Anticholinergic Burden in First-Episode Psychosis: A Comprehensive Examination of Cognition, Neuroimaging and Functional Outcomes

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ABSTRACT

The present thesis examined the multiple effects of anticholinergic burden (i.e., the cumulative effect of cholinergic blocking medications) over time in first-episode psychosis (FEP). Since high exposure to anticholinergics can contribute to greater cognitive decline and negative side effects, this thesis aimed to examine the adverse effects they may have following pharmacotherapy initiation on verbal memory (Study 1), hippocampal volume (Study 2), and functioning (Study 3). Exploring these interrelated dimensions provides insights for clinicians and researchers, offering an understanding of the complexities of pharmacotherapy in psychosis cross-sectionally and longitudinally. Study 1 included FEP patients (n=311; low anticholinergic burden [n=241] and high anticholinergic burden [n=70], defined by a Drug Burden Index (DBI) cut-off of 1) followed at the PEPP-Montreal clinic and healthy controls (n=128) who completed a neurocognitive battery, including parts of the Wechsler Memory Scale, at months 3 and 12 following program entry. Our cross-sectional results suggested that patients in the highest anticholinergic burden group had the poorest verbal memory performance compared to the other groups at month 3. Longitudinally, verbal memory performance improved over time in all groups. However, the difference between patients with low and high anticholinergic burden remained stable over time. Study 2 included FEP patients (n=82; low anticholinergic burden [n=64] and high anticholinergic burden [n=18], defined by a DBI cut-off of 1) followed at the PEPP-Montreal clinic and healthy controls (n=55) who underwent a 3T Magnetic Resonance Imaging (MRI) at months 3 and 12. Our cross-sectional and longitudinal results showed that the left fimbria hippocampal subfield volumes were reduced to a greater extent in patients with high anticholinergic burden than in patients with low anticholinergic burdens and controls. Study 3 included FEP patients (n=444; low anticholinergic burden [n=349] and high anticholinergic burden [n=95], defined by a DBI cut-off of 1) followed at the PEPP-Montreal clinic who completed the

Social and Occupational Functioning Assessment Scale (SOFAS) at months 3 and 12. Our results suggested that patients with a high anticholinergic burden have reduced functioning compared with those with a low anticholinergic burden. Our longitudinal findings indicated that although functioning may improve over time, patients exposed to a high anticholinergic burden have lower functioning than those in the low anticholinergic burden group. The overall observed associations between high anticholinergic burden and poorer verbal memory reduced hippocampal subfield volume, and impaired functioning provide further evidence for considering these dimensions when prescribing medications in FEP. In conclusion, our findings contribute to ongoing efforts to optimize treatment approaches and improve outcomes for individuals in the early stages of psychosis.

RÉSUMÉ

La présente thèse a examiné les nombreux effets d'une charge anticholinergique (l'effet cumulatif de médicaments bloquant les récepteurs cholinergiques) au fil du temps suite à un premier épisode de psychose (PEP). Comme l'exposition aux anticholinergiques peut contribuer à un déclin cognitif plus important et à une aggravation des effets secondaires, l'objectif de cette thèse était d'examiner les effets négatifs qu'ils peuvent avoir en début d'une pharmacothérapie sur la mémoire verbale (étude 1), le volume de l'hippocampe (étude 2) et le fonctionnement (étude 3). L'exploration de ces dimensions interdépendantes permet aux cliniciens et aux chercheurs de mieux comprendre la complexité de la pharmacothérapie liée à la psychose, de manière transversale et longitudinale. L'étude 1 incluait des patients avec un PEP (*n*=311; avec une charge anticholinergique faible [*n*=241] et avec une charge anticholinergique élevée [*n*=70], défini par un seuil du Drug Burden Index (DBI) de 1) suivis à la clinique PEPP-Montréal et des témoins sains (*n*=128) qui ont complété une batterie neurocognitive, incluant des parties de l'échelle de mémoire de Wechsler, au 3e et 12e mois. Nos résultats transversaux suggèrent que les patients du groupe ayant la charge anticholinergique la plus élevée avaient les performances de mémoire verbale les plus faibles par rapport aux autres groupes au 3e mois. De manière longitudinale, les performances de mémoire verbale se sont améliorées au fil du temps dans tous les groupes. Cependant, la différence entre les patients ayant une charge anticholinergique faible et élevée est restée stable au fil du temps. L'étude 2 incluait des patients avec un PEP (*n*=82; avec une charge anticholinergique faible [*n*=64] et avec une charge anticholinergique élevée [*n*=18], définie par un seuil du DBI de 1) suivis à la clinique PEPP-Montréal et des témoins sains (*n*=55) qui ont passé une Imagerie par Résonance Magnétique (IRM) 3T aux 3e et 12e mois. Nos résultats transversaux et longitudinaux ont montré que les volumes du sous-champ hippocampique de la fimbria gauche étaient plus réduits chez les patients à charge anticholinergique élevée que chez les

patients à faible charge anticholinergique et les témoins. L'étude 3 incluait des patients avec un PEP (n=444; avec une charge anticholinergique faible [n=349] et avec une charge anticholinergique élevée [n=95], défini par un seuil du DBI de 1) suivis à la clinique PEPP-Montréal et qui ont complété l'échelle d'évaluation du fonctionnement social et professionnel (SOFAS) au 3e et 12e mois. Nos résultats suggèrent que les patients ayant une charge anticholinergique élevée ont un fonctionnement réduit par rapport à ceux ayant une charge anticholinergique faible. Nos résultats longitudinaux indiquent que, bien que le fonctionnement puisse s'améliorer avec le temps, les patients exposés à une charge anticholinergique élevée ont un fonctionnement plus faible que ceux du groupe à faible charge anticholinergique. En général, les associations observées entre une charge anticholinergique élevée et une mémoire verbale plus faible, un volume réduit du de l'hippocampe et une altération du fonctionnement fournissent des preuves supplémentaires d'une nécessité de prendre en compte ces dimensions lors de la prescription des médicaments chez les personnes avec un PEP. En conclusion, nos résultats contribuent aux efforts en cours visant à optimiser le traitement et à améliorer le pronostic des personnes en début de psychose.

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CONTRIBUTION TO ORIGINAL KNOWLEDGE

This thesis provides a significant advancement in measuring anticholinergic exposure, particularly in the context of the early stages of psychosis following pharmacotherapy initiation. While most existing literature has focused on older populations, this study addresses a critical gap by examining the impact of high anticholinergic exposure on younger patients. In addition, this research proposes a global assessment of all medications taken daily by patients rather than limiting them to specific classes of medications, such as antipsychotics.

We also bring a new approach to understanding the impact of anticholinergic burden using comprehensive and longitudinal analysis, and quantitative assessment of anticholinergic burden using the Drug Burden Index (DBI), setting a new standard for future studies. This research is also novel in that it incorporates high-resolution 3T MRI scans, allowing precise examination of brain structures, particularly the hippocampus, a region closely linked to cognitive function and sensitive to the effects of medications.

CONTRIBUTION OF AUTHORS

This doctoral thesis is structured in a manuscript-based format. It consists of the published manuscript in the peer-reviewed Canadian Journal of Psychiatry (CJP), another manuscript under review at the peer-reviewed Psychiatry Research Neuroimaging (PRN) journal, and a third manuscript in preparation for journal submission. A fourth manuscript was published as a *Letter to the Editor* in the peer-reviewed Psychological Medicine (Psychol. Med.) journal (full article available in the Appendix Figure A). My first-author manuscripts have also been presented at international conferences, such as the Organization for Human Brain Mapping (OHBM) and the Schizophrenia International Research Society (SIRS).

1) Belkacem, A., Lavigne, K. M., Makowski, C., Chakravarty, M., Joober, R., Malla, A., Shah, J., & Lepage, M. (2023). Effects of Anticholinergic Burden on Verbal Memory Performance in First-Episode Psychosis. Canadian journal of psychiatry. Revue canadienne de psychiatrie, 68(12), 894–903.https://doi.org/10.1177/07067437231179161

The study was designed by A.B., K.L., and M.L., who also wrote the protocol, conducted a literature review, performed a statistical analysis, and prepared the first draft of this manuscript. M.C., M.CH., provided clinical and neurocognitive assessments, R.J., A.M., and J.S. All authors approved the final manuscript.

2) Belkacem, A., Lavigne, K., Raucher-Chéné, D., Makowski, C., Chakravarty, M., Joober, R., Malla, A., Shah, J. & Lepage, M. (2024). Association of Anticholinergic Burden with Hippocampal Subfields Volume in First-episode Psychosis. Psychiatry Research: Neuroimaging, under review.

A.B., K.L., and M.L. designed the study, wrote the protocol, conducted a literature review, performed a statistical analysis, and prepared the first draft of this manuscript. D.R-C., M.C., M. CH., R.J., A.M., and J.S. provided clinical expertise.

3) Belkacem, A., Lavigne, K., Joober, R., Malla, A., Shah, J. & Lepage, M. (2024). Effects of Anticholinergic Burden on Functioning in First-Episode Psychosis, in preparation.

A.B., K.L., and M.L. designed the study, wrote the protocol, and conducted a literature

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4) Belkacem, A., Lonergan, M., Feizi, S., & Brunet, A. (2023). Letter to the editor: the longitudinal effect of antipsychotic burden on psychosocial functioning in first-episode psychosis patients: the role of verbal memory. Psychological Medicine, 53(11), 5359–5360. https://doi.org/10.1017/S0033291723000065

A.B., M.L. and A.Br. conducted a literature review and prepared the first draft of this article. S.F. provided additional feedback. Guillaume Elgbeili (statistician) provided help on the statistical models.

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ACRONYMS

ADS	Anticholinergic Drug Scale
ACS	Anticholinergic Cognitive Scale
ARS	Anticholinergic Risk Scale
CPZeq	Chlorpromazine Equivalent Doses
DBI	Drug Burden Index
DUI	Duration of Untreated Illness
DUP	Duration of Untreated Psychosis
FEP	First-Episode Psychosis
GAF	Global Assessment of Functioning
GEE	Generalized Estimating Equation
ICV	Intracranial Volume
ISLT	International Shopping List Test
MCCB	MATRICS Consensus Test Battery
MRI	Magnetic Resonance Imaging
SAA	Serum Anticholinergic Activity
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SOFAS	Social and Occupational Functioning Assessment Scale
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1. Defining Schizophrenia and Psychosis

1.1.1. Epidemiology

Schizophrenia is a serious mental illness that can impact individuals worldwide, with a prevalence of up to 2% (Saha et al., 2005; McGrath et al., 2008). This condition is characterized by disruptions in thought processes, perceptions, and emotions, leading to an important loss of contact with reality, a state commonly referred to as psychosis (Kapur, 2003). Up to 3 out of every 100 young adults will experience a psychotic episode, highlighting the considerable societal impact (National Alliance on Mental Illness, 2008). Psychosis typically begins in the developmental years of adolescence and early adulthood, with a noted first appearance of psychotic symptoms, also known as first-episode psychosis (FEP). Individuals with schizophrenia and other related psychotic disorders often face several challenges that go beyond the clinical symptoms, including a significant decline in functioning and quality of life.

The exact causes of schizophrenia are still unknown. However, evidence suggests a complex interplay between genetic vulnerabilities and environmental factors (Lichtenstein et al., 2009; MacPherson, 2009). The diagnosis of schizophrenia is established through careful assessment of clinical symptoms following diagnostic guidelines set by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), highlighting the critical role of psychiatrists in providing accurate diagnosis.

1.1.2. SYMPTOMS

Symptoms of schizophrenia can be categorized into three domains: positive, negative, and cognitive deficits. Positive symptoms refer to a set of experiences that are outside of everyday perceptions and behaviours (Andreasen & Olsen, 1982). They can include hallucinations, delusions, and disorganized thoughts and behaviours (Andreasen & Olsen, 1982). Hallucinations are perceptions of things that are not present in reality (through any of the five senses). Delusions can be fixed, false, and resistant to reasoning, resulting in incorrect beliefs (Andreasen & Olsen, 1982). Disorganized thoughts and behaviours can be characterized as disruptions in thinking processes and actions, which may result in irrational speech and conduct (Andreasen & Olsen, 1982). Negative symptoms are reduced or absent functions usually present in healthy individuals. These symptoms can have a considerable impact on one's quality of life and can include flat affect (a lack of emotional expression), alogia (poverty of speech) and avolition (a low level of motivation or initiative; Andreasen & Olsen, 1982).

Cognitive deficits include impairments across multiple domains, impacting one's ability to process information, make decisions, and engage with their environment (Green et al., 2004; Benoit et al., 2015). These deficits extend beyond memory impairments and can involve difficulties with attention, executive function, and social cognition (Heinrichs & Zakzanis, 1998; Ranganath et al., 2018; Bora et al., 2010; Barch & Ceaser, 2012; Schaefer et al., 2013; Fioravanti et al., 2012; Nuechterlein et al., 2014). For example, individuals with schizophrenia may have a more challenging time sustaining attention on tasks, leading to difficulty focusing on appropriate information (Green et al., 2004; Bora & Murray, 2014). Executive function deficits may manifest as planning, problem-solving, and decision-making challenges that reduce one's ability to set goals and execute plans effectively (Bowie & Harvey, 2006). Deficits in social cognition may further impair one's

ability to accurately interpret social cues, understand others' perspectives and navigate interactions. This may lead to difficulties in building and maintaining interpersonal relationships, further contributing to social isolation (Bowie & Harvey, 2006; Green, 2006; Lepage and al., 2014).

1.1.3. Risk factors and Sex Differences

Several risk factors can contribute to the disease's development. Complications during pregnancy have been associated with an increased risk in the child (Brown & Derkits, 2010). Advanced paternal age is also associated with a higher likelihood of offspring (Malaspina et al., 2001). Urban upbringing has been identified as another risk factor, with studies showing a higher prevalence in urban regions than in rural areas (Van Os et al., 2010). This can suggest that environmental factors associated with urban living, such as social stressors, may play an important role. Substance abuse, particularly psychostimulants such as amphetamine, methamphetamine, and cocaine, can induce similar symptoms to those seen in psychosis and is therefore considered a potential risk factor (Breier et al., 1997). Cannabis use also represents a risk factor for psychosis, especially during adolescence (Colizzi et al., 2020). In predisposed individuals, it can heighten the risk of developing the disorder and disrupt normal brain maturation (Cunha et al., 2013). Adverse events during childhood or adolescence may disrupt normal brain development and further increase vulnerability.

Some sex differences also exist in schizophrenia. Women tend to develop symptoms later than men, with hormonal changes possibly playing a role (Leung et al., 2000; Riecher-Rossler et al., 2018). Women may report a more sudden onset, resulting in a shorter time between the beginning of symptoms and the first hospital admission. In

comparison, men can suffer from the disease earlier, with a more severe presentation and a greater likelihood of social isolation (Leung et al., 2000; Abel et al., 2010). However, despite these differences, the overall impact of the disease appears to be similar for both, with severe limitations and overall reduced quality of life (Leung et al., 2000; Falkenburg & Tracy, 2014; Seeman, 2021).

1.1.4. TREATMENT

Treating schizophrenia typically involves a comprehensive approach combining pharmacotherapy, psychotherapy, social support, cognitive interventions, rehabilitation programs, and social reintegration (Lieberman et al., 2005; Hofmann et al., 2012; Burlingame et al., 2020). This holistic approach helps address the complex and heterogeneous range of symptoms and functional impairments that come with the disease.

Medication is a critical part of the treatment, with antipsychotics being the first-line medication (Leucht et al., 2013). These medications can be divided into two categories: first-generation (typical) and second-generation (atypical) antipsychotics, each with a distinct pharmacological profile (Lieberman et al., 2003; Leucht et al., 2013). The choice of medication and dosage is tailored to the individual's unique symptomatology and response to the treatment, with continued monitoring. Along with pharmacological treatment, psychological interventions such as Cognitive-Behavioural Therapy (CBT) often help patients manage their symptoms, improve their ability to function, and address psychosocial stressors (Zimmermann et al., 2005; Hofmann et al., 2012; Bighelli et al., 2018).

1.2. COGNITIVE DEFICITS: CORE FEATURE

1.2.1. DEFINING VERBAL MEMORY

Nearly 70% of individuals with schizophrenia suffer from cognitive deficits (Heinrichs & Zakzanis, 1998; Tripathi et al., 2018). Cognitive impairments are distributed across various cognitive domains, each contributing significantly to an individual's ability to function (Green et al., 2004; Ranganath et al., 2008; Schaefer et al., 2013; Nuechterlein et al., 2014). Memory is one of them and helps with encoding, storing, and retrieving information (Aleman et al., 1999; Schwartz, 2020; Spencer, 2020; Cowan et al., 2021; Van Houdt et al., 2020).

Memory can be divided into various subtypes, each serving a specific role, with varying effects when they are impaired (Aleman et al., 1999; Norris, 2017; Zlotnik & Vansintjan, 2019). For example, short-term memory deficits can cause difficulty retaining information over short periods, further affecting activities such as following instructions and memorizing a phone number (Aleman et al., 1999; Cowan, 2008; Forbes et al., 2009; Norris, 2017). Impairments in long-term memory can affect one's ability to recall past experiences, details and events, where verbal memory was reported to be the most impaired cognitive domain (Aleman et al., 1999; Mesholam-Gately et al., 2009; Lee & Park, 2005; Henry & Crawford, 2005; Fioravanti et al., 2012; Antoniades et al., 2018; Bogie et al., 2023). For example, individuals may find it challenging to remember significant life events or details about their past, leading to problems in forming a coherent sense of self and identity. Other types of memory exist; for example, semantic memory impairments can result in difficulties in remembering basic facts, concepts, or vocabulary, further impacting one's ability to carry on a conversation or participate in academic activities (Aleman et al., 1999; Doughty & Done, 2009; McKenna et al., 2019). Similarly,

deficits in episodic memory, which involves recalling specific events or episodes from one's life, can result in difficulty remembering details about past events, such as where someone was and doing at a specific time (Elvevag & Goldberg, 2000; Toulopoulou et al., 2003; Achim & Lepage, 2005; Ranganath et al., 2008; Bacon & Izaute, 2009; Ragland et al., 2009; Raucher-Chené et al., 2022).

Memory impairments are present even in the early stages of the disease, and the pattern of impairments is similar to that seen in enduring schizophrenia, with verbal memory being one of the most affected cognitive domains (Mesholam-Gately et al., 2009; Schaefer et al., 2013; Bora & Murray, 2014; Nuechterlein et al., 2014; Antoniades et al., 2018). Verbal memory refers to the ability to encode, store, and recall information presented in a verbal form, such as words, sentences, and stories (Heinrichs & Zakzanis, 1998; Tracy et al., 2001; Toulopoulouand & Murray, 2004; Manglam & Das, 2013). It is essential for daily cognitive tasks, including language comprehension, learning, and overall communication (Heinrichs & Zakzanis, 1998). Studying verbal memory deficits is also important, as they are consistently reported in schizophrenia and FEP (Mesholam-Gately et al., 2009; Toulopoulouand & Murray, 2004; Antoniades et al., 2018; Bogie et al., 2023). Understanding these deficits makes it possible to comprehend the underlying mechanisms, such as abnormalities in associated brain regions.

Cognitive deficits in schizophrenia are not limited to impairments in memory. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS; Nuechterlein et al., 2004, Nuechterlein et al., 2008) conference recognized seven distinct cognitive domains, and they collectively represent different aspects of cognitive functioning that can be dysfunctional in schizophrenia: learning and verbal memory, learning and visual memory, working memory, processing speed, reasoning and problem-solving, attention, and social cognition (Green et al., 2004; Nuechterlein et al.,

2008). Overall, identifying these cognitive domains helps provide a standardized framework for assessing cognitive impairments in schizophrenia.

1.2.2. Cognitive Assessment Tools

Cognitive functioning can be assessed with several measurement tools, including standardized neuropsychological test batteries, computerized assessments, rapid screening tests, and clinical interviews. These instruments provide diverse approaches in evaluating the various affected cognitive domains, including the MATRICS Consensus Test Battery (MCCB; Marder & Fenton, 2004), Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 1999), Computerized CogState Schizophrenia Battery (CSB; Pietrzak et al., 2009) and Wechsler Memory Scale (WMS; Wechsler, 1945; Wechsler, 1997). The WMS was used and will therefore be discussed in more detail below.

WMS is a neuropsychological assessment tool adapted to evaluate memory function in individuals with schizophrenia. It consists of seven subtests that comprehensively assess different aspects of memory and assess it across different dimensions (Wechsler, 1997; Hoelzle et al., 2011). To assess verbal memory, the WMS includes the *Logical Memory* subtests. Participants are presented with stories and asked to recall them immediately after hearing them (Logical Memory I; Wechsler, 1997). This task measures one's ability to retain and retrieve information shortly after it is presented. Participants are also asked to recall the stories after a delay (Logical Memory II), followed by yes/no questions about the stories as a recognition task (Wechsler, 1997). This delayed recall portion provides valuable insight into the ability of the individual to retain and retrieve information over time.

1.2.3. Factors that Influence Cognitive Function

Multiple factors can influence cognitive functioning. Research suggests that women perform better on verbal memory tests, while men exhibit stronger visuospatial abilities (Leger & Neill, 2016; Buck et al., 2020). This highlights the necessity of accounting for sex differences when assessing cognitive performance. In addition, the level of education can be a factor that influences cognitive function as it shapes cognitive skills, particularly memory (Hakulinen et al.., 2019). However, people with schizophrenia often have fewer years of schooling due to the onset of the disorder during their academic years. Additionally, age is a critical factor to account for in neurocognitive performance (Pinkham et al., 2017). As a natural cognitive decline can occur over time, with global memory performance deteriorating by an average of 1-3% per year after age 25 (Salthouse, 2019). This age-related cognitive decline reinforces the importance of considering age-specific outcomes when assessing cognitive performance. Other factors influencing cognition have been identified, such as cannabis use (and other substances of abuse). Chronic use of cannabis may lead to deficits in attention, memory, and executive functions, impairing one's ability to perform complex tasks, make decisions, and process information efficiently, affecting overall cognitive performance (Cunha et al., 2013; Colizzi et al., 2020).

1.2.4. Cognitive Deficits and Functional Outcomes

Functioning can refer to one's ability to effectively achieve and maintain daily activities, social interactions, and occupational responsibilities (Green et al., 1996). Assessing functioning in schizophrenia and FEP is important and can be done using standardized tools, structured interviews, self-report measures, and observation ratings (Green et al., 2000). Clinicians can use scales such as the Social and Occupational Functioning

Assessment Scale (SOFAS; Rybarczyk, 2011) and the Global Assessment of Functioning (GAF; Startup et al., 2002) to measure one's social, occupational, and psychological functioning. The SOFAS was used and will therefore be discussed in more detail below.

SOFAS is a scale designed to evaluate social and occupational functioning, providing a single score ranging from 0 to 100, with higher scores indicating better functioning (Rybarczyk, 2011). Clinicians and researchers can use SOFAS to assess various aspects of an individual's functioning, including their ability to maintain relationships, manage daily activities, and participate in professional environments. This scale allows for a quantitative measure of functioning, allowing us to track changes over time and monitor the effectiveness of psychological interventions and pharmacotherapy. While SOFAS and GAF both assess functioning, SOFAS has a stronger focus on daily social and occupational aspects, while GAF considers a broader range of factors, including subjective psychological well-being, beyond the scope of our research (Startup et al., 2002; Rybarczyk, 2011)

It is worth mentioning that functioning is also closely linked to cognition in schizophrenia, as cognitive impairments can limit one’s ability to function (Green et al., 2000). A meta-analysis has also highlighted the importance of verbal memory in predicting functional outcomes (Mesholam-Gately et al., 2009). Those who experience difficulty encoding and retrieving verbal information may face challenges in communication and social interactions, and since everyday tasks rely on those skills, it could predict how well this person might function. Lepage et al. (2014) have also identified two outcome domains: functional and clinical. Functional outcomes refer to the broad range of life experiences, including social interactions, work engagement, and the ability to perform daily activities autonomously. In contrast, clinical outcomes only focus on the severity of symptoms and the individual's response to treatment. While various factors are essential, neurocognition

remains an important determinant of functional and clinical outcomes in schizophrenia, providing even more rationale for its attention and examination (Green et al., 2000; Lepage et al., 2014).

1.2.5. Cognitive Deficits in First-Episode Psychosis

Although cognitive deficits are well-documented in chronic schizophrenia, it is equally important to understand their presentation and severity in FEP (Barch & Caeaser, 2012; Fioravanti et al., 2012; Schaefer et al., 2013; Bora & Murray, 2014; Nuechterlein et al., 2014). The age of onset of psychosis is a crucial factor, as an earlier onset may result in more significant impairments (Hafner et al., 1993; Rajji et al., 2009). The duration of untreated psychosis (DUP) plays a pivotal role, as prolonged DUP is associated with worsened cognitive outcomes in FEP (Loebel et al., 1992). While cognitive deficits are a common feature of both FEP and schizophrenia, their differences in presentation suggest the need for tailored research and interventions that are designed to address the unique challenges associated with each stage of the disease.

1.3. HIPPOCAMPUS: INVOLVED IN VERBAL MEMORY

1.3.1. HIPPOCAMPAL DYSFUNCTION

The hippocampus, located in the temporal lobe of the brain, is a key site for memory processes, as discovered by the famous case of patient H.M. Following a surgical procedure for severe epilepsy, H.M. developed anterograde amnesia (inability to form new memories) as a result of surgical ablation of parts of his hippocampus (Scoville & Milner, 1957). Since this pivotal observation, extensive research has been done on hippocampal involvement in cognition (Heckers, 2001; Antonova et al., 2004; Flashman & Green, 2004; Boyer et al., 2007; Heckers & Konradi, 2010; Tamminga et al., 2010; Barch & Ceaser, 2012; Sheldon & Levine, 2016; Lieberman et al., 2018).

Evidence suggests that both schizophrenia and FEP are associated with abnormalities within the hippocampus (Siever & Davis, 2004; Boyer et al., 2007; Cannon, 2015; Lieberman et al., 2018). Structurally, a reduction in hippocampal volume relative to non-clinical controls has been consistently observed in both stages of the disease, suggesting progressive changes in its size and morphology (Bogerts et al., 1990; Nelson et al., 1998; Lawrie & Abukmeil, 1998; Steen et al., 2006; Mondeli et al., 2011; Adriano et al., 2012). Functionally, altered hippocampal activity during memory tasks has been recorded, reflecting alterations in the processing and retrieval of information (Jessen et al., 2003; Tregellas et al., 2014; Hutcheson et al., 2015; Zhao et al., 2018). These findings attest to the presence of hippocampal pathology in schizophrenia.

1.3.2. REDUCED HIPPOCAMPAL VOLUME

Magnetic Resonance Imaging (MRI) is a fundamental tool in research, offering a

non-invasive approach to obtaining in-depth images of brain structures (Smith et al., 2004). Structural MRI studies suggest reductions in grey matter density in several brain regions, including the temporal-medial lobe, thalamus, and prefrontal cortex, along with cortical thinning and gradual ventricular hypertrophy (Bogerts et al., 1990; Lawrie & Abukmeil, 1998; DeLisi et al., 2006; Steen et al., 2006; Galderisi et al., 2008; Olabi et al., 2011; Mondeli et al., 2011; Birur et al., 2017; Dietsche et al., 2017). An important reduction in hippocampal volume in schizophrenia is also consistently reported and is more pronounced than in other psychiatric disorders (Seidman et al., 2002; Pruessner et al., 2015; Adriano et al., 2012; Van Erp et al., 2016). This reduction in volume is believed to be associated with neurodevelopmental abnormalities and possible altered neuroplasticity (Weinberger & McClure, 2002; Harrison, 2004; Balu & Coyle, 2011). Findings from multiple studies also suggest a hemispheric discrepancy in hippocampal volume, with a greater reduction in the left hemisphere (Crow et al., 1989; Seidman et al., 2002; Angrilli et al., 2009; Okada et al., 2016; Pinto et al., 2023). This asymmetry is consistent with a proposed hypothesis of a dominant left hemisphere in schizophrenia and supports research that has found that the left hemisphere is responsible for language processing, semantic memory retrieval, and verbal memory processes (Langdon & Warrington, 2000; Niemann et al., 2000; Seidman et al., 2002; Angrilli et al., 2009).

Hippocampal volume has always been malleable and sensitive to various factors (e.g., stress and neurotoxicity), making it a robust marker for detecting any subtle abnormalities that could be associated with a particular factor (Pruessner et al., 2015). Repeated measures over time can also be achieved using hippocampal volumes, facilitating disease progression and tracking the treatment response. While other morphometric measures also provide valuable insights into specific aspects of the hippocampus, they don't offer the same level of comprehensive assessment of the hippocampal size. It is also a widely used measure in research and clinical settings, facilitating comparison between studies and reproducibility.

While the hippocampal volume measures the entire body size of the hippocampus in cubic millimetres (mm^3), it also provides information on the total amount of tissue present in this brain region. However, the hippocampus is composed of different subfields with potential region-specific functions and, therefore, abnormalities.

1.3.3. HIPPOCAMPAL SUBFIELDS

The development of high-resolution structural imaging techniques in recent years has allowed us to identify the different subfields that are part of the hippocampus (Winterburn et al., 2013; Pipitone et al., 2014). These subfields, which include the Cornu Ammonis (CA1, CA2, CA3, and CA4), dentate gyrus, and subiculum, are different subregions of the hippocampal circuitry and play specific roles in memory formation and retrieval (Heckers, 2001; Harrison, 2004; Haukvik et al., 2018; Olsen et al., 2019). The hippocampus is also abundant in white matter tracts, like the fornix, which connects the hippocampus to other brain regions, facilitating communication between them (Insausti & Amaral, 2004; Tamminga et al., 2010). Additionally, the fimbria, a white matter pathway located in the medial portion of the hippocampus, serves as a major exit pathway from the hippocampus, through which signals and information can be transmitted to other regions of the brain regions, like the hypothalamus and thalamus (Harrison, 2004; Tamminga et al., 2010; Dahmani et al., 2020). The alveus, a thin layer of white matter, forms the external surface of the hippocampus, providing structural support (Harrison, 2004).

Hippocampal subfields consist of separate regions with specialized functions (Atwood et al., 2023; Vargas et al., 2018). Subfields such as CA2, CA3, and the CA4/dentate gyrus are input structures that primarily encode new memories (Tamminga et al., 2010). In contrast, CA1 and the subiculum are considered output structures, playing a critical role in

memory retrieval processes (Tamminga et al., 2010; Roeske et al., 2021). Moreover, pattern separation and completion, facilitated by different hippocampal subfields, are essential for memory formation (Leutgeb et al., 2007; Tamminga et al., 2010; Yassa & Stark 2011; Makowski et al., 2020). Pattern separation allows for discrimination between similar memories, preserving their unique features, whereas pattern completion allows for retrieving complete memories from partial cues (Leutgeb et al., 2007; Tamminga et al., 2010; Neunuebel & Knierim, 2014). In this regard, episodic memory deficits that have been observed in schizophrenia and other related psychotic disorders have been linked to dysfunctional pattern completion and separation processes (Antonova et al., 2004; Nakahara et al., 2018; Sun et al., 2023). Given the interconnected nature of the hippocampus, if one subfield is reduced in volume or exhibits structural abnormalities, the entire hippocampal circuit can be disrupted, potentially causing abnormal information processing (Tamminga et al., 2010; Sun et al., 2023). Such disruptions can manifest as inappropriate associations, incorrect memories, and irrational thought patterns, all common symptoms of schizophrenia and FEP (Tamminga et al., 2010; Walter et al., 2016; Ho et al., 2017; Baglivo et al., 2018; McHugo et al., 2024).

1.4. ANTIPSYCHOTICS: FIRST-LINE MEDICATION

1.4.1. ANTIPSYCHOTICS: GENERAL MECHANISM OF ACTION

Antipsychotics are used to treat schizophrenia and related psychotic disorders. First-generation antipsychotics were the earliest medications developed and achieved their therapeutic effects predominantly by blocking dopamine D_2 receptors in the brain's mesolimbic pathway (from the ventral tegmental area to the limbic system; Kapur et al., 2006; Remington et al., 2021). This action leads to reduced dopaminergic activity, with observed improved positive symptoms (Kapur et al., 2006). However, this non-selective blockade of the D_2 receptors, particularly in other areas of the brain, like the nigrostriatal pathway, can induce important side effects such as extrapyramidal effects (e.g., parkinsonism, dystonia, and tardive dyskinesia; Leucht et al., 2013; Haddad & Correll, 2018).

In contrast, second-generation antipsychotics developed after first-generation antipsychotics have a more complex and advanced pharmacological profile (Lieberman et al., 2003; Kapur et al., 2006; Lally & MacCabe, 2015). Although they also act by blocking dopamine D_2 receptors, they can also modulate other neurotransmitters, including serotonin and acetylcholine (Lieberman et al., 2003). By targeting multiple neurotransmitters, these medications can potentially address a wider range of symptoms (Leucht et al., 2009). In addition, they tend to have a lower affinity for D_2 receptors compared to first-generation antipsychotics, creating a lower risk of extrapyramidal side effects (Lieberman et al., 2003; Goff et al., 2017). Given the effectiveness of antipsychotics in reducing positive symptoms, disrupted dopaminergic signalling (also known as the dopaminergic hypothesis) is believed to be an important consequence of schizophrenia (Bruijnzeel et al., 2014; Goff et al., 2017; Sabe et al., 2021; Correll et al., 2022; Spark et al., 2022).

1.4.2. BEYOND DOPAMINERGIC HYPOTHESIS OF SCHIZOPHRENIA

Second-generation antipsychotics also interact with other receptors, such as serotonin 5-HT_{2A} receptors (Leucht et al., 2009; Kaar et al., 2020; Ceskova, 2022). Blocking these receptors could better help with the disease's negative symptoms and cognitive deficits (Kapur et al., 2006; Leucht et al., 2009). For example, clozapine, a second-generation antipsychotic with high 5-HT_{2A} receptor affinity, has shown efficacy in treatment-resistant schizophrenia (Kane et al., 1988; Meltzer, 1997; Fakra & Azorin, 2012). Clozapine is one of the earliest second-generation antipsychotics to be developed and remains one of the most effective despite its critical adverse effects (Lewis et al., 2006; Wagner et al., 2020). Compared to first-generation antipsychotics, clozapine has a unique pharmacological profile that includes both antagonistic action of D_2 receptors and a potent antagonistic action of 5-HT_{2A} receptors (Lewis et al., 2006; Chan et al., 2021; Wagner et al., 2021). This dual mechanism is thought to contribute to its efficacy in treating both positive and negative symptoms of schizophrenia (Lewis et al., 2006; Lobos et al., 2010; Kane & Correll, 2016).

Antipsychotics can also interact with the cholinergic system through the antagonistic action of muscarinic acetylcholine receptors (Bymaster et al., 2003; Terry, 2008; Barak, 2009). These receptors are extensively distributed throughout the central nervous and peripheral systems (Caulfield, 1993; Terry, 2008; Dean & Scarr, 2020). Blockade of these receptors can lead to various side effects, including dry mouth, dizziness, nausea, and cognitive impairments (Ogino et al., 2014). Although antipsychotics have a more significant impact on dopaminergic and serotonergic signalling, their effect on the cholinergic system remains part of their overall pharmacological profile (Bymaster et al., 2003; Ozbilen & Adams, 2009). Although this is more consequential for first-generation antipsychotics, some second-generation antipsychotics, such as clozapine and olanzapine,

have a high affinity to those muscarinic receptors (Bymaster et al., 2003; Terry, 2008; Barak, 2009; Ozbilen & Adams, 2009; Lobos et al., 2010; Ogino et al., 2014). This highlights the important variability within second-generation antipsychotics. Not to mention that side effect profiles are not uniformly distributed among them, for example, olanzapine is associated with greater metabolic side effects, while risperidone tends to be associated with greater motor side effects (Rummel-Kluge et al., 2010). In contrast, third-generation antipsychotics, such as aripiprazole, have minimal anticholinergic burden. Their balanced partial agonist action on D_2 receptors and selective receptor profile result in a reduced affinity for muscarinic receptors, leading to fewer anticholinergic side effects (Kim et al., 2021).

1.4.3. PHARMACOTHERAPY

Antipsychotics are available in a multitude of delivery forms, including oral tablets, and intramuscular and intravenous injections (Seeman, 2002; Kapur et al., 2006, Kaar et al., 2020). Long-acting injectables are also available, providing an option for patients who may have challenges in compliance (Llorca et al., 2013; Correll et al., 2016). Antipsychotics are effective but can cause several side effects. Commonly reported adverse effects include weight gain, drowsiness, dry mouth, constipation, agitation, blurred vision, and dizziness (Kapur et al., 2006). In more severe cases, they can cause movement disorders such as tremors, increase the risk of metabolic disorders such as diabetes, and cause serious conditions such as tardive dyskinesia and neuroleptic malignant syndrome, associated with the use of high-potency antipsychotics, particularly in higher doses and during rapid dose escalation (Kaar et al., 2020). Such side effects can seriously impact one's quality of life and ability to adhere to the treatment. To minimize these risks, clinicians will often prescribe medication at the lowest effective dose and start with antipsychotic monotherapy

(Reus et al., 2016; Remington et al., 2017; Bjerre et al., 2018).

Other medications are also adjunctively used in psychosis, mainly to treat comorbidities (Kane & Correll, 2010; Remington et al., 2017). For example, mood stabilizers such as lithium can address impulsive behaviours and mood swings (Leucht et al., 2015). Antidepressants can also be used to target depressive symptoms (Helfer et al., 2016). Worth mentioning is that those medications, including antipsychotics, can have an anticholinergic action by blocking the muscarinic receptors in the central nervous system (Ozbilen & Adams, 2009; Chew et al., 2008; Ogino et al., 2014). As a result, when a person takes several medications simultaneously, there is cumulative exposure (Chew et al., 2008; Ogino et al., 2014). Given that cognitive deficits are an essential disease feature, this additional impact on cognition warrants further investigation.

1.5. Anticholinergic Burden: A Growing Focus

1.5.1. Anticholinergic Medication

The use of anticholinergic medications in treating psychosis is common (Bymaster et al., 2003; Terry, 2008; Ozbilen & Adams, 2009; Kane & Correll, 2010; Ogino et al., 2014; Dean & Scarr, 2020). Not only because of their antiparkinsonian effects (their ability to reduce extrapyramidal effects) but also because of their efficacy in helping a wide range of other symptoms (Desmarais et al., 2012; Hori et al., 2022). For example, among them, antihistamines, commonly used to treat allergies and other forms of inflammation, are available over-the-counter and have anticholinergic properties, along with certain antidepressants, cardiovascular medications, urinary incontinence medications, diuretics, and antipsychotics (Hori et al., 2022). Although anticholinergics can have therapeutic effects, they are also associated with a wide range of adverse effects, affecting both the peripheral and central nervous systems (Ozbilen & Adams, 2009). Frequently reported side effects include dry mouth, constipation, blurred vision, mental confusion and cognitive deficits (Desmarais et al., 2012; Ogino et al., 2014). In severe cases, it can lead to acute urinary retention, glaucoma, heat stroke, delirium, cardiac arrhythmias, and respiratory complications (Ogino et al., 2014).

A particular concern is the cumulative nature of anticholinergics, which can be increased with prolonged use or multiple exposure to medications with anticholinergic activity (Gray et al., 2015). High levels of exposure have been associated with an increased risk of adverse outcomes, including more significant cognitive deficits and functional impairment (Spohn & Strauss, 1989; Tracy et al., 1998; Fox et al., 2011; Ogino et al., 2014; Eum et al., 2017; Tsoutsoulas et al., 2017; Kim et al., 2019; Georgiou et al., 2021; Joshi et al., 2021; Khan et al., 2021; Haddad et al., 2023; Allott et al., 2024; Peralta et al.,

2024).

1.5.2. Anticholinergic Burden Assessment

Measuring the anticholinergic burden is important for evaluating their potential adverse effects, particularly in at-risk populations (Salahudeen et al., 2015). While the nature of cognitive decline in schizophrenia differs from the one observed in other psychiatric illnesses, effects on cognitive function remain the same. For example, in Alzheimer's disease, cognitive decline typically manifests as progressive memory loss and deterioration of cognitive functions over time (Gray et al., 2015; Kalia & Silva, 2015). In contrast, cognitive deficits in schizophrenia are characterized by impairments across multiple cognitive domains, and the trajectory of decline can differ between individuals and does not always progress on a linear trajectory or follow the same pattern that is seen in other psychiatric disorders (Kalia & Silva, 2015).

Several measures have been developed to assess anticholinergic activity, each providing unique perspectives on medication-induced effects. The Serum Anticholinergic Activity (SAA) uses the level of anticholinergic compounds present in the bloodstream and is measured using a radioreceptor assay, detecting the binding of anticholinergic agents (Mulsant et al., 2003). Other measures include the Anticholinergic Drug Scale (ADS), a categorical quantitative scale that assigns scores to medications based on their anticholinergic potency; it was designed by Carnahan et al. (2006) and ranks medications according to their likelihood of causing anticholinergic side effects with higher scores indicating more significant risk. Clinicians can estimate an individual's overall anticholinergic burden by manually calculating the sum of the scores for all medications taken by the individual (Carnahan et al., 2006). The Anticholinergic Risk Scale (ARS),

developed by Rudolph et al. (2008), is a screening tool used to assess the risk of anticholinergic adverse effects associated with medication use in older adults. The ARS scores medications with anticholinergic properties and assigns each medication a score based on its potential to cause anticholinergic side effects (Rudolph et al., 2008). The total manually calculated score estimates the anticholinergic burden and helps identify medications that may contribute to adverse outcomes (Rudolph et al., 2008). The Anticholinergic Cognitive Scale (ACS), developed by Boustani et al. (2008), focuses on the cognitive side effects of anticholinergic medications. It assigns a score to each medication based on its anticholinergic potency. The manually calculated cumulative score reflects the overall cognitive burden of anticholinergic medications (Boustani et al., 2008).

An additional measure of anticholinergic burden is the Drug Burden Index (DBI) developed by Hilmer et al. (2007). It consists of a quantitative scale to assess the cumulative burden of all medications with anticholinergic and sedative properties (Hilmer et al., 2007). It differs from other scales in that it considers the daily dosage of medications and automatically calculates the total score (Hilmer et al., 2007). To calculate the DBI, each medication is scored based on its anticholinergic and sedative potency (Hilmer et al., 2007). The total automatically calculated numerical score represents the medication's likelihood of impairing several outcomes, such as cognitive function (Hilmer et al., 2007; Hilmer, 2018). Higher scores indicate a more significant burden (Hilmer et al., 2007). Researchers and clinicians can calculate the total burden of anticholinergic and sedative medications based on the automatically calculated sum of the scores for all medications taken by a patient (Hilmer et al., 2007). The DBI provides a standardized approach to quantifying medication-induced cognitive impairments (Hilmer, 2018). A DBI score greater than 1 indicates moderate to high anticholinergic risk, while a score less than 1 indicates a lower risk (Hilmer, 2018). This index can be valuable in clinical settings where multiple medications are prescribed simultaneously, as it helps assess the combined impact

(Hilmer, 2018). Although antipsychotic monotherapy is encouraged and recommended by guidelines, observational and naturalistic studies consistently report high rates of polypharmacy in schizophrenia and FEP (Kane & Correll, 2010; Remington et al., 2017).

1.5.3. Anticholinergic Burden in Psychosis

Recent research suggests a significant correlation between high anticholinergic burden and cognitive deficits in schizophrenia and FEP (Spohn & Strauss, 1989; Tracy et al., 1998; Fox et al., 2011; Eum et al., 2017; Tsoutsoulas et al., 2017; Kim et al., 2019; Ballesteros et al., 2020; Joshi et al., 2021; Khan et al., 2021; Belkacem et al., 2023). In schizophrenia, while we know that patients commonly exhibit diminished central cholinergic activity and reduced expression of muscarinic receptors, anticholinergics, by blocking the action of acetylcholine, may aggravate the already present cognitive deficits in the disease (Hasselmo, 2006; Terry, 2008; Barak, 2009; Dean & Scarr, 2020). Research further suggests that a high anticholinergic burden could saturate M_1 muscarinic receptors, which are responsible for cognitive and verbal learning (Bakker et al., 2018; Dean & Scarr, 2020). In FEP, the effect of a high anticholinergic burden aligns with those seen in schizophrenia but can have some unique characteristics due to the early stage of the illness. A high anticholinergic burden can affect cognitive function in early psychosis, but its impact can be less severe than in chronic schizophrenia. This is because the brain is more capable of adapting and recovering from such exposure (Ortiz et al., 2017; Hori et al., 2022). Some studies suggest that discontinuing anticholinergics that block the M_1 receptor (e.g., biperiden) can improve verbal memory, indicating that their effects might be reversible (Desmarais et al., 2014). Vingerhoets et al. (2017) further established the role of M_1 receptors in cognition, showing that their blockade led to verbal memory deficits in both patients with psychotic disorders and healthy controls. In addition, the M_1 receptors

are highly distributed in the hippocampus; anticholinergic medications can, therefore, disrupt cholinergic signalling essential for maintaining the integrity of brain structures (Volpicelli et al., 2004; Scarr et al., 2016). Understanding the complex and dynamic interplay between anticholinergic medications, verbal memory, hippocampal volume, and functioning in psychosis is therefore crucial, given the unmet need to effectively treat cognitive deficits by current antipsychotics.

1.6. OBJECTIVES

The present thesis examined the effects of anticholinergic burden over time in individuals with FEP, focusing on three outcomes: verbal memory (Study 1), hippocampal volume (Study 2), and functioning (Study 3). Through these objectives, our studies attempted to address gaps in the early stages following pharmacotherapy initiation, cross-sectionally and longitudinally, from month 3 to month 12.

Study 1 provided a large-scale investigation of the effects of anticholinergic burden on verbal memory performance over time in FEP, as verbal memory deficits are common in FEP and associated with high anticholinergic burden. Study 2 explored the relationship between anticholinergic burden and hippocampal volume changes over time in FEP. Given the critical role of the hippocampus in memory, a reduction in hippocampal volume associated with a high anticholinergic burden could explain the underlying mechanisms of medication-induced effects. While reduced symptoms are essential, functioning is not permanently restored with pharmacotherapy. Therefore, an exploration in Study 3 of an association between a high anticholinergic burden and daily functioning over time in FEP was needed. Additionally, to encourage dialogue on future directions and clinical practices regarding anticholinergic use in early psychosis, we have included our published

commentary in the Appendix (Figure A; Belkacem et al., 2023).

Collectively, these studies aimed to address an essential gap in the current literature on the effects of anticholinergic burden on different outcomes in the early stages of psychosis after pharmacotherapy initiation. We hope to have provided useful knowledge and information to clinicians and researchers aiming to develop more effective pharmacotherapy.

CHAPTER 2

STUDY 1: EFFECTS OF ANTICHOLINERGIC BURDEN ON VERBAL MEMORY PERFORMANCE IN FIRST-EPISODE PSYCHOSIS[1]

[1] Belkacem, A., Lavigne, K. M., Makowski, C., Chakravarty, M., Joober, R., Malla, A., Shah, J., & Lepage, M. (2023). Effects of Anticholinergic Burden on Verbal Memory Performance in First-Episode Psychosis. Canadian journal of psychiatry. Revue canadienne de psychiatrie, 68(12), 894–903.https://doi.org/10.1177/07067437231179161

ABSTRACT

Antipsychotics are widely used to treat first-episode psychosis but may have an anticholinergic burden, that is, a cumulative effect of medications that block the cholinergic system. Studies suggest that a high anticholinergic burden negatively affects memory in psychosis, where cognitive deficits, particularly those in verbal memory, are a core feature of the disease. The present study sought to replicate this in a large cohort of well-characterized first-episode psychosis patients. We expected that patients in the highest anticholinergic burden group would exhibit the poorest verbal memory compared to those with low anticholinergic burden and healthy controls at baseline (3 months following admission). We further hypothesized that over time, at month 12, patients' verbal memory performance would improve but would remain inferior to controls. Methods: Patients (n=311; low anticholinergic burden [n=241] and high anticholinergic burden [n=70], defined by a Drug Burden Index cut-off of 1) and healthy controls (n=128) completed a clinical and neurocognitive battery including parts of the Wechsler Memory Scale at months 3 and 12. Cross-sectionally, using an analysis of variance, patients in the highest anticholinergic burden group had the poorest performance in verbal memory when compared to the other groups at month 3, $F(2,430)=52.33$, $P<0.001$. Longitudinally, using a Generalized Estimating Equation model, the verbal memory performance of all groups improved over time. However, patients' performance overall remained poorer than the controls. These findings highlight the importance of considering the anticholinergic burden when prescribing medications in the early stages of the disease.

2.1. INTRODUCTION

People living with psychosis receive several medications, including antipsychotics. Developing comorbidities in psychosis is not uncommon and consequently leads to increased medication burden. Commonly used in the treatment of psychosis, anticholinergics are among the medications prescribed to patients to counter the side effects of antipsychotics.[1,3] Evidence suggests that their substantial and cumulative effect, that is, anticholinergic burden, is associated with a significant decline in cognitive function.[4,8] Independent of the effect of anticholinergics, cognitive impairments represent one of the core features of schizophrenia and significantly influence functional outcomes.[9,13] Emerging evidence suggests that the anticholinergic burden from antipsychotics should be considered when prescribing medications. A high anticholinergic burden may be associated with more severe deficits in cognitive functions and, particularly, verbal memory.[14,17] While cross-sectional studies in first-episode psychosis (FEP) suggest an association between anticholinergic burden and verbal memory performance, few studies have examined this longitudinally after initiating medication in FEP patients. Thus, a longitudinal study that includes baseline and follow-up data on cognition and medication would help shed light on this matter.

This study aimed to determine whether cognitive decline is associated with anticholinergic burden in FEP in a cross-sectional and longitudinal setting. We examined the association between anticholinergic burden and verbal memory performance between patients with a high and low anticholinergic burden (defined as a Drug Burden Index [DBI] [18] cut-off of 1, as in previous research[14,19,21]) while covarying for factors known to affect performance (sex and age). We used cross-sectional and longitudinal data (3 and 12 months after clinical admission) to address our aims. We hypothesized that FEP patients with higher anticholinergic burden would show poorer verbal memory performance than

low anticholinergic burden and controls at month 3. We also hypothesized that both groups would show improvements in verbal memory performance over time but remain impaired relative to controls.

2.2. METHODS

2.2.1. PARTICIPANTS

FEP patients (n=311) were recruited from the Prevention and Early Intervention Program for Psychosis (PEPP-Montreal) clinic. Entry criteria include age 18 to 35 years, no antipsychotic treatment (max. 30 days), affective or nonaffective psychotic disorder (DSM-IV), good physical health, and ability to give consent in English or French. Exclusion criteria included minimal performance on neuropsychological tests (Intelligence Quotient [IQ] < 70), a medical history of a neurological disorder (including head injury with loss of consciousness), and a family history of neurological disorders. Nonclinical control subjects (n=128) were recruited through a centralized network of online postings for comparison purposes. Recruitment was restricted to the same catchment area to facilitate matching controls to patients. Controls were group-matched to the FEP patients on demographic variables (sex, age and parental socioeconomic status) at recruitment. Entry criteria included age 18 to 35 years, good physical health, not taking psychotropic medications, and being able to consent in English or French. Exclusion criteria include minimal performance on neuropsychological tests (IQ < 70), history of Axis I disorders (DSM-IV) according to the Non-Patient Edition of the Structured Clinical Interview for Axis I disorders of the DSM-IV,[22] first-order family history of psychotic disorder or hereditary neurological disease, diagnosis of substance abuse within the past 30 days, and medical history of neurological disorder (including head injury with loss of

consciousness). The Douglas Research Ethics Board approved this study, and all participants provided informed consent (written and verbal).

2.2.2. SETTING

After admission to the PEPP-Montreal clinic program between 2003 and 2022, participants underwent a systematic assessment protocol with several checkpoints over 2 years (see study[10] for more information). The first neurocognitive assessment took place on average 3 months after admission to the PEPP-Montreal clinic program. We considered it the baseline cognitive assessment since it was the first time cognitive performance was collected. For this study, we only considered data at baseline (month 3; *M*=2.07, *SD*= 0.89; FEP *n*=311, Controls *n*=128) and month 12 (*M*=12.83, *SD*=1.28; FEP *n*=107, Controls *n*=46) following PEPP-Montreal clinic admission once patients were clinically stabilized.

2.2.3. ASSESSMENTS

Patients were administered a Structured Clinical Diagnosis for DSM-IV (patient version).[22] In months 3 and 12, structured and semistructured instruments were used: the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS),[23,24] Duration of Untreated Psychosis (DUP), Duration of Untreated Illness (DUI) using the Circumstances of Onset and Relapse Schedule and Social and Occupational Functioning Assessment Scale (SOFAS).[25] We also assessed medication adherence using a validated method by Cassidy et al.[26] from a weekly adherence diary and several sources (e.g. families and case managers) at both assessments. Neurocognitive testing was performed at both assessments using the Wechsler Memory Scale.[27] The average of the scaled scores for Logical Memory I and II (*M*=10, *SD*=3) was used to

evaluate verbal memory performance. A qualified evaluator trained by a neuropsychologist administered this neuropsychological test. The anticholinergic burden may affect other cognitive domains. However, with the extensive literature on verbal memory, we focused on this cognitive domain to minimize the number of comparisons performed between groups for each cognitive domain.[28,29]

2.2.4. ANTICHOLINERGIC BURDEN

After carefully examining the available tools, we opted for the DBI to assess the anticholinergic burden. We consulted the systematic review of anticholinergic scales by Villalba-Moreno et al. [30] and concluded that the DBI was the only scale that considered the prescribed dose and the minimum effective dose, thus allowing us to quantify anticholinergic effects. [30] Furthermore, this scale allowed us to add and combine doses of multiple medications more easily, which was essential in this sample and provided a total cumulative burden. [20] The DBI also measures sedative medications, an important and unique feature relative to the other anticholinergic risk scales.[18,30] The DBI was validated by Hilmer et al. [18] study with a sample of 3075 patients, suggesting an association between anticholinergic burden (measured with DBI) and cognitive impairments. Notably, most negative associations were found with DBI and Anticholinergic Risk Scale (ARS).[30] Overall, this index is a useful evidence-based tool for assessing the effect of exposure to anticholinergic and sedative medications.[18,20,21,30,33] The anticholinergic burden of medications was calculated at months 3 and 12 using the DBI from a Web Portal Software Anticholinergic Burden Calculator (https://www.anticholinergicscales.es).[19,34] Patients were categorized into 2 groups according to a DBI score classification: a DBI score <1 indicating no to low anticholinergic burden and a DBI score >1 indicating moderate to high anticholinergic burden.[18,20] The DBI scale from the Anticholinergic Burden Calculator had

only 2 classifications (labelled medium/high). We also calculated the DBI score for 3 types of DBI: total DBI, antipsychotic DBI, and other medications DBI (see Appendix Table A for a representation of the 5 patients who showed the highest DBI scores). By separating the anticholinergic burden by medication type, we can identify which medications contribute most to the overall burden in early psychosis. Analyzing the 5 highest DBIs reveals potential prescription patterns predicting a higher anticholinergic burden.

2.2.5. ANTIPSYCHOTIC DOSAGE

The dosage of antipsychotics was measured using Chlorpromazine Equivalent doses (CPZ-eq doses).[34] CPZ-eq doses were calculated for the newer atypical antipsychotics,[35] with the antipsychotic comparison chart retrieved from https://www.rxfiles.ca/rxfiles and validated by psychiatrists at the Douglas Research Center. DBI and CPZ-eq scores were calculated for all medications taken by the patients daily, providing a cumulative score. For long-acting injectable antipsychotics, the daily dose was calculated with the total dosage divided by the number of days.[36] For example, if an injection was given every 4 weeks, the calculation was *X* mg/ 28 days.

2.2.6. STATISTICAL ANALYSES

To examine differences in clinical and demographic characteristics between groups, t-tests and one-way analysis of variances (ANOVAs) were performed. To examine cross-sectionally the association between anticholinergic burden and verbal memory performance at month 3, Pearson's correlations between total DBI and verbal memory performance were performed. In addition, univariate ANOVA was performed with groups as the independent variable, verbal memory performance as the dependent variable, and

sex and age as covariates. We also re-ran the same ANOVA model in patients while controlling for antipsychotic dosage. For significant interactions, contrast analyses were performed. In addition, a potential interaction between symptom severity and anticholinergic burden might exist; we, therefore, performed a stepwise regression using symptoms (SAPS and SANS) and anticholinergic burden (DBI) while covarying for sex and age to assess whether and by how much these predictors can explain the variability in verbal memory performance at month 3. As DBI is closely linked to medication and, therefore, symptoms, a single regression with all predictors and covariates might decrease the effect of DBI, hence the purpose of a step-by-step construction of our regression model. A Generalized Estimating Equation (GEE) model was used with assessment (months 3 and 12) as predictors and group as outcomes to examine this association longitudinally in a subset of participants.[37] Such a model has several advantages, including that no distributional assumption needs to be respected, supports non-normal and nested values, and does not require a balanced set (dealing with missing values).[37] The model was built with an independent working correlation matrix. In addition, sex and age were added as covariates. We re-ran the GEE model while controlling for antipsychotic dosage in patients and examined post hoc pairwise contrasts for significant interactions. The CPZ-eq variable was log-transformed (ln) due to its positive skewness. All statistical analyses were performed using SPSS Inc. (version 27, released in 2020).

2.3. RESULTS

2.3.1. DEMOGRAPHIC/CLINICAL

The sociodemographic and clinical characteristics of participants in month 3 are displayed in Table 1, whereas Table 2 presents data in month 12.

2.3.2. CROSS-SECTIONAL ASSOCIATION OF ANTICHOLINERGIC BURDEN

Pearson's correlations at month 3 revealed significant negative correlations between verbal memory and CPZ-eq (r=−0.174, $P<0.01$), as well as verbal memory and total DBI (r=−0.143, $P<0.05$). Pearson's correlations at month 3 revealed positive and significant correlations between CPZ-eq and total DBI (r=0.386, $P<0.01$). A correlation at baseline between verbal memory performance and DBI was calculated. The observed negative associations were for total DBI (r=−0.146, P=0.010) and antipsychotic DBI (r=−0.141, P=0.013), indicating a significant effect of antipsychotics on the observed anticholinergic effects. Univariate ANOVA revealed a cross-sectional association between anticholinergic burden and verbal memory performance between groups, $F(2,430)=52.33$, $P<0.001$ (Figure 1). Pairwise between-group comparisons revealed poorer verbal memory performance in patients with low DBI relative to controls at month 3 (Δ=3.11, 95% *CI*, 2.46 to 3.76, $P<0.001$). Pairwise between-group comparisons revealed poorer verbal memory performance in patients with high DBI compared to patients with low DBI at month 3 ($\Delta = 0.79$, 95% CI, 0.18 to 1.56, $P<0.05$). As an additional analysis, using the same ANOVA model, the results indicated that after controlling for antipsychotic dosage in patients only, this effect was insignificant, $F(1,260)=1.55$, P=0.214. Regarding a possible interaction between symptoms and anticholinergic burden, our results suggest that for every 1-unit increase in SAPS, verbal memory performance will decrease by 0.03

TABLE 1. Clinical and sociodemographic characteristics of participants at month 3

	FEP (*n*=311)		Controls (*n*=128)		FEP with longitudinal data (*n*=107)		FEP without longitudinal data (*n*=221)		FEP low DBI (*n*=241)		FEP high DBI (*n*=70)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	23.50	4.21	24.68	3.87	24.16	4.06	24.01	4.58	23.68	4.19	22.85	4.25
Male (*n*, %)	219[a]	66.77	85	66.40	73	68.22	146[a]	66.06	165	68.22	48	68.57
Education (years)[b**]	11.81	2.43	14.17	2.18	12.50	2.43	12.32	2.52	11.98	2.33	11.24	2.71
IQ (years)[c**]	95.93	15.54	108.56	13.29	99.57	15.06	95.69	15.28	96.59	15.47	93.66	15.65
Age at onset (years)	21.98	4.85	—	—	22.36	5.13	22.30	05.04	21.99	05.01	21.96	4.29
DUP (weeks)	53.79	107.74	—	—	59.72	127.00	57.01	119.25	58.87	113.51	36.33	83.37
DUI (weeks)[d*]	311.48	290.44	—	—	353.80	315.87	330.33	307.66	308.95	284.49	320.11	312.01
SAPS	13.23	13.96	—	—	15.30	15.42	14.65	14.87	13.66	14.14	11.72	13.30
SANS	21.84	13.97	—	—	21.96	13.98	21.40	13.68	21.16	14.06	24.25	13.46
SOFAS	44.20	17.77	—	—	42.17	16.18	42.67	16.18	45.07	17.74	41.13	17.62
Adherence (%)[e*]	80.42	33.45	—	—	81.36	34.00	80.30	30.09	75.90	36.72	95.91	6.39
CPZ-eq (mg)[f**]	378.51	359.69	—	—	356.17	301.85	366.35	322.46	340.99	339.80	483.02	394.09
Total DBI	0.72	0.52	—	—	0.65	0.53	0.68	0.54	0.50	0.32	1.48	0.37
Antipsychotic DBI	0.55	0.38	—	—	0.52	0.41	0.53	0.40	0.46	0.33	0.87	0.39
Other medications DBI	0.16	0.33	—	—	0.14	0.31	0.15	0.31	0.04	0.15	0.60	0.38
Verbal Memory WMS	7.52	3.14	10.79	3.06	7.86	3.20	7.79	3.22	7.70	3.15	6.92	3.03

Note. Abbreviations: CPZ-eq = Chlorpromazine Equivalent Doses, DBI = Drug Burden Index (score from the Anticholinergic Burden Calculator), DUI = Duration of Untreated Illness, DUP = Duration of Untreated Psychosis, IQ = Intelligence Quotient, SANS = Scale for the Assessment of Negative Symptoms (sum of toal scores for each subscale excluding attention), SAPS = Scale for the Assessment of Positive Symptoms (sum of total scores for each subscale), SD = Standard Deviation, SOFAS = Social and Occupational Functioning Assessment Scale (sum of total scores), WMS = Wechsler Memory Scale Third and Fourth Edition (average score between the scaled score Logical Memory I subtest and the scaled score Logical Memory II subtest (*M*=10; *SD*=3); [a]Missing sex information *n*=3, [b]T-tests revealed significant differences regarding years of education between patients (*M*=11.81, *SD*=2.43) and controls (*M*=14.17, *SD*=2.18), with patients having fewer years of education at month 3, $t(350)=8.90$, $P<0.001$, [c]T-tests revealed significant differences regarding IQ between patients (*M*=95.93, *SD*=15.54) and controls (*M*=108.56, *SD*=13.29), with patients having a lower IQ at month 3, $t(453)=8.18$, $P<0.001$, [d] T-tests reported differences regarding DUI between patients who remained in the study (*M*=362.17, *SD*=297.87, *n*=104) compared to patients who did not (*M*=286.28, *SD*=283.57, *N*=202), where patients with follow-up data had longer DUI, $t(304)=2.17$, $P<0.05$, [e]One-way ANOVA revealed differences between patient groups, where patients with high DBI had higher adherence ($F(1,60)=4.07$, $P<0.05$) compared to patients with low DBI at month 3, [f]One-way ANOVA revealed differences between patient groups, where patients with high DBI had higher antipsychotic dosage ($F(1,263)=8.25$, $P<0.05$) compared to patients with low DBI at month 3; $^{*}P<0.05$, $^{**}P<0.00$

TABLE 2. Clinical and sociodemographic characteristics of participants at month 12

	FEP with longitudinal data (*n*=107)		Controls (*n*=46)		FEP low DBI (*n*=48[a])		FEP high DBI (*n*=16[a])	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	24.71	4.05	26.42	4.40	24.98	4.03	23.77	4.04
Male (*n*, %)	73	68.22	30	65.00	16[b]	33.33[b]	8[c]	50.00[c]
Education (years)	11.92	2.83	14.11	1.86	12.30	2.64	10.73	3.15
SAPS	5.06	7.29	—	—	4.26	5.93	8.14	11.20
SANS	14.21	16.02	—	—	14.33	17.01	13.71	12.52
SOFAS	62.32	16.41	—	—	62.86	16.41	60.38	16.45
Adherence (%)	82.01	36.08	—	—	77.44	41.22	94.38	8.95
CPZ-eq (mg)	285.04	241.71	—	—	282.20	247.63	293.30	233.85
Total DBI	0.75	0.73	—	—	0.61	0.62	1.15	0.86
Antipsychotic DBI	0.52	0.39	—	—	0.46	0.37	0.70	0.38
Other medications DBI	0.23	0.49	—	—	0.15	0.41	0.45	0.63
Verbal Memory WMS	9.07	3.41	11.89	2.68	9.17	3.32	8.66	3.78

Note. Abbreviations: CPZ-eq = Chlorpromazine Equivalent Doses, DBI = Drug Burden Index (score from the Anticholinergic Burden Calculator), DUI = Duration of Untreated Illness, DUP = Duration of Untreated Psychosis, SANS = Scale for the Assessment of Negative Symptoms (sum of total scores for each subscale excluding attention), SAPS = Scale for the Assessment of Positive Symptoms (sum of total scores for each subscale), SD = Standard Deviation, SOFAS = Social and Occupational Functioning Assessment Scale (sum of total scores), WMS = Wechsler Memory Scale Third and Fourth Edition (average score between the scaled score Logical Memory I subtest and the scaled score Logical Memory II subtest (*M*=10; *SD*=3); [a]Missing medication information *n*=60, [b]Missing sex information *n*=24, [c]Missing sex information *n*=2.

(β=−0.03, P< 0.05), and for every 1-unit increase in SANS, verbal memory performance will decrease by 0.05 (β=−0.05, P< 0.001; R^2=0.11, F(4,314)=9.24, P< 0.001). Regarding anticholinergic burden, our results suggest that for every 1-unit increase in DBI, verbal memory performance will decrease by 0.75 (β=−0.75, P< 0.05; R^2=0.07, F(3,306)=7.36, P< 0.001).

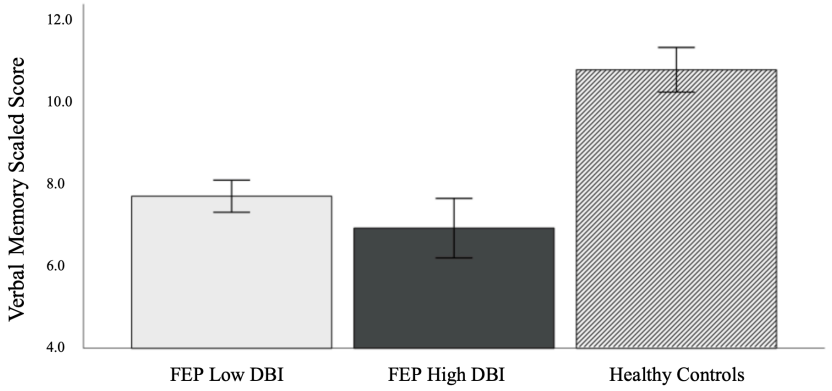

FIGURE 1. Cross-sectional association of anticholinergic burden on verbal memory performance between groups at month 3, P < 0.001.

2.3.3. LONGITUDINAL EFFECTS OF ANTICHOLINERGIC BURDEN

GEE analysis revealed a significant main effect of group (χ^2=51.26, df=2, P< 0.001), a significant main effect of time (χ^2=25.70, df=1, P< 0.001) and a marginally significant interaction between group and time (χ^2=5.92, df=2, P=0.052; Figure 2). Pairwise comparisons between groups revealed no significant mean difference between patients with high DBI and low DBI at month 12 (Δ=1.07, 95% *CI*, −1.07 to 3.22, P=0.322). Pairwise within-group comparisons revealed improved verbal memory performance in month 12 compared to month 3 for controls (Δ=1.04, 95% *CI*, 0.30 to 1.78, P< 0.05), for patients with low DBI (Δ=2.60, 95% *CI*, 1.49 to 3.70, P< 0.001), and patients with high DBI

(*Δ*=2.31, 95% *CI*, 0.37 to 2.26, *P*< 0.05). As an additional analysis, using the same ANOVA model, the results indicated that after controlling for antipsychotic dosage, it remained only significant for time (χ^2=18.06, *df*=1, *P*< 0.001).

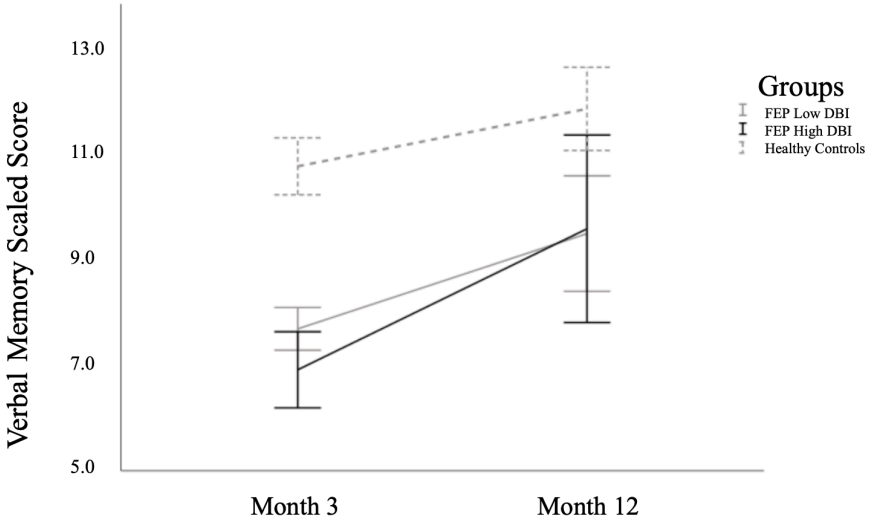

FIGURE 2. Longitudinal effects of anticholinergic burden on verbal memory performance between groups at months 3 and 12, *P* < 0.001.

2.4. DISCUSSION

Our findings suggest that patients with the highest anticholinergic burden group had the poorest verbal memory performance compared with those in the low anticholinergic burden group at month 3. This finding agrees with several cross-sectional studies investigating the association between anticholinergic burden and verbal memory.[5,7,14,17,28,38] However, this association is not maintained after controlling for antipsychotic dosage. Many of our FEP patients took multiple medications daily that could have a significant cumulative anticholinergic burden.[39,40] Approximately 132 of our patients received the same primary antipsychotic at months 3 and 12 with the same route of administration, though with some changes in dosage. However, it is possible that in our sample, at an early stage of the disease, the most used medications are antipsychotics and at higher doses than other medications, which is a limitation, and it remains challenging to dissociate from medication effects on verbal memory. Improvement in symptoms could also explain the increase in cognitive performance over time. Other factors have also been shown to influence verbal memory performance (e.g. age of onset, sex, and severity of negative symptoms). However, these did not differ significantly between our DBI patient groups.[41,44]

Evidence suggests that people with schizophrenia have reduced central cholinergic activity and reduced muscarinic receptor expression;[45,46] Thus, taking multiple medications with anticholinergic burden could saturate muscarinic receptors, especially the M_1 receptor, which are essential for cognitive and verbal learning.[46,48] Moreover, developing tolerance to an anticholinergic medication may occur in patients and increase binding to muscarinic receptors in the brain, which could have contributed to our results. In addition, severely ill patients are more likely to receive higher doses of medication.[49] This detail may also explain why, by adding antipsychotic dosage as a covariate, the initial results disappear.

However, controlling for antipsychotic dosage could also remove important information about the anticholinergic burden since both are calculated from the same dose of medication.[18,35,50] Differences between cross-sectional studies may be due to the use of different measures of anticholinergic burden.[30,51,52] Many studies examined the anticholinergic burden only by using a scale that does not consider the daily dose and does not examine the cumulative burden of all medications patients take. Our more comprehensive calculation of cumulative burden and our consideration of all medications' daily doses could explain the differences observed.

Our results suggest increased verbal memory performance in both controls and patients, which may indicate a practice effect over time. At month 12, no significant difference was observed between high and low anticholinergic burden on verbal memory performance. These results replicate previous longitudinal studies that also failed to find any effect of anticholinergic burden over time, including Ballesteros et al.,[14] who did not detect a significant effect of an anticholinergic burden on verbal memory at a 2-year follow-up, and Tracy et al.,[53] who reported no significant effect of serum anticholinergic levels on verbal memory after 1 week. However, some longitudinal studies have found that tapering high anticholinergic burden medications (e.g. biperiden) positively impacted cognition, with improved verbal memory.[2,3,54,55] As with cross-sectional studies, results from longitudinal studies are inconsistent; several reasons may account for this. Our sample, with an average age of 23.94 years, is younger than some longitudinal studies, such as the study by Tracy et al., 53, with an average age of 43.86 years. A younger sample may have increased central cholinergic activity and muscarinic receptor expression, resisting long-term consequences of anticholinergic burden.[46,56,57] Furthermore, a decrease in the density of receptors in the cholinergic system is more prevalent in severe and chronic schizophrenia than in the early stages of the disease. [58] We also believe that polypharmacy (due to the increased

medication burden with aging and changes in prescribing practices) may be an essential factor to consider in future studies, given the increased use of anticholinergics in recent years.[59,60]

A few limitations in this study can be identified. The sample size was small at month 12, making it challenging to maintain a representative sample in each group of participants over time. In addition, our first neurocognitive assessment took place 3 months after admission to the program and was considered baseline cognitive performance. However, we recognize this as a potential limitation of our study. Studying the effects of medication on cognition remains challenging as it is difficult to discriminate whether the changes are due to the severity of the illness or to the medication itself.[61] However, our studies did not find a significant difference in SAPS/SANS scores between high and low DBI groups. This similarity in illness severity between groups facilitates a clearer assessment of the relationship between anticholinergic burden and cognition.

Another key limitation is the lack of assessment for extrapyramidal symptoms (EPS). EPS, often associated with first-generation and occasionally second-generation antipsychotics, can affect motor control and attention, potentially skewing cognitive results over time.[62] EPS can also affect procedural learning (PL), which may further impact overall cognition.[63] Additionally, while patients with substance dependence (as defined in DSM-IV) were excluded, those with substance abuse were included.[64,65] This could confound results, as substance abuse may worsen EPS through interactions with treatment medications, which might impact cognition and introduce confounding variables in the relationship between anticholinergic burden and cognitive deficits.[62] Similarly, future studies should account for cannabis use, as it can impact cognition and psychosis itself and complicate the interpretation of the association between anticholinergic burden and

cognitive impairments.[66]

Furthermore, despite the many advantages of using the online calculator, it still has some limitations compared to other risk scales. For example, some medications, such as lurasidone, were not included in the calculator.[19] Our results may, therefore, differ if another anticholinergic burden scale was used. In addition, medications that can be taken as needed have yet to be included in the DBI and CPZ-eq calculations. The classification of the DBI at both assessments can also be considered a limitation. For example, a hypothetical patient could have a DBI of 0.98 (low DBI) at month 3 and a DBI of 1.02 (high DBI) at month 12 due to an increase in the medication dosage, leading to a somewhat arbitrary group definition. The study of medication dosage also has several limitations due to the variability of each individual and the pharmacological profiles of antipsychotic medications, resulting in the problematic calibration of dose equivalents. We also recognize that adopting a binary classification of DBI raises some limits to our study. We relied on the classification (medium/high) from the Anticholinergic Burden Calculator and the validated study by Hilmer et al. 18 We also performed statistical analyses with 3 groups of DBI, that is, low (0 to 1), medium (1 to 2), and high (>2) risk, but we did not have a sufficient sample in the latter group (n=8). However, adopting a categorical approach as opposed to a continuous measure of anticholinergic also has statistical advantages, where the distribution of values is manageable, and we do not assume linearity between our variables. In addition, as our patients were between 18 and 35 years old and in the early stages of the disease, we expect that there will be more medium-risk patients than high-risk, as many of them have just started treatment (max. 30 days), often at minimal therapeutic doses. Medications taken as needed (PRN) were not included in the calculations. Daily medication regimens were included in DBI calculations, but PRN anticholinergics were not. As a result, we may have missed temporary spikes in

anticholinergic burden from these as-needed medications. This could be a limitation, potentially leading to an underestimation of the true anticholinergic burden.

In summary, our cross-sectional results suggest that FEP patients in the highest anticholinergic burden group had the poorest verbal memory performance compared to those in the low anticholinergic burden group and healthy controls. Longitudinal findings indicate that although verbal memory performance in all groups improved over time, all FEP patient groups had poorer verbal memory performance than controls. However, the addition of antipsychotic dosage as a covariate removed these effects. Despite the effectiveness of antipsychotics in relieving psychotic symptoms, it appears that their anticholinergic properties, as well as those of other medications taken by FEP patients, may have a detrimental effect on cognitive performance. Studies with a more extended follow-up period that consider the occupancy of dopaminergic receptors and that consider adherence in the calculation of the DBI may be helpful to understand better how medication in FEP affects cognition. Given that cognitive deficits appear in the early stages of psychosis, our results highlight the need to consider the anticholinergic burden when prescribing medications.

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PREFACE TO CHAPTER 3

The observed association between a high anticholinergic burden and poorer verbal memory performance in high burden patients compared to low-burden patients and healthy controls highlights the need to investigate the effect of anticholinergic exposure on the hippocampus, as it is a key brain region that plays a critical role in memory processing, including verbal memory performance. Understanding the impact of anticholinergic medication on the hippocampus is important because this brain region is particularly vulnerable to the effects of medications. The hippocampus being one of the most important adult neurogenesis sites, is highly malleable, allowing it to adapt to changes in its environment. However, chronic exposure to certain medications, as they cross the blood-brain barrier, could disrupt this neuroplasticity, leading to alterations in its structure.

Understanding such complex mechanisms is essential to reduce the potential adverse effects of medications on the structure and function of the hippocampus, as it is also involved in cognition and memory, which are impaired in the disease. Researchers can develop strategies to minimize those structural changes and optimize pharmacotherapy by clarifying the underlying mechanisms and how medication can impact the hippocampus. Examining the various subfields within the hippocampus is crucial because they have different functions. Investigating individual subfields of the hippocampus can provide insight into which subfields may be more vulnerable to the effects of anticholinergic drugs than others, particularly in the early stages of the disease. Understanding subfields' different levels of vulnerability to anticholinergic exposure may provide a better comprehension of the specific mechanisms that underlie the verbal memory deficits observed in individuals exposed to these medications.

CHAPTER 3

STUDY 2: ASSOCIATION OF ANTICHOLINERGIC BURDEN WITH HIPPOCAMPAL SUBFIELDS VOLUME IN FIRST-EPISODE PSYCHOSIS[2]

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[2] Belkacem, A., Lavigne, K., Raucher-Chéné, D., Makowski, C., Chakravarty, M., Joober, R., Malla, A., Shah, J. & Lepage, M. (2024). Association of Anticholinergic Burden with Hippocampal Subfields Volume in First-episode Psychosis. Psychiatry Research: Neuroimaging, submitted and under review.

ABSTRACT

Polypharmacy is relatively common in early psychosis, but little attention has been paid to the anticholinergic burden of medication use (the cumulative effect of medications that block the cholinergic system). Evidence suggests that anticholinergic burden is associated with cognitive deficits and that hippocampal dysfunction may be involved in those impairments. We aimed to examine this association in a cohort of patients with first-episode psychosis. We hypothesized that patients with the highest burden would experience a more significant reduction in hippocampal volume compared to those with low burden and healthy controls, both at baseline (3 months) and at month 12. Patients (n=82; low burden [n=64] and high burden [n=18], defined by a Drug Burden Index cut-off of 1) followed at the PEPP-Montreal clinic, and controls (n=55) completed a 3T MRI at both timepoints. After controlling for antipsychotic dosage at both timepoints, results at baseline and over time revealed a greater reduction in left fimbria volumes in high burden patients compared to low-burden patients and controls. Overall, the associations observed between high anticholinergic burden and hippocampal volume provide further evidence for considering this dimension when prescribing medication in early psychosis.

3.1. INTRODUCTION

Comorbidities and persistent symptoms in the early stages of psychosis are common and can lead to increased polypharmacy. Among these medications, anticholinergics are often prescribed to reduce antipsychotic side effects, despite themselves having an anticholinergic burden (Bergman and Soares-Weiser, 2018). However, evidence suggests that their strong and cumulative effect (i.e., anticholinergic burden), along with other medications that block the cholinergic system (e.g., antidepressants), are associated with cognitive deficits in psychosis and schizophrenia (Ang et al., 2017; Ballesteros et al., 2021; Belkacem et al., 2023; Eum et al., 2017; Joshi et al., 2021; Ogino et al., 2014; Perlick et al., 1986).

While treatment of psychosis typically involves antipsychotic monotherapy as the gold standard approach, challenges such as unremitted and persistent positive symptoms may warrant the use of antipsychotic polypharmacy. Although the exact prevalence rates of polypharmacy may vary depending on the population studied, evidence suggests that it is relatively common in people with FEP. In their systematic review, Gallego et al. (2012) reported a prevalence rate of 19.6% of outpatients with schizophrenia receiving antipsychotic polypharmacy. Tiihonen et al. (2019) found a higher rate of 57.5% in a Finnish clinical population. In a Turkish study by Yazici et al. (2017), more than 70% of patients received multiple antipsychotics simultaneously. There may also be a tendency toward polypharmacy in psychosis, as clinicians seek to quickly stabilize the patient's symptoms. Other reasons may include a complex symptom presentation, a trial-and-error approach as patients are still in the early stages of their treatment, comorbidities such as depression, anxiety, and substance use disorders, and management of antipsychotic side effects by adding adjunctive medications. However, it is essential to note that the current

guidelines discourage polypharmacy. In addition, compared to continued antipsychotic monotherapy, antipsychotic augmentation may have some benefits in reducing symptoms, but there is still insufficient evidence to support this (Galling et al., 2017).

Independent of the effect of anticholinergics, hippocampal dysfunction is well-established in schizophrenia and can be considered a biomarker of psychosis (Adriano et al., 2012; Chan et al., 2011; Harrison, 2004; Heckers, 2001; Heckers and Konradi, 2010). Structural abnormalities in the hippocampus are also believed to be involved in cognitive impairments (Antoniades et al., 2018; Heckers, 2019; Voineskos et al., 2015) and may be sensitive to pharmacotherapy. For instance, Li et al. (2018) observed that following antipsychotic treatment, greater hippocampal volume reduction was more prominent in regions with a high density of dopamine D_2 receptors (e.g., dentate gyrus). They also observed an association between antipsychotic dosage and the degree of volume reduction, suggesting that patients with higher antipsychotic dosage had a more significant volume reduction (Li et al., 2018). While several studies have examined the relationship between hippocampal volume and antipsychotic dosage, only a few have looked into the relationship between hippocampal volume and the anticholinergic burden of medication (Li et al. (2018), Bodnar et al. (2016) and Navari et al. (2009). Kilimann et al. (2021) recently reported that as the anticholinergic burden increased, the hippocampal volume decreased in a population-based cohort of non-demented participants (N=3,087) aged 21-80. However, the effects of anticholinergic burden on brain volume can differ with pre-existing disorders, such as schizophrenia.

Therefore, examining anticholinergic burden in a cohort of young individuals with a first-episode of psychosis (FEP) is warranted, as cognitive deficits and reduced hippocampal volume are core features of the disease. Emerging data from Ballesteros et al.

(2020) and our recent study (Belkacem et al., 2023) suggest that anticholinergic burden should be considered when prescribing medications in early psychosis, as a high burden, may be associated with more severe deficits in cognitive function and, in particular, verbal memory. Individual hippocampal subfields are known to play different roles in memory, a core cognitive domain impaired in psychosis, and can also help pinpoint more nuanced volumetric changes over time that could be important in understanding the pathophysiology of psychosis. We explored this association while covarying for sex, age, and intracranial volume (ICV). We used cross-sectional and longitudinal data (3 and 12 months after clinical admission) to address our aims. We hypothesized that FEP patients with higher anticholinergic burden would show more significant hippocampal volume reductions compared to patients with low anticholinergic burden and healthy controls at month 3, as well as additional decreases over one year.

3.2. METHODS

3.2.1. PARTICIPANTS

FEP patients (n=82) were recruited from the Prevention and Early Intervention Program for Psychosis (PEPP-Montreal) clinic. Entry criteria include age 18-35 years, no antipsychotic treatment (max. 30 days), affective or non-affective psychotic disorder (DSM-IV), stable physical health, and ability to provide consent in English or French. Exclusion criteria included poor performance on neuropsychological tests (IQ<70), medical history of a neurological disorder (including head injury with loss of consciousness), and a family history of neurological disorders. For comparison purposes, control subjects (n=55) were recruited. Healthy, non-clinical participants were engaged through a centralized network of online postings (e.g., Kijiji). Recruitment was restricted to

in the same catchment area to facilitate matching controls to patients. Controls were also matched to patients on demographic variables (e.g., sex, age, handedness and parental socio-economic status) at recruitment. Entry criteria include age 18-35 years, stable physical health, not taking psychotropic medications, and being able to consent in English or French. Exclusion criteria include poor performance on neuropsychological tests (IQ<70), a history of Axis I disorders (DSM-IV) according to the non-patient edition of the Structured Clinical Interview for Axis I disorders of the DSM-IV (First and Gibbon, 2004), first-order family history of psychotic disorder or hereditary neurological diseases, diagnosis of substance abuse within the past 30 days, and medical history of a neurological disorder (including head injury with loss of consciousness). Medication data was not collected for controls, as we did not include those taking neuroleptic medications. The Douglas Research Ethics Board approved this study, and all participants provided informed consent (written and verbal).

3.2.2. SETTING

After admission to the PEPP-Montreal clinic (program between 2015 and 2022), participants underwent a systematic assessment protocol with several time points over two years after their entry (see Jordan et al. (2014) for more information). For this study, we only considered data collected in month 3 (baseline; M=2.02, SD=0.91; FEP n=82; controls n=55) and month 12 (M=12.91, SD=1.40; FEP n=44; controls n=46) following PEPP-Montreal clinic admission and once patients were clinically stabilized. Our sample size decreased over time (dropout rate ≈ 34.31%), significantly beyond the month 12 timepoint, due to various factors (e.g., subject dropout).

3.2.3. Assessments

FEP patients were administered a Structured Clinical Diagnosis for the DSM-IV patient version (First and Gibbon, 2004). In months 3 and 12, structured and semi-structured instruments were used, including the Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1984), the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1989), Duration of Untreated Psychosis (DUP), Duration of Untreated Illness (DUI) using the Circumstances of Onset and Relapse Schedule (CORS), and Social and Occupational Functioning Assessment Scale (SOFAS; Rybarczyk, 2018). Medication adherence was assessed with a validated method from Cassidy et al. (2010) using a weekly diary and sources of information (e.g., families and case managers) at both timepoints.

3.2.4. Anticholinergic Burden

After carefully examining the available tools to assess the anticholinergic burden, we opted for the Drug Burden Index (DBI; Hilmer et al., 2007), as recommended by the systematic review of anticholinergic scales by Villalba-Moreno et al. (2016). We concluded that the DBI was the best overall scale, as it considers the prescribed daily dose, allowing us to quantify the anticholinergic effect. Furthermore, this index allows us to add and combine daily doses of multiple medications and provide a cumulative burden (Hilmer, 2018; Hilmer et al., 2007). In addition, the DBI is the only scale that measures sedative medications, an important and unique feature relative to the other anticholinergic burden scales (Villalba-Moreno et al., 2016). The DBI was validated by Hilmer et al. (2007) in a study with 3,075 participants. Their study suggested an association between anticholinergic burden (measured with DBI) and cognitive impairments. Notably, most negative

associations were found for DBI compared to other scales (Hilmer et al., 2007). Overall, this index is a useful evidence-based tool for assessing the effect of exposure to anticholinergic and sedative medications. The anticholinergic burden of medications was calculated at months 3 and 12 using the DBI from a Web Portal Software Anticholinergic Burden Calculator© (https://www.anticholinergicscales.es; Villalba-Moreno et al., 2017). Patients were categorized into two groups according to the DBI score classification, i.e., a DBI score of less than 1 indicating no to low anticholinergic burden and a DBI score of more than 1 indicating moderate to high anticholinergic burden. The DBI scale from the calculator had only two classifications (labelled as medium/high; Villalba-Moreno et al., 2017). We also calculated the DBI score for three types of DBI: total DBI, antipsychotic DBI and other medications DBI (see supplemental Table A for a representation of the five patients who showed the highest DBI scores).

3.2.5. Antipsychotic Dosage

The dosage of antipsychotics was measured using Chlorpromazine Equivalent Doses (CPZ-eq). CPZ-eq doses were calculated with the Chlorpromazine Equivalent Doses for the Newer Atypical Antipsychotics, with the Antipsychotic Comparison Chart by Woods (2003) retrieved from https://www.rxfiles.ca and validated by psychiatrists at the Douglas Research Centre. The CPZ-eq was calculated for all antipsychotics taken, providing a cumulative score. For long-acting injectable antipsychotics, the daily dose was calculated with the total prescribed dosage divided by the number of required days. For example, if an injection was given every four weeks, the calculation was *X* mg/ 28 days.

3.2.6. NEUROIMAGING ASSESSMENT

Magnetic Resonance Imaging (MRI) scans were performed on a Siemens Magnetom Trio 3T scanner at the Douglas Mental Health Institute's Brain Imaging Centre. The anatomical scan was performed with a T1-weighted sequence (TR=2.300ms, TE=2.98ms, FOV=256mm, voxel size=1mm^3, flip angle=9 degrees) and T2-weighted sequence information (TR=2.500 ms, TE=198 ms, FOV=206 mm, voxel size=0.64mm^3). An evaluator and a radiology technician accompanied the participants at each timepoint. The hippocampal subfields in the right (R) and left (L) hemispheres (CA1, CA2/CA3, CA4/dentate gyrus, subiculum, stratum, hippocampus) and surrounding white matter (fimbria, fornix, mammillary body, and alveus) were segmented using the Multiple Automatically Generated Templates (MAGeT) algorithms (Pipitone et al., 2014). Automated neuroanatomical identification of brain regions is often based on one or a few manually segmented templates on a small number of individuals. It tends to increase the chances of inaccuracies due to the wide variability in the neuroanatomy of the brain. Although MAGeT operates similarly, its algorithm limits the estimation errors using a multi-atlas design (Pipitone et al., 2014). Twenty-one representative subjects were selected, and their MRI scans were registered to each of the five atlases, leading to 105 template models used for the study's entire sample (Amaral et al., 2018; Winterburn et al., 2013). Final segmentation was decided according to the anatomical label, which was the most common for a specific location.

3.2.7. STATISTICAL ANALYSES

To examine differences in clinical and demographic characteristics between groups, t-tests

and one-way ANOVAs were performed. T-tests were performed to determine whether patients with longitudinal data differed. Pearson's correlations were performed to examine cross-sectionally the association between DBI and hippocampal volume (subfields and surrounding white matter) between groups (low anticholinergic burden, high anticholinergic burden and controls). In addition, multivariate ANOVA was performed with groups as the independent variable and hippocampal volume as a dependent variable, with sex, age and ICV as covariates. We also re-ran the same model between patients while controlling for CPZ-eq. For significant interactions, contrast analyses were performed.

To examine this association longitudinally, a Generalized Estimating Equation (GEE) model was used with timepoints (months 3 and 12) as a predictor and group (low anticholinergic burden, high anticholinergic burden and controls) as the outcome. This model has several advantages, including supporting non-normal and nested data, not requiring a balanced set, and helping us deal with missing values, which is common in longitudinal studies (Crowder, 2010). Our model was built with an independent working correlation matrix. In addition, sex, age, and ICV were added as covariates. We re-ran the same model controlling for CPZ-eq for patient groups (low and high anticholinergic burden) and examined post hoc pairwise contrasts for significant interactions and a correction for multiple comparisons using the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995). The CPZ-eq variable was log-transformed (ln) due to its positive skewness. All statistical analyses were performed using SPSS Inc. (version 27, released in 2020).

3.3. RESULTS

3.3.1. DEMOGRAPHIC/CLINICAL

The sociodemographic and clinical characteristics of participants in month 3 are displayed in Table 3, whereas Table 4 presents data for month 12. In addition, the significant difference between participants with and without longitudinal data is reported in Table 1.

3.3.2. Cross-Sectional Association of Anticholinergic Burden

Pearson's correlations at month 3 revealed a significant correlation between total DBI and CPZ-eq (r=0.239, P<0.05). Pearson's correlations at month 3 revealed a significant negative correlation between other medication DBI and L CA4/dentate gyrus (r=-0.236, P<0.05), R fimbria (r=-0.244, P<0.05), L fimbria (r=-0.313, P<0.01), L hippocampus (r=-0.245, P<0.05) and total hippocampus (r=-0.235, P<0.05); between CPZ-eq and L subiculum (r=-0.279, P<0.05), L stratum (r=-0.240, P<0.05) and R alveus (r=-0.247, P<0.05).

Univariate ANOVA revealed a cross-sectional association between DBI and hippocampal volume between groups, with high DBI patients showing a greater reduction in volumes compared to low DBI patients and controls for R CA4/dentate gyrus (F(2,126)=6.72, P<0.05), L CA4/dentate gyrus (F(2,126)=4.48, P<0.05), R stratum (F(2,126)=3.49, P<0.05), L stratum (F(2,126)=6.05, P<0.05), L fimbria (F(2,126)=4.62, P<0.05), L CA1 (F(2,126)=3.94, P<0.05), L CA2CA3 (F(2,126)=3.38, P<0.05), R hippocampus (F(2,126)=3.32, P<0.05), L hippocampus (F(2,126)=4.40, P<0.05) and total hippocampus (F(2,126)=4.22, P<0.05). As an additional analysis, using the same model, the results indicated that after controlling for CPZ-eq as a covariate, this effect remained significant for L fimbria (F(1,64)=6.74, P<0.05; Figure 3) and at a trend level for L CA4/dentate gyrus (F(1,64)=3.67, P=0.06). Pairwise between-group comparisons at month 3 revealed a greater reduction in CA4/dentate gyrus bilaterally in high DBI patients

compared to controls (Δ=63.36, 95% *CI*: 11.21 to 115.50, P<0.05 and (Δ=67.22 mm³, 95% *CI*: 4.39 to 130.04, P<0.05, respectively); in L fimbria in high DBI patients compared to low DBI patients (Δ=11.48 mm³, 95% *CI*: 0.13 to 22.82, P<0.05) and in L stratum in high DBI patients compared to controls (Δ=64.49, 95% *CI*: 9.29 to 119.69, P<0.05).

TABLE 3. Clinical and sociodemographic characteristics of participants at month 3

	FEP (*n*=82)		Controls (*n*=55)		FEP with longitudinal data (*n*=44)		FEP without longitudinal data (*n*=42)		FEP low DBI (*n*=64)		FEP high DBI (*n*=18)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	24.77	4.26	24.98	4.50	23.80	4.03	24.86	4.69	25.35	4.30	23.70	3.89
Male (*n*, %)	51	61.45	36	65.45	26	63.41	25	59.52	37	61.67	11	61.11
Education (years)[a**, d*]	12.29	2.35	13.78	1.62	12.34	2.55	12.25	2.18	12.51	2.33	11.44	2.23
IQ (years)[b**, e*]	101.01	13.30	109.09	10.71	101.56	14.03	100.50	12.73	101.39	13.22	101.06	13.75
Age at onset (years)	22.85	6.45	—	—	23.80	4.03	21.91	8.13	23.29	4.30	23.03	3.97
DUP (weeks)	47.60	150.30	—	—	37.08	88.19	58.13	194.27	40.35	98.35	21.11	30.06
DUI (weeks)[c*]	407.01	355.46	—	—	492.19	316.46	321.83	375.29	384.38	363.81	482.67	308.29
SAPS	12.14	13.35	—	—	12.71	12.52	11.60	14.23	12.80	14.36	9.39	10.52
SANS	14.93	10.88	—	—	16.00	12.69	13.91	8.86	14.84	11.73	15.50	9.50
SOFAS	48.63	24.82	—	—	43.73	28.37	53.30	20.13	49.70	24.18	43.61	28.09
Adherence (%)[g*]	82.01	31.65	—	—	76.38	39.18	87.51	21.11	78.64	34.10	96.43	6.12
CPZ-eq (mg)	220.56	160.54	—	—	230.03	155.64	212.65	165.96	202.50	148.90	280.38	187.47
Total DBI[h**]	0.60	0.51	—	—	0.62	0.53	0.59	0.50	0.38	0.30	1.36	0.36
Antipsychotic DBI[i**]	0.40	0.39	—	—	0.39	0.42	0.40	0.35	0.30	0.30	0.73	0.44
Other medication DBI[j**]	0.21	0.37	—	—	0.22	0.34	0.20	0.39	0.08	0.21	0.66	0.46
Total Hipp volume (mm^3)[f*]	6693.49	710.60	6957.53	877.49	6862.84	706.99	6535.96	684.85	6777.13	722.91	6465.23	646.63
ICV (mm^3)	0.76	0.07	0.76	0.08	0.76	0.07	0.76	0.08	0.77	0.07	0.76	0.07

Note. Abbreviations: CPZ-eq = Chlorpromazine Equivalent Doses, DBI = Drug Burden Index (score from the Anticholinergic Burden Calculator), DUI = Duration of Untreated Illness, DUP = Duration of Untreated Psychosis, Hipp = Hippocampal, ICV = Intracranial volume, IQ = Intelligence Quotient, SANS = Scale for the Assessment of Negative Symptoms (sum of total scores for each subscale excluding attention), SAPS = Scale for the Assessment of Positive Symptoms (sum of total scores for each subscale), SD = Standard Deviation, SOFAS = Social and Occupational Functioning Assessment Scale (sum of total scores); [a]T-tests revealed significant differences regarding years of education between patients (*M*=12.29, *SD*=2.35) and controls (*M*=13.78, *SD*=1.62), with patients having fewer years of education, $t(138)=4.11$, $p<0.001$, [b]T-tests revealed significant differences regarding IQ between patients (*M*=101.01, *SD*=13.30) and controls (*M*=109.09, *SD*=10.71), with patients having a lower IQ, $t(138)=3.78$, $p<0.001$, [c]T-tests reported differences regarding DUI between patients who remained in the study (*M*=492.19, *SD*=316.46, *n*=41) compared to patients who did not (*M*=321.83, *SD*=375.29, *n*=41), where patients with follow-up data had longer DUI, $t(80)=2.22$, $p<0.05$, [d]T-tests reported differences regarding years of education between patients who remained in the study (*M*=13.20, *SD*=2.27, *n*=87) compared to patients who did not (*M*=12.36, *SD*=2.03, *n*=53), where patients with follow-up data had more years of education, $t(138)=2.20$, $p<0.05$, [e]T-tests reported differences regarding IQ between patients who remained in the study (*M*=105.86, *SD*=12.84, *n*=87) compared to patients who did not (*M*=101.43, *SD*=12.71, *n*=53), where patients with follow-up data had higher IQ, $t(138)=1.99$, $p<0.05$, [f]T-tests reported differences regarding total hippocampal volume between patients who remained in the study (*M*=6905.99, *SD*=806.88, *n*=86) compared to patients who did not (*M*=6614.74, *SD*=727.20, *n*=51), where patients with follow-up data had greater total hippocampal volume, $t(135)=2.12$, $P<0.05$, [g]One-way ANOVA reported differences regarding adherence between patients with low anticholinergic burden (*M*=79.17,

SD=33.65, *n*=60) compared to patients with high anticholinergic burden (*M*=96.43, *SD*=6.12, *n*=16), where patients with high anticholinergic burden had greater adherence, $F(1, 74)=4.13$, $p<0.05$,[h]One-way ANOVA reported differences regarding total DBI between patients with low anticholinergic burden (*M*=0.39, *SD*=0.30, *n*=64) compared to patients with high anticholinergic burden (*M*=1.36, *SD*=0.36, *n*=18), where patients with high anticholinergic burden had higher total DBI, $F(1, 80)=133.35$, $p<0.001$, [i]One-way ANOVA reported differences regarding antipsychotic DBI between patients with low anticholinergic burden (*M*=0.31, *SD*=0.30, *n*=64) compared to patients with high anticholinergic burden (*M*=0.73, *SD*=0.44, *n*=18), where patients with high anticholinergic burden had higher antipsychotic DBI, $F(1, 80)=21.09$, $p<0.001$, [j]One-way ANOVA reported differences regarding other medication DBI between patients with low anticholinergic burden (*M*=0.08, *SD*=0.211, *n*=64) compared to patients with high anticholinergic burden (*M*=0.66, *SD*=0.46, *n*=18), where patients with high anticholinergic burden had higher other medication DBI, $F(1, 80)=58.10$;*$p<0.05$,**$p<0.001$.

TABLE 4. Clinical and sociodemographic characteristics of participants at month 12

	FEP (*n*=44)		Controls (*n*=46)		FEP low DBI (*n*=32)		FEP high DBI (*n*=12)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	25.50	3.80	26.42	4.40	25.78	3.67	24.84	4.12
Male (*n*, %)	25	60.96	30	65.22	17	65.38	8	66.67
Education (years)[a**]	12.46	2.52	14.11	1.67	12.87	2.52	11.75	2.42
SAPS	6.20	9.64	—	—	4.91	9.30	7.08	9.09
SANS	13.43	14.61	—	—	11.78	12.11	17.67	20.75
SOFAS	65.26	18.34	—	—	69.31	15.46	57.67	22.90
Adherence (%)	83.78	33.95	—	—	75.93	41.08	96.43	7.46
CPZ-eq (mg)	233.08	191.42	—	—	185.20	137.87	312.29	250.49
Total DBI[b**]	0.70	0.81	—	—	0.28	0.33	1.82	0.61
Antipsychotic DBI[c**]	0.38	0.40	—	—	0.24	0.31	0.78	0.33
Other medication DBI[d**]	0.32	0.55	—	—	0.05	0.19	1.04	0.54
Total Hipp volume (mm^3)	6831.54	731.32	6951.60	881.74	6974.75	749.72	6546.45	565.30
ICV (mm^3)	0.76	0.07	0.76	0.08	0.76	0.08	0.76	0.04

Note. Abbreviations: CPZ-eq = Chlorpromazine Equivalent Doses, DBI = Drug Burden Index (score from the Anticholinergic Burden Calculator), Hipp = Hippocampal, ICV = Intracranial volume, SANS = Scale for the Assessment of Negative Symptoms (sum of total scores for each subscale excluding attention), SAPS = Scale for the Assessment of Positive Symptoms (sum of total scores for each subscale), SD = Standard Deviation, SOFAS = Social and Occupational Functioning Assessment Scale (sum of total scores);[a]T-tests revealed significant differences regarding years of education between patients (*M*=12.46, *SD*=2.51) and controls (*M*=14.11, *SD*=1.68), with patients having fewer years of education, $t(90)=3.70$, $p<0.001$, [b]One-way ANOVA reported differences regarding total DBI between patients with low anticholinergic burden (*M*=0.28, *SD*=0.33, *n*=32) compared to patients with high anticholinergic burden (*M*=1.82, *SD*=0.61, *n*=12), where patients with high anticholinergic burden had higher total DBI, $F(1, 42)=114.00$, $p<0.001$,[c]One-way ANOVA reported differences regarding antipsychotic DBI between patients with low anticholinergic burden (*M*=0.24, *SD*=0.31, *n*=32) compared to patients with high anticholinergic burden (*M*=0.78, *SD*=0.33, *n*=12), where patients with high anticholinergic burden had higher antipsychotic DBI, $F(1, 42)=25.64$, $p<0.001$,[d]One-way ANOVA reported differences regarding other medication DBI between patients with low anticholinergic burden (*M*=0.05, *SD*=0.19, *n*=32) compared to patients with high anticholinergic burden (*M*=1.04, *SD*=0.54, *n*=12), where patients with high anticholinergic burden had higher other medication DBI, $F(1, 42)=83.35$, *$p<0.05$; **$p<0.001$.

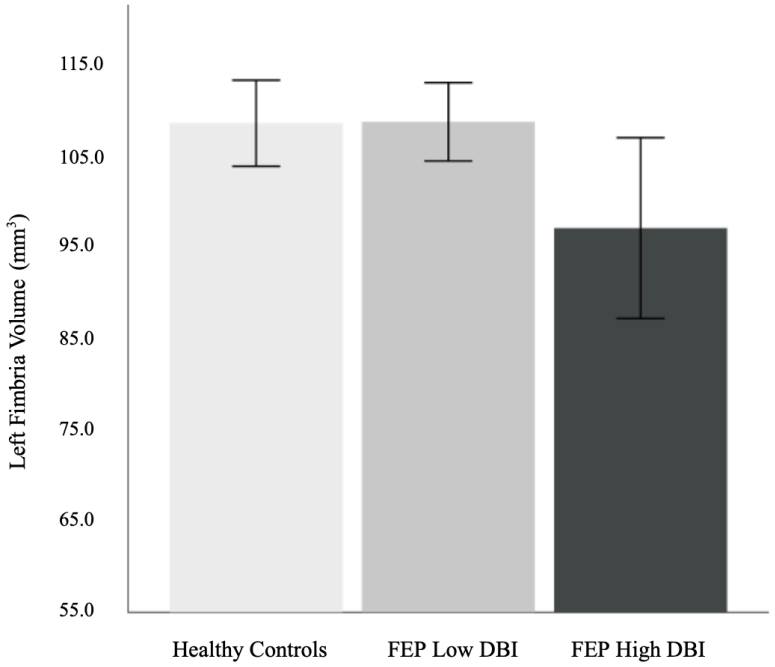

FIGURE 3. Left fimbria volume among groups at month 3, $P<0.05$.

3.3.3. Longitudinal Effects of Anticholinergic Burden

GEE analysis revealed a significant main effect of group for R CA4/dentate gyrus (χ^2=10.84, *df*=2, $P<0.05$); for R stratum (χ^2=9.50, *df*=2, $P<0.05$); for L CA4/dentate gyrus (χ^2=7.20, *df*=2, $P<0.05$); for L stratum (χ^2=13.45, *df*=2, $P<0.05$); for L CA2/CA3 (χ^2=9.44, *df*=2, $P<0.05$); for R hippocampus (χ^2=8.70, *df*=2, $P<0.05$); for L hippocampus (χ^2=10.79, *df*=2, $P<0.05$); for total hippocampus (χ^2=10.40, *df*=2, $P<0.05$). GEE analysis revealed a significant main effect of timepoint for L stratum (χ^2=6.94, *df*=1, $P<0.05$); for L fimbria

(χ^2=4.60, *df*=1, *P*<0.05); for L CA1 (χ^2=6.01, *df*=1, *P*<0.05); and L hippocampus (χ^2=5.54, *df*=1, *P*<0.05). The other main effects were non-significant. GEE analysis also revealed a trend-level interaction between the group and timepoint for L CA4/dentate gyrus (χ^2=5.69, *df*=2, *P*=0.058). GEE results are also presented in Figure 4.

Pairwise within-group comparisons revealed a greater reduction in L CA4/dentate gyrus for high DBI compared to controls at month 3 (Δ=71.17 mm³, 95% *CI*: 23.82 to 118.52, *P*<0.05) and for high DBI compared to low DBI at month 3 (Δ=49.31 mm³, 95% *CI*: 2.92 to 95.70, *P*<0.05). As an additional analysis, after adding CPZ-eq as a covariate, the main effect of group was significant for R CA2/CA3 (χ^2=3.83, *df*=1, *P*=0.050); for R stratum (χ^2=4.45, *df*=1, *P*<0.05); for L stratum (χ^2=5.87, *df*=1, *P*<0.05); for R alveus (χ^2=5.20, *df*=1, *P*<0.05); for R hippocampus (χ^2=4.29, *df*=1, *P*<0.05); for L hippocampus (χ^2=5.19, *df*=1, *P*<0.05); for total hippocampus (χ^2=5.00, *df*=1, *P*<0.05); the main effect of timepoint was significant for L stratum (χ^2=5.00, *df*=1, *P*<0.05) and for L CA1 (χ^2=3.96, *df*=1, *P*<0.05). The interaction between group and timepoint was significant for L fimbria (χ^2=4.30, *df*=1, *P*<0.05; Figure 4), with a greater reduction in L fimbria volume for high DBI compared to low DBI and controls at both timepoints. Our results remained significant after correcting for multiple comparisons, except for L stratum (group effect), L CA1 (timepoint effect with CPZ-eq as a covariate), R CA2/CA3 (group effect with CPZ-eq as a covariate) and L CA4/dentate gyrus (group and timepoint interaction).

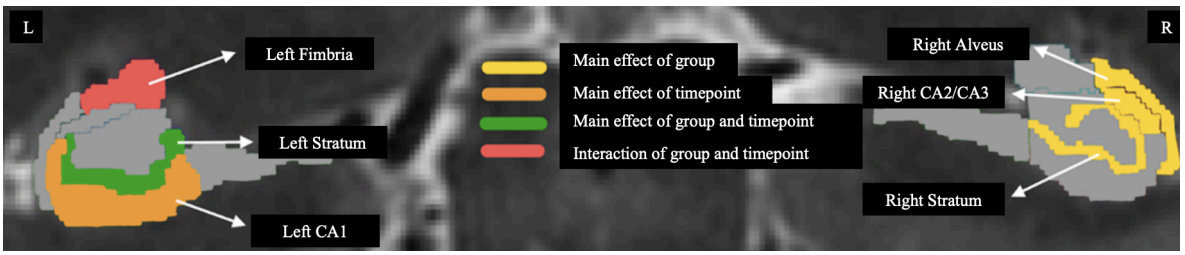

FIGURE 4. Generalized Estimating Equation (GEE) results after controlling for antipsychotic dosage for the left and right hippocampus using Multiple Automatically Generated Templates (MAGeT). Abbreviations: L = left, R = right; Coronal slice of left and right hippocampus using MAGeT algorithms (Pipitone et al., 2014) with GEE results after controlling for antipsychotic dosage for each subfield and surrounding white matter with significant main effects and interaction displayed.

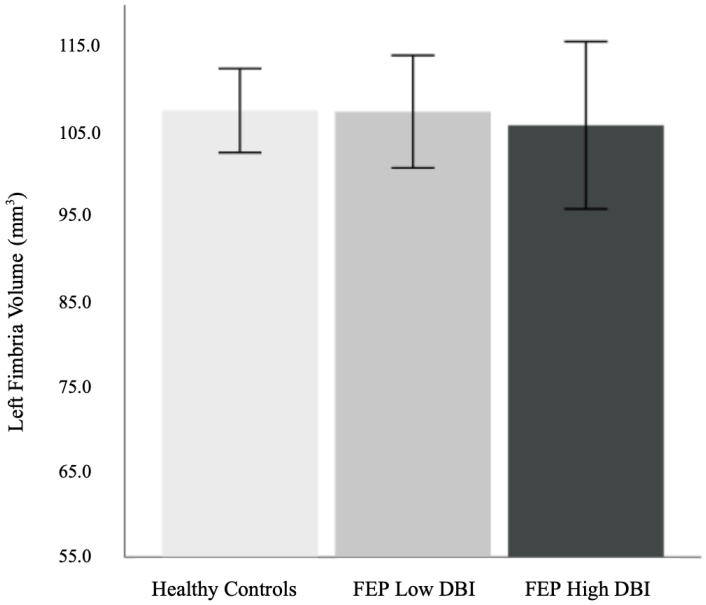

FIGURE 5. Left fimbria volume among groups at month 12, $P<0.05$.

3.4. DISCUSSION

Our study used high-resolution MRI and a longitudinal design to examine the association between hippocampal volume and anticholinergic burden in patients with a first episode of psychosis who recently started antipsychotic treatment. Early on and about 3 months following program entry, a significant association between anticholinergic burden and hippocampal volume was observed, with high anticholinergic burden patients showing a greater reduction in volumes compared to low anticholinergic burden patients and controls for several subfields of the hippocampus bilaterally. After controlling for antipsychotic dosage, results remained significant for L fimbria. After the introduction of pharmacotherapy, increased hippocampal volumes were observed in patients over time. However, patients with high anticholinergic burdens still had greater reduction volumes than the other groups. These results suggest that anticholinergic burden affects hippocampal volume early on following a first episode of psychosis.

Our results align with studies on hippocampal volume reduction in psychosis and schizophrenia (Adriano et al., 2012; Baglivo et al., 2018; Ebdrup et al., 2011; Heckers, 2001; Kawano et al., 2015; Pruessner et al., 2015; Wood et al., 2001). However, these changes seem more subtle in FEP and can be subfield-specific, which can be overlooked when looking at total hippocampal volumes, as many other studies have done (Sauras et al., 2017). Hippocampal subfields and surrounding white matter are all connected. Therefore, if a specific region is damaged or decreases in volume, it can lead to issues throughout the entire circuit (Meira et al., 2018). Evidence suggests that patients with schizophrenia display dysfunction in the trisynaptic circuitry, which involves the

CA4/dentate gyrus, CA1 and CA2/CA3 subfields (Brewer et al., 2013). A malfunction in this circuit can lead to inappropriate associations and generate false or illogical memories, which is strongly observed in psychosis (Tamminga et al., 2010). In line with our results, Kawano et al. (2015) also found that CA4/dentate gyrus volume was reduced in patients with schizophrenia (including FEP; *n*=19). In controls, newly generated neurons have been found, reflecting some evidence of neurogenesis in this subfield in humans.

Studies on the association between anticholinergic burden and hippocampal volume in early psychosis are rare. However, our results align with those performed in other clinical populations, such as in the study by Kilimann et al. (2021), suggesting that as the anticholinergic burden increased, the hippocampal volume decreased in a population-based cohort of non-demented participants aged 21-80. Risacher et al. (2016) cross-sectionally examined the association between anticholinergic medication use, cognitive functions and brain atrophy in cognitively normal older adults. They included 402 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and 49 from the Indiana Memory and Aging Study (IMAS; Risacher et al., 2016). Their results showed that anticholinergic use was associated with reduced cognition and brain atrophy (total cortical volume and temporal lobe cortical thickness; Risacher et al., 2016). Longitudinally, Chuang et al. (2017) followed 723 adults (mean baseline age 52.3 years) over an average of 20 years to investigate the effects of long-term use of anticholinergics on the risk of Alzheimer's disease and brain atrophy. Their results showed that individuals who were possibly high anticholinergic users had an increased risk of developing Alzheimer's disease and experienced greater brain atrophy rates than non-users (Chuang et al., 2017). Our study provides a unique perspective compared to previous research by providing a distinction

between low and high anticholinergic burden, calculated from all medications prescribed, including the most common first-line antipsychotics at baseline: aripiprazole, lurasidone, olanzapine, and risperidone. Nevertheless, Chuang et al. also conducted a study that explored similar aspects and did not observe an association between high anticholinergic burden and cortical atrophy. Chuang and colleagues (2017) explained that this might be due to a more heterogeneous group and that a high dose was administered for a short duration, resulting in more subtle changes in the brain.

The left fimbria represents a crucial pathway connecting the hippocampus to other brain regions. This structure is also rich in cholinergic receptors, particularly muscarinic receptors, which regulate synaptic plasticity, learning, and memory in the hippocampus (Antoniades et al., 2018). Hence, a volume reduction may disrupt hippocampal connectivity, potentially leading to memory impairments (Makowski et al., 2020; Totzek et al., 2024). Medications that block these receptors may lead to disruptions in cholinergic signalling. Therefore, prolonged exposure to anticholinergic use may contribute to structural changes in the hippocampus, such as a reduction in volume. Alternatively, individuals with a high anticholinergic burden may experience a more severe illness and greater cognitive impairments associated with structural changes in the hippocampus. Psychiatric disorders are also inherently characterized by progressive changes in brain structure (Navari et al., 2009). However, the finding that high anticholinergic exposure is associated with reduced left fimbria volume provides insight into the potential implications of a high medication burden in the treatment of psychosis. This may be of value to clinicians in selecting medications with less anticholinergic effects or in exploring alternative approaches to minimize adverse effects on brain structure. Changes in the

volume of the left fimbria could also be a potential biomarker for assessing treatment response and predicting outcomes in early psychosis. By incorporating neuroimaging data with clinical assessments, clinicians may be able to identify potential patterns of patients at greater risk for adverse outcomes and intervene earlier to optimize outcomes. In addition, observational studies like ours help to examine real-world treatment practices and outcomes and can be useful in complementing controlled trials by addressing the heterogeneity of medication response.

Evidence also suggests that patients with schizophrenia have reduced central cholinergic activity. An underlying mechanism that could explain the structural changes in the hippocampus is the loss of cholinergic input, which can affect neuroplasticity (Martin et al., 2000). This can also lead to difficulty in inducing long-term potentiation, which is important for cognitive function. In this regard, Cooper-Kuhn et al. (2004) found that cholinergic forebrain lesions in adult rats significantly decreased neurogenesis. We observed a greater reduction in left fimbria volume associated with high anticholinergic burden, which is also in line with other studies suggesting that fimbria-fornix lesions suppress cholinergic input, an important regulator of hippocampal activity (Dunnett and Bjorklund, 2017). We also note the possible involvement of the brain-derived neurotrophic factor (BDNF), which promotes neuronal cell survival and neurogenesis, and its activity may be modulated by cholinergic innervation (Kotani et al., 2006). A high anticholinergic burden may therefore reduce expression of this neurotrophic factor. For example, after introducing scopolamine (a medication with strong anticholinergic activity), Kotani et al. (2006) observed reduced BDNF in the hippocampus. Our results align with previous studies and provide new evidence for possible cholinergic involvement in adult

hippocampal neurogenesis in early psychosis.

A few limitations can be identified. Sample size may have precluded identifying significant volume decreases in other subfields with negligible effects. Regarding DBI calculations, some medications, such as lurasidone, were not included or added to the cumulative effect. Medications taken as needed (PRN) were not included in the calculations. Daily medication regimens were included in DBI calculations, but PRN anticholinergics were not. As a result, we may have missed temporary spikes in anticholinergic burden from these as-needed medications. This could be a limitation, potentially leading to an underestimation of the true anticholinergic burden. Medication data was not collected for controls, which can also be considered a limit. We also expected more low-risk than high-risk patients, as many have just started pharmacotherapy (max. 30 days), often at minimal therapeutic doses. In addition, the short 12-month follow-up period may be insufficient to detect long-term changes.

Our GEE model detected significant group effects across different hippocampal subfields independently of time. However, the one-year follow-up period may present a limitation in capturing a more nuanced pattern of reduced hippocampal volume. A longer follow-up period may be required to fully address the relationship between anticholinergic medication and hippocampal structures. We recognize that group differences observed at baseline may also be due to more severely ill patients (with more cognitive deficits) receiving higher doses of medication, resulting in increased anticholinergic exposure reflected in reduced hippocampal volumes. However, individuals with high anticholinergic burden continued to show reduced hippocampal volume compared to the other groups. Thus, the maintained group effect may indicate a potential contribution of anticholinergic

exposure to hippocampal structure, despite the effect over time. The finding of anticholinergic activity in early FEP, even if hippocampal changes in volume are so subtle, suggests potential long-term effects of anticholinergic exposure on brain volume that should be explored in extended longitudinal studies.

Another potential concern is the possibility of Type I Error due to multiple comparisons. However, we have taken cautious steps in our statistical modelling process and corrected for multiple comparisons using the Benjamini-Hochberg procedure and results for L fimbria remained significant even after adjustment (Benjamini & Hochberg, 1995). Our analysis includes additional pairwise comparisons within groups, which provides a more focused and controlled approach, increasing sensitivity to group differences. In addition, we considered sex and age and included an additional control for antipsychotic dosage, providing a more conservative approach to account for the weight of antipsychotics within the overall total anticholinergic burden for a better understanding of where the largest contribution of anticholinergic exposure may come from. Studying medication effects on brain structures is also challenging due to a difficulty in distinguishing changes from illness severity versus the medication itself. However, our studies did not find a significant difference in SAPS/SANS scores between high and low DBI groups. This similarity in illness severity between groups facilitates a clearer assessment of the relationship between anticholinergic burden and hippocampal volume.

DBI categorical classification at both timepoints can also be considered a limitation. For example, a hypothetical patient could have a DBI of 0.99 (low DBI) at month 3 and a DBI of 1.01 (high DBI) at month 12 due to an increase in the daily dose of the same medication, leading to a somewhat arbitrary group definition. Studying medication dosage also has

several limitations because of the variability of each individual and the pharmacological profiles of antipsychotic medications, making calibration of dose equivalents problematic. In addition, patients with substance dependence (as defined in the DSM-IV) were excluded, but those with substance abuse were included. This may be an important limitation, as an interaction between the substance used and medications taken as part of treatment may occur. Our results might also be different if another anticholinergic risk scale were used. We also recognize that adopting a binary classification of DBI raises some limits to our study. However, we relied on the classification (medium/high) from the Anticholinergic Burden Calculator© and the validated study by Hilmer et al. (2007). Nevertheless, we performed statistical analyses with 3 groups of DBI, i.e., low (0-1), medium (1-2), and high (2+). However, we did not have a sufficient sample in the latter group (n=8). Adopting a categorical approach instead of a continuous measure of anticholinergic burden also has statistical advantages where the distribution of values is manageable, and we are not assuming linearity between our variables.

Another possible limitation that is an important effect that we could not account for is that while the primary action of antipsychotics is to target dopamine receptors, blockade of muscarinic receptors in the cholinergic system can also occur as a secondary consequence of antipsychotics. Muscarinic receptors, including the brain and peripheral organs, are widely distributed throughout the body. As a result, antipsychotics can cause various anticholinergic side effects beyond their targeted therapeutic effect when they interact with those muscarinic receptors. The degree to which antipsychotics block muscarinic receptors may also vary from one medication to another. Some antipsychotics may have a greater affinity for muscarinic receptors than others, resulting in a greater likelihood of those side

effects. However, since muscarinic receptors are involved in several interconnected physiological processes, their blockade may sometimes be necessary when targeting other neurotransmitters.

While treatment of psychotic disorders typically promotes antipsychotic monotherapy as the gold standard approach, challenges such as incomplete symptom remission may warrant the use of antipsychotic polypharmacy, which involves the concurrent prescription of multiple antipsychotic medications. Although the exact prevalence rates of polypharmacy may vary depending on the population studied, evidence suggests that it is relatively common in people with FEP. In their systematic review, Gallego et al. (2012) reported a prevalence rate of 19.6% of outpatients with schizophrenia receiving antipsychotic polypharmacy. Tiihonen et al. (2019) found a higher rate of 57.5% in a Finnish clinical population. In a Turkish study by Yazici et al. (2017), more than 70% of patients received multiple antipsychotics simultaneously. Our study also looked at psychotropic polypharmacy, which is the simultaneous use of different medications that affect the mind and brain, such as antidepressants, mood stabilizers, and anxiolytics, and therefore not just antipsychotics. There may also be a tendency toward polypharmacy in psychosis, as clinicians seek to quickly stabilize the patient's symptoms. Other reasons may include a complex symptom presentation, a trial-and-error approach as patients are still in the early stages of their pharmacotherapy, comorbidities such as depression, anxiety, and substance use disorders, and management of antipsychotic side effects by adding adjunctive medications to counteract these effects. Nevertheless, current guidelines discourage polypharmacy.

Another possible limitation is that while the primary action of antipsychotics is to target

dopamine receptors, blockade of muscarinic receptors in the cholinergic system can also occur as an unintended consequence of the pharmacological properties of antipsychotics. Muscarinic receptors, including the brain and peripheral organs, are widely distributed throughout the body. As a result, antipsychotics can cause various anticholinergic side effects beyond their targeted therapeutic effects when they interact with those muscarinic receptors. The degree to which antipsychotics block muscarinic receptors may also vary from one medication to another. Some antipsychotics may have a greater affinity for muscarinic receptors than others, resulting in a greater likelihood of anticholinergic side effects. For instance, typical antipsychotics can have a higher affinity for muscarinic receptors than atypical antipsychotics. When multiple antipsychotics are used simultaneously, the combined blockade of muscarinic receptors may also become cumulative, leading to an increased risk of anticholinergic side effects. Long-acting injectable antipsychotics can also affect muscarinic receptors and may lead to a more prolonged and consistent blockade of muscarinic receptors over time compared to oral medications, which could potentially influence the occurrence and severity of those side effects. However, since muscarinic receptors are involved in several interconnected physiological processes, their blockade may sometimes be necessary when targeting other neurotransmitters.

Our study attempted to examine changes in hippocampal subfields and surrounding white matter volume in early psychosis as a function of anticholinergic burden. Findings suggest that high anticholinergic burden patients showed a greater reduction in volumes compared to low anticholinergic burden patients and healthy controls for L fimbria, even after controlling for antipsychotic dosage. Results also revealed that increased hippocampal

volumes were observed in patients over time after the introduction of pharmacotherapy. However, high anticholinergic burden patients still showed a greater reduction in L fimbria volumes compared to low anticholinergic burden patients and healthy controls, even after controlling for antipsychotic dosage. Despite the effectiveness of antipsychotics in treating psychotic symptoms, it appears that over time and at a high anticholinergic burden, they may not prevent the progressive hippocampal volume changes that occur with the disease. Further in-depth neuroimaging studies with a more extended follow-up period are needed to understand the effects of medication burden on the brain. Our study also highlights the need to consider the anticholinergic burden before prescribing medication for early psychosis.

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PREFACE TO CHAPTER 4

Given the observed associations between anticholinergic burden and cognitive deficits and reduced hippocampal volume, it is now important to examine the impact of anticholinergic burden on daily functioning. Daily functioning directly affects a person's quality of life. Impaired cognitive abilities, such as memory, attention, and executive functions, can affect a person's ability to perform daily tasks, maintain independence, and engage in social interactions. Therefore, it is essential to understand how anticholinergic burden may impact daily functioning to optimize pharmacotherapy, as functional outcomes are considered essential measures of treatment efficacy.

Although reducing symptom severity is crucial, it may not always provide a complete picture of the impact of treatment on patients' lives. Therefore, evaluating daily functioning is essential to comprehend how medication affects people's ability to perform their daily activities. By including measures of functioning in drug studies, researchers can more accurately determine the effectiveness of treatment and adapt interventions to improve patients' overall well-being.

CHAPTER 4

STUDY 3: EFFECTS OF ANTICHOLINERGIC BURDEN ON FUNCTIONING IN FIRST-EPISODE PSYCHOSIS[3]

[3] Belkacem, A., Lavigne, K., Joober, R., Malla, A., Shah, J. & Lepage, M. (2024). Effects of Anticholinergic Burden on Functioning in First-Episode Psychosis. Manuscript in preparation.

ABSTRACT

Treatment for a first-episode of psychosis (FEP) typically begins with antipsychotics. However, these medications and others (e.g., antidepressants) may have an anticholinergic burden, i.e., an accumulation of medications that block the cholinergic system. Recent evidence suggests that anticholinergic burden is associated with cognitive deficits, and some studies have reported an association between the two. However, very few have examined a link between the two in the early stages of the disease, whether cross-sectionally or longitudinally. We hypothesized that FEP patients with the highest anticholinergic burden would show the poorest levels of functioning compared to those in the low anticholinergic burden group at program entry (three months after admission). Longitudinally, we expected all groups to improve at month 12, but the high anticholinergic burden group would still have the lowest level of functioning. Patients (n=444) completed the Social and Occupational Functioning Assessment Scale (SOFAS) at both timepoints. They were divided into two groups; low anticholinergic burden (n=349) and high anticholinergic burden (n=95), based on a Drug Burden Index (DBI) cutoff of 1. Our results suggest that patients exposed to a high anticholinergic burden have reduced functioning compared with those with a low anticholinergic burden ($F(1,439)=4.40$, $P<0.05$). Our longitudinal results indicate that although functioning may improve over time, patients exposed to a high anticholinergic burden have reduced functioning compared to those in the other group ($\chi^2=5.52$, $df=1$, $P<0.05$). Our study highlights the need to properly assess exposure to anticholinergic burden when prescribing medication for psychosis.

4.1. INTRODUCTION

Functional impairments are common in schizophrenia, often occurring as early as in the first-episode of psychosis (FEP; Green et al., 2004; Lepage et al., 2014). These deficits include challenges in performing and maintaining daily tasks and participating in social interactions, such as scheduling appointments, following instructions, and managing finances. Tasks like these also require cognitive abilities such as verbal memory, attention and planning, some of which are regulated by the cholinergic system (Hasselmo, 2006).

While we know that individuals with schizophrenia and related psychotic disorders present with reduced central cholinergic activity, research has also shown that patients exposed to higher levels of cholinergic-blocking medications perform worse on cognitive assessments, particularly verbal memory (Tracy et al., 1998; Fox et al., 2011; Eum et al., 2017; Kim et al., 2019; Ballesteros et al., 2021; Joshi et al., 2021; Khan et al., 2021; Belkacem et al., 2023).

The relationship between anticholinergic medication and functional impairments in schizophrenia is complex, involving several mediating factors such as cognition. Anticholinergics act by blocking acetylcholine receptors in the brain, disrupting cholinergic signalling and can result in cognitive deficits (Hasselmo, 2006). The association between cognition and functioning is bidirectional, i.e., more significant cognitive deficits may impair functioning and vice versa (Green et al., 2004). For instance, disruptions in functioning, such as unemployment or social withdrawal, may lead to reduced cognitive

stimulation and engagement, which can also increase cognitive deficits over time.

Anticholinergic medications, which are prescribed through antipsychotics and other medication classes such as antidepressants and antihistamines, produce a cumulative effect known as anticholinergic burden (Desmarais et al., 2012). Consequently, individuals with FEP often find themselves exposed to multiple medications with anticholinergic properties and the burden is accumulated and heightened, further disrupting cholinergic signalling (Fox et al., 2014).

To assess anticholinergic burden, the Drug Burden Index (DBI) was used to quantify anticholinergic and sedative medication exposure, providing a comprehensive and practical approach. The validity of the DBI is supported by significant associations between DBI and cognitive impairments (Hilmer et al., 2007). Such findings suggest a potential cholinergic involvement in cognitive deficits and consequently concomitant functional impairments (Hasselmo, 2006). While the relationship between anticholinergic burden and functioning is not fully established, studying this in FEP has several benefits. Functional impairments are associated with worse long-term outcomes therefore identifying contributing factors, such as anticholinergic burden, could be useful for future studies.

Our study aimed to explore this association in FEP cross-sectionally and longitudinally. We hypothesized that patients with a higher anticholinergic burden would show worse functional outcomes compared to patients with a lower anticholinergic burden at month 3. With early patient care, we expected that both groups would show improvement in functioning over time, but the high anticholinergic burden group would remain inferior in functioning when compared to the low anticholinergic burden group.

4.2. METHODS

4.2.1. PARTICIPANTS

FEP patients (n=444) were recruited from the Prevention and Early Intervention Program for Psychosis (PEPP-Montreal) clinic. Entry criteria include age 18-35 years, no antipsychotic treatment (max. 30 days), affective or non-affective psychotic disorder (DSM-IV), good physical health, and ability to give consent in English or French. Exclusion criteria included: minimal performance on neuropsychological tests (IQ<70), a medical history of a neurological disorder (including head injury with loss of consciousness), and a family history of neurological disorders. The Douglas Research Ethics Board approved this study, and all participants provided informed consent (written and verbal).

4.2.2. SETTING

After admission to the PEPP-Montreal clinic program between 2003 and 2022, participants underwent a systematic assessment protocol with several checkpoints over two years (see the study by Jordan et al. (2014) for more information). The first neurocognitive assessment took place on average three months after admission to the PEPP-Montreal clinic program. For this study, we only considered data at month 3 (M=3.34, SD=4.55; n=444) and at month 12 (M=14.62, SD=3.18; n=88) following PEPP-Montreal clinic admission.

4.2.3. ASSESSMENTS

Patients were administered a Structured Clinical Diagnosis for DSM-IV and DSM-V (patient version; First & Gibbon, 2004). In months 3 and 12, structured and semi-structured instruments were used: the Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1989), Duration of Untreated Psychosis (DUP), Duration of Untreated Illness (DUI) using the Circumstances of Onset and Relapse Schedule (CORS). We also assessed medication adherence using a validated method reported by Cassidy et al. 2010 and colleagues involving a weekly adherence diary and several sources (e.g., families and case managers) at both assessments.

4.2.4. FUNCTIONING

To assess daily functioning (e.g., at work, in interpersonal relationships, in social activities, in self-care and daily living), we used the Social and Occupational Functioning Assessment Scale (SOFAS; Rybarczyk, 2018). SOFAS is a rating scale widely used in schizophrenia, ranging from 0 to 100, with higher scores indicating better functioning (Rybarczyk, 2018).

4.2.5. ANTICHOLINERGIC BURDEN

The Drug Burden Index (DBI; Hilmer et al., 2007) was chosen to assess anticholinergic burden based on the recommendation of the systematic review by Villalba-Moreno et al.

(2016). The DBI is unique in its comprehensive approach, taking into account prescribed daily doses and allowing for quantification of the anticholinergic effect. It combines daily doses of multiple medications in a distinctive way to provide a cumulative burden, including sedative medications, which makes it different from other scales (Villalba-Moreno et al., 2016). Hilmer et al. (2007) validated the DBI in a large study and found it to be associated with cognitive impairment, with the most significant correlations compared to other scales. A Web Portal Software Anticholinergic Burden Calculator© (https://www.anticholinergicscales.es; Villalba-Moreno et al., 2017) was utilized to calculate DBI scores at months 3 and 12. Patients were then categorized based on their DBI score, with a score of less than 1 indicating low anticholinergic burden and a score of greater than 1 indicating moderate to high anticholinergic burden, consistent with the 2 classifications provided by the website. DBI scores were also calculated for the total, antipsychotics, and other medications; details are provided in Appendix Table B.

4.2.6. ANTIPSYCHOTIC DOSAGE

Antipsychotic dosage was assessed using Chlorpromazine Equivalent Doses (CPZ-eq). CPZ-eq doses were calculated according to the Chlorpromazine Equivalent Doses for the Newer Atypical Antipsychotics (Woods, 2003) with the Antipsychotic Comparison Chart accessible at https://www.rxfiles.ca/rxfiles and were validated by psychiatrists at the Douglas Institute. CPZ-eq scores were calculated for all medications taken by patients daily, resulting in a cumulative score. In the case of long-acting injectable antipsychotics, the daily dose was determined by dividing the total dosage by the number of required days (e.g., *X* mg/ 28 days; Ozbilen, 2012).

4.2.7. Statistical Analyses

To compare clinical and demographical characteristics among groups (low vs high anticholinergic burden), we conducted t-tests. To explore the cross-sectional association between anticholinergic burden and functioning at month 3, we performed Pearson's correlations between the total DBI and SOFAS. We conducted an univariate ANOVA with groups as the independent variable, SOFAS as the dependent variable, and sex and age as covariates. We also considered the contribution of antipsychotics in functional impairments and repeated this model while adding CPZ-eq as an additional covariate. Additionally, we considered the potential interaction between symptom severity and anticholinergic burden. To examine this, we conducted a regression linear model, including symptoms (SAPS and SANS) and anticholinergic burden (DBI), while controlling for sex and age to understand their collective impact on functioning at month 3.

We used a Generalized Estimating Equation (GEE) model for a longitudinal assessment of this association, using timepoint (months 3 and 12) as predictor and group as outcome. The GEE model offers several advantages, including a reduced need for distributional assumptions, a lower risk of bias, the ability to handle non-normal and nested values, and the capacity to manage unbalanced data, making it appropriate for longitudinal data (Crowder, 2010; Patwary & Biswas, 2021). We used AR(1) working correlation structure for its relevance for a closely spaced repeated measure model and data with a natural order in time. We also included sex and age as covariates. We also reran the same GEE model while controlling for antipsychotic dosage using CPZ-eq. Post-hoc pairwise contrasts were examined for significant interactions. We applied a natural logarithm (ln) transformation to

the CPZ-eq variable to address positive skewness. All statistical analyses were conducted using SPSS Inc. (version 29, released in 2022).

4.3. RESULTS

4.3.1. DEMOGRAPHIC/CLINICAL

The sociodemographic and clinical characteristics of participants in months 3 and 12 are displayed in Table 5.

4.3.2. CROSS-SECTIONAL ASSOCIATION OF ANTICHOLINERGIC BURDEN

Pearson's correlations at month 3 revealed significant negative correlations between SOFAS and CPZ-eq (r=-0.282, P<0.01), and total DBI (r=-0.189, P<0.01). A significant positive correlation was observed between CPZ-eq and total DBI (r=0.403, P<0.01). Univariate ANOVA revealed a cross-sectional association between anticholinergic burden and functioning between DBI groups (F(1,439)=4.40, P<0.05; Figure 6). Using the same model, the results indicated that after controlling for antipsychotic dosage, this effect was no longer significant (F(1,374)=0.79, P=0.779). Pairwise comparisons between groups revealed significantly poorer functioning in high DBI compared to low DBI at month 3 (Δ=-31.31, 95% *CI*: -38.30 to 24.31, P<0.001). Regarding a possible interaction between symptoms and anticholinergic burden, our results suggest that for every 1-unit increase in SANS (higher scores indicating greater severity), functioning will increase by 0.008 (β=0.008, P<0.001, R^2=0.23, F(4,475)=6.33, P<0.001). No significant effect was found for SAPS (β=-0.003, P=0.072).

TABLE 5. Clinical and sociodemographic characteristics of participants at months 3 and 12

	Month 3 FEP (*n*=444)		Month 3 low DBI (*n*=349)		Month 3 high DBI (*n*=95)		Month 12 FEP (*n*=88)		Month 12 low DBI (*n*=68)		Month 12 high DBI (*n*=20)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	24.01	4.54	24.01	4.43	23.39	2.69	24.94	04.05	25.66	3.93	24.50	4.22
Male (*n*, %)	311[d]	70.05	241[e]	69.05	70	73.86	63	71.59	50	73.53	13	65.00
Education (years)	12.18	2.52	12.29	2.43	11.62	2.82	11.99	2.91	12.33	3.10	11.55	2.16
IQ (years)	97.81	15.24	98.64	14.82	96.02	15.58	—	—	—	—	—	—
Age at onset (years)	22.47	5.13	22.49	5.10	21.77	4.62	—	—	—	—	—	—
DUP (weeks)	56.87	115.94	57.13	122.34	55.65	108.09	—	—	—	—	—	—
DUI (weeks)	332.30	304.58	325.60	307.02	337.44	299.21	—	—	—	—	—	—
SAPS	15.25	15.15	15.04	15.07	13.81	14.81	4.76	7.22	3.33	5.54	07.08	09.09
SANS	21.35	13.66	20.91	13.65	24.35	14.06	15.14	16.95	11.54	12.70	17.67	20.75
SOFAS	43.87	14.78	43.34	15.98	39.22	16.07	62.73	17.50	65.16	16.54	58.75	19.18
Adherence (%)[a*]	84.23	28.37	75.90	36.73	95.92	6.40	91.88	21.43	74.16	42.57	96.43	7.46
CPZ-eq (mg)[b**]	356.76	327.86	325.53	291.34	506.40	395.19	268.29	206.24	258.49	207.14	311.33	216.25
Total DBI[c**]	0.67	0.54	0.46	0.33	1.48	0.40	0.67	0.48	0.44	0.33	1.65	0.54

Note. Abbreviations: CPZ-eq = Chlorpromazine Equivalent Doses, DBI = Drug Burden Index (score from the Anticholinergic Burden Calculator), DUI = Duration of Untreated Illness, DUP = Duration of Untreated Psychosis, IQ = Intelligence Quotient, SANS = Scale for the Assessment of Negative Symptoms (sum of total scores for each subscale excluding attention), SAPS = Scale for the Assessment of Positive Symptoms (sum of total scores for each subscale), SD = Standard Deviation, SOFAS = Social and Occupational Functioning Assessment Scale (sum of total scores); [a]T-tests revealed significant differences regarding adherence at month 3 between low DBI (*M*=75.90*, SD=36.73*) and high DBI (*M*=95.92*, SD*=6.40), with high DBI patients having higher adherence, *t*(60)=-2.02, *P*<0.05, [b]T-tests revealed significant differences regarding CPZ-eq at month 3 between low DBI (*M*=325.53*, SD*=291.34) and high DBI (*M*=506.40*, SD*=395.19), with high DBI patients having a higher antipsychotic dosage, *t*(417)=-5.01, *P*<0.001, [c]T-tests revealed significant differences regarding total DBI at month 12 between low DBI (*M*=0.44*, SD*=0.33) and high DBI (*M*=1.65*, SD*=0.54), with high DBI patients having a higher total DBI, *t*(104)=-13.12, *P*<0.001, [d]Missing sex information *n*=3,[e]Missing sex information *n*=3; * *P*<0.05, ** *P*<0.001.

4.3.3. LONGITUDINAL EFFECTS OF ANTICHOLINERGIC BURDEN

GEE analysis revealed a significant main effect of group (χ^2=5.52, *df*=1, *P*<0.05), and a significant main effect of timepoint (χ^2=39.99, *df*=1, *P*<0.001). No significant group and timepoint interactions were found (χ^2=1.74, *df*=1, *P*=0.187; Figure 6). Using the same model, the results indicated that after controlling for antipsychotic dosage, this effect remained significant for the main effect of timepoint (χ^2=33.12, *df*=1, *P*<0.001).

Pairwise comparisons between groups revealed marginally significantly poorer functioning in high DBI compared to low DBI at month 12 (Δ=-13.46, 95% *CI*: -27.25 to 0.32, *P*=0.056). Pairwise within-group comparisons revealed significantly improved functioning in month 12 compared to month 3 for low DBI (Δ=27.15, 95% *CI*: 20.69 to 33.61, *P*<0.001) and high DBI (Δ=17.84, 95% *CI*: 5.56 to 30.13, *P*<0.05).

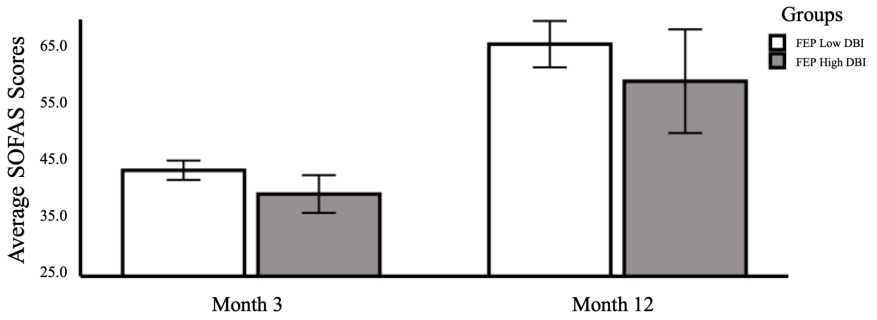

FIGURE 6. Cross-sectional and longitudinal effects of anticholinergic burden on functioning between groups at baseline and follow-up. Abbreviations: DBI = Drug Burden Index (score from the Anticholinergic Burden Calculator ©), SOFAS = Social and Occupational Functioning Assessment Scale (sum of total scores). GEE analysis revealed a significant main effect of group (χ^2=5.52, *df*=1, *P*<0.05) and a significant main effect of timepoint (χ^2=39.99, *df*=1, *P*<0.001)

4.4. DISCUSSION

Our study found a cross-sectional association between anticholinergic burden and functioning. Patients with the highest anticholinergic burden had worse functioning compared to those with the lowest burden at month 3. Our longitudinal analysis revealed that although patients with higher anticholinergic burden initially showed worse functioning, this difference was attenuated over time. Moreover, controlling for antipsychotic dosage further weakened this association.

Our cross-sectional association does align with previous research. Exposure to multiple medications with anticholinergic properties could block and saturate the M_1 receptor, inhibiting the typical acetylcholine response and further impacting the cognitive processes needed for functioning (Vingerhoets et al., 2017). The group with a higher anticholinergic burden could also potentially suffer from a more pronounced cholinergic disruption (e.g., greater severity of illness), explaining the poorer levels of functioning observed when compared to the other group (Khan et al., 2021). A weakened cholinergic system could further contribute to a vulnerability to high anticholinergic potency (Bakker et al., 2020; Tani et al., 2015). When controlling for antipsychotic dosage, we took into account their contribution to the total burden. This suggests that the relationship between DBI and CPZ-eq does not only come from their common calculation of the daily dosage but could also be attributed to a greater contribution of antipsychotics as a medication class when compared to other medications (Desmarais et al., 2012).

Our study did not find a strong longitudinal effect, even if at month 12 high anticholinergic burden patients still had poorer functioning, which is consistent with previous research in the initial stages of psychosis (Tracy et al., 1998; Ballesteros et al., 2021). Other longitudinal studies have also failed to find a long-term effect of high anticholinergic burden on functioning over similar follow-up periods. However, the majority of longitudinal studies (in schizophrenia e.g., Tracy et al. (1998)) examined the effects of anticholinergic medications in older adults, given the known and more severe adverse impact. In addition, because of age-related health conditions, older adults are also more likely to use anticholinergics (Chew et al., 2008). Age also is associated with changes

in pharmacokinetics and pharmacodynamics influencing the overall medication response. For example, hepatic metabolism tends to be slower with age, leading to prolonged exposure to medications, and alterations in receptor sensitivity, predisposing older individuals to a greater vulnerability to the effects of medication.

On the other hand, our study focused on a younger sample, aged 18-35 years, representative of individuals in the early stages of the disease. Despite our efforts in controlling for confounding factors like age, the significance of this variable cannot be underestimated. Younger individuals could have greater resilience to the long-term effects of anticholinergic medications on functioning and benefit from a more robust central cholinergic system when compared to an older population (Vingerhoets et al., 2017). However, by focusing on a younger cohort, we were able to address an important gap of age-related differences in medication response on functional trajectories. Further research in younger populations in FEP is warranted.

Several limitations can be identified. A significant reduction in sample size at month 12 presents challenges in maintaining a representative sample over time. This study collected various measures however, obtaining all of these data points simultaneously at follow-up, knowing the common risk of participant attrition in longitudinal studies, remains a challenge. As a result, participants with incomplete data were excluded from the analysis, leading to a further reduction in sample size at month 12. Determining whether changes in functioning over time are due to the underlying illness or to the actions of the medications also remains an important challenge. However, our studies did not find a significant

difference in SAPS/SANS scores between high and low DBI groups. This similarity in illness severity between groups facilitates a clearer assessment of the relationship between anticholinergic burden and functioning. In addition, although we excluded patients with substance dependence (as defined by the DSM-IV), individuals with substance abuse were not excluded.

While the DBI offers significant advantages, some limitations can be identified. The absence of certain medications, such as lurasidone, from the calculator's repository could lead to possible additional burdens. DBI and CPZ-eq calculations did not take into account medications taken on an "as needed" basis, overlooking the occasional exposure to medications with anticholinergic properties, potentially further underestimating the overall burden. Categorizing patients into two groups based on their DBI scores at each time point may also oversimplify the assessment of anticholinergic burden. Furthermore, since our patients are in the early stages of the disease, we expected a higher proportion of low/medium-risk patients rather than high-risk individuals, as treatment was initiated shortly after admission, often with minimal therapeutic doses, and within a maximum period of 30 days. Despite its limitations, DBI remains a powerful tool in quantifying anticholinergic burden and facilitating comparison and reproducibility between studies. Its standardized approach offers an additional framework for assessing anticholinergic burden.

In summary, our findings suggested that FEP patients exposed to higher levels of anticholinergic burden had poorer functioning when compared to those with lower burden. This association was notable in our cross-sectional analysis but not maintained

longitudinally. The fact that we observed these results as early as the first months following pharmacotherapy reinforces the importance of careful medication prescribing. Our study further supports the need for proactive measures to minimize polypharmacy in early psychosis.

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CHAPTER 5

GENERAL DISCUSSION

5. DISCUSSION

5.1. SUMMARY OF FINDINGS

Our findings revealed that the anticholinergic medication burden significantly impacts cognitive, neuroimaging, and functional outcomes in FEP. These findings highlight the relevance of considering anticholinergic burden when prescribing medication in early psychosis. Study 1 examined the effects on cognitive performance, showing that FEP patients with high anticholinergic burden had poorer verbal memory compared to those with lower burden and healthy controls. Study 2 investigated neuroimaging data, finding that patients with high anticholinergic burden had greater reductions in hippocampal volume, particularly in the left fimbria subfield, relative to those with lower burden and healthy controls. Study 3 addressed functional outcomes, revealing that a high anticholinergic burden was associated with reduced daily functioning at the first timepoint. These results suggest that a high anticholinergic burden is linked to cognitive deficits, structural brain changes, and decreased daily functioning, further providing evidence of the importance of monitoring anticholinergic use in treating FEP.

5.2. METHODOLOGICAL CONTRIBUTIONS

These studies propose a comprehensive method to investigate the anticholinergic burden in FEP, by adopting a multifactorial approach, we analyzed neurocognitive performance, neuroimaging data, and functional outcomes over time. This broader perspective allows

researchers to understand the diverse and interdisciplinary impact that a high anticholinergic burden can have (Lee et al., 2015). We also specifically focused on patients in the early stages of psychosis, ensuring that the sample was relatively naïve to medication (max. 30 days of medication use at the first timepoint). This approach minimizes the potential impact of confounding factors typically seen in chronic stages of the illness, providing clearer insights into the initial effects of pharmacological treatment (Ortiz et al., 2017).

Another methodological contribution is the integration of neurocognitive and neuroimaging data. This combination helps to establish a link between the biological processes in the brain and observable outcomes, such as memory and functional performance. By understanding which brain regions are affected by high anticholinergic burden, researchers can make connections to specific cognitive deficits. Our research also has methodological implications for broader research on psychiatric disorders where memory deficits are core features. By examining the effects of medication on memory and brain structure, researchers can gain insights into the underlying mechanisms of these disorders and potentially identify target brain regions or circuits for therapeutic interventions. Overall, these contributions suggest a more thorough and nuanced approach to understanding the impact of high anticholinergic burden in early psychosis. This approach can lead to more precise treatments and an improved understanding of the relationship between medication and cognitive outcomes.

A key methodological contribution is also the longitudinal aspect of our studies. By

following patients over an extended period, researchers can track changes and identify trends related to the effects of medication use. It also allowed us to capture the evolving effects of medication (Rindfleisch et al., 2008). This is particularly important in psychiatric populations, where medications may require extended periods to produce their full range of therapeutic or negative effects. Longitudinal studies are also crucial for observing subtle changes in the brain, as these changes often occur gradually (Fjell & Walhovd, 2010). By tracking the same individuals over time, we can more accurately detect patterns of progression. Additionally, this approach allowed us to control for cohort effects (results that can be influenced by age, culture, or other factors) that are more challenging to account for in cross-sectional studies. By also incorporating covariates (age, sex and others), we can further isolate the specific impacts of an anticholinergic burden on cognition and other outcomes (Rindfleisch et al., 2008). Using a longitudinal design provides a comprehensive view of how medications affect patients in a real-world setting, where dosages and regimens can change over time. This naturalistic and observational approach reflects the complexity of prescribing practices in psychiatric care. It allows us to understand the possible variability in patients' responses to medication initiation, providing a more accurate picture of clinical realities. Furthermore, this approach helps identify potential predictors or early signs that could guide future interventions. By observing certain patterns over time, we can form hypotheses about the mechanisms of action informing clinical decisions. However, we also included cross-sectional data in our research, as they complement the longitudinal findings by capturing those outcomes at specific points in time. Cross-sectional studies are also valuable as there is a reduced risk

of participant attrition, which can be challenging in longitudinal research.

A key contribution was also the use of multiple new measurement tools to enhance the accuracy and reliability of our analyses. For example, the DBI allowed us to quantify the anticholinergic burden of all medications taken by our patients, providing a quantitative, comprehensive and objective measure to examine its effects (Hilmer et al., 2007). This approach helped categorize patients based on their anticholinergic risk, allowing them to perform a direct comparison of outcomes between the groups. Additionally, the use of a 3T MRI scanner and MAGeT algorithms offered more precise neuroimaging data, facilitating a detailed assessment of structural changes in the hippocampal subfields (Pipitone et al., 2014). This technological advantage enhanced the reliability of our findings regarding the impact of anticholinergic burden on brain structure. The adoption of a GEE model also provided a robust analytical framework for analyzing our longitudinal data (Crowder, 2010). This approach allowed us to examine repeated measures over time, giving a more comprehensive view of how anticholinergic burden affects patients throughout their treatment. Moreover, working with a large sample in most of our studies improved the reliability and generalizability of our results. This approach helps us reduce variability and increase statistical power, allowing us to detect trends and patterns that might be significant and worth looking at further.

5.3. THEORETICAL CONTRIBUTIONS

The dopaminergic hypothesis has long been central to our understanding of symptoms of schizophrenia (Meltzer & Stahl, 1976; Baumeister & Francis, 2002; Toda & Abi-Dargham, 2007). However, in the present thesis, a shift in focus is proposed, to the cholinergic system and its underlooked greater role in memory (Raedler et al., 2007; Moncrieff, 2009; Lustig & Sarter, 2016; Yang & Tsai, 2017). Acetylcholine, a key neurotransmitter in the cholinergic system, is known to play an important part in learning and memory (Brandt & Flurie, 2020). Although its role is commonly known in Alzheimer's disease, however, its involvement in other psychiatric disorders like schizophrenia has not been as thoroughly explored (Francis et al., 1999; Craig et al., 2011; Hampel et al., 2018). Our theoretical emphasis on the cholinergic system could lead to new hypotheses regarding the mechanisms underlying memory deficits and cholinergic signalling in schizophrenia. This new framework could help further clarify and refine existing theories. By exploring a system that is typically associated with older populations and dementia, but less so with early-stage schizophrenia, we contribute by challenging current theories. This theoretical contribution encourages researchers to consider a broader range of mechanisms when studying schizophrenia, by suggesting that the cholinergic system might play a more significant role in the disease than previously thought, we also encourage future studies to look into other systems that may play in role. It opens new pathways for understanding and could lead to innovative approaches in developing treatments that target this system, ultimately enhancing our capacity to address cognitive impairments associated with

schizophrenia.

We have also contributed to the possibility of influencing prescription practices. We recommend considering the anticholinergic burden when prescribing medications, whether they are antipsychotic or not, in the context of psychosis, and we highlight the need to raise awareness about current prescribing practices (Scott et al., 2015). The issue of a tendency to overprescribe remains complex. Several factors may contribute to overprescription, including the pressure for quick interventions and high-dose treatments due to limited consultation time and restricted follow-up services in a given healthcare system (Sun et al., 2014). This pressure can often drive clinicians to prescribe more medication to reduce relapse rates (Kreyenbuhl et al., 2007; Sun et al, 2014). Additionally, a lack of continuous training and education may contribute to the problem of polypharmacy (Tani et al., 2013). Our results suggest that refining clinical guidelines, supported by observational studies like ours, is necessary to address them. Such studies can also potentially influence public health policies and foster discussions regarding better practices. By promoting a more balanced and well-informed approach to medication prescription by also involving the patients' feedback, these findings could lead to improved patient outcomes and more intentional use of medications in treating psychiatric conditions.

We also found that the issue of anticholinergic burden can arise right from the start of pharmacological treatment. These associations suggest a need for clinicians to identify and use medications with lower anticholinergic profiles (Fleischhacker & Uchida, 2014). A better understanding of the risks and negative effects of high anticholinergic burden can

help to encourage more vigilant monitoring and more frequent follow-ups. By improving those practices, clinicians can detect early signs of cognitive deficits induced by a high anticholinergic burden and adjust treatment accordingly (Mace & Taylor, 2015). Our research underscores the need for new guidelines that address the importance of minimizing anticholinergic burden and incorporating continued training programs. Cognitive deficits significantly impact daily functioning, they further impact a person's ability to participate in society and work. However, these deficits are not currently well managed by antipsychotics and therefore our findings may drive innovation in the identification of new procognitive drugs. Since our research findings can be directly applied to clinical practices, they provide an important contribution to patient care, treatment strategies, and healthcare guidelines. To reduce anticholinergic burden, clinicians should prioritize the lowest effective doses of second-generation antipsychotics with favorable anticholinergic side effect profiles (e.g., lurasidone) or consider third-generation antipsychotics (e.g., aripiprazole). Incorporating adherence into DBI calculations can provide a more accurate measure of the actual anticholinergic burden. Additionally, improving adherence can also indirectly reduce the need for a high anticholinergic burden. Future studies could also investigate anticholinergic burden as a potential indicator of disease severity, as patients with more severe or treatment-resistant profiles may require higher doses and multiple medications to manage their symptoms.

Furthermore, this emphasizes the importance of personalized treatment, as each patient may respond differently to new medications with anticholinergic properties (Mace & Taylor, 2015). Some patients could experience more significant negative effects than others.

It is crucial to consider these possibilities when assessing the broader impact of the anticholinergic burden. This individualized approach to treatment highlights the need for further careful monitoring and tailored strategies to minimize adverse outcomes (Meltzer, 2017). It reinforces the idea that a one-size-fits-all approach is not adequate for managing the complexities of medication in psychiatric care, and it calls for a comprehensive understanding of the risks associated with the anticholinergic burden (Mazza et al. 2021).

5.4. LIMITATIONS

Despite our robust methodology, we encountered several limitations. Some were common across all studies and others were unique to each. A major common limitation was participant attrition at the one-year follow-up mark. The disease's severity can make it difficult for patients to consistently participate in studies. First-line medications can cause significant side effects, while schizophrenia itself is often associated with cognitive deficits and a lack of insight into the condition, reducing compliance with treatment and making long-term study participation challenging (Iasevoli et al., 2018). Additionally, comorbidities like depression, anxiety, and substance abuse add further complexity to engaging in longitudinal studies. Other common limitations include excluding individuals with substance dependence but not those with substance abuse, which can complicate the interpretation of results, as interactions between these substances and prescribed medications could influence outcomes. The social stigma surrounding schizophrenia can also lead to isolation and a reluctance to engage with the healthcare system, contributing to

further participant attrition (Ertugrul & Ulug, 2004). Other factors like health and socioeconomic instability, unemployment, and limited access to technology and transportation further restrain consistent study participation (Szymczynska et al., 2017). To improve future longitudinal studies, strategies should address these limitations.

Some limitations were also specific to each study. In Study 1, the first cognitive assessment took place three months after their admission to the PEPP-Montreal clinical program. This delay was due to the program's protocol. However, we considered the first neurocognitive assessment as the baseline evaluation, while it does pose a potential limitation since initial cognitive changes due to the early care (not solely from medications, given that initial pharmacotherapy was limited to a max. of 30 days at the 3-month mark) may have occurred before testing. In the first two studies, we included a healthy control group to establish a reference point for normal cognitive performance (Study 1) and hippocampal volume (Study 2) before examining the effects of medication. However, we did not systematically collect medication data for the control group (those taking neuroleptic medications were not included). Additionally, controls were excluded from medication analyses, which focused solely on patient groups, limiting the insights we could gain from comparing controls with patients. In Study 2, a 12-month follow-up period might not be sufficient to detect significant structural changes, as such alterations often require more time to be observable, especially when isolating medication effects. Long-term medication use can lead to structural alterations but as the brain adapts and reorganizes itself through neuroplasticity, noticeable changes vary but can take time (that can involve synaptic remodelling and the formation of new neurons, also known as

neurogenesis). Furthermore, analyzing multiple subfields across both hemispheres increases the risk of Type 1 Error due to multiple comparisons, although we implemented statistical adjustments to address this.

When studying the effects of medications on cognition, brain, and functional outcomes, it can be difficult to differentiate the impact of the medications the one from the illness itself (Leucht et al., 2007). This challenge is even more relevant in complex disorders like schizophrenia, where symptoms are heterogeneous, and the effects of medication often overlap with those of the disease. To isolate the effects of medication more accurately, Randomized Controlled Trials (RCTs) could be needed in future studies (Correll et al., 2011). This approach, with a double-blind and a placebo-control group, could provide a robust framework for assessing the impact of anticholinergics (Correll et al., 2011). Gathering more comprehensive data at the admission of the program could also improve baseline assessment, allowing for a better understanding of the initial state of patients. Larger sample sizes would further enhance the generalizability of findings, which can be potentially achieved through collaboration among different research networks. Reproducing previous studies in future research, while adapting them to new contexts, can also contribute to the validation and generalization of results. For example, our first study was prompted by the study of Ballesteros and colleagues research done in Spain. However, we used a different statistical model suited to our sample, including a broader range of medications in the anticholinergic burden calculation, i.e., not just antipsychotics. Using covariates in our analyses helped control for confounding factors. In that regard, future studies could consider including additional covariates such as illness severity,

comorbidities and substance abuse. However, this can potentially introduce biases such as multicollinearity if these variables are strongly correlated, making it difficult to estimate the individual effects of each variable (Daoud, 2017; Kim, 2019). This issue can increase variance and lead to less reliable results (Paul, 2006). Overall, our findings suggest that future research in early psychosis should aim at improving methodology and clinical guidelines for prescribing medications, especially those with anticholinergic properties and associated risks.

CHAPTER 6

CONCLUDING REMARKS

6. CONCLUSION

In conclusion, our studies highlighted the pivotal role of anticholinergic medication burden as a factor in influencing cognitive, neuroimaging, and functional outcomes in FEP. These findings collectively provide a comprehensive understanding of the multi-dimensional impact of medication-induced effects and reinforce the importance of considering anticholinergic burden in medication prescription.

Study 1 revealed an impact of the anticholinergic burden on cognition by finding that FEP patients with a higher anticholinergic burden had poorer verbal memory performance compared to those with a lower anticholinergic burden, and healthy controls, indicating the potential additional cognitive deficits associated with anticholinergic medication use. To complement these findings, Study 2 examined associated alterations in hippocampal volume that might also be linked to a high anticholinergic burden. Our results showed that patients with high anticholinergic burden had more significant reductions in hippocampal volume, particularly in the left fimbria, compared to those with low burden and healthy controls. These results provided a potential mechanism by which anticholinergic medications may be associated with alterations in brain structure. In addition to cognitive and neuroimaging outcomes, Study 3 addressed a more general and daily functioning that could be associated with a high anticholinergic medication burden. Results suggested a higher anticholinergic burden to be associated with poorer functioning at the first timepoint.

Our studies collectively examined the interplay between anticholinergic burden, verbal memory, hippocampal volume, and functioning in the early stages of the disease following pharmacotherapy initiation. Our research supports the importance of a multidisciplinary approach to medication treatment, provides insight into the clinical decision-making process, and offers additional evidence to clinicians on considering anticholinergic burden in early psychosis.

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APPENDIX

TABLE A. Drug regimen of five FEP patients with the highest DBI scores

Table A. Drug Regimen of five FEP patients with the Highest DBI Scores

Patients (*n*=5)	Medication Name	Daily Dose (mg)	Total CPZ-eq (mg/day)	Total DBI	AP DBI	Other DBI
A	Quetiapine	400.00	532.00	2.52	0.89	1.63
	Lamotrigine	200.00				
	Pregabalin	425.00				
B	Aripiprazole[a]	19.05	253.90	2.55	0.66	1.89
	Lurasidone	100.00				
	Fluoxetine	30.00				
	Lorazepam	1.00				
	Clonazepam	0.12				
	Pregabalin	375.00				

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C	Quetiapine	600.00	1 002.00	2.71	0.92	1.79
	Citalopram	40.00				
	Benzatropine	50.00				
D	Olanzapine	35.00	2 104.05	2.92	1.79	1.13
	Haloperidol	15.00				
	Benzatropine	2.00				
	Diphenhydramine	25.00				
E	Quetiapine	50.00	245.07	3.03	1.04	1.99
	Paliperidone[a]	3.56				
	Fluoxetine	20.00				
	Zopiclone	7.50				
	Lithium	900.00				
	Lamotrigine	100.00				

Abbreviations: AP = Antipsychotic, CPZ-eq = Chlorpromazine Equivalent Doses, DBI = Drug Burden Index, Other = Other medication; [a] Long-acting injection.

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TABLE B. Drug regimen of five FEP patients with the highest DBI scores

Table A. Drug regimen of five FEP patients with the highest DBI scores

Patients (*n*=5)	Medication Name	Daily Dose (mg)	Total CPZ-eq (mg)	Total DBI AP DBI Other DBI
A	Olanzapine	12.00	340.00	2.25
	Lurasidone	20.00		0.71
	Citalopram	10.00		1.54
	Benzatropine	0.50		
	Pregabaline	175.00		
B	Paliperidone[a]	5.36	668.00	2.08
	Clozapine	200.00		1.58
	Pregabaline	150.00		0.50
C	Aripiprazole	19.00	253.27	1.37
	Lorazepam	2.50		0.66
				0.71
D	Ziprasidone	120.00	200.40	1.35
	Venlafaxine	112.50		0.75
				0.60
E	Aripiprazole	15.00	199.95	1.27
	Venlafaxine	150.00		0.60
				0.67

Note. Abbreviations: AP = Antipsychotic, CPZ-eq = Chlorpromazine Equivalent Doses, DBI = Drug Burden Index, FEP = first-episode psychosis, Other = Other medication; [a] Long-acting injection.

FIGURE A. Letter to the editor: the longitudinal effect of antipsychotic burden on psychosocial functioning in first-episode psychosis patients: the role of verbal memory (Belkacem et al., 2023)

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Letter to the editor: the longitudinal effect of antipsychotic burden on psychosocial functioning in first-episode psychosis patients: the role of verbal memory

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Ballesteros et al. (2020) investigated the relationship between antipsychotic medication dosage, anticholinergic burden and psychosocial functioning in patients with first-episode psychosis over time and whether cognitive deficits, a core feature of the disease, mediated this relationship. Despite important contributions to the existing literature, including a new method of calculating anticholinergic burden, we write to express our concerns and to offer some suggestions regarding the statistical analysis and theoretical framework.

This study followed 157 first-episode psychosis patients over two years. Several mediation models were performed to test the relationship between medication and psychosocial functioning, with six different cognitive domains as potential mediators. Mediation models were performed using 10 000 bootstrap samples. From this, a 95% confidence interval was obtained, and if zero was not included, the mediation was considered significant (Shrout & Bolger, 2002). For example, one of the models had attention as a mediator, symptom severity as a parallel mediator, antipsychotic dosage as the independent variable, psychosocial functioning as the dependent variable and anticholinergic burden as a covariate. Two models were found to be significant: model 1 with the mediator attention and model 5 with the mediator verbal memory. Despite the quality of the statistical method and the robustness of the performed tests, several points must be raised. Although zero is not included in the two significant models, the values obtained are very close to zero, indicating a minimal effect size. After correcting for multiple testing, these statistical results would likely be non-significant (Chaubey, 1993; Dai, Stanford, & LeBlanc, 2022). Indeed, the more tests performed, the more likely it is to find a significant effect that is not significant, also known as Type II Error (Chaubey, 1993). For each test performed, the researchers had a 5% chance of being wrong and finding a significant effect that was not there, which after six mediation models resulted in a non-negligible 26.5% probability of being wrong (Benjamini & Hochberg, 1995).

We also identified some key elements regarding medication. In reality, patients with psychosis present with multiple comorbidities and take several medications, such as antidepressants (Eum et al., 2017). The Drug Burden Index is an innovative way to measure anticholinergic burden. It is a valuable contribution to the literature as it is the only anticholinergic burden scale considering daily medication dosage. We also wonder whether the authors calculated the anticholinergic burden for all drugs taken by the patients, not just the antipsychotics (as suggested by the title). If not, we suggest calculating the total Drug Burden Index for all medications, as they are also likely to have an anticholinergic burden (Gerretsen & Pollock, 2011).

In addition, it might be beneficial to include more details on how the Drug Burden Index was calculated to facilitate reproducibility. We also noted that data on medication adherence were not provided, although they could offer useful information on treatment compliance.

It is also worth mentioning that patients with suicidal ideation and substance use disorders were included in this study. Although 40–50% of patients with schizophrenia have suicidal ideation, it is of interest to include them as it represents a strong ecological validity and provides data on this subgroup of patients who are often excluded from similar studies (Kovasznay et al., 1997; Skodlar, Tomori, & Parnas, 2008). Nevertheless, the inclusion of patients with substance abuse disorders may be a potential bias, as interaction may occur between the substance used and the medications taken in treatment, creating noise regarding the actual link between medications and psychosocial functioning (Baigent, Holme, & Hafner, 1995; Green, Noordsy, Brunette, & O'Keefe, 2008; Wilkins, 1997). We also observed that no information was provided as to whether this subgroup of patients had to abstain from substance use to participate in the study. We suggest conducting analyses with and without this subgroup to determine whether the results would differ, as substance misuse can affect psychosocial functioning and cognitive performance.

This study aimed to examine the effects of antipsychotic medication dosage and anticholinergic burden on psychosocial functioning in patients with early psychosis after two years of

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follow-up while considering cognitive impairments as a potential mediator. We note that the authors did not correct for multiple tests after running six mediation models, did not provide complete documentation on medication and overlooked the rationale for including patients with substance use disorders. We look forward to your response and hope some of our suggestions can be considered.

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