)	(9.78)	(10.00)	(7.70)
Choice	Total (N=47)	5.05	6.91	2.66	
		(13.33)	(10.74)	(5.59)	
	Pt ^d (n=23)	-4.94	-5.16	-2.66	-4.26
		(14.92)	(11.31)	(12.99)	(11.19)
	FM (n=9)	-1.53	-5.09	-5.04	-3.89
		(13.47)	(15.08)	(13.80)	(13.74)
Choice	NC (n=13)	-3.08	-3.21	-2.12	-2.80
		(7.98)	(12.31)	(10.98)	(8.22)
	Total (N=45)	-3.72	-4.58	-2.98	
		(12.79)	(12.15)	(12.37)	

table continues

		Pre-Randomization			
		-4a to -4b	-4a to -3	-4a to 0	Total
Measure	Group	M (<u>SD</u>)	<u>M</u> (<u>SD</u>)	<u>M</u> (<u>SD</u>)	<u>M</u> (<u>SD</u>)
Verbal STM					
Digit Span Forward	Pt (n=25)	15.83	13.75	19.26	16.23
		(25.63)	(25.91)	(35.66)	(23.96)
	FM (n=9)	9.44	5.45	16.34	10.41
		(19.93)	(19.72)	(17.46)	(16.25)
	NC (n=13)	7.80	12.22	7.50	9.17
		(18.21)	(22.41)	(10.06)	(15.58)
	Total (N=47)	12.38	11.74	15.45	
		(22.64)	(23.64)	(27.73)	
Visuospatial STM					
Circles Away	Pt (n=25)	4.22	-4.37	-6.25	-2.13
		(29.28)	(35.39)	(31.26)	(27.47)
10 Second Delay	FM (n=9)	-13.10	-13.37	-9.07	-11.84
		(42.07)	(20.90)	(38.62)	(29.23)
	NC (n=13)	2.65	-5.40	13.86	3.70
		(35.61)	(33.70)	(62.21)	(37.20)
	Total (N=47)	0.47	-6.38	-1.23	
		(33.63)	(32.21)	(43.23)	

table continues

Measure	Group	Pre-Randomization			
		-4a to -4b	-4a to -3	-4a to 0	Total
		M (SD)	M (SD)	M (SD)	M(SD)
Visual Memory	Pt (n=25)	12.16	11.81	20.34	14.77
Span Forward		(26.38)	(26.03)	(25.83)	(22.49)
	FM (n=9)	-5.22	2.30	-1.76	-1.56
		(12.07)	(16.74)	(10.34)	(11.05)
	NC (n=13)	4.57	9.35	9.69	7.87
		(10.00)	(12.56)	(18.86)	(9.98)
	Total (N=47)	6.73	9.31	13.16	
		(21.44)	(21.37)	(23.12)	
Attention					
D2 Test of Attention	Pt (n=25)	27.77	35.99	49.58	37.78
		(31.22)	(40.77)	(39.22)	(36.30)
	FM (n=9)	13.71	24.72	33.58	24.00
		(13.10)	(11.52)	(16.09)	(13.12)
	NC (n=13)	15.75	28.14	33.52	25.80
		(9.25)	(18.48)	(20.97)	(15.99)
	Total (N=47)	21.75	31.66	42.07	
		(24.56)	(31.66)	(32.06)	

table continues

Measure	Group	Pre-Randomization			
		-4a to -4b	-4a to -3	-4a to 0	Total
		M (SD)	M (SD)	M (SD)	M(SD)
Stroop	Pt (n=25)	0.44 (15.81)	7.07 (12.71)	5.80 (13.80)	4.44 (12.17)
	FM (n=9)	0.56 (6.66)	6.43 (11.90)	7.02 (14.44)	4.67 (9.11)
	NC (n=13)	-1.51 (8.80)	2.04 (12.06)	7.35 (11.67)	2.63 (7.63)
	Total (N=47)	-0.08 12.61	5.56 (12.32)	6.46 (13.10)	
Digit Span Distractability Test	Pt (n=25)	0.23 (41.45)	17.07 (57.56)	14.87 (61.01)	10.73 (47.28)
	FM (n=9)	19.21 (18.55)	14.19 (29.77)	28.79 (27.81)	20.73 (21.61)
	NC (n=13)	6.52 (11.71)	10.63 (24.45)	11.40 (10.72)	9.52 (11.71)
	Total (N=47)	5.60 (32.32)	14.74 (45.24)	16.58 (46.31)	

table continues

		Pre-Randomization			
		-4a to -4b	-4a to -3	-4a to 0	Total
Measure	Group	M (<u>SD</u>)	<u>M</u> (<u>SD</u>)	<u>M</u> (<u>SD</u>)	<u>M</u> (<u>SD</u>)
Visual working memory					
Visual Memory	Pt (n=25)	10.05	19.29	10.63	13.32
Span Backward		(37.46)	(38.75)	(36.61)	(36.18)
	FM (n=9)	1.13	5.37	1.23	2.58
		(15.11)	(16.70)	(15.80)	(12.85)
	NC (n=13)	10.24	7.43	16.03	11.23
		(14.73)	(18.82)	(21.73)	(15.92)
	Total (N=47)	8.39	13.35	10.32	
		(29.01)	(31.08)	(29.86)	
Verbal working memory					
Digit Span	Pt (n=25)	15.55	25.84	19.35	20.25
Backward		(44.15)	(70.65)	(55.01)	(49.16)
	FM (n=9)	7.62	13.81	17.06	12.83
		(18.58)	(29.28)	(29.90)	(23.56)
	NC (n=13)	3.30	8.98	6.16	6.15
		(23.83)	(26.44)	(19.11)	(19.57)
	Total (N=47)	10.64	18.87	15.27	
		(35.43)	(54.72)	(43.16)	

table continues

Measure	Group	Pre-Randomization			
		-4a to -4b	-4a to -3	-4a to 0	Total
		M (SD)	M (SD)	M (SD)	M(SD)
Letter Number Sequencing	Pt (n=25)	6.69	4.80	8.68	6.73
		(25.43)	(24.11)	(25.66)	(22.68)
	FM (n=9)	10.24	17.01	12.44	13.23
		(16.27)	(17.13)	(21.25)	(13.92)
	NC ^c (n=12)	14.19	12.48	18.75	15.14
		(19.15)	(22.97)	(19.46)	(18.22)
Total (N=46)		9.34	9.19	12.04	
		(22.18)	(22.74)	(23.29)	

Note. Pt = patients; FM = family members; NC = normal controls; STM = Short term memory.

^aAverage of right and left hand performance. ^bOne subject had carpal tunnel syndrome and could not complete the task. ^cMedian reaction times in ms. ^dTwo subjects (KB24 and JR25) were extreme outliers and were therefore not included in this analysis. ^eOne subject from the normal control group, VB10, was schooled in Italy and was not adequately familiar with the English alphabet to complete this task.

Appendix J

Means and Standard Deviations for Each Test in the Post-randomization Period

(Days 0, 28 and 56)

Measure	Group	Post-Randomization			
		0	28	56	Total
		<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Motor functioning ^a					
Grooved Peg Board	Ol (n=14)	74.46	74.43	73.96	74.29
		(15.49)	(12.17)	(12.92)	(12.51)
	Hal (n=11)	68.85	73.65	75.80	72.77
		(9.49)	(18.61)	(18.36)	(14.06)
	FM (n=9)	59.88	59.88	60.44	59.72
		(7.15)	(4.83)	(5.85)	(5.02)
	NC (n=13)	58.12	57.58	59.08	58.26
		(8.44)	(6.97)	(8.83)	(7.80)
	Total (N=47)	65.45	66.24	67.08	
		(1.64)	(1.72)	(1.81)	
Finger Tapping	Ol ^b (n=13)	46.91	47.14	48.00	47.35
		(7.31)	(5.23)	(6.64)	(6.04)
	Hal (n=11)	47.97	47.50	47.19	47.56
		(7.88)	(8.76)	(10.63)	(8.91)
	FM (n=9)	49.68	50.28	50.72	50.23
		(4.96)	(5.38)	(6.54)	(5.25)
	NC ^b (n=12)	49.55	49.00	48.31	48.95
		(4.41)	(3.89)	(3.55)	(3.70)
	Total (N=45)	48.43	48.35	48.43	
		(6.28)	(5.95)	(7.08)	

table continues

		Post-Randomization			
		0	28	56	Total
Measure	Group	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Reaction time ^c					
Simple	Ol (n=14)	380.96	379.15	373.62	377.91
		(51.08)	(70.37)	(34.03)	(41.11)
	Hal (n=11)	363.55	359.05	378.64	367.08
		(86.93)	(70.61)	(91.89)	(76.08)
	FM (n=9)	299.56	304.89	316.94	307.13
		(35.54)	(37.18)	(34.23)	(34.10)
	NC (n=13)	296.62	313.88	319.65	310.05
(37.90)		(43.56)	(43.66)	(39.22)	
	Total	337.03	341.37	348.48	
	(N=47)	(66.82)	(64.45)	(61.91)	
Choice	Ol ^d (n=13)	749.54	763.88	754.50	755.97
		(122.87)	(103.29)	(139.09)	(103.25)
	Hal ^d (n=10)	701.15	678.85	704.50	691.68
		(156.52)	(145.26)	(147.23)	(142.63)
	FM (n=9)	596.89	(55.07)	620.72	610.85
		(57.82)	620.00	(73.96)	(59.34)
	NC (n=13)	612.38	(114.77)	653.46	628.62
(90.27)		662.63	(102.34)	(90.64)	
	Total	668.63	(153.47)	687.44	
	(N=45)	(126.97)		(127.31)	

table continues

Measure	Group	Post-Randomization			
		0	28	56	Total
		<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Verbal STM					
Digit Span	Ol (n=14)	7.07	6.64	7.57	7.10
Forward		(1.94)	(2.21)	(1.55)	(1.70)
	Hal (n=11)	6.82	7.27	6.18	6.76
		(1.99)	(2.00)	(1.99)	(1.82)
	FM (n=9)	8.67	8.33	8.78	8.59
		(2.29)	(2.65)	(1.79)	(2.16)
	NC (n=13)	9.85	9.92	10.31	10.03
		(1.57)	(1.61)	(1.44)	(1.44)
	Total (N=47)	8.09	8.02	8.23	
		(2.26)	(2.43)	(2.25)	
Visuospatial STM					
Circles Away	Ol (n=14)	26.50	27.14	28.86	27.50
10 Second Delay		(11.20)	(10.52)	(10.20)	(9.95)
	Hal (n=11)	21.91	21.91	24.64	22.82
		(7.11)	(6.83)	(8.66)	(5.69)
	FM (n=9)	16.78	17.56	16.56	16.96
		(6.67)	(6.19)	(6.17)	(5.51)
	NC (n=13)	16.85	15.23	16.08	16.05
		(9.45)	(6.10)	(4.65)	(6.13)
	Total (N=47)	20.89	20.79	21.98	
		(9.76)	(9.01)	(9.47)	

table continues

		Post-Randomization			
Measure	Group	0	28	56	Total
		<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Visual Memory Span Forward	Ol (n=14)	8.64	8.71	8.64	8.67
		(2.37)	(2.40)	(2.68)	(2.23)
	Hal (n=11)	9.18	9.27	9.18	9.21
		(1.47)	(1.56)	(1.47)	(1.37)
	FM (n=9)	9.56	9.56	9.33	9.48
		(1.51)	(1.51)	(1.12)	(1.13)
	NC (n=13)	11.15	11.77	11.15	11.36
		(2.23)	(1.83)	(1.82)	(1.66)
Total (N=47)		9.64	9.85	9.60	
		(2.18)	(2.23)	(2.14)	
Attention					
D2 Test of Attention	Ol (n=14)	153.93	163.64	162.07	159.88
		(41.05)	(44.61)	(51.02)	(44.86)
	Hal (n=11)	166.36	162.27	160.36	163.00
		(46.32)	(42.65)	(40.02)	(41.20)
	FM (n=9)	222.89	224.00	222.33	223.07
		(46.03)	(48.71)	(45.92)	(46.53)
	NC (n=13)	251.31	246.46	247.77	248.51
		(52.61)	(56.29)	(57.79)	(55.08)
Total (N=47)		196.98	197.79	196.91	
		(61.54)	(60.48)	(62.19)	

table continues

Measure	Group	Post-Randomization			
		0	28	56	Total
		<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Stroop	Ol (n=14)	49.52	51.90	52.13	51.18
		(7.97)	(5.56)	(6.62)	(6.17)
	Hal (n=11)	50.67	52.32	52.35	51.78
		(6.36)	(5.39)	(5.38)	(4.99)
	FM (n=9)	54.76	56.09	55.80	55.55
		(7.90)	(6.22)	(5.74)	(5.45)
	NC (n=13)	60.54	59.74	61.11	60.46
		(9.08)	(10.80)	(10.19)	(9.30)
Total (N=47)		53.84	54.97	55.37	
		(8.95)	(7.96)	(8.14)	
Digit Span Distractability Test	Ol (n=14)	56.12	58.16	59.80	58.03
		(30.66)	(26.30)	(25.47)	(24.70)
	Hal (n=11)	63.12	77.92	67.79	69.61
		(27.98)	(25.01)	(29.25)	(25.78)
	FM (n=9)	86.67	80.95	84.44	84.02
		(22.90)	(18.74)	(23.82)	(19.20)
	NC (n=13)	94.07	91.65	93.85	93.19
		(15.84)	(20.12)	(11.24)	(15.08)
Total (N=47)		74.10	76.41	75.81	
		(29.38)	(25.88)	(26.47)	

table continues

Measure	Group	Post-Randomization			
		0	28	56	Total
		<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Visual working memory					
Visual Memory	Ol (n=14)	7.07	6.79	7.07	6.98
Span Backward		(2.56)	(2.52)	(2.62)	(2.41)
	Hal (n=11)	7.00	8.00	7.18	7.39
		(2.10)	(1.73)	(1.83)	(1.57)
	FM (n=9)	8.33	8.44	8.89	8.56
		(2.18)	(1.81)	(2.09)	(1.83)
	NC (n=13)	9.46	9.23	9.31	9.33
		(1.61)	(1.69)	(1.60)	(1.41)
	Total (N=46)	7.96	8.06	8.06	
		(2.33)	(2.16)	(2.27)	
Verbal working memory					
Digit Span	Ol (n=14)	5.43	5.86	6.00	5.76
Backward		(1.83)	(2.28)	(1.66)	(1.57)
	Hal (n=11)	6.45	6.55	6.82	6.61
		(2.16)	(2.42)	(2.36)	(2.19)
	FM (n=9)	8.56	8.78	8.22	8.52
		(2.51)	(2.54)	(2.49)	(2.38)
	NC (n=13)	8.62	10.31	9.46	9.46
		(1.85)	(2.02)	(2.11)	(1.51)
	Total (N=47)	7.15	7.81	7.57	
		(2.44)	(2.90)	(2.49)	

table continues

		Post-Randomization			
		0	28	56	Total
Measure	Group	<u>M (SD)</u>	<u>M (SD)</u>	<u>M (SD)</u>	<u>M(SD)</u>
Letter Number					
Sequencing	Ol (n=14)	9.93	9.50	10.21	9.88
		(3.08)	(2.28)	(2.29)	(2.23)
	Hal (n=11)	10.82	10.73	10.55	10.70
		(3.09)	(3.10)	(3.42)	(3.00)
	FM (n=9)	13.11	13.78	14.11	13.67
		(3.98)	(3.73)	(4.37)	(3.86)
	NC ^e (n=12)	14.83	15.17	15.92	15.31
		(2.08)	(2.52)	(2.47)	(2.17)
	Total (N=46)	12.04	12.11	12.54	
		(3.58)	(3.65)	(3.90)	

Note. Ol = olanzapine; Hal = haloperidol; FM = family members; NC = normal controls; STM = Short term memory.

^aAverage of right and left hand performance. ^bOne subject had carpal tunnel syndrome and could not complete the task. ^cMedian reaction times in ms. ^dTwo subjects (KB24 and JR25) were extreme outliers and were therefore not included in this analysis. ^eOne subject from the normal control group, VB10, was schooled in Italy and was not adequately familiar with the English alphabet to complete this task.

Appendix K

Mean Percent Change Scores from Day 0 to 28 and from Day 0 to 56

		Post-Randomization		
		0 to 28	0 to 56	Total
Measure	Group	M (<u>SD</u>)	M (<u>SD</u>)	<u>M(SD)</u>
Motor functioning ^a				
Grooved Peg Board	Ol (n=14)	1.31	.77	1.04
		(12.83)	(13.87)	(12.85)
	Hal (n=11)	4.18	7.47	5.83
		(17.14)	(16.42)	(16.37)
	FM (n=9)	1.71	1.78	1.74
		(7.64)	(10.53)	(8.49)
NC (n=13)	-0.55	1.87	0.66	
	(5.22)	(7.07)	(5.44)	
	Total (N=47)	1.54	2.84	
		(11.43)	(12.34)	
Finger Tapping	Ol ^b (n=13)	1.59	3.02	2.32
		(10.09)	(9.29)	(9.01)
	Hal (n=11)	-1.05	-2.52	-1.79
		(6.95)	(8.87)	(7.28)
	FM (n=9)	1.26	2.01	1.63
		(5.03)	(7.39)	(4.02)
NC ^b (n=12)	-0.92	-2.21	-1.56	
	(4.77)	(5.89)	(4.98)	
	Total (N=45)	0.21	0.007	
		(7.11)	(8.15)	

table continues

		Post-Randomization		
		0 to 28	0 to 56	Total
Measure	Group	M (<u>SD</u>)	M (<u>SD</u>)	<u>M</u> (<u>SD</u>)
Reaction time ^c				
Simple	OI (n=13)	-0.07	-0.89	-0.48
		(15.02)	(13.10)	(10.13)
	Hal (n=11)	0.79	5.15	2.97
		(17.02)	(14.97)	(15.03)
	FM (n=9)	2.00	5.96	3.98
		(7.03)	(3.60)	(4.88)
	NC (n=13)	5.94	8.14	7.04
(7.33)		(11.51)	(9.03)	
	Total	2.24	4.44	
	(N=46)	(12.40)	(12.08)	
Choice	OI ^d (n=13)	3.34	1.21	2.27
		(16.25)	(12.75)	(12.21)
	Hal ^d (n=10)	-2.21	1.46	-0.37
		(15.14)	(14.14)	(13.77)
	FM (n=9)	3.15	4.06	3.60
		(3.58)	(7.87)	(5.26)
	NC (n=13)	1.93	7.14	4.54
(14.72)		(10.86)	(11.14)	
	Total (N=45)	-0.28	3.55	
		(19.30)	(11.62)	

table continues

		Post-Randomization		
Measure	Group	0 to 28	0 to 56	Total
		M (<u>SD</u>)	M (<u>SD</u>)	<u>M</u> (<u>SD</u>)
Verbal STM				
Digit Span Forward	Ol (n=14)	-7.69	12.85	2.56
		(22.08)	(30.33)	(17.04)
	Hal (n=11)	9.00	-8.66	0.17
		(24.53)	(17.34)	(17.51)
	FM (n=9)	-4.29	3.28	-0.51
		(18.65)	(13.90)	(14.13)
	NC (n=13)	0.97	5.30	3.13
		(7.57)	(9.47)	(6.50)
	Total (N=47)	-0.74	3.89	
		(19.62)	(21.10)	
Visuospatial STM				
Circles Away 10 Second Delay	Ol (n=14)	9.26	12.97	11.11
		(35.11)	(19.08)	(23.52)
	Hal (n=11)	10.92	22.29	16.60
		(51.08)	(57.63)	(52.66)
	FM (n=9)	10.00	2.95	6.47
		(33.12)	(28.44)	(26.06)
	NC (n=13)	-2.99	7.51	2.26
		(27.28)	(38.85)	(29.65)
	Total (N=47)	6.40	11.72	
		(36.54)	(37.50)	

table continues

Measure	Group	Post-Randomization		
		0 to 28 M (SD)	0 to 56 M (SD)	Total M(SD)
Visual Memory Span Forward	Ol (n=14)	2.25 (16.51)	2.80 (27.57)	2.52 (19.03)
	Hal (n=11)	1.00 (8.01)	0.77 (12.40)	0.88 (7.11)
	FM (n=9)	0.72 (12.25)	-0.55 (17.03)	0.009 (12.81)
	NC (n=13)	8.18 (21.14)	3.42 (24.96)	5.80 (22.22)
	Total (N=47)	3.30 (15.60)	1.85 (21.53)	
Attention				
D2 Test of Attention	Ol (n=14)	6.86 (11.76)	4.67 (11.92)	5.77 (11.17)
	Hal (n=11)	-0.55 (19.16)	-1.79 (15.65)	-1.17 (17.23)
	FM (n=9)	0.37 (6.21)	-0.14 (6.20)	0.12 (6.07)
	NC (n=13)	-1.92 (7.49)	-1.76 (6.24)	-1.84 (6.46)
	Total (N=47)	1.45 (12.39)	0.46 (10.88)	

table continues

Measure	Group	Post-Randomization		
		0 to 28 M (SD)	0 to 56 M (SD)	Total M(SD)
Stroop	Ol (n=14)	6.11 (12.31)	6.04 (8.13)	6.08 (9.34)
	Hal (n=11)	3.87 (9.16)	4.05 (10.10)	3.96 (7.88)
	FM (n=9)	3.63 (13.15)	3.03 (12.70)	3.33 (11.78)
	NC (n=13)	-1.00 (12.06)	1.05 (8.24)	0.03 (8.90)
	Total (N=47)	3.14 (11.69)	3.62 (9.50)	
Digit Span Distractability Test	Ol (n=14)	27.17 (63.15)	26.87 (95.55)	27.02 (72.70)
	Hal (n=11)	42.74 (55.90)	11.23 (56.41)	26.98 (47.50)
	FM (n=9)	-2.29 (23.60)	-0.14 (26.36)	-1.21 (22.17)
	NC (n=13)	-3.71 (12.41)	1.71 (13.61)	-1.00 (7.06)
	Total (N=47)	16.63 (48.24)	11.08 (59.72)	

table continues

		Post-Randomization		
		0 to 28	0 to 56	Total
Measure	Group	M (<u>SD</u>)	M (<u>SD</u>)	<u>M(SD)</u>
Visual working memory				
Visual Memory	Ol (n=14)	-1.97	0.97	-0.51
Span Backward		(21.96)	(22.19)	(17.91)
	Hal (n=11)	22.35	8.64	15.49
		(37.60)	(30.73)	(32.43)
	FM (n=9)	3.25	9.26	6.26
		(14.33)	(24.17)	(16.15)
	NC (n=13)	-1.18	-0.78	-0.98
		(17.26)	(13.82)	(13.37)
	Total (N=47)	4.94	3.87	
		(25.60)	(22.71)	
Verbal working memory				
Digit Span	Ol (n=14)	13.44	20.50	16.97
Backward		(39.22)	(45.48)	(38.88)
	Hal (n=11)	2.71	8.64	5.67
		(23.49)	(28.27)	(23.76)
	FM (n=9)	5.44	-3.97	0.74
		(25.84)	(6.31)	(13.72)
	NC (n=13)	22.84	13.16	18.00
		(30.50)	(29.39)	(26.79)
	Total (N=47)	12.00	11.01	
		(31.24)	(32.63)	

table continues

Measure	Group	Post-Randomization		
		0 to 28	0 to 56	Total
		M (SD)	M (SD)	M(SD)
Letter Number				
Sequencing	Ol (n=14)	0.71	9.01	4.86
		(26.29)	(31.66)	(27.28)
	Hal (n=11)	1.10	-2.33	-0.61
		(20.34)	(7.07)	(17.44)
	FM (n=9)	7.32	7.69	7.50
		(19.77)	(14.87)	(13.30)
	NC ^e (n=12)	2.51	7.76	5.13
		(12.30)	(13.48)	(11.93)
	Total (N=46)	2.57	5.71	
		(20.10)	(21.43)	

Note. Ol = olanzapine; Hal = haloperidol; FM = family members; NC = normal controls; STM = Short term memory.

^aAverage of right and left hand performance. ^bOne subject had carpal tunnel syndrome and could not complete the task. ^cMedian reaction times in ms. ^dTwo subjects (KB24 and JR25) were extreme outliers and were therefore not included in this analysis. ^eOne subject from the normal control group, VB10, was schooled in Italy and was not adequately familiar with the English alphabet to complete this task.

Appendix L

Concomitant Medications: Olanzapine Group

Baseline		Day 28		Day 56	
Patient Code	Baseline Antipsychotic Medication(s) / dose(s)	Concomitant Medications / dose(s)	Dose	Concomitant Medications	Dose Concomitant Medications
MSJ16	olanzapine 20 mg/day	citalopram, 40mg; Risp 2mg qhs; (PRNS: haldol, 10mg; lorazepam 2mg; benztropine 1mg	20	coumadin 6 mg	20 coumadin 6mg
SB17	risperidone 6 mg/day	cogentin 2 mg PRN; methotrimeprazine 100 mg/day	15	none	20 none
BH21	clozapine 250 mg/day	nozinan, 75mg	10	none	15 none
LL22	olanzapine 7.5 mg/day	orap, 6mg; glyburide 5mg; clonazepam, 1.5mg; cogentin 2mg	20	zopiclone 7.5	20 zopiclone 7.5
JR25	olanzapine	none	10	none	10 none
MK27	risperidone 4mg/day; haloperidol 15 mg/day	lorazepam 6mg	2.5	none	15 none
TSC30	neuroleptic naive	none	2.5	none	2.5 none
DS32	off medications > 1 month	none	5	cogentin 2 mg PRN	5 cogentin 2 mg PRN
NX33	olanzapine 10 mg	lorazepam 4 mg/day	20	zopiclone 3.75 mg PRN	20 zopiclone 3.75 mg PRN
EL35	neuroleptic naive	effexor, XR 150mg	5	cogentin 2 mg PRN	5 cogentin 2mg PRN
TB37	risperidone 3 mg/day	Paxil, 30mg; lorazepam 6mg; zopiclone 7.5mg	5	none	5 none
VC38	olanzapine 10 mg/day	celexa	10	zopiclone 7.5	10 zopiclone 7.5
AG38	risperidone 4 mg/day	celexa 20mg; lorazepam 1mg	7.5	Cogentin 4 mg; zopiclone 7.5 mg	7.5 Cogentin 4mg; zopiclone 7.5
LP40	risperidone 6 mg/day; loxapac 125 mg/day	Kemadrin 15mg	10	none	10 none

table continues

Concomitant Medications: Olanzapine Group

Patient Code	Baseline		Dose	Day 28		Day 56	
	Baseline Antipsychotic Medication(s) / dose(s)	Concomitant Medications / dose(s)		Concomitant Medications	Dose	Concomitant Medications	
NL18	neuroleptic naive	none	2.5	Zopiclone 7.5	2.5	Zopiclone 7.5	
AP19	neuroleptic naive	none	2.5	none	5	none	
EL20	quetiapine 800 mg/day	cogentin 2mg; clonazepam 0.5mg; ranitidine 300mg	10	cogentin IM	10	cogentin IM	
AR23	olanzapine 20 mg/day	ativan 1mg; zoloft 50mg; cogentin 2mg	20	zopiclone 15 mg; cogentin 2 mg PRN	Early Termination		
KB24	risperidone 4 mg/day	acetaminophen 650mg; haldol 5mg prn; lorazepam 1mg prn	20	zopiclone 15mg	15	none	
AS26	quetiapine 800 mg/day	PRNs: benztropine, 1mg; trazodone, 50mg; clonazepam, 0.5mg	5	cogentin 2 mg PRN; zopiclone 15 mg PRN	5	cogentin 2 mg PRN; zopiclone 15 mg PRN	
VS29	risperidone 4mg/day	cogentin 1mg	5	cogentin 2 mg PRN; zopiclone 7.5 mg bid/PRN	5	cogentin 2 mg PRN; zopiclone 7.5 mg bid/PRN	
LL31	olanzapine 5 mg/day	effexor 37.5mg	5	cogentin 2 mg; zopiclone 7.5 mg	5	cogentin 2 mg; zopiclone 7.5 mg	
MLL34	risperidone 2 mg/day	none	2.5	none	2.5	colace 200 mg	
SB36	quetiapine 400mg/day	paroxetine 7.5 mg PRN	5	zopiclone 7.5 mg; cogentin 2 mg	Early Termination		
DF41	olanzapine 20mg/day; haloperidol 3 mg/day	none	15	cogentin 4 mg; zopiclone 7.5 mg	15	cogentin 3 mg; zopiclone 7.5 mg	
RA42	olanzapine 20 mg/day; haloperidol 10 mg/day	lorazepam 1mg; divalproex Na 1000mg	7.5	cogentin 4 mg; zopiclone 7.5 mg	17.5	cogentin 3 mg; zopiclone 7.5 mg	
CG43	quetiapine 400 mg/day	epival 500 mg	5	none	10	none	