Effects of Antipsychotic Medication on Cardiovascular Function and Fitness in Individuals with Schizophrenia

by

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Abstract

**Background:** Individuals living with schizophrenia have consistently demonstrated impaired cardiovascular fitness. It is of particular interest whether antipsychotic medications significantly contribute to the reduced cardiovascular fitness in these individuals. A comprehensive review of the literature and meta-analysis was performed to examine the overall dose-dependent effect of antipsychotics on cardiovascular fitness. Also, it was tested in our participants with schizophrenia whether this dose-dependent effect might be independent of body mass index (BMI) and whether cardiovascular fitness might be further reduced in those exposed primarily to clozapine versus other antipsychotics.

**Methods:** For our comprehensive review and meta-analysis, an electronic search of the literature was performed to identify studies that examined the effects of antipsychotics on cardiovascular fitness. For our original research investigation, 30 participants with schizophrenia or schizoaffective disorder stabilized on antipsychotics were recruited. The patients were divided into the clozapine (n = 15) and non-clozapine (n = 15) groups, and a group of healthy age- and sex-matched controls (n = 15) was included. All current antipsychotic doses were converted to chlorpromazine equivalents (CPZE). Each participant completed maximal symptom-limited exercise testing on a cycle ergometer for the assessment of peak aerobic power (VO$_2$peak).

**Results:** The meta-analysis revealed an overall significant dose-dependent effect of antipsychotics on cardiovascular fitness in a total of 294 participants (correlation coefficient: -0.29, 95% CI: -0.43 to -0.14, p < 0.001). In our patients, after controlling for BMI, every 100-mg·d$^{-1}$ increase in CPZE was associated with approximately a 1-mL·kg$^{-1}$·min$^{-1}$ reduction in VO$_2$peak (p = 0.046). Moreover, the clozapine group demonstrated further reduced VO$_2$peak as compared to the non-clozapine group, even after controlling for BMI and CPZE (p = 0.042).

**Conclusion:** In conclusion, antipsychotics affect cardiovascular fitness in a dose-dependent manner, and this effect is independent of BMI in individuals with schizophrenia. Also, those receiving clozapine have further reduced cardiovascular fitness than those receiving other antipsychotics. Potential mechanisms are not clear, but it is suggested that altered activity of peripheral adrenergic and muscarinic receptors, as well as altered metabolism, by antipsychotics may contribute to the impaired cardiovascular fitness in individuals with schizophrenia.
Preface

I, David Kim, completed the writing of this thesis with the guidance of my supervisor (Dr. Darren Warburton) and committee members (Drs. Donna Lang and Ric Procysyn). My supervisory committee provided support for the conception and implementation of this research. Data for this study represent a subset of data from an ongoing research trial, titled the Psychosis, Exercise, and Hippocampal Plasticity (PEHP) study, for which Dr. Donna Lang is the principal investigator and Dr. Darren Warburton is a study chair. The research protocol was registered with ClinicalTrials.gov (Identifier: NCT01392885) and was approved by the University of British Columbia’s Clinical Research Ethics Board (Certificate H10-02919).

Versions of the “Comprehensive Review and Meta-Analysis” and “Original Research Investigation” will be submitted for peer review. David Kim will be primarily responsible for writing the manuscripts and Dr. Darren Warburton will be the corresponding author. The co-authors (including my committee members) made significant contributions to the collection of the data and will play an active role in providing edits for the manuscripts.
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<th>Description</th>
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<tr>
<td>BD</td>
<td>Bipolar disorder</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BZTE</td>
<td>Benztropine equivalent</td>
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<tr>
<td>CPZE</td>
<td>Chlorpromazine equivalent</td>
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<tr>
<td>FGA</td>
<td>First-generation antipsychotic</td>
</tr>
<tr>
<td>HALE</td>
<td>Haloperidol equivalent</td>
</tr>
<tr>
<td>HALalpha₁E</td>
<td>Haloperidol equivalent for alpha₁-adrenergic receptor antagonism</td>
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<tr>
<td>HALalpha₂E</td>
<td>Haloperidol equivalent for alpha₂-adrenergic receptor antagonism</td>
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<tr>
<td>SCZ</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>SGA</td>
<td>Second-generation antipsychotic</td>
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<tr>
<td>VO₂max/peak</td>
<td>Maximal or peak aerobic power</td>
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<tr>
<td>6MWT</td>
<td>6-minute walk test</td>
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</table>
Acknowledgements

First, I would like to offer sincere thanks to my supervisor, Dr. Darren Warburton, for his support throughout my master’s program here at the University of British Columbia. Under his supervision, I was exposed to a variety of opportunities and was able to gain valuable experience throughout my years. With his guidance, my knowledge of cardiovascular and exercise physiology has been enriched, and I could acknowledge how clinically important this field of research was to the psychiatric populations. Without Dr. Warburton’s guidance, I would not have been introduced to my committee members and subsequently to a new topic that I have grown to become very passionate about. The topic was schizophrenia and although I was not at first familiar with this area, my committee members, Drs. Donna Lang and Ric Procyshyn, have actively helped me learn the important concepts.

I sincerely thank Dr. Lang for allowing my direct involvement in her ongoing research, from which I could learn much about the effects of exercise in schizophrenia. I thank her for allowing me to use her data, and without them the current thesis would not have been developed. I sincerely thank Dr. Procyshyn for his excellent mentorship and constant encouragement throughout my program. My knowledge of psychopharmacology has been enriched through his teaching, and his everyday guidance has eventually led me to select this field as my primary research interest. Without the knowledge of all my supervisory committee members, I would not have been able to complete my project and develop the current thesis.

Second, I thank Kai Kaufman for her active assistance with my project and Melissa Woodward for being my excellent research partner. I also thank all my lab members, but would like to give special thanks to Bradley Hansen, Andrew Perrotta, Lauren Buschmann, Andrew Jeklin, and Amanda de Faye for their constant support and encouragement throughout my program.

Most importantly, I would like to offer sincere thanks to my immediate family members, Jeongha Kim, Meeok Kim, and Minji Kim, for your love and support. My father, Jeongha Kim, has always been my role model as a professor, and I would not have chosen the path of research without your guidance and inspiration.
Chapter 1: Introduction

1.1 Schizophrenia

Schizophrenia is a severe mental disorder that affects approximately 1% of the general population.\(^1\) The onset of illness is usually in late adolescence and early adulthood.\(^2\) The economic burden associated with treatment and lost productivity in individuals with schizophrenia was estimated to be $6.85 billion in 2004 and is predicted to be greater nowadays.\(^3\) Individuals with schizophrenia demonstrate positive, negative, and cognitive symptoms that affect their overall quality of life. Positive symptoms include delusions and hallucinations, and negative symptoms include social withdrawal, reduced thought or speech formation, and loss of emotion and volition.\(^1\) According to the dopamine hypothesis of schizophrenia, positive symptoms are thought to be associated with hyperfunction of the dopaminergic neurons connecting the ventral tegmental area to the nucleus accumbens (i.e., mesolimbic pathway).\(^4\) The negative as well as cognitive symptoms are thought to be associated with hypofunction of the dopaminergic neurons connecting the ventral tegmental area to the frontal cortex (i.e., mesocortical pathway).\(^4\) Moreover, the glutamate hypothesis of schizophrenia explains that the symptoms may originate as a result of hypofunction of the N-methyl-D-aspartate (NMDA) receptor located on the gamma-aminobutyric acid (GABA)-ergic inhibitory interneuron, leading to increased glutamatergic activity in the striatum and cortex.\(^5,6\) As a result, positive, negative, and cognitive symptoms may arise. Some of the cognitive symptoms associated with schizophrenia include lack of concentration, attention, and memory.\(^7\)

Antipsychotic medications are the first line of treatment for schizophrenia. They are classified as first- and second-generation antipsychotics, and all act as antagonists at dopamine
D_2_ receptors. The fact that these D_2_ antagonists have helped improve psychotic symptoms supports the dopamine hypothesis of schizophrenia.\textsuperscript{4} However, first-generation antipsychotics often cause resistance as well as neuromotor side effects (i.e., extrapyramidal symptoms).\textsuperscript{8} Such adverse effects associated with first-generation antipsychotics are largely absent in second-generation antipsychotics. Some of the unique properties of second-generation antipsychotics include partial agonism of 5-HT_{1A} receptors, strong antagonism of 5-HT_{2A} relative to D_2 receptors, and rapid dissociation from D_2 receptors, all of which help alleviate extrapyramidal symptoms.\textsuperscript{9,10} Although antipsychotics improve positive symptoms, they remain ineffective for negative and cognitive symptoms.\textsuperscript{11} Moreover, antipsychotic medications cause various cardiovascular (e.g., tachycardia, orthostatic hypotension, cardiotoxicity, and sudden cardiac death) and metabolic (e.g., weight gain, dyslipidemia, insulin resistance, and type 2 diabetes) adverse effects.\textsuperscript{8,12,13}

1.2 Cardiovascular and Metabolic Abnormalities in Schizophrenia

1.2.1 Cardiovascular Aspect

Cardiovascular system is closely regulated by the autonomic nervous system. For example, regulation of heart rate involves both intrinsic properties and the autonomic nervous system. The parasympathetic nervous system slows down heart rate, whereas the sympathetic nervous system accelerates it.\textsuperscript{14} The variability in the time intervals between heartbeats is known as heart rate variability.\textsuperscript{15} Generally, a greater degree of variability indicates healthier autonomic control of the heart.\textsuperscript{15} Heart rate variability can be further analyzed to assess the parasympathetic and sympathetic control of the heart.\textsuperscript{15} Individuals with schizophrenia not only demonstrate
reduced heart rate variability, but also autonomic imbalance in the form of decreased parasympathetic and increased sympathetic activity.\textsuperscript{16} Such autonomic imbalance has been found in both antipsychotic-naive and antipsychotic-treated individuals.\textsuperscript{16} Some studies have reported exacerbated autonomic function in individuals with schizophrenia following antipsychotic treatment.\textsuperscript{17-19} Antipsychotics demonstrated dose-dependent effects on parasympathetic activity, where the high-dose group had a larger reduction in parasympathetic activity than the moderate-dose (p = 0.010) and low-dose (p < 0.001) groups.\textsuperscript{19} Moreover, high plasma norepinephrine levels, which indicate an increase in sympathetic activity, often follow antipsychotic treatment.\textsuperscript{20,21}

As a result of such autonomic imbalance (i.e., decreased parasympathetic and increased sympathetic activity), elevated resting heart rate, also known as tachycardia, is often seen in individuals with schizophrenia receiving antipsychotics.\textsuperscript{13} For example, treatment with clozapine is frequently associated with tachycardia.\textsuperscript{22} This is likely the result of high anticholinergic and antiadrenergic effects associated with clozapine.\textsuperscript{13} The parasympathetic control of heart rate is largely mediated by the interaction between acetylcholine and muscarinic M\textsubscript{2} receptors located on the sinoatrial node.\textsuperscript{23} The sympathetic control of heart rate is largely mediated by the interaction between norepinephrine, that is released from presynaptic terminals, and cardiac beta\textsubscript{1}-adrenergic receptors.\textsuperscript{14} The release of norepinephrine is closely regulated via negative feedback by presynaptic alpha\textsubscript{2}-adrenergic receptors.\textsuperscript{24} Therefore, antagonism of muscarinic M\textsubscript{2} receptors and presynaptic alpha\textsubscript{2}-adrenergic receptors by antipsychotics can lead to tachycardia.\textsuperscript{13}
1.2.2 Metabolic Aspect

Individuals with schizophrenia are highly susceptible to cardiometabolic disorder. There is a 2-4 fold increase in the risk of developing metabolic syndrome in these individuals.\textsuperscript{25,26} Such increased risk can be attributed to a combination of unhealthy lifestyle factors and adverse effects of antipsychotics. Approximately 60-90\% of individuals with schizophrenia are smokers, and they not only smoke more than the general population, but also more than individuals with other mental disorders.\textsuperscript{27,28} The prevalence of obesity is also high among those with schizophrenia. Approximately 60-70\% of these individuals are overweight or obese.\textsuperscript{29} Such weight gain may be promoted by unhealthy lifestyle factors, such as unbalanced diet and physical inactivity/sedentary behavior.\textsuperscript{30-32} Some antipsychotics have been associated with marked weight gain.\textsuperscript{12} Clozapine was associated with a gain of 4.45 kg, olanzapine 4.15 kg, chlorpromazine 2.58 kg, risperidone 2.10 kg, haloperidol 1.08 kg, and ziprasidone 0.04 kg after 10 weeks of treatment.\textsuperscript{33} As compared to untreated patients, the rate of metabolic syndrome in antipsychotic-treated patients was 7.7-31.7\% higher, with the highest rate of 51.9\% in those treated with clozapine.\textsuperscript{34}

1.3 Cardiovascular Fitness in Schizophrenia

Cardiovascular fitness largely depends on cardiovascular and metabolic capabilities.\textsuperscript{35,36} The maximal (or peak) volume of oxygen consumed by working tissues per unit time (\(\text{VO}_2\text{max/peak}\)) is a precise measure of cardiovascular (aerobic) fitness.\textsuperscript{36} Maximal (or peak) aerobic power (\(\text{VO}_2\text{max/peak}\)) is directly proportional to the amount of blood pumped by the heart per unit time (i.e., cardiac output) and to the difference between the arterial and venous oxygen content.\textsuperscript{36} The 6-minute walk test (6MWT) is an alternative metric that estimates
cardiovascular fitness by taking into account a total distance (m) travelled over a 6-minute period.\textsuperscript{37} Although an indirect measure, 6MWT is often preferred in clinical settings because it is convenient and as accurate as the direct measure, VO\textsubscript{2}max/peak.\textsuperscript{37}

Many studies, using the VO\textsubscript{2}max and 6MWT methods, have demonstrated impaired cardiovascular fitness in individuals with schizophrenia.\textsuperscript{38-44} A recent meta-analysis has found that VO\textsubscript{2}max/peak was reduced in these individuals (n = 154) by a standardized mean difference of -0.96 (95% CI: -1.29 to -0.64) as compared to healthy individuals (n = 182).\textsuperscript{44} As cardiovascular fitness largely depends on cardiovascular and metabolic capabilities, the impaired cardiovascular fitness in these individuals can be due to the fact that they are at increased risk of cardiovascular and metabolic abnormalities (as mentioned above). However, it is of particular interest whether antipsychotics have direct effects on cardiovascular fitness.

Although a number of factors impair cardiovascular fitness in schizophrenia, it is not clear whether antipsychotics have a direct impact. Some studies have reported dose-dependent associations between antipsychotics and cardiovascular fitness in individuals with schizophrenia, where higher doses were associated with lower 6MWT scores or VO\textsubscript{2}max/peak.\textsuperscript{38-40,45} Yet, some studies have not found such an association.\textsuperscript{42,46} It is of interest whether these associations are overall significant and independent of some of the covariates of antipsychotic treatment and cardiovascular fitness, such as body mass index (BMI).\textsuperscript{12,47} Moreover, as clozapine is particularly associated with cardiovascular and metabolic adverse effects among other antipsychotics,\textsuperscript{48} it is of interest whether clozapine exposure may further impair cardiovascular fitness than exposure to other antipsychotics in individuals with schizophrenia.
1.4 Objectives and Hypotheses

Objective and Hypothesis 1:
To conduct a comprehensive review of the literature and meta-analysis to address the inconsistency of the results pertaining to the effects of antipsychotics on cardiovascular fitness.
Hypothesis 1: Antipsychotics will demonstrate an overall significant dose-dependent effect on cardiovascular fitness.

Objective and Hypothesis 2:
To examine the association between antipsychotic dose and peak aerobic power (VO$_2$peak) in our participants with schizophrenia, controlling for BMI.
Hypothesis 2: Antipsychotics will demonstrate a significant dose-dependent effect on VO$_2$peak even after controlling for BMI.

Objective and Hypothesis 3:
To compare VO$_2$peak in our participants with schizophrenia receiving clozapine versus other antipsychotics.
Hypothesis 3: Those receiving clozapine will demonstrate further reduced VO$_2$peak as compared to those receiving other antipsychotics.
Chapter 2: Methods

2.1 Comprehensive Review and Meta-Analysis

An electronic search of the literature, using the Medline, EMBASE, and Cochrane databases, was performed to identify studies that examined the effects of antipsychotics on cardiovascular fitness. The search was not limited to patients with schizophrenia, but also included those with other mental disorders taking antipsychotics. The following search terms were used: “antipsychotic” or “neuroleptic” and “fitness” or “exercise test” or “oxygen consumption” or “VO\textsubscript{2}”. Studies were further included using the references from relevant articles. Our own result was included in the review and meta-analysis.

Studies were included if they examined 1) the association between antipsychotic dose and any measure of cardiovascular fitness, 2) cardiovascular fitness in antipsychotic-treated versus untreated individuals, and 3) effects of different antipsychotics on cardiovascular fitness. From each relevant article, the following information was extracted: author, publication year, study location, sample size, demographics, medication information, fitness measure, and outcomes. A meta-analysis was performed using MedCalc®.

2.2 Original Research Investigation

2.2.1 Participants and Setting

Data for this study represent a subset of data from an ongoing study (Psychosis, Exercise, and Hippocampal Plasticity) that aims to determine the effects of aerobic and resistance exercise on hippocampal volumes and severity of psychotic symptoms in a population of patients with
psychosis compared to healthy age- and sex-matched controls. Patients for this study were recruited from the British Columbia Psychosis Program in Vancouver, Canada. This is a 25-bed provincial inpatient unit that offers specialized treatment to individuals with refractory psychosis. Patients were eligible for enrollment into the study if they had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, were fluent in English, were between the ages of 19 and 45 years, and could provide written informed consent. Patients were excluded from the study if they 1) had a history of organic disorders (e.g., dementia, severe head injury, or developmental disorders), 2) had a DSM-IV diagnosis of substance dependence (prior 12 months), 3) had a history of angina, heart attack, or transient ischemic attack, 4) had a history of severe head injury leading to loss of consciousness for greater than 5 minutes, or 5) were already enrolled in a regular exercise program. The research protocol was registered with ClinicalTrials.gov (Identifier: NCT01392885) and was approved by the University of British Columbia’s ethics review board. Severity of symptoms in our patients was rated using the Positive and Negative Syndrome Scale (PANSS).

2.2.2 Antipsychotic Medication

All patients included in this study were stabilized on second-generation antipsychotics, including clozapine (n = 20), aripiprazole (n = 6), olanzapine (n = 7), quetiapine (n = 4), asenapine (n = 1), risperidone (n = 1), and paliperidone (n = 5), and some were augmented with first-generation antipsychotics, including haloperidol (n = 2), loxapine (n = 3), and flupenthixol (n = 3). The mean antipsychotic dose 7 days prior to the day of assessment was calculated for each patient and converted to chlorpromazine equivalent (CPZE), according to the Clinical
Handbook of Psychotropic Drugs (21st ed.). Converting antipsychotic doses to dose equivalents (e.g., CPZE) is useful when there are different kinds of antipsychotics.

Those receiving clozapine greater than 50% of total CPZE comprised the clozapine group, and those receiving other antipsychotics or clozapine less than 50% of total CPZE comprised the non-clozapine group. In addition to CPZE, it was possible to calculate the anticholinergic loads (i.e., benztropine equivalent (BZTE) for muscarinic receptor antagonism) and antiadrenergic loads (i.e., haloperidol equivalent for alpha$_1$-adrenergic (HALalpha$_1$E) and alpha$_2$-adrenergic (HALalpha$_2$E) receptor antagonism) using the methods provided elsewhere in order to compare the antagonist loads at the muscarinic and adrenergic receptors between the clozapine and non-clozapine groups.

2.2.3 Physical Assessment

Physical assessments involved measuring body weight, height, blood pressure, heart rate, and VO$_2$peak. Each participant completed a Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) before performing maximal symptom-limited exercise testing on a cycle ergometer. All participants were cleared for physical activity participation and exercise stress testing via the PAR-Q+ as verified via a physician.

The exercise test began with a power output of 30 W with an increase of 10 W/min until volitional fatigue. The participants were required to maintain at the minimum speed of 60 rpm throughout the test. Expired gas and ventilatory parameters were acquired using a calibrated metabolic cart (Medisoft Ergocard Clinical®), allowing for the determination of VO$_2$peak. Every minute during the exercise test, rating of perceived exertion was recorded as well as heart rate using a single-lead ECG system. Oxygen pulse, which is a surrogate for stroke volume and the
difference between the arterial and venous oxygen content, was calculated by dividing VO$_2$peak by peak heart rate.$^{53}$$

2.2.4 Statistical Analysis

The following statistical analyses were performed using Statistical Package for the Social Sciences® (Ver. 24). P-values less than 0.05 were considered significant. Independent t-test was performed to test for any differences between patients and healthy controls. Pearson correlation analysis was performed to examine the associations between CPZE and the physical variables, and partial correlation analysis was performed to examine these associations after controlling for potential confounding factors. Hierarchical multiple regression analysis was performed to examine the associations of a dose increase with changes in the physical variables after controlling for potential confounding factors. Analysis of variance with Fisher’s least significant difference (LSD) post-hoc test was performed to test for any differences between the clozapine, non-clozapine, and healthy control groups. Independent t-test was performed to compare the clinical variables between the clozapine and non-clozapine groups, and analysis of covariance was performed to compare the physical variables between the clozapine and non-clozapine groups after controlling for potential confounding factors.
Chapter 3: Results

3.1 Comprehensive Review and Meta-Analysis

A total of 631 studies were identified and 11 studies met our inclusion criteria. The outcomes of the comprehensive review are presented in Table 1. A number of studies have examined the association between antipsychotic dose (in dose equivalent) and 6MWT score or VO_{2}\text{max}/peak.\textsuperscript{38-40,42,45,46,54,55} Owing to the limited number of studies, a meta-analysis was performed only on the studies that reported correlation coefficients between antipsychotic dose and cardiovascular fitness. Three studies were removed from the analysis because one did not report a correlation coefficient,\textsuperscript{54} and the other two were suspected to use the same sample as the study by Vancampfort et al. (2012).\textsuperscript{38-40} The meta-analysis revealed an overall significant inverse association between antipsychotic dose and cardiovascular fitness in a total of 294 participants (\textit{fixed effects}: correlation coefficient: \(-0.29, 95\% \text{ CI: } -0.39 \text{ to } -0.18, p < 0.001; \textit{random effects}: \text{correlation coefficient: } -0.29, 95\% \text{ CI: } -0.43 \text{ to } -0.14, p < 0.001\) (Table 2, Figure 1). The test for heterogeneity did not reach significance (\(p = 0.162\)).

A few studies compared cardiovascular fitness between antipsychotic-treated and untreated individuals. Carlsson et al. (1968) found that individuals with schizophrenia receiving high doses (range: 1500-3600 mg·d\(^{-1}\)) of chlorpromazine, a first-generation antipsychotic, demonstrated decreases in stroke volume and cardiac output as well as smaller increases or even rapid drops in blood pressure during exercise as compared to untreated individuals.\textsuperscript{56} Holmelo et al. (2014) found that estimated VO_{2}\text{max} was lower in antipsychotic-treated individuals with schizophrenia as compared to untreated individuals, although the result was not statistically significant (45 vs. 48 mL·kg\(^{-1}\)·min\(^{-1}\), \(p = 0.29\)).\textsuperscript{57} Yet, they found that inpatients had significantly
lower estimated VO$_2$\textsubscript{max} than outpatients (42 ± 10 vs. 50 ± 8 mL·kg$^{-1}$·min$^{-1}$, p < 0.001), where antipsychotic use was significantly higher among the inpatients (p = 0.002). Vancampfort et al. (2016) found that antipsychotic-treated individuals with bipolar disorder had significantly lower VO$_2$\textsubscript{max} than untreated individuals (22.9 ± 6.9 vs. 29.0 ± 6.7 mL·kg$^{-1}$·min$^{-1}$, p = 0.057). Lastly, only one study, by Strassnig et al. (2011), attempted to test for any differences in VO$_2$\textsubscript{max} across different antipsychotic medications but did not find significance (F = 0.94, p = 0.47).

Other than the study by Gomes et al. (2016), all studies that examined the relationship between BMI and cardiovascular fitness reported a significant inverse association (Table 1). No studies included in our comprehensive review, however, have tested whether the inverse association between antipsychotic dose and cardiovascular fitness was independent of BMI. We provide the result of the partial correlation analysis in the following section.
### Table 1. Comprehensive Review Outcomes

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Participants:</th>
<th>Antipsychotic Medications</th>
<th>Fitness Measures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample Size (% Male)</td>
<td>Mean Age, BMI ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancampfort et al., 2011, Belgium</td>
<td>n = 71 (66%)</td>
<td>Age: 37.4 ± 10.1 yr BMI: 26.0 ± 5.3 kg/m²</td>
<td>CPZE: 626.0 ± 377.0 mg·d⁻¹ -SGA / FGA / combination</td>
<td>6MWT</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Correlation between 6MWT score and: 1) CPZE: r = -0.37, p = 0.003 2) BMI: r = -0.52, p &lt; 0.001</td>
</tr>
<tr>
<td>Vancampfort et al., 2012, Belgium</td>
<td>n = 93 (73%)</td>
<td>Age: 34.6 ± 9.7 yr BMI: 24.9 ± 4.4 kg/m²</td>
<td>CPZE: 655.3 ± 416.1 mg·d⁻¹ -SGA / FGA / combination</td>
<td>6MWT</td>
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<tr>
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<td></td>
<td>Correlation between 6MWT score and: 1) CPZE: r = -0.38, p &lt; 0.001 2) BMI: r = -0.40, p &lt; 0.001</td>
</tr>
<tr>
<td>Nilsson et al., 2012, Sweden</td>
<td>n = 10 (100%)</td>
<td>Age: 34.7 ± 7.9 yr BMI: 28.5 ± 6.3 kg/m²</td>
<td>HALE: 7.0 ± 3.9 mg·d⁻¹ -SGA / FGA</td>
<td>VO₂max (estimated)</td>
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<td></td>
<td></td>
<td></td>
<td>VO₂max (estimated) was not correlated with either HALE or body weight (correlation coefficients not provided).</td>
</tr>
<tr>
<td>Scheewe et al., 2012, The Netherlands</td>
<td>n = 63 (73%)</td>
<td>Age: 29.2 ± 7.2 yr (Group 1); 30.1 ± 7.7 yr (Group 2) BMI: 26.6 ± 6.6 kg/m² (Group 1); 26.0 ± 5.5 kg/m² (Group 2)</td>
<td>Treated for at least 4 weeks. -HALE: 8.1 ± 5.8 mg·d⁻¹ (Group 1); 8.2 ± 4.6 mg·d⁻¹ (Group 2) -SGA / FGA / combination</td>
<td>VO₂peak</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Correlation between VO₂peak and: 1) HALE in males: r = -0.173, p = 0.263 (n = 46) 2) HALE in females: r = -0.201, p = 0.473 (n = 17) 3) BMI in males: r = -0.67, p &lt; 0.001 (n = 46) 4) BMI in females: r = -0.54, p = 0.03 (n = 17)</td>
</tr>
<tr>
<td>Vancampfort et al., 2013, Belgium</td>
<td>n = 80 (69%)</td>
<td>Age: 36.8 ± 10.0 yr BMI: 26.3 ± 5.5 kg/m²</td>
<td>Treated for at least 4 weeks. -CPZE: 687.2 ± 406.0 mg·d⁻¹ -Medication not specified.</td>
<td>6MWT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Correlation between 6MWT score and: 1) CPZE: r = -0.42, p &lt; 0.001 2) BMI: r = -0.61, p &lt; 0.001</td>
</tr>
<tr>
<td>Vancampfort et al., 2014, Belgium</td>
<td>n = 47 (69%)</td>
<td>Age: 34.2 ± 11.2 yr BMI: 25.8 ± 4.3 kg/m²</td>
<td>CPZE: 649.6 ± 410.3 mg·d⁻¹ -SGA / FGA / combination</td>
<td>VO₂max (estimated)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Correlation between VO₂max (estimated) and: 1) CPZE: rho = -0.28, p = 0.055 2) BMI: rho = -0.53, p &lt; 0.001</td>
</tr>
<tr>
<td>Gomes et al., 2016, Portugal</td>
<td>n = 51 (76%)</td>
<td>Age: 39.9 ± 7.1 yr BMI: 29.1 ± 4.8 kg/m²</td>
<td>Treated for at least 4 weeks. -CPZE: 391.4 ± 347.1 mg·d⁻¹ -Medication not specified.</td>
<td>6MWT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Correlation between 6MWT score and: 1) CPZE: r = -0.02 (p &gt; 0.05) 2) BMI: r = -0.25 (p &gt; 0.05)</td>
</tr>
<tr>
<td>Vancampfort et al., 2016, Belgium</td>
<td>n = 20 (30%)</td>
<td>Age: 47.9 ± 7.9 yr BMI: 26.4 ± 5.2 kg/m²</td>
<td>CPZE: 367 ± 217 mg·d⁻¹ -Medication not specified.</td>
<td>VO₂max</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Correlation between VO₂max and: 1) CPZE: r = -0.64, p = 0.044 (n = 10) 2) BMI: r = -0.64, p = 0.002 (n = 20)</td>
</tr>
<tr>
<td>Kim et al., 2016, Canada</td>
<td>n = 30 (67%)</td>
<td>Age: 31.0 ± 6.6 yr BMI: 27.8 ± 5.6 kg/m²</td>
<td>CPZE: 731.3 ± 386.5 mg·d⁻¹ -SGA / FGA / combination</td>
<td>VO₂peak</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Correlation between VO₂peak and: 1) CPZE: r = -0.53, p = 0.003 2) BMI: r = -0.52, p = 0.003</td>
</tr>
</tbody>
</table>
### Table 1 (Continued). Comprehensive Review Outcomes

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Participants: Sample Size (% Male)</th>
<th>Antipsychotic Medications</th>
<th>Fitness Measures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies that examined cardiovascular fitness between antipsychotic-treated and untreated individuals.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carlsson et al., 1968, Sweden&lt;sup&gt;56&lt;/sup&gt;</td>
<td>SCZ (Treated): n = 8 (100%) Age: 31.4 ± 9.9 yr BMI: 25.8 ± 5.2 kg·m&lt;sup&gt;-2&lt;/sup&gt; SCZ (Untreated): n = 9 (100%) Age: 28.8 ± 8.2 yr BMI: 22.9 ± 5.0 kg·m&lt;sup&gt;-2&lt;/sup&gt;</td>
<td>Chlorpromazine: 2362.5 ± 678.1 mg·d&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>VO&lt;sub&gt;2&lt;/sub&gt;max, ventilation, cardiac output, blood pressure during maximal exercise on a cycle ergometer.</td>
<td>1) Further decreases in stroke volume and cardiac output in treated as compared to untreated patients. 2) Smaller increases and rapid drops in blood pressure during exercise in treated as compared to untreated patients.</td>
</tr>
<tr>
<td>Holmemo et al., 2014, Norway&lt;sup&gt;57&lt;/sup&gt;</td>
<td>SCZ (Treated): n = 32 SCZ (Untreated): n = 18</td>
<td>No specific information.</td>
<td>VO&lt;sub&gt;2&lt;/sub&gt;max (estimated)</td>
<td>1) Lower, but not significant, VO&lt;sub&gt;2&lt;/sub&gt;max (estimated) in those taking antipsychotics (45 vs. 48 mL·kg&lt;sup&gt;-1&lt;/sup&gt;·min&lt;sup&gt;-1&lt;/sup&gt;, p = 0.29). 2) Lower VO&lt;sub&gt;2&lt;/sub&gt;max (estimated) in inpatients vs. outpatients (42 ± 10 vs. 50 ± 8, p &lt; 0.001), where antipsychotic use was higher among inpatients vs. outpatients (p = 0.002).</td>
</tr>
<tr>
<td>Vancampfort et al., 2016, Belgium&lt;sup&gt;58&lt;/sup&gt;</td>
<td>BD (Treated): n = 10 BD (Untreated): n = 10</td>
<td>CPZE: 367 ± 217 mg·d&lt;sup&gt;-1&lt;/sup&gt; -Medication not specified.</td>
<td>VO&lt;sub&gt;2&lt;/sub&gt;max</td>
<td>Lower VO&lt;sub&gt;2&lt;/sub&gt;max in those taking antipsychotics (22.9 ± 6.9 vs. 29.0 ± 6.7 mL·kg&lt;sup&gt;-1&lt;/sup&gt;·min&lt;sup&gt;-1&lt;/sup&gt;) (p = 0.057).</td>
</tr>
<tr>
<td><strong>Studies that examined effects of different antipsychotics on cardiovascular fitness.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strassnig et al., 2011, USA&lt;sup&gt;41&lt;/sup&gt;</td>
<td>SCZ: n = T17 (41%) Age: 43.2 ± 9.9 yr BMI: 37.2 ± 7.3 kg·m&lt;sup&gt;-2&lt;/sup&gt;</td>
<td>SGA / combination</td>
<td>VO&lt;sub&gt;2&lt;/sub&gt;max</td>
<td>There was no difference in VO&lt;sub&gt;2&lt;/sub&gt;max across antipsychotic medications (F = 0.94, p = 0.47).</td>
</tr>
</tbody>
</table>

BD: bipolar disorder; BMI: body mass index; CPZE: chlorpromazine equivalent; FGA: first-generation antipsychotic; HALE: haloperidol equivalent; SCZ: schizophrenia; SGA: second-generation antipsychotic; VO<sub>2</sub>max/peak: maximal or peak oxygen consumption; 6MWT: 6-minute walk test.
Table 2. Meta-Analysis of Dose-Dependent Effects of Antipsychotics on Cardiovascular Fitness

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Correlation coefficient</th>
<th>95% CI</th>
<th>z</th>
<th>p</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancampfort, 2012</td>
<td>93</td>
<td>-0.380</td>
<td>-0.542 to -0.191</td>
<td></td>
<td></td>
<td>32.97</td>
</tr>
<tr>
<td>Scheewe, 2012a</td>
<td>46</td>
<td>-0.173</td>
<td>-0.441 to 0.124</td>
<td></td>
<td></td>
<td>15.75</td>
</tr>
<tr>
<td>Scheewe, 2012b</td>
<td>17</td>
<td>-0.201</td>
<td>-0.622 to 0.310</td>
<td></td>
<td></td>
<td>5.13</td>
</tr>
<tr>
<td>Vancampfort, 2014</td>
<td>47</td>
<td>-0.280</td>
<td>-0.525 to 0.00780</td>
<td></td>
<td></td>
<td>16.12</td>
</tr>
<tr>
<td>Gomes, 2016</td>
<td>51</td>
<td>-0.0200</td>
<td>-0.294 to 0.257</td>
<td></td>
<td></td>
<td>17.58</td>
</tr>
<tr>
<td>Vancampfort, 2016</td>
<td>10</td>
<td>-0.640</td>
<td>-0.905 to -0.0174</td>
<td></td>
<td></td>
<td>2.56</td>
</tr>
<tr>
<td>Kim, 2016</td>
<td>30</td>
<td>-0.530</td>
<td>-0.748 to -0.210</td>
<td></td>
<td></td>
<td>9.89</td>
</tr>
<tr>
<td>Total (fixed effects)</td>
<td>294</td>
<td>-0.289</td>
<td>-0.394 to -0.177</td>
<td>-4.916</td>
<td>&lt;0.001</td>
<td>100.00</td>
</tr>
<tr>
<td>Total (random effects)</td>
<td>294</td>
<td>-0.290</td>
<td>-0.426 to -0.141</td>
<td>-3.739</td>
<td>&lt;0.001</td>
<td>100.00</td>
</tr>
</tbody>
</table>

The authors reported correlation coefficients for males (a) and females (b), separately. The test for heterogeneity did not reach significance ($p = 0.162$).

Figure 1. Forest plot of dose-dependent effects of antipsychotics on cardiovascular fitness.
3.2 Original Research Investigation

Thirty individuals diagnosed with either schizophrenia or schizoaffective disorder were included in our investigation and were divided into the clozapine (n = 15) and non-clozapine (n = 15) groups. A group of healthy age- and sex-matched controls (n = 15) was also included. The demographic, clinical, and physical characteristics of the three groups are presented in Table 3. The use of clozapine was 87.3% and 6.5% in the clozapine non-clozapine groups, respectively (Table 3). The mean age and BMI of the patients (n = 30) were 31.0 ± 6.6 yr and 27.8 ± 5.6 kg·m⁻², respectively, none of which were significantly different from those of the healthy controls.

3.2.1 Cardiovascular Fitness in Schizophrenia

As compared to the healthy controls, the patients (n = 30) demonstrated significantly lower VO₂peak (absolute: 1.85 ± 0.81 vs. 2.74 ± 0.67 L·min⁻¹, p < 0.001; relative: 22.7 ± 9.8 vs. 37.3 ± 10.2 mL·kg⁻¹·min⁻¹, p < 0.001) (Figure 2). Although no differences were found in resting systolic and diastolic blood pressure, the patients demonstrated significantly higher resting heart rate than the healthy controls (93.6 ± 13.7 vs. 78.4 ± 13.2 bpm, p < 0.001) (Figure 3). At the peak of exertion, the patients demonstrated significantly lower peak heart rate (138.2 ± 24.5 vs. 179.4 ± 11.5 bpm, p < 0.001) (Figure 3), power output (139.5 ± 49.2 vs. 198.8 ± 42.4 W, p < 0.001), ventilation (63.8 ± 28.4 vs. 104.5 ± 23.2 L·min⁻¹, p < 0.001), and respiratory exchange ratio (1.10 ± 0.16 vs. 1.29 ± 0.09, p < 0.001) as compared to the healthy controls. However, oxygen pulse (13.1 ± 4.5 vs. 15.3 ± 3.7 mL·beat⁻¹, p = 0.121) and rating of perceived exertion (8.4 ± 1.7 vs. 9.2 ± 1.0, p = 0.125) were not significantly different between the patients and healthy controls.
Table 3. Demographics and Physical Outcomes

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Clozapine</th>
<th>Non-Clozapine</th>
<th>Healthy Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>(male/female)</td>
<td>(10/5)</td>
<td>(10/5)</td>
<td>(10/5)</td>
</tr>
<tr>
<td>(smoker/nonsmoker)</td>
<td>(7/8)</td>
<td>(9/6)</td>
<td>(2/13)</td>
</tr>
<tr>
<td>(schizophrenia/schizoaffective disorder)</td>
<td>(10/5)</td>
<td>(4/11)</td>
<td>N/A</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>31.0 ± 7.5</td>
<td>31.0 ± 6.0</td>
<td>30.9 ± 7.5</td>
</tr>
<tr>
<td>Duration of illness (yr)</td>
<td>11.5 ± 5.0</td>
<td>10.1 ± 5.9</td>
<td>N/A</td>
</tr>
<tr>
<td>PANSS total score</td>
<td>96.7 ± 14.5</td>
<td>94.1 ± 14.5</td>
<td>N/A</td>
</tr>
<tr>
<td>Antipsychotic Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Clozapine</td>
<td>87.3 ± 14.7c</td>
<td>6.5 ± 11.5</td>
<td>N/A</td>
</tr>
<tr>
<td>CPZE (mg·d⁻¹)</td>
<td>771.8 ± 271.9</td>
<td>690.8 ± 481.6</td>
<td>N/A</td>
</tr>
<tr>
<td>BZTE (mg·d⁻¹)</td>
<td>43.2 ± 19.2e</td>
<td>3.1 ± 4.1</td>
<td>N/A</td>
</tr>
<tr>
<td>HALalpha¹E (mg·d⁻¹)</td>
<td>682.4 ± 309.5c</td>
<td>238.7 ± 337.7</td>
<td>N/A</td>
</tr>
<tr>
<td>HALalpha²E (mg·d⁻¹)</td>
<td>9583.4 ± 4313.6c</td>
<td>1560.3 ± 2842.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Physical Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>28.7 ± 4.7</td>
<td>27.0 ± 6.4</td>
<td>25.3 ± 5.2</td>
</tr>
<tr>
<td>Resting systolic blood pressure (mm Hg)</td>
<td>116.9 ± 13.7</td>
<td>117.1 ± 14.2</td>
<td>117.2 ± 7.1</td>
</tr>
<tr>
<td>Resting diastolic blood pressure (mm Hg)</td>
<td>79.3 ± 9.1</td>
<td>77.5 ± 11.5</td>
<td>77.9 ± 4.4</td>
</tr>
<tr>
<td>Resting heart rate (bpm)</td>
<td>99.1 ± 9.4a,f</td>
<td>88.1 ± 15.3g</td>
<td>78.4 ± 13.2</td>
</tr>
<tr>
<td>Peak heart rate (bpm)</td>
<td>126.5 ± 19.3b,f</td>
<td>149.9 ± 24.2i</td>
<td>179.4 ± 11.5</td>
</tr>
<tr>
<td>Oxygen pulse (mL·beat⁻¹)</td>
<td>12.1 ± 3.9d</td>
<td>14.2 ± 4.9</td>
<td>15.3 ± 3.7</td>
</tr>
<tr>
<td>VO₂:peak (L·min⁻¹)</td>
<td>1.68 ± 0.72a,f</td>
<td>2.12 ± 0.83g</td>
<td>2.74 ± 0.67</td>
</tr>
<tr>
<td>VO₂:peak (mL·kg⁻¹·min⁻¹)</td>
<td>18.9 ± 7.9a,f</td>
<td>26.5 ± 10.3b</td>
<td>37.3 ± 10.2</td>
</tr>
<tr>
<td>Power output (W)</td>
<td>121.7 ± 52.0a,f</td>
<td>157.3 ± 40.4g</td>
<td>198.8 ± 42.4</td>
</tr>
<tr>
<td>Ventilation (L·min⁻¹)</td>
<td>56.1 ± 27.1f</td>
<td>71.6 ± 28.5h</td>
<td>104.5 ± 23.2</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>1.07 ± 0.13f</td>
<td>1.14 ± 0.19h</td>
<td>1.29 ± 0.09</td>
</tr>
<tr>
<td>Rating of perceived exertion</td>
<td>8.5 ± 1.8</td>
<td>8.3 ± 1.7</td>
<td>9.2 ± 1.0</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation. Significant differences between: 1) Clozapine and Non-Clozapine: a p ≤ 0.05; b p < 0.01; c p < 0.001; 2) Clozapine and Healthy Control: d p < 0.05; e p < 0.01; f p < 0.001; 3) Non-Clozapine and Healthy Control: g p < 0.05; h p < 0.01; i p < 0.001.
Figure 2. Comparison of VO₂peak between schizophrenia and healthy control. *p < 0.001 between schizophrenia and healthy control. Error bars indicate standard deviation.

Figure 3. Comparison of resting and peak heart rate between schizophrenia and healthy control. Resting heart rate: *p < 0.001 between schizophrenia and healthy control. Peak heart rate: b p < 0.001 between schizophrenia and healthy control. Error bars indicate standard deviation.
3.2.2 Relationship between Antipsychotics and Cardiovascular Fitness

Antipsychotic dose (in CPZE) demonstrated significant associations with various physical variables (Table 4). There was a significant inverse association between CPZE and relative (but not absolute) VO\textsubscript{2}peak (r = -0.53, p = 0.003) (Figure 4). Also, BMI demonstrated a positive association with CPZE (r = 0.48, p = 0.008) and an inverse association with relative VO\textsubscript{2}peak (r = -0.52, p = 0.003) (Figure 5). After controlling for BMI, the association between CPZE and relative VO\textsubscript{2}peak remained significant (r = -0.37, p = 0.046). While BMI accounted for 27% of the variability in relative VO\textsubscript{2}peak, CPZE accounted for additional 10% (ΔR\textsuperscript{2} = 0.10, p = 0.046). After controlling for BMI, every 100-mg·d\(^{-1}\) increase in CPZE was associated with approximately a 1-mL·kg\(^{-1}·\text{min}^{-1}\) reduction in relative VO\textsubscript{2}peak (B = -0.92, SE = 0.44, p = 0.046). Also, CPZE demonstrated opposing associations with resting (r = 0.37, p = 0.046) and peak heart rate (r = -0.44, p = 0.014) (Figure 6); however, none of these associations remained significant after controlling for BMI (Table 4).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Correlation with CPZE</th>
<th>Controlling for BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.48**</td>
<td>/</td>
</tr>
<tr>
<td>Resting systolic blood pressure</td>
<td>0.08</td>
<td>-0.14</td>
</tr>
<tr>
<td>Resting diastolic blood pressure</td>
<td>0.18</td>
<td>0.06</td>
</tr>
<tr>
<td>Resting heart rate</td>
<td>0.37*</td>
<td>0.32</td>
</tr>
<tr>
<td>Peak heart rate</td>
<td>-0.44**</td>
<td>-0.30</td>
</tr>
<tr>
<td>Oxygen pulse</td>
<td>-0.25</td>
<td>-0.31</td>
</tr>
<tr>
<td>VO\textsubscript{2}peak (absolute)</td>
<td>-0.36</td>
<td>-0.36</td>
</tr>
<tr>
<td>VO\textsubscript{2}peak (relative)</td>
<td>-0.53**</td>
<td>-0.37*</td>
</tr>
<tr>
<td>Work load</td>
<td>-0.36</td>
<td>-0.32</td>
</tr>
<tr>
<td>Ventilation</td>
<td>-0.30</td>
<td>-0.29</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>-0.17</td>
<td>0.01</td>
</tr>
</tbody>
</table>

\(p < 0.05; \quad \star p < 0.01\)
Figure 4. Correlation between chlorpromazine equivalent and VO$_2$peak. Pearson’s $r = -0.53$, $p = 0.003$.

Figure 5. BMI as a covariate of chlorpromazine equivalent and VO$_2$peak. A) Correlation between chlorpromazine equivalent and BMI. Pearson’s $r = 0.48$, $p = 0.008$. B) Correlation between BMI and VO$_2$peak. Pearson’s $r = -0.52$, $p = 0.003$. 
Figure 6. Correlation between chlorpromazine equivalent and resting (square) and peak (circle) heart rate. Resting heart rate: Pearson’s $r = 0.37$, $p = 0.046$. Peak heart rate: Pearson’s $r = -0.44$, $p = 0.014$.

3.2.3 Comparison between Clozapine versus Non-Clozapine Exposure

The use of clozapine was 87.3% and 6.5% in the clozapine non-clozapine groups, respectively (Table 3). No significant differences were found between the three groups in age and BMI (Table 3). No significant differences were found between the clozapine and non-clozapine groups in duration of illness ($p = 0.515$), symptom severity ($p = 0.636$), and CPZE ($p = 0.575$) (Table 3). On the other hand, BZTE ($p < 0.001$), HALalpha$_1$E ($p < 0.001$), and HALalpha$_2$E ($p < 0.001$) were significantly higher in the clozapine group as compared to the non-clozapine group (Table 3).

As compared to the healthy control group, the clozapine ($p < 0.001$) and non-clozapine ($p = 0.003$) groups demonstrated significantly lower relative VO$_2$peak, with the clozapine group demonstrating significantly lower relative VO$_2$peak than the non-clozapine group ($p = 0.035$) (Figure 7). Although no significant differences existed between the three groups in resting systolic and diastolic blood pressure, resting heart rate was significantly higher in the clozapine
(p < 0.001) and non-clozapine (p = 0.047) groups as compared to the healthy control group, with the clozapine group demonstrating significantly higher resting heart rate than the non-clozapine group (p = 0.024) (Figure 8). Peak heart rate was significantly lower in the clozapine (p < 0.001) and non-clozapine (p < 0.001) groups as compared to the healthy control group, with the clozapine group demonstrating significantly lower peak heart rate than the non-clozapine group (p = 0.002) (Figure 8).

As compared to the healthy control group, power output was significantly lower in the clozapine (p < 0.001) and non-clozapine (p = 0.016) groups, with the clozapine group demonstrating significantly lower power output than the non-clozapine group (p = 0.037). Only the clozapine group demonstrated significantly lower oxygen pulse at 25% of peak power output (p = 0.05), at 50% (p = 0.020), and at 100% (p = 0.047) as compared to the healthy control group (Figure 9). No significant differences were observed in rating of perceived exertion between the three groups (Table 3).

Our analysis demonstrated that BMI and CPZE were significant correlates of VO₂peak (Table 4). BMI and CPZE, although not significant, were higher in the clozapine group than the non-clozapine group (Table 3). The clozapine group demonstrated significantly lower VO₂peak than the non-clozapine group even after controlling for BMI and CPZE (F₁,₂₈ = 4.55, p = 0.042). Also, the clozapine group demonstrated significantly higher resting heart rate (F₁,₂₈ = 4.95, p = 0.035) and lower peak heart rate (F₁,₂₈ = 7.70, p = 0.010) after controlling for BMI and CPZE. Power output was no longer significantly different between the clozapine and non-clozapine groups after controlling for BMI and CPZE despite a trend (p = 0.062).
Figure 7. Comparison of VO$_2$peak between clozapine, non-clozapine, and healthy control. Fisher’s LSD $^a$p < 0.05 between clozapine and non-clozapine; $^b$p < 0.001 between clozapine and healthy control; $^c$p < 0.001 between non-clozapine and healthy control. Error bars indicate standard deviation.

Figure 8. Comparison of resting and peak heart rate between clozapine, non-clozapine, and healthy control. Resting heart rate: Fisher’s LSD $^a$p < 0.05 between clozapine and non-clozapine; $^b$p < 0.001 between clozapine and healthy control; $^c$p < 0.05 between non-clozapine and healthy control. Peak heart rate: Fisher’s LSD $^d$p < 0.01 between clozapine and non-clozapine; $^e$p < 0.001 between clozapine and healthy control; $^f$p < 0.001 between non-clozapine and healthy control. Error bars indicate standard deviation.
Figure 9. Oxygen pulse vs. power output in clozapine, non-clozapine, and healthy control. Fisher’s LSD $^a p = 0.05$ between clozapine and healthy control; $^b p = 0.020$ between clozapine and healthy control; $^c p = 0.047$ between clozapine and healthy control. Error bars indicate standard deviation.
Chapter 4: Discussion

4.1 Comprehensive Review and Meta-Analysis

Our comprehensive review and meta-analysis suggest that antipsychotics have significant dose-dependent effects on cardiovascular fitness. However, as cardiovascular fitness testing requires a certain degree of muscular exertion (and therefore requisite strength), it should be considered whether antipsychotics have effects on musculoskeletal fitness. Some studies have reported that antipsychotics can impact musculoskeletal fitness as well as gait parameters.\textsuperscript{58-60} The authors suggest that this may be due to the neuromotor side effects (i.e., extrapyramidal symptoms) caused by antipsychotics.\textsuperscript{60} In fact, musculoskeletal fitness accounted for a significant portion of the variability in 6MWT scores in individuals with schizophrenia.\textsuperscript{40} Therefore, when using the tests that require a large amount of body movement (e.g., 6MWT or VO\textsubscript{2}max on a treadmill) to assess cardiovascular fitness in those taking antipsychotics, one should note the effects these drugs might have on musculoskeletal fitness.

Antipsychotic-treated individuals tend to have impaired cardiovascular fitness as compared to the untreated. However, limitations existed in some of our included studies. Other than the study by Carlsson et al. (1968),\textsuperscript{56} the main investigation of the rest of the studies was not about comparing cardiovascular fitness between antipsychotic-treated versus untreated individuals.\textsuperscript{55,57} Therefore, it is not known whether the divided groups had well-matched characteristics. This might have been the reason that Holmemo et al. (2014) did not find a significant difference in estimated VO\textsubscript{2}max between the treated versus untreated individuals with schizophrenia, although significantly lower estimated VO\textsubscript{2}max was observed in inpatients versus outpatients where antipsychotic use was significantly higher among the inpatients.\textsuperscript{57}
Vancampfort et al. (2016) have found significantly lower VO$_2$max in antipsychotic-treated individuals with bipolar disorder as compared to the untreated, although such reduced VO$_2$max might have been secondary to the significantly lower energy expenditure (i.e., lower levels of physical activity) in their treated group.\(^5\)

Strassnig et al. (2011) reported that there was no difference in VO$_2$peak across different antipsychotic medications.\(^4\) However, most of the patients included in their study were obese (i.e., BMI = 37.2 ± 7.3 kg·m$^{-2}$). This is much higher than the mean body mass indices of the patients examined in the rest of our included studies (range: 22.9 ± 5.0 to 29.1 ± 4.8 kg·m$^{-2}$) (Table 1). This implies that BMI must have had a large impact on cardiovascular fitness in the patients examined by Strassnig et al. (2011), to an extent that different antipsychotics failed to have significant effects.\(^4\)

Other than the study by Gomes et al. (2016),\(^4\) all studies that examined the relationship between BMI and cardiovascular fitness reported a significant inverse association (Table 1). One of the common side effects of antipsychotics is weight gain (or an increase in BMI),\(^2\) and increased BMI in turn is associated with decreased cardiovascular fitness.\(^3\) Unfortunately, no studies included in our comprehensive review have tested whether antipsychotics have significant dose-dependent effects on cardiovascular fitness even after controlling for BMI.

**4.2. Original Research Investigation**

In our investigation, antipsychotics demonstrated an inverse dose-dependent association with cardiovascular fitness, which is in agreement with previous studies (Table 1). However, our study provides new important information. The dose-dependent association between antipsychotics and cardiovascular fitness was independent of BMI. Controlling for BMI is
important in this case as BMI can be associated with antipsychotic treatment and cardiovascular fitness.\cite{12,47} An increase in BMI can result from antipsychotic treatment, as weight gain is a common side effect of a number of antipsychotics.\cite{12} Some studies have also shown that antipsychotic-associated weight gain can be a dose-dependent phenomenon.\cite{61} With regards to cardiovascular fitness, BMI has been well recognized as a strong limiting factor.\cite{47} As expected, our analyses demonstrated that BMI was positively associated with CPZE ($r = 0.48$, $p = 0.008$) and inversely associated with VO$_2$peak ($r = -0.52$, $p = 0.003$). Therefore, it is likely that BMI could have been the major driving force for the significant inverse associations between antipsychotic dose and cardiovascular fitness reported in previous studies that did not control for BMI (Table 1). However, our analysis demonstrated that the association between CPZE and VO$_2$peak remained significant even after controlling for BMI ($\Delta R^2 = 0.10$, $p = 0.046$).

Our investigation has also found that individuals with schizophrenia exposed primarily to clozapine demonstrated significantly reduced VO$_2$peak than those exposed primarily to other antipsychotics. The two groups did not significantly differ in BMI or CPZE, although both were slightly higher in the clozapine group. A more precise analysis showed that VO$_2$peak remained significantly reduced in the clozapine group as compared to the non-clozapine group even after controlling for BMI and CPZE ($F_{1,28} = 4.55$, $p = 0.042$).

### 4.3 Mechanisms

#### 4.3.1 Antipsychotics

Antipsychotics may impair cardiovascular fitness via antagonizing several receptors (Table 5). One study showed that antipsychotics may disrupt thermoregulation during exercise,
possibly by altering vascular function.\textsuperscript{62} The patients were treated with either haloperidol or fluphenazine, both of which are antiadrenergic but not anticholinergic.\textsuperscript{50,51,62} The authors suggest that heat intolerance observed in these patients during exercise might have been in part due to the antiadrenergic effects of haloperidol and fluphenazine on blood vessels, inhibiting blood flow from the core to the periphery.\textsuperscript{62} Many antipsychotics tend to be strong antagonists at alpha\textsubscript{1}-adrenergic receptors (Table 5).\textsuperscript{51} Alpha\textsubscript{1}-adrenergic receptors located on vascular smooth muscle cells are involved in peripheral vasoconstriction,\textsuperscript{63} which is required during exercise not only for thermoregulation but also for increasing blood flow from non-working vascular beds (e.g., in visceral organs and inactive muscles) to the working skeletal muscle.\textsuperscript{64} Antagonism of alpha\textsubscript{1}-adrenergic receptors by antipsychotics may inhibit this process and lead to limited skeletal muscle blood flow during exercise.

Our results indicate that antipsychotics may impair VO\textsubscript{2}peak by affecting heart-rate response. Cardiac output, which is a product of stroke volume and heart rate, is a key determinant of VO\textsubscript{2}max.\textsuperscript{35,36} Antipsychotic dose was positively associated with resting heart rate (r = 0.37, p = 0.046) and inversely associated with peak heart rate (r = -0.44, p = 0.014) (Figure 6). In other words, larger doses were associated with smaller changes in heart rate during exercise (i.e., chronotropic incompetence). Therefore, the decreased VO\textsubscript{2}peak observed in our patients could have been secondary to the effects that antipsychotics might have on heart-rate response.

Antagonism of alpha\textsubscript{2}-adrenergic receptors by antipsychotics may provide one mechanism for altered regulation of heart rate at rest and during exercise (Table 5).\textsuperscript{51} As presynaptic alpha\textsubscript{2}-adrenergic receptors exert negative feedback on norepinephrine release, antagonism of these receptors can lead to increased sympathetic activity.\textsuperscript{13,24} Subsequently, there
can be increased stimulation of cardiac beta\textsubscript{1}-adrenergic receptors, leading to increased resting heart rate.\textsuperscript{65} It is less clear as to how antipsychotics contribute to smaller increases in heart rate during exercise. Previous studies demonstrated that administration of alpha\textsubscript{2}-adrenergic receptor antagonists,\textsuperscript{66} as well as second-generation antipsychotics,\textsuperscript{67} in rat brain and heart resulted in desensitization of beta-adrenergic receptors likely due to increased exposure to norepinephrine. Therefore, it can be speculated that long-term treatment with antipsychotics might have led to desensitization of cardiac beta\textsubscript{1}-adrenergic receptors in our patients. Such a decrease in cardiac beta\textsubscript{1}-adrenergic receptor sensitivity may contribute to smaller increases in heart rate during exercise (i.e., chronotropic incompetence).

Furthermore, it has been shown that some second-generation antipsychotics, including clozapine, olanzapine, and risperidone, induced fat oxidation possibly by inhibiting glucose oxidation and subsequently reduced basal VO\textsubscript{2} in mice.\textsuperscript{68} Glucose is an important source of energy during a bout of strenuous exercise, such as that performed for the assessment of VO\textsubscript{2max}.\textsuperscript{69} Since antipsychotics can prevent glucose from being used as a fuel, this may contribute to lower VO\textsubscript{2}peak in individuals treated with antipsychotics. It has also been shown that first- and second-generation antipsychotics can impair adenosine triphosphate (ATP) production at the mitochondrial level by inhibiting complex I of the mitochondrial electron transport chain.\textsuperscript{70}
Table 5. Affinities of Antipsychotics for Adrenergic and Cholinergic Receptors

<table>
<thead>
<tr>
<th></th>
<th>Alpha₁</th>
<th>Alpha₂</th>
<th>Beta₁</th>
<th>Beta₂</th>
<th>M₁</th>
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</thead>
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<td></td>
</tr>
<tr>
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</tr>
<tr>
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<td>++</td>
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<tr>
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<td>−</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Quetiapine</td>
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<td>−</td>
<td>−</td>
<td>++</td>
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</tr>
<tr>
<td>Risperidone</td>
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<td>−</td>
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</tr>
<tr>
<td>Paliperidone</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>Haloperidol</td>
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<tr>
<td>Loxapine</td>
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<td>+</td>
<td>−</td>
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<tr>
<td>Flupenthixol</td>
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<td>++</td>
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<td>+++</td>
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</tr>
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</table>

Ki (nM) >10,000 = −; 1000–10,000 = +; 100–1000 = ++; 10–100 = +++; 1–10 = ++++; unknown = ?
Lower the Ki, stronger the affinity. Data are from the Psychoactive Drug Screening Program (PDSP) Ki Database and Clinical Handbook of Psychotropic Drugs (21st ed.).

4.3.2 Clozapine

Although there was no significant difference in CPZE (p = 0.575), the clozapine group was exposed to significantly higher anticholinergic loads (p < 0.001), as well as higher antiadrenergic loads at the alpha₁ (p < 0.001) and alpha₂ (p < 0.001) receptors, as compared to the non-clozapine group (Table 3). Such increased receptor antagonist loads might have contributed to the further impaired cardiovascular function and fitness in the clozapine group. The clozapine group demonstrated significantly higher resting heart rate than the non-clozapine group. This is consistent with the fact that clozapine has high anticholinergic as well as antiadrenergic loads compared to other antipsychotics. Antagonism of cardiac M₂ receptors blocks parasympathetic input, whereas antagonism of presynaptic alpha₂-adrenergic receptors increases sympathetic outflow. Together, sympathetic activity can be largely increased by clozapine, leading to tachycardia.
Increased anticholinergic loads associated with clozapine may pose additional physiological barriers to cardiovascular fitness. Epinephrine is a hormone that plays important roles during exercise. Its concentration rises during exercise to increase heart rate, as well as blood flow to the working skeletal muscle via vasodilation. Epinephrine is primarily released from the adrenal medulla, and this release is mediated by muscarinic receptors. Therefore, increased anticholinergic loads in the clozapine group might have inhibited the release of epinephrine during exercise.

Clozapine-treated patients might be even less likely to be heat-tolerant during exercise. Higher antagonist loads at alpha\textsubscript{1}-adrenergic receptors in the clozapine group might have further restricted blood flow not only from non-working to working tissues during exercise, but also from the core to the periphery. Moreover, sweat production, which is mediated by muscarinic receptors, might have been impaired in the clozapine group during exercise. As sweating facilitates evaporative cooling during exercise, blocking sweat production may require more blood to be delivered to the skin for convective cooling (i.e., heat loss via ambient flowing air), which can in turn result in less blood flow to the working skeletal muscle. In fact, decreased sweating is a common side effect of anticholinergic agents, such as clozapine.

Cardiac output might have been further reduced in the clozapine group. Since clozapine is associated with higher antagonist loads at alpha\textsubscript{2}-adrenergic receptors, desensitization of cardiac beta\textsubscript{1}-adrenergic receptors might have been more likely to occur in the clozapine group than the non-clozapine group. This might have in part contributed to the further reduced peak heart rate in the clozapine group. Also, one study observed particularly impaired left ventricular function in the clozapine group as compared to the non-clozapine and healthy control groups. This is partly consistent with our result where the clozapine group demonstrated altered oxygen-
pulse response (i.e., impaired stroke volume and oxygen delivery/uptake) during exercise (Figure 9). In fact, clozapine is particularly known among other antipsychotics to cause cardiotoxicity, from which symptoms of heart failure can emerge.⁷⁶

### 4.4 Implications

In addition to the effects of antipsychotics, several unhealthy lifestyle factors may also contribute to impaired cardiovascular fitness in individuals with schizophrenia. There is increased prevalence of smoking and obesity in schizophrenia, which can directly affect cardiovascular fitness.⁷⁷-²⁹ Increased BMI in these individuals can be secondary to unbalanced diet,³⁰ physical inactivity/sedentary behaviour,³¹,³² and adverse effects of antipsychotics.¹² Therefore, the combination of the effects of antipsychotics and unhealthy lifestyle factors may contribute to the reduced cardiovascular fitness in individuals with schizophrenia.

Such reduced cardiovascular fitness may increase the risk of cardiovascular disease and premature mortality in schizophrenia.⁷⁷-⁸⁰ In fact, cardiovascular disease has been a causal factor for the reduced lifespan in individuals with schizophrenia.⁸¹ Mounting evidence demonstrates that cardiovascular (aerobic) fitness is a strong predictor of cardiovascular disease and premature mortality. For example, Kokkinos and colleagues have demonstrated that a survival benefit of 8-20% for every 1-MET increase in cardiovascular fitness (where 1 MET = 3.5 mL·kg⁻¹·min⁻¹).⁷⁸,⁷⁹ For every 1-MET increase in cardiovascular fitness, mortality risk was 12% lower for the entire cohort, 15% for those <60 yr, and 11% for those ≥60 yr.⁷⁸,⁷⁹ Increased cardiovascular fitness across the lifespan reduces greatly the risk of at least 25 chronic medical conditions and premature mortality.⁸⁰ Therefore, the independent effects of antipsychotics on cardiovascular fitness may, at least in part, explain the early rates of mortality in schizophrenia.
4.5 Limitations

There are several limitations that require consideration. First, the sample size was small. Second, the use of antipsychotics was heterogeneous. However, this heterogeneity could be moderated by converting the doses of different antipsychotics to dose equivalents. Second, smoking status is not matched in the healthy control group (i.e., a much smaller number of smokers), although it is well matched between the clozapine and non-clozapine groups. Third, plasma levels of antipsychotics were not obtained, which might have been more representative of drug levels in the body than dose equivalents. However, in the case of having different antipsychotics, calculating the dose equivalent can be more convenient and appropriate. Fourth, some adjunct medications, such as fluvoxamine and beta-blockers, might have affected plasma levels of antipsychotics and cardiovascular fitness, respectively. However, only a small number of patients were treated with fluvoxamine (n = 4) and beta-blockers (n = 2). Fifth, lower respiratory exchange ratio, as seen in the clozapine and non-clozapine groups (Table 3), might represent that the patients did not try as hard as the healthy controls. However, the fact that rating of perceived exertion, although slightly lower in the patients, was not significantly different across the groups may indicate similar work effort in all participants. Lastly, the use of Fisher’s LSD post-hoc test might have increased the chance of incorrect rejection of a true null hypothesis (i.e., type 1 error).

4.6 Future Research

As demonstrated by our results, cardiovascular fitness in those treated with clozapine was particularly impaired. Since the sample size was small, future studies should investigate the effects of clozapine on cardiovascular fitness in a larger sample, as well as the effects of small
doses of different antipsychotics on cardiovascular fitness in healthy individuals. Also, it should be examined whether plasma levels of antipsychotics are better correlates of cardiovascular fitness. It is also of interest whether clozapine-treated individuals are more heat-intolerant and demonstrate lower plasma levels of epinephrine during exercise than those treated with other antipsychotics. Any interventions intended to improve cardiovascular fitness in individuals with schizophrenia, such as exercise, should note whether the improvement is similar between those receiving higher doses of antipsychotics or taking clozapine and those receiving lower doses or taking other non-clozapine antipsychotics. In fact, a previous study has noted that individuals with schizophrenia receiving high doses of chlorpromazine seemed to benefit less from exercise training as compared to untreated individuals. If those treated with clozapine do not benefit the same way as those treated with other antipsychotics, exercise prescription should be designed more specifically for the former.

4.7 Conclusions

In conclusion, antipsychotic medications affect cardiovascular fitness in a dose-dependent manner, and this effect is independent of BMI in individuals with schizophrenia. Also, individuals with schizophrenia receiving clozapine have further reduced cardiovascular fitness as compared to those receiving other antipsychotics. Potential mechanisms are not clear, but it is suggested that altered activity of peripheral adrenergic and muscarinic receptors, as well as altered metabolism, by antipsychotics may contribute to the impaired cardiovascular fitness in individuals with schizophrenia.
Bibliography


