LONGITUDINAL RELATIONS AMONG ANTICHOLINERGIC DRUG BURDEN, NEUROCOGNITION, AND COMMUNITY FUNCTIONING IN OUTPATIENTS WITH SERIOUS MENTAL ILLNESS

by

Axel Benjamin Bouchard

A DISSERTATION

Presented to the Faculty of

The Graduate College at the University of Nebraska

In Partial Fulfillment of Requirements

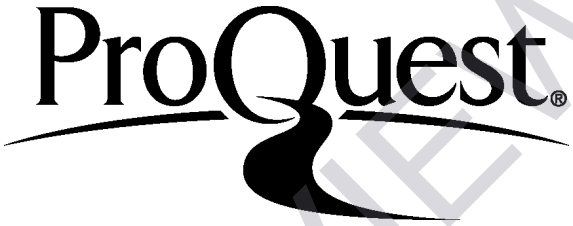
For the Degree of Doctor of Philosophy

Major: Psychology

Under the Supervision of Professor William D. Spaulding

Lincoln, Nebraska

August, 2016



LONGITUDINAL RELATIONS AMONG ANTICHOLINERGIC DRUG BURDEN, NEUROCOGNITION, AND COMMUNITY FUNCTIONING IN OUTPATIENTS WITH SERIOUS MENTAL ILLNESS

Axel Benjamin Bouchard, Ph.D.

University of Nebraska, 2016

Adviser: William D. Spaulding

The present study is the first to examine the links among anticholinergic drug burden, neurocognition, and community functioning in outpatients with serious mental illness (SMI). Although drugs with anticholinergic properties are understood to have deleterious effects on cognition, relatively little is known of their long-term consequences, particularly with respect to treatment outcome and higher-order processes such as social behavior. This is of particular import to people with SMI, who are commonly prescribed multiple drugs with anticholinergic properties.

Method. This project utilized longitudinal archival data from 88 outpatients with SMI. The aim was to determine the following: (a) whether anticholinergic burden predicts treatment outcome, as measured by trajectories of community functioning; (b) whether some people are more vulnerable to adverse anticholinergic effects than others; and (c) whether anticholinergic burden has an effect on community functioning independent of neurocognition.

Results. There was mixed support for the hypotheses. Community functioning increased, on average, over the course of treatment; however, the overall linear trajectory was higher or lower depending on levels of anticholinergic burden. Participants with

greater anticholinergic burden had lower levels of community functioning, even when controlling for illness severity.

Contrary to one of the hypotheses, anticholinergic burden was not associated with any measure of neurocognition. Neurocognition did not predict levels of overall community functioning; however, associations were found between neurocognition and specific domains of community functioning. Finally, medical burden and neuropathology were identified as significant moderators of the association between anticholinergic burden and community functioning. However, the pattern of the interactions suggested that medical conditions masked, rather than exacerbated, the negative effects of anticholinergic burden.

Conclusions. This project extends the relatively sparse literature on anticholinergic burden and real-world functioning to SMI populations and psychiatric rehabilitation outcomes. The findings suggest that anticholinergic burden may impact community functioning independent of neurocognition.

DEDICATION

For my family and friends

ACKNOWLEDGEMENTS

I would first like to express my gratitude to my advisor, Dr. William Spaulding, for his mentorship and support throughout my time at the University of Nebraska-Lincoln. I would also like to thank the other members of my committee, Drs. Debra A. Hope, Arthur Maerlender, Scott Napolitano, and Cynthia Willis-Esqueda, for their time and input on this project. I am also grateful to Dr. Rebecca Brock for providing statistical consultation.

Last but not least, I would also like to thank past and present members of the Serious Mental Illness Research group at the University of Nebraska-Lincoln, without whom this project would not have been possible.

TABLE OF CONTENTS

LIST OF MULTIMEDIA OBJECTS

CHAPTER 1: INTRODUCTION

Serious mental illness (SMI) is a broad category, and it encompasses a number of psychiatric diagnoses associated with significant functional impairment, including schizophrenia-spectrum disorders, major depression, bipolar disorder, and personality disorders. SMI carries immense personal and societal costs which may be exacerbated by the iatrogenic effects of psychiatric treatment. Under the current treatment paradigm, treatment of mental illness has arguably become synonymous with long-term administration of psychotropic drugs. However, these drugs have adverse effects and provide little clinically significant benefit to cognitive functioning, quality of life, or molar deficits in social functioning (Buchanan et al., 2010). Indeed, a number of commonly prescribed medications have known deleterious effects on various cognitive domains, including attention, psychomotor speed, and memory (Stein & Strickland, 1998). There is even some evidence to suggest that certain drugs decrease individuals' response to cognitive remediation (e.g., Vinogradov et al, 2009) and psychosocial skills training (e.g., Corrigan & Penn, 1995)

One drug class (i.e., those drugs that modify cholinergic activity within the central nervous system and periphery) is receiving increasing attention from researchers, in part due to recent findings linking these drugs to increased risk for dementia and other neurodegenerative conditions (e.g., Campbell & Boustani, 2015; Yoshiyama et al., 2012). The growing push to examine the anticholinergic effects of drugs – and more broadly, to address potentially harmful prescribing practices – appears to be the result of two separate yet complementary streams of research. The first involves a growing

understanding of molecular, neurophysiological processes in both normal functioning and illness, including the role of the cholinergic system in psychotic and affective disorders. The second research stream involves concern regarding polypharmacy, particularly the compounding effects of multiple drugs with anticholinergic properties on cognition and physical health (also called anticholinergic drug burden). Although the latter stream has generally come from the fields of gerontology and pharmacology, the implications for clinical psychology, psychiatry and the treatment of people with SMI are profound. The following research questions are of particular interest:

1. Does exposure to drugs with anticholinergic properties predict treatment response, as measured by changes in community functioning over time?

2. Does neurocognition explain the association between anticholinergic drug burden and changes in community functioning, or are there other pathways by which drugs with anticholinergic properties might affect social behavior?

The notion that drugs may have downstream effects beyond neurocognition (and physical side effects) is embedded within a biosystemic understanding of mental illness. This biosystemic model is outlined below.

The Biosystemic Model of Mental Illness

The use of the Biosystemic Model as a framework for understanding mental illness is supported by a large body of research in psychopathology and is explained in greater detail in Spaulding, Sullivan, and Poland (2003). This model rests on the following assumptions: first, humans operate within a biosystem that maintains its equilibrium through complex interactions and adjustments at both molecular and molar levels; second, the system's individual components are interconnected; third and finally,

problems or vulnerabilities at one level inevitably spread to other parts of the system. While the human biosystem can cope with a few vulnerabilities and their sequelae at any given time, it may become dysregulated and eventually collapse in the face of compounding problems at various levels of functioning, resulting in “disease” and the abnormal behaviors characteristic of mental illness. This biosystem can be thought of as comprising five distinct yet interconnected levels: physiology, neurocognition, social cognition, social behavior, and person-environment interactions.

The biosystemic model has a number of important implications for psychopathology research and the treatment of mental illness. It views behavior, and abnormal behavior by extension, as the products of highly complex albeit quantifiable systemic interactions. Thus, abnormal behavior is not prima facie proof of brain dysfunction. Rather than beginning with the assumption of a single cause, biology is treated as just one among many possible factors that play an important role in the etiology and progression of mental illness. One aim of psychopathology research, then, should be to test theories regarding specific linkages within the biosystem.

In order to demonstrate the use of this model and its application to the present study, the five levels of the biosystem are introduced below and applied to schizophrenia, beginning with the most molecular level of the biosystem, physiology. Schizophrenia-spectrum disorders are characterized by positive, negative, and disorganized symptoms; these core symptoms have known, deleterious effects on individuals' interpersonal functioning and quality of life. Negative symptoms, in particular, are associated with poor functional outcomes for individuals diagnosed with schizophrenia-spectrum disorders (Hegelstad et al., 2012; Bromet et al., 2005). These encapsulate functions that

are either absent or occur at a level well below the norm and can include various aspects of emotion and motivation (e.g., abulia, anhedonia, apathy), behavior (e.g., impoverished speech, blunted affect), and neurocognition (e.g., cognitive deficits in attention, language processes, and executive functions) (Silverstein, Spaulding, & Mendito, 2006). These signs and symptoms manifest across all levels of the biosystem, as outlined below.

Physiology. Physiology is the medium upon which psychological information is maintained, and it involves nerve cells and their associated electrochemical and epigenetic interactions. In neurodevelopmental disorders such as schizophrenia, abnormalities at the level of neurophysiology often result in widespread impairment, particularly as new systems are built upon disordered physiology. For instance, abnormal neurophysiology in schizophrenia has been linked to various neurotransmitter systems, including dysfunction of the dopaminergic system and resultant impairment in reward processing (Strauss, Waltz, & Gold, 2014), and the hypofunction of NMDA receptors, which ultimately contributes to neurocognitive deficits and other characteristic negative and positive features of schizophrenia (Cohen, Tsien, Goff, & Halassa, 2015; Coyle, 2012). Likewise, treatments that target and ameliorate dysfunction at the neurophysiological level can have downstream effects on higher-order processes. Conversely, these same treatments may introduce additional vulnerability into the biosystem, compounding dysfunction already present at the physiological level. In this sense, pharmacotherapy is a superordinate, molecular dimension that can affect various levels of the biosystem, including social behavior. This notion forms the basis of the present study.

Neurocognition. The neurocognitive level of functioning refers broadly to the brain's information processing abilities, and it involves the methods by which more molecular physiological processes organize themselves and influence an individual's psychological state. Neurocognitive deficits are well documented in schizophrenia and have been found in nearly all measurable domains, including visuospatial ability, visual and auditory attention, verbal and nonverbal memory, motor performance, language test performance, general intelligence, and executive functioning (Heinrichs & Zakzanis, 1998). Cognitive impairment in individuals with schizophrenia is one of the strongest predictors of problems with medication adherence (Jeste et al., 2003), decisional capacity (Palmer & Jeste, 2006), community functioning (Gioia & Brekke, 2009), and performance of instrumental activities of daily living (Green, 1996). Consequently, it is recognized as an important treatment target for this population. By extension, factors that impair neurocognition – including the adverse effects of certain medications – may have deleterious effects on the real-world functioning of people with schizophrenia. This concept forms another basis for the present study.

Social cognition. Social cognition is the process of thinking about people (Fiske, 1995), and it includes exclusively "social" neurocognitions such as facial perception and complex language (Spaulding, Sullivan, & Poland, 2003, p. 103, 157). It also involves aspects of social perception (e.g., intuiting the emotions and intentions of others) as well as individuals' abilities to understand how their own behavior can positively or negatively impact others' reactions to them. When there are deficits in this aspect of social cognition, individuals may lack the capacity to learn from and utilize interpersonal feedback to modify their behavior and generalize learning to other social situations. Thus,

impairments at this level of the biosystem necessarily affect social behavior and, by extension, community functioning.

Social behavior and person-environment interactions. People with schizophrenia often exhibit significant impairments at more molar levels of the biosystem. At the level of social behavior, these impairments take the form of deficient instrumental and internal skills, which can make it difficult for them to (a) regulate their own emotions and behavioral activation patterns, and (b) effectively navigate their social environments (Spaulding, Sullivan & Poland, 2003). They may also exhibit constrained role performance (i.e., the social roles they engage in are often quite limited, as are the scripts and metascripts they access to engage in those roles).

Ultimately, individuals with schizophrenia experience problems in several areas of community functioning involving the capacity to maintain reciprocal relationships and develop functional abilities necessary for community life, including personal hygiene, meal preparation, and budgeting skills, as well as the abilities to navigate public transportation systems and access community services. Deficient skills and impoverished behavioral repertoires are therefore crucial treatment targets in people with schizophrenia (Silverstein, Spaulding, & Menditto, 2006). Unfortunately, a person's ability to learn from his or her experiences (and from psychosocial treatments by extension) is contingent upon his or her cognitive functioning. Thus, the potential effects of impaired neurocognition on treatment outcome forms the final basis for the present study.

The Current Study

A biosystemic understanding of the adverse effects of psychotropic drugs begins with the recognition that although they affect molecular mechanisms, their effects

reverberate across other, higher-order domains of functioning. By extension, superordinate molecular dimensions (e.g., measures of anticholinergic drug burden) might capture some of the vulnerability that psychotropic drugs introduce into the biosystem. The purpose of this study is to explore the relations among anticholinergic drug burden (a molecular process), neurocognition (a proximal domain with known vulnerability to anticholinergic drugs), and community functioning (a higher-order domain that reflects an individual's ability to successfully live in the community).

This manuscript is organized into several sections. Chapter Two discusses the current treatment atmosphere, the influence of the medical model of mental illness, and its effects on pharmacotherapy. It concludes by drawing attention to the robust association between polypharmacy and total exposure to drugs with anticholinergic properties. Chapter Three provides an introduction to the cholinergic system and mechanisms of action of drugs with anticholinergic properties, concluding with a review of their adverse effects. Afterward, the concept of anticholinergic burden is introduced. The limitations of the extant literature are reviewed in Chapter Four, and the research hypotheses are subsequently introduced. The study method is detailed in Chapter Five. Findings are reported in Chapter Six, and their implications are discussed in Chapter Seven.

CHAPTER 2: PSYCHOTROPIC MEDICATION IN THE TREATMENT OF SERIOUS MENTAL ILLNESS

Contemporary treatment of mental illness is dominated by the allopathic paradigm, which posits the following: first, mental illness is a disease; second, the cause of this disease mechanistically leads to its consequences (i.e., brain processes directly cause the signs and symptoms associated with mental illness); third and finally, because mental illness follows the laws of medicine, it can be treated with a "magic bullet" approach targeting brain processes (Spaulding, Sullivan & Poland, 2003, p. 42-43).

Such beliefs are pervasive in psychiatric treatment settings and influence the care that people with mental illness receive. For example, a recent mixed methods study involving 800 mental health workers found significant links between their causal attributions (i.e., what they believe to be the cause of mental illness) and their beliefs about treatment (Bouchard, 2015). Biological attributions were associated with (a) greater emphasis on symptom management as the goal of treatment; (b) greater endorsement of psychotropic medication and inpatient hospitalization; and (c) lower likelihood of believing that mental illness could be cured. Of note, nearly two-thirds (63.1%) of all attributions made by mental health workers in the study were biological in nature, whereas just 15.2% of attributions invoked environmental causal agents such as trauma, social isolation, and stress (Bouchard, 2015). Consistent with the allopathic paradigm, the most common beliefs among respondents related to cause and treatment emphasis were that psychiatric symptoms could only be managed with medication because mental illness is a chronic, incurable disease.

Other researchers have found similarly high adherence to the medical model among treatment providers (for a review, see Schulze, 2007). More recently, Lebowitz and Ahn (2014) found that clinicians were less likely to agree with positively-valenced adjectives of hypothetical clients when they read vignettes containing genetic and neurobiological descriptors (versus historical information), suggesting that biological explanations of mental illness evoke less empathy from clinicians than psychosocial explanations. Biological descriptors were also associated with greater confidence in the effectiveness of pharmacotherapy for depression and anxiety (Lebowitz & Ahn, 2014). Overall, these findings highlight the predominance of the medical model of mental illness and raise concerns regarding its treatment implications.

The belief that abnormal behavior is a disease process that follows the laws of medicine, necessarily results in the promotion of biomedical interventions aimed at purported molecular mechanisms of illness (i.e., dysfunction in one or more neurotransmitter systems). By attributing cause solely to biological factors in this fashion, treatment providers can fall into the trap of assuming that people with mental illness are a homogeneous group. When the signs and symptoms of mental illness are taken as prima facie evidence of brain dysfunction, the social and environmental processes that influence behavior are all too frequently ignored. Ultimately, this results in a one-size-fits-all approach to the treatment of serious mental illness, typically involving the adjustment of medication type and dosage and, in the case of high-risk patients, psychiatric hospitalization (Spaulding, Sullivan, & Poland, 2003; Spaulding, Sullivan, Poland, & Ritchie, 2010).

The following sections explore these treatment implications in greater detail. Of note, almost all people with a serious mental illness diagnosis receive psychotropic medication (e.g., West et al., 2005), and large percentages of these individuals receive two or more antipsychotics in addition to other drugs (e.g., Constantine, Andel, & Tandon, 2010). These medications have a number of adverse effects that can decrease quality of life and interfere with treatment outcome (e.g., Vinogradov et al., 2009). In recent years, an increasing amount of attention has been devoted to drugs with anticholinergic properties, in large part due to the widespread, sometimes serious peripheral and central effects they induce. Beginning on page 21 is a brief review of the literature on the cholinergic system, the mechanisms of action of anticholinergic drugs, and their adverse effects. Finally, gaps in the current literature are discussed in relation to the present study.

Current Trends in Polypharmacy

Antipsychotics and other psychotropic drugs are ubiquitous in the treatment of SMI. The following review of the literature on polypharmacy raises concerns regarding its consequences and supports the following assertions. First, the prevalence of antipsychotic polypharmacy (APP) varies across treatment settings and countries but appears to be increasing on the whole, in terms of both its incidence and duration. Second, polypharmacy involving combinations of antipsychotics with other psychotropic drug families, also called cotherapy, is standard practice in psychiatry. Third, although APP and cotherapy are associated with illness-related factors such as severity and comorbidity, prescriber attitudes and practices suggest that polypharmacy is driven less by ideographic, patient-centric dimensions than it is by heuristics developed over the

course of clinical practice. Fourth and finally, the health and monetary costs of APP and cotherapy outweigh their purported benefits. These assertions are explored in greater detail in the following sections.

Prevalence of antipsychotic polypharmacy. In their review of 147 studies on global APP practices, Gallego and colleagues (2012a) outline trends in APP from the 1970s to 2009 as well as current prevalence rates in various regions. Although the global median for APP prevalence rates was found to be 19.6%, significant variability was observed across regions. Specifically, APP prevalence over three decades was estimated to be 16% in North America, 16.4% in Oceania, 23% in Europe, and 32% in Asia. However, the reviewed studies also indicate that, since the 1980s, APP rates in North America have increased by 34%, decreased by 65% in Asia, and remained relatively unchanged in Europe, suggesting that current prevalence of APP in the United States may be even higher than the previous figures suggest.

Utilization of first- versus second-generation antipsychotics. In addition to the widespread increase in APP noted above, prescribing patterns worldwide have changed with respect to antipsychotic generation (and combinations thereof). For example, Bernardo and colleagues (2012) examined the prevalence of APP in Catalonia, Spain over the course of a single year. Among 117,811 outpatients receiving at least one antipsychotic medication, 9,855 (13.8%) were simultaneously prescribed two or more antipsychotics. Among these individuals, 615 (6.2%) received five or more, 1,029 (10.4%) received four, 2,519 (25.6%) received three, and 5,692 (57.8%) received two. With respect to antipsychotic generation and polypharmacy, 6,106 (62.0%) received a combination of first- and second-generation antipsychotics, 1,050 (10.6%) received only

first-generation antipsychotics (FGAs), and the remaining 2,699 (27.4%) received a combination of second-generation antipsychotics (SGAs).

Similar patterns of antipsychotic distribution have been observed worldwide. For example, an analysis of antipsychotic polypharmacy data from the South London and Maudsley NHS Foundation Trust revealed that, among individuals with a serious mental illness diagnosis receiving APP, 64.8% received only second-generation antipsychotics while 32.5% received a combination of first- and second-generation antipsychotics (Kadra et al., 2015). A similar distribution of SGA utilization was observed in an inception cohort study of Danish outpatients who met inclusion criteria following their first episode of schizophrenia. In this study, the percentage of subjects treated with at least one SGA increased by nearly a factor of five in the span of just ten years, from 15.3% in 1996 to 89.2% in 2005. A commensurate decline in FGA utilization was observed over the same time frame, reflecting gradual replacement of FGAs with SGAs (Nielsen et al., 2010).

Duration of antipsychotic polypharmacy. Although polypharmacy duration is often not examined in retrospective epidemiological analyses (Gallego et al., 2012a), there is evidence to suggest that APP is often used for prolonged periods of time. For example, in the multi-site U.S. Schizophrenia Care and Assessment Program (US-CAP) study, the average duration of APP over the course of one year was 155.7 days, and a majority of patients (57.7%) received APP for 60 days or more over a one-year period. In contrast, just 35.7% were treated with monotherapy for 300 days or longer (Faries et al., 2005).

Other researchers have observed comparable durations of APP. For example, a three-year, retrospective cohort study of California and Georgia Medicaid recipients with schizophrenia revealed that the prevalence of APP was 40% and that, on average, the duration of APP for these individuals was 149 days (Ganguly et al., 2004). Fisher and colleagues (2014) observed a similar duration of APP in U.S. patients with commercial health plans undergoing psychiatric treatment for schizophrenia. For the 23.2% of patients who concurrently received 2 or more antipsychotics over a one-year time frame, the mean duration of APP was 163 days. In contrast, for individuals receiving just one antipsychotic, the average duration of monotherapy was 253 days (Fisher et al., 2014). These findings suggest that short-term use of APP – either during the acute phase of illness or for the purpose of switching from one antipsychotic to another (i.e., cross-titration) – is common even in individuals receiving primarily monotherapy, which may account for the variability in APP prevalence across studies (Kadra et al., 2015).

Use of concomitant medications. Another important facet of polypharmacy is the addition of antidepressants, anxiolytics, and other psychotropic medications to preexisting antipsychotic regimens (often referred to in the literature as cotherapy or concomitant medication use). Whereas some studies have demonstrated that the duration of concomitant medication tends to be shorter than that of APP (Vares et al., 2011), others reveal longer patterns of use similar to those observed in APP (Möller et al., 2014).

Duration notwithstanding, the prevalence of concomitant medication is quite high at any given point in time, by some estimates as high as 50% (Möller et al., 2014). For example, a group of Austrian researchers examining prescribing patterns in an inpatient psychiatric hospital found that between 1989 and 2001, approximately 25% of inpatients