Effects of Acute Aerobic Exercise on the Pharmacokinetics of the Anti-anxiety/Anti-depressant Drug Sertraline.

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Department of Exercise Sciences
University of Toronto

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Abstract

This study examined the effects of 30 minutes of cycle exercise at 65% $\dot{V}O_{2\text{max}}$ on the pharmacokinetics of the S.S.R.I. sertraline. Blood samples were taken over 48 hours from 14 healthy males (23.9±2.5 years, 80.3±12.6 kilograms) following oral ingestion of a single 100 mg dose of sertraline. Participants completed two sertraline trials separated by at least two weeks; one trial while resting and the other trial with exercise as described above. With exercise, the absorption rate constant and volume of sertraline in the central compartment decreased, while the elimination half-life increased. Maximum concentration, time of maximum concentration, and area under the curve were unchanged. Fitness level had little impact on the concentration of sertraline, as compartmental modeling was unchanged when relative $\dot{V}O_{2\text{max}}$ was added as a covariate. However, controlling for participant body weight improved the model estimate. These results indicate that acute aerobic exercise has the potential to change the concentration of sertraline in vivo.
Acknowledgments

I would like to express my deepest gratitude to all individuals who supported me throughout this academic endeavor. The successful completion of this research project would not have been possible without the mentorship and guidance of my supervisor and thesis committee, dedication of enthusiastic and committed study participants, assistance of lab members, and steadfast support of my family.

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<th>Description</th>
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<tr>
<td>ADME</td>
<td>absorption, distribution, metabolism, and excretion</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve (concentration vs. time graph)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;</td>
<td>area under the curve extrapolated to infinity</td>
</tr>
<tr>
<td>CL</td>
<td>clearance</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>maximum concentration</td>
</tr>
<tr>
<td>CYP450</td>
<td>cytochrome P450</td>
</tr>
<tr>
<td>DMS</td>
<td>desmethylsertraline</td>
</tr>
<tr>
<td>EHBF</td>
<td>estimated hepatic blood flow</td>
</tr>
<tr>
<td>F</td>
<td>bioavailability</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>Hb</td>
<td>haemoglobin</td>
</tr>
<tr>
<td>Hct</td>
<td>hematocrit</td>
</tr>
<tr>
<td>ICG</td>
<td>Indocyanine green dye</td>
</tr>
<tr>
<td>k</td>
<td>rate constant</td>
</tr>
<tr>
<td>kg</td>
<td>kilograms</td>
</tr>
<tr>
<td>m</td>
<td>metres</td>
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<tr>
<td>mg</td>
<td>milligrams</td>
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<td>min</td>
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</table>
mL  millilitres
mmHg  millimetres of mercury
ng  nanograms
PK  pharmacokinetics
t₁/₂β  elimination half life
tₘₐₓ  time to maximum concentration
µg  micrograms
µM  micromolar
Vd  Volume of distribution
SD  standard deviation
SSRI  selective serotonin reuptake inhibitor
VO₂  rate of oxygen consumption
VO₂ₘₐₓ  maximum rate of oxygen consumption
W  Watts
1 Introduction

Health Canada reported in 2009 that one in ten Canadians is affected by a mental health disorder, with anxiety and depression being most common (Canada, 2009). The prevalence of these conditions among athletes is similar to that of the general population (Reardon & Factor, 2010). It is recognized that regular exercise can have an independent therapeutic effect in managing mental illness, and is frequently recommended in conjunction with drug treatment (Blumenthal et al., 1999). Yet little is known about the effects of exercise on the pharmacokinetics and drug efficacy of prescription drugs used in these conditions. It is likely that several criteria used to characterize drugs are influenced by exercise, e.g. drug absorption, distribution, metabolism, and excretion (ADME). Health Canada regulates drug release to the public to ensure drug safety, efficacy, and quality. This approval process is based on pre-clinical and clinical trial data submitted by those requesting drug approval (Canada, 2006), but there is no requirement to include exercise as a component of any of these trials.

Sertraline came to market following the usual approval process by Health Canada. It is in the class of the selective serotonin reuptake inhibitors, and was the most commonly prescribed anti-anxiety/anti-depressant in the United States in 2010, with over 33 million prescriptions (National, 2011). The cytochrome P450 (CYP) family are the main enzymes responsible for the metabolism of sertraline, specifically CYP3A4 (DeVane, Liston, & Markowitz, 2002).

It is well established that CYP enzymes are affected by exercise and the related hyperemia (Hillig et al., 2002). It is also well established that acute exercise changes the rate and distribution of blood flow throughout the body (Saltin et al., 1998), which in turn should affect the ADME of a drug (Lenz, 2011). During physical activity, blood is shunted away from
internal organs and towards working muscles to provide oxygen, and to subcutaneous tissue in order to regulate body temperature (Daneshmend, Jackson, & Roberts, 1981). At all intensities of physical activity, blood flow decreases to the liver and kidney, as demonstrated in multiple studies (for review see Peng & Cheung, 2011). Therefore, drug pharmacokinetic indices that are based on resting blood flow quantities (such as Volume of Distribution (Vd), and Clearance (CL)) could be altered when an individual exercises, particularly at high intensity (Lenz, 2010).

Animal pharmacokinetic studies have shown that the F of sertraline is approximately 25%, indicating that sertraline is highly extracted by the liver and therefore its metabolic clearance is mainly blood flow-dependent (Tremaine, Welch, & Ronfeld, 1989). Because the liver receives most of the blood supply perfusing the splanchnic region and is positioned between the gastrointestinal tract and the general circulation, the metabolism of drugs that require extensive hepatic extraction is significantly dependent upon blood flow through the liver and therefore these drugs tend to be less available to the systemic circulation (Pang & Rowland, 1977). This pre-systemic hepatic drug metabolism occurs as the drug first moves through the liver and is termed the first-pass effect (Gibaldi, Boyes, & Feldman, 1971).

The reduction in visceral blood flow during exercise may significantly alter the clearance of flow-limited drugs (Khazaeinia, Ramsey, & Tam, 2000; van Baak, 1990). Thus, the shunting of blood away from the liver that accompanies exercise is likely to alter the metabolism of sertraline. Exercise may alter the pharmacokinetics of a drug such that serious over- or under-estimation of dosing may result. A comprehensive understanding of how exercise changes ADME is necessary in order to predict both efficacy and risks of sertraline administration.
2 Literature review

Based on an extensive review of PubMed using the search criteria “exercise,” “physical activity,” “pharmacokinetics,” and “sertraline,” no studies could be found that mirror the present study. Therefore it is suggested that there has yet to be a direct assessment of the effects of acute aerobic exercise on the pharmacokinetics of sertraline. However, relevant aspects and components of the present study have been researched, and these topics are explored in this literature review in order to establish the background to the present research project.

In this review of literature the use of exercise and physical activity both independently and combined with pharmaceutical medications for the prevention and treatment of anxiety and depression are examined. The definitions and equations for standard pharmacokinetic variables used to assess drugs are outlined followed by a review of sertraline specifically, including the mechanism of action and pharmacokinetics of this drug. The effect of exercise on blood distribution is reviewed, so that current knowledge about the effect of exercise on a drug’s disposition can be more fully explored.

While above topics formed the basis for inclusion criteria in this review of literature, certain research studies and findings were excluded based on elements that were not pertinent to the present study. Since humans were used as the test subjects, animal studies were excluded for the most part. Studies conducted using females were similarly omitted, since only males were used in the present study (due to financial restraints, as discussed in the methods section). Exclusions to these delimitations were if any study directly assessed the interactions of exercise and sertraline, be it with males or females, or with humans or other species. As mentioned previously, no such studies were found.
When discussing the efficacy of different treatments for anxiety and depression, reports that involved conditions other than depression/anxiety were excluded since these confounders may complicate findings and extrapolations (e.g. use of exercise and/or pharmaceuticals in treating depression in cardiac rehabilitation patients). Similarly, studies involving drug interaction were not considered, since the inclusion criteria for volunteers in the present study require that potential participants not be taking any other medications.

In examining the different pharmacokinetic adaptations possible as a result of the combination of exercise and sertraline, exercise and drug metabolism studies with drugs other than sertraline were excluded. While a drug may be similar to sertraline in certain regards, it will differ in others. For example, a drug may be similar to sertraline in that its extraction is also flow-limited, but its hepatic metabolism may occur through different enzymes. For example, the beta-blocker propranolol is also flow-limited, however different hepatic enzymes are responsible for its metabolism (CYP1A2/2D6). Since no other drug exhibits pharmacokinetics that are identical to sertraline, comparisons based on certain factors while omitting others requires extreme caution.

2.1 Exercise as a therapeutic modality for anxiety and/or depression

It has been suggested that vigorous physical activity can positively affect populations with both clinical and nonclinical mental health disorders (Blumenthal, Williams, Needels, & Wallace, 1982; DiLorenzo et al., 1999; Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005; King, Taylor, & Haskell, 1993; Roth & Holmes, 1987; Taylor, Sallis, & Needle, 1985; Trivedi et al., 2011). These proposed psychological benefits include improved confidence, a sense of well-being, anxiety reduction, and positive effects on depressed mood and intellectual functioning (Strohle,
2009). These beneficial effects of physical activity could have important benefits for primary prevention by making people less susceptible to different factors that may produce mental illness. Physical activity could also have secondary preventive effects in improving functioning in people with mental illness. The dual benefits of physical activity for both the prevention and/or treatment of mental health conditions was investigated in a major longitudinal study with close to 2,000 individuals over a five-year span. Even after adjusting for factors such as age, sex, ethnicity, financial strain, chronic conditions, disability, body mass index, alcohol consumption, smoking, and social relations, increased levels of physical activity were protective for both the incidence and prevalence of depression (Strawbridge, 2002).

Improvements in depressed individuals have been attributed to diversion, social reinforcement, and amplified neurotransmission of catecholamines and/or endogenous opiates (Hughes, 1984). Experimental studies involving both acute and chronic exercise of vigorous intensities have consistently demonstrated a reduction in state of temporary or transient anxiety (Folkins, 1976; Lichtman & Poser, 1983; Morgan, 1979).

Reductions in trait anxiety following chronic exercise training have also been shown to occur (Blumenthal et al., 1982; Schwartz, Davidson, & Goleman, 1978). One study even reported that acute exercise was as effective in reducing anxiety as cognitive-behavioural therapy, a common and well-established drug-free treatment for anxiety (Lobitz et al., 1983). Exercise is thought to reduce anxiety by diversion, social reinforcement, and improved response to stress because of decreases in muscle tension, heart rate, skin conductance, and catecholamine, glucocorticoid, or lactate production (Hughes, 1984). Acute and chronic exercise have been shown to reduce physiological responses to stress, suggesting that exercise training may produce improvements
in the physiological responses to stress greater than or equal to those produced by some relaxation techniques (Sinyor et al., 1983).

Despite the reported beneficial effects of exercise for mental health disorders, the combination of exercise and drug treatment has received limited attention. Mather et al. found that in patients with a diagnosis of mood (affective) disorder who were taking antidepressants, 10 weeks of group exercise classes resulted in a modest reduction in depression symptoms compared to a control group receiving health education classes (Mather et al., 2002). A similar study by Blumenthal et al. found that 16 weeks of group exercise training in older patients with major depression was as effective as antidepressant treatment with sertraline (Blumenthal et al., 1999). Furthermore, there was no difference in the reduction of depression scores between these two groups and a third group that received a combination of exercise and sertraline. This lack of an additive effect in the combination group may have been due to improper dosing of sertraline as a result of the exercise intervention.

As outlined above, exercise is often recommended and prescribed as an alternative or adjunct treatment with pharmaceuticals for management of anxiety and/or depression. For this reason, more insight and information is needed as to how exercise can influence the pharmaceutical drugs used to treat these conditions. In order to examine one such drug, it is necessary to understand the standard variables used to characterize how drugs move into and out of the body.

### 2.2 Definition of standard pharmacokinetic variables

Pharmacokinetics (PK) is defined as ‘what the body does to the drug’ (Quan, 2008). Since this definition is rather ambiguous, it is helpful to think of pharmacokinetics as defining the onset, intensity, and duration of a drug’s effect as it moves into, through, and out of the body.
Pharmacokinetics can be generally described by measuring the time course and mechanism of a drug’s ADME, and more specifically defined using the following criteria: bioavailability \( (F) \), volume of distribution \( (V_d) \), maximum concentration \( (C_{\text{max}}) \), time to maximum concentration \( (t_{\text{max}}) \), area under the curve \( (AUC) \) graph, elimination half-life \( (t_{1/2}) \), and clearance \( (CL) \). These pharmacokinetic indices will be influenced by an individual’s sex, age, weight, height, ethnicity, disease status, body composition, total body water, muscle mass, and other factors such as organ blood flow and blood composition.

### 2.2.1 Bioavailability \( (F) \)

The oral bioavailability is the percentage of the dose administered that reaches the systemic circulation unchanged. Factors that affect bioavailability include the dosage form (e.g. bioavailability increases with liquid formulations and decreases with time-release capsules), the chemical structure of the drug, the extent of first-pass metabolism before reaching the systemic circulation, and the absorption and dissolution characteristics of the drug itself (Quan, 2008). The measure of extraction ratio is equal to 1 minus the bioavailability. Therefore, a drug that is substantially altered before reaching the systemic circulation will have a low bioavailability and a high extraction ratio. However, \( F \) also depends on the amount of drug that is not absorbed, in addition to what is extracted by first pass organs.

### 2.2.2 Volume of distribution \( (V_d) \)

The volume of distribution quantifies how a drug disperses throughout the body’s different tissue compartments. It can be expressed by dividing the amount of drug in the body by the plasma drug concentration (Quan, 2008). The distribution of a drug will be impacted by changes
in plasma volume and amount of blood protein. The apparent volume of distribution of a drug can be quantified by the following equation:

\[ V_d = V_P + V_T \times \frac{f_U}{f_{UT}} \]

Where \( V_d \) is the apparent volume of distribution, \( V_P \) is plasma water (~3 litres in humans), \( V_T \) is volume of tissue water (~39 litres in humans), \( f_U \) is the unbound fraction of drug in the blood, and \( f_{UT} \) is the unbound fraction of drug in the tissue (Persky, Eddington, & Derendorf, 2003).

### 2.2.3 Maximum concentration (\( C_{max} \)), time to maximum concentration (\( t_{max} \)), and the area under the curve (AUC) graph

\( C_{max} \) is identified as the highest plasma drug concentration measured at any time after drug administration, and is measured in \( \mu g/L \). \( t_{max} \) is noted as the first time of occurrence of \( C_{max} \), and is measured in hours. The AUC is the integration of plasma drug concentration over time, and can be calculated with the linear trapezoidal rule. The area from zero hour to infinity (AUC) is calculated by extrapolating the AUC to infinity by the addition of the final measureable concentration divided by the terminal phase rate constant, as determined by linear regression (Demolis et al., 1996).

### 2.2.4 Elimination half-life (\( t_{1/2} \))

The half-life quantifies the amount of time that it takes for the plasma drug concentration or amount of drug in the body to decrease by one-half and is measured in hours. The half-life yields information about the disposition of the drug (Quan, 2008). For example, it can be used to determine the time it takes to reach steady state drug concentration, when the rate of drug
administration is equal to the rate of drug elimination. To achieve 90% of steady-state, it takes roughly 3.3 half-lives (Quan, 2008). Half-life can be calculated using the following equation, where CL is the clearance of the drug:

\[ t_{1/2} = \frac{\ln 2}{k_e} \]

2.2.5 Clearance (CL)

Clearance is the ability to remove drug from the plasma or the body and is expressed as volume per unit time. Factors affecting clearance include cardiac output, drug-drug interactions, hepatic and renal function, plasma protein binding, renal replacement therapy, and weight of the individual (Quan, 2008). Hepatic clearance is determined by the equation:

\[ CL_H = Q_H \times \frac{f_U \times CL_{INT}}{Q_H + f_U \times CL_{INT}} \]

Where \( Q_H \) is hepatic blood flow, \( f_U \) is unbound fraction of the drug, and \( CL_{INT} \) is the intrinsic clearance of free drug.

2.3 Sertraline

Sertraline is in the class of the selective serotonin reuptake inhibitors (SSRI). It enhances serotonergic transmission, a property that appears to explain its antidepressant activity. It was the most commonly prescribed anti-anxiety/anti-depressant in the United States in 2010, with over 33 million prescriptions (National, 2011). It was introduced to the market as a treatment for
major depressive disorders, but is now also indicated in the management of panic, obsessive-compulsive and post-traumatic stress disorders (Meyer et al., 2004).

2.3.1 Mechanism of action

The chemical name for sertraline is (1S, 4S)-4-(3,4-dichlorophenyl)-N-methyl-1, 2,3,4-tetrahydronaphthalen-1-amine, and its structure is shown below.

Sertraline is a derivative of napthalenamine that serves to inhibit the presynaptic reuptake of serotonin from the synaptic cleft, more specifically the re-uptake of 5-hydroxytryptamine (5-HT) (Warrington, 1991). Therapeutic doses (50-200 mg/day) taken by patients for one month resulted in 80-90% inhibition of serotonin transporter in the striatum region of the forebrain (Meyer et al., 2004). By inhibiting the active transport mechanism for serotonin reuptake, sertraline increases serotonin concentrations in synaptic clefts and prolongs its activity at postsynaptic receptor sites; inhibition of reuptake leads to reduced serotonin turnover via a negative feedback mechanism (Murdoch & McTavish, 1992).

2.3.2 Pharmacokinetics of sertraline

The literature-reported PK parameters of sertraline from studies using a similar dosage and population are summarized in Table 1. Sertraline is absorbed slowly when taken orally, reaching maximum plasma concentrations at 4-8 hours following administration (DeVane et al., 2002). It undergoes extensive first-pass metabolism to form N-desmethyleralsertraline (DMS), a metabolite
that is only weakly active and accumulates to a greater extent in plasma than the parent drug at steady-state concentrations (DeVane et al., 2002). CYP2B6 and CYP3A4 appear to be the key enzymes involved in the biotransformation of sertraline to desmethylsertraline (its major inactive metabolite, which has negligible clinical effects) (Obach, Cox, & Tremaine, 2005). Absolute bioavailability was estimated to be greater than 44%, with relative bioavailability reportedly equivalent between tablets and oral solution (DeVane et al., 2002). Co-administration with food resulted in a 25% greater peak plasma concentration and 31% faster time to peak concentration since an increase in hepatic blood flow as a result of increased digestion may allow more unabsorbed drug to escape first-pass hepatic uptake and metabolism (Ronfeld, Wilner, & Baris, 1997).
Table 1. Literature-reported PK parameters of sertraline.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Population</th>
<th>Dosage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ ($\mu g \cdot L^{-1}$)</td>
<td>$24.5 \pm 65$</td>
<td>Healthy males</td>
<td>Single 100 mg, oral</td>
<td>(Ronfeld, Wilner, et al., 1997)</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>$7.0 \pm 2.1$</td>
<td>Healthy males</td>
<td>Single 100 mg, oral</td>
<td>(Ronfeld, Wilner, et al., 1997)</td>
</tr>
<tr>
<td>$t_{0.5\beta}$ (h)</td>
<td>20.0</td>
<td>Healthy males</td>
<td>Single 100 mg, oral</td>
<td>(Ronfeld, Wilner, et al., 1997)</td>
</tr>
<tr>
<td>$AUC_{\text{inf}}$ ($\mu g \cdot h \cdot L^{-1}$)</td>
<td>$664 \pm 203$</td>
<td>Healthy males</td>
<td>Single 100 mg, oral</td>
<td>(Ronfeld, Wilner, et al., 1997)</td>
</tr>
<tr>
<td>$\text{CL/F}$ ($L \cdot h^{-1} \cdot kg^{-1}$)</td>
<td>$1.41 \pm 0.36$</td>
<td>Healthy males</td>
<td>21 days x 200mg, oral</td>
<td>(Ronfeld, Tremaine, &amp; Wilner, 1997)</td>
</tr>
<tr>
<td>$V_d$ (L/kg)</td>
<td>~20</td>
<td>Animals</td>
<td>n/a</td>
<td>(Levine, Jenkins, &amp; Smialek, 1994)</td>
</tr>
<tr>
<td>$k_e$ (h$^{-1}$)</td>
<td>$0.0309 \pm 0.0071$</td>
<td>Healthy males</td>
<td>30 days x 100mg, oral</td>
<td>(Warrington, 1991)</td>
</tr>
</tbody>
</table>

Abbreviations: $C_{\text{max}}$ = maximum plasma concentration; $t_{\text{max}}$ = time to $C_{\text{max}}$; $t_{0.5\beta}$ = terminal elimination half-life; $AUC_{\text{inf}}$ = area under the plasma concentration-time curve from zero to infinity; $\text{CL/F}$: intrinsic clearance (estimated oral clearance); $V_d$: volume of distribution; $k_e$: elimination rate constant; $\mu g$: micrograms; h: hours; kg: kilograms; $\beta$: beta (elimination rate constant).

At dosages of 50 to 200 mg, a linear relationship exists between the ingested amount and plasma concentrations in healthy men following a single oral dose (Warrington, 1991). Sertraline is highly bound to plasma proteins, at approximately 98% (Ronfeld, Wilner, et al., 1997; Warrington, 1991). The volume of distribution in animals was measured at 25 l/kg, implying extensive tissue distribution (Warrington, 1991). A post-mortem study on human cadavers reported liver tissue concentrations of sertraline and DMS that were 20 to 50 fold above peripheral plasma concentrations, reflecting their high lipophilicity (Levine et al., 1994).
Multiple cytochrome P450 (CYP450) isoforms are involved in the metabolism of sertraline (Figure 1). An in vitro study found CYP2C9 and CYP2C19 to be significantly affected by CYP inhibitors and/or CYP antibodies, while sertraline has a moderate to high potency in the inhibition of CYP2D6 (Xu et al., 1999). N-demethylation of sertraline occurs with CYP3A4, CYP2D6, CYP2C9, CYP2B6, and CYP2C19, as shown in human microsomes and cDNA-expressed human CYP isoforms (DeVane et al., 2002). The isoform CYP2D6 contributed most to the relative $V_{\text{max}}/K_m$ values (Kobayashi et al., 1999). However, it is important to note that sertraline is metabolized by several CYP enzymes in vivo, meaning that there should be no single agent that could significantly alter the pharmacokinetics of sertraline, nor should there be any single drug-metabolizing enzyme genetic polymorphism (DeVane et al., 2002).

![Figure 1. Metabolic scheme of sertraline (Kobayashi et al., 1999).](image)

Clearance of sertraline is typical for a drug that is highly extracted from the liver; elimination occurs via formation of a ketone and an alcohol, which are mostly excreted by the kidneys as
conjugates. The half-life ranges from 22 to 36 hours (Warrington, 1991). A possible overdose effect, called serotonin syndrome, is caused by excessive serotonin and is characterized by tremor, rigidity, hypertonicity, myoclonus, variable autonomic responses and possibly generalized seizures (DeVane et al., 2002).

2.4 Exercise and splanchnic blood flow

A number of pharmacokinetic indices are affected by measurements of liver and kidney blood flow at rest. For example, measurements of a drug’s F, Vd, and CL are all affected by resting liver blood flow and function. However, systemic blood flow is drastically redistributed during exercise; splanchnic blood flow is reduced, and proper liver functioning is delayed, meaning that hepatic extraction ratio of a drug may decrease with exercise due to a reduction in hepatic blood flow. As a result there may be a higher plasma concentration and a lower Vd (Somani et al., 1990). In order to fully appreciate these and other potential changes to a drug’s pharmacokinetics, the redistribution of blood flow away from the drug metabolizing organs during exercise will be further explored.

2.4.1 Blood flow alterations during an acute bout of exercise

At rest, the body circulates roughly five litres of blood per minute (Saltin et al., 1998). At various intensities of physical activity, the amount and distribution of blood flow changes substantially. One method used to quantify these changes within the splanchnic region is by measuring the concentration of infused indocyanine green dye (ICG). ICG is removed from the systemic circulation entirely by the liver. Due to the high binding rate of ICG to plasma proteins, the dye allows for a measure of liver and splanchnic perfusion by monitoring changes
in the ICG plasma disappearance rate. ICG has a high extraction ratio and does not undergo biotransformation prior to excretion in bile (Daneshmend et al., 1981).

In a classic study by Rowell, changes in hepatic blood flow in response to exercise were estimated from changes over resting values of plasma clearance rate of ICG after a single injection (Rowell, Blackmon, & Bruce, 1964). During exercise at intensities ranging from 26-97% of maximal aerobic power (\(\dot{V}O_{2\text{max}}\)), peripheral venous concentration of ICG decreased linearly when plotted on a semi-logarithmic scale against time, but the half-life was extended compared to resting values (Rowell et al., 1964). The prolongation of ICG clearance by the liver was inversely correlated with exercise intensity, expressed as oxygen intake relative to the individual’s \(\dot{V}O_{2\text{max}}\). The decrease in ICG clearance during exercise was primarily the result of decreased estimated hepatic blood flow (EHBF), rather than a decrease in extraction ratio of ICG. EHBF fell from a mean of 1,614 mL/min at rest to a range of 820 to 390 mL/min during exercise at various intensities (Rowell et al., 1964). In a separate study, ICG blood clearance decreased significantly from a mean of 1484 mL/min while sitting to 716 mL/min during exercise, a decline of 52%, and plasma half-life of the dye was significantly increased from 3.7 min at rest to 5.9 min during exercise (Daneshmend et al., 1981).

One of the mechanisms for this redistribution of blood flow during exercise is the alteration in vascular resistance in different regions of the body. For example, during cycling exercise at 75% \(\dot{V}O_{2\text{max}}\), splanchnic blood flow decreased 0.6 L/min (43%) compared to rest, while splanchnic resistance (the ratio of mean arterial pressure to splanchnic blood flow) increased 71 mmHg min/L (126%) (Perko et al., 1998). Overall, this study demonstrated a more than doubling of splanchnic vascular resistance with a concurrent 43% reduction in blood flow to the region during submaximal cycling. The celiac artery was predominately responsible for this response,
with a 165% increase in resistance and a 50% (0.42 L/min) reduction in blood flow. Splanchnic blood flow was measured using two separate techniques, ICG elimination and duplex ultrasound, and the difference between estimates using these two techniques was not significant.

While exercise is one of the stressors that may lead to a redistribution of blood flow, there are other stressors that may also result in alterations in blood flow, both independently and combined with exercise. These stressor conditions can include heat and/or fluid deprivation, as the plasma half-life for ICG increased significantly under each of these conditions when compared to rest (Swartz, Sidell, & Cucinell, 1974). The half-life was prolonged under each condition of stress, as the combination of heat plus exercise resulted in the longest prolongation, followed by exercise alone, heat alone, resting without fluid ingestion, and finally resting alone (Swartz et al., 1974). The data also indicated that the effects of different stressors were additive, such that the effect of exercise and heat was equal to the combined effects of exercise and heat separately.

Further, the plasma clearance of ICG showed marked reductions under all stress conditions tested, with these reductions corresponding to the increases in half-life. The combined effects of heat and exercise appeared to have similar additive effects in reducing the plasma clearance of ICG. If plasma clearance is a valid estimate of liver plasma flow, then findings indicate that liver plasma flow is reduced by the stresses used in the study (Swartz et al., 1974).

Overall, each stress exerts an effect on the clearance of ICG and combining stressful conditions generally supplements this effect. Also, the plasma clearance of ICG was significantly changed under conditions that had little effect on the Vd of ICG, indicating that reduced perfusion of the liver occurred despite little or no contraction of plasma volume (Swartz et al., 1974).
The preceding paragraphs indicate that drastic alterations in splanchnic blood flow can occur with physical exertion. Such alterations have the potential to significantly alter pharmacokinetic parameters that are calculated using measurements of blood flow to this region (such as Vd and CL). An additional potential confounder due to exercise and physical activity is the chronic changes in blood flow distribution that may occur as a result of exercise training.

2.4.2 Blood flow alterations during acute exercise following training

Chronic exercise training has the potential to modify the exercise-induced alterations in splanchnic and renal blood flow, such that the reduction in blood flow is attenuated in those with a higher aerobic fitness (McAllister, 1998). In examining the effects of aerobic fitness on acute exercise-induced reductions in splanchnic and renal blood flows, an appropriate condition must be selected for comparison of the sedentary and trained states. The magnitude of decrease in blood flow to these organs is directly related to relative exercise intensity (McAllister, 1998). Thus, at the same relative \( \dot{V}O_2\text{max} \), blood flow would be expected to be similar between trained and sedentary individuals. Therefore, any comparison to assess the effects of training should examine blood flow at the same absolute rather than relative submaximal exercise intensity.

The mechanisms for this attenuated response have not been fully elucidated. One possibility is a reduction in sympathetic nervous system outflow to vascular beds in the trained state. This mechanism is likely involved, since sympathetic outflow is directly related to relative exercise intensity, which decreased for a given workload following training (McAllister, 1998). Another possibility is an attenuated increase in plasma levels of norepinephrine, vasopressin and angiotensin II, all potent vasoconstrictors. This alteration would reduce the splanchnic and renal vasoconstrictor response at a given submaximal exercise intensity.
In the aforementioned study by Rowell et al., three months of physical training resulted in a 10% attenuation in the reduction of liver blood flow (40% to 30% reduction in blood flow) when exercising at the same absolute workload as that used during pre-training testing (Rowell et al., 1964). The reduction in liver blood flow was even less (25%) for highly trained endurance athletes studied simultaneously at the same absolute workload. Similar results were reported by Clausen (Clausen, 1977). The alterations in blood flow distribution as a result of exercise training have the potential to alter the pharmacokinetics of sertraline, especially for an individual who begins a training program concurrently with starting sertraline in an effort to treat anxiety and/or depression.

2.5 Effect of exercise on drug disposition and pharmacokinetics

Two significant elements contribute to a drug’s disposition within the body: the capacity of drug metabolizing systems, and the rate of delivery of drug to the liver (Daneshmend et al., 1981). In accordance with the preceding review of literature both of these factors will likely be affected by physical activity. When a highly active drug metabolizing system is present for a certain drug, its bioavailability is low and its hepatic extraction ratio is high. For this reason, the elimination kinetics of sertraline will be critically sensitive to changes in hepatic blood flow and there will be extensive first-pass metabolism after oral administration. Therefore, when assessing the effect of exercise on sertraline’s pharmacokinetics, it is also important to highlight changes that occur during bouts of acute physical activity, since a number of changes to sertraline’s ADME will occur when the body shifts from a state of rest to physical activity.
2.5.1 Bioavailability and absorption

Preabsorption bioavailability occurs before systemic or biophasic availability and can be considered as an in vivo analogue of an in vitro drug dissolution profile. For example, for a drug that is administered orally as a tablet or capsule, preabsorption bioavailability is called gastrointestinal availability and refers to the time course of the rates and extent of dissolution of the drug into the gastrointestinal fluids (Smolen, 1976). When determining this oral bioavailability of a drug, it is important to recognize that a variety of factors can affect the results of bioequivalency trials, including posture, type and frequency of food intake, mobility of the human subjects, and pathophysiological conditions (Riegelman & Rowland, 1973). Certain features result in a drug having a low oral bioavailability. These may include: low lipid solubility (if the drug is highly ionized), degradation by the acidic medium of the stomach, metabolism by gut wall enzymes, and metabolism by the liver before entering the systemic circulation (Pleuvry, 2005). Additional factors that influence drug bioavailability may include: drug formation (i.e. particle size, tablet size, enteric coating and pressure used by the tableting machine may affect drug dispersion), physicochemical interactions with other drugs or food resulting in binding of the drug and decreased absorption, and various individual factors such as malabsorption syndromes or altered intestinal mobility.

Before an orally administered drug is able to be absorbed, it must pass through the stomach. The low pH environment in the stomach results in acidic drugs being mostly unionized. However, because of the small surface area and quick gastric emptying, the stomach does not participate significantly in drug absorption. The main site of absorption of orally administered drugs is the small intestine, as its large surface area (250 m²) and epithelium allow for particles to readily filter through the membrane wall (Chillistone & Hardman, 2008). Oral bioavailability is
dependent not only on the ability of a drug to pass through the gut mucosa, but also on the degree of metabolism the drug undergoes by enzymes in the gut wall and/or in the liver. This is known as first-pass metabolism and occurs before orally ingested drugs are able to reach the systemic circulation. The first-pass metabolism effect may be increased or decreased by induction or inhibition of liver enzymes (Chillistone & Hardman, 2008).

Absorption requires the movement of drug across the membranes dividing the absorption site from circulation, most often through the process of diffusion. The rate of absorption is dependent on the permeability constant (which is contingent on both the drug molecule and the membrane), the membrane surface area, and the concentration gradient across the membrane (van Baak, 1990). The permeability constant is dependent on the partition coefficient of a drug between the lipid membrane and aqueous environment. This concentration gradient is maintained as blood flow removes drug that passes through the membrane, maintaining continuous absorption.

Since blood flow to the internal organs is reduced during exercise, the absorption of drug may be slowed due to a decrease in removal of drug and the ensuing reduction in the concentration gradient between the two separate environments. For drugs such as sertraline that are highly lipid soluble, movement through the membrane may be so quick that blood flow would be the rate-determining step for absorption, rather than the penetration of the membrane itself (van Baak, 1990). The rate at which the drug is delivered to the absorption site may also influence the absorption rate.

Overall, physical activity may alter diffusion itself, the rate of delivery to the absorption site, and/or the blood flow responsible for removing drug from that site (van Baak, 1990).
2.5.2 Gastric emptying

Exercise has the potential to alter a number of factors that are important in the regulation of the absorption of drugs from the gastrointestinal tract. For example, gut motility regulates the time that the drug stays at the absorption site, while intestinal blood flow controls the removal of drug from the absorption site.

An additional consequence of redistribution of blood flow that will affect drug absorption is based on gastric emptying. Gastric emptying regulates the rate of delivery to the absorption site (the small intestine for most drugs). While gastric emptying is based on a number of factors such as calories, meal osmolality, and meal temperature, it is generally accepted that emptying of fluids is slightly accelerated during light exercise and emptying of solids is delayed during heavy exercise (Moses, 1990). However, the type of exercise may also be a determining factor, since mechanical movement of fluid within the stomach will influence gastric motility. Indeed, running at 50-70% of \( \dot{V}O_{2\text{max}} \) showed increased gastric emptying rate compared to rest (Neufer et al., 1986), but cycling exercise performed at 40-70% of \( \dot{V}O_{2\text{max}} \) did not alter gastric emptying rate compared to rest (Costill & Saltin, 1974).

The rate of gastric emptying is one of the rate-limiting steps affecting the absorption of orally administered drugs, depending on the solubility of the drug. For a drug with saturated absorption kinetics and/or a tight ‘absorption window,’ accelerated gastric emptying may result in a decline in overall systemic bioavailability (Queckenberg & Fuhr, 2009). Exercise has the potential to decrease the absorption rate of drugs that exhibit a perfusion rate-limited absorption from the gastrointestinal tract (van Baak, 1990).

An additional factor that can influence gastric emptying is the position of the body. Posture can
limit gastric emptying, suggesting that posture can have a significant influence on drug absorption (Queckenberg & Fuhr, 2009). This occurs as a result of several factors. The shift in body position from recumbent to upright leads to a significant increase in levels of hemoglobin, hematocrit, erythrocytes, leucocytes, and platelets, as a result of changes in the concentration and redistribution of blood volume (Hagan, Diaz, & Horvath, 1978; Penev & Kereshka, 1988). For example, a change of posture from lying to standing led to a significant decrease in ICG clearance from 1214 mL/min to 763 mL/min and an increase in ICG half-life from 4.2 min to 5.7 min (Daneshmend et al., 1981).

The implications for individuals progressing from a highly recumbent/sitting, sedentary lifestyle to that of an active one with much more standing time may therefore involve adaptations occurring as a result of postural stability improvements and the ensuing alterations in drug pharmacokinetics brought about by alterations in blood composition. For example, total plasma concentrations of highly protein bound drugs such as imipramine and desipramine increased significantly following 40 min of standing compared to supine position (Abalan et al., 1990). Sertraline is highly protein bound, indicating that its plasma concentration may be altered when an individual shifts from the recumbent to the standing position. The plasma protein binding of sertraline, along with its movement into different tissues, is described by its distribution.

### 2.5.3 Distribution

The distribution of a drug to the site of action depends on variables that affect the delivery of the drug to the intended tissue, the movement of that drug through the tissue membrane, and the binding of that drug to plasma proteins. Physical activity alters drug binding to plasma proteins and tissues; since water moves from the plasma into the tissue, plasma protein concentration may increase during exercise (van Baak, 1990). This occurs due to increased osmolality in the
active tissue and increased hydrostatic pressure and fluid lost as sweat. Therefore, drug
distribution may be substantially altered, particularly for drugs such as sertraline that are highly
dependent on protein binding.

Considering that sertraline is 98% protein bound, the increase in blood protein that results due to
chronic aerobic exercise will have a substantial effect on its pharmacokinetics. Albumin binding
of a drug may reduce the maximal availability of free drug, but it also has the potential to
enhance the duration of the pharmacological effect of the drug in the body. With chronic
exercise, the rise in blood plasma and protein will alter the volume of distribution of sertraline.
$V_T$ will be increased as a result of the gain in total body water, and $f_U$ will be decreased due to
the rise in albumin and other blood proteins. Since both of these distribution parameters will
change with chronic exercise, distribution is likely to be more affected by chronic aerobic
physical activity than by acute bouts of exercise.

### 2.5.4 Hepatic metabolism

Since blood flow is altered drastically during and immediately following physical activity,
pharmacokinetic parameters affected by blood flow will be most influenced during this period.
The metabolism of drugs that require extensive hepatic extraction is significantly dependent
upon blood flow through the liver and therefore tend to be less available to the systemic
circulation. Therefore, changes to hepatic blood flow as a result of physical activity can
significantly modify the metabolism of high extraction drugs (Lenz, 2011). A change in
clearance of these types of drugs (including sertraline) due to physical activity only happens
during the exercise session or time of blood flow changes (Lenz, 2011). The reduction in
visceral blood flow during exercise can significantly alter the clearance and secretion of flow-
limited drugs (Khazaeinia et al., 2000; van Baak, 1990).
Organ clearance is calculated as

\[
\frac{CL_{intrinsic} f_U}{Q + CL_{intrinsic}}
\]

where \( Q \) indicates the organ blood flow, \( f_U \) indicates unbound fraction of the drug, and \( CL_{intrinsic} \) refers to the intrinsic maximal capacity of the organ to remove drug by all pathways without any flow limitations. This index is a distinctive characteristic for a drug in a given situation and reflects three parameters: the partitioning of the drug into the organ from the blood, the size of the organ, and the intrinsic overall rate of elimination by the biochemical processes, i.e. \( V_{max}/K_m \) (Rowland, Benet, & Graham, 1973). When the \( CL_{intrinsic} \) is very large relative to the flow (equal to an extraction ratio >0.8), the actual clearance is not reflective of the activity of the drug metabolizing enzymes but rather the rate of blood flow to the liver. For this reason, changes in this rate will result in nearly proportional changes in the measured clearance. For these types of flow-limited drugs, changes in hepatic blood flow lead to relatively small but proportional changes in the extraction ratio. Conversely, when hepatic blood flow is much greater than \( CL_{intrinsic} \) (equal to an extraction ratio <0.2), clearance is roughly equal to this parameter and is essentially independent of flow. These types of drugs, that do not require extensive hepatic extraction, function virtually independently of hepatic blood flow and are usually more available to the systemic circulation (Lenz, 2011). For these types of capacity limited drugs, changes caused by flow tend to be balanced by an opposite and larger curvilinear alteration in the extraction ratio (Wilkinson, 1975).

Metabolism of these types of drugs depends on hepatic enzyme activity coupled with the unbound fraction of drug present in the blood plasma. Therefore, blood flow alterations that
occur during bouts of physical activity are of less importance. Instead, metabolism of these drugs may be more substantially altered by alterations in physical conditioning; improvements in physical fitness have been shown to stimulate hepatic oxidative metabolism (Villa, Bayon, & Gonzalez-Gallego, 1999). This change, coupled with the change in plasma volume, indicate that it is reasonable to assume that metabolism and pharmacokinetics of low hepatic extraction drugs could be altered in patients progressing from untrained to trained conditions.

2.5.5 Excretion

Drug excretion is another pharmacokinetic parameter that will be altered by acute bouts of physical activity. The major routes of drug excretion from the body are in the urine and bile, but may also occur through sweat, expired air, breast milk or seminal fluid (Lenz, 2011). Elimination through the urine is linked to renal function, and is dependent on glomerular filtration, tubular secretion, and tubular reabsorption. Glomerular filtration rate depends on the amount of blood flow to the kidneys, which is influenced by intensity of physical activity (Lenz, 2011). Glomerular filtration rate has been shown to decrease by 30% during physical activity, as the intensity of physical activity is inversely related to the amount of renal blood flow and therefore the rate of filtration (van Baak, 1990). A similar study reported a 53% decrease in renal blood flow with exhaustive physical activity, compared to pre-exercise renal blood flow (Suzuki et al., 1996). At 30 and 60 min post-exercise, renal blood flow returned to 80% of resting levels. Decreased creatinine clearance and urine volume were also reported immediately following and at 30 minutes post-exercise (Suzuki et al., 1996). The decrease in glomerular filtration rate and renal function that accompanies acute aerobic exercise is unlikely to have a significant effect on the pharmacokinetics of sertraline, since the major metabolite of sertraline,
DMS, may accumulate to a greater degree as a result of delayed elimination, but this metabolite is only weakly active and its effects are negligible.

### 2.6 Summary and Questions

Exercise has wide-ranging benefits that include utility as a preventive and therapeutic tool in the treatment of mental health disorders. These disorders are also treated using pharmaceuticals, such as the anti-anxiety/anti-depressant drug sertraline. While the pharmacokinetics of sertraline at rest are well documented, the alterations to its pharmacokinetics that may occur with exercise are unknown. It is clear that exercise can cause a drastic redistribution of blood flow away from the internal organs and towards working muscle, but the effect that this may have on sertraline’s ADME is unclear. There remain many outstanding issues regarding the effect of acute aerobic exercise on the pharmacokinetics of sertraline. It is also unclear whether aerobic fitness has any impact on the pharmacokinetics of sertraline. A comprehensive understanding of how exercise may change ADME would facilitate an improved understanding of the efficacy and risks of sertraline administration.
3 Purpose and Hypotheses

3.1 Purpose

To date, the effects of physical activity on the pharmacokinetics of sertraline have not been examined. The purpose of this study was to quantify the alterations in the pharmacokinetics of sertraline that occur due to acute aerobic exercise. Furthermore, since improvements in physical fitness have been shown to stimulate hepatic oxidative metabolism (Villa et al., 1999), a secondary purpose was to examine the effects of aerobic fitness of the participants on sertraline metabolism.

A more complete understanding of how acute and/or chronic exercise influence the pharmacokinetics of sertraline will allow health care providers to provide more accurate drug/exercise dosing recommendations. An individual with a mental health issue may be able to relieve his or her symptoms more effectively by augmenting pharmaceutical treatment with exercise, and athletes taking this drug may begin to understand more fully how their exercise training impacts the effectiveness of their pharmaceutical medication.

3.2 Hypotheses

It was hypothesized that sertraline pharmacokinetics would be significantly affected by acute exercise as demonstrated by greater blood concentrations ($C_{\text{max}}$) of sertraline for a longer duration ($t_{\text{max}}$). Due to the redistribution of blood flow that occurs during exercise, the liver will receive less blood flow, meaning that less sertraline may be delivered to the liver. As well, there may be a diminished metabolic capacity of the liver during exercise. These combined effects
were predicted to result in a higher concentration of sertraline with a delayed breakdown of sertraline, leading to an increase in $C_{\text{max}}$ and $t_{\text{max}}$.

It was also hypothesized that more aerobically fit participants would have different pharmacokinetics than unfit participants. As the body adapts to chronic exercise, enzyme activity may change as a result of the change in the ability of the body to utilize oxygen, especially in areas with a high content of mitochondria, such as the liver. Hepatic oxidative metabolism of sertraline may therefore be impacted. The increase in blood volume with chronic exercise training (Convertino, 1991) may also impact the pharmacokinetics of sertraline.
4 Materials and Methods

4.1 Experimental design overview

The study design is depicted graphically in Figure 2. During this repeated measures study, participants were asked to report to the laboratory at U of T on seven separate occasions over a three-week period. During the first visit, participants underwent basic anthropometric testing along with a direct determination of $\dot{V}O_{2\text{max}}$ on a cycle ergometer by means of a graded exercise test.

During the second and fifth visits, separated by at least 14 days, participants were given 100 mg of sertraline, administered orally as a tablet. On either the second or fifth visit, participants rested quietly following drug administration; during the other visit, participants exercised following drug administration. The order of these rest and exercise trials was balanced such that half of the participants rested on the second visit and exercised on the fifth, and half of the participants exercised on the second visit and rested on the fifth. Blood sampling occurred during the second to seventh visits as outlined below. Prior to experimental testing, each volunteer was assessed by the study physician to ensure no contraindications to participation.
The chosen study design represented a proof-of-principle approach, as this area of research is in its primary stage. Since this study is the first to examine the interaction between exercise and sertraline, it was decided to limit the scope of the project to one that examines the effects of a single acute bout of aerobic exercise on the PK of sertraline. It is acknowledged that there are a myriad of other factors that should also be considered (e.g. frequency, intensity, duration, mode, training status).

4.2 Participants

Healthy male volunteers aged 18-40 years were recruited to participate in this study. The sample size was chosen based on the assumption that any exercise-associated changes in pharmacokinetics would be at least as great as those reported for diurnal and fed/fasted effects. Based on the pharmacokinetic differences calculated between morning and evening and fasted and fed sertraline administration (Ronfeld, Wilner, et al., 1997), it was calculated that fifteen subjects would be sufficient to detect significant changes in the pharmacokinetics of sertraline within a participant between rest and exercise trials, with a statistical power of 80% and a 0.05
level of significance. Participant attrition during the trials of about 25% was considered and therefore it was proposed to recruit 19 participants.

Sertraline is contraindicated for those under the age of 18 and for pregnant females, therefore the inclusion of female participants would have required pregnancy tests to be conducted at the beginning of each visit to avoid these potential risks. The associated financial cost precluded the inclusion of female participants in the participant pool. In order to participate, the study physician assessed all volunteers to rule out of the possibility of contraindications against sertraline administration.

Participants were informed of the protocol and of all risks and discomforts that they may experience through participation. Prior to experimentation each participant completed a written informed consent and a Physical Activity Readiness Questionnaire (PAR-Q). The PAR-Q is a validated short questionnaire that helped to determine whether the participant was healthy enough to partake in strenuous physical activity. Fitness was not a participant selection criterion. Potential participants were also screened by the study physician, who performed a full physical examination and reviewed results of the participants’ 10-lead electrocardiogram, prior to enrolment in the study.

4.3 Experimental design

The following experimental design overview depicts the first drug administration visit as the resting trial and the second drug administration visit as the exercise trial, however the order of these trials were equally randomized for each participant, with seven participants beginning with the rest trial and the other seven participants beginning with the exercise trial.
4.3.1 Day 1 – Basic anthropometric testing and determination of $\dot{V}O_{2\text{max}}$

On day 1 of testing, participants came in to the laboratory for anthropometric testing including measurements of height, weight, and percent body fat estimated from a bioimpedance device (Omron® Fat Loss Monitor, Model HBF-306CAN, Toronto, Canada). On this visit participants also underwent testing on the cycle ergometer in order to determine $\dot{V}O_{2\text{max}}$ and to estimate the power output, in watts (W), corresponding to 65% $\dot{V}O_{2\text{max}}$.

4.3.2 Determination of $\dot{V}O_{2\text{max}}$

Following a self-directed warm-up, participants began the $\dot{V}O_{2\text{max}}$ test on the cycle ergometer, starting at zero Watts. This test involved continuous bicycle exercise, with the participant maintaining a pedaling frequency of 70-90 revolutions/min. The workload increased by 25 Watts every minute until either 1) the investigators terminated the test as participants were not able to maintain the target intensity (defined as being unable to keep the pedaling cadence above 60 revolutions/min) or 2) the participant reached volitional fatigue. During the test, participants were connected to a Metamax Cortex 3B (Metamax Cortex, Leipzig, Germany) metabolic apparatus for the measurement of their $\dot{V}O_2$. $\dot{V}O_{2\text{max}}$ was defined as the highest 30-second average recorded, meaning that the peak $\dot{V}O_2$ was considered as the $\dot{V}O_{2\text{max}}$. A true $\dot{V}O_{2\text{max}}$ value may have been higher had a different protocol been used for its assessment. Heart rate was also monitored throughout the test via heart rate telemetry.

4.3.3 Determination of wattage corresponding to 65% $\dot{V}O_{2\text{max}}$

Following a 10-15 minute rest period, participants began cycling at 50W for five minutes. The power output increased to 100W, 150W, and 200W, with each stage lasting five minutes.
During the test, participants were connected to a Metamax Cortex 3B metabolic apparatus for the measurement of oxygen uptake. Since oxygen uptake and power output are directly related, a linear regression model was used to calculate the power output corresponding to 65% of the subject’s VO$_{2\text{max}}$.

### 4.3.4 Day 4 - Resting drug administration

On day 4 (minimum three days following the initial exercise tests), participants returned to the laboratory at 7:30 am to be given a 100 mg dose of sertraline (Teva-Sertraline 100 mg, Sertraline HCl). Participants underwent basic anthropometric testing again to ensure no significant changes from baseline values. Participants were given a standardized light breakfast and lunch while reading/studying independently or resting quietly during the next ten hours, predominately in a seated position. During this time blood samples were taken as outlined below and as depicted in Figure 3. Water was ingested *ad libitum*. Participants were encouraged to maintain their normal exercise regimens during the two-week washout period, and were instructed not to exercise the day before coming into the laboratory for the drug administration protocols.

![Figure 3. Resting sertraline administration experimental protocol.](image-url)
4.3.5 Blood sampling

Blood samples sufficient to produce 4mL of plasma were obtained from each participant just before administration of sertraline (0 hour) and at 1, 2, 4, 6, 8, 10, 24, and 48 hours following administration. Blood samples were collected in a heparinized tube via a flexible catheter inserted into an antecubital vein (BD Nexiva Closed IV Catheter System, NJ, USA). Plasma aliquots were frozen at -30°C during the day of collection, and at -80°C afterwards until being shipped on dry ice to the commercial laboratory where the assay was performed. Hematocrit (Hct) and haemoglobin (Hb) measurements were made in conjunction with each blood sample in order to calculate relative changes in plasma volume according to the method outlined by Dill and Costill (1974) using the following formula:

$$\Delta PV, \% = 100 \left[ \left( BV_{before} \left( \frac{Hb_{before}}{Hb_{after}} \right) - BV_{after} \left( Hct_{after} \right) \right) - PV_{before} \right] \div PV_{before}$$

where $\Delta PV$ is the relative change in plasma volume, expressed as a percent change from the 1-hour blood sampling time point of that day, $BV_{before}$ represents the blood volume at the 1-hour blood sampling time point (a volume of 1L was used), $Hb_{before}$ is the Hb at the 1-hour blood sampling time point, $Hb_{after}$ is the Hb at the respective blood sampling time point, $BV_{after}$ is the ratio of the change in Hb to the 1L initial value, $Hct_{after}$ is the percent Hct at the respective blood sampling time point, and $PV_{before}$ is the difference between the 1L initial total volume and the red cell volume (from the initial percent Hct).

4.3.6 Days 5 & 6 – 24 hour blood sampling

Participants returned to the laboratory at 7:30am for the 24- and 48-hour blood sampling.
4.3.7 Days 6-18 - Washout period

The resting drug administration visit and the exercising drug administration visit were separated by a washout period of at least 14 days in order to ensure that all sertraline has been metabolized and excreted from the body (Ronfeld, Wilner, et al., 1997).

4.3.8 Day 18 - Exercise and drug administration

On day 18 (fourteen days following the resting drug administration), participants returned to the laboratory for the exercising drug administration. Participants came to the laboratory at 7:30am and underwent basic anthropometric testing again to ensure no significant changes from baseline values. They were then given the same standardized light breakfast with the 100 mg dose of sertraline. Four hours following drug administration, participants exercised at 65% of their \( \dot{V}O_2_{max} \) for 30 minutes (Figure 4). This intensity and duration of exercise was chosen since it has been shown to cause a significant redistribution of blood flow away from the liver (Rowell et al., 1964). Blood sampling occurred at the same time intervals outlined previously. A standardized lunch was given to participants, and water intake was *ad libitum*. Participants were instructed not to exercise the day before coming into the laboratory for the drug administration protocols.

![Figure 4. Exercise and sertraline administration experimental protocol.](image)
4.3.9 Days 19 & 20 – 24 hour blood sampling

Participants returned to the laboratory at 7:30am for the 24- and 48-hour blood sampling.

4.4 Measurements

4.4.1 Basic anthropometric measurements

- *Body mass* was measured using a standard scale at the beginning of each visit.
- *Height* was measured using a tape measure.
- *Body fat percentage* was estimated using the Omron® Fat Loss Monitor which uses total body impedance for its calculations.
- *Oxygen uptake, carbon dioxide production, and minute ventilation* were measured using an automated portable metabolic system (Metamax Cortex, Leipzig, Germany) during the \( \dot{V}O_{2\text{max}} \) protocol. Before each \( \dot{V}O_{2\text{max}} \) protocol, gas analyzers were calibrated using gases of known concentrations. \( \dot{V}O_2, \ CO_2, \) and minute ventilation were calculated.
- *Exercise* was done on a Lode Excalibur Sport 925900 (Groningen, The Netherlands) cycle ergometer. The participants used the same footwear and ergometer configuration for every session.
- *Heart rate* was measured continuously throughout each exercise session with heart rate telemetry via a Polar heart rate strap.

4.4.2 Blood Sampling

Blood samples were obtained from an antecubital vein using an indwelling flexible catheter with a 3-way stopcock system which was kept patent via infusion of saline (0.9% sodium chloride) following each sample taken.
4.4.3 Blood Analysis

The assays of plasma sertraline concentration and DMS concentration were all performed at an industrial analytical chemistry laboratory (PharmaCadence Analytical Services, Hatfield, PA, USA). Analysis was done by liquid chromatography-mass spectrometry, with an assay limit of quantification of 1ng/mL.

Measurements of Hb and Hct were done on each blood sample to enable calculations of changes in plasma volume from the baseline sample (Dill & Costill, 1974). Before centrifuging the vacutainers containing the whole blood, blood samples were taken from the vacutainers and transferred into capillary tubes to be spun within the hematocrit rotor to determine hematocrit levels within each sample.

Blood samples were loaded into the capillary tubes, and the capillary tubes were stored within the micro-hematocrit rotor, within the fridge, until the samples were ready to be spun within the centrifuge.

For determination of blood hemoglobin concentration, the microcuvette was filled in one continuous process. Excess blood was wiped from the outside of the microcuvette with a clean, lint-free wipe, using care not to touch the open end of the microcuvette (which could result in blood being drawn out of the microcuvette). The filled microcuvette was placed in the cuvette holder. After 15-60 seconds, the haemoglobin value of the sample was displayed. This value was recorded within the individual participant data sheet.
4.4.4 Code for labelling blood samples

Each plasma sample that was aliquoted into the eppendorf tubes was labelled with the date and study code in order to remain organized and allow for easy identification of samples.

Sample vacutainer label:
- Date YY/MM/DD, ex. 13/4/19
- Code, ex. 03E4
  - The first two digits (e.g. 03) correspond to the participant number, i.e. the third participant will be given the label “03”
  - The next letter (e.g. E) corresponds to the type of drug administration protocol, i.e. exercise (E) or rest (R)
  - The next number (e.g. 4) corresponds to the sample number, i.e. sample 4 (11:30am).

4.4.5 Statistical analysis and pharmacokinetic analysis

Statistical analysis of the raw-assayed drug concentration data was performed using a two-way (trial by hour) repeated measures analysis of variance (ANOVA) to determine the effect of trial (i.e. rest or exercise) and hour (blood sampling intervals at 0, 1, 2, 4, 6, 8, 10, 24, and 48 hours) on sertraline concentration.

PK variables using the observed drug concentration data were calculated as follows: $C_{\text{max}}$ was taken directly from the experimental data; $t_{\text{max}}$ was defined as the first occurrence of $C_{\text{max}}$. The rate constant ‘$k$’ was calculated using least-squares regression of the log concentration-time data
during the terminal log-linear phase of the last sampling points. \( \text{AUC}_{\text{inf}} \) was determined using the linear trapezoidal rule, and \( t_{1/2} \) was calculated as 0.693/k.

To determine the influence of aerobic fitness on the PK of sertraline, relative \( \dot{\text{V}}\text{O}_2\text{max} \) was added as a covariate to the ANOVA model. Furthermore, participants were ranked according to relative \( \dot{\text{V}}\text{O}_2\text{max} \), and split into two groups of seven, depending on whether the participant was above or below the group median. Differences in PK parameters between these two groups were examined separately for both the rest as well as the exercise trials.

Paired sample t-tests were used to assess differences in PK variables (\( C_{\text{max}}, t_{\text{max}}, \text{AUC}, \text{and } t_{1/2} \)) between trials. All comparisons were based on a 95% confidence interval \( (P < 0.05) \), and values are expressed as mean ± SD (IBM Statistical Package for Social Sciences, Version 20).

### 4.4.6 The pharmacokinetic compartmental models used to fit the raw assayed drug concentration data

Population modeling was performed by Dr. Sandy Pang and Qi Yang using ADAPT 5 PK/PD Systems Analysis Software (BMSR Biomedical Simulations Resource, Version 5). A single as well as multi-compartment approach was used to model the data set. The two main compartments included the central compartment and the peripheral compartment. Additional compartments included the gut and metabolite. Figure 5 shows a schematic representation of the two compartment model: \( k_a \), the absorption rate constant of the parent drug from the gut to the central compartment; \( k_{12} \) and \( k_{21} \), the distribution rate constants of the parent drug that is transferred between the central (1) and peripheral (2) compartments; \( k_m \), the rate constant of the parent drug in the central compartment that is transferred to the metabolite compartment; \( k'_{10} \), also referred to as \( k_e \), the elimination rate constant from the central compartment without \( k_m \);
$k_{[M]}$, the elimination rate constant from the metabolite compartment; and $V_1$, the apparent Vd by the oral route. The one compartment model was identical to the two-compartment model, except that it did not include the peripheral compartment, and therefore did not include $k_{12}$ and $k_{21}$.

**Figure 5.** Schematic representation of the multi compartment model used to model the observed sertraline concentration data using ADAPT 5.

Abbreviations: $k_a$: absorption rate constant; $k_{12}$ and $k_{21}$: the rate constants between the central (1) and peripheral (2) compartments, respectively; $k_m$: the rate constant between the central and metabolite (3) compartment; $k'_{10}$: the elimination rate constant from the central compartment without $k_m$; $k_{[M]}$: the elimination rate constant from the metabolite compartment; and $V_1$: the apparent Vd by the oral route.
Transit between compartments can be represented by the following rate equations:

\[
\frac{dX_1}{dt} = \frac{dV_1C_1}{dt} = \left(k_aF_dose_{p0}\right) + \left(k_{21}V_2C_2\right) - V_1C_1(k_{12} + k_m + k_{10}')
\]

**Equation 1:**

\[
\frac{dX_2}{dt} = \frac{dV_2C_2}{dt} = (k_{12}V_1C_1) - (k_{21}V_2C_2)
\]

**Equation 2:**

\[
\frac{dX_3}{dt} = \frac{dV_mC_M}{dt} = (k_mC_mC_M) - (k_{M}V_mC_M)
\]

**Equation 3:**

\[
\frac{dF_{dose_{p0}}}{dt} = -(k_aF_{dose_{p0}})
\]

**Equation 4:**

In an effort to improve the accuracy of the drug concentrations of the predicted model, the measured anthropometric variables from Table 2 were separately added to the model as covariates in order to adjust for the size of the central compartment. The only variable that was significantly able to improve the estimate of apparent Vd of the central compartment was participant body weight. The size of the central compartment was normalized using allometric scaling; apparent Vd was multiplied by the participant body weight divided by the mean body weight of the group.

PK variables for the predicted drug concentration data were calculated as follows: \(C_{\text{max}}\) was taken as the maximum value of drug concentration from the predicted line of best fit. \(t_{\text{max}}\) was the time point that this concentration occurred. \(\text{AUC}_{\text{inf}}\) was calculated using the linear trapezoidal rule of the predicted drug concentration vs. time graph, and included the measure of
\( \text{AUC}_{\text{extrapolated}} \), which was derived using the elimination rate constant \( \beta \) of the extrapolated predicted drug concentration data. \( t_{\frac{1}{2}} \beta \) was also calculated using this elimination rate constant.
5 Results

5.1 Participant Characteristics

Fifteen volunteers were recruited by word of mouth, and one volunteer responded to the study flyer on the faculty website. Of those fifteen volunteers, thirteen were briefed about the study, pre-screened by the primary study investigator, medically screened by the study physician, and completed all aspects of experimental testing as participants. One of those fifteen volunteers did not advance past the study briefing due to scheduling restraints, and the other did not pass the medical screening and was therefore excluded from participation in the study. The volunteer recruited from the online study flyer also completed all of the pre-study screening procedures and completed all aspects of the experimental testing as a participant.

Overall, fourteen healthy males (23.9 ± 2.52 years of age, 80.3 ± 12.6 kg) successfully completed both trials of the study (Table 2). These fourteen participants were medically screened by the study physician and cleared to participate. All participants had normal resting blood pressure and can be considered as moderately aerobically fit with a mean VO$_{2\text{max}}$ of 50.5 ± 9.71 mL·kg$^{-1}$·min$^{-1}$ (Table 2).
Table 2. Participant characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.9 ± 2.53</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.81 ± 0.09</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.3 ± 12.6</td>
</tr>
<tr>
<td>BMI (kg•m⁻²)</td>
<td>24.5 ± 2.93</td>
</tr>
<tr>
<td>Body Surface Area (m²)</td>
<td>2.0 ± 0.19</td>
</tr>
<tr>
<td>Resting Blood Pressure (mmHg)</td>
<td>115/70 ± 6.2/9.09</td>
</tr>
<tr>
<td>Percent Body Fat</td>
<td>14.7 ± 4.41</td>
</tr>
<tr>
<td>Absolute $\dot{V}O_{2\text{max}}$ (L•min⁻¹)</td>
<td>4.03 ± 0.86</td>
</tr>
<tr>
<td>Relative $\dot{V}O_{2\text{max}}$ (mL•kg⁻¹•min⁻¹)</td>
<td>50.5 ± 9.71</td>
</tr>
<tr>
<td>Average $\dot{V}O_2$ from the 30-min exercise session (mL•kg⁻¹•min⁻¹)</td>
<td>32.2 ± 7.01</td>
</tr>
<tr>
<td>Percent of $\dot{V}O_{2\text{max}}$ exercised at during the 30-min exercise session</td>
<td>63.6 ± 5.31</td>
</tr>
<tr>
<td>Power output during the 30-minute exercise session (W)</td>
<td>154 ± 45.4</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>12</td>
</tr>
<tr>
<td>Caribbean</td>
<td>1</td>
</tr>
<tr>
<td>Chinese</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are means ± SD.

Abbreviations: $\dot{V}O_{2\text{max}}$: maximum rate of oxygen consumption.
5.2 Relative changes in plasma volume

Exercise has been demonstrated to affect plasma volume as a function of intensity and duration of exercise. Significant changes in plasma volume would directly affect the expression of drug concentration therefore it was important to assess whether plasma volume changes needed to be factored into the expression of sertraline concentration. Using the method outlined by Dill and Costill (Dill & Costill, 1974), relative changes in plasma volume were estimated from measures of Hb and Hct, with the 1-hour blood sampling interval used as the initial value to compare same day samples. There was not a significant main effect of trial or of the interaction effect between trial and hour on relative changes in plasma volume (Table 3). There was however a change in relative plasma volume within a day; Mauchley’s test indicted that the assumption of sphericity was met ($X^2 (20) = 26.74, p = 0.172$), and there was a significant effect of hour (i.e. time of day) on relative change in plasma volume, $F (2, 60) = 2.51, P = 0.031$.

To elucidate mechanisms for potential changes in drug concentration, the correlations between observed sertraline concentration and relative change in plasma volume at that point in time were examined; no significant correlations were found.

Since no differences in relative change in plasma volume were evident between trials, drug concentration data did not need to be corrected.
Table 3. Mean relative changes in plasma volume at each blood sampling time point during each trial for all participants, expressed as a percentage change from the 1-hour blood sampling time point of that trial.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Relative Changes in Plasma Volume: Mean Percentages ± SD At Blood Sampling Time Points (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Rest</td>
<td>-1.80 ± 4.93</td>
</tr>
<tr>
<td>Exercise</td>
<td>0.909 ± 5.06</td>
</tr>
</tbody>
</table>

Note: there were no significant differences in relative changes in plasma volume between the rest and exercise trials, at the corresponding blood sampling time point (P < 0.05).

5.3 Sertraline Concentration

5.3.1 Main effects of trial and hour on raw assayed sertraline concentration

There was not a significant main effect of trial or of the interaction effect between trial and hour on the concentration of sertraline or desmethylsertraline (Figures 6 and 7). Paired sample t-tests were conducted to compare model-independent pharmacokinetic variables between trials based on observed drug concentration data. No significant differences were found between rest and exercise trials (Table 4). As to be expected with an acute drug administration, there was a significant difference in drug concentration within a trial, depending on hour, F (1.71, 22.23) = 63.1, P < 0.001; Mauchley’s test indicted that the assumption of sphericity was not met (X² (35) = 198.1, p < 0.001), therefore the Greenhouse-Geisser correction was applied.
Significant differences that only involved the independent variable of hour are not presented, since diurnal changes in the concentration of a single acute administration of sertraline have been previously established (Ronfeld, Tremaine, et al., 1997; Ronfeld, Wilner, et al., 1997).

There was not a significant improvement in the repeated measures ANOVA when relative $\dot{\text{VO}}_{\text{2max}}$ of the participants was added as a covariate, indicating that there was no difference in the concentration of sertraline between participants of various aerobic fitness levels. Furthermore, after dividing the participants into two groups based on relative $\dot{\text{VO}}_{\text{2max}}$, paired samples t-tests revealed that there were no significant differences in any of the PK parameters between groups, during either the rest or exercise trials.

**Figure 6.** Mean raw assayed sertraline and desmethylsertraline concentrations between trials across all sampling time points.

Abbreviations: $\mu$g/L: micrograms•Litre$^{-1}$; h: hours
Figure 7. Mean raw assayed sertraline and desmethylsertraline concentrations between trials across all sampling time points, plotted using a semi-logarithmic scale in order to view the t_{1/2}β.

Abbreviations: µg/L: micrograms•litre⁻¹; h: hours
### Table 4. Model-independent PK parameters. Comparison of pharmacokinetic parameters of sertraline and desmethylsertraline derived from raw assayed drug concentration data during the rest and exercise trials following a single 100 mg dose administered in tablet form.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sertraline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ ($\mu g \cdot L^{-1}$)</td>
<td>33.1 ± 12.8</td>
<td>33.72 ± 15.73</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>7.42 ± 2.1</td>
<td>6.74 ± 2.02</td>
</tr>
<tr>
<td>$t_\beta$ (h)$^a$</td>
<td>19.7 ± 5.89</td>
<td>18.51 ± 2.75</td>
</tr>
<tr>
<td>$\text{AUC}_{\text{inf}}$ ($\mu g \cdot h \cdot L^{-1}$)$^b$</td>
<td>1000 ± 427</td>
<td>950 ± 438</td>
</tr>
<tr>
<td><strong>Desmethylsertraline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ ($\mu g \cdot L^{-1}$)</td>
<td>11.0 ± 3.07</td>
<td>9.92 ± 2.37</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>21.5 ± 13.2</td>
<td>20.6 ± 10.6</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Note: There were no significant differences in any parameter between the rest and exercise trials ($P < 0.05$).

Abbreviations: $C_{\text{max}}$ = maximum plasma concentration; $t_{\text{max}}$ = time to $C_{\text{max}}$; $t_\beta$ = terminal elimination half-life; $\text{AUC}_{\text{inf}}$ = area under the plasma concentration-time curve from zero to infinity; $\mu g$: micrograms; mL: millilitres; h: hours; $\beta$: beta (elimination rate constant).

$^a$Estimated from the last 2 drug sampling time points (24 and 48 h), see Figure 7 for plot of elimination phase.

$^b$Sum of $\text{AUC}_{48h}$ (calculated using the linear trapezoidal rule) and $C_{48h}/(0.693/t_\beta)$.
6 Discussion

To our knowledge, this is the first study to examine the effects of exercise of any type on sertraline pharmacokinetics. Considering the variations in dosing regimens reported in previous studies (50-400 mg, administered acutely or chronically, with or without increasing the amount of drug by titration), the values of the pharmacokinetic parameters found in the present study (Table 4, Appendix P) are within the expected range (Demolis et al., 1996; Hiemke & Hartter, 2000; Mandrioli, Mercolini, & Raggi, 2013; Murdoch & McTavish, 1992; Obach et al., 2005; Perry & Benfield, 1997; Preskorn, 1997; Ronfeld, Tremaine, et al., 1997; Ronfeld, Wilner, et al., 1997; Van Harten, 1993; Warrington, 1991). Comparisons of the present study’s results to those of these other studies of sertraline pharmacokinetics should consider that the current study is the only one to date where the PK parameters have been calculated based on the computed sertraline concentrations derived from the ADAPT 5 data fitting model. All the previous reports of the PK of sertraline are based solely on the assayed drug concentrations.

This study’s dose of 100 mg was substantially less than the frequently used dosage of 200 mg, and this study involved only a single administration, rather than the roughly 14 days of continuous dosing needed to reach a steady state concentration. Another difference between this study and others is that participants in the present study ingested sertraline after an overnight fast, in contrast with the co-administration with food as done in other studies. However, there are equivocal reports of the effects of co-ingestion with food in previous studies as to the effect on absorption of sertraline (Murdoch & McTavish, 1992; Ronfeld, Wilner, et al., 1997).
Notwithstanding the differences in the above studies, given that the PK parameters reported in this study are within the normal range reported by others, there is confidence in the assessment of the effects of exercise that was carried out in the present study.

6.1 Relative changes in plasma volume

Participants demonstrated no difference in relative changes in plasma volume between rest and exercise trials. Previous studies using cycle ergometry exercise have reported decreases in plasma volume of about 12% (Lindinger et al., 1994) and 17% (McMurray, 1983) during exercise of a similar intensity and duration, and a return to normal levels within 60 minutes of completion of the exercise (McMurray, 1983; Novosadova, 1977). This effect may have occurred in the present study, since relative changes in plasma volume were estimated from blood samples taken immediately before and two-hours after the start of the exercise session.

A substantial decrease in plasma volume as a result of exercise may have artificially inflated the concentration values for sertraline, without a genuine change in the amount of drug. Had the exercise session been more exhausting or dehydrating, the effect on relative changes in plasma volume may have become more pronounced (Dill & Costill, 1974).

6.2 Raw assayed sertraline data vs. modeled sertraline data

The results presented in Table 4 were calculated using the raw assayed sertraline concentration data, similar to what was reported in previous studies of the PK of sertraline (Demolis et al., 1996; DeVane et al., 2002; Hiemke & Hartter, 2000; Murdoch & McTavish, 1992; Perry & Benfield, 1997; Preskorn, 1997; Ronfeld, Tremaine, et al., 1997; Ronfeld, Wilner, et al., 1997; Warrington, 1991). From the statistical analysis of the raw assayed blood concentrations, none
of the PK parameters of sertraline changed due to the acute aerobic exercise trial, when compared to rest (Table 4).

This method of assessing pharmacokinetic variables has been considered simplistic by some in that drug concentration values are solely a function of the time interval at which blood was sampled. The observed drug concentrations represent a snapshot of 9 periods within the 48-hour sampling interval, and may not reflect the \textit{in vivo} drug concentration changes that can be expected based on an understanding of the relevant physiology. Without such considerations the change in drug concentration between sampling points is unknown, and as such must be assumed to increase or decrease linearly between the observed values. Similarly, the $C_{\text{max}}$ and $t_{\text{max}}$ derived from the observed data are a function of the time-points chosen for blood sampling; it is possible that higher values existed between sampling points.

The use of computer-simulated data fitting based on compartmental modeling allows for an improved interpretation of the drug concentration-time data since the drug concentration vs. time profile was produced based on parameters from the present study, such as the participant weights, the time of blood sampling intervals, the raw assayed sertraline concentrations, as well as the molecular weight of sertraline. This method of data analysis allows for a more accurate prediction of $C_{\text{max}}$, $t_{\text{max}}$, $AUC_{\text{inf}}$, $t_{1/2}\beta$, and drug concentration following the 48-hour sample, therefore improving all of the PK parameter estimates. As well, this method of analysis provides estimates of the rate constants within the compartmental model, allowing for inferences on the ADME of sertraline.

Results from the repeated measures ANOVA of observed drug concentrations were included to demonstrate the initial statistical data analysis, but because of the improved sophistication of the computer-simulated data fitting, the estimated drug concentration data is discussed in more
detail. Results of the rate constants derived from the data fitting as well as the PK parameters based on data fitting can be found in Appendices K-P.

6.2.1 Comparison of the one vs. two compartment models

In order to determine which pharmacokinetic compartmental model provided a better fit for the data, an F-test was performed (Boxenbaum, Riegelman, & Elashoff, 1974). A two-compartment model is assumed to provide a better fit for the data, since more compartments implies greater specificity. However, the F-test indicates whether the two-compartment model provides a statistically significant improved fit compared to the one compartment model. Results of the F-test indicated that there was no statistically significant improvement in fit using the two compartmental model, $P < 0.05$, $F (3,1) = 199.5$.

Additionally, the results of the rate constants from the one compartmental model were in accordance with predicted physiological changes that occur during acute aerobic exercise, such as a decrease in $k_a$ due to decreased absorption and a decrease in $V_1$ due to decreased distribution (Appendix N).

For these reasons, the rate constants and volume of sertraline in the central compartment from the one compartmental model as well as the PK parameters derived from the sertraline concentrations predicted from the one compartmental model are discussed. A comparison of the changes in rate constants and volume of sertraline in the central compartment between the one and two-compartment models is shown in Appendix O.
6.2.2 Model rate constants and Vd central compartment

Paired sample t-tests were conducted to compare rate constants and the apparent Vd of the central compartment between trials for the one and two compartment models. Significant differences in $k_a$, $k_{10}$, $k_m$, $k_{10}$, $V_1$, and $k_{V(M)}$ were found between trials for the one compartment model (Appendix N). The rate constants and apparent Vd for the central compartment for each participant along with the predicted population mean for both the one compartment and two compartment models is shown in Appendix K.

6.3 Effect of trial on the pharmacokinetic variables using modeled sertraline concentration data

This study has demonstrated that an acute bout of aerobic exercise on a cycle ergometer performed for 30 minutes at 65% of $\dot{VO}_{2\text{max}}$ alters the $t_{0.5}\beta$ of a single, orally ingested 100 mg dose of the selective serotonin reuptake inhibitor sertraline (Appendix P). The hypothesis that exercise would lead to a higher $C_{\text{max}}$ and longer $t_{\text{max}}$ of sertraline was not supported by the present study, although an increase in the $t_{0.5}\beta$ did occur during the exercise trial. The secondary hypothesis that more aerobically fit participants would exhibit different pharmacokinetics compared to unfit participants was not supported.

6.3.1 Effect of exercise on the absorption of sertraline

The $k_a$ of sertraline was decreased with exercise (Appendix N), suggesting that the rate of transport of parent sertraline out of the intestine and into the central compartment may be decreased by acute aerobic exercise.
Conflicting reports exist as to the effect of exercise on the absorption of orally administered drugs, since this aspect of the drug-exercise interaction has not been extensively studied. Some studies have reported an increase in the absorption of drugs, specifically following acute exercise of high intensity. For example, the rate of absorption of sulfamethizole, tetracycline, and doxycycline was likely increased when participants played basketball for 50 minutes per hour, for 4 hours, at a mean heart rate of 130-140 beats per minute (Ylitalo, Hinkka, & Neuvonen, 1977). The $C_{\text{max}}$ of these drugs was also increased, as a result of increased absorption coupled with delayed elimination. A similar study demonstrated an increase in the $k_a$ of caffeine following acute aerobic exercise (Kamimori et al., 1987).

Other studies have reported a decrease in the absorption of drugs administered orally when combined with exercise. The absorption of antipyrine, aminopyrine, and salicylic acid were all decreased with acute aerobic exercise (Brouns, Saris, & Rehrer, 1987; Hurwitz et al., 1983). Similarly, midazolam absorption decreased with moderate intensity aerobic exercise, as evidenced by decreased $C_{\text{max}}$ and $k_a$, and an increased $t_{\text{max}}$, in comparison with rest (Stromberg et al., 1992). Absorption from the gastrointestinal tract may be slowed as a result of exercise, since gastric emptying is slowed and bowel transit time is decreased (Costill & Saltin, 1974). This implies that a drug such as sertraline will have decreased ability to enter the blood stream from the intestine. Overall, results of this study support the previous reports that acute aerobic exercise diminishes the absorption of orally administered drugs.

6.3.2 Effect of exercise on the distribution of sertraline

The volume of parent drug in the central compartment was decreased during the exercise trial (Appendix N). Sertraline is 98% protein bound within the blood plasma (Ronfeld, Tremaine, et al., 1997; Warrington, 1991). This has implications for its volume of distribution, especially
during or after an acute bout of exercise. Exercise has the potential to alter the composition of the blood, which may impact the distribution of a drug, according to the following equation:

\[ V_d = V_p + \Sigma V_T \left( \frac{f_{u_{plasma}}}{f_{u_{tissue}}} \right) \]

Despite the fact that plasma volume was not shown to change in the present study, there may have been changes that occurred and were not demonstrated due to the time of the blood sampling intervals. The earliest blood sample following the exercise session was taken two hours following the onset of exercise, meaning that plasma volume may have decreased, undetected, following the exercise session, and then returned to normal by the time of the blood sample. As is common during acute aerobic exercise, a decrease in plasma volume can lead to an increase in albumin and other blood proteins (Lindinger et al., 1994). This can lead to an increase in protein binding of a drug, thereby reducing the fraction of unbound drug in the plasma. Taken together, these potential exercise-induced changes in the composition of the blood may have led to the observed decrease in the volume of distribution of sertraline during the exercise trial (Appendix N).

While the volume of distribution of sertraline may have been impacted during the exercise trial, the impact of this change on distribution is still unknown, specifically possible changes in the distribution of sertraline in the brain. Sertraline exerts its effects by inhibiting uptake of serotonin at the serotonin receptors of the brain (Murdoch & McTavish, 1992), and the efficacy of sertraline in this regard is presumed to be a function of its ability to bind with these receptors. Cerebral blood flow is elevated up until the exercise intensity of the present study, and then decreases with heavy exercise (Ogoh & Ainslie, 2009). These changes need to be considered when assessing possible exercise-induced changes in the receptor binding ability of sertraline.
6.3.3 Effect of exercise on the metabolism and excretion of sertraline

The total elimination rate constant ($k_{10}$) of sertraline was increased during the exercise trial (Appendix N). When considered in conjunction with the finding that the volume of sertraline in the central compartment decreased during the exercise trial (Appendix N), the increased total elimination rate constant may be explained by a possible lack of change in the clearance of sertraline between trials. Sertraline’s bioavailability of roughly 44% is one of the lowest amongst all S.S.R.I.s (Hiemke & Hartter, 2000). This was predicted to be a favourable quality a priori, since any differences in hepatic blood flow as a result of exercise would alter the first-pass metabolism of sertraline to the greatest extent. However, results of this study indicated that this was not the case. Since the value of 44% is close to 50%, the equation for bioavailability ($F = Q / (Q + CL_{int})$) indicates that the $CL_{int}$ of sertraline must not have been changed dramatically. Hepatic blood flow must approach $CL$, meaning that exercise may not have affected $CL$, since $CL$ and $Q$ change by approximately the same amount. Wilkinson (1975) notes that when $CL_{int}$ is large compared to flow, corresponding to a bioavailability of roughly 20% or less, $CL$ does not reflect the activity of the CYP enzymes, but rather the hepatic blood flow rate, and changes in this rate will result in nearly proportional alterations in the measured clearance.

Without a direct measurement of changes in hepatic blood flow as a result of exercise, it is difficult to ascertain the impact of changes in blood flow on hepatic function, as well as the impact of exercise on hepatic enzyme function, irrespective of changes in blood flow. Furthermore, the combined influence of changes in blood flow on the enzymatic function of the liver also remains uncertain. Inter-individual differences in the hepatic oxidation of sertraline can exist due to numerous factors.
Differences in the aerobic fitness of participants may have accounted for differences in the activity of hepatic enzymes, which could contribute to the inter-individual discrepancies in sertraline concentration. For example, three months of aerobic physical training led to a correlation between the change in \( \dot{V}O_{2\text{max}} \) and relative change in aminopyrine metabolism, an indication that chronic exercise stimulated hepatic oxidative metabolism (Boel et al., 1984).

The interaction between physical activity and hepatic enzyme activity is still in question. Demethylation and hydroxylation may be affected to a different extent by various stimuli, such as aging or alcoholic cirrhosis (Jorquera et al., 1998). A similar effect may be present in highly trained individuals, such as the endurance trained athletes in the study by Villa et al., which would explain the difference in the clearance of antipyrine in those individuals compared to sedentary controls (Villa et al., 1999). The participants in the present study may not have experienced this effect, since they were not as highly trained as those in the Villa et al. study.

Contributing to the inter-individual variation in enzyme activity is the potential for genetic polymorphisms in the CYP450 enzymes, specifically CYP2D6 and 2C19. Individuals with several active gene copies metabolize drugs more rapidly, whereas those lacking functional CYP2D6 genes metabolize CYP2D6 substrates at a lower rate (Eichelbaum, Ingelman-Sundberg, & Evans, 2006). The PK parameters of similar SSRIs such as fluoxetine and paroxetine have been correlated with CYP2D6 genotype (Eichelbaum et al., 2006). Similarly, there was a difference in AUC\(_{\text{inf}}\), \( t_{1/2} \), and oral CL of sertraline between CYP2C19 poor and extensive metabolizers (Wang et al., 2001). Without controlling for hepatic enzyme function by genotyping participants, the effects of external stimuli such as exercise on the concentration of sertraline are challenging to interpret.
It has been reported that the prevalence of “sertraline poor metabolizers” (individuals with defective enzymes that are responsible for metabolizing sertraline) is higher in Asian populations (13-23%) compared to Caucasian populations (2-5%) (de Morais et al., 1994). It is interesting to note that the one participant of Chinese ethnicity (participant 15) in the present study was the only participant to become ill during the study period, 4 hours following the ingestion of sertraline. The $k_a$ and $k_{10}$ of this participant were unchanged between trials (Appendix K), indicating that movement of sertraline from the intestine into the liver and the conversion of parent drug to metabolite were both reduced, possibly as a consequence of CYP2C19 polymorphism. It has been reported that poor metabolizers of sertraline with a homozygous mutant CYP2C19 genotype exhibited severe side effects of intestinal disturbances (nausea, vomiting, diarrhea) (Xu et al., 1999). A probable cause of these side effects is that poor CYP2C19 metabolizers cannot immediately metabolize sertraline to inactive desmethylsertraline metabolite, resulting in an accumulation of sertraline and potentially the development of sertraline-associated toxicity (Xu et al., 1999).

6.3.3.1 Implications of the increased elimination half-life of sertraline during the exercise trial

The elimination half-life of sertraline increased by 30.5% during the exercise trial compared to the rest trial (Appendix P). This change likely represents a physiologically significant difference, since a change in the magnitude of the elimination half-life by almost one-third during the exercise trial likely has potential implications for the dosing regimen of sertraline. However, proper interpretation of the effect of a change of this magnitude is only possible with a consideration of the impact that this change may have on the pharmacodynamics of sertraline. A 30.5% increase in the half-life of sertraline is likely to influence its pharmacodynamics,
thereby impacting its efficacy and clinical implications. While the direct impact of an increase in the elimination half-life of sertraline when combined with acute aerobic exercise is still unknown, it is likely that a change of this magnitude is biologically significant, in addition to being statistically significant.

Although the present study involved administration of a single 100 mg dose of sertraline, certain inferences can be made about the implications that changes in the elimination half-life of sertraline may have when the drug is administered chronically to elicit a steady-state concentration. The elimination phase of a drug has a greater impact on its AUC$_{\text{inf}}$ than the $C_{\text{max}}$ achieved, since the elimination phase ($\beta$), is much longer than the absorption phase ($\alpha$). When comparing the pharmacokinetics of a drug administered acutely vs. chronically, the measure of AUC$_{\text{inf}}$ is most important, since the steady-state concentration of a drug will be stable when a constant dose is administered chronically. Therefore, although the $C_{\text{max}}$ of the drug may change when the dosing regimen is changed, the AUC$_{\text{inf}}$ will not change accordingly. For this reason, the AUC$_{\text{inf}}$ (and the elimination half-life contributing to this AUC$_{\text{inf}}$) is the most important PK parameter to consider when attempting an extrapolation of PK parameters that are based on an acute drug ingestion trial, to expected PK parameters that are based on a chronic dosing trial. This assumption indicates that because the AUC$_{\text{inf}}$ of sertraline in the present study was unchanged between rest and exercise trials, no change in the AUC$_{\text{inf}}$ of sertraline would result if chronic dosing of sertraline was combined with a similar exercise intervention.
6.4 Study limitations

6.4.1 Inter-individual responses to exercise

There exists the potential for large inter-individual variation in the physiological responses to exercise, despite all participants exercising at 65% of their $\dot{V}O_{2\text{max}}$. This variation may have influenced the extent of change in hepatic blood flow of participants based on their aerobic fitness; this was not controlled for. The ability of a given participant to tolerate the exercise session varied. The disruption to resting metabolic rate and systemic blood flow would have varied accordingly (McAllister, 1998), effectively varying the impact of the exercise between participants and the resulting influence on the concentration of sertraline. Relative $\dot{V}O_{2\text{max}}$ is the most commonly used physiological variable for standardizing the strain on the cardiovascular and aerobic metabolism systems between individuals, although it is acknowledged that there are physiological systems that may respond very differently to exercise at the same percent of $\dot{V}O_{2\text{max}}$, especially in individuals at the extreme ranges of aerobic fitness, such as the participants in the present study whose relative $\dot{V}O_{2\text{max}}$ values ranged from 35-71 mL/kg/min.

6.4.2 Effect of posture on sertraline pharmacokinetics

A potential confounding variable during the resting drug administration protocol was the difference in a participants’ posture between the rest and exercise trials. During the resting drug administration protocol, participants were seated comfortably, while during the exercise drug administration protocol, participants performed upright cycle ergometry for a period of 30 minutes. This change in posture may influence the pharmacokinetics of a drug (Queckenberg & Fuhr, 2009). To correct for this confounder, participants could have been asked to sit on the cycle ergometer for 30 minutes during the resting drug administration protocol, without
exercising. It was acknowledged that this approach lacks external validity, and was not in accordance with the ‘sedentary lifestyle’ that the present study was attempting to mimic during the resting drug administration protocol.

6.4.3 Dose of sertraline administered

A limitation in the design of this study involved the dose of sertraline administered to participants. The amount of drug administered was not standardized relative to the exercise intensity performed by the participants, or the body weight of the participant.

Despite the fact that each participant cycled at a similar relative intensity based on his $\dot{V}O_2_{\text{max}}$, the 100 mg dose administered was the same for all participants, regardless of aerobic fitness level. Similarly, this dosage was not adjusted based on the body weight of the participant. Considering the between-participant differences in sertraline concentration, it is reasonable to conclude that the variance in drug concentration would have been reduced had the administered dose been relative to some established criteria, such as body weight (Holford, 1996). Using the findings of the present study in combination with similar previous studies (Ronfeld, Tremaine, et al., 1997; Ronfeld, Wilner, et al., 1997), it is recommended that a dose of 1.22 mg of sertraline per kg body weight be administered in future studies in order to achieve a less variable $C_{\text{max}}$ irrespective of participant body weight.

While the mixture of absolute and relative experimental interventions was more practical for the present study design, it is acknowledged that this design lacked the superior method of standardizing the dosage based on certain relevant factors (e.g. weight) that would have led to a more stringently controlled experimental design. Had this been the case, a confounding variable
would be removed and the conclusions drawn based on the experimental intervention of exercise would become more robust.

6.4.4 Measures used to determine participant composition

While it is believed that measures of height, weight, $\dot{V}O_2$, and blood pressure were accurate, the measure of percent body fat may have been incorrect due to the measurement device used. The use of a handheld bioimpedance device to predict body fat percentage is less than ideal compared to other established methods (caliper measurement of skin-folds, hydrostatic weighing, Bod Pod), and results may have been altered by the time of day of the recording as well as the hydration status of the participant. Had a more accurate method for determining participant body fat percentage been used, this variable may have become a covariate added to the predicted drug concentration model, and therefore could have been used to standardize sertraline concentration between participants.

While a more accurate reading of percent body fat would have been ideal, two crucial variables that would aid in understanding results were not readily quantifiable. Based on the methods of previous reports, had the present study determined hepatic enzyme function of participants (Wang et al., 2001) as well as hepatic blood flow during exercise (Daneshmend et al., 1981; Rowell et al., 1964; Villa et al., 1999), a clearer picture would be afforded when interpreting variations in drug metabolism that exist between individuals, as well as variations due to any experimental intervention, such as exercise.
6.4.5 Participant compliance

Although it is virtually impossible to control for participants’ engagement in physical activity outside of the laboratory immediately before and during the blood-sampling time period, participants were asked to abstain from exercise the day prior to coming into the laboratory for the study, and to maintain their usual daily activity levels throughout the duration of the entire study. Similarly, diet was uncontrolled outside of the laboratory, which has the potential to influence sertraline concentration (Ronfeld, Wilner, et al., 1997). Smoking, alcohol, and/or illicit drug use outside of the laboratory was not reported by any participants, but may have occurred unbeknownst to the study investigators.

6.4.6 Generalizability of results

The present study consisted of a rather homogenous population of participants: young, athletic males, between the ages of 20-30, and free of known disease. For this reason, caution must be exercised when applying the findings of this study to individuals outside of these parameters, such as females or older individuals, who have shown different sertraline pharmacokinetics compared to young males (Ronfeld, Tremaine, et al., 1997). Results of this study are not readily applicable to dosing regimens of sertraline other than a single 100 mg capsule, administered to individuals free of hepatic or renal disease as well as not having any diagnosed mental health disorders.

6.5 Future perspectives and clinical implications

The interaction of exercise and pharmacokinetics involves complex relationships between numerous physiological systems. This study suggests that exercise has the potential to affect
sertraline pharmacokinetics, which in turn alter the efficacy of a very frequently prescribed medication used to treat mental health disorders.

Future research is warranted on the influence of genotype and exercise on sertraline metabolism, thereby elucidating the interaction between hepatic enzyme activity and exercise on sertraline metabolism. These findings may be further substantiated with research that incorporates a measure of hepatic blood flow during exercise, allowing for a determination of the effect that changes in blood flow may have on the ability of hepatic enzymes to metabolize sertraline. A longitudinal study of this nature would clarify the time-course of these potential effects.

By sequentially determining the effect of these factors on the metabolism of sertraline, more confounding variables such as dosing regimen, gender, age, and chronic exercise can be added to the study design, lending greater external validity to the findings from such studies.

Research in this area should work towards understanding what effect acute and/or chronic exercise can have on the pharmacokinetics and pharmacodynamics of sertraline in patients with hepatic, renal, and mental health diseases. With this understanding, the proper frequency, intensity, duration, and type of exercise can be prescribed in combination with sertraline treatment, allowing for the maximum possible benefits that exercise and drug treatment provide, while at the same time minimizing possible adverse reactions to medication.
7 Study conclusions

The purpose of this study was to clarify the alterations in the pharmacokinetics of sertraline that occur due to acute aerobic exercise and to determine if aerobic fitness has an impact on the metabolism of sertraline. To our knowledge, this is the first study to investigate the interaction of exercise with sertraline pharmacokinetics. Thus, it is also the first study to report that acute aerobic exercise at 65% of $\dot{V}O_{2\text{max}}$ alters the $t_{\frac{1}{2}\beta}$, but not the $C_{\text{max}}$, $t_{\text{max}}$ or $AUC_{\text{inf}}$, of sertraline. Furthermore, aerobic fitness level appears to have little impact on the concentration of sertraline, as there was no difference in sertraline’s PK parameters between individuals of various aerobic fitness levels. Research on the relationship between exercise, hepatic blood flow, and hepatic enzyme activity would aid in interpreting these findings.

Factors contributing to the increased $t_{\frac{1}{2}\beta}$ of sertraline may have included decreased absorption and distribution with exercise. An increase in the concentration of plasma proteins during exercise may have contributed to the decreased distribution of sertraline during the exercise trial.

This study has demonstrated the need for future research to elucidate the effects of the various physiological changes that occur due to physical activity on the metabolism of sertraline, administered both acutely and chronically, in various populations. Research in this area has the potential to aid in the treatment and ease the burden for individuals suffering from mental health disorders. There is also the potential to sensitize drug regulatory authorities responsible for approving and monitoring the safety and efficacy of drugs as to the potential interaction between exercise and medication.
References


### SECTION A – GENERAL INFORMATION

1. **TITLE OF RESEARCH PROJECT**

Effects of acute aerobic exercise on the pharmacokinetics of the anti-anxiety/anti-depressant drug sertraline

2. **INVESTIGATOR INFORMATION**

**Investigator:**

<table>
<thead>
<tr>
<th>Title: Mr.</th>
<th>Name: Ethan Ruderman</th>
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**Level of Project**

- Faculty Research
- CBR/CBPR Research
- Post-Doctoral Research
- Student Research: Doctoral  Masters

**Student Number** 996181849

**Faculty Supervisor/Sponsor:**

<table>
<thead>
<tr>
<th>Title: Prof &amp; Dean</th>
<th>Name: Ira Jacobs</th>
</tr>
</thead>
</table>

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Phone: 416-978-5909  Institutional e-mail: ira.jacobs@utoronto.ca

**Co-Investigators:**

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<th>Name: Doug Richards</th>
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</table>

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<thead>
<tr>
<th>Title: Prof</th>
<th>Name: K.Sandy Pang</th>
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</thead>
</table>

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Phone: 416-978-6164  Fax: Institutional e-mail: ks.pang@utoronto.ca

*Please append additional pages with co-investigators’ names if necessary.*
3. UNIVERSITY OF TORONTO RESEARCH ETHICS BOARD:

Health Sciences ☑ Social Science, Humanities and Education ☐ HIV
REB ☐
Please consult http://www.research.utoronto.ca/for-researchers-administrators/ethics/human/boards-committees/ to determine which Research Ethics Board (REB) your proposal should be submitted.

4. LOCATION(S) WHERE THE RESEARCH WILL BE CONDUCTED:

If the research is to be conducted at a site requiring administrative approval/consent (e.g. in a school), please include all draft administrative consent letters. It is the responsibility of the researcher to determine what other means of approval are required, and to obtain approval prior to starting the project.

University of Toronto ☑
Hospital ☐ specify site(s)
School board or community agency ☐ specify site(s)
Community within the GTA ☐ specify site(s)
International ☐ specify site(s)
Other ☐ specify site(s)

The University of Toronto has an agreement with the Toronto Academic Health Sciences Network (TAHSN) hospitals regarding ethics review of hospital-based research where the University plays a peripheral role. Based on this agreement, certain hospital-based research may not require ethics review at the University of Toronto. If your research is based at a TAHSN hospital please consult the following document to determine whether or not your research requires review at the University of Toronto. http://www.research.utoronto.ca/for-researchers-administrators/ethics/human/at-a-glance/where-to-apply-tahsn-institutions/

5. OTHER RESEARCH ETHICS BOARD APPROVAL(S)

(a) Does the research involve another institution or site? Yes ☑ No ☐
(b) Has any other REB approved this project? Yes ☑ No ☐
   If Yes, please provide a copy of the approval letter upon submission of this application.
   If No, will any other REB be asked for approval?
      Yes ☑ (please specify which REB) No ☐
      Please note that REB approvals from other sites must be submitted to the ORE at U of T

6. FUNDING OF THE PROJECT

(a) Please check one:

<table>
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<th>Funded ☑</th>
<th>Agency: Ontario Ministry of Tourism, Culture, and Sports: Research Program in Applied Sport Science</th>
<th>Fund #: 4 TBD (6 digits)</th>
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<td>Applied for funding ☐</td>
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<tr>
<td></td>
<td>Agency:</td>
<td>Submission date:</td>
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<td>Agency:</td>
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</tbody>
</table>
If unfunded, please provide an explanation why no funding is needed?

If one protocol is to cover more than one grant, please include all fund numbers:

(b) If waiting for funding, do you wish to postdate ethics approval to the release of funds?
   Yes ☐ No ☒

(c) For funded research, will more than one protocol be submitted to cover all research funded by the respective grant? Yes ☐ No ☒
   Please list these protocols by title and RIS # (if known):

7. CONTRACTS

Is there a University of Toronto funding or non-funded agreement associated with the research?
   Yes ☐ No ☒
   If Yes, please include a copy of the agreement upon submission of this application.

Is there any aspect of the contract that could put any member of the research team in a potential conflict of interest? Yes ☐ No ☒
   If yes, please elaborate under #10.

8. PROJECT START AND END DATES

Estimated start date for this project: October 2012
Estimated completion of involvement of human participants for this project: June 2013

9. SCHOLARLY REVIEW

(Please note: for submissions to the HIV REB from community investigators, scientific review is a pre-requisite for ethics review. If your study is unfunded, please contact the OHTN to arrange a scientific review prior to completing your ethics submission.)

Please check one:

☒ The research has been approved by a thesis committee or equivalent (required for thesis research)
☒ The research has undergone scholarly review prior to this submission for ethics review
   Research Program in Applied Sport Science (Specify review committee – e.g., departmental research committee, CIHR peer-review committee, OHTN scientific review, etc)
☐ The research will undergo scholarly review prior to funding
   (Specify review committee – e.g., departmental research committee, CIHR peer-review committee, OHTN scientific review, etc)
☐ The research will not undergo scholarly review

10. CONFLICTS OF INTEREST

(a) Will the researcher(s), members of the research team, and/or their partners or immediate family members:
   (i) Receive any personal benefits (e.g. financial benefit such as remuneration, intellectual property rights, rights of employment, consultancies, board membership, share ownership, stock options, etc.) as a result of or in connection to this study? Yes ☐ No ☒
(ii) If Yes, please describe the benefits below. (Do not include conference and travel expense coverage, or other benefits which are standard to the conduct of research.)

(b) Describe any restrictions regarding access to or disclosure of information (during or at the end of the study) that has been placed on the investigator(s). This includes controls placed by sponsor, funding body, advisory or steering committee.

Restrictions have not been placed on the investigators or disclosure of information.

(c) Where relevant, please explain any pre-existing relationship between the researcher(s) and the researched (e.g. instructor-student; manager-employee; minister-congregant). Please pay special attention to relationships in which there may be a power differential.

N/A

(d) Please describe the decision-making processes for collaborative research studies. If Terms of Reference exist, please attach them.

SECTION B – SUMMARY OF THE PROPOSED RESEARCH

11. RATIONALE

Describe the purpose and scholarly rationale for the proposed project, and, if relevant, the hypotheses/research questions to be examined. The rationale for doing the study must be clear.

Health Canada reported in 2009 that one in ten Canadians is affected by a mental health disorder, with anxiety and depression being most common. In addition to pharmacotherapy, the therapeutic effects of exercise are also well established and frequently prescribed together with drug treatment in managing mental illness. Yet little is known about the effects of exercise on the pharmacokinetics and drug efficacy of prescription drugs used in these conditions. The physiological responses to exercise include those that have the potential to affect common criteria used to characterize drugs, e.g. drug absorption, distribution, metabolism, and excretion (ADME).

Moreover, the cytochrome P450 (CYP) family are the main enzymes responsible for the metabolism of one of the most commonly prescribed drugs used in the management of mental illness, i.e. sertraline (DeVane, Liston, & Markowitz, 2002). It is well established that CYP enzymes are affected by exercise and the related hyperemia (Hillig et al., 2002).

It is also well established that acute exercise changes the rate and distribution of blood flow throughout the body (Saltin, Rådegran, Koskoluou, & Roach, 1998), which in turn should affect ADME (Lenz, 2011). During physical activity, blood is shunted away from internal organs and towards working muscles to provide oxygen, and to subcutaneous tissue in order to regulate body temperature (Daneshmend, Jackson, & Roberts, 1981). At all intensities of physical activity, blood flow decreases to the liver and kidney (Peng & Cheung, 2011). Based on this knowledge it is highly probably that drug pharmacokinetic indices that are based on resting blood flow (such as Volume of Distribution (Vd) and Clearance (Cl)) will be altered when an individual exercises, particularly at high intensity (Lenz, 2010).
Animal pharmacokinetic studies have shown that the bioavailability of sertraline was approximately 25%, indicating that sertraline is highly extracted and therefore its metabolic clearance is mainly blood flow-dependent (Ronfeld, Tremaine, & Welch, 1989). The metabolism of drugs that require extensive hepatic extraction is significantly dependent upon blood flow through the liver and therefore tend to be less available to the systemic circulation. The reduction in visceral blood flow during exercise can significantly alter the clearance and secretion of flow-limited drugs (Khazaenia, Ramsey, & Tam, 2000; van Baak, 1990). Thus, the shunting of blood away from the liver that accompanies exercise is likely to alter the metabolism of the flow-limited drug sertraline.

Given this theoretical basis, it is tempting to speculate that exercise may alter the pharmacokinetics of drugs such that serious over- or under-estimation of an effective or optimal dose may result. A comprehensive understanding of whether exercise actually affects ADME is necessary in order to predict and anticipate both efficacy and risks of drug administration.

To date, the effects of physical activity on the pharmacokinetics of sertraline have not been examined. The proposed study seeks to quantify the alterations in the pharmacokinetics of sertraline that occur due to acute aerobic exercise. Furthermore, since improvements in physical fitness have been shown to stimulate hepatic oxidative metabolism (Villa, Bayon, & González-Gallego, 1999), a secondary purpose is to examine the effects of training status and fitness level of the participants on sertraline metabolism.

12. METHODS

Please describe all formal and informal procedures to be used. Describe the data to be gathered, where and how they will be obtained and analyzed. If research includes intentions to publish in other than standard academic venues, please indicate.

Experimental Design

After being approved by the study physician for participation as participants in this investigation, volunteers will be asked to report to the exercise physiology research laboratory in the Faculty of KPE at U of T on five separate occasions over a three-week period. During the first visit height and body mass will be registered and bioimpedance measurements will be made to enable the estimation of total body water, lean body mass and percent body fat. Also on this visit, direct determination of participants’ maximal aerobic power (VO\textsubscript{2max}) will be made on a cycle ergometer by means of a graded exercise test.

During the second and fifth visits, separated by 14 days, participants will be asked to orally ingest an acute 100mg of sertraline in a tablet. On either the second or fifth visit, participants will rest quietly following drug administration; during the other visit, participants will exercise following drug administration. The order of these rest and exercise trials will be balanced such that half of the participants will rest on the second visit and exercise on the fifth, and half of the participants will exercise on the second visit and rest on the fifth. Blood sampling will occur during the second to seventh visits as outlined below. Prior to experimental testing, each participant will be assessed by the study physician to ensure there are no medical contraindications to participation.

Cycle Ergometer
All exercise protocols will be performed on a Lode Excalibur Sport 925900 (Groningen, The Netherlands) electronically controlled cycle ergometer. The participants will use the same footwear and ergometer configuration for every session.

**Submaximal Exercise Test**
Following a 10-minute warm up at a self-selected light intensity, participants will begin cycling at 50 watts for three minutes. The intensity will increase to 100, 150, and 200 watts, with each stage lasting five minutes. During the test, participants’ expired respiratory gases will be monitored via a portable oxygen uptake monitoring system that will calculate respiratory oxygen uptake and carbon dioxide production. Since oxygen uptake increases linearly with submaximal power output, the oxygen uptake data from this submaximal test will be used together with a linear regression model to calculate the power output corresponding to 65% of the participant’s VO$_{2\text{max}}$. The calculation of the VO$_{2\text{max}}$ is described in the next paragraph.

**Determination of VO$_{2\text{max}}$**
Following the submaximal VO$_{2\text{max}}$ determination, participants will rest for 15 minutes. Participants will then begin the VO$_{2\text{max}}$ test on the cycle ergometer, starting at zero watts. The workload will be increased by 30 watts every minute until either 1) the investigators terminate the test as participants are not able to maintain the target intensity or 2) the participant reaches volitional fatigue. During the test, participants will be connected to the respiratory gas system described above for the continuous measurement and registration of oxygen uptake. VO$_{2\text{max}}$ will be defined as the highest 30-second average VO$_2$ recorded. Heart rate will also be monitored throughout the test via heart rate telemetry.

**Resting Drug Administration**
On day 4 or 18 (three days following the initial exercise tests), participants will return to the laboratory in a 12-hour post-absorbptive state at 7:30 am and be given a 100 mg dose of sertraline together with a standardized light breakfast. Participants will undergo basic anthropometric testing again to ensure no significant changes from baseline values. **Participants will then read/study independently or rest quietly for the next ten hours, predominately in a seated position. They may engage in sedentary activities such as reading, computer use, videos, DVDs, music, etc.** Wi-Fi access will be provided for their use. They will be provided with a standardized light lunch. During this time blood samples will be taken as outlined below. Water will be ingested *ad libitum,* and participants will keep a food log to track dietary intake on the day before coming to the laboratory, and instructed to repeat this diet as closely as possible when returning to the laboratory for the second drug administration visit. Participants will also be encouraged to maintain their normal exercise regimens during the two-week period between drug administration trials. Participants will be instructed not to exercise the day before coming into the laboratory for the drug administration protocols.

**Blood Sampling**
Ten milliliter venous blood samples will be collected repeatedly after sertraline ingestion. Each such sample should be sufficient to produce 4 ml of plasma which has been shown to be sufficient for the subsequent assay of drug concentration (Démolis et al., 1996; Ronfeld et al., 1997). Blood will be obtained from each participant just before the ingestion of sertraline (0 hour) and at 1, 2, 4, 6, 8, 10, 24, and 48 hours following sertraline ingestion. **This**
number of blood samples is the minimum number of samples needed to determine the standard pharmacokinetic parameters of sertraline, such as the area under the curve (AUC, ng/ml h⁻¹), the maximum plasma concentration of the drug (C_max, ng/ml), the time required for the drug to reach its maximum blood concentration (t_max, h), and the drug half-life (t_½, h) (Démolis et al., 1996; DeVane et al., 2002; Ronfeld et al., 1997). A flexible intravenous catheter will be inserted into an antecubital vein prior to drug ingestion and will be used for collection of the samples from time 0 through 10 hours post drug ingestion. The catheter will be kept patent with heparinized saline between samples. The samples at 24 and 48 hours will also be obtained via venipuncture but with standard vacutainers. The blood will be centrifuged and plasma aliquots will be stored at -20°C until assayed. Concentrations of sertraline and desmethylsertraline will be measured in plasma by a gas chromatographic method (Tremaine & Joerg, 1989). Hematocrit and hemoglobin measurements will be made in conjunction with each blood sample in order to calculate relative changes in plasma volume.

**Washout Period**

The resting drug administration visit and the exercising drug administration visit will be separated by a washout period of at least 14 days in order to ensure that all sertraline has been metabolized and excreted from the body (Ronfeld, Wilner, & Baris, 1997).

**Exercise and Drug Administration**

On day 4 or 18 (fourteen days following the previous drug administration), participants will return to the laboratory for the trial involving drug administration combined with a bout of acute exercise. The procedures will be identical to those described above for the resting drug administration trial until the 4 hour time point after drug ingestion. At that time the participants will exercise at 65% of their VO₂max for 30 minutes. Blood sampling will occur at the same time intervals outlined previously. A standardized lunch will be given to participants, water intake will be ingested ad libitum, and participants will be encouraged to duplicate their dietary intake the day before coming into the laboratory as outlined in their food log. Participants will be instructed not to exercise the day before coming into the laboratory for the drug administration protocols.

**Statistical Analysis and Pharmacokinetic Analysis**

Results will be presented as mean values ± standard deviation (SD). Differences will be considered significant when p ≤ 0.05. A repeated measures analysis of variance (ANOVA) (Group x Condition) will be performed to evaluate the differences in pharmacokinetic indices between resting and exercise conditions. Standard pharmacokinetic indices will be calculated, including AUC (ng/ml h), C_max (ng/ml), t_max (h), and t_½ (h). Significant interactions will be followed up with appropriate post hoc analysis. All statistics will be calculated using SPSS.

Healthy male participants aged 18-40 years will be recruited to participate in this study. The sample size was chosen based on the assumption that any exercise-associated changes in pharmacokinetics will be at least as great as those reported for diurnal and fed/fasted effects. Based on the pharmacokinetic differences calculated between morning and evening and fasted and fed sertraline administration (Ronfeld, Wilner, & Baris, 1997), it was calculated that fifteen participants would be sufficient to detect significant changes in the pharmacokinetics of sertraline within participants between rest and exercise conditions, with a statistical power of 80% and a 0.05 level of significance. Participant attrition during the trials of about 25% was considered and therefore it is proposed to recruit 19 participants.
Attach a copy of all questionnaires, interview guides or other non-standard test instruments. Please include a list of appendices here for all additional materials submitted (e.g., Appendix A – Informed Consent; Appendix B – Interview Guide, etc.):

Appendix A – Informed Consent
Appendix B – Physical Activity Readiness Questionnaire (PAR-Q)
Appendix C – Sertraline Information for Patients
Appendix D – Recruitment Poster

13. PARTICIPANTS OR DATA SUBJECTS

(a) Describe the participants to be recruited, or the subjects about whom personally identifiable information will be collected. Where recruitment is required, please describe inclusion and exclusion criteria. Where the research involves extraction or collection of personally identifiable information, please describe from whom the information will be obtained and what it will include. Strategies for recruitment are to be described in section #15.

19 healthy male participants aged 18-40 will be recruited to volunteer in this study. Sertraline is contraindicated for those under the age of 18 and for pregnant females, therefore the inclusion of female participants would require pregnancy tests to be conducted at the beginning of each visit to avoid these potential risks. The associated financial cost precluded the inclusion of female participants in the participant pool. The study physician (D. Richards, MD) will perform a standard medical examination on each volunteer to confirm that there are no medical contraindications to taking sertraline and participating as a participant. Participation is contingent on volunteers’ agreement to meet with the study physician for a standard medical screening.

Participants must be free of any condition that can be aggravated by exercise as identified by the PAR-Q. Participants will be informed of the protocol and of all risks and discomforts that they may experience through participation. Prior to experimentation each participant will complete a written informed consent and a Physical Activity Readiness Questionnaire (PAR-Q). The PAR-Q is a validated short questionnaire that will help to determine whether the participant is healthy enough to partake in strenuous physical activity. A normal body mass index (BMI), between the values of 18.5 and 24.9, will be a pre-requisite for participation as a participant. Fitness will not be a participant selection criterion.

(b) Is there any group or individual-level vulnerability related to the research that needs to be mitigated (for example, difficulties understanding informed consent, history of exploitation by researchers, power differential between the researcher and the potential participant)?

N/A

14. EXPERIENCE

(a) Please provide a brief description of (i) the principal investigator’s, (ii) the research team’s and (iii) the people who will have contact with the participants’ experience with this type of research. If there has not been previous experience, please describe how the individual/team will be prepared.

Principle Investigator – Ethan Ruderman
Mr. Ethan Ruderman is well accustomed with maximal and sub-maximal laboratory testing protocols to measure the physiological responses of healthy humans to exercise. He is well trained with the equipment to be used in this study as well as all pertinent safety and emergency procedures. **Mr. Ruderman has undergone training in an exercise physiology lab to become familiar with exercise testing protocols and is proficient with the related instrumentation and exercise testing protocols. He has completed and been certified in advanced venipuncture and phlebotomy at the Michener Institute.** His past experience has prepared him to execute the protocols safely and efficiently.

Co-Investigator – Professor Ira Jacobs
Dr. Ira Jacobs has conducted human exercise physiology research for over 30 years, resulting in over 200 publications. His research with healthy humans has investigated physiological responses and adaptations to acute exercise, to physical training programs, and physiological responses to stressors and various drugs. He is well trained in all of the methods and instrumentation required for completion of this study, and in the identification of physiological and behavioural symptoms that indicate that a participant should not continue with an experiment because of associated health risks.

Co-Investigator – Dr. Doug Richards, MD
Dr. Doug Richards is a clinical sport medicine physician. Educated in medicine at U of T (Class of 779), he has worked at the University of Toronto’s David L. MacIntosh Sports Medicine Clinic since 1984, and has been its medical director since 1989. He has been a professor in U of T’s Faculty of Kinesiology and Physical Education at the University of Toronto since 1991. Dr. Richards will be the study physician.

Co-Investigator – Professor K. Sandy Pang
K. Sandy Pang, Ph.D., received her B.Sc. (Pharmacy from the University of Toronto and Ph.D. (Pharm Chem) in the area of pharmacokinetics with Dr. Malcolm Rowland from the University of California at San Francisco. She received further postdoctoral training as a Fogarty fellow at the National Institutes of Health, Bethesda, MD, under the sponsorship of Dr. James R. Gillette. After working the next four years at the Texas Medical Centre, Houston, she returned to Toronto. She is now Professor of Pharmacy and Pharmacology at the Faculties of Pharmacy and Medicine at the University of Toronto. Dr. Pang applied pharmacokinetic theory to understand the roles that transporters and enzymes play in the disposition of drugs and metabolites in eliminating organs.

(b) For projects that will involve community members (for example, Peer Researchers) in the collection and/or analysis of data, please describe their status within the research team (e.g. are they considered employees, volunteers or participants?) and what kind of training they will receive.

The primary investigator (Ethan Ruderman) will perform all data collection and analysis in conjunction with the co-investigator (Dr. Ira Jacobs).

15. RECRUITMENT

Where there is recruitment, please describe how, by whom, and from where the participants will be recruited.

Where participant observation is to be used, please explain the form of insertion of the researcher into the research setting (e.g. living in a community, visiting on a bi-weekly basis, attending organized functions). Please make it explicit where it is reasonable to anticipate that all or some of the participants who will be recruited will not speak English or will speak English as a second language. Describe any translation of recruitment materials, how this will occur and whether or not those people responsible for recruitment will speak the language of the participants.
Attach a copy of all posters, advertisements, flyers, letters, e-mail text, or telephone scripts to be used for recruitment. This copy should be exactly as it will appear for recruitment.

Volunteers will be recruited by informing students, colleagues, and personal contacts about the research and by posting announcements on bulletin boards within the Faculty and on the Faculty website where opportunities to participate in research experiments are announced. (Appendix D).

16. COMPENSATION

(a) Will participants receive compensation for participation?

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</table>

(b) If Yes, please provide details and justification for the amount or the value of the compensation offered.

If participants complete the study, they will be reimbursed a flat fee of $200 for their time and any expenses incurred.

(c) If No, please explain why compensation is not possible or appropriate.

(d) Where there is a withdrawal clause in the research procedure, if participants choose to withdraw, how will compensation be affected?

If a subject withdraws before completing all of the requirements of the study, any incurred expenses will be reimbursed such as those related to transportation, but the $200 compensation will not be paid.

SECTION C –DESCRIPTION OF THE RISKS AND BENEFITS OF THE PROPOSED RESEARCH

17. POSSIBLE RISKS

Risks to participants as individuals or as members of a community may include:

(a) Physical risks (including any bodily contact or administration of any substance); Yes ✗ No

(b) Psychological/emotional risks (feeling uncomfortable, embarrassed, anxious or upset); Yes No ✗

(c) Social risks (including possible loss of status, privacy and/or reputation); and/or Yes No ✗

(d) Legal risks (potential of apprehension or arrest or being identified as a member of a legally-compromised group).

Please describe the risks involved in the study, and what steps will be taken to ensure that they will be managed and/or minimized.
Maximal and Submaximal Exercise: Participants may experience muscular fatigue, nausea, light-headedness and general discomfort. There is a very small risk of death during an exercise test (<0.5 per 10,000 tests). These risks and side effects will be minimized by 1) the initial medical screening procedures, 2) the PAR-Q health questionnaire, and 3) following standard laboratory procedures for exercise testing. Potential participants who exhibit a condition that can be aggravated by exercise as determined by the PAR-Q will be excluded from participating in the study. A trained and experienced member of the research team who is certified in First Aid and CPR will conduct all testing. Should an emergency occur, research personnel will follow standard emergency procedures and alert the Emergency Medical System if it is required.

Sertraline: The study physician will ensure that each participant included in the study has no contraindications to the ingestion of sertraline. Previously reported side effects include nausea, headache, dry mouth, diarrhea, sleep disturbance and loss of appetite. Other effects may include drowsiness, sexual problems, nervousness and tremor. Although the side effects are unlikely following a single acute administration, participants will be instructed to immediately advise Mr. Ruderman if they notice any signs of being unwell while in the laboratory. Before the participants leave the laboratory, they will be reminded that should any symptoms arise, they should immediately contact emergency medical services if the symptoms are severe, and otherwise contact Mr. Ruderman, who will contact the appropriate authorities, such as the study physician, to request his advice. The full list of side effects and precautions are indicated in the Zoloft monograph (Appendix C), and a copy of this information will be given to each participant. Should participants feel distressed after taking the drug, they can also contact emergency services at 911 or Campus Police, or Kids Help Phone at 1-800-668-6868.

Blood sampling: The risks associated with blood samples obtained with a needle and syringe may include one or all of the following: local discomfort, occasional dizziness and nausea, and subcutaneous bruising. Blood clots attached to the walls of a blood vessel, and infections are very rare but are also potential risks. Only individuals to whom the blood sampling has been formally delegated by the study physician will be taking the blood samples; these individuals have undergone formal phlebotomy (blood sampling) training and are experienced with the venous blood sampling techniques to be used in this study.

Blood Loss. The amount of blood sampled over the study period will total less than 100 millilitres for each of the two 48 hour trials where blood is sampled, amounting to 180 millilitres over the course of the 3 week study. This is not considered a significant physiological or health challenge given that it will be spread out over a minimum of a 3 week period, and thus is unlikely to result in any adverse effects. To minimize risks, however, hematocrit and hemoglobin levels, which are classical indices of anemia and dehydration, will be measured each time blood is sampled. If these parameters are lower than normal (hematocrit <36% and hemoglobin <12.0 g/dL), the study physician, Dr. Doug Richards, will be immediately telephoned and informed of the values. The physician will advise the participant in accordance with standard medical practice. This advice may preclude continuation in the study as a participant.

18. POSSIBLE BENEFITS
Discuss any potential direct benefits to the participants from their involvement in the project. Discuss any potential direct benefits to the community, including any capacity building which is integrated into the study design. Comment on the potential benefits to the scientific/scholarly community or society that would justify involvement of participants in this study.

Those participants who are interested in their aerobic fitness level will benefit from participation in this study, as they will receive a report describing their maximal aerobic power and other physiological variables measured during the VO\textsubscript{2max} test. This report will highlight their individual physiological responses to increasing exercise intensity, which can be used to help the participants understand their current training status and fitness level. In addition, this study could potentially improve our understanding of how the dosing regimen of a drug is altered by exercise, benefiting the medical community as well as individuals engaged in physically demanding occupations, recreational physical activity, and competitive sport. Should this research support the experimental hypothesis, a reassessment of conventional dosing of sertraline may be necessary, leading to greater effectiveness of a prevalent drug. This research also has the potential to sensitize drug regulatory agencies to the effects of exercise on drug efficacy.

**SECTION D – THE INFORMED CONSENT PROCESS**

**19. THE CONSENT PROCESS**

Describe the process that will be used to obtain informed consent. Please note that it is the quality of the consent, not the format that is important. If the research involves extraction or collection of personally identifiable information from a research participant, please describe how consent from the individuals or authorization from the data custodian will be obtained. If there will be no written consent, please provide a rationale for oral or implied consent (e.g., discipline, cultural appropriateness, etc.) and explain how consent will be recorded.


Where applicable, please attach a copy of the Information Letter/Consent Form, the content of any telephone script, screening materials, introductory letters, letters of administrative consent or authorization and/or any other material which will be used in the informed consent process. If any of the information collected in the screening process - prior to full informed consent to participate in the study - is to be retained from those who are excluded or refuse to participate in the study, please describe how those individuals will be informed of this.

All of the information collected during the screening process will be destroyed should the individual refuse to participate or is excluded from participating by the researchers. Each participant will have the study protocols and potential risks described to them in person before beginning any aspects of the study. Either Dr. Jacobs or Mr. Ruderman will personally meet and speak with each participant prior to beginning the study, and will verbally describe the study before giving the potential participant the consent form to examine.

**20. COMMUNITY AND/OR ORGANIZATIONAL CONSENT, OR CONSENT BY AN AUTHORIZED PARTY**
(a) If the research is taking place within a recognized community or an organization which requires that formal consent be sought prior to the involvement of individual participants, explain whether consent from that community/organization will be sought. Describe this consent process and attach any relevant documentation. If consent will not be sought, please provide a justification and describe any alternative forms of consultation that may take place.

(a) If any or all of the participants are children and/or are not competent to consent, describe the process by which capacity/competency will be assessed, the proposed alternate source of consent - including any permission/information letter to be provided to the person(s) providing the alternate consent – as well as the assent process for participants.

Participants in this study will be 18 years of age or older.

21. DEBRIEFING and DISSEMINATION

(a) If deception or intentional non-disclosure will be used in the research study, please justify. Please consult Guidelines for the Use of Deception and Debriefing in Research

Deception will not be used as part of the experimental design.

Please provide a copy of the written debriefing form, if applicable.

The participants will not be engaged in a formal debriefing session when they complete the requirements of the study.

(b) Will participants and/or communities be given the option of withdrawing their data following the debriefing? Please explain.

Participants will have the option of withdrawing their data from the study following the debriefing. If a participant chooses to participate in the study, but later decides to withdraw before completing all of its requirements, the participant will be asked to confirm that any data already collected may in fact be used for the study outcomes.

(c) Please explain what information/feedback will be provided to participants and/or communities after their participation in the project is complete. (e.g., report, poster presentation, pamphlet, etc.)

Participants will be informed of their current fitness levels and anthropometric measurements, if they so desire. Further, participants will be asked if they are interested in the results of their drug trials, and will be informed of the results if they so desire.

22. PARTICIPANT WITHDRAWAL

(a) Where applicable, please describe how the participants will be informed of their right to withdraw from the project. Outline the procedures which will be followed to allow them to exercise this right.

Members of the research team will verbally inform the participants, in person or over the telephone, of their right to withdraw from the project and to decline to answer any questions they choose, before implementing the prescreening procedures. A member of the research team will again remind the participants of their rights verbally and in writing while reviewing and signing the informed consent form together. If a participant chooses to participate in
the study, but later decides to withdraw before completing all of its requirements, the participant will be asked to confirm that any data already collected may in fact be used for the study outcomes.

(b) Indicate what will be done with the participant’s data and any consequences which withdrawal may have on the participant.

Should the participant decide to withdraw from the study before completion, their relationship with the researchers and the University of Toronto will not be affected at any point in time. The partial data set that has been collected will be kept on file.

(c) If participants will not have the right to withdraw from the project at all, or beyond a certain point, please explain. Ensure this information is included in the consent process.

Participants will have the right to withdraw from the study at any time for any reason.

SECTION E – CONFIDENTIALITY AND PRIVACY

23. CONFIDENTIALITY

(a) Will the data be treated as confidential? Yes ☑ No ☐

(b) Describe the procedures to be used to protect anonymity of participants or informants, where applicable, or the confidentiality of data during the conduct of research and dissemination of results. Data security measures must be consistent with UT’s Data Security Standards for Personally Identifiable and Other Confidential Data in Research. All identifiable electronic data outside of a secure server environment must be encrypted, consistent with the standards described at: http://www.utoronto.ca/security/UTORprotect/encryption_guidelines.htm.

All records, including personal information as well as the research data collected, will be maintained in strict confidence and will only be accessible to the investigators involved in this study. All files (electronic and hard copy) will be encoded to protect participant confidentiality. Hard copies will be kept at the University of Toronto (55 Harbord St.) for storage upon study completion. All electronic files will be stored and encrypted on a desktop computer utilizing File Vault technology. The research data collected will be used as part of scholarly publications and presentations. Subject names or other identifiable information will not be included in any research dissemination.

(c) Describe any limitations to protecting the confidentiality of participants whether due to the law, the methods used or other reasons (e.g., duty to report)

The investigators do not foresee any limitations in protecting the confidentiality of the participants.

(d) Explain how written records, video/audio recordings, artifacts and questionnaires will be secured, how long they will be retained, and provide details of their final disposal or storage. Describe the standard data security procedures for your discipline and provide a justification if you intend to store your data for an indefinite length of time. If the data may have archival value, discuss this and whether participants will be informed of this possibility during the consent process.

Written records, including personal information as well as the research data collected, will be kept on site at the University of Toronto (55 Harbord St.) to be stored for 7 years after which they will be
destroyed (shredded) by the investigators. Electronic data sets, cleared of all personal information, will be kept indefinitely for future data mining and analysis.

(d) If participant anonymity or confidentiality is not appropriate to this research project, please explain. Also, explain how identifiable data in written records, video/audio recordings, artifacts, questionnaires, etc. will be secured.

All data collected will be treated as confidential and will be handled in accordance with the procedures outlined above (Section E, 23, a-d).

24. PRIVACY REGULATIONS
For research involving extraction or collection of personally identifiable information, provincial, national and/or international laws may apply. I will report any apparent mishandling of personally identifiable information to the Office of Research Ethics. My signature as Principal Investigator, in Section G of this protocol form, confirms that I am aware of, understand and will comply with all relevant laws governing the collection and use of personally identifiable information in research.

SECTION F – CONTINUING REVIEW OF ONGOING RESEARCH

RISK MATRIX: REVIEW TYPE BY GROUP VULNERABILITY AND RESEARCH RISK – check one:

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<td>3</td>
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</table>

See the Instructions for Ethics Review Protocol Submission Form for detailed information about the Risk Matrix.

Explain/justify the level of risk and group vulnerability reported above:

Although there are potential risks involved in this study, the investigators believe that the probability of injury or other health risk is low. First, the research team is well trained in the protocols employed in this study and are fully versed in the pertinent emergency procedures. Second, all participants recruited will be comfortable with maximal and submaximal intensity exercise. Third, all venous catheter insertions will be performed by the study physician, or by a trained individual delegated by the study physician. Finally, having the study physician pre-screen potential participants prior to inclusion into the study will mitigate the risks associated with sertraline administration.

Review Type

Based on the level of risk, these are the types of review that a protocol may receive:

Risk level= 1: Delegated Review (formerly expedited); Risk level = 2 or 3: Full Board Review
For both delegated and full reviews (SSH&E, HS, or HIV REB), please submit one electronic copy of your protocol and appendices (e.g., recruitment, information/consent and debriefing materials, and study instruments) as a single Word document or a pdf. Please ensure that the electronic signatures are in place and e-mail to new.ethics.protocols@utoronto.ca

All other submissions, which are not new (e.g., revisions and continuing review submissions), as well as general inquiries, should be sent to ethics.review@utoronto.ca

The deadline for delegated review (SSH&E or HS) is EVERY Monday, or first business day of the week, by 4 pm. HIV REB reviews all protocols at full board level but applies proportionate review based on the level of risk.

REB meeting and submission due dates are posted on our website (SSH&E, HS or HIV).

Please note that the final determination of Review Type and level of monitoring will be made by the University of Toronto REB and the Office of Research Ethics.

SECTION G – SIGNATURES

The faculty supervisor/sponsor and his/her respective Departmental Chair/Dean or designate must sign below:

As the Investigator on this project, my signature confirms that I will ensure that all procedures performed under the project will be conducted in accordance with all relevant University, provincial, national and international policies and regulations that govern research involving human participants. I understand that if there is any significant deviation from the project as originally approved I must submit an amendment to the Research Ethics Board for approval prior to its implementation.

For U of T student researchers, my signature confirms that I am a registered student in good standing with the University of Toronto. My project has been reviewed and approved by my advisory committee (where applicable). If my status as a student changes, I will inform the Office of Research Ethics.

Signature of Investigator: _______________________________ Date: August 28, 2012

***For Graduate Students, the signature of the Faculty Supervisor is required. For Post-Doctoral Fellows and Visiting Professors or Researchers, the signature of the Faculty Sponsor is required. ***

As the Faculty Supervisor of this project, my signature confirms that I have reviewed and approve the scientific merit of the research project and this ethics protocol submission. I will provide the necessary supervision to the student researcher throughout the project, to ensure that all procedures performed under the research project will be conducted in accordance with relevant University, provincial, national or international policies and regulations that govern research involving human participants. This includes ensuring that the level of risk inherent to the project is managed by the level of research experience that the student has, combined with the extent of oversight that will be provided by the Faculty Supervisor and/or On-site Supervisor.

As the Faculty Sponsor for this project, my signature confirms that I have reviewed and approve of the research project and will assume responsibility, as the University representative, for this research project. I will ensure that all procedures performed under the project will be conducted in
accordance with all relevant University, provincial, national or international policies and regulations that govern research involving human participants.

Signature of Faculty Supervisor/Sponsor: ___________________________ Date: August 28, 2012

As the **Departmental Chair/Dean**, my signature confirms that I am aware of the proposed activity and that it has received appropriate review prior to submission. My administrative unit will follow guidelines and procedures which ensure compliance with all relevant University, provincial, national or international policies and regulations that govern research involving human participants. My signature also reflects the willingness of the department, faculty or division to administer the research funds, if there are any, in accordance with University, regulatory agency and sponsor agency policies.

Print Name of Departmental Chair/Dean (or designate): Ira Jacobs

Signature of Departmental Chair/Dean: ___________________________ Date: August 28, 2012 (or designate)
Appendix B

PROTOCOL REFERENCE # 28123

October 15, 2012

Dr. Ira Jacobs
FACULTY OF PHYSICAL EDUCATION AND
HEALTH

Mr. Ethan Ruderman
FACULTY OF PHYSICAL EDUCATION AND
HEALTH

Dear Dr. Jacobs and Mr. Ethan Ruderman,

Re: Your research protocol entitled, "Effects of acute aerobic exercise on the pharmacokinetics of the anti-anxiety/anti-depressant drug sertraline"

ETHICS APPROVAL

Original Approval Date: October 15, 2012
Expiry Date: October 14, 2013
Continuing Review Level: 2

We are writing to advise you that the Health Sciences Research Ethics Board (REB) has granted approval to the above-named research protocol, for a period of one year. Ongoing research under this protocol must be renewed prior to the expiry date.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events in the research should be reported to the Office of Research Ethics as soon as possible.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 15 to 30 days prior to the expiry date of your current ethics approval. Note that annual renewals for studies cannot be accepted more than 30 days prior to the date of expiry.

If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your research.

Yours sincerely,

Judith Friedland, Ph.D.
REB Chair

Daniel Gyewu
REB Manager
# Appendix C

## Medical Directive &/or Delegation Template

**Template for Use by Physicians or Authorizers with Ordering Authority**

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<tr>
<td>09 January 2013</td>
<td>09 January 2014</td>
</tr>
</tbody>
</table>

**Sponsoring/Contact Person(s)**

*(name, position, contact particulars):*

Doug Richards, MD, Medical Director at the David L. MacIntosh Sports Medicine Clinic, doug.richards@utoronto.ca

<table>
<thead>
<tr>
<th>Order/Delegated Procedure:</th>
<th>Appendix Attached: □ Yes □ No</th>
<th>Title:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood sampling from healthy volunteers for the purpose of a research experiment either by one-time venipuncture using vacutainers or similar system or by venous catheterization. All venous sampling to be done from a superficial forearm vein (i.e. cubital, cephalic, basilic).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Authorized Implementers:**

Ira Jacobs, DrMedSc, Professor and Dean, Faculty of Kinesiology and Physical Education, University of Toronto
Ethan Ruderman, MSc Candidate, Faculty of Kinesiology and Physical Education, University of Toronto

**Recipient Patients:**

Volunteers participating as subjects in the research project approved by The University of Toronto’s Research Ethics Board, Protocol ID 28123, entitled: “Effects of acute aerobic exercise on the pharmacokinetics of the anti-anxiety/anti-depressant drug sertraline.”

**Indications:**

Volunteers participating as subjects in the research project approved by The University of Toronto’s Research Ethics Board, Protocol ID 28123, entitled: “Effects of acute aerobic exercise on the pharmacokinetics of the anti-anxiety/anti-depressant drug sertraline.”

**Consent:**

All volunteers will have read and signed the informed consent form associated with the protocol approved by The University of Toronto Research Ethics Board, Protocol ID 28123, entitled: “Effects of acute aerobic exercise on the pharmacokinetics of the anti-anxiety/anti-depressant drug sertraline.”

**Documentation and Communication**

Any complications or unexpected responses to the blood sampling must be immediately communicated to Dr. Richards via telephone. Dr. Richards will inform the implementers of his location and how he can be contacted at all times.

**Review and Quality Monitoring Guidelines:**

The implementers have attended and received course certificates from the Michener Institute for Applied Health Sciences indicating that they have successfully completed the courses entitled “Basic and Advanced Venipuncture.”

**Approving Physician(s):**

Appendix Attached: □ Yes □ No
Appendix D

Consent to Participate in a Research Study

Study Name: Effects of acute aerobic exercise on the pharmacokinetics of the anti-anxiety/anti-depressant drug sertraline

Researchers: Ethan Ruderman (MSc Candidate); Ira Jacobs, DrMedSc; Doug Richards, MD, K. Sandy Pang, PhD.

Sponsors: University of Toronto, Department of Exercise Sciences, Faculty of Kinesiology and Physical Education

Invitation to participate: You are being invited to participate in a research study. Before you decide to be a part of this study, you need to understand the risks and benefits involved so that you can make an informed decision. This consent form provides information about the research study. One of the Principal Investigators for this research study (either E. Ruderman or I. Jacobs) will be available to answer your questions and provide further explanations. If you agree to take part in the research study, you will be asked to sign this consent form. This process is known as informed consent.

Purpose of the research: The purpose of this study is to clarify if one bout of moderate intensity exercise alters the amount of drug in the body and/or the duration that that drug is in the body. We are also interested to see if a person’s fitness level has any impact on these measures. The drug is an anti-anxiety/anti-depressant called sertraline, trademark names Zoloft and Lustral.

What you will be asked to do in the research: If you are eligible and agree to participate in this study you will make 7 visits in total to the laboratory during a 3-week period. These visits will be used to provide a study overview, receive clearance for participation from the study physician, perform basic height and weight measurements and a VO$_{2\text{max}}$ test, and perform two trials of drug administration, one while resting and the other with a thirty-minute bout of exercise. During these two trials, blood samples will be taken throughout the day, and at 24 and 48 hours following the drug administration.

Day 1 – Review and sign the consent form, physician clearance, and basic testing

On Day 1 of the study, one of the investigators will explain the study to you and will answer any questions you have. You will be asked to fill out a PAR-Q form. The PAR-Q is a short questionnaire that will help to determine whether you are healthy enough to perform the physical exercise protocols used in this study. You will be asked to read, review, and sign the consent form if you are interested in participating. The study physician will then assess you to
ensure you are able to participate in the study. Next, you will come in to the laboratory for anthropometric testing including measurements of height, weight, total body water, and percent body fat. On this visit you will also undergo testing on the cycle ergometer in order to assess your aerobic fitness. This visit will take about 2 hours to complete.

*Determinations of VO$_{2\text{max}}$ and Wattage at 65% VO$_{2\text{max}}$*

You will complete submaximal and maximal exercise tests on a bike to determine your VO$_{2\text{max}}$, a measure of your cardiovascular fitness level. You will be connected to a metabolic cart during the entire test by breathing from and into a mouthpiece. The test will stop when either: 1) the investigators stop the test as you are not able to maintain the target intensity or 2) you are too tired to continue exercising.

**Day 4 – Resting or Exercise Drug Administration**

On day 4 (three days following the maximal exercise test), you will return to the laboratory at 7:30am and be given a 100 mg dose of sertraline. Breakfast and lunch will be provided to you during this visit. Basic anthropometric measures such as weight and percent body fat will be repeated on this visit. Either during this visit or visit 5, you will exercise for 30 minutes at a moderate intensity, halfway through the 10-hour visit. **You will then read/study independently or rest quietly for the next ten hours, predominately in a seated position.** You may engage in sedentary activities such as reading, computer use, videos, DVDs, music, etc. Wi-Fi access will be provided for your use. During this time, blood samples will be taken as outlined below. You can take food and water as needed, and you will be asked to keep a food log to track dietary intake. This visit will take about 10 hours to complete.

**Day 5 – 24 hour blood sampling**

On day 5 you will come into the laboratory at 7:30am for one blood sample to be taken. This visit will take about 15 minutes to complete.

**Day 6 – 48 hour blood sampling**

On day 6 you will come into the laboratory at 7:30am for one blood sample to be taken. This visit will take about 15 minutes to complete.

**Day 5-18 – Washout Period**

The resting drug administration visit and the exercising drug administration visit will be separated by a washout period of at least 14 days in order to ensure that all sertraline has been metabolized and excreted from the body.

**Day 18 – Exercise or Resting and Drug Administration**

On day 18 (fourteen days following the previous drug administration visit), you will return to the laboratory for the exercising/resting drug administration. This visit will mirror Day 4 visit, however participants who did not exercise on Day 4 will exercise during this visit, and vice versa. Should this be the exercise visit, four hours following drug administration, you will exercise at 65% of your VO$_{2\text{max}}$ for 30 minutes. Blood sampling will occur at the same time intervals outlined previously. **You will then read/study independently or rest quietly for the next ten hours, predominately in a seated position.** You may engage in sedentary activities such as reading, computer use, videos, DVDs, music, etc. Wi-Fi access will be provided for your use.
**Day 19 – 24 hour blood sampling**

On day 19 you will come into the laboratory at 7:30am for one blood sample to be taken. This visit will take about 15 minutes to complete.

**Day 20 – 48 hour blood sampling**

On day 20 you will come into the laboratory at 7:30am for one blood sample to be taken. This visit will take about 15 minutes to complete.

**Blood Sampling:** Blood samples will be taken just before administration of sertraline (0 hour) and at 1, 2, 4, 6, 8, 10, 24, and 48 hours following administration on each of the trial days. Blood samples will be collected from a catheter which will be inserted into a superficial vein in your arm by the study physician, or by the trained person that the physician delegates. The catheter is flexible and will remain in your arm for the duration of the day on Day 4 and Day 18. The catheter will not be needed to take the single blood sample on Days 5, 6, 19, and 20.

During each visit to the laboratory we will ask you questions to find out if you have done anything between visits that would prevent your continuing in the study such as: taking prescription drugs, smoking, donating blood, etc.

**Possible risks and discomforts**

**Maximal and Submaximal Exercise:** You may experience muscular fatigue, nausea, light-headedness and general discomfort during exercise testing. There is a very small risk of death during an exercise test (0.5 per 10,000 tests). These risks and side effects will be minimized by: 1) the initial medical screening procedures, 2) the PAR-Q health questionnaire, and 3) following standard laboratory procedures for exercise testing. Potential participants who exhibit a condition that can be aggravated by exercise as determined by the PAR-Q will be excluded from participating in the study. Should an emergency occur, research personnel will follow standard emergency procedures and alert the Emergency Medical System if required.

**Sertraline:** There are known contraindications to the use of sertraline, such as individuals under the age of 18 or females who are pregnant/nursing. The study physician will ensure that each participant included in the study has no contraindications against taking sertraline. Previously reported side effects include nausea, headache, dry mouth, diarrhea, sleep disturbance and loss of appetite. Other effects may include drowsiness, sexual problems, nervousness and tremor. Although the side effects are unlikely following a single acute administration, participants will be instructed to immediately advise Mr. Ruderman if they notice any signs of being unwell while in the laboratory. Before the participants leave the laboratory, they will be reminded that should any symptoms arise, they should immediately contact Mr. Ruderman, who will contact the appropriate authorities, such as the study physician. The full list of side effects and precautions are indicated in the Zoloft monograph (Appendix C), and a copy of this information will be given to each participant. Should participants feel distressed after taking the drug, they can also contact emergency services at 911 or Campus Police, or Kids Help Phone at 1-800-668-6868.
Blood sampling: It is possible that you could develop an infection from the blood draw, or you could bruise in that area. These risks are small since we use standard medical precautions (including: use of sterile needles; properly cleaning the skin area with alcohol prior to drawing the blood; personnel wearing gloves; following aseptic conditions; no reusing of tubes, needles, or gauze, etc.). Blood samples will be drawn by an experienced member of the research team who has been trained to take blood samples and authorized by a physician to do so.

Blood loss: It is possible for you to have reduced blood volume over the course of the study. However, the amount of blood taken during the three-week period for the testing visits is small and it is unlikely to result in any adverse effects. The amount of blood sampled over the study period will total less than 100 millilitres for each of the two 48 hour trials where blood is sampled, amounting to 180 millilitres over the course of the 3 week study. This is not considered a significant physiological or health challenge given that it will be spread out over a minimum of a 3 week period, and thus is unlikely to result in any adverse effects.

The study is a more than minimal-risk research project and therefore we have adopted several procedures for your safety. In the event a First Aid Emergency occurs while you are in the laboratory, a phone call to 911 and/or Campus Police will be made. First aid/CPR may be given by one of the trained members of the research team who will be present during all lab visits.

Possible benefits of the research and benefits to you

Those participants who are interested in their aerobic fitness level will benefit from participation in this study, as they will receive a report describing their maximal aerobic power and other physiological variables measured during the VO_2max test. This report will highlight their individual physiological responses to increasing exercise intensity, which can be used to help the participants understand their current training status and fitness level. In addition, this study could potentially improve our understanding of how the dosing regimen of a drug is altered by exercise, benefiting the medical community as well as individuals taking this drug who are engaged in physically demanding occupations, recreational physical activity, and competitive sport. Should research findings support the experimental hypothesis, than a reassessment of conventional dosing of sertraline may be necessary, leading to a more effective use of a commonly prescribed drug. This research also has the broader potential to sensitize drug regulatory agencies and prescribing health professionals to the effects of exercise on drug efficacy.

Voluntary participation: Your participation in the study is completely voluntary and you may choose to stop participating at any time. Your decision not to volunteer will not influence the nature of the ongoing relationship you may have with the researchers or study staff or the nature of your relationship with the University of Toronto either now, or in the future.

Blood samples: By volunteering to participate in this study you are indicating that you are aware and agree that blood specimens will be obtained as described above. These samples will be used for measuring levels of sertraline, as well as other substances naturally present in the
blood. These samples are stored frozen in the lab with your study identification code. It is standard practice to keep your samples even after they have been analyzed.

**Secondary use of data:** I consent/do not consent (circle one) to the use of this study’s experimental data involving me in unidentified form in future related studies provided review and approval have been given by the Office of the Vice-President, Research at the University of Toronto. If I agree, the results collected from my physiological monitoring and performance tests will be entered into an electronic database in a form that is anonymous and cannot be linked back to my name. The objective of the database is to facilitate the creation of normative values for the various tests that are used routinely in our research laboratory.

**Participant Signature**  
__________________________

**Date**  
________________

**Withdrawal from the study:** You can stop participating in the study at any time, for any reason, if you so decide. If you decide to stop participating, you will receive a prorated compensation of the time you were in the study. Your decision to stop participating, or to refuse to answer particular questions, will not affect your relationship with the researchers, the University of Toronto, or any other group associated with this project. In the event you withdraw from the study, you will have the option of withdrawing your data from the study following the debriefing. If you choose to participate in the study, but later decides to withdraw before completing all of its requirements, you will be asked to confirm that any data already collected may in fact be used for the study outcomes.

**Compensation:** You will receive financial compensation for your time in the laboratory. If you complete the entire protocol, you will receive an honorarium of $200.00. If you withdraw early or are terminated from the study, you will receive a pro-rated amount of compensation for the amount of time you completed in the study. Financial compensation from this study is taxable, however, T4A slips are issued only for amounts in excess of $500.00 remuneration per year.

**Confidentiality:** All information you supply during the research will be held in confidence and unless you specifically indicate your consent, your name will not appear in any report or publication of the research.

Data will be collected using several methods, including questionnaires and computers, as well as blood samples. Upon being enrolled in the study, you will receive an individualized study code. Only the study code will be used for identification purposes on any forms or materials collected during the study. Your data will be safely stores in a locked facility and only research staff will have access to this information. Your data files will be stores for at least ten years after the completion of the study after which they will be destroyed by shredding at a commercial document destruction firm. Confidentiality will be provided to the fullest extent possible by law.

**Questions about the research?** If you have questions about the research in general or about your role in the study, please feel free to contact Ethan Ruderman (MSc Candidate) by email at ethan.ruderman@mail.utoronto.ca or Dr. Ira Jacobs by email at ira.jacobs@utoronto.ca.
If you have questions about how you have been treated as a research participant, please do not hesitate to contact the Office of Research Ethics: Daniel Gyewu, d.gyewu@utoronto.ca or 416 946 5606.

Do you have any food allergies?  
Yes:_________  No:_________  
If yes, please describe:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

Legal rights and signatures:

I _______________________________, consent to participate in the study titled “Effects of acute aerobic exercise on the pharmacokinetics of the anti-anxiety/anti-depressant drug sertraline” being conducted by Ethan Ruderman (MSc Candidate) and Dr. Ira Jacobs. I have read about and understood the nature of this project and wish to participate. I am not waiving any of my legal rights by signing this form. My signature below indicates my consent.

Participant Signature  Date
________________________________________________________________________  ________________________________

Principle Investigator Signature  Date
________________________________________________________________________  ________________________________
Appendix E

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

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<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
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<tbody>
<tr>
<td>1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?</td>
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<tr>
<td>2. Do you feel pain in your chest when you do physical activity?</td>
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<tr>
<td>3. In the past month, have you had chest pain when you were not doing physical activity?</td>
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<tr>
<td>4. Do you lose your balance because of dizziness or do you ever lose consciousness?</td>
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<tr>
<td>5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?</td>
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<tr>
<td>6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?</td>
<td></td>
</tr>
<tr>
<td>7. Do you know of any other reason why you should not do physical activity?</td>
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</table>

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:
- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

**NO to all questions**

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:
- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

**DELAY BECOMING MUCH MORE ACTIVE:**
- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

**PLEASE NOTE:** If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

---

Please note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

© Canadian Society for Exercise Physiology  www.csep.ca/forms
Zoloft®  
sertraline HCl  
Antidepressant—Antipanic—Antiobsessional  
Pfizer  

Date of Revision: November 17, 2011

Information for the Patient:

Please read this information before you start to take your medicine, even if you have taken this drug before.

What you should know about ZOLOFT:

ZOLOFT (sertraline hydrochloride) belongs to a family of medicines called SSRIs; Selective Serotonin Reuptake Inhibitors.

ZOLOFT has been prescribed to you by your doctor to relieve your symptoms of depression, panic disorder or obsessive-compulsive disorder. Treatment with these types of medications is most safe and effective when you and your doctor have good communication about how you are feeling.

What you should tell your doctor before taking ZOLOFT:

All your medical conditions, including a history of seizures, liver or kidney disease, diabetes or abnormal bleeding;

Any medications (prescription or nonprescription) which you are taking or have recently taken (within the last 14 days), especially monoamine oxidase inhibitor antidepressants (e.g. phenelzine sulfate, tranylcypromine sulfate or moclobemide) or any other antidepressants, pimozide (an antipsychotic drug), drugs used to treat diabetes, drugs used to thin the blood
(anticoagulants), the antibiotic linezolid, methylthioninium chloride (methylene blue) or drugs that affect serotonin (including but not limited to fentanyl, fenfluramine and tryptophan);

If you are pregnant or thinking about becoming pregnant, or if you are breast-feeding;

Your habits concerning alcohol consumption;

Any natural or herbal products you are taking (e.g. St-John’s Wort).

How to take ZOLOFT:

It is very important for you to take ZOLOFT exactly as your doctor has instructed. The usual starting dose is 50 mg of ZOLOFT/day for depression and obsessive-compulsive disorder. If you are taking ZOLOFT for panic disorder, your doctor may start you at 25 mg/day. Your doctor may decide to increase the dose up to 200 mg/day.

Never increase or decrease the amount of ZOLOFT you, or those in your care if you are a caregiver or guardian, are taking unless your doctor tells you to and do not stop taking this medication without consulting your doctor (see under Precautions when taking ZOLOFT:). You should continue to take your medicine even if you do not feel better, as it may take approximately four weeks for your medicine to work.

ZOLOFT should be taken with food; either in the morning or evening. You should swallow the capsule whole; do not chew it.

Keep taking ZOLOFT until your doctor tells you to stop. Your doctor may tell you to continue to take your medicine for several months. Continue to follow your doctor’s instructions.

If you miss taking a dose of ZOLOFT, do not worry, just take the next dose when you normally do. Do not take 2 doses at once. It is important to discuss with your doctor what you should do if you miss several doses of ZOLOFT.

You should avoid taking St. John’s Wort if you are taking ZOLOFT.

When not to use ZOLOFT:

Do not use ZOLOFT if you are allergic to it or to any of the components of its formulation (see list of components at the end of this section). Stop taking the drug and contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effect.

Precautions when taking ZOLOFT:
You may experience some side effects such as nausea, headache, dry mouth, diarrhea, sleep disturbance and loss of appetite. Other effects may include drowsiness, sexual problems, nervousness and tremor. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

**Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately; do not discontinue your medication on your own.**

ZOLOFT does not usually affect people's normal activities. However, some people feel sleepy while taking it, in which case they should not drive or operate machinery.

Avoid alcoholic drinks while taking ZOLOFT.

Contact your physician before stopping or reducing your dosage of ZOLOFT. Symptoms such as dizziness, abnormal dreams, electric shock sensations, agitation, anxiety, difficulty concentrating, headache, tremor, nausea, vomiting, sweating or other symptoms may occur after stopping or reducing the dosage of ZOLOFT. Such symptoms may also occur if a dose is missed. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of ZOLOFT to alleviate the symptoms.

Post-marketing cases of loss of blood sugar level control including both higher and lower-than normal sugar level have been reported in patients receiving SSRIs including ZOLOFT, with and without pre-existing diabetes. Symptoms associated with low blood sugar level in your blood include weakness, hunger, anxiety, sweating, numbness or tingling in your extremities. These are early warning symptoms and should not be ignored. Contact your doctor if you experience these symptoms.

Post-marketing reports indicate that some newborns whose mother took an SSRI (Selective Serotonin Reuptake Inhibitors), or other newer antidepressants, such as ZOLOFT, during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support, and tube feeding. Reported symptoms include: feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying. In most cases, the newer antidepressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the antidepressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact
your doctor as soon as you can.

If you are pregnant and taking an SSRI, or other newer antidepressant, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important you do NOT stop taking these medications without first consulting your doctor.

What to do in case of overdose:

If you have taken a large number of capsules all at once, go to the nearest hospital emergency department or nearest poison control center immediately, even though you may not feel sick, and take your medicine with you.

How to store ZOLOFT:

Store at room temperature (15 to 30°C) in a dry place.

Keep the container tightly closed.

Keep out of reach of children.

If your doctor decides to stop ZOLOFT treatment, return any leftover medicine to your pharmacist to safely dispose of it. Keep it only if your doctor tells you to do so.

What ZOLOFT contains:

ZOLOFT is available as 25 mg (yellow capsule), 50 mg (white and yellow capsule) and 100 mg (orange capsule). Sertraline is the active ingredient. Nonmedicinal ingredients include: cornstarch; lactose (anhydrous); magnesium stearate; sodium lauryl sulfate. Capsule shells contain gelatin, titanium dioxide and dye D & C Yellow #10. Capsules 25 and 50 mg also contain dye FD & C Yellow #6 and capsules 100 mg also contain dye FD&C #40. The capsules do not contain tartrazine or gluten.

Who manufactures ZOLOFT:

ZOLOFT capsules are manufactured by: Pfizer Canada Inc.
Reminder:

This medicine has been prescribed only for you. Do not give it to anybody else. If you have any further questions, please ask your doctor or pharmacist.

Availability:

The capsules are available as follows:

<table>
<thead>
<tr>
<th>Strengths (Capsules)</th>
<th>Sizes</th>
<th>Colors (Body/Cap)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg</td>
<td>#4</td>
<td>yellow/yellow</td>
</tr>
<tr>
<td>50 mg</td>
<td>#4</td>
<td>white/yellow</td>
</tr>
<tr>
<td>100 mg</td>
<td>#2</td>
<td>orange/orange</td>
</tr>
</tbody>
</table>

Capsule shells contain gelatin, titanium dioxide and dye D & C Yellow #10. Capsules 25 and 50 mg also contain dye FD & C Yellow #6, and capsules 100 mg also contain FD & C Red #40. They are tartrazine free. The drug is supplied in white high density polyethylene bottles of 100 capsules. Also, the 50 and 100 mg strengths are available in bottles of 250 capsules each.

Signature: ____________________________________________________

The Information for the Patient handout is developed by the pharmaceutical manufacturer in accordance with the requirements of Health Canada. The Canadian Pharmacists Association does not assume any legal liability and makes no representations or warranties concerning the accuracy, completeness, timeliness, reliability or usefulness of this information.

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Appendix G

The Graduate Department of Exercise Science at the University of Toronto is conducting a study to examine the effects of aerobic exercise on the metabolism of a drug in the body in young, healthy male participants. We will be studying whether exercise changes blood levels of the anti-anxiety/anti-depressant drug sertraline (brand name Zoloft/Lustral) in the body.

**Who Can Participate:**

- Participants must be **young** (age 18-40 years)
- **Healthy** (normal Body Mass Index – 18.5-24.9)
- **Males**
- Participants must not be taking any medications and have no prior history of anxiety, depression, and/or any other mental health disorders

**What’s Involved:**

- Participants must be capable of cycling for 30 minutes (0.5 hours) at a moderate intensity
- The study will include 7 visits to the laboratory spread out over three weeks, with each visit being of varying duration
- Blood samples from an arm vein
- Participants will receive financial compensation following completion of the study

**Where:**

- All testing will be conducted at the Athletic Centre, 55 Harbord Street

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**What’s In It for You?**

- Measurement of your VO$_{2\text{max}}$ and percent body fat.
- You will be making a significant contribution to exercise science through your participation in the study.

**Further Questions?**

Please feel free to contact the investigator with further questions concerning the study and your possible participation.

Contact:

Ethan Ruderman - 416 277 6155

Email: ethan.ruderman@mail.utoronto.ca
Appendix H

Study Meals

**Breakfast:**
Ensure Plus/Complete – vanilla or chocolate
*Total nutrition:* 350 Calories, 11g fat, 51g carbohydrates, 13g protein

**Morning Snack:**
Apple and Banana
*Total nutrition:* 242 Calories, 0g fat, 62g carbohydrates, 2g protein

**Lunch:**
Dempsters 12 grain whole-wheat bagel, peanut Butter and jam
Medium sized clementine
Dole canned apple juice
*Total nutrition:* 545 Calories, 12.5g fat, 99g carbohydrates, 14g protein

OR

Michelina’s – various choices
Medium sized clementine
Dole canned apple juice
*Total nutrition:* 535 Calories, 13g fat, 91g carbohydrates, 13g protein

**Afternoon Snack:**
Cliff bar – various choices
Premier Protein bar – various choices
*Total nutrition:* 530 calories, 11g fat, 69g carbohydrates, 41g protein

*Total nutritional intake for the entire day:*
1,627 Calories, 35g fat, 269g carbohydrates, 70g protein
Nutritional Information

Ensure:

1 Large Apple (3 ¼ inch diameter)

1 Large Banana (8 inches)
### Bagel Nutrition Facts

<table>
<thead>
<tr>
<th>Nutrition</th>
<th>Amount</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>Total Fat</td>
<td>2.5 g</td>
<td>4%</td>
</tr>
<tr>
<td>Saturated Fat</td>
<td>0.4 g</td>
<td>2%</td>
</tr>
<tr>
<td>Trans Fat</td>
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<tr>
<td>Polyunsaturated</td>
<td>0 g</td>
<td></td>
</tr>
<tr>
<td>Monounsaturated</td>
<td>0 g</td>
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</tr>
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<tr>
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<tr>
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<td>Sorbitol</td>
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### Kraft Peanut Butter Packet

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<tr>
<td>Polyunsaturated</td>
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<tr>
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<td>Protein</td>
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### Kraft Jam Packet

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<tr>
<td>Polyunsaturated</td>
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<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>0 mg</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>0 mg</td>
<td></td>
</tr>
<tr>
<td>Total Carbs</td>
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<tr>
<td>Dietary Fiber</td>
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### Dole canned juice

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<td>Calories</td>
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<td></td>
</tr>
<tr>
<td>Total Carbohydrates</td>
<td>79.2g</td>
<td>26%</td>
</tr>
<tr>
<td>Fiber</td>
<td>3.9 g</td>
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<tr>
<td>Sugars</td>
<td>48.1 g</td>
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<td>Protein</td>
<td>10.0 g</td>
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*Based on a 2000 calorie diet
### Michelina’s Clemintine

**Nutrition Facts**

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</tr>
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<td>Total Fat / Lipides</td>
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<tr>
<td>Saturated / saturated</td>
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</tr>
<tr>
<td>Sodium / Sodium</td>
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<tr>
<td>Carbohydrate / Glucides</td>
<td>56 g</td>
</tr>
<tr>
<td>Fiber / Fibres</td>
<td>2 g</td>
</tr>
<tr>
<td>Sugars / Sucres</td>
<td>3 g</td>
</tr>
<tr>
<td>Protein / Protéines</td>
<td>12 g</td>
</tr>
<tr>
<td>Vitamin A / Vitamine A</td>
<td>15 %</td>
</tr>
<tr>
<td>Vitamin C / Vitamine C</td>
<td>15 %</td>
</tr>
<tr>
<td>Calcium / Calcium</td>
<td>6 %</td>
</tr>
<tr>
<td>Iron / Fer</td>
<td>10 %</td>
</tr>
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</table>

*Based on a 2000 calorie diet

See more extended nutritional details

---

### Cliff bar

**Nutrition Facts**

<table>
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<tr>
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<tbody>
<tr>
<td>Calories / Fat / Sodium</td>
<td>18 g</td>
</tr>
<tr>
<td>Carbohydrate / Fiber</td>
<td>14 g</td>
</tr>
<tr>
<td>Sugar / Sucrose</td>
<td>32 g</td>
</tr>
<tr>
<td>Protein / Protein</td>
<td>8 g</td>
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</table>

Ingredients: Organic Brown Rice Syrup, CRP® (Soy Rice Crisps) Soy Protein

---

### Premier Protein bar

**Nutrition Facts**

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<tr>
<th>Amount</th>
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</thead>
<tbody>
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<td>Calories / Fat / Sodium</td>
<td>18 g</td>
</tr>
<tr>
<td>Carbohydrate / Fiber</td>
<td>14 g</td>
</tr>
<tr>
<td>Sugar / Sucrose</td>
<td>32 g</td>
</tr>
<tr>
<td>Protein / Protein</td>
<td>8 g</td>
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</tbody>
</table>

Ingredients: Organic Brown Rice Syrup, CRP® (Soy Rice Crisps) Soy Protein

---

*Percent Daily Values are based on a 2000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.

Calories: 2,000 2,500
## Appendix I

### Sertraline concentration of each participant at rest

<table>
<thead>
<tr>
<th>Time</th>
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<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>24</th>
<th>48</th>
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<tbody>
<tr>
<td><strong>Participant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1R</td>
<td>0.01</td>
<td>&lt; 0</td>
<td>1.42</td>
<td>8.58</td>
<td>17.33</td>
<td>20.26</td>
<td>19.79</td>
<td>8.99</td>
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<td>2.37</td>
<td>24.91</td>
<td>22.68</td>
<td>21.81</td>
<td>25.67</td>
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</tr>
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<td>N/A</td>
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<td>10.77</td>
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<td>12.42</td>
<td>9.88</td>
<td>5.12</td>
<td>2.33</td>
</tr>
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<td>N/A</td>
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<td>14.07</td>
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<td>4.27</td>
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<td>14.03</td>
<td>5.96</td>
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<td>57.12</td>
<td>51.77</td>
<td>13.25</td>
<td>12.42</td>
<td>9.88</td>
<td>5.12</td>
</tr>
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<td>1.01</td>
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<td>N/A</td>
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Values are concentration (ng/mL)

### Sertraline concentration of each participant with exercise

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<th>8</th>
<th>10</th>
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<td>22.34</td>
<td>20.41</td>
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<td>22.61</td>
<td>16.99</td>
<td>16.26</td>
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<td>4.12</td>
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<td>21.92</td>
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Values are concentration (ng/mL)
Appendix J

Relative changes in plasma volume of each participant at rest

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<td>-0.7</td>
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</tr>
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<td>4R</td>
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<td>11.5</td>
<td>16.0</td>
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<tr>
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<td>-4.7</td>
<td>-4.1</td>
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<td>-11.8</td>
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<td>-17.2</td>
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<td>11.1</td>
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Values are percentages

Relative changes in plasma volume of each participant with exercise

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Values are percentages
### Appendix K

Comparison of the effect of condition on the model rate constants and apparent Vd for each participant from the two compartment model.

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<th>$k'_{10}$ Exercise</th>
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<th>$V_1$ Exercise</th>
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**Population**

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<th>( k_{21} ) Exercise</th>
<th>( k_m ) Rest</th>
<th>( k_m ) Exercise</th>
<th>( k_{(M)} ) Rest</th>
<th>( k_{(M)} ) Exercise</th>
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**Participant values** are predicted parameter ± SE. **Population means** are values ± SD.

**Abbreviations:** L: litres; h: hours; NS: not significant; \( k_a \): absorption rate constant from the gut to the central compartment; \( k_{12} \) and \( k_{21} \): the rate constants between the central (1) and peripheral (2) compartments, respectively; \( k_m \): metabolite formation rate constant; \( k'_{10} \): the elimination rate constant of drug from the central compartment without \( k_m \); \( k_{(M)} \): the elimination rate constant from the metabolite compartment; and \( V_1 \): the apparent Vd by the oral route.
Comparison of the effect of condition on the model rate constants and apparent Vd for each participant from the one compartment model.

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Table Continued

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<td>0.1603</td>
<td>0.168</td>
<td>0.205</td>
<td>0.1894</td>
<td>0.1911</td>
</tr>
<tr>
<td>3</td>
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<td>0.2209</td>
<td>0.195</td>
<td>0.232</td>
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<td>0.2529</td>
</tr>
<tr>
<td>4</td>
<td>0.1323</td>
<td>0.1466</td>
<td>0.175</td>
<td>0.223</td>
<td>0.1652</td>
<td>0.1783</td>
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<tr>
<td>5</td>
<td>0.155</td>
<td>0.2155</td>
<td>0.176</td>
<td>0.22</td>
<td>0.1869</td>
<td>0.2471</td>
</tr>
<tr>
<td>6</td>
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<td>0.1927</td>
<td>0.173</td>
<td>0.207</td>
<td>0.1991</td>
<td>0.2237</td>
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<td>0.16</td>
<td>0.197</td>
<td>0.2014</td>
<td>0.2511</td>
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<td>0.153</td>
<td>0.213</td>
<td>0.1642</td>
<td>0.1665</td>
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<tr>
<td>9</td>
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<td>0.1534</td>
<td>0.162</td>
<td>0.223</td>
<td>0.1869</td>
<td>0.1849</td>
</tr>
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<td>10</td>
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<td>0.142</td>
<td>0.15</td>
<td>0.21</td>
<td>0.1547</td>
<td>0.1725</td>
</tr>
<tr>
<td>11</td>
<td>0.1569</td>
<td>0.1613</td>
<td>0.175</td>
<td>0.209</td>
<td>0.1884</td>
<td>0.1923</td>
</tr>
<tr>
<td>12</td>
<td>0.1362</td>
<td>0.1329</td>
<td>0.15</td>
<td>0.209</td>
<td>0.1677</td>
<td>0.1639</td>
</tr>
<tr>
<td>13</td>
<td>0.1188</td>
<td>0.116</td>
<td>0.156</td>
<td>0.218</td>
<td>0.1521</td>
<td>0.1475</td>
</tr>
<tr>
<td>14</td>
<td>0.115</td>
<td>0.144</td>
<td>0.123</td>
<td>0.198</td>
<td>0.1464</td>
<td>0.174</td>
</tr>
</tbody>
</table>

Participant values are predicted parameter ± SE
Population mean are values ± SD
**Appendix L**

**Table L.** Comparison of the effect of trial on the two compartment model mean rate constants and mean apparent Vd.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group Mean</th>
<th>t-statistic</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>(Degrees of Freedom)</td>
</tr>
<tr>
<td>$k_a$ (h$^{-1}$)</td>
<td>0.137 ± 0.0182</td>
<td>0.210 ± 0.0535</td>
<td>-5.89 (13)</td>
</tr>
<tr>
<td>$k_{10}^\prime$ (h$^{-1}$)</td>
<td>0.0392 ± 0.00890</td>
<td>0.0627 ± 0.0102</td>
<td>-9.98 (13)</td>
</tr>
<tr>
<td>$k_m$ (h$^{-1}$)</td>
<td>0.357 ± 0.0312</td>
<td>0.321 ± 0.0216</td>
<td>5.19 (13)</td>
</tr>
<tr>
<td>$k_{10}$ (h$^{-1}$)</td>
<td>0.396 ± 0.0313</td>
<td>0.383 ± 0.0220</td>
<td>1.723 (13)</td>
</tr>
<tr>
<td>$k_{12}$ (h$^{-1}$)</td>
<td>0.729 ± 0.0268</td>
<td>0.822 ± 0.0441</td>
<td>-11.3 (13)</td>
</tr>
<tr>
<td>$k_{21}$ (h$^{-1}$)</td>
<td>2.539 ± 0.109</td>
<td>2.95 ± 0.122</td>
<td>-20.9 (13)</td>
</tr>
<tr>
<td>$V_1$ (L)</td>
<td>30.3 ± 0.00910</td>
<td>40.1 ± 0.00679</td>
<td>-6.80 (13)</td>
</tr>
<tr>
<td>$k_{[M]}$ (h$^{-1}$)</td>
<td>0.263 ± 0.0202</td>
<td>0.254 ± 0.0102</td>
<td>1.30 (13)</td>
</tr>
</tbody>
</table>

Group mean values are mean ± SD.

Abbreviations: L: litres; h: hours; NS: not significant; $k_a$: absorption rate constant from the gut to the central compartment; $k_{10}^\prime$: the elimination rate constant from the central compartment without $k_m$; $k_m$: the rate constant between the central and metabolite (3) compartment; $k_{10}$ the elimination rate constant sum of $k_{10}^\prime$ and $k_m$; $k_{12}$ and $k_{21}$: the rate constants between the central (1) and peripheral (2) compartments, respectively; $k_{[M]}$: the elimination rate constant from the metabolite compartment; and $V_1$: the apparent Vd by the oral route.
Appendix M

Figure M shows the predicted population concentration vs. time curve for sertraline and desmethylsertraline at rest and exercise, extrapolated to 96 hours. Paired sample t-tests were conducted to compare pharmacokinetic variables between trials. Significant differences in the t½β of sertraline between trials were found (Table M). No significant differences in the relevant PK parameters of desmethylsertraline were found.

Figure M. Predicted population semilogarithmic plot of plasma sertraline and desmethylsertraline concentrations during both trials based on the two-compartment model, extrapolated to 96 hours. Graph courtesy of Qi Yang.

Abbreviations: µM: micromolar (micromoles•Litres⁻¹); h: hours
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Exercise</th>
<th>t-statistic (Degrees of Freedom)</th>
<th>Significance</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sertraline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ ($\mu g\cdot L^{-1}$)</td>
<td>21.5 ± 6.41</td>
<td>25.6 ± 8.51</td>
<td>-2.94 (13)</td>
<td>$P &lt; 0.05$</td>
<td>19.1%</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>9.57 ± 1.36</td>
<td>8.6 ± 1.27</td>
<td>1.78 (13)</td>
<td>NS</td>
<td>n/a</td>
</tr>
<tr>
<td>$t_{1/2}\beta$ (h)</td>
<td>23.8 ± 5.45</td>
<td>19.5 ± 3.18</td>
<td>3.19 (13)</td>
<td>$P &lt; 0.01$</td>
<td>-18.1%</td>
</tr>
<tr>
<td>$AUC_{\text{inf}}$ ($\mu g\cdot h\cdot L^{-1}$)</td>
<td>1095 ± 473</td>
<td>935 ± 386</td>
<td>2.12 (13)</td>
<td>NS</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Desmethylsertraline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$AUC_{\text{inf}}$ ($\mu g\cdot h\cdot L^{-1}$)</td>
<td>739 ± 256</td>
<td>792 ± 305</td>
<td>-1.27 (13)</td>
<td>NS</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Abbreviations: NS: not significant; $C_{\text{max}}$: maximum plasma concentration; $t_{\text{max}}$: time to $C_{\text{max}}$; $t_{1/2}\beta$: terminal elimination half-life; $AUC_{\text{inf}}$: area under the plasma concentration-time curve from zero to infinity; $\mu g$: micrograms; L: litres; h: hours; $\beta$: beta (elimination rate constant).
Appendix N

**Table N.** Comparison of the effect of trial on the model mean rate constants and mean apparent Vd from the one compartment model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group Mean</th>
<th>t-statistic</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>(Degrees of Freedom)</td>
</tr>
<tr>
<td>$k_a$ (h$^{-1}$)</td>
<td>0.0353 ± 0.00182</td>
<td>0.0279 ± 0.00359</td>
<td>12.2 (13)</td>
</tr>
<tr>
<td>$k'_{10}$ (h$^{-1}$)</td>
<td>0.0319 ± 0.000798</td>
<td>0.0312 ± 0.000533</td>
<td>3.74 (13)</td>
</tr>
<tr>
<td>$k_m$ (h$^{-1}$)</td>
<td>0.144 ± 0.0182</td>
<td>0.169 ± 0.0380</td>
<td>-3.16 (13)</td>
</tr>
<tr>
<td>$k_{10}$ (h$^{-1}$)</td>
<td>0.176 ± 0.0178</td>
<td>0.200 ± 0.0383</td>
<td>-3.07 (13)</td>
</tr>
<tr>
<td>$V_1$ (L)</td>
<td>8.63 ± 2.50</td>
<td>7.25 ± 2.37</td>
<td>2.42 (13)</td>
</tr>
<tr>
<td>$k_{[M]}$ (h$^{-1}$)</td>
<td>0.164 ± 0.0174</td>
<td>0.213 ± 0.010</td>
<td>-14.0 (13)</td>
</tr>
</tbody>
</table>

Group mean values are mean ± SD

Abbreviations: L: litres; h: hours; NS: not significant; $k_a$: absorption rate constant from the gut to the central compartment; $k'_{10}$: the elimination rate constant from the central compartment without $k_m$; $k_m$: the rate constant between the central and metabolite compartment; $k_{10}$: the elimination rate constant sum of $k'_{10}$ and $k_m$; $V_1$: the apparent Vd by the oral route; and $k_{[M]}$: the elimination rate constant from the metabolite compartment;
### Appendix O

**Table O.** Comparison of the trends in rate constants and volume of sertraline in the central compartment between the one and two compartment models.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>One Compartment</th>
<th>Two Compartment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest → Exercise</td>
<td>Rest → Exercise</td>
</tr>
<tr>
<td>$k_s (\text{h}^{-1})$</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>$k_{10} (\text{h}^{-1})$</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>$k_m (\text{h}^{-1})$</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>$k_{10} (\text{h}^{-1})$</td>
<td>↑</td>
<td>NS</td>
</tr>
<tr>
<td>$k_{12} (\text{h}^{-1})$</td>
<td>n/a</td>
<td>↑</td>
</tr>
<tr>
<td>$k_{21} (\text{h}^{-1})$</td>
<td>n/a</td>
<td>↑</td>
</tr>
<tr>
<td>$V_i/F (\text{L})$</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>$k_{(M)} (\text{h}^{-1})$</td>
<td>↑</td>
<td>NS</td>
</tr>
</tbody>
</table>
**Figure P.** Predicted population semilogarithmic plot of plasma sertraline and desmethylsertraline concentrations during both trials based on the one compartment model, extrapolated to 96 hours. Graph courtesy of Qi Yang.

Abbreviations: $\mu$M: micromolar (micromoles $\cdot$ Litres$^{-1}$); h: hours
Table P. Comparison of pharmacokinetic parameters of sertraline and desmethylsertraline during the rest and exercise conditions based on data estimated from one compartment ADAPT 5 model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Exercise</th>
<th>t-statistic (Degrees of Freedom)</th>
<th>Significance</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sertraline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ ($\mu\text{g}\cdot\text{L}^{-1}$)</td>
<td>21.4 ± 6.91</td>
<td>19.6 ± 6.86</td>
<td>1.81 (13)</td>
<td>NS</td>
<td>n/a</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>11.5 ± 0.926</td>
<td>11.7 ± 1.72</td>
<td>-0.606 (13)</td>
<td>NS</td>
<td>n/a</td>
</tr>
<tr>
<td>$t_\beta$ (h)</td>
<td>20.0 ± 1.17</td>
<td>26.1 ± 4.52</td>
<td>-6.46 (13)</td>
<td>$P &lt; 0.001$</td>
<td>30.5%</td>
</tr>
<tr>
<td>$\text{AUC}_{\text{inf}}$ ($\mu\text{g}\cdot\text{h}\cdot\text{L}^{-1}$)</td>
<td>997 ± 353</td>
<td>1086 ± 589</td>
<td>-0.994 (13)</td>
<td>NS</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Desmethylsertraline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{AUC}_{\text{inf}}$ ($\mu\text{g}\cdot\text{h}\cdot\text{L}^{-1}$)</td>
<td>448 ± 109</td>
<td>538 ± 288</td>
<td>-1.40 (13)</td>
<td>NS</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Values are mean ± SD

Abbreviations: NS: not significant; $C_{\text{max}}$: maximum plasma concentration; $t_{\text{max}}$: time to $C_{\text{max}}$; $t_\beta$: terminal elimination half-life; $\text{AUC}_{\text{inf}}$: area under the plasma concentration-time curve from zero to infinity; $\mu\text{g}$: micrograms; L: litres; h: hours; $\beta$: beta (elimination rate constant).
Subject 5

Subject 6

Drug Concentration (μM)

Time (h)

Drug Concentration (μM)

Time (h)
Appendix R

Subject 1

Subject 2