University of Alberta

Is Atomoxetine effective in treating nicotine withdrawal?
A double-blind, placebo-controlled, fixed-dose study

by

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Dedication

This work is dedicated to my lovely husband Mehti Dadashov and my dear children Seymur and Kamilla, whose love, inspiration and great support made this project successful.

I also dedicate these theses to my dear parents Vera Stadnik and Valeriy Stadnik, whose deepest love and couching has been navigating me throughout my life.

Abstract

Drugs that affect noradrenaline neurotransmission are used as therapy for smoking cessation. A recent study in individuals with attention-deficit and hyperactivity disorder (ADHD) suggested that atomoxetine, a noradrenaline reuptake inhibitor, may reduce cravings in individuals with ADHD who also smoked. The present double-blind, placebo-controlled, fixed-dose study investigated the effect of atomoxetine on nicotine withdrawal in otherwise healthy smokers, who has no psychiatric condition, and wish to stop smoking. A total of 17 individuals received either 40 mg atomoxetine (9 participants) or placebo (8 participants) treatment for 21-days. Study results indicated that, although none of the participants stopped smoking, there was clinical improvement in the atomoxetine treated group compared to the placebo group. Analysis showed significant differences between groups with regards to nicotine dependence and smoking urges. These differences were not seen in mixed model and in a last-observation carried forward analysis. Of note was that all participants in the placebo group completed the study while more than half of the participants in the atomoxetine group dropped out due to side-effects. It is concluded that atomoxetine deserves further study as a drug to help individuals stopping smoking, but given the high drop-out rate, a lower dose may be required.

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All things in our life happen according to the plans of the Lord Almighty. I believe that His plans for me were to meet those great people, whose encouragement, guidance and continual support provided me with the great opportunity to complete this thesis.

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My deepest gratitude to my beloved family: my parents, my husband and my lovely children, whose love and enormous support has been inspiring and encouraging me during my study.

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Abbreviations

AADAC	Alberta Alcohol and Drug Abuse Commission
ADHD	attention deficit hyperactivity disorder
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	aspartate aminotransferase
BDI	Beck Depression Inventory
BMI	body mass index
bpm	beats per minute
x	by
CBT	cognitive-behavioral therapy
CDS	Cigarette Dependence Scale
CIDI	Composite International Diagnostic Interview
CNS	central nervous system
COBh	blood carboxyhemoglobin
COPD	chronic obstructive pulmonary disease
CPP	conditioned place preference
CTUMS	Canadian Tobacco Use Monitoring Survey
CWS	Cigarette Withdrawal Scale
DA	dopamine
dBP	diastolic blood pressure

DNB	dorsal noradrenergic bundle
DSM-IV	Diagnostic and Statistical Manual version IV
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
fMRI	functional magnetic resonance imaging
FTND	Fagertrőm Test for Nicotine Dependence
GABA	γ-Aminobutyric acid
GGT	gamma-glutamyl transpeptidase
HAM-D	Hamilton Rating Scale for Depression
HIV	Human immunodeficiency virus
HR	heart rate
ICD	International Classification of Diseases
ICSS	intracranial self-stimulation
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
LC	locus ceruleus
LF	lost for follow-up
LOCF	last-observation carried forward
LOE	loss of efficacy
LSD	lysergic acid diethylamide
MADRS	Montgomery-Åsberg Depression Rating Scale
MAO-A	monoamine oxidase A
MAO-B	monoamine oxidase B

MINI	Mini International Neuropsychiatric Interview
MNWS	Minnesota Nicotine Withdrawal Scale
MWF	Minnesota Withdrawal Form
NA	noradrenaline
nAChRs	nicotinic acetylcholine receptors
NACTRC	Northern Alberta Clinical Trail Research Centre
NCSW	Number of cigarettes smoked per week
NDSS	Nicotine Dependence Syndrome Scale
NET	noradrenaline transporters
NHLBI	National Heart Blood and Lung Institute
NMDA	N-Methyl-D-aspartate
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone)
NNN	N'-nitrosonornicotine
NRT	nicotine-replacement therapy
PD	patient decision
PECNM	protocol entry criteria not met
PET	positron emission tomography
PFC	prefrontal cortex
PhD	physician decision
PHS	Public Health Services
PT	protocol violation
QSU	Questionnaire for Smoking Urges

RIA	radioimmunoassay
sBP	systolic blood pressure
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SCID-P	Structured Clinical Interview for DSM-IH-R patients
SCO	expired air carbon monoxide
SD	standard deviation
SD	sponsor decision
SE	side effects
SES	Rosenberg Self-Esteem Scale
SMR	standardized mortality ratio
SPECT	single photon emission computed tomography
US	United States
VNB	ventral noradrenergic bundle
WHO	World Health Organization
WK	week
WSWS	Wisconsin Smoking Withdrawal Scale

CHAPTER 1

INTRODUCTION

1.1. Introduction

Smoking is recognized as a global concern. Nicotine addiction affects not only tobacco users, but also their families and society in general. Impacting both mental and physical health, smoking addiction generates high cost associated with multidimensional measures, significantly affecting economy of countries world-wide (Koob & Le Moal, 2006).

Even though the number of smokers has been declining over several decades, global epidemiological data provided by World Health Organization (WHO) showed that in 1998 weighed smoking prevalence rates ranged from 21.8 % to 34.4% among various WHO world regions (Corrao et al, 2000), where weighted smoking prevalence rate for each WHO region were weighted by the number of smokers aged 15 and above. Moreover, it was predicted that world-wide annual smoking-related deaths will reach roughly three million people per year in the industrialized and seven million per year in the developing countries by 2030, despite declines in smoking prevalence rates (Mackay & Eriksen 2002).

Using tobacco leaves for a variety of purposes, including ceremonial, medicinal and pleasurable, has likely occurred for more than eight thousand years. However, it is only recently that civilizations have been able to appreciate the perilous consequences of tobacco consumption. It has only relatively recently

become clear that smoking is a globally growing problem that leads to serious health consequences (Report of the Surgeon General 1988). Furthermore, the etiology of many disorders has been recognized as being smoking-related, and additionally that nicotine dependence is one of the strongest addictions (Britton, 2000).

Since the majority of countries have acknowledged the severe impact produced by tobacco products, multiple actions to reduce tobacco addiction have been introduced. These include taxation, a supply reduction policy, reduction of drug demand, and harm reduction to try and decrease ease of use and availability. However, one of the most important steps was the recognition that smoking is a strong addiction, which requires a multifactorial treatment approach.

For several decades researchers have been attempting to find effective therapies for smoking cessation. One of the key scientific approaches has been to elucidate the role of neurotransmitters involved in nicotine dependence and addiction. Based on the effects on specific neurotransmitter systems, various smoking cessation medications have been introduced to the market.

Several studies have pointed out that alterations in noradrenaline (NA) neurotransmission in the hypothalamic paraventricular nucleus (Fu et al., 2001; Zhao et al., 2007), amygdala (Fu,Y. 2003; Zhao et al., 2007), extended amygdala that includes the bed nucleus of the stria terminalis, central medial amygdala and posterior part of the medial nucleus accumbens (Koob, 2009; Smith & Aston-Jones 2008) and fronto-parietal cortical regions (Summers,K.L. 1995) could be a one of the contributors to the process of nicotine dependence (Benowitz et al,

2008; Picciotto & Corrigall, 2002; Wonnacott et al, 1991; Wonnacott et al, 2006), drug craving (Zhao et al, 2007), relapse (Smith & Aston-Jones 2008), and withdrawal (Benowitz et al, 2008; Koob, 2009). Although the exact role of this neurotransmitter in nicotine dependence is still uncertain, it has been demonstrated that drugs affecting synthesis, release and inhibition of NA reuptake are also clinically effective (Carrozzi et al, 2008; Hughes et al, 2007a).

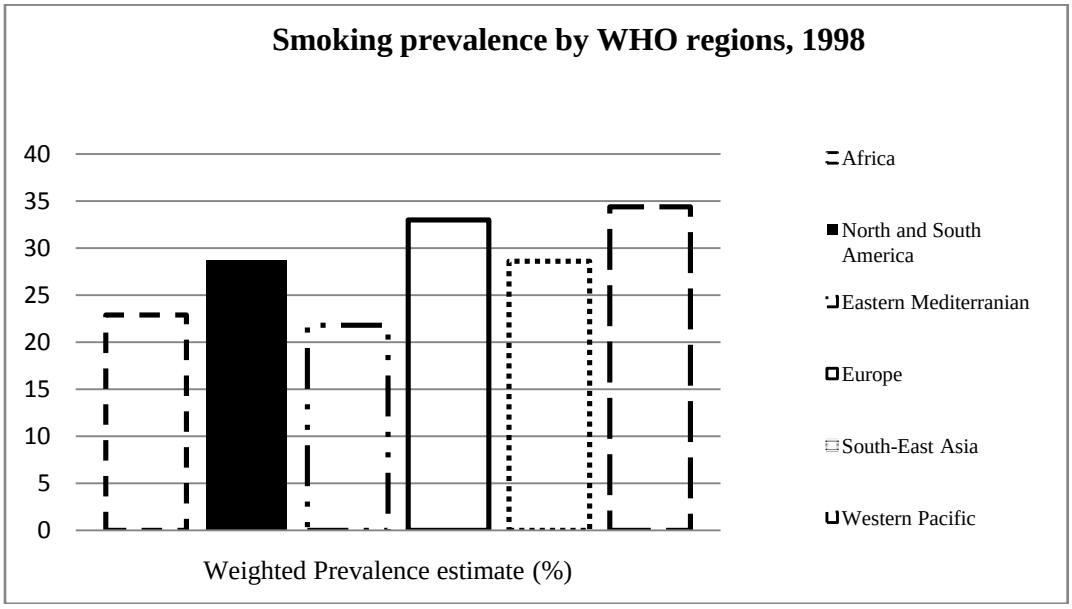
Despite numerous medications available for the treatment of nicotine addiction, the efficacy of current pharmaceutical aids remains wanting; therefore, there is still room for new medications for smoking cessation to be discovered. In the present research we explored a new treatment option, namely atomoxetine therapy for smoking cessation.

1.1.1. Epidemiology of nicotine addiction

1.1.1.1. World-wide situation.

The Tobacco Control Country Profile database created by the American Cancer Society and WHO revealed that in 1998 approximately 23% of African, 29% of American, 22% of Eastern Mediterranean, 33% of European, 29% of South East Asian and 34% of Western Pacific world regions population were smokers (Corrao et al, 2000) (Figure 1.1).

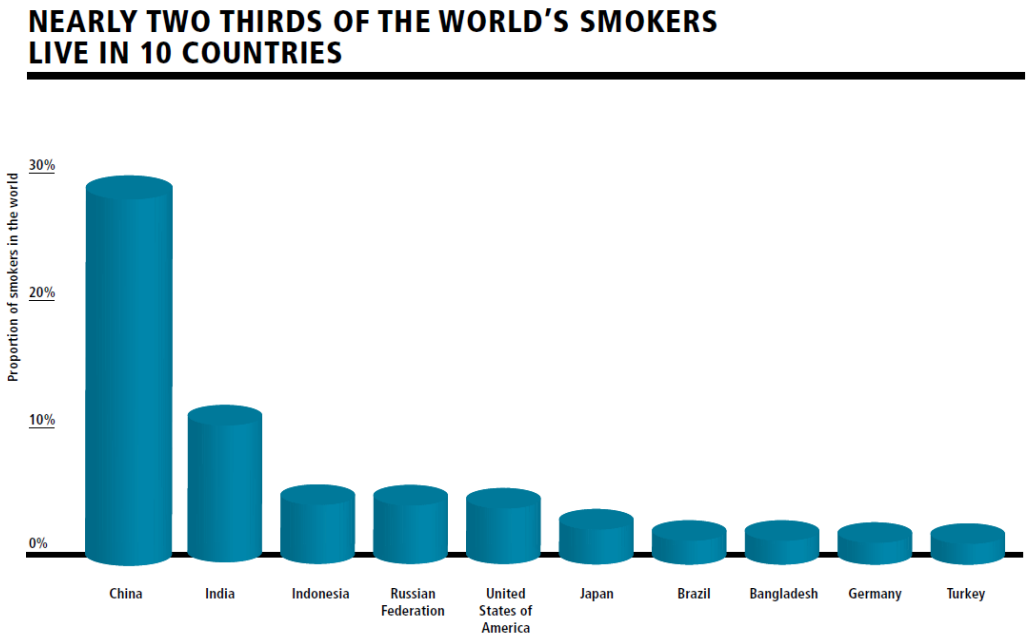
Figure 1.1. Smoking prevalence by WHO regions, 1998



Source: Corrao et al, 2000

The WHO Report on the Global Tobacco Epidemic, 2008, revealed that the prevalence of smoking varies from country to country with around two thirds of the world's smokers being concentrated in only 10 countries (Figure 1.2.).

Figure 1.2. Ten countries, where nearly two third of smokers live.



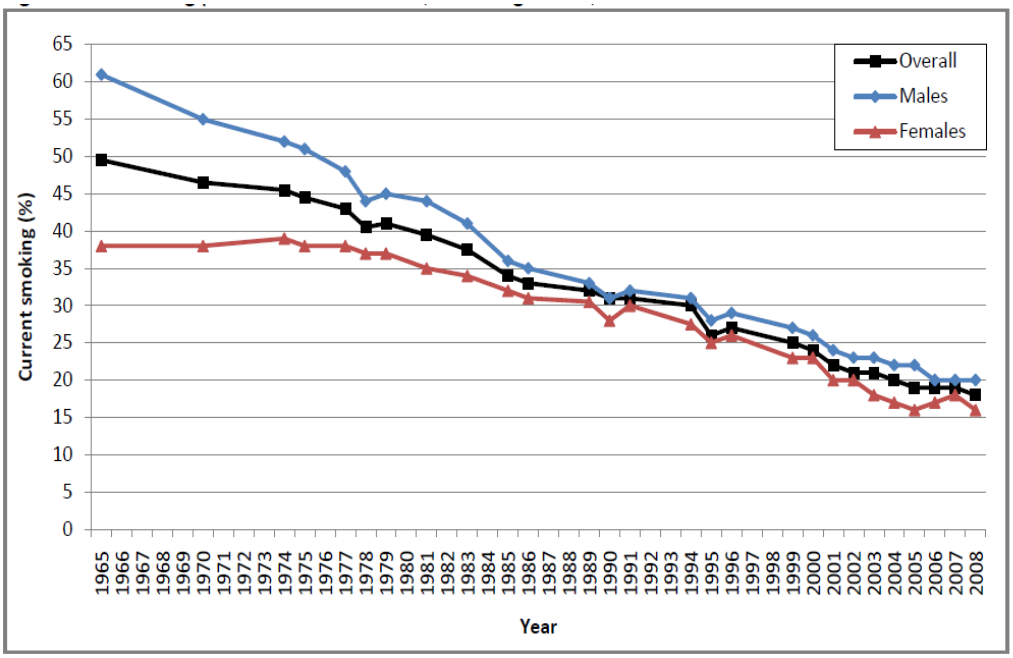
Source: WHO Report on the Global Tobacco Epidemic, 2008.

1.1.1.2. Prevalence of smoking in Canada

Canada belongs to the group of countries where smoking was very prevalent over the past four decades. Nevertheless, in line with world trends, since 1965 the total percentage of smokers has been decreasing in Canada (Figure 1.3.) (Physicians for a Smoke-Free Canada, 2009; Reid & Hammond, 2009).

According to the latest federal survey the percentage of both daily and occasional smokers has been decreasing in Canada. This declining trend was seen in both genders and across different age groups (Figure 1.3, Figure 1.4, Figure 1.5, Figure 1.6) (Reid & Hammond, 2009).

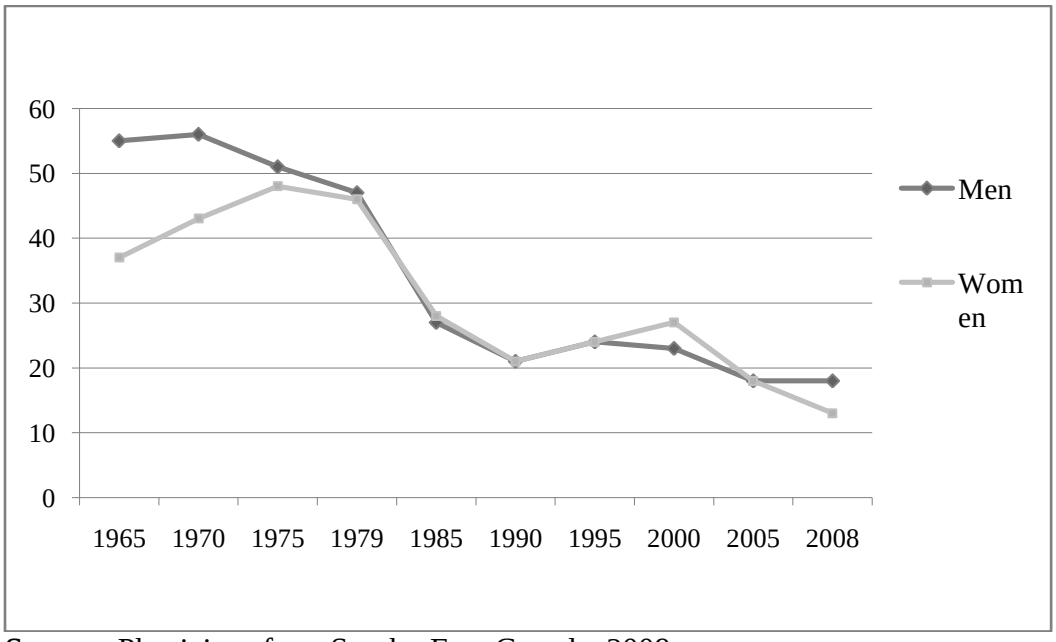
Figure 1.3. Prevalence of smoking in Canada, age 15+years, 1965-2008



*Includes daily and non-daily smokers

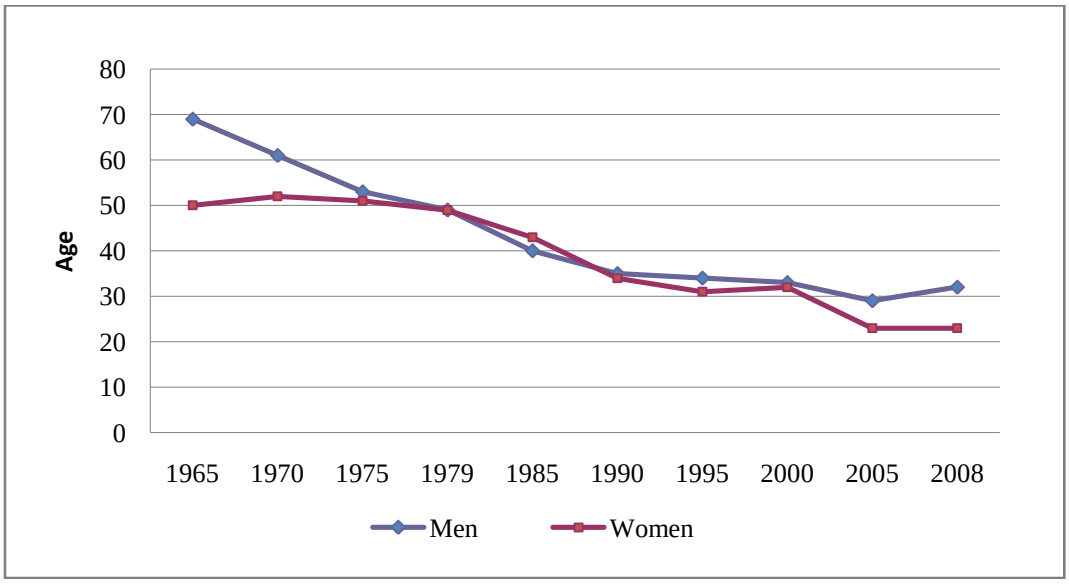
Source: Reid & Hammond, 2009.

Figure 1.4. Percentage of Canadians who smoke (daily or occasional), 15-19 years age group, 1965-2008



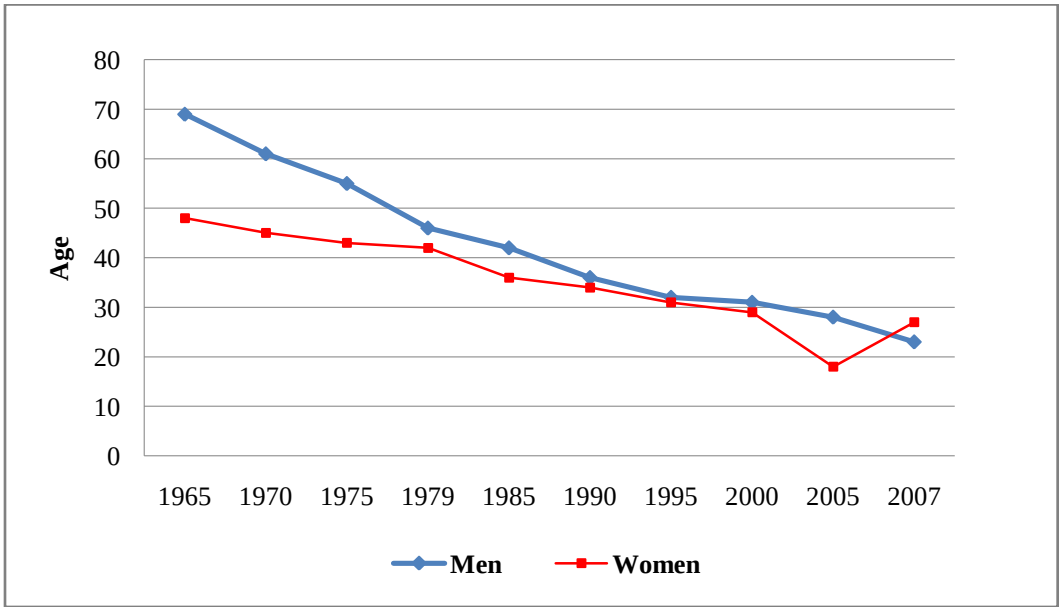
Source: Physicians for a Smoke-Free Canada, 2009.

Figure 1.5. Percentage of Canadians who smoke (daily or occasional), 20-24 years age group, 1965-2008



Source: Physicians for a Smoke-Free Canada, 2009.

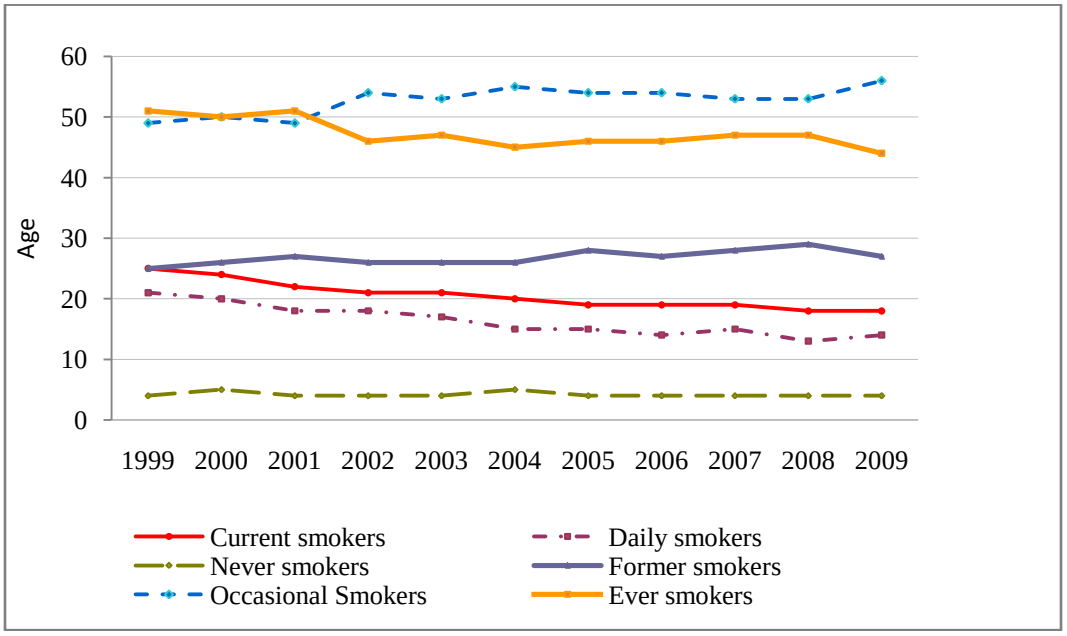
Figure 1.6. Percentage of Canadians who smoke (daily or occasional), 25-44 years age group, 1965-2008



Source: Physicians for a Smoke-Free Canada, 2009.

During the past ten years the proportions of smokers in different smoking categories, such as daily, occasional, current and former smokers, also underwent some changes consistent with less frequent smoking and more frequent quitting (Figure 1.7) (Canadian Tobacco Use Monitoring Survey 2009, CTUMS-11 Years of Data)

Figure 1.7. Smoking Status, Selected Percentages, Age 15+ years, Canada, 1999-2009



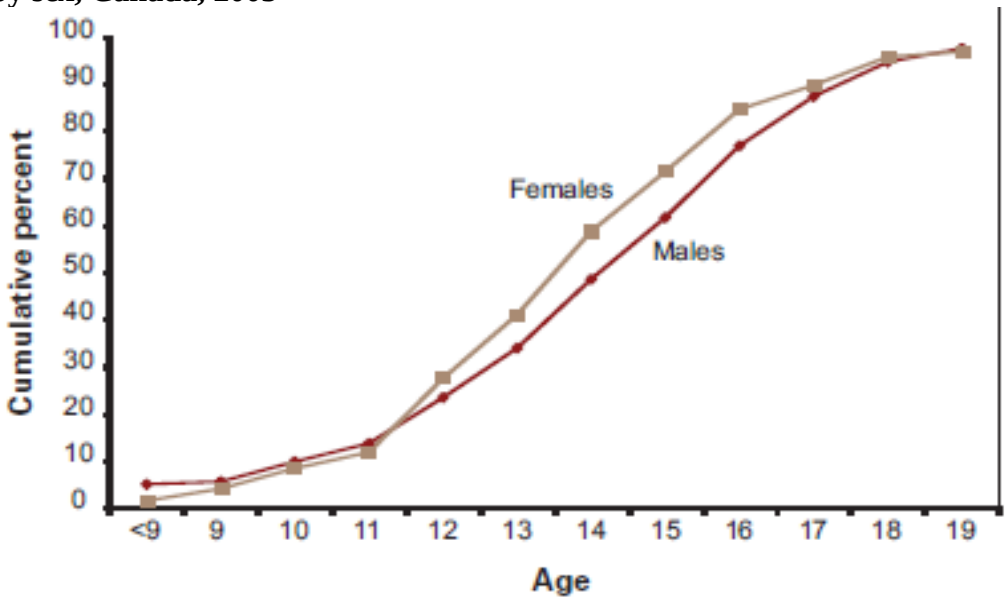
Source: Canadian Tobacco Use Monitoring Survey 2009, CTUMS-11 Years of Data.

Note: Figure 1.7 contains combined data on different groups of smokers such as current and former, daily and occasional, as well as smokers, who never and ever smoked.

Nevertheless, in total, 18% of Canadians are still smokers (Canadian Tobacco Use Monitoring Survey 2009, CTUMS-11 Years of Data). The National Youth Smoking Survey revealed that the average age at which children smoked their first cigarette has been rising over past 15 years. Even though youth survey data on average age of smoking initiation was not consistently reported, changes

have been observed. Thus, in the period 1994-2002 the average age of children who smoked a whole cigarette for the first time was 11 years. In contrast, 2008 - 2009 survey data showed that for those in grades 10-12 the average age was 14.1 years (Summary of results of the Youth Smoking Surveys for 1994-2009 years). Moreover, the only other available data (a monitoring survey in 2003) demonstrated that 66% of current smokers in Canada had their first cigarette by age 15 and almost 90% by age 19 years (Figure 1.8).

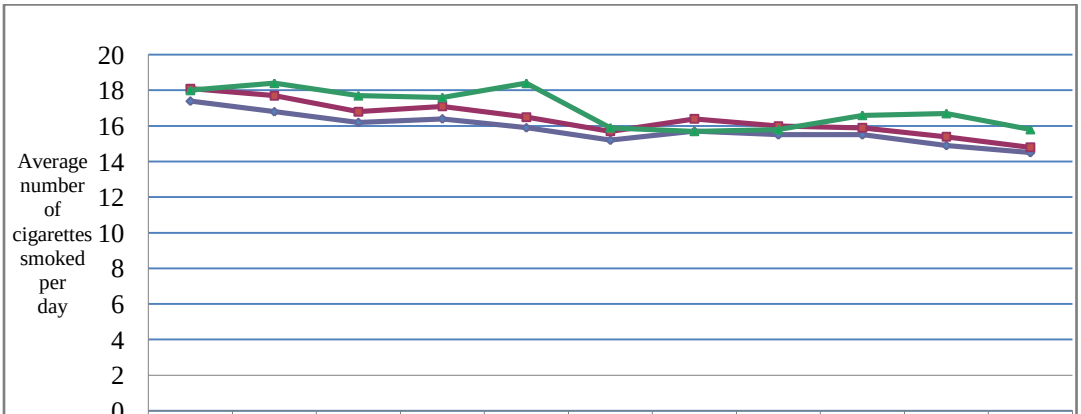
Figure 1.8. Age of smoking first cigarette, Current smokers, age 20-24 years, by sex, Canada, 2003



Source: Canadian Tobacco Use Monitoring Survey. Smoking in Canada.

National statistical data also showed that the average number of cigarettes smoked per day was more than 15 cigarettes per day during the period 1999 until 2008, for age groups 15+, 25+ and 55+, but in the last two years (2008 and 2009) the average number of cigarettes smoked per day decreased to less than 15 cigarettes per day (Figure 1.9).

Figure 1.9. Average Number Of Cigarettes Smoked Per Day Among Daily Smokers, By Age Groups, Age 15+, 25+, and 55+ years, Canada, 1999-2009

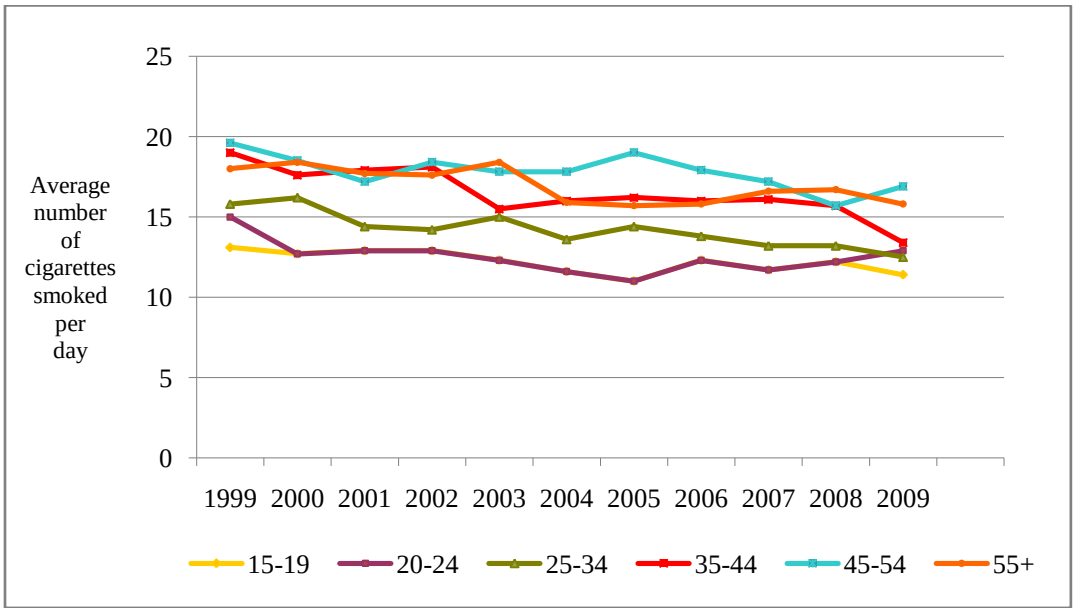


	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
15+	17.4	16.8	16.2	16.4	15.9	15.2	15.7	15.5	15.5	14.9	14.5
25+	18.1	17.7	16.8	17.1	16.5	15.7	16.4	16	15.9	15.4	14.8
55+	18	18.4	17.7	17.6	18.4	15.9	15.7	15.8	16.6	16.7	15.8

Source: 1) Tobacco Use in the 1998 National Household Survey on Drug Abuse. 2) Canadian Tobacco Use Monitoring Survey 2009.

When smokers are re-grouped by age categories as 15-19, 20-24, 25-34, 35-44, 45-54 and 55+, one can observe that according the National Institute on Drug Abuse classification of smoking severity, Canadian smokers who are older than 35 years of age belong to the "moderate" category on smoking severity for almost the entire decade, while smokers younger than 35 years of age were mostly "light" smokers (Figure 1.10).

Figure 1.10. Average Number Of Cigarettes Smoked Per Day Among Daily Smokers, By Age Groups, Age 15+, Canada, 1999-2009



Source: Canadian Tobacco Use Monitoring Survey 2009.

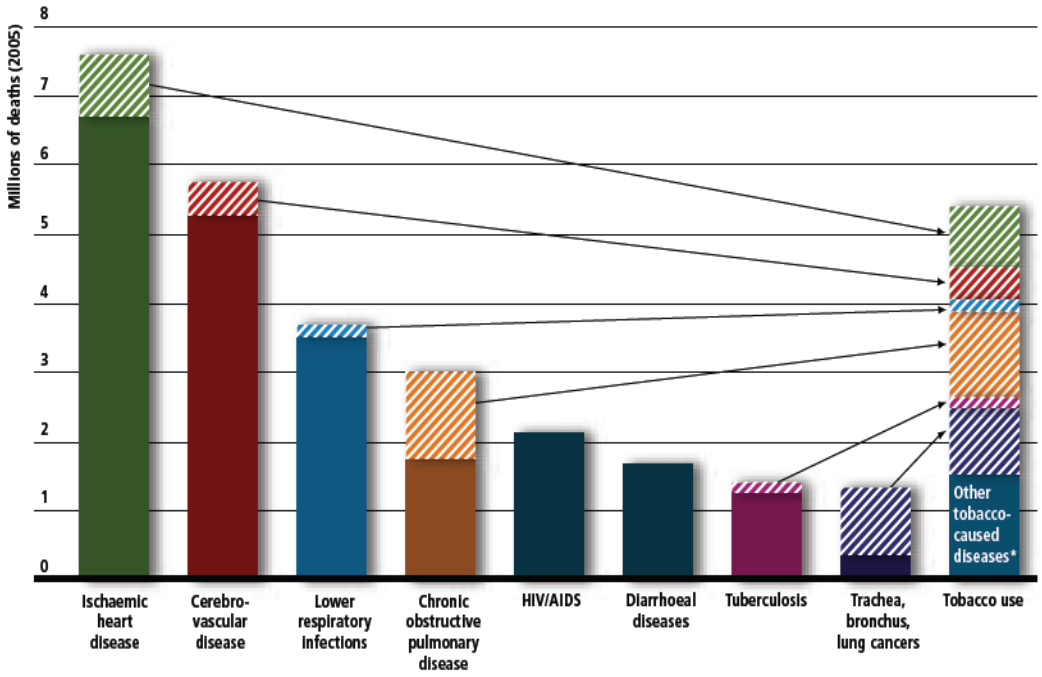
1.1.2. Health effects associated with use of tobacco products

The first time smoking was officially referred to as a growing health and social concern was in the Report of the U.S. Surgeon General, Luther L. Terry, in 1964. Since that time various health consequences of tobacco products have been well described and documented. In the 1979 report of the U.S. Surgeon General, smoking was recognized as involving nicotine addiction, and it was also linked with the development of various diseases in both active and passive smokers (Report of Surgeon General report, 1989).

Global statistics, collected by the World Health Organization (WHO), identified eight leading causes of the death world-wide. Use of tobacco was

recognized as a risk factor for six of eight of these causesincluding cancers and infections of the respiratory tract, chronic obstructive pulmonary diseases, ischemic heart diseases, cerebro-vascular diseases, and tuberculosis (Figure 1.11).

Figure 1.11. Tobacco Use is a Risk Factor for Six of the Eight Leading Causes of Death in the World.



Source: WHO Report on the Global Tobacco Epidemic, 2008.

Tobacco use was also reported to be a risk factor and a major cause of three leading causes of death in Canada: lung cancer, ischemic heart disease, and respiratory disease (Health Canada. Tobacco Use, 2007). In Canada approximately 85 per cent of lung cancer deaths are related to smoking (Lung Cancer Brochure-4 panel). Smoking also accounts for up to 90 % of all

underlying causes of chronic obstructive pulmonary disease (Health Canada, COPD). The risk of developing heart diseases and strokes is also significantly higher among smokers (Smoking in Canada Backgrounder).

Active smoking in women was linked to breast cancer and the development of earlier menopause compared to non-smokers. Moreover, smoking females have up to a 30% reduction in their fertility rates (Health Canada. Sleeping with a killer, 2008). Smoking also increases the risks associated with pregnancy outcomes (National Clearinghouse on Tobacco and Health), and by affecting pregnancy also leads to increased rates for various complications such as miscarriages, preterm delivery, and placenta abnormalities, resulting in increased perinatal mortality rates (DiFranza et al., 1995; Murin et al., 2011; Hayashi et al., 2011; Health Canada. Sleeping with a killer, 2008; Sochaczewska et al., 2010).

Although several epidemiological studies failed to demonstrate that the increase in congenital anomalies or birth defects were directly related to smoking, one cohort study showed that the babies of smoking mothers tended to have lower birth weights (Health Canada. Sleeping with a killer, 2008).

1.1.3. Exposure to environmental tobacco smoke

The magnitude of the harm produced by second hand smoke exposure is believed to be as significant as that from active smoking. Passive exposure to tobacco smoke produces substantial impact on the health of people who only passively inhale smoke (which contains more than 4,000 various chemicals, many

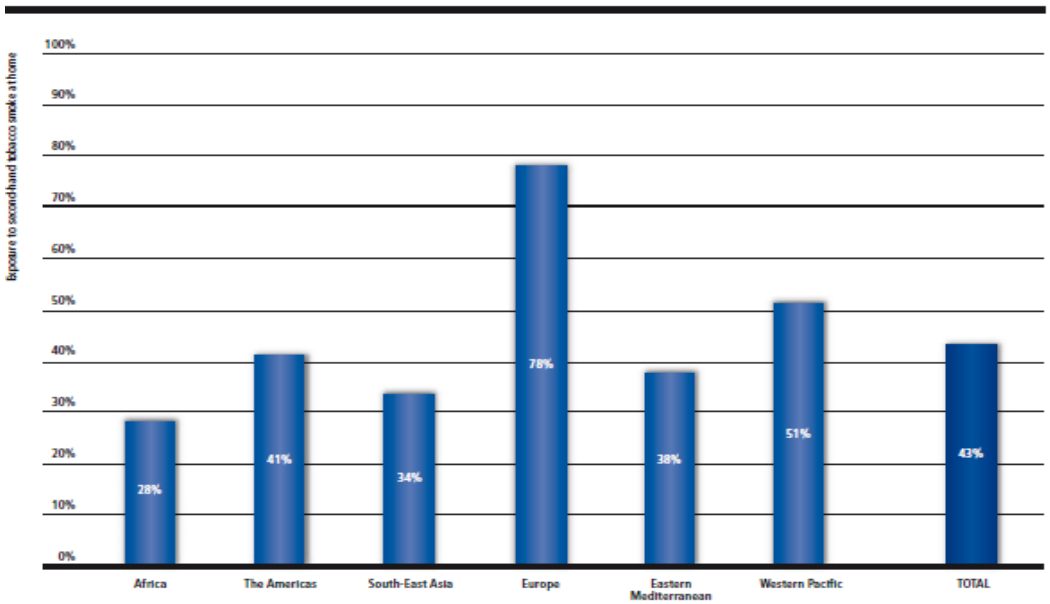
of which have harmful and cancerogenic). For example, passive smokers who are regularly exposed to cigarette smoke have 25% more probability of developing respiratory problems and 10% more of them develop heart diseases when compared to unexposed populations (Smoking in Canada Backgrounder).

Passive exposure to cigarette smoke in pregnant females was shown to lead to lower birth weights. Moreover, children of mothers exposed to passive smoking during pregnancy have an 80% increased risk of developing central nervous system tumors (Health Canada. Sleeping with a killer, 2008). Currently, many children around the world are exposed to passive smoking. Exposure usually occurs either at home or at day care. The health impact due to second hand smoke is even more extensive for children because of their developing status and small body size (Health Canada. A National Strategy 1999). Moreover, passive exposure also affects the attitudes of children towards smoking in their life, with children of smoking parents being more likely to smoke than children of non-smoking parents (Smoking in Canada Backgrounder).

In 2008 around 43% of children world-wide were exposed to smoke at their homes. The European, American and Western Pacific regions were leading regions in terms of children's smoke exposure (Figure 1.12) (WHO Report on the Global Tobacco Epidemic, 2009). In 2009, according to a Canadian survey, 5% of children aged up to 11 years old were exposed to second hand smoke at home. This represented a very considerable drop over a 10-year period, since the proportion of exposed children was 26% in 1999 (Health Canada. Overview of

Historical Data, 1999-2009 http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/index-eng.php).

Figure 1.12. Average Percentage of 13-15 Year-Olds Living in A Home Where Others Smoke, by WHO Regions, 2008



Source: WHO Report on the Global Tobacco Epidemic, 2009.

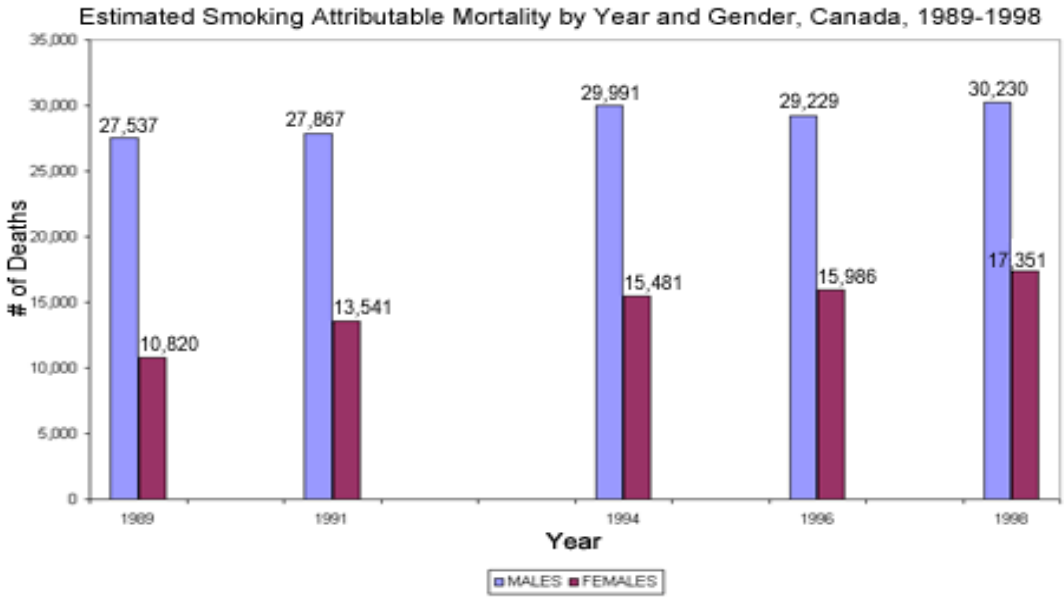
1.1.4. Smoking-associated mortality

Makomaski Illing and Kaiserman reported that smoking was responsible for 22% of all deaths in Canada in 1998 (The Mortality Attributable to Tobacco Use in Canada and its Regions (1998) study; Makomaski Illing & Kaiserman, 2004). In their study researchers gathered smoking-attributable mortality data from twenty two adult smoking-related diseases (including cancers, cardiovascular and respiratory diseases) and four pediatric diseases that were linked to maternal smoking. Smoking attributable mortality estimates were

analyzed since 1989 till 1998. Study results revealed that the number of smoking-related deaths has been steady rising since 1989(Makomaski Illing & Kaiserman, 2004).

In 1998 out of 47,581 smoking-attributable deaths in Canada, lung cancer was responsible for 35%, ischemic heart disease for 20% and chronic airway obstruction for 14% (Increase in Deaths in Canada Due to Smoking, 1998). Deaths due to smoking in Canada vary by years and by gender (Figure 1.13). For these reasons, smoking is referred as the most important cause of preventable illness, disability and premature death in Canada (National Clearinghouse on Tobacco or Health).

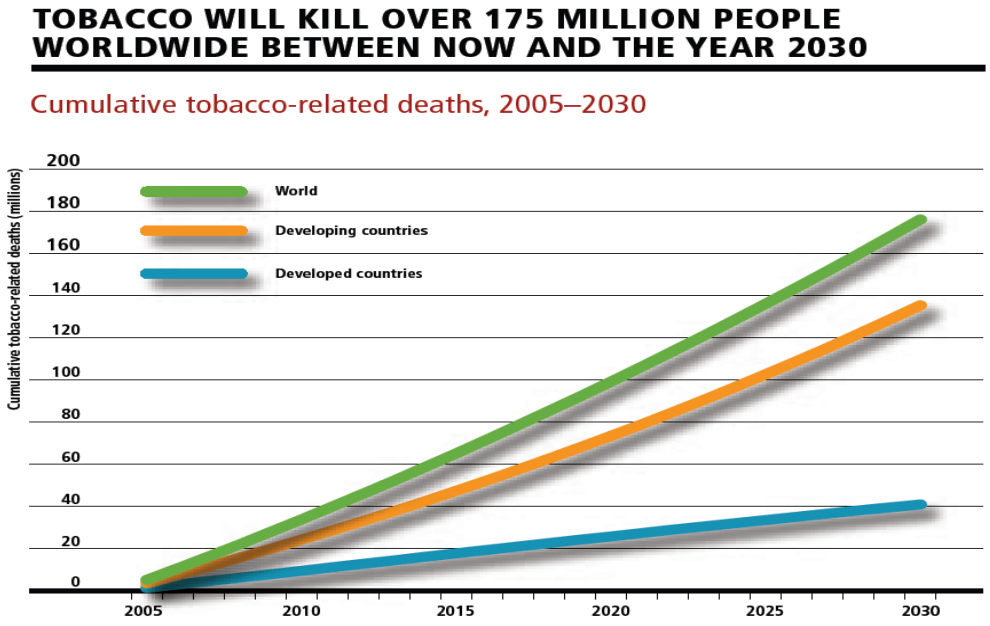
Figure 1.13. Estimated Smoking Attributable Mortality by Year and Gender, Canada, 1989-1998



Source: Increase in Deaths in Canada Due to Smoking, 1998.

Furthermore, there have been suggestions that globally, deaths due to tobacco use will increase dramatically over the period 2009 – 2030, particularly in developing countries (Figure 1.14)

Figure 1.14. Postulated tobacco-related deaths world-wide, WHO 2009



Source: WHO Report on the Global Tobacco Epidemic, 2009.

1.1.5. Economic impact of smoking

In a comprehensive report on social costs related to substance abuse (The Costs of Substance Abuse in Canada, 2002), it was shown that since 1966 there have been continuous increases in the costs associated with tobacco product use in Canada. This was $2.0 billion in 1991 (Kaiserman, 1997) compared to $17 billion in 2002. In 2002 smoking accounted for about 43% of all substance abuse costs in Canada. The large majority (74%, i.e. $12.5 billion) of that amount was related to

indirect costs associated with productivity lost due to illnesses and premature deaths among smokers, while 23% was spent for acute treatment and drug prescriptions for tobacco users.

1.2. Nicotine and its effects on the brain

1.2.1. Nicotine is the primary addictive component of the tobacco smoke

Cigarettes contain dried tobacco leaves along with various additives. When lit the burning cigarettes releases smoke that includes more than 4,000 various chemicals. Even though one cannot exclude the possibility that other components of tobacco smoke are responsible for the addictive properties of tobacco, nicotine has been shown to exhibit highly addictive properties in the large number of studies. It is considered to be the primary component responsible for the development of addiction to tobacco (Lowinson et al, 1997; Koob and le Moal 2006; Benowitz, 1999a).

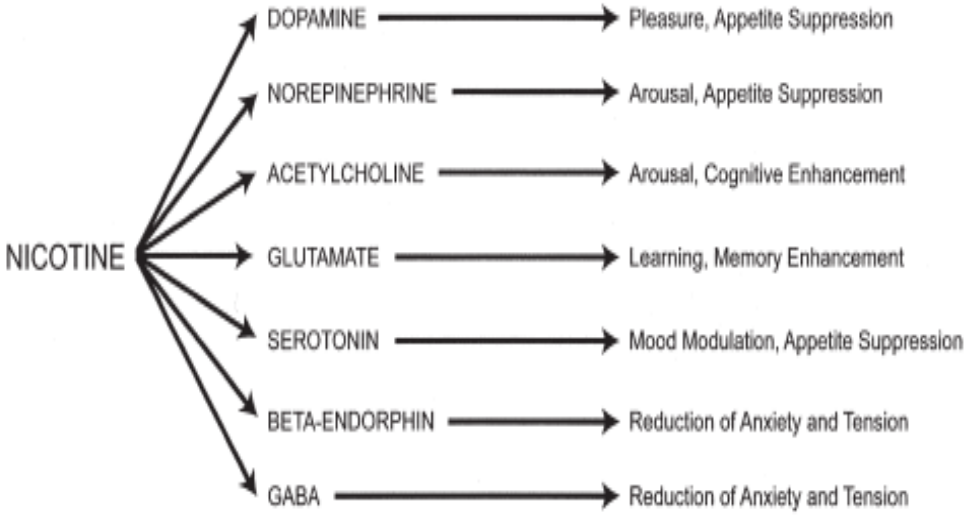
When compared to other drugs of abuse, nicotine has been shown to possess stronger addictive properties than other common drugs of abuse including heroin, cocaine, alcohol and caffeine (Britton et al., 2000).

1.2.2. Neurobiology of nicotine addiction

When cigarette smoke is inhaled, nicotine, which is carried by tar droplets, becomes rapidly absorbed through the alveolar surface of the lung and reaches the brain within 10-20 seconds (Benowitz et al., 2009). Nicotine has high

affinity to nicotinic acetylcholine receptors (nAChRs). When binding to their numerous subtypes, nicotine causes stimulation within the central nervous system with subsequent release of a diverse number of neurotransmitters (Wonnacott et al., 1997). Nicotine also produces activation of various brain regions such as frontal lobes, cingulate, prefrontal cortex, nucleus accumbens, hippocampus, thalamus, ventral tegmentum, amygdala, and substantia nigra (Stein et al., 1998; Li et al., 2008; Neuhaus et al., 2006; Ray et al., 2008; Suarez et al., 2009; Sharma and Brody, 2009; Rose et al., 2003;Musso et al., 2007; Gozzi et al., 2006)), as well as modulation of several neurotransmitter systems, which together likely mediate the numerous psychoactive effects of nicotine (Benowitz, 1999, Benowitz et al., 1999; 2008; Waters and Sutton, 2000; Zhao et al., 2007; Fu et al., 2001) (Figure 1.15)

Figure 1.15. Links between nicotine and effects of various neurotransmitters



(Adopted from permission of Dr. N.L. Benowitz, 1999)

In the present research study noradrenaline is the neurotransmitter of interest, and for this reason the research reviewed in detail in the following section focuses on this neurotransmitter in addition to reviewing the major known effects of nicotine on a variety of brain regions.

1.2.3. Nicotine-induced changes in the regional brain activity

Application of various imaging modalities in both animals and humans, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) have demonstrated that acute and chronic nicotine administration induce changes in regional brain activity.

Acute administration of nicotine has been shown to produce activation of several neuro-anatomical regions in animals including prefrontal, frontal, cingulate, piriform, somatosensory and rhinal cortices, amygdala, nucleus accumbens, ventral-tegmental area, substantia nigra, thalamus, putamen and caudal-ventral hippocampal regions (Gozzi et al, 2006; Suarez et al, 2009). Repetitive or chronic nicotine treatments of animals showed the activation of the following regions: striatum, nucleus accumbens, lateral septum, hippocampus, prefrontal cortex, cingulated cortex, ventral pallidum and ventral tegmentum (Calderan et al, 2005; Li et al, 2008).

In human PET and MRI studies it was similarly found that acutely administered nicotine activated frontal, prefrontal and visual cortices, insula, frontal and cingulate gyrus, thalamus, hippocampus, striatum, cerebellum and

reticular system (Domino et al, 2000a; Sutheraland et al, 2011; Domino et al, 2000; Rose et al, 2003). Chronic use of nicotine leads to effects on prefrontal and cingulate cortices, nucleus accumbens, amygdala, medio-dorsal and lateral posterior thalamus (Brody, 2006; Calderan et al, 2005; Stein et al, 1998; Stein et al, 2001; Sharma et al, 2009).

Thus, the overlap between animal and human imaging data regarding nicotine-evoked changes in regional brain activity implies that brain regions forming neuronal circuits are involved in nicotine's effects on the brain. Moreover, the activation of structurally distinct regions in acute and chronic nicotine use may reflect neuroanatomical changes corresponding to the duration of nicotine use. Furthermore, psychoactive effects associated with nicotine administration probably are mediated by nicotine-activated neuronal circuits mapped by neuroimaging studies. These circuits are closely structurally interconnected and in some cases overlap.

Changes evoked by nicotine involve various neurotransmitter systems with modulation of the neurotransmitters' release in diverse brain regions. Animal studies show that nicotine-induced noradrenergic release occurs following nicotine administration in almost same cortical and subcortical brain regions that were shown to become activated in imaging studies, namely the fronto-parietal (Summers and Giacobini 1995), prefrontal and medial temporal cortices, hippocampus (Singer et al, 2004; Shearman et al, 2005), hypothalamus (Mitchell, 1993; Fu et al, 1997; Fu, 2003; Lena et al, 1999; Jacobs et al, 2002), amygdala (Mitchell, 1993; Lena et al, 1999; Fu et al, 1998; Jacobs et al, 2002; Shearman et

al, 2005), substantia nigra, cingulate cortex, and pontine nucleus (Toth et al, 1992).

Nicotine-evoked noradrenaline (NA) release in diverse brain regions was reported to occur via both direct and indirect mechanisms. For example, the activation of nAChRs by nicotine can lead to direct increase of NA in hippocampal terminals, while indirect mechanisms might work though GABA and glutamate release (Wonnacott et al, 2006; Clarke and Reuben, 1996). The presence of two distinct nicotinic mechanisms of NA release demonstrates the complexity of the modulation of NA release by activated nicotinic receptors. Taken together with the neuroimaging and other research data on the topography of nicotine-induced NA release, this suggests that brain regions where the nicotine-induced NA release was demonstrated might not always correspond with the brain regions where the nicotine elicits its direct effect on the nAChRs. This is due to the possibility that NA release in a given brain area can arise via direct activation of nicotinic receptors in this brain region, or via nicotine-induced activation of remotely located nAChRs which is then mediated through an indirect mechanism.

1.2.4. Molecular mechanism of nicotine - stimulated noradrenaline release

Within the central nervous system nicotine binds to nicotinic acetylcholine receptors (nAChRs) which, when they are activated, modulate the release of various transmitters including noradrenaline (Picciotto et al, 1998).

There is a large molecular diversity of nAChRs, which in turn is explained by various arrangements of α and ß subunits. In the mammalian brain there are nine α (α2- α10) and three β (β2-β4) subunits expressed. The combination of two, three or more of these subunits can form numerous subtypes of nAChRs. If nicotinic acetylcholine receptor is formed by the subunits of the same type (either α or β), it called homopentamer receptors, while nicotinic acetylcholine receptors composed of various subunits (various α and β), then the receptor is called heteropentemer. Among three major α4β2, α3β4 and α7 subtypes of nAChRs, α4β2 subtype accounts for approximately 90% and the α4β2 subtype is found to possess a very high affinity for nicotine. This subtype is found in the cortex, striatum, cerebellum, lateral geniculate nucleus, amygdala, superior colliculus, hippocampus and thalamus (Brody et al, 2006; Dome et al, 2010; Benowitz, 2010).

The great structural variation of nAChRs explains their distinct physiological properties and biological functions. Thus, genetic animal studies suggested that α and β subunits are responsible for modulation of specific aspects of addictive, reinforcing, cognitive and other properties of nicotine, as well as for various aspects of nicotine addiction and withdrawal. For example, the β2 subunit plays a role in the affective component, the β4 subunit in the somatic component, α7 in the physical component of nicotine withdrawal (grooming, chewing, scratching, and tremor), and the α7 subunit has a role in mediating the reinforcing actions of acute nicotine (Kenny et al, 2001). The β2 subunit is also involved in mediating the reinforcing properties of nicotine (Picciotto et al, 1998), while the

α4 subunit plays a role in the sensitivity to nicotine and nicotine self-administration, with the α6 subunit being linked to nicotine reward (Gozzi et al, 2006; Dome et al, 2010).

The nicotinic receptors, which modulate release of NA, are mostly heteropentamer receptors located pre-synaptically on noradrenergic synapses (Dome et al, 2010). Animal studies, which have aimed to describe and localize nAChRs in central nervous system (CNS), reported that α3-α7 and β2-β4 subunits are specifically expressed in the locus ceruleus of rats (Lena et al, 1999; Vizi et al, 1999, Azam et al, 2007). Interestingly, as the locus ceruleus sends multiple noradrenergic projections to other parts of the brain, including the hippocampus, it was found that hippocampal nAChRs have similar combination of subunits to those of the locus ceruleus. Thus, α3β4, α3β2, β2-β4 α4, and α7 subunits have been proposed to be closely involved in nicotine-induced NA release in the hippocampus (Clarke and Reuben, 1996; Luo et al, 1998; Vizi et al, 1999; Azam et al, 2007; Fu et al, 1999). However, it is currently unknown whether noradrenergic nerve terminals in other brain regions that originate from the locus ceruleus will also contain similar combination of receptor subunits.

Several studies investigating mechanisms of nicotine-evoked Na release in various brain regions uncovered some details of this mechanism. It was shown that nicotine can elicit release from noradrenaline terminals of the hippocampus by direct activation of nAChRs containing α3 and β4 subunits and by indirect activation of nAChRs containing α7 subunits by producing GABA and glutamate release (Wonnacott, 2006; Clarke and Reuben, 1996). In contrast, Zhao and

colleagues found that direct nicotine administration to glutamate afferents and NMDA receptors in nucleus tractus solitarius evoked NA release in hypothalamic paraventricular nucleus and amygdala (Zhao et al, 2007). Thus, the release of NA can be elicited either through direct activation of nAChRs but additionally nicotine-evoked NA release can occur in remote areas of the brain connected to these. This data suggests the complexity of the mechanisms related to nicotine-evoked NA release that are still largely unknown and poorly understood. What is clear, however, is that through a variety of mechanisms, nicotine causes release of noradrenaline in many brain areas.

Furthermore, imaging studies added additional complexities to this puzzle. A PET human study on the distribution of the density of noradrenaline transporters showed the highest densities in three brain regions: locus ceruleus, thalamus and striatum; however, there was a surprising mismatch between high level of noradrenaline transporters and NA itself in the nucleus accumbens (Tong et al, 2007) which may relate to a possible specific role for NA playing a role in the mechanisms underlying reward, addiction, pleasure, and aggression (Logan et al., 2007 ; Tong et al, 2007: Lajtha and Sershen, 2010; Berridge and Robinson, 2003; Robinson and Berridge, 2003; Berridge and Waterhouse, 2003). These studies may also suggest that the region-specific mechanisms of NA depletion might play some role in the mechanism of action of this neurotransmitter in the brain.

In summary, to date there is evidence for some aspects regarding the molecular mechanism of nicotine-stimulated noradrenaline release in the central nervous system. However, more studies are required before a comprehensive understanding of the relationship of the interaction between nicotine and noradrenaline release is fully understood. Still, given the role of noradrenaline in addiction, the importance of this is clear.

1.3. Role of noradrenaline in addiction

1.3.1. Noradrenergic system and noradrenaline

Noradrenaline is a catecholamine with several functions. It can act as a neurotransmitter within the central nervous system or as a stress hormone. Noradrenaline is the principal neurotransmitter of the noradrenergic system within the brain that is represented by two main nuclei: the locus ceruleus (LC) and the caudal raphe nuclei (ponto-medullar nuclei). Originating in these centers, noradrenergic neurons link to many brain regions: projections from LC are named the dorsal noradrenergic bundle (DNB), and bring noradrenergic innervation to the cerebral cortex, limbic system, hippocampus, cerebellum, and forebrain. Noradrenergic neurons from the caudal raphe nuclei are known as the ventral noradrenergic bundle (VNB), and supply the hypothalamus, midbrain, and extended amygdala (Weinshenker and Schroeder, 2007).

The functional role of such extensive noradrenergic projections to diverse brain regions is associated with NA involvement in the regulation of many processes including arousal, attention, vigilance, memory, learning, response to stress, and mood (Ramos et al, 2007; Weinshenker and Schroeder, 2007; Levine et al, 1990; Berridge and Waterhouse, 2003). Additionally the noradrenergic system is involved in reward and drug addiction (Berridge and Waterhouse, 2003; Weinshenker and Schroeder, 2007; Safuoglu and Sewell, 2009).

1.3.2. Role of noradrenergic system in neurobiology of addiction in general and nicotine addiction specifically

The neurobiology of addiction to multiple different drugs has been explained primarily through the mechanisms underlying the reinforcing and rewarding properties of the specific addictive substances. Neuroanatomically, this mechanism is represented by reward circuitry that consists of mesolimbic and mesocortical pathways. Dopaminergic projections from ventral tegmentum to the nucleus accumbens, amygdala, hippocampus and prefrontal cortex form mesolimbic dopaminergic pathways that are believed to play a critical role in the reward and reinforcing properties of addictive drugs (Wise et al, 1998; Corrigall et al, 1994; Di Chiara and Imperato, 1988; Koob, 1992; Koob, 1996; Nestler, 2001; Sofuoglu & Sewell, 2009). The same mechanism is also thought to underlie the addiction to nicotine (Laviolette and van der Kooy, 2003; Corrigall et al, 1994; Nisell et al, 1994; Kenny and Markou, 2006; Singer et al, 2004; Wise et al, 1996; Benwell and Balfour, 1997).

However, it is not just dopamine. The relationship between the noradrenergic system and reward mechanisms have been reported by a number of authors who have pointed out that the major noradrenergic nucleus, the locus ceruleus, sends its projections to ventral tegmental and nucleus accumbens, thus influencing these reward and reinforcing pathways (Berridge et al, 1997; Berridge and Waterhouse, 2003; Wise et al, 1998). Moreover, the release of dopamine in the nucleus accumbens induced by all addictive substances is considered to be a common mechanism in the development and maintenance of the addiction; yet, it was demonstrated by Grenhoff that the firing of midbrain dopamine cells is modulated by noradrenergic neurons from the locus ceruleus (Grenhoff et al, 1993). This discovery, along with other similar research data, led Weinshenker and Schroeder to propose the role of noradrenaline pathways in stimulant additions (Weinshenker and Schroeder, 2007).

Several authors also pointed at the contributory role of the noradrenergic projections from the locus ceruleus in cocaine, amphetamine and opiate addictions (Berridge and Waterhouse, 2003; Safuoglu and Sewell, 2009). Systemic nicotine administration also leads to the activation of the locus ceruleus (Mitchell, 1993). Moreover, acute, repeated and chronic nicotine administrations produce the release of dopamine in the nucleus accumbens (Benwell and Balfour, 1997) that is linked to the rewarding and reinforcing properties of nicotine (Benwell and Balfour, 1997; Kenny and Markou, 2006; Laviolette and van der Kooy, 2003). Thus, taken together, the data suggests the participation of noradrenergic neuronal mechanisms in nicotine addiction. Indeed, Weinshenker

and Schroeder suggested that noradrenaline was the key mediator of both natural and drug-induced reward. Their conclusion was based on a review of studies which aimed to understand, identify and describe the neurochemical basis of addiction and reward circuits. Other supporting evidence comes from anatomical, electrophysiological, and pharmacological studies data which all suggest that NA pathways support intracranial self-stimulation (ICSS) and modulate drug-induced changes in ICSS thresholds. Studies on psychostimulant-induced locomotor activity and sensitization along with conditioned place preference (CPP) paradigm, which is standard pre-clinical model aimed to demonstrate that after initial conditioning experimental animals spend significantly more time in the drug-paired than in vehicle-paired context, also demonstrate that NA is crucial for many aspects of drug reward (Weinshenker and Schroeder, 2007). These authors concluded that there are functional connections between noradrenergic and dopaminergic systems which are critical for both reward and addiction.

The link between addiction and noradrenergic neurotransmission is also supported, indirectly, by studies that have shown the role of NA in a range of cognitive functions (Chamberlain et al, 2006; Ordway et al, 2007; Hajos 2003; Singer et al, 2004; Ramos et al, 2007; Hyman et al, 2006; Rezvani and Levin, 2001). Since appropriate cognitive functioning is an essential component of the motivation and reward processes, noradrenaline was suggested as an important neurotransmitter of the reward mechanism (Serchen, 2009; Tong et al, 2007; Ventura et al, 2003; Singer et al, 2004; Hyman et al, 2006). Moreover, a series of imaging studies found the involvement of the same frontal network being

activated during intoxication and craving while being deactivated during the withdrawal phase in drug addicts(Goldstien and Volkow, 2002; Volkow, 2002; Neuhas et al, 2006).

Knowing that noradrenaline is involved in addictions in general, it is important to see how it is also linked to nicotine's effects specifically. Clinical and imaging studies have shown that acute administration of nicotine enhances memory and attention, producing activation of brain regions involved in these cognitive processes. In contrast, nicotine withdrawal exhibits the opposite changes (Neuhas et al, 2006; Stein et al, 1998; Sharma and Brody, 2009; Sherman et al, 2005; Xu et al, 2005). Thus, the findings that the same regions are involved in both nicotine use and withdrawal suggests that they are likely to play a clinical role.

Converging evidence from animal studies suggest that this process likely occurs through the nicotinic modulation of a number of neurotransmitters in the areas of the brain responsible for cognitive functions, particularly via changes in noradrenaline release in the hippocampus, ventral tegmental area, prefrontal and medial temporal cortices (Singer et al, 2004; Sershen, 2009). Indeed, trying to differentiate the nicotine-induced changes of NA in areas of the brain responsible for cognitive (memory and learning) and reward functions, Sershen suggested that elevated level of noradrenaline, but not dopamine, in the shell of the nucleus accumbens plays an important role in the reward mechanism. Furthermore, similar nicotine-induced changes of noradrenaline concentrations were noted by

Pagliusi(Pagliusi et al., 1996), implying the key role for noradrenaline in nicotine-induced reward mechanisms.

Another line of evidence that noradrenaline signaling in essential in the neurobiology of additions, and nicotine addiction in particular, comes from pharmacological studies examining intracranial self-stimulation that found alterations of ICSS threshold, and self-administration of addictive drugs, were mainly due to their ability to alter noradrenaline reuptake or release or both. Moreover, numerous clinical trials with drugs altering NA reuptake have shown their effectiveness in the treatment of stimulant addictions (Safuoglu and Sewell, 2009). Furthermore, these medications were also shown to enhance cognitive functions while producing their effects (Safuoglu et al, 2010).

1.3.3. Withdrawal

Being an essential component of the drug addiction process, withdrawal is a syndrome that arises either upon reduction or cessation of an addictive substance, and is represented by behavioral, affective, cognitive, and physical symptoms. Acute and prolonged withdrawal from many addictive substances has been shown to be characterized by significant distress and impairment in many areas of functioning (Buchhalter et al, 2005; Hughes et al., 2003; Highes, 2007b; Hughes, 2007c; Shiffman et al, 2004; Shiffman et al, 2006; Koob, 2009a).

Thus, withdrawal process produced deleterious effect on several cognitive functions in abstinent smokers (Shiffman et al, 2006; Xu et al, 2006; Xu et al, 2007) that was also evident in imaging studies demonstrating simultaneous

changes in cognitive areas of the smokers' brain during the withdrawal period (Goldstein and Volkow, 2002).

There are many biological and behavioral theories of withdrawal. Thus, according to the opponent process theory of addiction, addictive drugs including nicotine activate the mesolimbic dopaminergic system. This includes the nucleus accumbens and amygdala. This hypothesis suggests that during withdrawal there are downregulations of the mesolimbic dopamine system with a subsequent decrease in dopamine and serotonin concentrations (Koob, 2009; Koob et al. 1997; Koob and Le Moal 1997; Koob and Le Moal 2001; Robinson and Berridge, 2003; Liu and Jin, 2004). Supporting this proposal, several authors have reported that neuronal activity of mesolimbic dopaminergic neurons is decreased in rats during the withdrawal period, with diminished level of dopamine in the nucleus accumbens (Liu and Jin, 2004).

One study found an increased level of noradrenaline in hypothalamic and preoptic noradrenergic nerve terminals during acute nicotine withdrawal (Anderson et al, 1989). Changes in amygdala were reported in animals exposed to chronic nicotine administration, with intermittent changes in NA levels during withdrawal in both hypothalamus (Sharp and Matta, 1993; Fu et al, 2001) and amygdala (Fu et al, 2003).

Indirect support for the role of noradrenaline during withdrawal comes from studies during alcohol withdrawal which have shown the central role of noradrenaline dysregulation in both clinical and pre-clinical studies (Patkar et al, 2003).

Craving has also been proposed to be one of the main symptoms of nicotine addiction (Donny, 2008), and it has been suggested that craving should be included in the diagnostic criteria of addictions (Rosenberg, 2009). However, there is relatively little data on the neural basis of craving. There may be a link to noradrenaline release since craving is associated with the activation of a number of brain regions (Goldstein and Volkow, 2002) as well as reward (Due et al, 2002), and can be suppressed by noradrenaline reuptake inhibitors, at least in nicotine-induced craving. This may be in large part because nicotine consumption produces an increase in noradrenaline secretion in orbito-frontal cortex (Volkow and Fowler, 2000), which in turn is believed to mediate the intensity of craving and determine the degree of reward (Lee, 2007; Wallis, 2007). On the another hand, dysfunction of this brain region is thought to be associated with compulsive behavior (Pagliusi, 1996; Lajtha and Sershen, 2010; Roesch and Olson, 2007). These findings may represent part of the complex structure and mechanism involved in nicotine addiction, but further support links between noradrenaline, nicotine, and addiction.

1.4. Pharmaceutical aids for smoking cessation

Since harmful impact on health of smokers was first demonstrated and the addictive role of nicotine in tobacco products were first recognized many researchers have sought effective methods to treat nicotine addiction. Among these, both pharmacological and non-pharmacological methods have been proposed.

At the present time there are many pharmacological therapies available for smoking cessation. In development of these several objectives were pursued: smoking cessation medications have to alleviate the withdrawal symptoms and the craving as well as attenuate the reinforcing effects of tobacco smoke, particularly nicotine (Perkins et al, 2006; Perkins et al, 2001).

All medications for smoking cessation can be divided into two major groups: nicotine-replacement agents and non-replacement agents. The therapeutic effects of replacement agents mainly incorporate the replacement of nicotine delivered during smoking with the avoidance of delivery of other smoke components that have been shown to be cancerogenic. Nictotine-replacement therapies (NRT) supply nicotine via various routes, such as a patch or in gum. Thus, nicotine-replacement medications provide the replacement of the neuropharmacological and reinforcing effects of nicotine along with the substitution of additional effects that smokers experience during smoking, and that they desire during abstinence from smoking (Henningfield et al, 2005). However, the drawback of using this type of product is that the addiction to nicotine isn't addressed, along with relatively poor efficacy in terms of the alleviation of withdrawal symptoms when compared to other first-line agents (Fant et al, 2009; Carrozzi et al, 2008; Wu et al, 2006; Mills et al, 2009).

In terms of the non-replacement agents, there are first-line and second-line treatments, based upon success in several clinical studies. In current practical guidelines, varenicline and bupropion are first-line medications for smoking cessation while second-line treatments include nortriptyline and clonidine

(Carrozzi et al, 2008; PHS Guideline Update Panel, Liaisons, and Staff. 2008). Interestingly, drugs modulating NA release such as bupropion, nortriptyline, and clonidine are considered to be efficacious and are included in both first-line and second-line groups.

1.4.1. Bupropion

Bupropion is an antidepressant that acts as nonselective inhibitor of dopamine and noradrenaline transporters (Warner and Shoab, 2005). It also possesses antagonist actions at nAChRs (Dwoskin et al, 2006).

Among numerous pharmacological mechanisms of action of bupropion that are thought to be related to the efficacy of this drug in smoking cessation are its effects on noradrenaline release. Bupropion increases NA concentrations in the nucleus accumbens, hypothalamus, striatum and prefrontal cortex probably via two mechanisms. Firstly, via NA reuptake inhibition at the noradrenaline transporter and secondly via enhancement of NA release (Gobbi et al, 2003; Warner and Shoab, 2005; Paterson, 2009). Additionally, bupropion has downstream effects on serotonergic signaling in dorsal ralph nuclei that are consistent with the reported serotonergic effects of bupropion (Paterson, 2009).

Bupropion also inhibits the excitability of dopaminergic neurons in the ventral tegmental area (Mansvelder et al, 2007), altering the reinforcing, rewarding and reward-enhancing properties of nicotine as well as alleviating somatic signs of withdrawal in animal studies (Paterson et al, 2008). Numerous human trials have shown that bupropion not only attenuates affective and somatic

symptoms of withdrawal syndrome in abstinent smokers (Dwoskin et al, 2006), but also prolongs abstinence, increases cessation rates, and reduces the craving and smoking urges and reduces relapse rates (Richmond and Zwar, 2003; Paterson, 2009; Aubin et al, 2004). Subjective rating of smoking (Cousins et al, 2001) and withdrawal rates were also decreased in smokers treated with bupropion (Gonzales et al, 2006; Jorenby et al, 2006; West et al, 2008). These have been shown to be realted to a decrease in smoking (Hurt et al, 1997) and the reduction in frequency and amount of smoking even in these who did not achieved complete abstinence (Aubin et al, 2004; George and O'Malley, 2004).

In a systematic review and meta-analysis, bupropion was described as the best therapeutic treatment for smoking cessation compared to placebo, along with other first line agents (Wu et al, 2006). The effectiveness of bupropion was shown to be similar to nicotine-replacement agents when compared with a placebo group (Schmelzle et al, 2008). Other reviewers found that the effectiveness of NA reuptake inhibiting medications for smoking cessation, namely bupropion, nortriptyline and clonidine, were only inferior to varenicline but were comparable to the nicotine-replacement therapy (Corrozzi et al, 2008; PHS Guideline Update Panel, Liaisons, and Staff, 2008). In agreement with this, a meta-analysis of 69 randomized controlled trials had similar results (Eisenberg et al, 2008). Furthermore, in a meta-analysis and meta-regression of 168 randomized controlled trials, Mills and colleagues showed that, when indirect comparisons (comparison of the effectiveness of bupropion and varenicline based on indirect comparison of their effectiveness when compared with NRT or versus each other)

were applied, the efficacy of bupropion was superior to the nicotine-replacement therapies and inferior only to treatment with varenicline (Mills et al, 2009).

Interestingly others have not been able to differentiate between the effectiveness of bupropion compared to nicotine replacement therapy due to problematic data (Ranney et al, 2006; Hughes et al, 2007a), and at least one other reviewer considers bupropion less effective than nicotine-replacing agents in terms of the safety, tolerability and the cost for these medications (Lancaster et al, 2008).

In terms of combination therapies, the findings are also not clear, with one reviewer finding that bupropion was the only drug in which efficacy for smoking cessation was comparable to that of combined therapies (Shah et al, 2008). Similarly, combination therapy of cognitive-behavioural therapy (CBT) with bupropion was shown to be more effective than that of CBT with nortriptyline or placebo (Haggstram et al, 2006). Studies have also examined the combination therapy of bupropion and nicotine replacing agents (Corelli et al, 2006).

Overall, the differences and controversies between the results of different meta-analyses and reviews can be attributed to many reasons: the aims of the study, the methodology, inclusion and exclusion criteria of the analyzed studies, outcome measures, differences in the analyzed groups of participants and their characteristics in terms of smoking history, peculiarities of pharmacotherapeutic regimens and their combinations with psychotherapeutic interventions, and even the language of assessed articles. Thus, although the mentioned-above disparities lead to diverse conclusion, the consensus remains that bupropion is an effective

agent for smoking cessation that has its unique therapeutic conditions and applications. However, the exact degree of its effectiveness, and its possible advantages and disadvantages compared to other drugs or therapies, and its use in combination, all remain unclear.

Taken together, therefore, it can be seen that there is converging evidences that bupropion has effects on NA metabolism and that this mechanism explains its behavioral effects which are the attenuation of nicotine withdrawal and the increase of abstinence. This is likely to be mediated via its well documented influence on noradrenergic systems and impact on signaling in midbrain dopaminergic neurons. This role of NA reuptake in the mechanism of action of bupropion is significant for the amelioration of nicotine withdrawal and for lowering rewarding properties of nicotine. It also suggests that other drugs which can alter NA reuptake, such as nortriptyline, atomoxetine, and desipramine would imply that the noradrenergic system is a promising target for the treatment of nicotine addiction (Paterson, 2009).

1.4.2. Nortriptyline

Nortriptyline belongs to the class of tricyclic antidepressants. It has both noradrenaline and serotonin reuptake inhibiting qualities with a mainly noradrenergic effect (Escobar-Chavez et al, 2010). Despite these pharmacological actions nortriptyline is considered to be a second line agent due to its side effects, and is usually recommended for smoking cessation when first line medication could not be tolerated by smokers (Herman and Safuoglu, 2010).

Foulds and colleagues presenting data from Cochrane Database of Systematic Reviews reported that nortriptyline is a more effective medication for smoking cessation compared to bupropion, clonidine and nicotine-containing products. They also indicated that nortriptyline is considered a second line agent only due to its side effects. The efficacy of nortriptyline they assert is due to its effects on the NA system, providing further support that NA modulators can be effective for smoking cessation (Foulds et al, 2006).

In an extensive review on antidepressants effective for smoking cessation, Hughes and colleagues analyzed ten studies with nortriptyline compared to placebo (Hughes et al, 2007a). They reported that the abstinence rate with nortriptyline treatment was similar to that of bupropion, although authors of some of the referenced studies suggested that bupropion was more efficient (Hall et al, 2002; Hughes et al, 2007a). Another review, of five randomized clinical trials with nortriptyline, suggested that nortriptyline should be a first-line agent (Wagena et al. 2005), although this conclusion is not supported by all reviewers (Lancaster et al, 2008).

Studies to date suggest that there is little support to argue that combination therapy of nortriptyline with nicotine replacement drugs is more effective than monotherapy with either alone (Aveyard et al, 2008; Hughes et al, 2007a), although Prochazka found this combination successfully increased cessation rates (Prochazka et al, 2004). Hall reported abstinence rates at one year of 42% to 50% when nortriptyline was combined with psychotherapeutic support and transdermal nicotine respectively (Hall et al, 2004).

Recent studies report that a reduction of nortriptyline side effects can be achieved through the limitations of plasma fluctuations of this drug by using non-oral routes of administration. Transdermal administration of nortriptyline is suggested to provide the reduction of side effects and be a promising direction for further application of nortriptyline for smoking cessation (Melero et al, 2009; Escobar-Chavez et al, 2010).

1.4.3. Other antidepressants

Desipramine is a tricyclic antidepressant which is also a preferential inhibitor of noradrenaline reuptake. To a lesser degree it also inhibits serotonin reuptake and is an antagonist of nAChRs (Rana et al, 1993; Izaguirre et al, 1997). It may also have actions on noradrenaline transporters and these effects, as well as those on adrenergic and dopaminergic receptors, are essential in desipramine's putative mechanism of action for the treatment of stimulant addictions (Weddington et al, 2010; Safuoglu and Sewell, 2009; Srisurapanont et al, 2001).

Aside from its use as antidepressant, a few studies have examined the effectiveness of desipramine in the treatment of stimulant addictions. The results of desipramine trials for treatment of cocaine dependence are inconclusive and controversial, suggesting the possibility that desipramine might prolong the abstinence in cocaine users (Arndth et al, 1992; Arndth et al, 1994; Gawin et al, 1989; Levin and Lehman, 1991; Weddington et al, 2010). In addition, Srisurapanont and colleagues evaluated the use of desipramine for the treatment of amphetamine dependence, hypothesizing that the mechanism of action of

amphetamines involves the increase of monoamines' release, block of their uptake, or both; however, they found no benefits (Srisurapanont et al, 2001).

In terms of the possible use of desipramine in smoking cessation, there is only one animal study, which suggested there may be beneficial effects of desipramine as an anti-smoking agent (Paterson et al, 2008).

Reboxetine is an antidepressant with highly potent and selective effects on noradrenaline transporters and to a lesser degree serotonin and dopamine transporter inhibiting properties. This medication was examined by Szerman who published promising results regarding the use of reboxetine for cocaine dependence (Szerman et al, 2005). A few preclinical studies indicated that this drug might also be effective for the reduction of nicotine-self-administration (Rauhut et al, 2002) and, therefore for smoking cessation (Miller et al, 2002). However, to date there have been no human trials for smoking cessation.

Moclobemide is a reversible monoamine oxidase A inhibitor (MAO-A) inhibitor that increases the levels of noradrenaline and serotonin levels in the brains of smokers. The effectiveness of this antidepressant was proposed because of earlier animal and human studies that demonstrated decreased levels of MAO-A and monoamine oxidase B inhibitor (MAO-B) in the brains of chronic smokers compared to non-smokers (Fowler et al, 2003; Frishman, 2009). Interestingly, although there have been no specific clinical trials of moclobemide in smoking cessation, previous trials with MAO-B inhibitors demonstrated their ability to reduce smoking rates, craving and smoking behavior (Hughes et al, 2004; George et al, 2003; Frishman, 2009). This effect was hypothesized to be related to their

dopaminergic activity and the role of dopamine in nicotine addiction. Nonetheless, knowing that brain MAO-A is mainly located in dopaminergic, noradrenergic and serotonergic neurons, the evaluation of MAO-A inhibitors in smoking cessation seems to be of greater interest (van Amsterdam et al, 2006; Fowler et al, 2003).

1.4.4. Varenicline (Champix)

Varenicline (Champix) is relatively novel pharmacological agent that was approved for smoking cession in Canada in April 2007 (Health Canada. New safety information regarding Champix (varenicline tartrate) - For the Public).

Varenicline was shown to be more effective than placebo, bupropion and nicotine replacement therapy (NRT) in several trials (Grassi et al., 2011; Xi, 2010). The clinical superiority of varenicline is likely due to unique aspects of its mechanism of action.

Varenicline is selective partial agonist of α4β2 and α3β4 as well as full agonist at α7 nicotinic acetylcholine receptors (nAChR) as well as and 5-HT3 serotonergic receptors (Champix Product monograph).

It is believed that the activation of α4β2 subtype of nAChR is primarily responsible for the therapeutic effect of varenicline in smoking cessation (Xi, 2010). Varenicline producing partial activation of the same receptors that nicotine acts upon, blocks rewarding effects of nicotine and alleviates withdrawal symptoms of nicotine (Champix Product monograph; Turner, Castellano, & Blendy, 2011; Xi, 2010).

Being a weaker, and only partial agonist, of these nicotinic receptors varenicline also affects neurotransmission of dopamine, noradrenaline, and serotonin (Rollema, Wilson, Lee, Folgering, & Flik, 2011). This results in prolonged release of dopamine and noradrenaline (Cinemre et al., 2010).

The literature on the effect of varenicline on the release of monoaminergic neurotransmitters is extremely limited. It was shown that the activation of α4β2 nAChR and the release of dopamine in mesolimbic region by varenicline blocks the rewarding effects of nicotine and alleviates symptoms of nicotine withdrawal (Cinemre et al., 2010). However, varenicline's mechanism of action is related to the release of other neurotransmitters such as noradrenaline and serotonin, but has been studied less rigorously.

For example, Patterson and colleagues reported that varenicline produces an enhancement of cognitive function and mood during nicotine withdrawal (Patterson et al., 2009). Philip and colleagues demonstrated the augmentation effect of varenicline when administered simultaneously with antidepressants for smokers who suffer from depression (Philip, Carpenter, Tyrka, Whiteley, & Price, 2009). In their review, summarizing the relationship between nicotinic acetylcholine receptors, smoking and depression, Phillip and colleagues suggested that the mechanism of action of varenicline could best be explained by its effect on several subtypes of nAChR and the subsequent modulation of monoaminergic neurotransmission (Philip, Carpenter, Tyrka, & Price, 2010).

Unfortunately, there are not currently studies published that directly examine the effects of varenicline on noradrenergic neurotransmission.

In summary, the mechanism of action of varenicline appears unique, but there is some evidences that some of its clinical benefits can be explained through activation of monoaminergic neurotransmitters interactions, including noradrenaline. Although currently very limited, these findings suggest the need for further research of the potential role of alterations in noradrenergic neurotransmission on nicotine addiction.

1.4.5.Summary

In summary, analysis of the mechanism of action and the effectiveness of diverse antidepressants that have been shown to be clinically useful for smoking cessation lead to the conclusion that there is a critical role for the noradrenergic system in the pathophysiology of nicotine addiction. This also leads to the suggest that there is a potential role for relatively untried noradrenaline inhibitors in this situation, such as atomoxetine. To date there has been a single small preliminary study examining this possibility in which atomoxetine was found to reduce nicotine withdrawal symptoms and craving (Ray et al, 2009). Further consideration of the possible role of atomoxetine is therefore warranted.

CHAPTER 2

ATOMOXETINE

In 2002 atomoxetine became the first non-stimulant drug to be approved by the FDA for the treatment of attention deficit hyperactivity disorder (ADHD). Interestingly it was approved for use in both adults and children (Garland and Kirkpatrick, 2004). Atomoxetine is a relatively specific noradrenaline reuptake inhibitor (Wong et al, 1982) that has been shown to be clinically effective in ADHD. It has also been used clinically for some other disorders, but it has not officially been approved for any of these.

2.1. Pharmacokinetic characteristics of atomoxetine

It is important to understand the pharmacokinetics of atomoxetine as there are dramatic differences between extensive and poor metabolizers of this drug, which may have clinical implications, as well as requiring several exclusion factors in the present study design.

Atomoxetine was originally known as substance LY1 39603 or (-) isomer of LY1 35252, (±)-N-methyl--y-(2-methylphenoxy) phenylpropylamine hydrochloride (Wong et al, 1982). It is a specific inhibitor of presynaptic noradrenaline reuptake (Strattera product monograph, Eli Lilly Canada Inc, 2009), with high affinity for the noradrenaline transporter (Sauer et al, 2005).

Nonetheless, the complete mechanism of action of this drug is still uncertain (Garnock-Jones and Keating, 2009).

After adjustment for body weight the pharmacokinetic properties of atomoxetine are similar in adults, adolescents and children (Witcher et al, 2003). After oral administration, the maximum plasma concentration of atomoxetine is reached within 2 hours of oral administration, with a half-life fluctuating widely between extensive metabolizers (5 hours) and poor metabolizers (21 hours) (Witcher et al, 2003; Sauer et al, 2005). Oral bioavailability also varies dramatically between these two groups. Food slows absorption of atomoxetine (Sauer et al, 2005; Garnock-Jones and Keating, 2009).

Animal studies demonstrate that atomoxetine is distributed in all body tissues, with its maximum concentration occurring approximately one hour after oral administration. A decline in radiolabelled atomoxetine is seen in most organ tissues after approximately after eight hours, including rat brain (Sauer et al, 2005). Moreover, atomoxetine crosses the placenta and is excreted into the milk of lactating rats (Sauer et al, 2005).

Human studies showed that almost 99% of atomoxetine, 67% of its major metabolite (4-hydroxyatomoxetine) and 99% of its minor metabolite (N-desmethylatomoxetine) are bound to albumin in plasma (Strattera package insert, 2003; Sauer et al, 2005).

Atomoxetine is metabolized by the liver mainly through oxidation reactions. Cytochrome P450 enzymes are responsible for the metabolic biotransformation of atomoxetine in humans (Ring et al, 2002). The major

oxidative metabolite of atomoxetine is 4-hydroxyatomoxetine (Farid et al, 1985); and, CYP2D6 is the enzymatic pathway primarily responsible for the metabolism of atomoxetine to 4-hydroxyatomoxetine (Ring et al, 2002). For a minor metabolite of atomoxetine, *N*-desmethylatomoxetine CYP2C19 is a primary enzyme (Ring et al, 2002).

Biotransformation of atomoxetine has been shown to be dependent on the polymorphic expression of the P450 enzymes. The level of activity of CYP2D6 differentiates the types of metabolizers, as this is the primary mechanism for metabolism in extensive metabolizers (Ring et al, 2002). In contrast, however, atomoxetine is mainly metabolized through CYP2C19 in poor metabolizers. Nonetheless, in general the biotransformation of atomoxetine is not different in poor and extensive metabolizers, except that the status of enzymatic pathways CYP2D6 and CYP2C19 will affect the amount of formed metabolites, rate of formation, and percent of excreted metabolites (Sauer et al, 2005; Garnock-Jones and Keating, 2009).

Sex and race do not influence the pharmacokinetic characteristics of atomoxetine, although it should be noted that approximately 1% of Asian, 2% of Arabic, 2% of African-American, 3% of African, and 7% of the Caucasian population are poor metabolizers (Strattera package insert, 2003; Sauer et al, 2003; Cui et al, 2007; Jose de Leon, 2007; Sauer et al, 2005).

Due to dependency on CYP2D6 for metabolism, drugs that interact with this can alter atomoxetine's metabolism. Thus, for example, co-administration with potential inhibitors of CYP2D6 leads to an increase in the plasma concentration of atomoxetine with creation of a profile analogous to poor metabolizers. In contrast, atomoxetine does not itself inhibit the metabolism of other drugs which are metabolized by CYP2D6 or CYP3A (Sauer et al, 2005; Ring et al, 2002).

Atomoxetine is primarily cleared from the body through urine, and to some extend in faeces. Excretion of unchanged atomoxetine by the kidneys accounts for 3% of total excretion and is not an important route for the atomoxetine's clearance. The route of excretion for atomoxetine's metabolites varies between extensive and poor metabolizers, because of the distinct principal metabolites as well as the different rates at which metabolic products are formed (Sauer et al, 2005).

As metabolic transformation occurs in the liver, and clearance of atomoxetine's metabolites occurs via the kidneys, any functional impairment of these organs will affect excretion. Thus, in patients with impaired liver function reduced doses of up to 50 % of recommended does are recommended. Interestingly, even though the plasma concentration of atomoxetine was reported to be 65% higher in patients with end-stage renal disease, the company does not recommend reduced doses in this situation (Strattera package insert, 2003; Sauer et al, 2005).

2.2. Pharmacodynamic properties of atomoxetine

Atomoxetine is a highly selective and potent inhibitor of the presynaptic noradrenaline transporter (Wong et al, 1982; Garnock-Jones and Keating, 2009), acting both centrally and peripherally (Gehlert et al, 1993; Zerbe et al, 1985; Sauer et al, 2005). Supporting this, animal studies have shown that atomoxetine increases extracellular NA concentrations in many brain regions including prefrontal and occipital cortices, lateral hypothalamus, dorsal hippocampus and

cerebellum (Swanson et al, 2006; Koda et al, 2010; Bymaster et al, 2002). The affinity of atomoxetine and its primary metabolite (4-hydroxyatomoxetine) for the noradrenaline transporter are similar, but the less common metabolite seen in poor metabolizers (*N*-desmethylatomoxetine) has a much lower affinity (Sauer et al, 2005). These differences may also, in part, explain clinical differences seen between these two groups.

Atomoxetine possesses a low affinity for multiple other neurotransmitters including serotonin, dopamine, choline, GABA, adenosine transporters, and ion-channels (Wong et al, 1982; Gehlert et al, 1993; Garnock-Jones and Keating, 2009; Sauer et al, 2005). Thus, actions of atomoxetine which increase levels of other neurotransmitters are an indirect effect mediated via increased noradrenaline release (Swanson et al, 2006; Koda et al, 2010). Its inability to raise the concentration of dopamine in the prefrontal cortex is probably linked to its low abuse potential, a finding that has been supported in clinical trials (Bymaster et al, 2002; Swanson et al, 2006; Koda et al, 2010; Garnock-Jones and Keating, 2009).

Atomoxetine's clinical benefits are believed to be due to noradrenergic augmentation in the prefrontal cortex (Chamberlain et al, 2007; de Jong, et al, 2009; Faraone et al, 2005). This proposal has been supported by an fMRI imaging study in healthy volunteers where atomoxetine activated the right inferior frontal gyrus (Chamberlain et al, 2009). In animal models atomoxetine improves attention and decreases impulsivity (Robinson et al, 2008; Navarra et al, 2008; Garnock-Jones and Keating, 2009). These findings support the potential of this drug in the treatment of ADHD.

2.3. Atomoxetine for the treatment of ADHD

Testing this, several short-term clinical trials in both children and adults found that atomoxetine treatment was superior to placebo. Significant improvement was noted in many variables including ADHD symptoms, response rates, and scores of inattention, hyperactivity and impulsivity. Additionally, quality of life and clinical global impression were also significantly improved when compared with treatment and placebo groups. Longer-term clinical trials of atomoxetine compared to placebo also demonstrated that patients on atomoxetine therapy had longer mean time to relapse and exhibited no evidence of drug tolerance (Garnock-Jones and Keating, 2009). Thus, compared to placebo, atomoxetine has repeatedly demonstrated efficacy which is what underlies its approval and continued use.

However, a more vexed problem is the comparison to psychostrimulants. In such comparison studies, the disadvantages of atomoxetine include a longer onset of action. Interestingly, the same drug can have different findings compared to atomoxetine. For example, osmotically- or extended-release methylphenidate preparations have shown repeated benefits compared to atomoxetine, while the efficacy of atomoxetine did not significantly differ from immediate release methylphenidate (Garnock-Jones and Keating, 2009). In ADHD patients, some studies have also reported that atomoxetine improves executive functioning along with subjective improvement in many ADHD symptoms (Brown et al, 2009) and visuospatial working memory (de Jong, et al, 2009), although not all investigators

found atomoxetine improved neurocognitive symptoms (Ray et al, 2009; Friedman et al, 2008).

The observed effects of atomoxetine on noradrenaline release in prefrontal cortex, which are also the regions involved in attention and memory, have been suggested to underlie its clinical efficacy in ADHD (Bymaster et al, 2002). Supporting this, Neuman and colleagues reported that atomoxetine reversed attentional deficits caused by noradrenergic lesions in medial prefrontal cortex of animals (Newman et al, 2008).

2.4. Atomoxetine for the treatment of other conditions

In addition to its utility in ADHD, atomoxetine has been examined in other areas including possibly a use as an antidepressant (Wong et al, 1982) when evaluated on healthy volunteers (Zerbe et al, 1985). When tested in an open-label study in depressed patients, and in placebo-controlled trials as an augmentation agent for ADHD patients with co-morbid depression, atomoxetine was shown to be beneficial by some researchers (Chouinard 1984; Spencer et al, 2006; Bangs et al.,2007; Garnock-Jones and Keating, 2009). However, it failed as a stand-alone antidepressant in major clinical studies. More recently a possible niche use in depression has been suggested, after Reimherr and colleagues found that patients resistant to sertraline treatment benefited from augmentation therapy with atomoxetine. What was interesting about this study is that it only applied to those with an S/S genotype, and this may be important since this genotype is found to

be associated not only with an increased risk of depression, but also with poor impulse control and extreme aggressive behavior (Reimherr et al, 2010).

In other therapeutic areas, atomoxetine was shown to be efficacious and well tolerated in n eating disorders. During a 10 week randomized, double blind, placebo-controlled trial it significantly reduced binge-eating episodes and frequency, body weight, body mass index (BMI), obsessive-compulsive features and overall severity of illness. Although the mechanism of action for atomoxetine in binge-eating disorder is unknown, it was suggested that the effectiveness of tricyclic antidepressants with preferential NA reuptake inhibiting properties in both bulimia and anorexia nervosa might be a clue suggesting that atomoxetine may work in the same manner (McElroy et al, 2007).

Others have suggested that atomoxetine may improve cognitive functions in schizophrenia patients (Morein-Zamir et al, 2005), although this does not appear to be widely replicated.

Earlier preclinical studies showed a possible benefit of noradrenergic drugs in the attenuation of drug self-administration in animals, along with the modification of reinforcing properties of stimulants (Weinshenker and Schroeder, 2007). Both findings might suggest a beneficial role for noradrenergic medications in the treatment of stimulant addictions. This notion was further strengthened by data showing that atomoxetine may be preferred in the treatment of addictions because it does not increase dopamine concentrations in striatum and nucleus accumbens (Bymaster et al. 2002), suggesting a low abuse potential. This was also supported by clinical trials among drug users treated with either

stimulants, such as methylphenidate and phentermine, or with atomoxetine where the latter was not abused (Jasinski et al, 2008; Heil et al, 2002; Lile et al, 2006).

A few clinical trials of atomoxetine have been carried out to date to assess the efficacy of atomoxetine in the treatment of substance disorders co-morbid with ADHD produce, although with mixed results. Still, the attenuation of some subjective effects of psychostrimulants by atomoxetine suggest that further exploration of the efficacy of atomoxetine in addictions is warranted (Safuoglu and Sewell, 2009; Levin et al, 2009; Thursdone et al, 2010).

2.5. Atomoxetine for the treatment of addictions and nicotine withdrawal

Taking this all together there are several lines of converging evidence which suggest that atomoxetine may have promise in the treatment of nicotine withdrawal.

One line of evidence relates to the available epidemiological and clinical data about patients with ADHD. It was noted that the prevalence of smoking in ADHD children and adults is higher than in their peers. The degree of the severity of nicotine-induced withdrawal symptoms among smokers with ADHD is greater that in smokers without this disorder (Pomerlau et al, 1995; Lambert and Hartsough, 1998; Reichel et al, 2007; Ray et al, 2009). Moreover, more frequent relapses were associated with the presence of ADHD-type symptoms in smokers (Ray et al, 2009), while the presence of inattentive type symptoms during the nicotine-withdrawal period were associated with a greater desire and urge to smoke (Lerman et al, 2001).

Clinical trials with atomoxetine in human subjects represent another potentially supportive line of evidence. Thus, testing the relationship between stimulants and smoking, Vansikel came to the conclusion that, unlike methylphenidate, atomoxetine does not increase cigarette smoking dose-dependently (Vansikel et al, 2007). Analyzing the cognitive effects of atomoxetine in ADHD smokers, Ray reported an unexpected reduction in subjective withdrawal symptoms and in smoking urges among smokers treated with atomoxetine versus placebo (Ray et al, 2009).

Studies on smoking cessation with the utilization of drugs that possess noradrenaline reuptake qualities represent perhaps the strongest line of evidence suggesting possible efficacy of atomoxetine for this condition. For example, many preclinical and clinical experiments with drugs that are noradrenergic reuptake inhibitors, including bupropion, desipramine, nortriptyline, and reboxetine have shown that these drugs are effective in attenuating the affective, behavioral, cognitive, and physical symptoms of nicotine-evoked withdrawal.

Finally, animal experiments with atomoxetine have found the reversal of deficits seen during nicotine withdrawal, such as contextual fear conditioning and alleviation of attentional deficits (Davis and Gould, 2007; Reichel et al, 2007).

Thus, there appears sufficient evidence to warrant a study of atomoxetine for smoking cessation. The one proviso is that it must be safe to administer to often otherwise healthy individuals.

2.6. Safety profile of atomoxetine

Given that this drug has some reports of serious side-effects, we decided to carry out a comprehensive safety review. This included every publication (n=198) in which atomoxetine had been used in the treatment of a wide variety of disorders. This review was conducted to determine the extent of all treatment-associated adverse events reported in the medical literature. Articles were retrieved from PubMed and MedLine sources by utilization of the following key words: *atomoxetine, side effects, adverse events, adults.* Retrieved articles consisted of 87 articles reporting studies conducted in adult subjects, and 111 articles reporting on studies in children and adolescents. Since we only studied adults, in this section we only report the summary of this analysis for the adult studies only.

Although there were a total of 87 articles, only 35 articles on individual studies were included in the analysis of treatment-associated adverse events in adults. The rest of the articles were literature reviews or other articles that captured the same information as contained in the 35 individual studies. Fifteen out of 35 studies were randomized placebo-controlled trials, four were case reports, three studies were about overdoses of atomoxetine, and thirteen were neither placebo-controlled nor randomized studies. Out of all individual placebo-controlled trials in adults, twelve studies contained data on treatment-associated adverse events, while only seven studies provided information on the frequency of treatment-associated adverse events in both placebo and atomoxetine arms (see Table 1). Moreover, only three analyzed studies had a comparatively large number of participants (72-270).

All studies examined different time periods of atomoxetine administration: from one day up to 6 months of treatment duration. The dose range given during the studies varied from 25 mg to 160 mg per day.

Table 2.1. Most commonly observed adverse events of atomoxetine (incidence of 5% or greater and at least twice the incidence in placebo patients) in 7 randomized, double blind, placebo-controlled studies in adult subjects.

Treatment - Associated Adverse Events	Number of randomized patients	Number taking atomoxetine	Length of Treatment	Dose Range	Frequency Of Adverse Events (%) Atomoxetine Arm	Frequency Of Adverse Events (%) Placebo Arm	Reasons For Discontinuation	Reference
1Dry mouth 2.Insomnia 3.Nausea 4.↓ appetite 5.Constipation 6.Erectile Dysfunction 6.↓ libido 7.Dizziness 8.Sweating	536	269	10 weeks	60-120 mg	21.2 20.8 12.3 11.5 10.8 9.8 7.1 6.3 5.2	6.8 8.7 4.9 3.4 3.8 1.2 1.9 1.9 0.8	AE=23 LF=19 PD=18 PV=2 PhD=2 SD=14 LOE=8	Michelson et. al., 2003
1.↓ appetite 2. Dry mouth 3.Fatigue 4.↑ HR	26	12	12 weeks	25-100 mg	50 40 25 17	21.4 0 0 0	AE=2 LF=2 PD=2 Other=4	Gadde et. al., 2006
1.Dry mouth 2.Nausea 3.Nervousness 4.Insomnia 5.Constipation 6.Sweating 7.Dizziness 8.Hypertantion 9.Dyspepsia 10.Hot flash 11.Depression 12.Urinary hesitancy 13.Eructation	40	20	10 weeks	40-120 mg	55 40 35 35 20 20 15 10 10 10 10 10 10	20 10 15 15 10 0 0 5 5 5 0 0 0	AE=4	McElroy et. al., 2007

Treatment-Associated Adverse Events	Number of randomized patients	Number taking atomoxetine	Length of Treatment	Dose Range	Frequency Of Adverse Events (%) Atomoxetine Arm	Frequency Of Adverse Events (%) Placebo Arm	Reasons For Discontinuation	Reference
1.Nauses 2. Other AE	410	271	6 months (double-blind)	40-100 mg	28.4 14.0	5.8 2.2	AE=14 % LF=16 % PD=10.5% LOE=11%	Adler et al., 2008
1.Dry mouth 2. Insomnia 3. Nausea 4. ↓ Appetite 5.↓ Libido 6. Erectile dysfunction 7.Dizziness	536	unknown	10 weeks	Up to 120 mg	21 21 12 12 7 10 6	7 9 5 3 2 1 1	Unknown	Adler et al., 2007
1.Nausea 2. Dry mouth 3. Fatigue 4. ↓ Appetite 5. Dizziness 6. Constipation 7. Urinary hesitancy 8. Erectile dysfunction	551	250	6 months	25-100 mg	32 28 16 14 10 7 6 11	9 8 8 3 4 3 0.4 3	Due to AE=17.2% atomoxetine arm And 5.6% in placebo arm	Adler et al., 2009a
1. Insomnia 2. Nausea 3. Dry mouth 4. Dizziness 5. Initial insomnia 6. Erectile dysfunction	442	224	14 weeks	40-100 mg	17 16 15.6 7.5 5.7 5.2	9 7.6 4.3 2.4 2.8 0.8	AE=35 LF=59 PD=23 PV=4 PhD=0 SD=0 LOE=17 PECNM=2 Other=9	Adler et al., 2009b

See Table 1 for abbreviations: sBP- systolic blood pressure, dBP- diastolic blood pressure; HR-heart rate; AE-adverse event; LF-lost for follow-up; PD-patient decision; PV-protocol violation; PhD-physician decision; SD-sponsor decision; LOE-loss of efficacy; PECNM-protocol entry criteria not met

As dose range and length of treatment varied widely, only three studies which had a large number of participants were considered for the treatment-associated adverse events analysis in adults. For convenience, adult studies were classified as placebo-controlled or non placebo-controlled; while treatment-associated adverse events were grouped according to their frequency, impact on particular organ system, and type of atomoxetine ingestion. To be easily comparable to the adverse events reported by the manufacture (Eli Lilly) as well as other studies, we classified these treatment-associated adverse events in the same manner as reported elsewhere. In particular, we identified side-effects that occur most commonly (incidence of 5% or greater and at least twice the incidence in placebo patients), commonly (incidence of 2% or greater and not observed at an equivalent incidence among placebo-treated patients) and were rare reported adverse events.

2.6.1. Treatment-associated adverse events in adult studies

The most commonly reported adverse events associated with the use of atomoxetine in adults were: dry mouth (15.6-55%), decreased appetite (12-50%), insomnia (17-35%), nervousness (35%), constipation (7-20%), erectile dysfunction (5.2-11%), nausea (12.3-40%), dizziness (6-15%), decreased libido (7.0-7.1%), sweating (5.2-20%), fatigue (16-25%), increased heart rate (17%), hypertension (10%), hot flashes (10%), depression (10%), and urinary problems (6-10%).

Analyzed results were relatively consistent with the reported data from the manufacturer and for those treatment-associated adverse events reported in trials of 10 weeks duration, namely: dry mouth (15%), insomnia (11%), urinary hesitancy and/or retention and dysuria (8%) decreased appetite (7%), nausea (7%), constipation (6%) and erectile dysfunction (6%).

Three rare adverse reactions were found as case reports, with the details as follows: sudden death due to cardiac arrhythmia, hyponatremia, and hemospermia. None of these were clearly due to atomoxetine alone. In addition, Ely Lilly and Company has reported various post-marketing spontaneous adverse events in adult patients with ADHD (in the Compendium of Pharmaceuticals and Specialties, 2009).

The following treatment-associated adverse events were associated with the use of atomoxetine in adults, and were observed with a frequency between 1:100 and 1:1,000: tachycardia, abdominal pain, constipation, dry mouth, nausea, chills, fatigue, weight loss, decrease in appetite, dizziness, insomnia, and difficulty in micturition. Other rare side-effects were observed with a frequency of less than 1:1,000 in adult populations and were: QT prolongation on electrocardiogram (ECG) (in 0.01%), dyspepsia, flatulence, hepatobiliary events, liver function test abnormalities, lethargy, sudden death, overdose, insomnia, seizure, sinus headache, syncope, early morning awakening, decrease libido, sleep disorders, and suicidality.

In summary, atomoxetine appears safe, although there are some significant effects that occur rarely in adults treated over the longer term. In the presentation to the ethics review board at the University of Alberta, all of this evidence was presented. Following review, the ethics review board concurred that it was safe and appropriate to give this drug for up to 2 weeks to smokers wishing to stop smoking, provided they had read all of the relevant information contained within the informed consent form.

2.7. Conclusion

In conclusion, we observed that numerous direct and indirect lines of evidence suggest that atomoxetine is well-tolerated, safe, and an efficacious medication for the treatment of ADHD. Given that both addictions and the nicotine withdrawal syndrome are both characterized by similar signs and symptoms, and that both appear to benefit from treatment with drugs that modulate noradrenergic neurotransmission, we proposed to conduct a pilot placebo-controlled, double-blind (subjects, co-investigator and investigator) randomized trial with atomoxetine for the treatment of smoking cessation. Our expectation was that atomoxetine would increase the abstinence rate as well as alleviating withdrawal symptoms and craving in abstinent smokers.

CHAPTER 3.

STUDY METHODOLOGY

3.1. STUDY HYPOTHESES

The primary study hypothesis was that more subjects in the atomoxetine treatment group would be able to remain abstinent from cigarette smoking for a twenty-one day treatment period compared to those who received placebo.

There were four secondary hypotheses in the study:

A. That there would be a difference in the frequency or severity of withdrawal syndromes in cigarette smokers between those who received atomoxetine compared to those who received placebo.
B. That there would be a difference in other symptoms, including craving and smoking urges, between those who received atomoxetine compared to those who received placebo.
C. That there would be a correlation between success at stopping smoking during the study and alleviation of withdrawal symptoms observed during the treatment period.
D. That the safety of atomoxetine in the study population would be similar to that seen in other studies in adults.

3.2. STUDY POPULATION

The study population was defined as healthy volunteers who wanted to quit smoking and met the DSM-IV criteria for nicotine dependence. The study population was sampled as much as possible from the general population and was intended to be recruited primarily using advertising of the study on posters and via media advertisements (see Appendix 12. Poster).

Inclusion and exclusion criteria were used to ensure an appropriate study population, as well as ensuring that the two study groups were as similar as possible for a variety of potential biases both related to their nicotine dependence as well as other general health and life-style related issues.

3.3. SAMPLE SIZE CALCULATION

In order to determine the differences between treatment and placebo groups, the sample size was calculated by a power analysis. This was based on the reduction in self-reported smoking urges as measured by the questionnaire for smoking urges (QSU) that was found in a previous study of the effects of atomoxetine in smoking cessation in patients with ADHD (Ray et al., 2009). In this study the baseline QSU was 72 with a standard deviation of 19, while following treatment with atomoxetine it was 82 with a standard deviation of 17. Assuming that the study should be powered sufficiently to detect a similar change in magnitude, a sample size calculation was made using these values and an Alpha error level of 5% (corresponding to a 95% confidence interval) and a Beta error level of 10% (the probability of incorrectly failing to reject the null

hypothesis that there is no difference in the average values). Using this information the number of subjects required to reach statistical significance was calculated as 56. To account for drop-outs, a total of 60 subjects in each arm were felt to be required. Thus, it was the intention to recruit a total of 120 subjects, 60 in each arm.

3.4. SCREENING

Screening of volunteers for study eligibility was conducted in accordance with standard clinical practice guidelines, and utilized widely used standardized scales and semi-structured interviews. A standardized format was also used to record all data.

During screening the following information was collected:

- Demographic data
- Contact details for the potential subject
- Smoking history with enough history to determine if the individuals met diagnostic criteria for nicotine dependence according to DSM – IV classification
- Psychiatric history including other substance use/abuse
- The Mini International Neuropsychiatric Interview (Appendix 6. The Mini International Neuropsychiatric Interview)
- Medical history
- Inclusion/Exclusion criteria

- Physical examination records (see Appendix 13. Physical Exam Form)
- Concomitant medications use (see Appendix 14. Concomitant Medications)

The following demographic information was collected during the screening interview: gender, age, socio-economic status (educational level, income, and occupation), marital status, ethnicity, and residence location.

Detailed smoking, substance use/abuse, medical and psychiatric histories were also gathered during the interview.

3.4.1. Diagnostic and Statistical Manual version IV (DSM-IV)

To ensure diagnostic accuracy, The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used (First et al., 1997) to confirm that volunteers met diagnostic criteria of DSM-IV for nicotine dependence. Only those individuals who met diagnostic criteria for nicotine dependence were eligible for study participation. DSM-IV criteria were also used to determine if nicotine withdrawal occurred. The following are the DSM-IV criteria for nicotine dependence and nicotine withdrawal:

3.4.1.1. DSM-IV Diagnostic Criteria for Nicotine Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by 3 (or more) of the following, occurring at any time in the same 12–months period:

1. Tolerance, as defined by either of the following:
    a) A need for markedly increase amounts of the substance to achieve intoxication or desired effect
    b) Markedly diminished effect with continued use of the same amount of the substance
2. Withdrawal, as manifested by either of the following:
    a) The characteristic withdrawal syndrome for the nicotine
    b) The same substance is taken to relive or avoid withdrawal symptoms
3. The substance is often taken in the large amount or over a long period of time than was intended
4. There is s persistent desire or unsuccessful efforts to cut down or control substance use
5. A great deal of the time is spent in activities necessary to obtain the substance, use it or recover from its effects
6. Important social, occupational, or recreational activities are given up or reduced because of the substance use
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

Specifiers:

- With physiological dependence: evidence of tolerance or withdrawal

- Without physiological dependence: no evidence of tolerance or withdrawal, but compulsive use is what describes the dependence for these individuals (Criteria 3-7).

Course specifiers:

1. Early full remission (1 month at least, but < 12 months, none of criteria for dependence met)
2. Early partial remission (1 month at least, but < 12 months, with presence of 1 or more criteria for dependence, but full criteria have not been met)
3. Sustained full remission (> 12 months, none of criteria for dependence met)
4. Sustained partial remission (>12 months, with presence of 1 or more criteria for dependence, but full criteria have not been met)
5. On agonist therapy
6. In a controlled environment (jail, therapeutic community, locked unit in hospital and etc.)

3.4.1.2. DSM-IV Diagnostic Criteria for Nicotine Withdrawal

A. Daily use of nicotine for at least several weeks

B. Abrupt cessation of nicotine use, or reduction in amount of nicotine used, followed with 24 hours by four (or more) of the following signs:

   1. Dysphoric or depressed mood

2. Insomnia
3. Irritability, frustration or anger
4. Anxiety
5. Difficulty concentrating
6. Restlessness
7. Increased heart rate
8. Increase appetite or weight gain
9. Other

C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational or other important areas of functioning

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

3.2.1.3. DSM-IV Diagnostic Criteria for Nicotine Dependence – strengths and weaknesses

Although we have used DSM-IV throughout, there are issues with nicotine dependence and withdrawal criteria. Some of the key concerns are discussed below.

The concept of mental disorders has evolved considerably as increasing knowledge has been accumulating through clinical practice, research, and statistical data. Due to rapidly changing and constantly increasing knowledge of psychiatric diseases, DSM classification has been revised several times. The last

version of DSM, DSM-IV, was introduced in 1994. However, it is being revised with a new edition due to be released (DSM-V) in 2013, and the current version is recognized to have a number of weaknesses. These issues can be considered as structure- and content-related.

From a structural point of view, the length of the DSM-IV means that it is inconvenient and impractical in clinical practice. The symptom–based approach also contributed to the excessive description of the addiction disorders and in some instances to the poor boundaries between distinct nosologic entities. The research data show that nicotine is an addictive substance with the highest level of dependence compared to other psychoactive substances (Britton, 2000). It has also been shown that there is a substantial difference between the dependence/withdrawal symptoms produced by nicotine and other psychoactive substances. However, despite these findings, neither nicotine nor other addictive substances have separate descriptions of diagnostic criteria in DSM-IV.

One of the commonest content-related disadvantages of DSM-IV is its phenomenological approach. This symptom-based approach to classification does not fully reflect the etiology and pathogenesis of nicotine dependence. Moreover, it does not capture some typical symptoms that occur. For example, craving, which is a key symptom, was never included in the DSM-IV leading to the gaps between clinically observed phenomenon and the diagnostic criteria.

Others have suggested that the nicotine withdrawal definition in DSM-IV is not complete. One group of researchers has strongly argued that the current criteria mainly reflects late secondary signs and omits subclinical and early

clinical presentations (DiFranza et al., 2010). These authors suggest that it is of paramount importance to reflect the earliest clinical manifestations of addiction in order to reveal them and prevent progression (DiFranza et al., 2010). Moreover, the intensity of the symptoms of nicotine dependence have never been reflected in the DSM, although as described by DiFranza and colleagues, the spectrum of intensity (degree of the desire) combined with description of periodicity (frequency, which the desire appears with) and latency (period of time between being satiated by nicotine and next wanting/craving period) can reflect the pathophysiology of the nicotine addiction (DiFranza et al., 2010).

Others have suggested that another disadvantage of the DSM-IV is that the classification was mostly based on the medical model of mental disorders. Utilization of alternative conceptual frameworks such as dimensional (approach that allows to view the disorder as combination of cognitive and emotional dimensions and determines position of the patients on the spectrum of these dimensions), holistic (method that units social, spiritual an pharmacological approaches and considers them as equal entities) and perspectival (approach that views mental disorders in the light of four perspectives: disease, dimensions, behavior and life story and considers the treatment of mental disorders based on these perspectives) models could be used to better understand the mental disorders in general and nicotine addiction in particular, compose diagnostic criteria, reveal earliest signs/symptoms, and apply suitable treatment (Encyclopedia of mental disorders. Diagnostic and Statistical Manual of Mental Disorders)

Another weakpoint of DSM-IV is the data that was used in its development. While in most areas, pharmacological field trials were one of the key sources of information during development of DSM-IV criteria (Frances et al., 2000), this was not the case with nicotine addiction and withdrawal. This raises issues regarding the validity and, subsequently, the generalizability of the classification. In contrast, it seems to be prudent to use a combination of clinically and research-based information for the diagnostic criteria in the next version. For example, DiFranza had proposed new nicotine dependence criteria relying on forty distinct smoking research studies (DiFranza et al., 2010). This could be combined with data from general clinical practice, as suggested by Kirk and Kutchins, to serve as more reliable source for future classification (Kirk and Kutchins, 1994).

Another issue is that the gender, race and ethnicity issues of nicotine dependent individuals has also never been considered in DSM–IV, even though it has been shown that these parameters can affect the metabolism of nicotine and its primary metabolites, thus potentially impacting the manifestation and progression of nicotine dependence (Benowitz, 1999; Benowitz, 2002; Benowitz et al., 2009; Perez-Stable et al., 1990; Perez-Stable et al., 1998; Wagenknecht et al., 1990;).

The presence of the vague diagnostic subcategory "nicotine-related disorders not otherwise specified" can introduce confusion during diagnosis, and could significantly affect scientific and statistical data.

Despite these drawbacks the DSM-IV possesses several advantages: 1) the classification serves as a standardized diagnostic tool and is widely-used by various entities, whose work constantly involves the use of a consistent description for nicotine dependence; 2) it provides detailed descriptions of currently known psychiatric conditions including nicotine dependence and withdrawal; 3) the system has been widely accepted and used as a common language to communicate various clinical and research-based results; 4) the classification has been constantly undergoing revisions and has been under regular critique by professionals in the mental health and addiction areas.

Lastly, the composition of the diagnostic criteria for nicotine dependence and nicotine withdrawal in the DSM-IV has impacted understanding of nicotine addiction over the past two decades. There are many publications and studies that have been carried out based upon the existing diagnostic criteria. This existing database allows meaningful comparisons between the data in the present study and previous ones that have used the same diagnostic criteria.

Therefore, despite the issues identified, the DSM-IV has been used in the present study for inclusion/exclusion criteria, to characterize the study population, to describe nicotine dependence and nicotine withdrawal syndrome, to monitor changes in withdrawal symptoms during the abstinence in both treatment arms, and to determine conclusions.

3.4.2. Mini International Neuropsychiatric Interview (M.I.N.I.)

The Mini International Neuropsychiatric Interview (M.I.N.I.) is a brief structured interview that was employed in our study to exclude other psychiatric disorders in the study subjects during the screening visit (see Appendix 6. The Mini International Neuropsychiatric Interview).

This interview was developed by American and French psychiatrists and has been widely used since its introduction in 1990 (Sheehan et al., 1998; Sheehan et al., 1997; Sheehan et al., 2010). The main goal of the authors was the creation of the psychiatric structured interview that possessed multiple advantages over the existing instruments.

Indeed, when compared to other semi-structured diagnostic interviews available in psychiatry, the M.I.N.I. is often preferred due to its simplicity of use, brevity, and cost efficiency. Moreover, it is compatible with diagnostic criteria including DSM-IV and ICD-10 (Sheehan et al., 1998). The M.I.N.I. allows quick evaluations and determination of outcomes not only in clinical settings, but also in experimental and observational studies (Sheehan et al., 1998; van Vliet & de Beurs, 2007).

The M.I.N.I. was shown to be valid and reliable in eliciting symptom criteria in both ICD-10 and DSM-IV. When compared to the Structured Clinical Interview for DSM-IH-R patients(SCID-P) and the Composite International Diagnostic Interview for ICD-10 (CIDI), the M.I.N.I. was reported to have good inter-rater and test-retest reliability (Lecrubier et al., 1997). In addition, Pinninti and colleagues demonstrated that administration of this questionnaire was

feasible and well accepted by patients in outpatient conditions compared to the usual methods of asking questions (Pinninti et al., 2003).

For study purposes, the M.I.N.I. International Neuropsychiatric Interview version was used. This consists of 19 modules which were developed to evaluate 17 Axis I DSM-IV disorders: major depressive disorder, dysthymic disorder, panic disorder and phobias, obsessive-compulsive disorder, general anxiety disorder, alcohol and other drug dependence and abuse disorders, psychotic disorder, eating disorders, hypomania/mania, antisocial personality disorder, post-traumatic stress disorder and suicidality. This version can be administered by raters with various degree of training (Sheehan et al., 1998; de Azevedo Marques & Zuardi, 2008).

3.4.3. Study Inclusion Criteria and rationale for these

The following inclusion criteria were used in the study:

1. Patients who want to quit smoking
2. Diagnosis of nicotine dependence according to DSM –IV criteria
3. The individual smokes between 10-25 cigarettes per day, and has done so for at least the previous 12 months
4. Aged between 21-60
5. Signed informed consent

The first inclusion criterion was introduced to limit the study population to smokers who actively wanted to stop smoking. A strong motivation to stop smoking is important for individuals who enter studies to try and decrease drop-out rates, particularly in a drug study where side-effects may occur.

The second criterion was chosen to ensure study subjects had nicotine dependence. Issues with these criteria have been noted previously.

The degree of nicotine dependence is somewhat arbitrary, but the choice we made is consistent with nicotine dependency based on national statistical data (Health Canada. Tobacco Use Statistics). These have shown that the average number of cigarettes smoked per day is approximately 15, and this number remained stable over a prolonged period (1999 until 2008). However, it should be noted that in the most recent two years for which data is available (2008 and 2009) the average number of cigarettes smoked per day decreased slightly to 14.9 and 13.3 respectively. According the U.S. National Institute on Drug Abuse smoking levels can be classified as light (less than 15 cigarettes per day), moderate (15 -24 cigarettes per day) and heavy (25 and more cigarettes per day) (National Household Survey on Drug Abuse, 1998).

These lower levels have been considered to be at a mild smoking level, but then this appears to be the range of the majority of smokers in Canada. Thus, the statistical information demonstrates that in Canada the majority of daily smokers have been moderate to mild smokers, across different age categories. For these reasons both groups were included in the study, thus reflecting of the use across Canada. However, those, who had very mild and/or occasional

smoking, were excluded as they may be less addicted. For this reason it was specified that individuals must smoke at least 10 cigarettes per day. Similarly, to avoid a very wide range of individual consumption, and to exclude those who are categorized as heavy smokers, the upper cut-off of 25 per day was set up.

This study was carried out according to the highest ethical standards, and was approved by the Health Research Ethics Board (Panel A) of the University of Alberta. It was conducted in compliance with local regulations, Good Clinical Practice and in accordance with the ethical principles summarized in the Declaration of Helsinki (1964) revised in Tokyo in 2004 (Appendix 11. The Declaration of Helsinki).

The age restriction for the study was 21-60 years of age for two main reasons:

Firstly, Canadian statistical data for last decade showed that the majority of current smokers belonged to the age groups that fall between 20 and 55 years of age (Reid et al., 2009). Moreover, according to latest Canadian Tobacco Use Monitoring Survey (CTUMS) (2003) the vast majority of individuals tried their first cigarette at the age of 19 years. Thus, these numbers suggest those over 21 would be the most appropriate lower age cut-off for the time by which dependence to nicotine will have developed, and a more or less regular pattern of smoking established. We were concerned that younger adults (those aged 18-21) may not have an established smoking pattern and therefore withdrawal symptoms may be less likely to be manifested.

Secondly, the upper limit of the age group, this was based on research data on nicotine and its primary metabolite cotinine. Studies on the influence of age on the metabolism and clearance of nicotine and cotinine have demonstrated that the half-life of nicotine is longer in neonates (Dempsey et al., 2000) and is decreased in older individuals (>65) (Molander et al., 2001), but there is no difference in the steady-state nicotine plasma levels or its clearance in individuals between 18 to 69 years of age (Gourlay & Benowitz, 1996). Similarly, there has been shown to be decreased renal clearance of cotinine in people older than 65 years, due to diminished glomerular filtration related to aging (Molander et al., 2001). For these reasons we felt that to decrease any risk of this being problematic, the appropriate upper age limit for this study was 60 years.

3.4.4. Study Exclusion Criteria and rationale for these

Exclusion criteria were based on the information from several sources, and were designed to minimize any risks involved when using atomoxetine in this study population. The following data had provided the basis for the exclusion criteria:

- safety reports provided by Elly Lilly, the pharmaceutical manufacturer of atomoxetine
- atomoxetine (Strattera) product monograph (Appendix 1. Strattera Product Monograph)

- comprehensive literature review of experimental and observational studies in over 200 studies that had involved atomoxetine. This was a detailed review in which side-effects from every study were considered, and ranked. This was considered critical as until this was done it was not clear that it would be safe to give this drug to otherwise healthy individuals. This information was provided in detail to the ethics review board in their consideration of this study protocol.
- detailed review of all available articles on atomoxetine side effects in both adults and children
- all relevant case reports

Although there were many side effects reported, we selected any of these that were potentially dangerous or likely to cause severe medical problems to the study subjects. More common, but less significant, side effects such as, abdominal cramps, fatigue, and decreased appetite were not included in the exclusion criteria. However, each subject was warned about all potential side effects of atomoxetine.

The following exclusion criteria were used (and the reason for this are given except where self-evident):

3.4.1.1. Any current Axis I psychiatric disorders

This selection criterion was used to exclude other major psychiatric conditions in the study group so as to avoid potential issues with applicability of the study.

3.4.1.2. History of intolerability, hypersensitivity or allergy to atomoxetine

3.4.1.3. Presence of narrow angle closure glaucoma

In the Product Monograph it was reported that the use of atomoxetine was associated with an increased risk of mydriasis (Strattera Product Monograph, 2009). Additionally, Alhatem and colleagues also published one case report about mydriasis in short-term atomoxetine monotherapy noticing that to date the only one animal study done by Kreuser and colleagues has found atomoxetine-induced mydriasis in healthy rats (Alhatem & Decker, 2008). Mydriasis is an excessive dilation of the pupil due to a shift in muscle tone of dilator or constrictor. Mydriasis is considered to be a risk factor for the narrow angle glaucoma, which is characterized by the progressive damage of the optic nerve with gradual irreversible loss of vision. Excessively dilated pupils increase the eye fluid pressure and create the mechanical obstruction of these fluids that leads to the progression of the optic nerve damage.

Atomoxetine most likely induces mydriasis because of its noradrenaline reuptake inhibitor actions. Via an increase in noradrenaline levels, atomoxetine can stimulate the sympathetic fibres of dilator muscle, thus inducing mydriasis.

As angle closure glaucoma is a serious condition that leads to disability, it is important to minimize the risk of this, and hence those individuals who had this condition were excluded in order to avoid potential optic nerve damage.

3.4.4.4. Use of monoamine oxidase inhibitors (MAOI) or other drugs that affect brain monoamine concentration

This criterion was included because the use of MAO inhibitors or other substances that can affect concentration of monoamines in the brain (for example, tricyclic antidepressants, amphetamines, alcohol) cannot be combined with atomoxetine (Strattera Product Monograph, 2009, Nardil product monograph, Parnate product monograph, Selegeline product monograph, Moclobemide product monograph). As is well recognized, such interactions can cause serious, or even fatal, reactions in study subjects. These adverse reactions can occur if MAO inhibitors and atomoxetine are taken at the same time, or within 2 weeks of initiation/discontinuation of either one. This two-week period is based upon product monographs for the most commonly used MAOIs [Phenelzine (Nardil), Tranylcypromine (Parnate), Moclobemide (Aurorix, Manerix, Moclodura), Selegiline (Selegiline, Eldepryl, Emsam] as well as for Strattera (atomoxetine). All were reviewed and confirmed a recommended two week washout period between either initiation or discontinuation of the above-mentioned drugs (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php).

To ensure that this did not occur, subjects were not simply asked whether or not they took such medications, but the list of all available MAOIs was presented to each study subject at the screening visit.

3.4.4.5. Use of atomoxetine within the 30 days prior to screening.

This criterion was designed to avoid any overlap or/and accidental atomoxetine overdose if atomoxetine use had occurred prior to, or within, 30 days of study therapy initiation. To determine the safest period required for the complete elimination of atomoxetine from the body over 200 publications were reviewed in detail.

It was found that the length of the washout period or interval between atomoxetine initiation (various doses) and use of other drugs in different atomoxetine clinical trials ranged from 0 to 28 days. This is despite the fact that that in poor metabolizers the mean half-life of atomoxetine was about 62 hours, with the majority of the dose eliminated within 72 hours (Sauer et al., 2003; Sauer et al., 2005).

Most studies documented a one or two week drug-free interval, although two studies applied a 28-day drug-free period (Brown et al., 2009; Adler et al., 2008). Two studies used a one week washout and a 2 weeks placebo lead-in period giving a total of 21-days washout (Reimherr et al., 2005; Michelson et al., 2003).

Given these differences, we examined the most appropriate length for a washout in the current study, particularly examining the time needed for a clinical response to atomoxetine treatment and the time required for discontinuation of atomoxetine.

Regarding the response time to atomoxetine, it was found that this took from 1 to 4 weeks before clinically noticeable responses occurred (Kelsey et al.,

2004; Prasad et al., 2008; Wernicke et al., 2004; Michelson et al., 2003; Strattera Product Monograph, 2009). It is believed that this time is required for formation/accumulation of poorly understood neuroregulatory changes. It is well recognized that, similarly to the mechanism of action of antidepressants, this time course is much longer than that required to demonstrate blockade of the presynaptic noradrenaline transporter by atomoxetine (Michelson et al., 2003).

In studies on atomoxetine discontinuation most studies report a 4 week period after atomoxetine was stopped. However, although no clear explanations for this length of time were provided in the studies, it is probable that the same neuroregulatory changes would be responsible in the determination of the length of the discontinuation period (Wernicke et al., 2004; Michelson et. al., 2003).

Thus, based on the literature, and to ensure that any risks are the lowest possible, it was decided that in the present study an interval period of at least 30 days between previous doses of atomoxetine and current participation would be required.

3.4.4.6. Suicidal risk (presence of suicidal ideation).

The frequency of suicidal ideation with atomoxetine is uncertain. Post-market spontaneous adverse event reports, as reported in the Strattera Product monograph, indicate that less than 0.01% of adult patients with ADHD who are treated with atomoxetine experience suicidality - defined in the product monograph as completed suicide, suicidal ideation, suicide attempt, or suicidal depression (Strattera Product Monograph, 2009). However, short-term placebo-

controlled trials in children and adolescents with ADHD clearly showed an increased risk (0.4%) of suicidal ideation in atomoxetine treatment group compared to placebo (0%) (Strattera. Highlights of prescribing information, 2008).

This data led to a public warning from Eli Lilly Canada Inc., jointly with Health Canada, in September 2005, about behavioral and emotional changes. These include potential suicidal behavior among patients of all ages who taking atomoxetine (Strattera product monograph, 2009).

In 2008 a meta-analysis of suicide-related behaviours in pediatric atomoxetine trials suggested a similar finding. In this study the frequency of suicidal ideation was 0.37% (5/1357) in children/adolescents taking atomoxetine versus 0% (0/851) in the placebo group (Bangs et al., 2008).

In 2009 McCarthy and colleagues in their study aimed to identify cases of death among patients taking stimulants and atomoxetine and examine any associations between these and sudden death. In the cohort of 18,637 patient-years they found that the standardized mortality ratio (SMR) for suicide among patients aged 11-14 years was very significantly greater in these younger patients (161.91) compared to patients aged 15-21 years (1.84) (McCarthy et al., 2009).

Based on the collected safety data detailed above, we excluded any individuals with suicidal ideations, thoughts or attempts present during screening. In addition, we specifically mentioned this risk to every subject and inquired about it at every visit.

3.4.4.7. Abnormal vital signs including systolic BP>140 mmHg or diastolic >90Hg

Atomoxetine affects noradrenaline, and this is involved in control of both pulse and blood pressure. A fairly frequent side-effect of atomoxetine has also been pyrexia and chills. For this reason, careful note of blood pressure, pulse, and temperature were made at every visit using best practices, as described below.

Blood pressure

Normal reference range for blood pressure is considered to be between 90-140 mmHg for systolic and between 40-90 mmHg for diastolic pressure (Chowdhury and Merani, 2010). Abnormal vital signs are determined as an increase of systolic blood pressure more that 140 mm Hg or diastolic more than 90 mm Hg as well as a decrease of systolic blood pressure less than 90 mm Hg or diastolic blood pressure less than 40 mm Hg. In the present study,a wall-mounted sphygmomanometer at the Northern Alberta Clinical Trail Research Centre (NACTRC) was utilized as it is regularly serviced and calibrated. To ensure this was measured consistently we utilized the following technique.

Measuring technique

Blood pressure was measured at the baseline visit initially in both arms. Differences of 5-10 mm between both arms were considered normal. The arm with the higher measurement was used for subsequent readings. The use of

appropriate cuff size was ensured. The cuff was completely deflated when applied. The subject was positioned comfortably with their arm slightly flexed at the elbow and free of constricting sleeve. Their arm was placed such that the brachial artery was at the level of the heart. The center of the cuff bladder was placed over the brachial artery. For the first measure a palpatory reading was taken to determine proper inflation and the initial level of the reading. Then, the cuff was deflated completely to allow the blood pressure to normalize. After 20 seconds the cuff was inflated rapidly to 30 mm Hg above the previously determined palpatory reading. The readings then were recorded in the patient's file.

Importance of blood pressure control in the atomoxetine clinical trial

High blood pressure is an exclusion criterion for the present study because in several clinical trials atomoxetine has been shown to produce cardiovascular effects in children, adolescents and adults in both short-term and long-term studies (Strattera Product Monograph, 2009).

Additionally, more recent literature that was not captured in the Strattera Product monograph was reviewed. One open-labelled atomoxetine study in adults, who had subthreshold and/or late onset ADHD, demonstrated clinically and statistically significant changes in both blood pressure and heart rate in patients treated with atomoxetine (Surman et al., 2010). Similarly, another study found that atomoxetine treatment produced small, but statistically significant, changes in blood pressure in patients with Huntington disease (Beglinger et al.,

2009). In a review, small, statistically significant, changes of blood pressure were found in pediatric and in adult patients (Garnock-Jones et al., 2009; Adler et al., 2009; Adler, Spencer et al., 2009). In contrast, other studies with atomoxetine did not find any significant changes in blood pressure in ADHD adults receiving treatment with atomoxetine (Johnson et al., 2010; Adler et al., 2009). Some studies have also suggested that the risk is not large, since it has been suggested that atomoxetine may attenuate cocaine-induced and dextroamphetamine-induced hypertension (Sheehan et al., 2010; Sofuoglu & Sewell, 2009; Sofuoglu et al., 2009a; Stoops et al., 2008).

Taking this together, while there is no current research on possible changes in those with pre-existing hypertension, and the data on the effect of atomoxetine is not clear cut, given the clear possible risks of even a small increase in blood pressure, particularly in those who are hypertensive and who smoke, all potential subjects whose resting blood pressure was outside the normal range were excluded from the study.

Pulse Rate

In the present study radial pulse measurement was used. The commonly accepted pulse range of between 45 and 100 beats per minute was utilized. A rate of more than 100 beats per minute was considered to indicate tachycardia and less than 45 beats per minute to indicate bradycardia (Chowdhury and Merani, 2010). It is recognized that age, body mass index, sex, physical

condition, emotional state, food and drinks, medications, diseases, as well as the presence of nicotine itself, can all affect the heart rate.

Radial pulse measuring technique

The subject was seated comfortably when pulse was measured. Their arm was supported to ensure that the wrist was at the same level as the heart. The pulse was assessed by the tips of the first three fingers placed at the wrist area 2 cm above the base of the thumb. An appropriate amount of pressure was applied to the radial artery to feel its pulsation. Pulse rate was then measured during a complete one minute period.

Importance of heart rate variability in atomoxetine clinical trials

In the product monograph (Strattera Product Monograph, 2009) there are warnings and precautions about use of atomoxetine in individuals with pre-existing cardiovascular diseases. Moreover, based on the summary of several clinical trials in children, adolescents, and adults treated with atomoxetine, the presence of any symptomatic cardiovascular condition is considered to be a contraindication for the use of atomoxetine.

In a more detailed literature review it was confirmed that atomoxetine therapy, in a variety of age groups, altered heart the rate in children, adolescents and adults (Kratochvil et al., 2008; Wernicke et al., 2002; Arnold et al., 2006; Chamberlein et al., 2007; Garnock-Jones et al., 2009). However, not all trials found a statistically significant change in pulse rate (Quintana et al., 2007; Johnson et al., 2010).

Temperature

Among treatment-emergent adverse events in acute adults trials atomoxetine was shown to induce both pyrexia and chills (Strattera Product Monograph, 2009). Additionally, a meta-analysis reported pyrexia in acute atomoxetine therapy in children with ADHD (Kratochvil et al., 2008). Thus, it was important to monitor and record the temperature of study participants during the study.

Aural temperature measuring technique

Tympanic membrane (aural) thermometer was used to measure the core body temperature of the trial participants. It is believed that the auditory channel is an ideal site for obtaining the core temperature of the body compared to other measurements. This method is considered to be ideal because tympanic membrane shares the same blood supply with the hypothalamus. Moreover, studies conducted with this type of thermometer showed that reproducibility of the aural thermometer was better than for oral and axillary electronic thermometers (Chamberlain et al., 1995; Kiya et al., 2007; Bock et al., 2005; Keir et al., 1998).

In the present study, the subject was seated comfortably when aural temperature was evaluated. A disposable cover was attached to the thermometer during each ear temperature measurement. Temperature was measured until the reading appeared on the display. Temperature was recorded in Celsius.

The reference range for aural temperature measurement was 35.9^0c – 37.6^0c for individuals 11-65 years of age (Braun Owner's Manual ThermoScan IRT 3520; Chamberlain, 1994).

3.4.4.8. Concomitant use of CYP2D6 inhibitors or knowledge that study participant is poor CYP2D6 metabolizer.

Pharmacokinetic studies demonstrate that atomoxetine does not affect the CYP2D6 enzyme system. However, its biotransformation occurs through the CYP2D6 system. Therefore, combined use of atomoxetine with medications that can influence CYP2D6 system can alter the pharmacokinetics of this drug (Ring et al., 2002; Sauer et al., 2003; Sauer et al., 2004; Sauer et al., 2005; Belle et al., 2002).

Inhibitors of the CYP2D6 enzymatic pathway increase plasma concentrations of atomoxetine and its metabolites (Sauer et al., 2005) that may subsequently lead to increased risk of atomoxetine side effects.

Although there is no current published information about possible interactions between CYP2D6 inducing substances and atomoxetine, co-administration of atomoxetine will probably result in reduction of atomoxetine concentrations in plasma (Mann et al., 2008). Any such in decrease of atomoxetine concentrations would lead to diminution of therapeutic effect.

For these reasons, we ensured that no subject used any drugs that interacted with CYP2D6. Thus, during the screening visit study volunteers were presented with a list of potential medications (Appendix 13.Physical Exam

Form,Appendix 14.Concomitant Medications, Appendix 19. List of CYP2D6 inhibitors and inducers. Apperndix20. List of pharmaceutical drugs) that incorporate a comprehensive list of CYP2D6 inhibitors and inducers. In addition, all subjects were questioned about current use of medications that might alter the CYP2D6 enzymatic pathway.

During screening visit volunteers were also questioned to assist possible determination of their CYP2D6 status. It is well recognized that approximately 7 % of Caucasian, 3% of African, 2% of Black, 2% of Arabic and less than 1% of East Asians are poor CYP2D6 metabolizers. Compromised activity of this liver enzymatic system can lead to an increase of atomoxetine plasma concentration that may be as much as 4-5 times higher compared to extensive metabolizers. This is emphasized by findings that co-administration of CYP2D6 inhibitors and atomoxetine in poor metabolizers significantly increase the number of adverse events (Ring et al., 2002; Sauer et al., 2003; Sauer et al., 2005; Cui et al., 2007).

3.4.4.9. Current use of drugs that increase blood pressure, current use of Albuterol, stimulants, drugs that affect gastric pH, drugs that highly bound to plasma protein

As already mentioned above in 4.4.7, atomoxetine hydrochloride was shown to exhibit cardiovascular effects in various age groups; therefore, co-administration of atomoxetine and drugs that possess blood pressure increasing characteristics should be avoided.

In this regard the latest available literature on co-administration of atomoxetine with various stimulants is problematic. For example, several reports showed that atomoxetine attenuates stimulant-induced blood pressure rises when combined with cocaine, amphetamine, or dextroamphetamine administration (Sofuoglu & Sewell, 2009; Sofuoglu et al., 2009a; Stoops et al., 2008), while other studies demonstrated that atomoxetine increases heart rate in amphetamine and cocaine users (Stoops et al., 2008; Jasinski et al., 2008).

Due to the potential risks, and the uncertainty in the literature, in the present study we excluded any individuals who were also taking other drugs that may increase blood pressure, including other stimulants.

3.4.4.10. Current use of any recreational or illegal drugs not necessary meeting DSM-IV criteria for substance abuse disorder or use of controlled substance maintenance therapy

There i s a very limited literature about combined use of atomoxetine and illicit drugs. A few studies have examined atomoxetine therapy for individuals with ADHD who also use marijuana (Kratochvil et al., 2006; Tirado et al., 2008; Wilens et al., 2006), although only one study described the combined administration of atomoxetine and marijuana as well as the side effects associated with it. In this study it was found that atomoxetine is not effective for the treatment of marijuana dependence, and was characterized by clinically significant adverse events related to gastrointestinal tract (Tirado et al., 2008).

There have also been a small number of reports regarding the co-administration of atomoxetine and stimulants. One study found that intranasal cocaine administration during atomoxetine therapy could attenuate the predicted cocaine-induced increase in systolic blood pressure, but enhance cocaine-induced increases in heart rate. In contrast, Jasinski and colleagues showed that atomoxetine use significantly increased heart rate and blood pressure in stimulants abusers (Jasinski et al., 2008). Moreover, atomoxetine was shown to produce dose-dependent increases in blood pressure and heart rate in lysergic acid diethylamide (LSD), phenobarbital, chlorpromazine, and alcohol users comparing to placebo (Heil et al., 2002). Thus, limited data about physiological changes due to co-administration of atomoxetine and various drugs of abuse led to the decision that illicit drug use should be an exclusion criterion for participants' safety.

3.4.4.11. Alcohol use that meets DSM-IV criteria for alcohol dependence or alcohol abuse

Although in the Strattera product monograph it is noted that consumption of ethanol and atomoxetine hydrochloride will not affect intoxication effects of ethanol, some side effects of atomoxetine such as dizziness, drowsiness, light-headedness can be worsened by alcohol use (http://www.drugs.com /cdi/atomoxetine.html). Additionally, as it was noted in paragraph 4.4.7. atomoxetine can influence blood pressure and heart rate in light alcohol users compared to a placebo group (Heil et al., 2002). Moreover, ADHD patients with

alcohol-use disorder tend to experience atomoxetine associated treatment-emergent adverse events more frequently (Wilens et al., 2008; Adler et al., 2009a). Therefore, taking into consideration safety of participants, the use of alcohol during the study participation was considered as an exclusion criterion. It was recognized that this limitation may reduce the potential eligibility for many subjects.

3.4.4.12. Pregnancy and lactation period

There are very limited data about the effects of atomoxetine on fertility and reproduction. To date there are no animal studies that showed impairment in fertility in animal studies, although decreased fetus survival in rats has been reported (Alessi & Spalding, 2003). Similarly, in the available human data only three normal pregnancies with healthy newborns have been reported and one was lost to follow-up (Alessi & Spalding, 2003; Humphreys et al., 2007). Animal studies demonstrated that atomoxetine can be excreted in the milk (Strattera Product Monograph, 2009); however, there are no studies to our knowledge that examined this in the humans.

Taking this together, pregnancy and lactation were an exclusion criterion.

3.4.4.13. Neurological disorders such as tics and Tourette syndrome

Use of atomoxetine in ADHD patients with co-morbid tics and Tourette syndrome

In 2002, examining the mechanism of action of atomoxetine and its potential efficacy in ADHD, Bymaster concluded that due to an absence of effect on dopamine (DA) in the striatum and nucleus accumbense atomoxetine should not affect motor tracts (Bymaster et al., 2002). For similar reasons atomoxetine was suggested as a possible therapeutic alternative for the treatment of ADHD with co-morbid tic and Tourette disorders (Allen & Michelson, 2002; Block et al., 2009; Castellanos & Acosta, 2004).

Studies have been carried out, which include an 18-week placebo-controlled, double-blind trial, and results show significant symptom improvement in ADHD patients with co-morbid Tourette syndrome and tics (Allen & Michelson, 2002; Block et al., 2009; Feldman et al., 2005). Subsequent post-hoc subgroup analysis from this database revealed results consistent with these original findings (Spencer et al., 2008). Moreover, it has also been suggested that atomoxetine be used as an alternative therapeutic option if tic disorder is present (Wolraich et al., 2007).

Nonetheless, twelve case reports found that atomoxetine can develop/exacerbate tics in children with ADHD (Lee et al., 2004; Sears & Patel, 2008; Ledbetter, 2005; Parraga et al., 2007) when administered alone, as well as precipitate/exacerbate dyskinesias when combined with other dopaminergic, noradrenergic or serotonergic drugs (Ledbetter, 2005; Jaworowski et al., 2006; Parraga et al., 2007; Parraga et al., 2008).

For these reasons, and because of ongoing uncertainty in the literature, in the present study any individuals who had either tics or Tourette syndrome were excluded.

3.4.4.14. Seizures

Use of atomoxetine in ADHD patients with co-morbid seizure disorders

Preclinical data regarding the effect of atomoxetine on convulsive behaviour suggests an increased risk of seizure in animals treated with high doses of atomoxetine (Torres et al., 2008). Similarly, the majority of published case reports suggest that atomoxetine overdose causes seizures in children and adolescents, although the confirmatory serum levels were not always performed (Sawant & David, 2002; Spiller et al., 2005; Kashani & Ruha, 2007). Interestingly, the majority of documented cases reported the presence of pre-existing seizure disorders (12 out of 17 case reports of atomoxetine treatment-associated seizures; Graham & Coghill, 2008). Additionally, an increase in epileptic seizures within 2 weeks of treatment initiation in one out of seventeen children with epilepsy was reported (Torres et al., 2008).

In the post-marketing follow up, the frequency of seizure in children and adolescents (0.01%) is much higher than in adult population (0.0035%) (Strattera Product Monograph, 2009).

In the retrospective analysis of 31 clinical trials and post-market spontaneous adverse event reports from two independent Eli Lilly databases

(published from November 2002 to November 2004), Wernicke et al. concluded that the risk of seizure is not increased in ADHD adults who were treated with atomoxetine, provided that they did not have a past seizure history (Wernicke et al., 2007).

Taking into account the available research data regarding precipitation of seizures potential subjects with a pre-existing seizure history were excluded.

3.4.4.15. Aggressive behaviour and hostility

Aggression is viewed as one of the most common signs of ADHD in children (Polzer et al., 2007). On another hand, ADHD can co-occur with many co-morbid conditions such as oppositional defiant disorder (30-50%) and conduct disorder (25-50%) that are also characterized by aggression, hostility and antisocial behaviour (Ebert et al., 2008). Approximately 70% of children with childhood onset ADHD continue to exhibit symptoms in adulthood that puts them at risk for aggression and other types of antisocial behaviour in adulthood (Ebert et al., 2008).

The published literature has examined impacts of various pharmacological treatments on aggression in children and adults with ADHD. The majority of studies suggest that therapy decreases the aggression, hostility and antisocial behaviour, while some studies showed that medications can worsen the situation (Polzer et al., 2007).

Atomoxetine has been a therapeutic option, whose use has been associated with more frequently observed aggressive behaviour among children

and adolescents (Strattera Product Monograph, 2009; Polzer et al., 2007), especially in children with a positive family and personal history of verbal and physical aggression (Henderson & Hartman, 2004).

In adults a meta-analysis of aggression or hostility in three randomized controlled trials concluded that the risk of aggression and hostility in ADHD adults treated with atomoxetine was not different from placebo (Polzer et al., 2007). However, in contrast, in a 10 week adult open-labelled trial with atomoxetine, approximately 10% discontinued their participation due to aggression and hostility, and 10 % experienced it as an adverse event (Johnson et al., 2010).

Taking this information together it is difficult to draw firm conclusions about the potential risks of hostility and aggression in adults treated with atomoxetine, especially if the there is a previous history of such behaviour. Therefore, potential subjects with a history of aggression (determined by history or assessed by MINI questionnaire) and/or antisocial behaviour were excluded from study participation.

3.4.4.16. History of urine outflow obstruction from bladder

Symptoms of urinary retention and hesitancy in ADHD adults treated with atomoxetine were reported as occurring in more than 5% or subjects (Strattera Product Monograph, 2009).

In addition, two randomized placebo-controlled studies reported urinary hesitancy as atomoxetine-associated adverse events in more than 5% (Adler et al., 2008) and in 10 % (McElroy et al., 2007) of study participants. One open-labelled atomoxetine trial in adults with subthreshold and/or late onset ADHD found that 13% had the side-effect of urinary hesitancy (Surman et al., 2010). Indeed, this side-effect is so well recognized in children that it has been utilized in the treatment of children with nocturnal enuresis (Sumner et al., 2006).

It is recognized that worsening of urinary retention/hesitancy can lead to severe complications such as acute urinary retention, infections, acute and chronic kidney failure, and urinary incontinence (LeBlond et al., 2008).

For these reasons subjects with a positive history of urinary retention or hesitancy were excluded from study participation.

3.5. RANDOMIZATION AND CODING

In order to avoid selection bias, the assignment of subjects to the two study groups was done on the basis of a chance/random process. Randomization was determined according to a code generated by computer (http://www.randomizer.org/form.htm). Two copies of the generated code were kept in a separate locked compartments, and were not opened until the study was completed.

Double blinding was employed to ensure the precaution that neither study subjects nor study staff was aware of group assignment, to achieve more accurate study results and to eliminate various biases such as placebo effect or

information bias (systematically introduced bias when information about subjects in both placebo and atomoxetine arms is gathered differently by the interviewer, who is not blinded)

Participants were randomized and assigned to either atomoxetine or placebo-treatment arm during the baseline visit. Coding of study subjects (study subject number) was done by assigning unique alphanumeric sequential code to each participant. Alphanumeric sequential code was of six characters length as 001 XXX, 002 XXX and etc, with XXX representing the subject's initials. Where subjects had only two initials, the middle initial was the letter A. Where subjects had more than 3 initials (such as 2 middle names or double-barrelled last name), the first three initials in their name was used.

3.6. VISIT DETAILS

3.6.1. Screening Visit

All volunteers who expressed their wish to participate in the study were contacted by telephone. Once they understood the general principles of the study, and there were no obvious issues during pre-screening by telephone, they were invited to the screening visit.

Complete information about the study objectives, procedures, requirements, risks and benefits was provided to volunteers during the screening meeting. This material was presented in clear and simple language. Comprehensive information about the mechanism of action of study medication and its side effects was also explained.

A Written Informed Consent Form was collected for each study participant by the study sub-investigator before initiation of his/her participation. The Informed Consent From was obtained in accordance with local regulations, and all study information was approved by the Health Research Ethics Board of the University of Alberta.

Upon signing the Informed Consent Form, the subjects underwent a screening interview that included:

- Screening questionnaire consisting of demographic data, smoking history, medical history, psychiatric history, and social history of the patient.
- Screening questionnaire with study inclusion and exclusion criteria.
- Structured Clinical Interview for Diagnostic and Statistical Manual (DSM-IV) to confirm that the subject met appropriate diagnostic criteria of DSM-IV for nicotine dependence
- Mini International Neuropsychiatric Interview (M.I.N.I.) to exclude other psychiatric disorders.

Upon completion of the interview subjects had a physical exam that also included the following measurements:

- weight (kg),
- blood pressure (mmHg),
- pulse (bpm).

Please refer to Appendix 13. Physical Exam Form

Subjects also underwent cotinine saliva test to confirm their smoking status. Those volunteers, whose screening interview and cotinine saliva test

showed that they were eligible for trial participation, were contacted by the co-investigator and invited for a Baseline visit (see Appendix 17.Cotinine saliva test record form).

3.6.2. Baseline Visit (Day 1=Week 0)

The Baseline visit occurred within 7 days of the screening visit. Complete information about smoking history along with detailed information on medical, psychiatric, and social history of each participant were collected during this visit. This was to complete any missing information from the screening visit (see Appendix 18. Patient Baseline Form).

The following questionnaires were employed to determine the baseline ratings for subjects:

- Severity of nicotine dependence - utilizing the Cigarette Dependence Scale (see Appendix 7. The Cigarette Dependence Scale)
- Withdrawal symptoms - utilizing the Cigarette Withdrawal Scale (see Appendix 8. The Cigarette Withdrawal Scale)
- Smoking urges and craving - utilizing the Questionnaire for Smoking Urges (see Appendix 3. The Questionnaire for Smoking Urges)
- Depression symptoms - utilizing the Montgomery-Åsberg Depression Rating Scale (see Appendix 4. Montgomery-Åsberg Depression Rating Scale)
- Level of self-esteem - using the Rosenberg Self-Esteem Scale (see Appendix 9. Rosenberg Self-Esteem Scale).

Additionally, participants underwent a repeat physical exam that included measurement of vital signs (blood pressure, pulse, temperature) and weight.

The biochemical measure of the primary nicotine metabolite, cotinine, was carried out from a salivary sample to establish its baseline level. This baseline level was used for evaluation at subsequent visits as well as monitoring measure of compliance and self-reporting.

As a subjective monitoring measure, a Self-Monitoring Dairy was used. At the baseline visit each participant received a Self-Monitoring Dairy (see Appendix 5. Self-Monitoring Dairy) to record data for one week and was instructed to fill it out every day, as well as to return it at the next follow-up visit.

At the baseline visit (Day1=Week 0) participants underwent randomization and were assigned to either atomoxetine or placebo-treated group. The same day, the drug was dispensed as a 7±2 day supply, with a total of 9 capsules in each container to allow for delayed visits.

Subjects were instructed to return for follow-up after a one-week (±2 days) period and bring the container and the rest of the pills (if any). Participants were also instructed about the administered daily dose of the atomoxetine, with each subject receiving 40 mg once a day.

All subjects were provided with the Alberta Alcohol and Drug Abuse Commission (AADAC) information and brochures about support services and self-help groups for individuals who are in the process of quitting smoking.

Subjects were also instructed that the follow up visit would be held every seven days (±2 days) during the 21-day treatment period. Thus, each subject had 3 additional follow-up visits (Day 7=Week 1, Day 14=Week 2, Day 21=Week3).

Participants were advised to report all side effects to the study medication and reminded that they were free to drop out of the study at any time if they wish.

3.6.3. Follow up visits (Day 7=Week 1, Day 14=Week 2)

At Day 7 and Day 14 visits, the following questionnaires were used in order to evaluate changes in:

- Severity of nicotine dependence - utilizing the Cigarette Dependence
- Withdrawal symptoms - utilizing the Cigarette Withdrawal Scale
- Smoking urges and craving - utilizing the Questionnaire for Smoking Urges
- Depression symptoms - utilizing the Montgomery-Åsberg Depression Rating Scale
- Level of self-esteem - using the Rosenberg Self-Esteem Scale

Participants underwent a repeat physical exam that included measurement of vital signs (blood pressure, pulse, temperature) and weight.

Saliva cotinine test was repeated to monitor compliance and to verify self-reporting of smoking.

The Patient Visit Form (see Appendix 10. Patient Visit Form) and Adverse Event Form (see Appendix 15. Adverse Event Form) were filled out,

the Self-Monitoring Dairy was collected and a new one was provided for the next week. Participants were instructed to fill out the dairy every day and return it during the next follow-up visit.

Atomoxetine was dispensed as a 7±2 day supply, with a total of 9 capsules in a container to allow for delayed visits (see Appendix 16. Dispensation/Compliance Form). Subjects were again instructed to return for follow-up after a one-week (±2 days) period and bring the container and the rest of the pills (if any). Participants were also instructed to report all side effects occurring during the interval between study visits.

3.6.4. Final visit (Day 21=Week 3)

At Day 21, the following questionnaires were administered in order to evaluate changes in:

- Severity of nicotine dependence - utilizing the Cigarette Dependence Scale
- Withdrawal symptoms - utilizing the Cigarette Withdrawal Scale
- Smoking urges and craving - utilizing the Questionnaire for Smoking Urges
- Depression symptoms - utilizing the Montgomery-Åsberg Depression Rating Scale
- Level of self-esteem - using the Rosenberg Self-Esteem Scale

Participants underwent a final physical exam that included measurement of vital signs (blood pressure, pulse, temperature) and weight.

The saliva cotinine test was repeated to monitor compliance and verify self-reporting of smoking.

The Patient Visit Form and Adverse Event Form were filled out; the Self-Monitoring Dairy was collected.

Participants were also instructed to report any events that occurred within the subsequent 2 weeks following the last dose of study medication.

3.7. COMPLIANCE

Study medication was dispensed for a first time at baseline visit (Week 0) to each study participant. During weeks 1, 2, and 3 the number of tablets returned (if any) was recorded in the Dispensation/Compliance Form (see Appendix 16.Dispensation/Compliance Form).

Self-reporting was used as a method to monitor medication compliance. In situations where pills were returned or treatment interruption occurred, volunteers were interviewed and the reasons such as relapse or adverse event were recorded.

3.8. CONCOMITANT TREATMENT

During the screening visit each participant was questioned about current use of medications, over-the-counter drugs, herbal remedies and supplements.

Information was recorded in the Concomitant Medication Form attached to each individual participant's file (see Appendix 14. Concomitant Medications).

At the baseline visit of each study participant, possible side effects associated with atomoxetine treatment particularly were explained in detail, as well as the potential risks of combining atomoxetine with other drugs. Participants were instructed that in case of a new drug initiation or emergency situation they needed to inform their family physician, or any other medical practitioner, that they are currently participating in a double-blind randomized placebo-controlled trial with atomoxetine.

After the screening visit each recorded concomitant medication was checked to ensure that they would not produce drug-drug interactions with atomoxetine and were not considered to be a contraindication for the use of atomoxetine. In any situations of uncertainty, the co-investigator discussed this information with the primary investigator, and if approved, patients were phoned back and informed that they can continue with their participation.

3.9. EFFICACY ASSESSMENT

Several measurement tools were used to evaluate the effectiveness of the study drug.

3.9.1. Primary endpoint

The number of subjects remaining abstinent from cigarette smoking for a twenty-one day period compared to the placebo treatment.

3.9.2. Secondary endpoints

- Changes in frequency and severity of withdrawal syndromes comparing to the baseline measurement in cigarette smokers of both groups
- Changes in craving and smoking urges compared to the baseline measurement in both treatment groups
- Any correlation between success at stopping smoking during the study and alleviation of withdrawal symptoms observed during the treatment period.
- Percent of adverse events among cigarette smokers in both treatment groups.

3.9.3. Methodology for the assessment of baseline status, the progress and study outcomes.

3.9.3.1. Collection of baseline and follow-up information

The collection, analysis and interpretation of the information gathered during the study are the primary purpose in a research project.

We based our approach on previously published information, and relied upon standardized widely-used measurements. Thus, we chose to utilize several commonly-used questionnaires as well as a self-monitoring dairy to allow the study results to be comparable with other available research information.

Measurement instruments were selected taking into consideration the following characteristics: sensitivity, specificity, validity, reliability, reflection of DSM-IV criteria, ease and convenience of use in both clinical and research settings, and that they were widely reported in literature as a standardized measurement.

Similarly, previously published information was reviewed to determine current recommendations regarding the specificity of the assessment for nicotine dependence, nicotine withdrawal and craving, and other aspects such as the frequency of follow-ups and type of the assessment. Following this review it was determined that the best approach was the utilization of multiple-item instruments with weekly follow-up periods. (Shiffman et al., 2004; Hughes et al., 2003).

We therefore employed five standardized self-reporting questionnaires (QSU, SES, CDS, CWS, and self-monitoring dairy) which had the advantages of simplicity of use, feasibility, and applicability in many settings. The advantages and disadvantages of each instrument had to be considered, and these are discussed for each measurement tool we used.

3.9.3.2. Outcome assessment

Outcomes in smoking cessation studies can vary according to the goals and objectives of each particular trial. Many outcome measure have been proposed to evaluate the efficacy of interventions for quitting smoking (Hughes et al., 2003), and, it is still arguable what measures are important, reliable and should be recommended for use in these types of trials.

In terms of objectivity/neutrality of the outcomes, we found that some researchers believe that subjective methods such as self-reporting are valid outcome measures and can be employed independently, while others prefer to employ objective measures such as biochemical validation (Velicer et al., 1992).

From our point of view, we believed the most advanced approach is when both methods are combined. Previous studies have also concluded that the results tend to yield more correct information about outcomes and subjective measures when a combination of both outcome measures occurs (Stevens & Munoz, 2004).

In addition, others have shown that three out of four self-reporting outcome measures yield similar results (Velicer & Prochaska, 2004). It is widely agreed that when several outcome measures are evaluated simultaneously, it allows more accurate conclusions about abstinence in study subjects to be made (Velicer et al., 1992; Hughes et al., 2003; Stevens & Munoz, 2004).

Thus, to assure the greatest level of accuracy for the outcome measurements in our study we combined self-reported questionnaires and a self-monitoring dairy with objective measurement of a biological marker for smoking, namely the cotinine saliva test.

Outcomes in smoking cessation studies can vary greatly in part because of variability in the number of lapses and relapses. One can also raise the question of how to define "failure" in a smoking cessation study. As our study was pilot project, we expected lapses and even failures to occur as the outcomes.

Failure is defined as the outcome that is different from the goals of the study treatment (Hughes et al., 2003). The definition of failure varies between studies and ranges from complete abstinence ("not-even-a-puff") to continuous smoking for 2 consecutive weeks. Clearly, these are large differences. In the latter case, such smoking characteristics as number of cigarettes, smoking

frequency and its duration are considered to help define if a treatment is considered a "failure". Nonetheless, a review found no differences, at least in terms of effect sizes, for various thresholds defining failure (Hughes et al., 2003).

After consideration we decided to use the relapse definition from the U.S. National Heart Blood and Lung Institute (NHLBI) which defines relapse as any smoking on seven consecutive days. This criterion has been among the most widely used criteria employed in studies on smoking cessation and, consequently, was recommended by reviewers for the employment in smoking cessation trails (Hughes et al., 2003).

To help allow us to determine whether or not patients were "failures" in terms of the outcome measures we utilized the cotinine saliva test as an objective measure of the study outcome and self-reporting verification tool.

We also clearly realized that the advantage of complete abstinence is that it can be verified though the use of biomarkers such as cotinine. However, it should be realized that if other "slips-allowed" definitions are used the failure cannot be biochemically verifiable as lapses are allowed. In the case when subjects report no smoking, except on the day before and the day of follow-up, he/she would not meet the NHLBI criterion for failure and thus would be considered a success, even though they would produce a positive biochemical value.

3.9.3.3. Methodology of the determination of severity of smoking dependence and withdrawal

Determination of the severity of nicotine dependence and nicotine withdrawal was done using standardized scales. Analysis of literature showed that the scales mentioned below are widely used, well validated and reliable. The following three scales were therefore employed in this study to determine severity of smoking dependence and withdrawal symptoms:

- Severity of nicotine dependence was assessed by utilizing the Cigarette Dependence Scale
- Severity of withdrawal symptoms was assessed by utilizing the Cigarette Withdrawal Scale
- Severity of smoking urges and craving was assessed by using the Questionnaire for Smoking Urges

3.9.3.3.1 The Cigarette Dependence Scale (CDS)

The Cigarette Dependence Scale-12 was developed in 2003 as a self-administered scale to measure cigarette dependence (Etter et al., 2003). This 12-item questionnaire was created to reflect not only the main components of nicotine dependence syndrome captured by DSM-IV and ICD-10, but also to incorporate other aspects that are not covered by DSM-IV or other commonly used questionnaires (Etter et al., 2009). It was also intended to measure the intensity of any dependence to nicotine.

There are other scales that have been used commonly such as the Fagertrőm Test for Nicotine Dependence (FTND) and the Nicotine Dependence Syndrome Scale (NDSS). However, there are three major reasons why the CDS-12 was used in the current study. Firstly, the CDS-12 has a higher test-retest reliability, had greater internal consistency, and has stronger associations with age and craving compared to the FTDN (Etter et. al., 2003). Secondly, it has been shown that the Nicotine Dependence Syndrome Scale (NDSS) has at least three items for which the reliability coefficient is significantly lower than for the CDS-12 (Courvoisier & Etter, 2008). Thirdly, it has been shown that CDS-12 scores are strongly associated with the objective measurement of cotinine levels in saliva (Etter et al., 2003). Moreover, when compared to other scales CDS-12 had the best predictive validity (Courvoisier & Etter, 2010).

Before the study was initiated, permission was granted by the author of the CDS-12 to use the scale in the present study.

3.9.3.3.2. The Cigarette Withdrawal Scale (CWS)

Introduced by Etter and colleagues in 2004, the Cigarette Withdrawal Scale (CWS) has been shown to be a reliable and valid self-reporting tool to assess cigarette withdrawal symptoms. The scale is a 21-item, six-dimension instrument: depression-anxiety, craving, irritability-impatience, difficulty concentrating, appetite-weight gain and insomnia (Etter & Hughes, 2006).

The CWS possesses three main advantages over other existing scales. Firstly, it includes six subscales that incorporate the main components of

nicotine dependence and tobacco withdrawal reflected in DSM-IV and ICD-10. Secondly, it has been shown to predict relapse among smokers. Thirdly, it has been shown to be sensitive to changes over time (Etter et al., 2005).

The scale was demonstrated to be analogous in its psychometric properties (reliability and validity) to other popular cigarette withdrawal scales such as the Minnesota Withdrawal Form (MWF) and the Wisconsin Smoking Withdrawal Scale (WSWS) (Etter & Hughes, 2006). However, it is briefer than the WWS and is more reliable than single-item MWF scales (Etter, 2005).

Before the study was initiated, permission was granted by the author of the CWS to use the scale in the present study.

3.9.3.3.3. The Questionnaire for Smoking Urges (QSU)

As craving is considered a major symptom during nicotine withdrawal, and is viewed as a predictor of relapse (Cox et al., 2001), it is important to measure this aspect. For this reason a 10-item version of the Questionnaire for Smoking Urges (QSU) was utilized to measure the intensity, duration and frequency of craving for smoking in the study subjects.

The QSU was developed in 2001 as a short version of a previously created 32–item questionnaire, and has became a widely employed self-reported tool for measurement of smoking urges (Cox et al., 2001; Toll et al., 2006; Toll et al., 2004). The 10-item version was shown to possess internal consistency of data regarding different stages of smoking and good reliability for the desire to

smoke. Moreover, the 10-item scale was shown to reflect the multidimensional character of craving (Toll et al., 2006).

Comparative research study also revealed that QSU is sensitive to withdrawal symptoms and, in comparison with other commonly used scales, has a high test re-test reliability compared the Shiffman Scale, greater sensitivity compared to the Minnesota Nicotine Withdrawal Scale, and, as concluded by authors, analogous sensitivity to abstinence compared to both the Shiffman Scale and the Minnesota Nicotine Withdrawal Scale (West & Ussher, 2009).

3.9.3.3.4. The Montgomery-Åsberg Depression Rating Scale (MADRS)

Many studies have found a strong association between depressive symptoms and smoking (Brownell et al., 1986; Gehricke et al., 2007; Gullion et al., 2007). Depressed mood has been shown to serve as a risk factor for smoking initiation, maintenance (Stevens et al., 2005; Gehricke et al., 2007) and less successful recovery from this habit (Gehricke et al., 2007). It has also been reported that negative affects, including depressive mood, can predict relapse in smokers (Swan et al., 1996; West et al., 1989; Brownell et al., 1986).

Depressed mood is also considered to be one of the key characteristics of nicotine withdrawal syndrome, as well as an important symptom for monitoring of abstinence progress (Shiffman et al., 2004a; West et al., 1984).

Therefore, in our research we decided to examine the presence of mood changes/fluctuations in study participants, as well as the influence of mood on the craving experienced during nicotine withdrawal.

Currently there are many scales employed for the assessment of depressive symptoms in the patients in both clinical and research settings, although only three are considered to be superior to other instruments, especially when response to antidepressant treatment needs to be assessed: the Montgomery-Åsberg Depression Rating Scale (MADRS), the Hamilton Rating Scale for Depression (HAM-D) and the Beck Depression Inventory (BDI) (Lenderking et al., 2008).

In our research, the Montgomery-Åsberg Depression Rating Scale (MADRS) was utilized because of advantages it has over the other two.

The Montgomery-Åsberg Depression Rating Scale (MADRS) was developed in 1979 mainly with the purpose of measuring overall severity of depressive symptoms and their changes during antidepressant treatment (Davidson et. al., 1986; Svanborg & Åsberg, 2001). Additionally, existing problems with the currently available scales, particularly the Hamilton Rating Scale for Depression (HAM-D), provided another reason.

All three scales measure depressive symptoms reliably, although are of different lengths. The MADRS is a10-item scale compared to the Hamilton Rating Scale for Depression which can be 17 or 21items, and the Beck Depression Inventory which has 21items. The scores of the MADRS are highly correlated with scores from both the Hamilton Rating Scale for Depression (HAM-D) and the Beck Depression Inventory (BDI) (Montgomery & Åsberg, 1978; Svanborg & Åsberg, 2001). Moreover, the validity of the MADRS was found to be very similar to that of the HAM-D (Davidson et al., 1986).

Additionally, there are problems with the HAM-D, which include its length, the scale and the scope of diagnostic symptoms it measures, its poorer test-retest reliability, and its reliance on physical symptoms (Lenderking et al., 2008).

The MADRS is also considered to be superior to the Beck Depression Inventory (BDI) because of the more comprehensive coverage of core symptoms of depression such as sadness, inner tension, lassitude, pessimism and suicidal thoughts in adults (Svanborg & Asberg, 2001).

The MADRS was shown to be reliable when used by various health care workers; the inter-rater reliability was comparable to that found between psychiatrists (Åsberg et al., 1978; Montgomery and Åsberg, 1978).

3.9.3.4. The Rosenberg Self-Esteem Scale (SES)

According to a widely respected model of development, self-esteem is a personal factor that influences adolescent risk behaviour (Neumark-Sztainer et al., 1997). For a number of reasons we believe that it is important to measure self-esteem in this study.

Self-esteem can be characterized as an attitude, perception, understanding and evaluation of an individual's attributes, qualities and abilities that can range from being satisfied to unsatisfied with these personal characteristics (Kawabata et al., 1998; Guillon et al., 2007). Many studies demonstrated that self-esteem can be in a reciprocal relationship with other

personal, socio-environmental and behavioural factors (Neumark-Sztainer et al., 1997).

It was shown that self-esteem impacts the adaptational abilities of individuals to changes in the surrounding environment, although studies have been somewhat inconsistent regarding how self-esteem shapes person's abilities to cope with stressful situations or threats to an individual's self-image. In some situations, self-esteem can serve as either risk factor, while in others it serves as a protective mechanism (Gibbons et al., 1997; Wild et al., 2004). It is well recognized that adolescence is a transitional period, and is associated with an increase in risk behaviours including drinking, cigarette smoking, drug use, and early sexual activity (McGee & Williams, 2000).

Smoking is the third most common health compromising behaviour in female adolescents, after eating problems and alcohol use. It is the fourth most common health compromising behaviour in male adolescents after alcohol, sexual activities, and cannabis use subsequently (McGee & Williams, 2000).

Several studies have shown a strong association between low self-esteem and substance abuse (Neumark-Sztainer et al., 1997; Donnelly et al., 2008) in general, and smoking in particular (McGee & Williams, 2000). It was also suggested that low self-esteem might influence smoking habits by being an independent determinant of smoking initiation among adolescents (O'Loughlin et al., 2009; Carvajal et al., 2000; Kawabata et al., 1998). It can be associated with higher smoking rates in this age category (Martinez Maldonado et al., 2008) and can help to distinguish smokers and non-smoking adolescents (Guillon et

al., 2007). It is also noteworthy that self-esteem is variable over time, and it can impact motivation for poor health behaviours (McGee & Williams S, 2000; Wild et al., 2004).

In fact, there may be a reciprocal relationship between negative experiences such as smoking, and lowered self-esteem (Neumark-Sztainer et al., 1997; Donnelly, et al., 2008). Indeed, it has been suggested that there is a strong relationship between cigarette smoking and self-esteem (Jones & Hartmann, 1985). Another study found similar results showing less school competency among students who ever smoked, used alcohol or other drugs compared to those who never had this experience (Emery et al., 1993). However, it was difficult for the authors to conclude any clear causal relationships between smoking and low-self esteem due to the cross-sectional nature of the study.

Although there have been no studies to date examining the relationship between low self-esteem and susceptibility to relapse, nonetheless studies which have targeted an improvement in self-esteem have been shown to be beneficial during smoking cessation (Kawabata et al., 1999; Carvajal et al., 2000; Donnelly et al., 2008; Emery et al., 1993).

Given the strength of the literature suggesting that lowered self-esteem may impact smoking in a number of ways it thus seems prudent to evaluate changes in self-esteem for study participants in smoking cessation trials.

To measure the level of self-esteem, the Rosenberg Self-Esteem Scale was employed in the study. This instrument was developed by Rosenberg in 1989 to assess self-reported feeling of self-worth or self-value. According to

Maryland University, where Dr. Rosenberg worked, the scale has been commonly employed in various studies mainly in treatment outcome trials (http://www.bsos.umd.edu/socy/Research/rosenberg.htm).

The Rosenberg Self-Esteem Scale is an easily administered, brief, self-report questionnaire that consists of 10 items reflecting self-esteem. The scale has been translated into many languages (Dittmann et al., 2009) and is commonly utilized in treatment outcome studies (http://www.emcdda. europa.eu/html.cfm/index3676EN.html).

The Rosenberg Self-Esteem Scale is considered a reliable instrument that has been validated across a variety of age groups, in both genders, in different languages, and for diverse clinical groups including substance abusers (Dittmann et al., 2009; http://www.emcdda.europa.eu/html.cfm/index3676EN.html).

Permission to use the Self-Esteem Scale for educational and professional research was obtained from the website of the University of Maryland. This permission was given by the wife of the late Dr. Rosenberg (http://www.bsos.umd.edu/socy/Research/rosenberg.htm).

3.9.3.5. Self- monitoring diary

A Self-monitoring diary was employed in the study as a self-reporting tool that allowed investigators to fulfill several goals:

Using the diary allowed prospective information to be obtained about the withdrawal period for study subjects in general. This also provided an opportunity to gather data about the presence of any lapses as well as various

factors associated with them such as situational changes, mood, changes in cravings, and the amount and frequency of any smoking.

Additionally, the dairy allowed collecting consistent data between study visits. As the intervals between visits were 7 ± 2 days, the collection of continuous information recorded regularly by participants on a daily basis between study visits was important for analysis of study outcomes.

Lastly, self-reporting of symptoms during withdrawal allows a more accurate determination of whether a subject is a study "failure" according to the criteria outlined earlier.

The Self-monitoring diary was given to each study subject at every visit starting from the baseline visit.

3.9.3.6. Cotinine

Analysis of cotinine in saliva was utilized in the current study based upon recommendations made in previous studies examining the best research methods to measure smoking cessation (Velicer et al., 1992; Stevens & Munoz, 2004). It has been noted by many authors that the accuracy of using self-reporting methods alone to measure cessation is very problematic, and studies should use a combination of both self-reporting and biochemical measurements, preferably cotinine (Velicer et al., 1992; Stevens & Munoz, 2004; Gorber et al., 2009; Paek et al., 2009).

The pharmacokinetic and pharmacodynamic properties of nicotine and its metabolites have been well studied. Below we review the attributes of cotinine

that make this particular metabolite of nicotine a preferred biomarker for nicotine exposure.

3.9.3.6.1. Pharmacokinetics of cotinine

When inhaled, nicotine is quickly absorbed by the human body and appears in the blood stream within seconds. Nicotine is metabolized by the liver which leads to the production of its six primary metabolites, including cotinine (Benowitz et al., 2009).

Cotinine is considered to be the major metabolite and accounts for approximately 75% of all biproducts of nicotine's metabolism (Hukkanen et al., 2005; Benowitz et al., 2009).

The blood concentration of cotinine (250-300 ng/ml) on average is much higher than that of typical peak concentration of nicotine, 19-50 ng/ml (Benowitz et al., 2009), with the average half-life of cotinine (16-17 hours) being on average about 14 hours longer than half-life of nicotine (2 hours) (Hukkanen et al., 2005).

As in the case of nicotine, in human adult subjects cotinine was shown to be mainly metabolized through CYP2A6. Therefore, drugs and foods that are converted though the same pathway of enzymes influence metabolism of both nicotine and cotinine (Benowitz et al., 2009). The metabolism rate of cotinine is slower than that of nicotine and is influenced by very similar factors as the metabolism of nicotine. These factors are related to:

1) Characteristics of the smoker including age, gender, race, BMI and body composition, body organ functions, and genetic variation of liver enzymes (McCarty et al., 1992; Hukkanen et al., 2005; Benowitz, 1996; Roethig et al., 2009; Benowitz et al., 2009; Benowitz et al., 2008);
2) Characteristics of consumed cigarettes: the brand, the length of cigarette, ingredients, and delivery system (McCarty et al., 1992; Hukkanen et al., 2005);
3) Smoking patterns: smoking rate and topography (for example, puff duration and volume, frequency of inhalation and retention time and etc.) (McCarty et al., 1992);
4) Diet and physical activities of the smoker (McCarty et al., 1992; Benowitz et al, 2009);
5) Simultaneous consumption of medications and illicit drugs by the smoker (Hukkanen et al., 2005; Benowitz et al., 2009).

Approximately 12% of cotinine is excreted by the kidneys in an unchanged form, while the rest is transformed into various metabolites of cotinine. Cotinine is filtrated in the kidneys with the glomerular filtration rate exceeding the level of renal clearance of cotinine. Cotinine is extensively absorbed in renal tubules because only 5% of it is protein-bound. Renal excretion of cotinine can be influenced by urinary pH, disturbed renal clearance and urinary flow rate (Benowitz et al., 1982; 2009a).

3.9.3.6.2. Cotinine versus other biomarkers of nicotine exposure

We reviewed various literature sources to determine what biomarker(s) would best reflect the tobacco smoke exposure.

Biomarkers are defined as exogenous substances or their metabolites that can be measured in various body tissues or fluids or products of metabolism (such as exhaled air) of study subjects and are then used to infer information about changes in the body (Jaakkola & Jaakkola, 1997; Florescu et al., 2009). Consequently, biomarkers represent a spectrum that reflects the impact on the body, and incorporates biomarkers of exposure, biologically effective doses, and those suggesting potential harm or outcome (disease) (Shields, 2002).

Moreover, the higher the values of specificity and sensitivity of tests with particular biomarkers, the higher the reliability of that biomarker (Jarvis et al., 1987). Thus, we found the comparison of four biomarkers that revealed high specificity and sensitivity of cotinine as a biomarker for discriminating true smoking status (Table 3.1).

Due to nature of our study we wanted to evaluate the most commonly studied biomarkers of mainstream smoke, which is directly inhaled by cigarette smokers (Jaakkola & Jaakkola, 1997). Knowing that mainstream smoke contains numerous gaseous (carbon monoxide, nitrogen oxides, formaldehyde, benzene, pyrene, phenantrene, acetone, hydrogen cyanide) and particle (particulate matter, cholesterol, anabatine, nicotine, phenol, benzopyrene and benzoanthracene) components (Scherer et al., 1990; Smith & Fischer, 2001), a number of substances have been suggested as useful biomarkers of tobacco smoke uptake.

These include tobacco alkaloids, their metabolites, carbon monoxide, thiocyanate, carboxyhaemoglobin, and tobacco-specific nitrosamines (Hatkusami et al., 2003; Benowitz et al., 2009; Roethig et al., 2009; Florescu et al., 2009).

Table 3.1. Optimum Cut off, Sensitivity, and Specificity Values for Each Marker in Discriminating True Smoking Status

Chemical marker	Cut off value	Sensitivity(%)	Specificity(%)	95% CI for % accuracy
Carbon monoxide				
ECO (ppm) [1]				
COBh (%)[2]	8	90	89	86.2-91.7
	1.6	86	92	83.0-89.2
Nicotine				
Plasma (ng/ml)	2.3	88	99	89.4-93.8
Saliva (ng/ml)	21.8	90	99	91.6-95.2
Urine (ng/ml)	58.6	89	97	93.3-96.3
Cotinine				
Plasma (ng/ml)	13.7	96	100	98.3-99.1
Saliva (ng/ml)	14.2	96	99	98.5-99.3
Urine (mg/ml)	49.7	97	99	98.4-99.2
Thiocyanate				
Plasma (mol/L)	78.0	84	91	81.1-87.9
Saliva (mmol/L)	1.6	81	71	66.0-76.0
Urine (mol/L)	118.0	59	89	67.0-77.0

[1]ECO – expired air carbon monoxide; [2]COBh – blood carboxyhemoglobin

Adopted from Jarvis et al., 1987

However, an examination of the literature revealed that cotinine is the preferred biomarker of cigarette smoke exposure in active and even passive smokers, having numerous advantages over other smoke components, including primary alkaloids of tobacco or its metabolic by-products (Dhar, 2004).

It is useful to compare the properties of the primary alkaloid of tobacco (nicotine) with its primary metabolite (cotinine) to evaluate the advantages of cotinine as a biomarker of smoke exposure.

When absorbed into the blood, nicotine undergoes rapid metabolic transformation in the liver. Primary metabolism of nicotine leads to the formation of six main metabolites, of which cotinine constitutes 75%. Oxidation of nicotine leads to the formation of nicotine-N-oxide, which comprises 4 to 7% of all nicotine metabolites, while the glucuronidation pathway produces nicotine-glucuronide that forms 3 to 5% of all nicotine metabolites. 4-oxo-4(3-pyridyl)-butanoic acid is another metabolite that represents approximately 2% of all nicotine metabolites. Finally, nicotine isomethonium ion and nornicotine represent less than 2% of all nicotine primary metabolites together (Kyerematen & Vesell, 1991; Hukkanen et al., 2005). Thus, to determine minute blood concentrations of the primary nicotine metabolites, excluding cotinine, laboratory assays to identify their presence in the human tissues/liquids would be challenging and expensive. Besides, we did not find any studies that identified the above mentioned primary metabolites of nicotine, except cotinine, as biomarkers of nicotine exposure.

Numerous aforementioned factors can influence the metabolism of both nicotine and cotinine. Age is one of them. We found that age extremes (<18 and >69) can have an impact on plasma steady-concentration and clearance of nicotine, although no differences were found between the ages 18 to 69 (Gourlay and Benowitz, 1996; Benowitz et al., 2009). Moreover, the blood half-life of

nicotine was shown to be influenced by age, while the blood half-life of cotinine remained similar in different age groups (Dempsey et al., 2000).

Metabolic properties of both substances are different, even though cotinine is the primary metabolite of nicotine. Several metabolic characteristics of cotinine make it more suitable to be used as a biomarker of nicotine exposure than nicotine itself. For example, slow metabolic rate and a long half-life make the blood concentration of cotinine less variable throughout the day (half-life of cotinine is 16-17 hours vs. 2-3 hours for nicotine) (Benowitz, 1996). Thus, sampling time will influence the cotinine blood concentration to a lesser degree compared to nicotine assays when sampling closely tied to smoking time (Jaakkola et al., 1999; Swan et al., 1993; Bramer & Kallungal, 2003; Hukkanen et al., 2005).

Moreover, higher concentrations of cotinine in the bloodstream makes laboratory tests for the metabolite more sensitive, even when passive exposure occurs, while also making it possible to quantify cotinine in blood. Therefore, in contrast with nicotine assays, cotinine assays are less expensive, more convenient in term of sampling time, as well as more sensitive and specific (Florescu et al., 2009; Watts et al., 1990; Bramer and Kallungal, 2003).

Regarding urine analysis, the determination of cotinine in urine is preferred to urine nicotine assay, as the urinary excretion of nicotine is shorter than that of cotinine (Dhar, 2004).

Many authors reported that cotinine and nicotine can be measured in various body fluids; however, cotinine measurements are more sensitive (Steven

and Munoz, 2004), accurate and specific for nicotine exposure in both active and passive smokers (Jenkins and Counts 1999; Ziegler et al. 2004; Dhar, 2004; Helzer et al., 2007; Jacob et al., 1999; Florescu et al., 2009).

We evaluated available research data on the primary and minor alkaloids of tobacco in order to determine which substance was found to serve better as a biomarker.

Tobacco contains numerous alkaloids. Nicotine is considered to be a principal alkaloid, while nornicotine, anabasine, anatabine, myosmine and metylanabasine are minor ones. Nornicotine is a metabolite and an alkaloid, simultaneously (Benowitz et al., 2009; Hukkanen et al., 2005; Jacob et al., 1999; Jacob et al., 2002).

Several studies described the pharmacokinetic and pharmacodynamic properties of minor alkaloids in humans. However, metabolic properties were mostly described in animals (Hukkanen et al., 2005).

It was shown that the plasma/serum concentration of anabasine, anabatine and nornicotine is significantly lower than that of nicotine and cotinine. Urine concentrations of anabasine and anabatine were also significantly lower compared to that of nicotine and cotinine, regardless of the nicotine delivery route (Jacob et al., 2002). Moreover, the plasma concentration of minor alkaloids is lower than their concentration in urine (Benowitz , 2002; Yue et al., 2010; Jacob et al., 1999). Thus, because of higher urine concentrations and the predominant urinary excretion of minor alkaloids, they are mostly measured in

the urine. Urinary pH has a significant impact on the excretion level of minor alkaloids (Benowitz et al., 2009).

Half-lives of anabasine (16 hours) and anatabine (10 hours) are quite long (Benowitz, 2002) which makes them suitable to be used as biomarkers of nicotine uptake. However, these minor alkaloids are present only in tobacco products, but not in nicotine replacement therapy (NRT) medications which make their utilization limited, especially for validation of self-reporting (Jacob et al., 1999).

Although the sample size was very small, Jacob and colleagues showed that urinary measurements of anabasine and anatabine correlated well with the levels of nicotine intake in active smokers (Jacob et al., 1999). However, in a subsequent study the author demonstrated fair to poor correlations between urine concentration of anabasine, anatabine and self-reported tobacco use in cigarette smokers, although it was mentioned that the correlation is better when smokeless tobacco or nicotine replacement therapy were used (Jacob et al., 2002).

Moreover, on average, the urine concentration of minor alkaloids was two times higher in smokeless users versus smokers. The results allowed the authors to conclude that anabasine and anatabine as biomarkers were better utilized in abstinent smokers treated with nicotine replacement therapy (Jacob et al., 2002) and that these minor alkaloids might be better used for monitoring of treatment with NRT or validating self-reporting smoking in NRT users (Jacob et al.. 1999).

Schutte-Borkovec and colleagues showed that myosmine - one of the minor alkaloids of tobacco - can be measured in various tissues of human body. However, this biomarker is not as specific for tobacco smoke exposure as cotinine and nicotine when measurements of myosmine are compared in nails, plasma or urine samples from both smokers and non-smokers. In addition, the presence of myosmine in various dietary sources may influence the results (Schutte-Borkovec et al., 2009; Shah & Karnes, 2010).

We compared available data on laboratory assays on various smoke components proposed as useful biomarkers of tobacco smoke exposure.

Carbon monoxide is a toxic constituent that can be determined during the gas phase of mainstream cigarette smoking (Roethig et al., 2009; Florescu et al., 2009). Carbon monoxide can be measured in the exhaled air and in the blood as carboxyhemoglobin. Both methods were considered to make a distinction between active smokers and non-smokers (Jaakkola and Jaakkola, 1997). However, each particular assay has some disadvantages that make them less popular compared to cotinine.

The carboxyhemoglobin assay is not favoured due to the invasive nature of the procedure (Stevens and Munoz, 2004), while exhaled carbon monoxide is considered to be most useful as a biomarker of nicotine exposure because when measured in exhaled air it does not undergo metabolic activation (Shields, 2002). Moreover, the assay is simple and non-invasive with almost immediate results. However, the main disadvantages of this method are non-specificity for cigarettes smoking (Shields, 2002), short-half life and diurnal variability of

carbon monoxide that influences sampling time and makes the sensitivity of the assay low in cases of infrequent and/or irregular smoking. Even though expired carbon monoxide and carboxyhemoglobin are highly correlated, environmental exposure, atmospheric pollutions, physical activities and lactose intolerance were shown to influence the levels of carbon monoxide and carboxyhemoglobin (Benowitz, 2002; Gilbert, 1993). The assay was also shown to produce up to 16% false-negative results (Velicer et al., 1992).

Detoxification of hydrogen cyanide present in mainstream cigarette smoke during both gaseous and particulate phases leads to the formation of an end-product called thiocyanate (Galanti et al., 1997). Thiocyanate was also introduced as a biomarker of nicotine exposure. However, despite the long half-life of thiocyanate, the test did not become popular due to the influence of diet and industrial exposure on the level of thiocyanate. Also, the test was shown to have a low specificity in terms of light smoking detection (Gillies et al., 1982; Velicer et al., 1992; Benowitz, 2002) and is considered to be the least reliable biomarker (Gilbert D., 1993). In addition, when compared with cotinine assays regarding the accuracy of smoking self-reporting, thiocyanate measurements in blood and saliva, the thiocyanate test yields less accurate results (Haley et al., 1983).

Nitrosamines are carcinogenic compounds identified in both smokeless tobacco and tobacco smoke. There are three main sources of nitrosamines derived from tobacco. Tobacco-specific nitrosamines are a group of nitrosamines

that were found in tobacco products and tobacco smoke and are not associated with volatile nitrosamines or nitrosamines from agricultural chemicals.

There are seven tobacco-specific nitrosamines that serve as biomarkers of exposure. These are found in the particulate phase of mainstream smoke. Two of the tobacco-specific nitrosamines, NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) and NNN (N'-nitrosonornicotine), have been studied extensively and are described as the most prevalent strong carcinogens (Shields, 2002; Shah and Karnes, 2010).

NNK, NNN and their metabolites have been quantified in various body tissues and fluids; however, plasma measurements were most frequently applied in clinical studies and reported as the most suitable assays for these substances. Although the testing method is invasive and expensive compared to the cotinine saliva test that we chose for our study, its main disadvantage is related to the poor correlation between smoke exposure and the levels of NNK and its single metabolite (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) (Shepperd et al., 2009).

Several assay methods have been mentioned in reviews, although the validity and reliability of them are still questionable (Shah and Karnes, 2010). Shah and Karnes indicated that there are many challenging aspects that need to be resolved through further studies in order to conclude any preferable biological matrices, effective and reliable analytical techniques, commonly agreed unit measurements, and other aspects that make recent information about bioanalysis of nitrosamines inconclusive and vague (Shah and Karnes, 2010).

Thus, summarizing the data about potential biomarkers for smoke uptake, we observed that they mostly posses less advantages when compared to cotinine. Moreover, the assays that are utilized for these substances are technically demanding and time consuming (Bramer and Kallungal, 2003).

Thus, there is evidence that cotinine would be a better biomarker of smoke uptake due to the specificity of its pharmacokinetic and metabolic properties. We reviewed the literature about biological mediums that would be most appropriate for cotinine measurements.

Cotinine was shown to be detected in diverse body fluids such as urine, serum, (Etzel et al., 1990), cervical mucus (Binnie et al.. 2004), semen (Vine et al., 1993) saliva (Jenkins and Counts 1999; Dhar 2004; Montalto & Wells, 2007) in addition to amniotic fluid, infant meconium and urine (Kohler et al., 2010; Gorber et al., 2009) as well as in nails and hair (Benowitz et al., 2009). Cotinine concentrations from a variety of different sources, including urine, blood and saliva, have been shown to be highly correlated with each other (Gorber et al., 2009) and therefore any of these measurements can be used. The measurements of cotinine in these mediums and in semen were shown to be correlated in both passive and active smokers (Bramer and Kallungal, 2003). However, according to the review completed by Gorber and colleagues, the most consistent sensitivity was found in studies with saliva assays (86%), followed by studies that analysed cotinine in blood (76%) and, finally, in trials that used urine as a medium to measure cotinine level (75%) (Gorber et al., 2009).

Saliva cotinine assay was found to be a reliable alternative to plasma cotinine for the validation of smoking status (Haley et al., 1983; Gorber et al., 2009), as well as being useful in distinguishing between active smokers and non-smokers (Binnie et al., 2004; Bramer and Kallungal, 2003).

In addition to the assay per se, the convenience, the simplicity, the cost, the time and the invasiveness of the test are also components that were weighed considerably in determining the most suitable medium selection. For all these reasons, in the current study salivary cotinine levels were used.

To obtain a saliva sample is more convenient for study subjects, relatively quick, and the performance of the assay is simple compared to blood and urine tests. A saliva cotinine test lacks the biological hazard risks that are associated with blood test. Moreover, blood samples are costly to obtain. Usually assays with blood and urine as the medium are more expensive and time consuming.

Other body fluids and tissues, such as amniotic fluids, semen, cervical mucus and spinal fluids (Dhar P., 2004) were used for assessing the concentration of cotinine; however, the tests require special equipment and training, and are time-consuming and invasive.

According to the latest systematic review on the relationship between self-reported and cotinine-assessed smoking status conducted by Gorber and colleagues, a majority of recent research studies utilized the measurement of cotinine in saliva compared to urine and blood. It appears that the saliva cotinine assay becomes the matrix of choice due to its non-invasiveness, relative

simplicity, and convenience (Gorber et al., 2009; Binnie et al., 2004; Berny et al., 2002).

The data regarding which saliva assay would be best in terms of convenience, simplicity, cost, and time required for analysis was also evaluated.

Different assay methods can be utilized to measure the concentration of cotinine in saliva: colorimetry, chromatography, enzyme-linked immunosorbent assay (ELISA), and radioimmunoassay (RIA) (Dhar, 2004;).

Analysing the numerous pros and cons of each specific assay are summarized by Dhar , it is clear that advantages and disadvantages of each test can be related not only to the properties of the assay per se, but also depend on the analysed medium and the task that researcher wants to investigate. Therefore, the choice of the analytical technique will depend on the goal of the study. For example, colorimetry, which is analytical method that uses color reagents to determine the concentration of the chemical compounds in a solution (Housecroft and Constable, 2006),was deemed not to be an ideal method to monitor exposure to environmental tobacco smoke, although it can provide extensive information about the total metabolites of nicotine while being a simple and inexpensive method (Dhar, 2004).

Taking into account characteristics of each assay method related to the cost, the simplicity, the convenience and time required for obtaining results, quick chromatographic methods like the strip test seem to be the technique of choice for studies like ours.

Chromatography is a laboratory technique that measures the quantity of analytes in the biological fluids by separation of analyzed components that distributed between two phases. when chromatography methods is classified with regards to the physical state of mobile phase There are two subtypes of this method: gas and liquid chromatography (IUPAC Nomenclature for Chromatography, IUPAC Recommendations 1993). These chromatographic assays were reported to be a very sensitive and specific method that utilizes inexpensive reagents that do not require any laboratory equipment. Relative to the colorimetric method, the chromatographic process is much more sensitive in terms of cotinine quantification in saliva (0.1 ng ml^{-1}) compared to colorimetry (100 ng ml^{-1}). In addition, the colorimetric method analyses nicotine and its metabolites displaying results as "cotinine equivalents" which makes results less accurate (Gilbert et al, 1993).

In contract to RIA and ELISA, some chromatography processes are less time consuming and do not need to be processed in the laboratory. Moreover, ELISA, being a very accurate and sensitive method, was shown to be less specific than chromatography (Watt et al, 1990; Wielkoszynski et al, 2009). The chromatography based script tests require a very brief training session on how to perform the test and analyze the results; they are also significantly more cost effective than assay methods done in laboratories.

In our study the NicAlert™ Saliva Nicotine Test was chosen for assessment of cigarette smoke exposure and to confirm accuracy of self-reporting by study subjects. We found two studies that demonstrated the

NicAlert™ test as a valid, highly sensitive and specific method to determine self-reported smoking status as well as to distinguish between active and passive smokers (Montalto and Wells, 2007; Helzer, 2007). Cooke and colleagues also reported that the NicAlert™ test is valid and reliable when compared with the more costly and time-consuming gas-chromatography technique (Cooke et al., 2008). One of the important advantages of this assay is that the test is very simple and requires no training to complete.

The NicAlert™ test, as indicated by the manufacturer, is the first saliva-based assay in the world. The test utilizes at the point of contact, a chromographic lateral flow strip device that is highly sensitive to cotinine and can detect 6 ranges of cotinine concentrations in saliva within 15 minutes. Each strip is divided into six reactive chromo-graphic (color change) zones that can detect cotinine in a semi-quantitative fashion. Results are visibly obtained and are presented as 6 levels according to concentration of cotinine: level 0: 1-10 ng/ml, level 1: 10-30 ng/ml, level 2: 30-100 ng/ml, level 3: 100-200 ng/ml, level 4: 200-500 ng/ml, level 5: 500-2000 ng/ml, level 6: 2000+ ng/ml.

Unfortunately, we did not find detailed information whether these levels of cotinine correspond to the number of smoked cigarettes. However, we found some information summarized by Bramer and colleagues, describing that saliva cotinine level less that 5 ng/ml typical for passive smokers, between 10 and 100 ng/ml noticed in infrequent active and regular active smokers with low nicotine intake, while saliva cotinine level more than 100 ng/ml likely indicates regular active smoking (Bramer et al., 2003). Moreover, Blackford and colleagues

analysed csaliva cotinine in light and regular smokers from different countries and demonstrated that saliva cotinine level in light smokers who smokes between 13.8 and 18.5 cigarettes a day is between 140.6 and 225.3, while in regular smoker who smoke between 17.5 and 20.6 cigarettes per day saliva cotinine level was 188.4 and 249.1 ng/ml (Blackford et al., 2006).

3.9.3.6.3. Protocol of the determination of cotininte in saliva (NicAlert test procedure)

A test was performed according to the manufacturer's instructions.

Materials

Specimen: Saliva

Saliva collection kit: funnel for saliva deposit, 2 ml saliva collection container, snap top for the saliva tube container

Accutest ® NicAlert ™ Strip test

NicAlert Saliva testing card

Gloves

Storage

Accutest ® NicAlert ™ Strip test were stored in a special pharmaceutical storage room at the Northern Alberta Clinical Trials and Research Centre at the required temperature and out of direct sunlight in sealed foil pouches, as specified by the manufacturer.

Specimen collection

The study subject was asked to provide his/her saliva into the funnel device until the collection container was filled at least one third with saliva. Then the funnel was removed from the collection container and its larger open end was plugged with a stopper.

Saliva was handled as if potentially infectious or biohazardous. The obtained saliva was stored at room temperature and analysed within 15-30 minutes after collection.

Cotinine saliva assay procedure

After confirming the expiration date on the package, the NicAlert™ strip test device was properly positioned on a dry flat surface of NicAlert Saliva testing card with the numbered levels facing up.

- Eight drops of saliva from the collection container was squeezed on an absorbent cotton wick end of the test strip until the wick end was completely saturated and visible sample migration across the test strip was noticed with results appearing on the panel.

- The strip was left to rest until the red area transferred up into the white area above it and red bands appeared. After approximately 20 minutes, when the blue band disappeared and the test readings were fully developed, test results were observed and the scoring level was recorded in the subject's file.
- Test results were interpreted according to the following table (Table 3.2) that was developed by the manufacturer to assist in the interpretation of the result and in obtaining the appropriate concentration range for cotinine in the saliva of study subjects:

Table 3.2. Cotinine equivalents for each level.

Level	Cotinine Equivalent (ng/ml)
0	1 - 10
1	10 -30
2	30 – 100
3	100 – 200
4	200 – 500
5	500 – 2000
6	>2000

Source: Accutest ® NicAlert ™ Nicotine/Cotinine Lateral Flow Type Chromographic Assay using Human Saliva. Instruction.

3.10. ETHICS AND REGULATORY APPROVALS

Approval for study implementation was obtained from Health Canada on October 20, 2009.

The study protocol, Information Sheet and Consent Form, investigator documents such as questionnaires and recoding forms were submitted to the

Health Research Ethics Board (Biomedical Panel) of the University of Alberta in accordance with local regulations. Additionally, Administrative and Operational approvals were obtained from Alberta Health Services. Health Ethics Research Board approval was received on November 13, 2009. The study was initiated on March 1, 2010 and subject recruitment was finished on 30 October 2010.

The study was conducted in compliance with the protocol, Good Clinical Practice guidelines and the applicable regulatory requirements. The study was also performed in accordance with the ethical principles summarized in the Declaration of Helsinki (1964) revised in Tokyo in 2004 (Appendix 11. The Declaration of Helsinki).

3.11. STATISTICAL ANALYSIS

The proposed analysis included a calculation of means of the following measurements: cotinine saliva concentrations at each visit and scores on each of the questionnaires (Cigarette Dependence Scale, Cigarette Withdrawal Scale, Questionnaire of Smoking Urges, Montgomery-Åsberg Depression Rating Scale, Rosenberg Self-Esteem Scale). The mean was calculated for study groups (placebo versus atomoxetine-treatment group and completed versus dropout group). Multilevel mixed-effects linear regression model was employed to compare the data from groups to determine if there are statistically significant differences between them.

Multilevel mixed-effects linear regression model was utilized in the study as, due to nature of our trial, the serial repeated mean measurements of the

same variable collected at several points in time and the comparison of mean measurements between two groups are essential. The use of this model was also desirable due to the following characteristics of the model:

- applies only to experiments where two or more factors are under the study
- combines both fixed and random effects
- allows using maximal available research data
- compares the results with incomplete data

Additionally, statistical examination occured to determine if there are other statistically significant correlations namely: Dr. Joyce asked to revise following:

- Correlations between the subjects who obtain abstinence from smoking and their scores on each of the questionnaires
- Correlations between the subjects who obtain abstinence from smoking and saliva cotinine concentrations.

T tests (two sample, paired t test) were utilized to explore the significant differences between group measurements at some point of the time.

For the statistical analysis, the statistical software package STATA SE/11 version was used. Performed statistical tests were considered statistically significant with the alpha equal to 0.05.

CHAPTER 4

RESULTS

4.1. RECRUITMENT

Volunteers were recruited through community and clinic-based efforts according to protocol inclusion and exclusion criteria.

Strenuous efforts were made to recruit enough individuals for the study during a 8-month period. Six hundred posters were printed and distributed at the following locations:

- University of Alberta – over 50 different locations
- University of Alberta Hospital – over 30 different locations
- Misericordia Hospital
- Six community shopping malls in multiple locations
- Eight medical and community centers.

Moreover, twelve paid advertisements during the eight month study duration appeared in the METRO daily newspaper. The co-investigator also personally went to multiple sites to interact with individuals who were smoking to hand out an additional 300 posters to those who might be interested. In addition, the author contacted the following services in Edmonton to notify them about study implementation and to ask for assistance in referring potential subjects, and whenever possible, met with these groups (Table 4.1). The co-investigator also met with representatives of Nicotine Anonymous groups to provide detailed information for group members. In addition, seven radio

stations (Table 4.2) were contacted in order to request free advertisement about study implementation, where the wording of the advertisement was the same as in the poster.

Table 4.1 – Organizations contacted

NAME OF ORGANIZATION	CONTACT INFORMATION
Smoker's Help Line	Phone: 1-866-332-2322
Alberta Health Services – Tobacco Cessation Clinics	Phone: 780-342-4154 Fax: 780-342-4100
Tobacco Cessation Program, Faculty of Medicine and Dentistry, University of Alberta Dentistry/Pharmacy Centre	Phone: 780-492-2100
Tobacco Reduction and Cessation Support Group, Alberta Health Services - Mental Health Program	Phone: 780-429-7830
Quit Core	Phone: 1-866-710-7848
Nicotine Anonymous :	West Edmonton Ebenezer United Church Hall, 163 St. & 106 Ave. Phone: 780-443-3020 or North East Edmonton Henwood Treatment Centre 18750 – 18th Street Phone: 780-422-9069 South Edmonton Evangel Pentecostal Assembly church 4461 50th Street, Phone: 780-462-6403 Downtown Edmonton Alano Club 10728 124th Street Phone: 780-902-8872
ASTEP - Alberta Spit Tobacco Education Program	Phone: 1-866-332-2322
Small Steps Matter	Phone: 1-866-332-2322 Website: http://tobacco.aadac.com/about_quitting/pregnancy
Smoker's Help Line	Phone: 1-866-332-2322
One Step at a Time	Phone: 1-866-332-2322 Website: http://tobacco.aadac.com

A Tribe Called Quit	Nechi Institute at 1-800-459-1884 Website: http://www.ayn.ca/quit
Tobacco Reduction and Cessation Support Group, Edmonton Mental Health	Phone: 780-401-4169
AADAC Recovery Centre, 10302-107 Street NW	Phone: 780-427-4291 (24 hours) Fax: 780-422-2881
AADAC Counseling & Prevention Services	10010-102A Avenue NW Phone: 780-427-2736 Fax: 780-427-4180
Enhanced Services for Women (ESW)	10010-102A Avenue NW Phone: 780-415-0786 or 780-415-0776 Fax: 780-427-4180
George Spady Centre Society	10015-105A Avenue NW Phone: 780-424-8335 Fax: 780-426-1203 E-mail: admin@gspady.ab.ca Website: http://www.gspady.ab.ca/

Table 4.2 – Radio Stations contacted

RADIO STATION	CONTACT INFORMATION
630 CHED	5204 - 84th St, Edmonton , T6E 5N8 Phone: 780-440-6300
92.5 JOE FM	5204 - 84 St, Edmonton , T6E 5N8 Phone: 780-428-1104
CJSR	Phone: 780-492-2577
CKUA RADIO NETWORK	4th Floor - 10526 Jasper Ave, Edmonton , T5J 1Z7 Phone: 780-428-7595
COOL 880 THE BOSS	5204 - 84 St, Edmonton , T6E 5N8 Phone: 780-424-8800
SHINE FM CJRY	Suite #204, 4207 98 St, Edmonton , T6E 5R7 Phone: 780-466-4930
THE BEAR ROCKS	#100 - 18520 Stony Plain Rd, Edmonton, T5S 2E2 Phone: 780-486-2800

4.2. SELETION AND SCREENING

The recruitment period started on March 1st, 2010 and ended on October 30th, 2010. During the 8-month recruitment period 114 calls were received from potential subjects. There were significant drop-outs during this process as some subjects realized that their personal situation would not allow them to participate in the study. Of the total of 114 potential subjects, 59 decided not to participate any further.

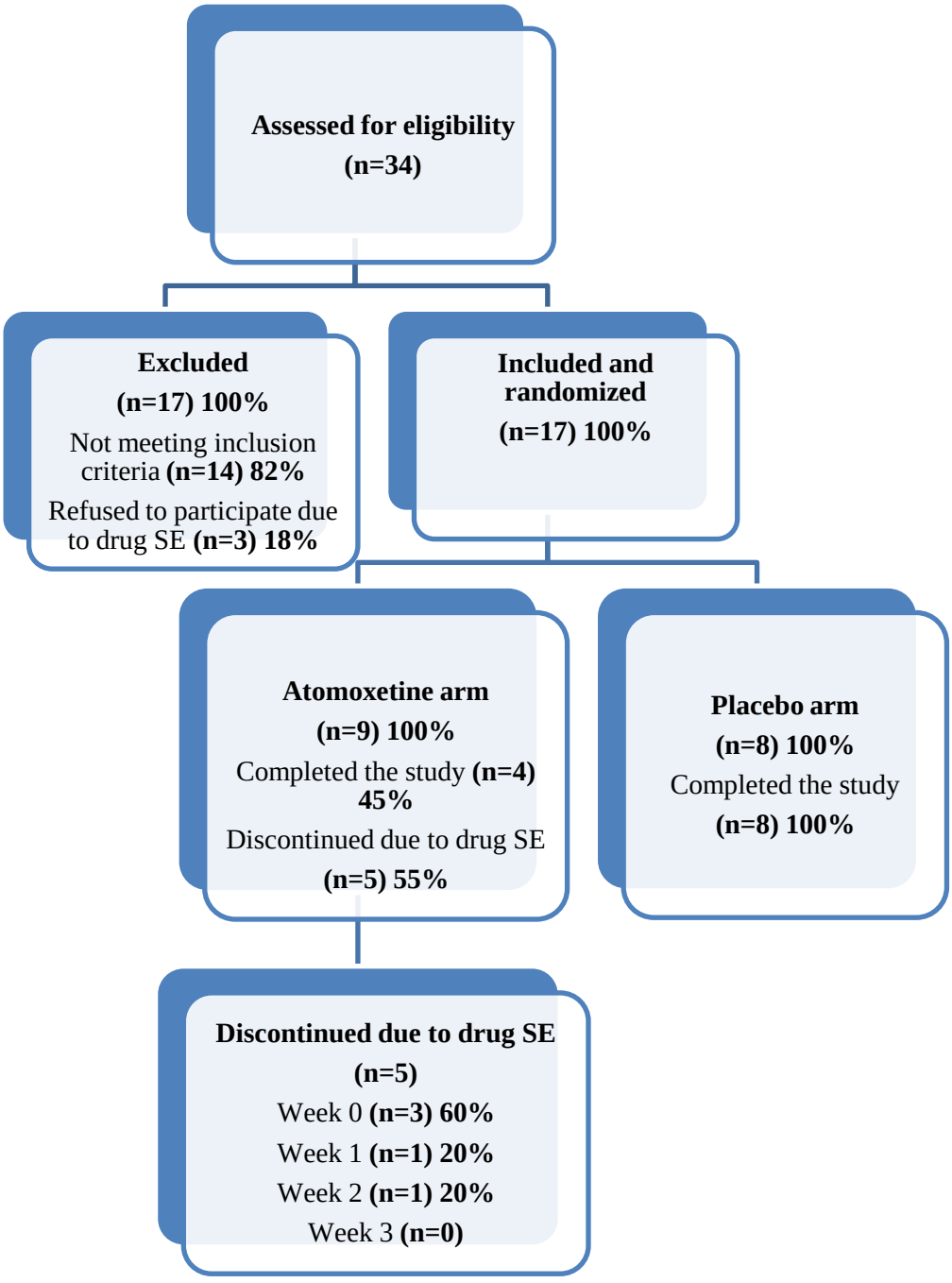
Of the remaining 55 subjects, an additional 21 were pre-screened over the phone, but could not participate because some of these potential subjects were either on medications that were contraindicated or had medical conditions that excluded them from participation.

A total of 34 potential subjects attended for a complete screening visit. However, 14 did not meet both inclusion and exclusion criteria for the study.

Thus, a total of 20 people entered the study. Of these 20, three individuals attended only the baseline visit, but dropped out before initiating study medication, and have therefore been considered as screening failures. Dr. Joyce asked: What happened to power?

The study population, therefore, consists of 17 subjects who were randomized to receive double-blind medication. Of these, a total of 5 dropped out within a 3-week study due to adverse events, and a total of 12 subjects completed the study (Figure 4.1).

Figure 4.1. Demonstrating number of potential patients in terms of assessment, recruitment, study completion and data analysis



4.3. ANALYSIS OF DATA FOR ALL STUDY PARTICIPANTS

4.3.1. Demographic characteristics of study participants

The demographic characteristics of the study participants are summarized in Table 4.3. There were no statistically significant differences between the groups.

The majority of participants was Caucasian (88.2%) and lived in Edmonton. Mean age was 41.9 years, almost, 60% of participants were female. Approximately 88% of participants had college and university degrees, and a similar percentage was employed. Regarding the financial situation, the large majority of participants had a low or moderate income. Single or divorced individuals constituted 65% of all study participants.

Of randomized patients, 9 individuals (52.9%) were randomized to the atomoxetine arm and 8 (47.1 %) to the placebo arm. The comparison of demographic characteristics between the two groups showed that both consisted of around 88% Caucasian with similar mean ages. Gender proportions were slightly different with a higher percentage of males, 55.6%, in the atomoxetine group compared to only 37.5% in the placebo group.

Rates of unemployment were also somewhat different in both groups, although in both groups the majority was employed, with 33.3% of the atomoxetine group being unemployed or students compared to 12.5% in the placebo group.

Marital status characteristics differed more between the two groups; 55.6% were married or living in a common-law relationship in the atomoxetine group and 12.5% in the placebo group.

Table 4.3. Demographic characteristics of study participants

Characteristics	Atomoxetine arm (n=9)	Placebo arm (n=8)	P value (<0.05)
Age in years:			
Mean (SD)	40.9 (11.9)	43 (9.9)	0.699[3]
Range	25-57	31-58	
Gender: n (%)			
Male	5 (55.6)	3 (37.5)	0.637[2]
Female	4 (44.5)	5 (62.5)	
Ethnicity: n (%)			
White	8 (88.9)	7 (87.5)	1.000
Other[1]	1(11.1)	1 (12.5)	
Education: n (%)			
High school	2 (22.2)	0 (0)	0.471
College/University	7 (77.8)	8 (100)	
Occupation: n (%)			
Student/Unemployed	3 (33.3)	1 (12.5)	0.576
Employed	6 (66.7)	7 (87.5)	
Income: n (%)			
Low/Moderate	7 (77.8)	7 (87.5)	1.000
High	2 (22.2)	1 (12.5)	
Marital status: n (%)			
Married/common law	5 (55.6)	1 (12.5)	0.131
Single/divorced	4 (44.5)	7 (87.5)	

[1] Other subgroup incorporates the following ethnicities: one Asian in atomoxetine and one Métis individual in placebo arm.
[2]Fisher's exact test for used to compare the proportions.
[3]T-test was used to compare the mean ages of both groups.

However, despite these numerical differences, there were no statistically significant differences (see Table 4.3). A *t-test* was used to compare the mean ages between the groups, while Fisher's exact test was used to compare other demographic characteristics.

4.3.2. Clinical characteristics of study participants

The clinical characteristics of participants are summarized in Table 4.4. There were no statistically significant differences between clinical characteristics

Table 4.4. Clinical characteristics of all study participants

Clinical characteristics	Atomoxetine arm (N=9)	Placebo arm (N=8)	P value
History of mental disorders **n (%)**[1]	0 (0)	2 (25)	0.206
Co-morbid general medical conditions **n (%)**	5 (55.6)	4 (50)	1.000
Health concerns/problems related to smoking[2]	1(11.1)	3(37.5)[2]	0.294
Alcohol use/abuse **n (%)**[2]	9(100)	7 (87.5)	0.471
Substance use/abuse **n (%)**	1(11.1)	0 (0)	1.000
Use of medications for the treatment of medical conditions throughout the study **n (%)**	6 (66.7)	3 (37.5)	0.347
Participation in other clinical drug trials with simultaneous other medications use during the study **n (%)**	0 (0)	0 (0)	
Family history of mental health conditions other than nicotine dependence **n (%)**	3 (33.3)	2 (25)	1.000
Family history of smoking **n (%)**[3]	9 (100)	8 (100)	

[1]None of participants had current mental health illness or was taking medications for their treatment.
[2]All but one participant used alcohol on regular basis. Screening with MINI questionnaire revealed absence of alcohol abuse or dependence; yet, all participants agreed to avoid its use one week before and during the entire study participation.
[3]All participants had family history of smoking where at least one of the members of their family was a smoker.

and the family history of participants in both treatment groups (Fisher's exact test).

4.3.3. Smoking-related history for all participants

All seventeen participants met criteria for nicotine dependence according to DSM-IV classification. In terms of specifiers, all of them had nicotine dependence with physiological dependence. Summary of their current and past smoking behaviour is shown in Table 4.5.

Among all study participants, only one individual in the atomoxetine group and 3 individuals in the placebo group reported the development of respiratory problems related to smoking. One individual in the placebo group was diagnosed with COPD.

Table 4.5. Smoking data for all study participants

Characteristics	Atomoxetine arm (N=9)	Placebo arm (N=8)	P value
Length of every day smoking, in			
Mean (SD)	20.9 (11.3)	23.1 (8.4)	0.655
Range	5-40	11-36	
Number of cigarettes per day, n (%)			
Mean (SD)	19.1 (5.5)	19.1 (5.0)	0.979
Range	11-27.5	12-27	
Age of smoking initiation:			0.984
Mean (SD)	16.3 (2.8)	16.4 (5.8)	
Range	13-21	11-29	
Number of quitting attempts:			
Mean (SD)	4.7 (3.2)	5.9 (5.8)	0.596
Range	2-10	2-20	
Median length of the recent attempt			
Median	3	13,8	0.409
Range	2-3650[3]	3-180	
Percentile 25	2	7	
Percentile 50	3	13.8	
Percentile 75	510	120	
Median of average length of quitting			
Median	60	19.3	0.630
Range	2-7300[3]	1-365	
Percentile 25	2.25	11.4	
Percentile 50	60	19.3	
Percentile 75	2230	78	
Use of smoking cessation	8 (88.9)	7 (87.5)	1.000
Help of smoking cessation	6 (66.7)[1]	7 (87.5)[1]	0.467

[1]One smoker from atomoxetine treatment arm and one smoker from placebo group did not use any medication for smoking cessation.
[2] Two smokers from atomoxetine treatment arm did not experience any help with the use of smoking cessation pharmaceutical aids.[3]One of the participants from atomoxetine treatment arm had smoke free period that lasted almost 20 years, while another participant from placebo arm had smoke free period about 10 years.

4.4. STATISTICAL ANALYSIS

The aim of a statistical analysis is to examine the data and determine if any numerical differences that are seen are likely to represent real differences or are likely to be chance findings. Traditionally, a level of 0.05 is taken to represent statistical significance, i.e. that there is a less than 1 in 20 chance that any such differences occur due to chance alone. However, another clearly known fact about statistical analysis is that the larger the number of data points the more robust any findings are, but with fewer data points the findings are often less robust. Given the small number of subjects that were entered into this study it should be recognized that statistical analysis is problematic. Indeed, as discussed in the methodology section, an initial sample size calculation suggested that at least 54 individuals in each treatment arm were required, whereas we only achieved 8 on one arm and 9 in another.

Nonetheless, there several statistical analyses undertaken as described in the methodology section. The first, and most rigorous, was a mixed-effects model to determine possibly statistically significant differences between subjective and objective outcome measurements in both treatment groups. In the mixed-effects model the following variables were considered as independent factors:

- Treatment (atomoxetine and placebo groups)
- Time (baseline, visit 1, visit 2)Baseline mean score of the outcome variable

- Interactions between treatment and time Interaction between baseline mean score of the outcome variable and time

Additionally, a further problem of clinical studies is how to deal with data from those individuals who drop-out during studies. The most widely accepted method of doing this is to use a "last-observation carried forward" (LOCF) analysis, in which the final observation of the subject is used throughout all the remaining time periods for which no further data is available. Possibly the least rigorous is a completer analysis, which shows the data for only those individuals who complete each study time point.

In terms of the results there were two analyses that were completed using a *t*-test, firstly a comparison between all data at baseline compared to the data at the final visit (paired *t*-test). The second analysis was an examination between the results for those in the atomoxetine treatment arm compared to those in the placebo treatment arm at each time point (two-sample *t*-test), both for the LOCF analysis and for the completer analysis. For each area considered there is a graph of the data for this final analysis. However, it should be noted that as there were no drop-outs in the placebo treatment arm the LOCF and completer analysis is the same for this group, whereas in the atomoxetine treatment arm they differ. This is why in the various graphs there are only 3 sets of data shown.

4.5. DETAILED RESULTS

4.5.1. Total results for mixed-effects model analysis

A summary of the statistical results for the mixed-effects model are shown in Table 4.6 for each variable that was measured. However, as can be seen with the graphs in the following sections, a statistically significant finding (such as a change with Time for the CDS score) reflected the variability of the data, and did not indicate clinically relevant findings between the two treatment arms. For this reason, the results from the mixed-effect model analysis are not shown with each variable considered, but are summarized below.

Table 4.6 Statistically significant results revealed by the mixed-effects model with of subjective outcome measures

Outcome (Dependent variable)	Predictors (Independent variable)	P values	Coefficient	SE
The Cigarette Dependence Scale (CDS) score	Time	0.001	-0.647	0.135
	Treatment	0.982	-0.965	4.396
	CDS Baseline	0.159	0.492	0.349
	Time×Treatment	0.572	-2.238	3.962
	CDS Baseline×Treatment	0.534	-2.806	4.510
The Cigarette Withdrawal scale (CWS) score	Time	0.283	0.183	0.171
	Treatment	0.344	-6.213	6.559
	CWS Baseline	0.001	0.613	0.113
	Time×Treatment	0.408	-5.518	6.666
	CWS Baseline×Treatment	0.304	-4.044	3.933
Questionnaire of Smoking Urges (QSU) score	Time	0.290	-2.626	2.482
	Treatment	0.612	40.735	80.381
	QSU Baseline	0.001	0.514	0.083
	Time×Treatment	0.718	27.769	77.016
	QSU Baseline×Treatment	0.581	-20.221	36.666
Montgomery-Åsberg Depression Rating Scale (MADRS) score	Time	0.001	0.172	0.046
	Treatment	0.641	0.698	1.494
	MADRS Baseline	0.001	1.185	0.292
	Time×Treatment	0.378	1.349	1.532
	MADRS Baseline×Treatment	0.555	0.621	1.053
Rosenberg Self-Esteem scale (SES) score	Time	0.313	-0.038	0.037
	Treatment	0.362	1.814	1.988
	SES Baseline	0.001	0.825	0.085
	Time×Treatment	0.401	1.666	1.984
	SES Baseline×Treatment	0.246	0.861	0.742
Number of cigarettes smoked per week	Time	0.001	-4.651	0.762
	Treatment	0.451	11.999	15.918
	Number of cigarettes Baseline	0.233	0.248	0.208
	Time×Treatment	0.910	1.412	12.507
	Number of cigarettes Baseline×Treatment	0.499	10.756	15.912

4.5.2. Results of differences between baseline and final scores

Another way to examine the significance of changes between the two groups is to determine if the difference over time varies between the two groups. For example, the mean baseline score in the atomoxetine group on the Cigarette Dependence Scale scores was 54.1 and the final score (after 3 weeks) was 26.8, meaning that the mean decrease was 27.3. In contrast, the mean baseline score for the placebo group was 49.8 and the mean final score was 42.3, meaning that the mean decrease was only 7.5. Carrying out a statistical analysis of all of these differences, data in Table 4.7 shows that there were the differences over time between two groups with regards to majority subjective and all objective outcome variables were not statistically significant; the only statistically significant difference between both treatment groups was found with regards to cigarette dependence score.

Analogous situation was seen when the LOCF values were used for both subjective and objective outcome variables. This is shown in Table 4.8.

Table 4.7 Statistical results for differences between atomoxetine treatment group and placebo treatment grou

Outcome score (Dependent variable)	Mean (SD) of Delta[1] [mean of baseline, mean at week3]		P-value (2-tailed)[2]
	Atomoxetine arm[3]	Placebo arm	
The Cigarette Dependence Scale (CDS)	27.3 (10.2) [54.1, 26.8]	7.5 (8.2) [49.8, 42.3]	0.005
The Cigarette Withdrawal scale (CWS)	-0.8 (14.5) [40.8, 38.8]	-5.5 (22.8) [44.1, 49.6]	0.714
Questionnaire of Smoking Urges (QSU)	124.4 (214.6) [367.6, 133.8]	4.4 (227.9) [276.4,	0.402
Montgomery-Åsberg Depression Rating Scale (MADRS)	-0.5 (2.5) [1.6, 1.5]	-3.0 (4.0) [1.3, 4.3]	0.286
Rosenberg Self-Esteem scale (SES)	-1.0 (2.8) [23.3, 22.8]	1.3 (3.0) [22.1, 20.9]	0.243
Number of cigarettes smoked per week	126.1 (57.1) [133.4, 11.3]	89.4 (41.4) [133.9, 44.5]	0.228
NicAlert saliva (cotinine) test	1.5 (1.0) [4.1, 2.8]	0.8 (0.9) [4.5, 3.8]	0.214
Systolic blood pressure	-3.0 (14.6) [116.4, 112.5]	4.8 (13.7) [107.5, 102.8]	0.386
Diastolic blood pressure	-3.8 (7.5) [72.8, 76.3]	-0.8 (7.2) [68.1, 68.9]	0.517
Heart rate	-0.8 (5.7) [66.8, 71.5]	-2.1 (9.0) [70.0, 72.1]	0.789
Respiratory rate	-1.5 (3.4) [14.7, 16.0]	-0.5 (2.1) [14.8, 15.3]	0.536
Body temperature	0.2 (0.3) [36.4, 36.3]	-0.1 (0.4) [36.1, 36.3]	0.176
Body weight	13.1 (30.4) [80.9, 76.9]	-0.3 (1.4) [67.9, 68.2)	0.227

[1]Delta = Baseline score-Final score,
[2]2-tailed t-test was used as there was no certainty about the direction of the parameter values that the data will support.
[3]Mean for participants, who have completed study

Table 4.8 Statistical results for differences between atomoxetine treatment group (LOCF analysis) and placebo treatment group

Outcome score (Dependent variable)	Mean (SD) of Delta[1] [mean ot baseline, mean at week3]		P-value (2-tailed)[2]
	Atomoxetine arm	Placebo arm	
The Cigarette Dependence Scale (CDS)	13.4 (14.8) [54.1, 40.7]	7.5 (8.2) [49.8,	0.330
The Cigarette Withdrawal scale (CWS)	-0.7 (9.7) [40.8, 41.4]	-5.5 (22.8)	0.180
Questionnaire of Smoking Urges (QSU)	55.7 (147.4) [367.6, 311.9]	4.4 (227.9)	0.585
Montgomery-Åsberg Depression Rating Scale (MADRS)	-2.2 (4.2) [1.6, 3.8]	-3.0 (4.0) [1.3, 4.3]	0.701
Rosenberg Self-Esteem scale (SES)	-0.3 (2.9) [23.3, 23.7]	1.3 (3.0) [22.1,	0.289
Number of cigarettes smoked per week	108.7 (39.9) [133.4, 24.7]	89.4 (41.4)	0.343
NicAlert saliva (cotinine) test	0.8 (1.0) [4.1, 3.4]	0.8 (0.9) [4.5, 3.8]	0.952
Systolic blood pressure (sBP)	-4.1 (12.0) [116.4, 120.6]	4.8 (13.7)	0.175
Diastolic blood pressure (dBP)	-0.3 (9.1) [72.8, 76.3]	-0.8 (7.2) [68.1,	0.315
Heart rate	-2.8 (6.8) [66.8, 69.6]	-2.1 (9.0) [70.0,	0.868
Respiratory rate	-1.6 (2.6) [14.7, 16.2]	-0.5 (2.1) [14.8,	0.373
Body temperature	-0.1 (0.4) [36.4, 36.5]	-0.1 (0.4) [36.1,	0.613
Body weight	-0.3 (0.7) [80.9, 81.2]	-0.3 (1.4) [67.9,	0.942

[1]Delta = Baseline score-Final score,
[2]2-tailed t-test was used as there was no certainty about the direction of the parameter values that the data will support.

4.5.3. Results of two-sample *t*-test for each subjective and objective outcome measures

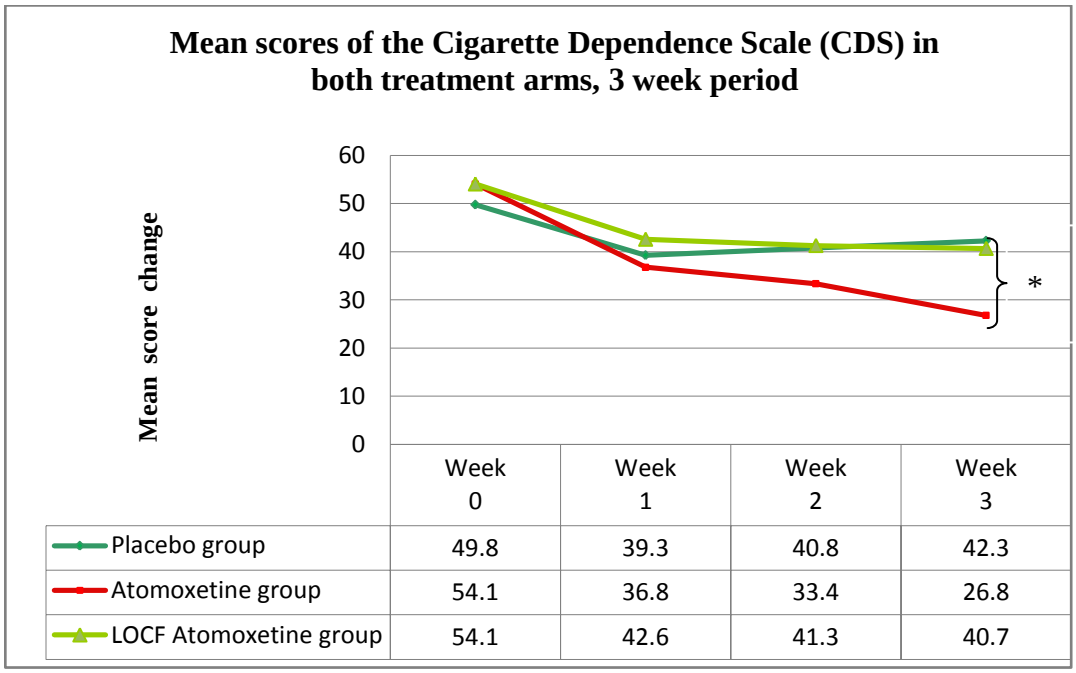
In addition to the two methods already described, a third way to examine the possible statistical significance of any differences is to analyze the results at each time point to see if they are statistically significant. To do this we utilized a two-sample *t*-test to compare results between the groups at each time point. This was done both for the group of individuals who completed each visit ("Atomoxetine group") as well as for those who stopped the study early and whose missing data was completed using an LOCF analysis ("LOCF atomoxetine group").

These are shown for each of the 6 key outcome measures, the Cigarette Dependence Scale (CDS), Cigarette Withdrawal Scale (CWS), Questionnaire of Smoking Urges (QSU), Montgomery-Åsberg Depression Rating Scale (MADRS), Rosenberg Self-Esteem scale (SES), and the Number of cigarettes smoked per week (NCSW).

4.5.3.1. Cigarette Dependence Scale (CDS) scores

The changes over time for the CDS scale are shown in Figure 4.2. The results showed that there was a statistically significant difference between the atomoxetine treatment arm compared to those in the placebo group at the end of the study (26.8 vs. 42.3, p = 0.023). However, this difference was not statistically significant in an LOCF analysis.

Figure 4.2. Mean scores on the Cigarette Dependence Scale (CDS) in both treatment arms, during the 3 week study period

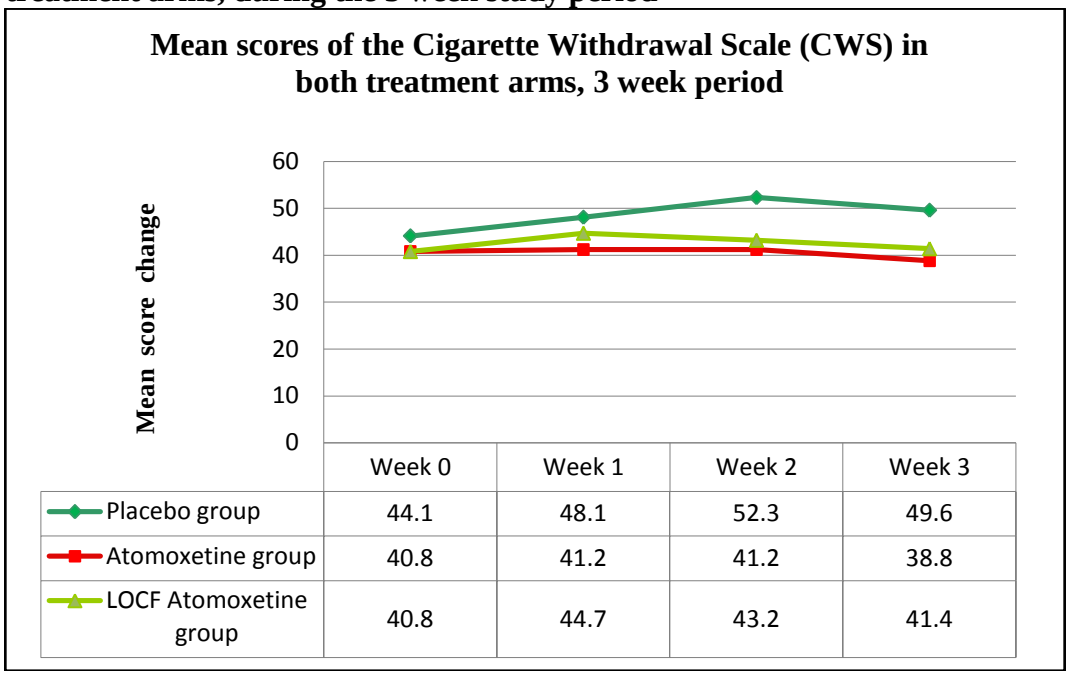


* Two-sample t-test demonstrated statistically significant difference ($p<0.05$) between the Atomoxetine and Placebo groups.

4.5.3.2. Cigarette Withdrawal Scale (CWS) scores

The CWS examines the severity of withdrawal symptoms. The change over time for the CWS scale is shown in Figure 4.3. It can be seen that there were no significant changes in the CWS scale over time or between the two groups either when comparing completers only or when considering LOCF. These results suggest that those study participants, who completed the study and received atomoxetine, may have experienced a reduction in their nicotine withdrawal symptoms compared to those who received placebo, but the data is by no means clear in this regard.

Figure 4.3. Mean scores on the Cigarette Withdrawal Scale (CWS) in both treatment arms, during the 3 week study period

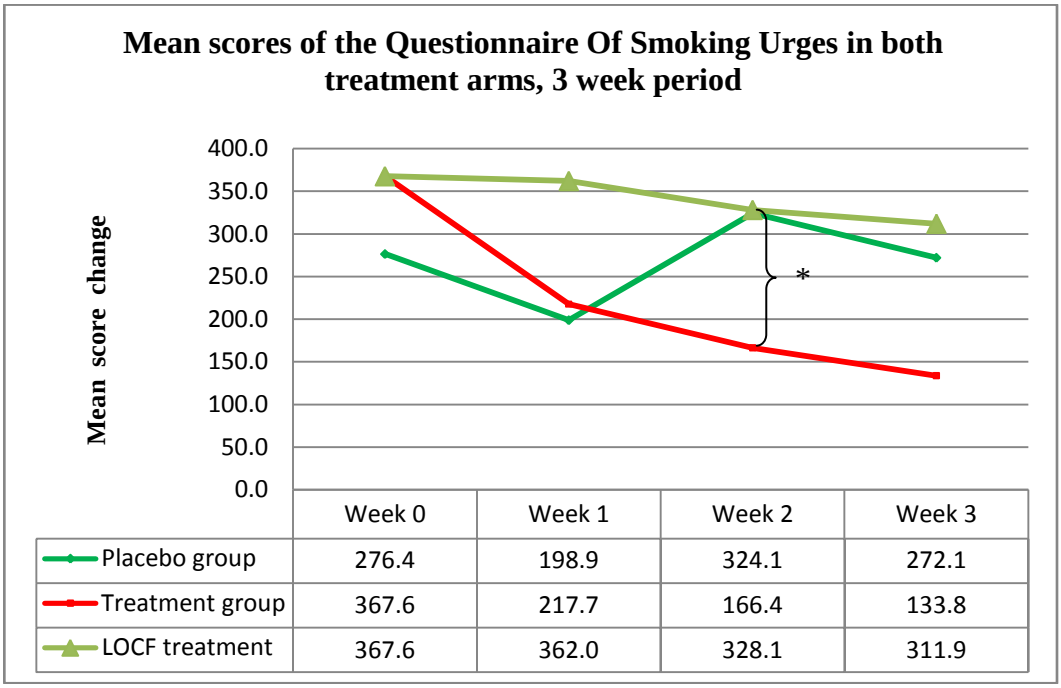


	Week 0	Week 1	Week 2	Week 3
Placebo group	44.1	48.1	52.3	49.6
Atomoxetine group	40.8	41.2	41.2	38.8
LOCF Atomoxetine group	40.8	44.7	43.2	41.4

4.5.3.3.Questionnaire of Smoking Urges (QSU) score

The QSU is a subjective measure for nicotine withdrawal symptoms and smoking urges that is considered one of the important measures of nicotine-induced abstinence. The changes over time for the QSU scale are shown in Figure 4.4.

Figure 4.4. Mean scores of the QSU in both treatment arms, 3 week period



	Week 0	Week 1	Week 2	Week 3
Placebo group	276.4	198.9	324.1	272.1
Treatment group	367.6	217.7	166.4	133.8
LOCF treatment	367.6	362.0	328.1	311.9

*Two-sample t-test demonstrated statistically significant differences ($p<0.05$) between the treatment groups.

It can be seen that at week 2 there is a reduction in the QSU scores in the treatment group (from a baseline measurement of 368 to 134), and this was accompanied by a statistically significant difference between the atomoxetine treatment arm and placebo treatment arm at week 2 ($p=0.049$). However, the difference narrowed at week 3 and just failed to reach statistical significance at the final visit ($p=0.058$).

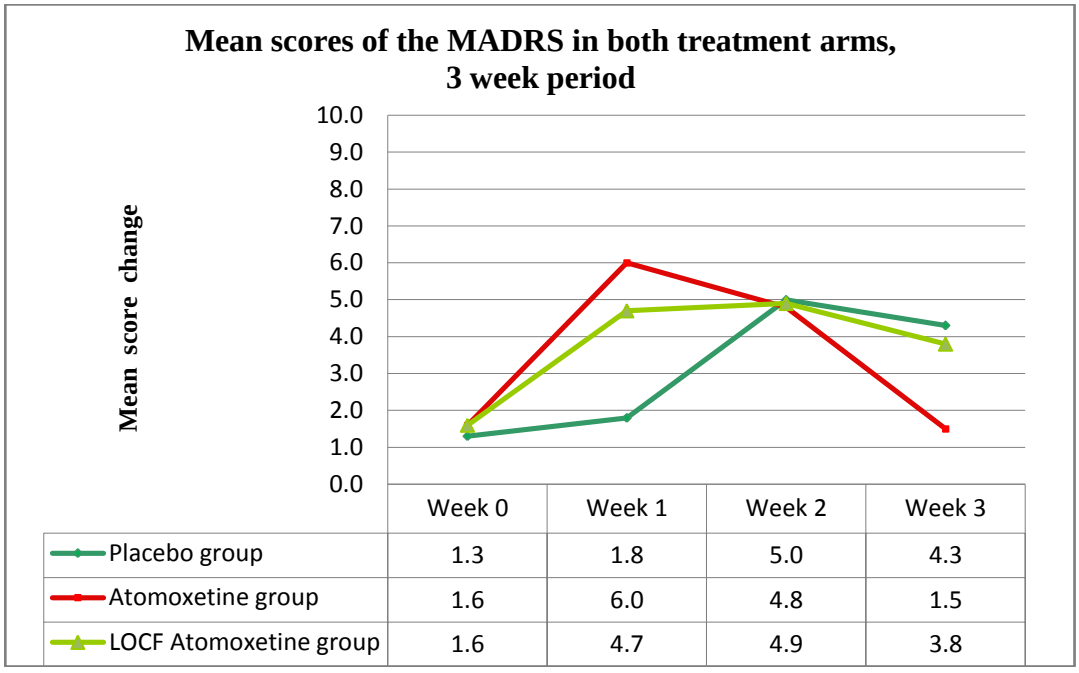
In contrast, there were no statistically significant differences between the placebo group and the LOCF treatment group at any time point, and at week 1 the LOCF groups scores were in fact higher, although this was not statistically significant ($p=0.115$).

4.5.3.4. Montgomery-Åsberg Depression Rating Scale (MADRS) score

The Montgomery-Åsberg scale is a measure of depressive mood that has been shown to be sensitive to change in a variety of drug studies. In the present study all individuals remained below the thresholds for major depressive disorder throughout the study.

The changes over time for the MADRS score are shown in Figure 4.5. Although there was an initial increase in scores on the MADRS in the atomoxetine treatment group at week 1, and a decrease at the end of the study, however, no statistically significant difference neither with two-sample t-test, nor with LOCF analysis at any time-point.

Figure 4.5. Mean scores of the MADRS in both treatment arms, 3 week period

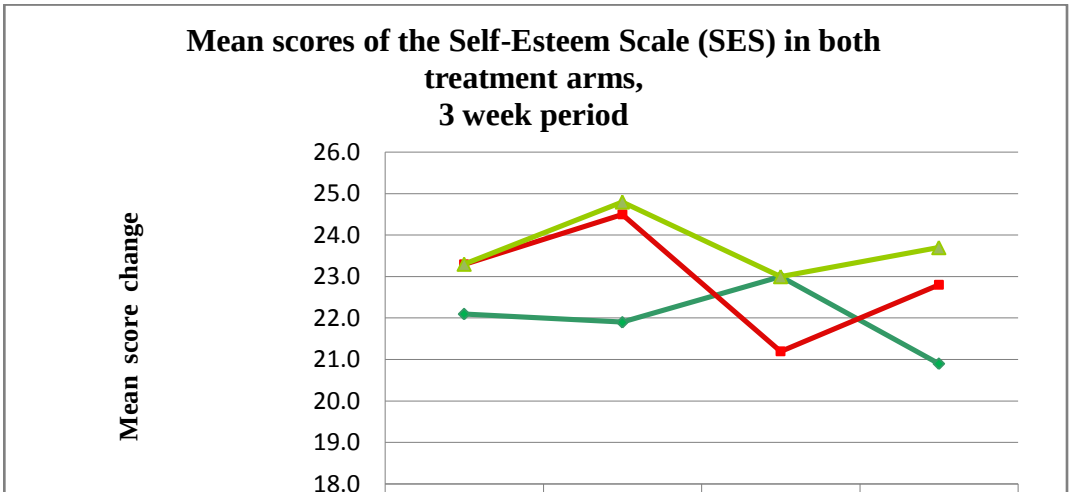


4.5.3.5.Rosenberg Self-Esteem Scale (SES)

It was of interest to determine if self-esteem changed with treatment. The change over time for the Rosenberg SES is shown in Figure 4.5.

It can be seen that in terms of self esteem, the participants randomized to atomoxetine group had higher self-esteem scores comparing to the placebo group at both the beginning and end of the study, although these differences were small and were not statistically significant. There was also some variation in mean self-esteem during the study in the atomoxetine group, which may have reflected the scores from those individuals who dropped out.

Figure 4.6. Mean scores of the SES in both treatment arms, 3 week period



	Week 0	Week 1	Week 2	Week 3
Placebo group	22.1	21.9	23.0	20.9
Atomoxetine group	23.3	24.5	21.2	22.8
LOCF Atomoxetine group	23.3	24.8	23.0	23.7

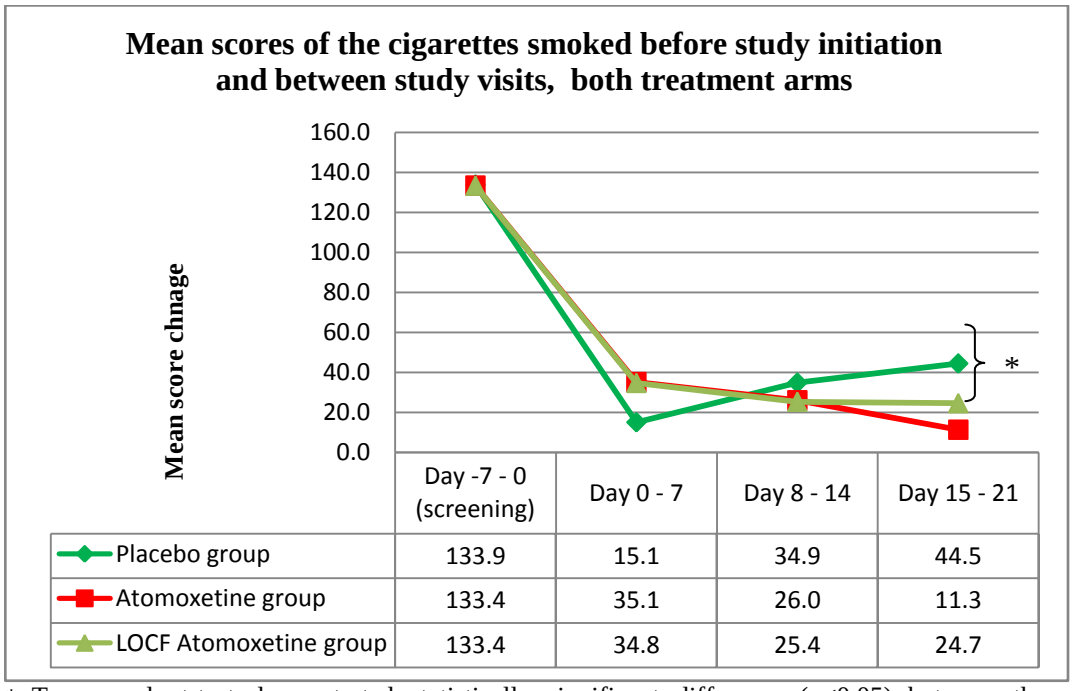
4.5.3.6.Number of cigarettes smoked per week

In terms of the self-reported number of cigarettes smoked, groups were similar at the beginning of the study (mean number of cigarettes smoked per week by smokers randomized into atomoxetine group was 133. 4 and by placebo was 133.9).

There was an initially higher number of cigarettes smoked in the atomoxetine treatment group during the first week of the study treatment (35.1) compared to the number smoked per week in the placebo group during the same period (15.1). As the study progressed the number of cigarettes smoked in the atomoxetine treatment group decreased (11.3), while it increased more in the placebo group (44.5). This difference at the end of the study was statistically significant (p=0.015).

However, when the last observation carried forward (LOCF) analysis was considered, there were no statistically significant differences (p=0.082). It should also be noted that during the study none of the participants stopped smoking completely. The change over time for the number of cigarettes smoked per day is shown in Figure 4.7.

Figure 4.7. Mean scores of cigarettes smoked between study visits, both arms, 3 week period



	Day -7 - 0 (screening)	Day 0 - 7	Day 8 - 14	Day 15 - 21
Placebo group	133.9	15.1	34.9	44.5
Atomoxetine group	133.4	35.1	26.0	11.3
LOCF Atomoxetine group	133.4	34.8	25.4	24.7

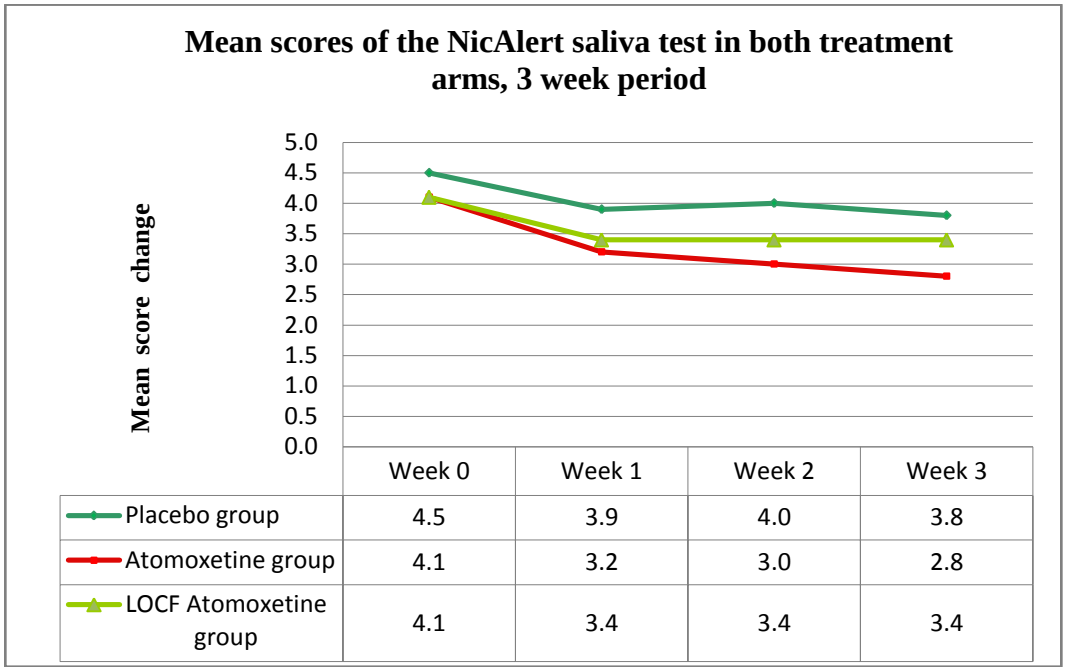
* Two-sample t-test demonstrated statistically significant difference ($p<0.05$) between the Atomoxetine and Placebo groups.

4.5.3.7.Salivary cotinine

Cotinine in saliva was the primary objective measurement, as it accurately reflects the concentration of nicotine in the human body and was measured using the NicAlert test. The cotinine test is therefore a very useful way of validating the self-report smoking (Figure 4.8).

To be considered valid, the decrease in smoking should be accompanied by decreases in cotinine levels, as measured in the NicAlert test. The change over time for NicAlert test is shown in Figure 4.8, and it can be seen that indeed in the atomoxetine group there was a greater decrease over time.

Figure 4.8. Mean scores of NicAlert saliva test, both arms, 3 week period



	Week 0	Week 1	Week 2	Week 3
Placebo group	4.5	3.9	4.0	3.8
Atomoxetine group	4.1	3.2	3.0	2.8
LOCF Atomoxetine group	4.1	3.4	3.4	3.4

The placebo group had a mean decrease of 0.7 on the NicAlert test, while the atomoxetine treatment group had a mean decrease of 1.3. However, when comparing the mean scores of the two groups at week 3 there was only a trend; and, the difference did not reach statistical significance (p=0.069).

These findings are consistent with the reported reduction in the number of cigarettes smoked in the atomoxetine treated group, although perhaps not as dramatic a reduction.

When using LOCF there were no statistically significant differences between the atomoxetine treatment group and the placebo group.

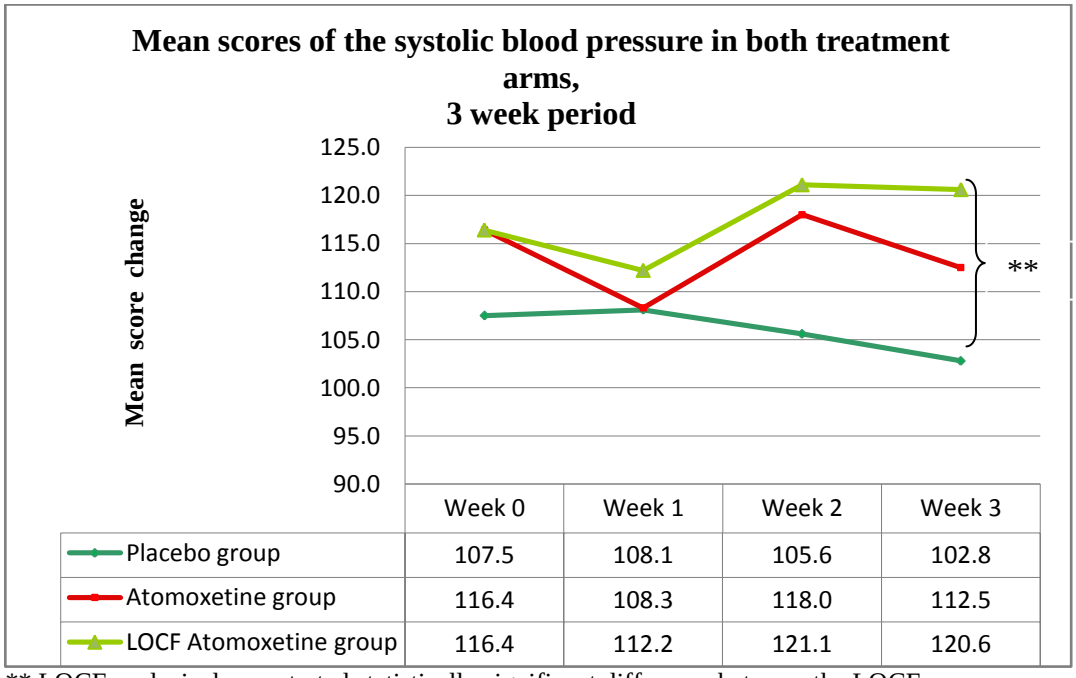
4.5.4. Other measurements

Measurement was also made of systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature, and body weight. These measurements were secondary outcome measures, but can indicate possible safety issues with the treatment drug and are therefore important to consider.

4.5.4.1. Systolic blood pressure

As seen in Figure 4.9, the baseline systolic blood pressure was higher in the atomoxetine treatment group compared to the placebo group (116 mmHg vs. 108 mmHg), but this was not statistically significant, and there were no statistically significant differences at any time point.

Figure 4.9. Mean scores of systolic blood pressure, both arms, 3 week period



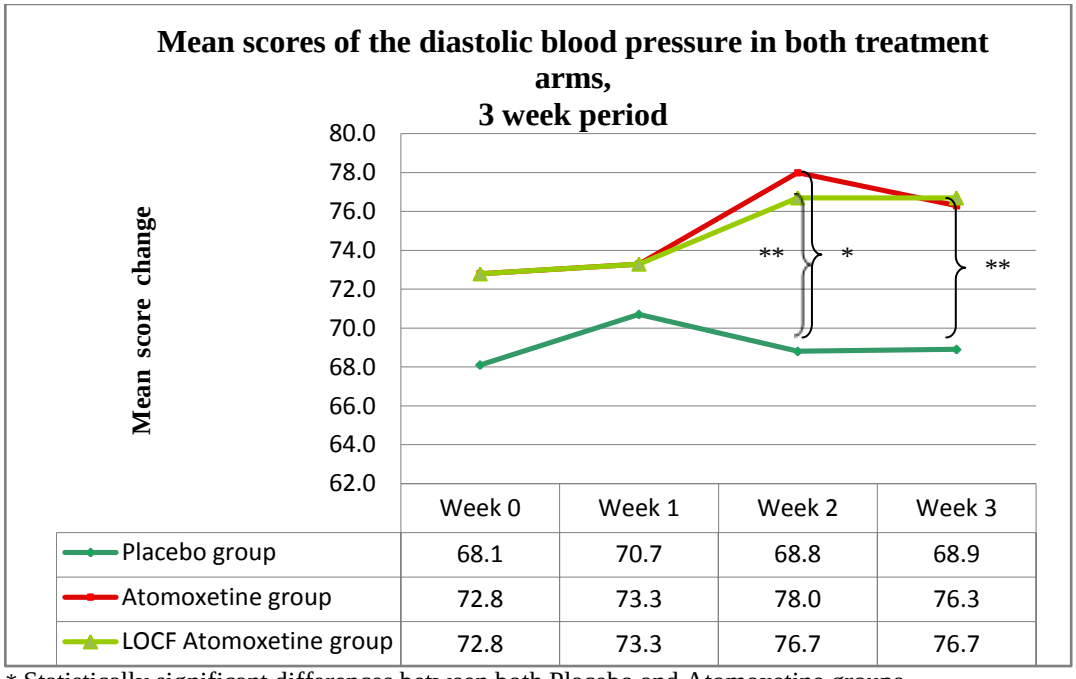
** LOCF analysis demonstrated statistically significant difference between the LOCF Atomoxetine and Placebo group.

In contrast, the LOCF analysis showed that for individuals who were randomized to the atomoxetine group there was an increase in mean systolic blood pressure during the study (from 116 mmHg at baseline to 121 mmHg), and that at the end of the study this was significantly greater than the placebo group (p=0.007).

4.5.4.2. Diastolic blood pressure

Both treatment groups had similar diastolic blood pressure measurements at baseline (p value 0.196). Examining the change in diastolic blood pressure (Figure 4.10) it can be seen that at week 2 there was a statistically significantly

Figure 4.10. Mean scores of diastolic blood pressure, both arms, 3 week period



	Week 0	Week 1	Week 2	Week 3
Placebo group	68.1	70.7	68.8	68.9
Atomoxetine group	72.8	73.3	78.0	76.3
LOCF Atomoxetine group	72.8	73.3	76.7	76.7

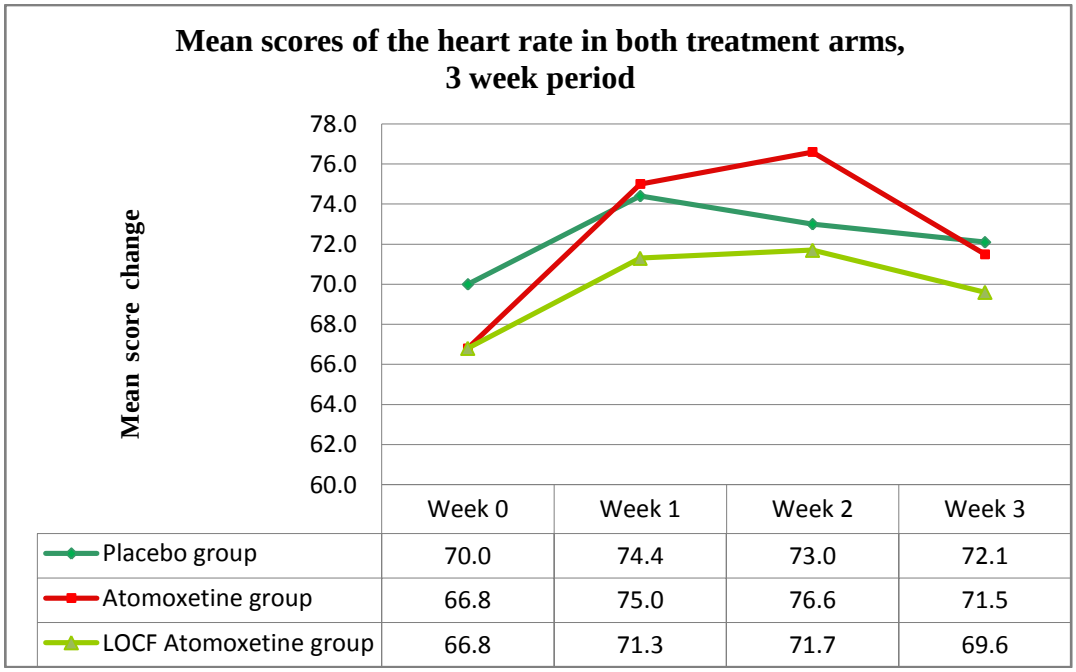
* Statistically significant differences between both Placebo and Atomoxetine groups.
** Statistically significant differences between both Placebo and LOCF Atomoxetine groups.

greater diastolic blood pressure in the atomoxetine treated group (p=0.004) that did not reach statistical significance at the final visit (p=0.053). However, with the LOCF analysis, diastolic blood pressure was significantly greater in individuals treated with atomoxetine at both week 2 and week 3 (p=0.002 and p=0.009, respectively).

4.5.4.3.Heart rate

As shown in Figure 4.11, all participants in both treatment arms experienced some increase in their heart rate during the study, although this was only minimally increased at the end of the study period, and throughout it remained within normal physiological limits. At no point, there were any statistically significant differences between the groups in terms of mean heart rate.

Figure 4.11. Mean scores of heart rate, both arms, 3 week period

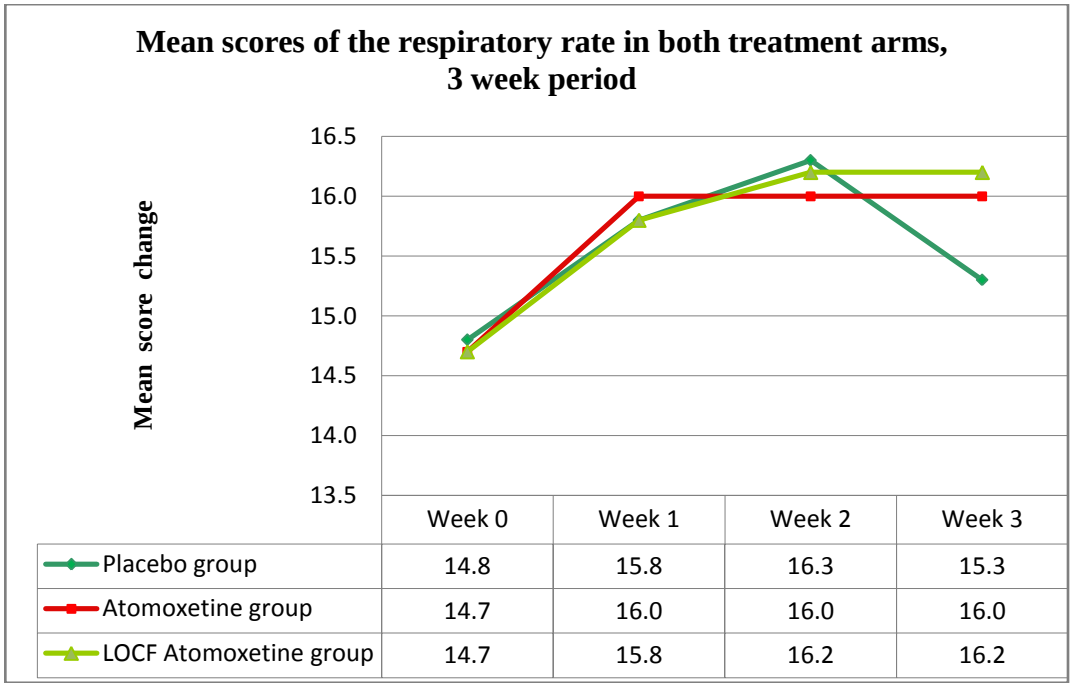


	Week 0	Week 1	Week 2	Week 3
Placebo group	70.0	74.4	73.0	72.1
Atomoxetine group	66.8	75.0	76.6	71.5
LOCF Atomoxetine group	66.8	71.3	71.7	69.6

4.5.4.4. Respiratory rate

As shown in Figure 4.12 there was an increase in all treatment groups during the first two weeks, but there were no statistically significant differences between the two groups in terms of respiratory rate during the study demonstrated by nether two-sample t-test, nor by LOCF analysis.

Figure 4.12. Mean scores of respiratory rate, both arms, 3 week period

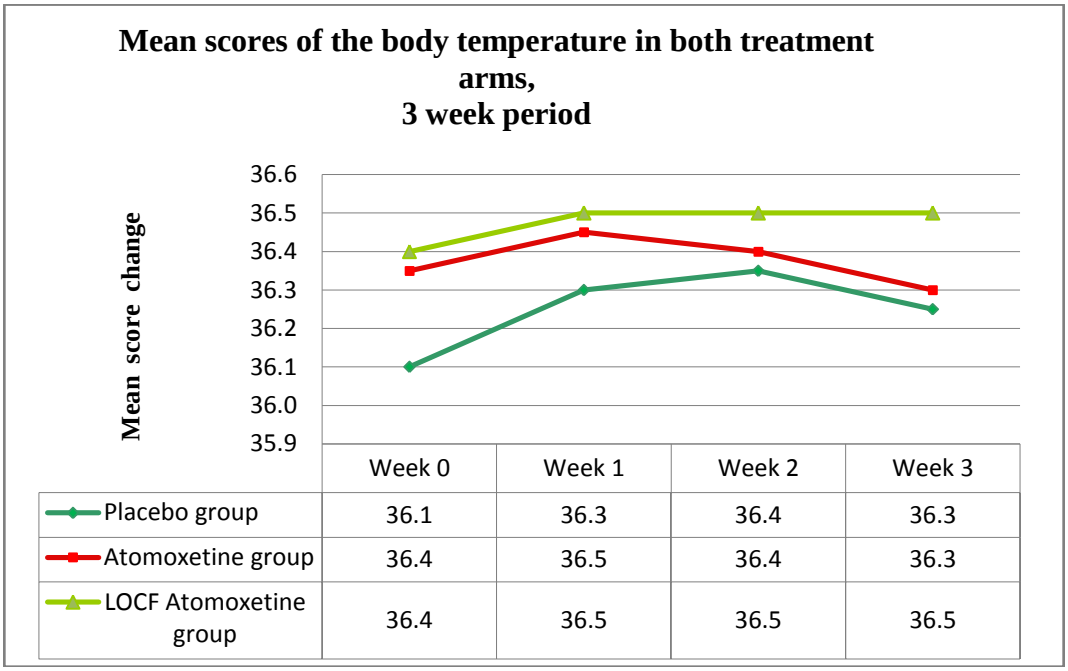


	Week 0	Week 1	Week 2	Week 3
Placebo group	14.8	15.8	16.3	15.3
Atomoxetine group	14.7	16.0	16.0	16.0
LOCF Atomoxetine group	14.7	15.8	16.2	16.2

4.5.4.5. Body temperature

As per Figure 4.13, individuals from both treatment groups did not experience an increase of their body temperature above normal limits. Statistical analysis showed no difference between the groups in terms of body temperature.

Figure 4.13. Mean scores of body temperature, both arms, 3 week period



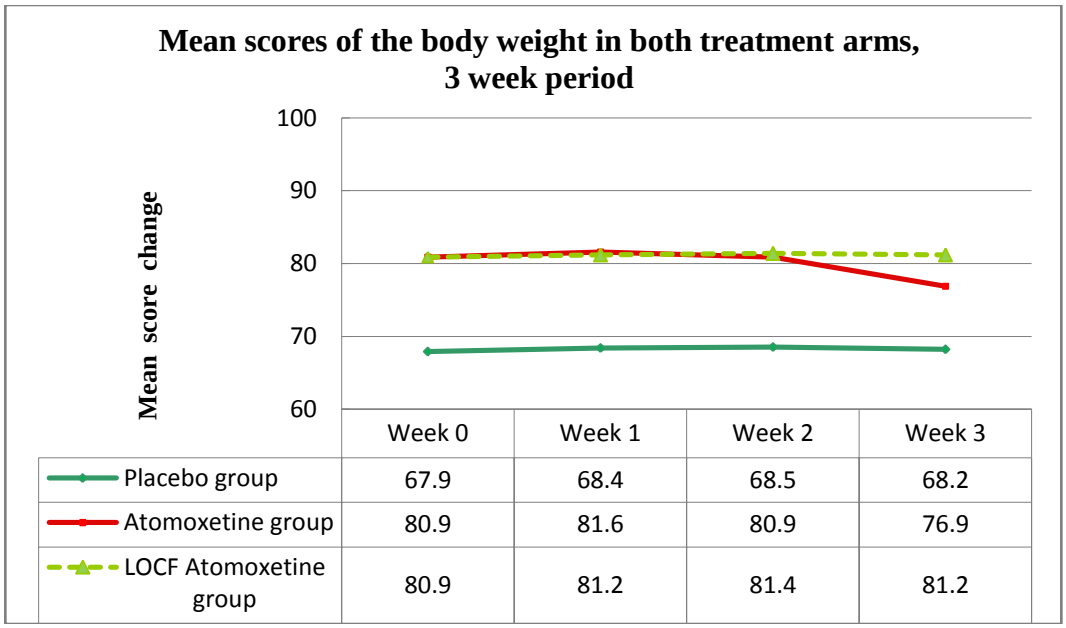
	Week 0	Week 1	Week 2	Week 3
Placebo group	36.1	36.3	36.4	36.3
Atomoxetine group	36.4	36.5	36.4	36.3
LOCF Atomoxetine group	36.4	36.5	36.5	36.5

4.5.4.6. Body weight

Body weight was measured at each visit, and the mean scores are shown in Figure 4.14. There was a small (0.5 kg) increase in weight in the placebo group during the 3-week study period. In contrast there was a decrease in weight in the atomoxetine group (4 kg) which occurred entirely between the second and third weeks. Such a rapid and dramatic reduction would be very hard to explain, and in all likelihood is an artifact explained by a change in mean weight in the

subjects who remained in the study. This is also supported by the LOCF assessment which shows only a 0.2 kg decrease in weight during the same period.

Figure 4.14. Mean scores of weight during 3 week study period



	Week 0	Week 1	Week 2	Week 3
Placebo group	67.9	68.4	68.5	68.2
Atomoxetine group	80.9	81.6	80.9	76.9
LOCF Atomoxetine group	80.9	81.2	81.4	81.2

4.6. ADVERSE EVENTS REPORTED BY PARTICIPANTS IN THE STUDY

Several participants discontinued their participation during the study due to adverse events. When the data was analyzed it became apparent that all discontinuations occurred in those receiving atomoxetine, and were entirely due to the side-effects of atomoxetine. Three participants dropped out during the first week of taking the drug, one individual dropped out during the second week, and one more participant discontinued his participation during the third week of the

study. Thus, more than 50% of those started on atomoxetine were not able to tolerate it at the dose used, which is the recommended starting dose for adults.

In total we gathered information about 65 adverse events. None of them were serious. When at the end of the study the code was broken, we analyzed adverse events that occurred in both treatment arms. It can be seen that the most frequent adverse event was insomnia, followed by dizziness, fatigue, nausea, decreased concentration, and headache. These were all anticipated adverse events.

Analysis showed that individuals who dropped out from the study were not significantly different from those who completed the study in terms of co-morbid general medical conditions ($p=0.728$), use of medications for the regular treatment of medical problems ($p=0.169$), use of alcohol ($p=0.536$), use of other addictive substances ($p=0.536$), or in terms of history of mental health disorders, either personal ($p=0.362$) or family ($p=0.610$).

Table 4.9. Adverse events recorded during the study among participants

Adverse events	Total	n (%)	
		Atomoxetine arm (n=9)	Placebo arm (n=8)
Insomnia	7	5 (55.6)	2 (25)
Dizziness	5	2 (22.2)	3 (37.5)
Fatigue	4	2 (22.2)	2 (25)
Nausea	4	2 (22.2)	2 (25)
Decrease concentration	4	2 (22.2)	2 (25)
Headache	4	2 (22.2)	2 (25)
Dry mouth	3	3 (33.3)	0 (0)
Diaphoresis	3	2 (22.2)	1(12.5)
Anxiety/nervousness	2	3 (33.3)	0 (0)
Common cold	2	1 (11.1)	1(12.5)
Urinary retention	2	2 (22.2)	0 (0)
Increased energy, feeling "high"	2	2 (22.2)	0 (0)
Paraesthesias (tingling sensation)	2	2 (22.2)	0 (0)
Restless	2	2 (22.2)	0 (0)
Irritability	2	2 (22.2)	0 (0)
Sadness/ low mood	2	1 (11.1)	1(12.5)
Diarrhea	1	1 (11.1)	0 (0)
Constipation	1	1 (11.1)	0 (0)
Sexual dysfunction	1	1 (11.1)	0 (0)
Chills	1	1 (11.1)	0 (0)
Tense	1	1 (11.1)	0 (0)
Feeling that time goes fast/ speedy	1	1 (11.1)	0 (0)
Decreased appetite	1	1 (11.1)	0 (0)
Reckless	1	1 (11.1)	0 (0)
Stomach pain	1	1 (11.1)	0 (0)
Fall	2	0 (0)	2 (25)
Sinusitis	1	0 (0)	1(12.5)
Bladder infection	1	0 (0)	1(12.5)
Heart palpitation	1	0 (0)	1(12.5)
Other (assault, car accident)	4	2 (22.2)	0 (0)

CHAPTER 5

DISCUSSION, STUDY LIMITATIONS, AND CONCLUSIONS

5.1. STUDY OBJECTIVES

The primary objective of the study was to determine if more subjects who received atomoxetine would be able to remain abstinent from cigarette smoking for a twenty-one day treatment period compared to those who received placebo.

There were four also secondary objectives in the study:

A. Determining if there was a difference in the frequency or severity of withdrawal syndromes in cigarette smokers randomly treated with either atomoxetine or placebo.
B. Assessing the effect of atomoxetine on withdrawal symptoms, including craving and smoking urges.
C. Determining if there was any correlation between successes at stopping smoking during the study and alleviation of withdrawal symptoms observed during the treatment period.
D. Determining the safety of atomoxetine in the study population.

However, before discussing the results, it is important to recognize the significant study issues that limit the usefulness and generalization of the study. These cover several areas, but clearly the small numbers of individuals entered

into the study is the primary concern. The sample size calculation completed prior to the study starting suggested that there needed to be at least 54 individuals in each study arm, and this was not achieved.

5.2. LIMITATIONS OF THE STUDY

A randomized, placebo-controlled, double-blind study design was used to make our groups as similar as possible and eliminate a number of biases related to the selection processes. Nevertheless, the study still has several significant limitations and potential biases, of which five will be discussed.

First of all, the number of participants did not come close to the proposed numbers indicated by the sample size calculation that would be required to have power to identify statistically significant results. It was a major surprise how difficult it proved to recruit individuals to take part in the study, despite strenuous, novel, and continued approaches to recruit patients. This involved visits to multiple organizations, going to places where smokers were based, and placing over 600 posters in a variety of locations. It is perhaps somewhat ironic that despite the widespread pressure to stop smoking, it appears that individual smokers are not as motivated as may be thought. On multiple occasions individuals declined to even hear details about the study, despite purporting to be interested. This difficulty led to the major limitation of the study, namely the fact that only 17 individuals actually took part in the double-blind component of the study.

The second major limitation of the study is linked to the first point, and that is that the statistical findings were far from robust. Because of the small numbers it is very difficult to be confident that even where statistically significant findings were found that they have clinical relevance. In certain, very unusual, situations very small numbers of clinical findings can have a more widespread relevance. For example, when the chances of survival from a spefic cancer over 6 months are usually only 10%, then were an increase to 80% in only a few individuals following administration of a novel medication would be considered of wider significance. However, for most situations this does not apply. In the standard case, as with the present situation, small numbers of subjects means the wide variances that occur between individuals cannot be controlled for.

Furthermore, in the present study there were different findings when completers only were considered as opposed to the last-observation carried forward analysis. The results also varied depending if a mixed-effects model were used or if comparisons were made based upon the change in scores rather than the total scores. All of these findings make it clear that the results were not robust, and should be taken as possibly indicative of utility only.

A third major limitation was the large drop-out rate among the atomoxetine-treatment group. The recommended starting dose for atomoxetine is 40 mg. This was the dose used in the present study. However, less than 50% of those who started on this dose were able to tolerate it for 3 weeks. If this study was to be repeated it would be strongly recommended that a slow dose titration

over 2 – 3 weeks would be carried out. The large number of side-effects experienced by those who took part in the study is a testament to how significantly otherwise healthy individuals were affected. Of interest is the fact that this dose is recommended for all teens and adults over 70 kg, but the mean starting weight of the subjects in the atomoxetine group was 81 kg. The small number of subjects who started the study, and the even smaller number of those treated with atomoxetine who completed it (n=4) affected the statistical power of the study and made the results far less reliable. The limited sample also prevented us from generalization and extrapolation of acquired results. Thus, our findings should be interpreted very cautiously.

Fourthly, the duration of the study was 21 days, during which the effects of atomoxetine on nicotine withdrawal were examined. The duration of the study may not have been long enough to assess the effect of atomoxetine on nicotine withdrawal, especially, taking into account that the first 3-4 weeks of abstinence are considered to be an acute nicotine withdrawal period that represents the high-risk period for relapse. Ideally, far longer study periods would show utility (or otherwise) of atomoxetine in achieving and maintaining abstinence. Thus, in future studies, a 6 or 12 months duration of atomoxetine therapy for nicotine withdrawal may be required to determine any differences between the natural progression of nicotine withdrawal and the time required to observe the therapeutic effect of atomoxetine. Therefore, it should be appreciated that the length of treatment in the present study was experimental and not sufficient

enough to determine a definitive therapeutic effect of atomoxetine on smoking cessation.

Fifthly, because the groups were small, there were differences between them which could have affected the results. Thus, the atomoxetine and placebo group differed (even if not statistically significantly) in terms of gender, education, occupation, income, marital status, history of mental disorder, number with health concerns from smoking, use of medication for medical conditions, length they had been smoking, median length of attempts to quit smoking, median length of previous attempts to stop smoking, and helpfulness of previous medication for smoking cessation. While these differences may not have been statistically significant on an individual basis, in small groups of subjects such differences can conceivably have a significant cumulative effect that could impact the results.

The discussion of the results that follows should take these significant study limitations into account.

5.3. DISCUSSION OF STUDY RESULTS

Despite the significant limitations outlined, the results were of interest, being the first double-blind, placebo-controlled, study to examine the effects on atomoxetine for more than 7 days. Furthermore, there were several indications that in those individuals who could tolerate the side-effects of atomoxetine, there were significant possible advantages compared to placebo. Nonetheless, it was also clear that we failed in our primary study objective. Thus, none of our

volunteers was able to remain abstinent for the 21 day period, so even for those who could tolerate this drug, the benefits were not as great as hoped.

Despite this, it should be recognized that those who stayed on atomoxetine for 21 days had some benefits that taken together would support suggestions that this drug is potentially effective. Thus, they had a reduction in the cigarette dependence scale (CDS) (from a mean of 54 to 27); had a small reduction in the cigarette withdrawal scale (2.0) compared to an increase in the placebo group (5.5); had a marked reduction in the questionnaire of smoking urges (from 368 to 134) while the placebo group had a very minor reduction (from 276 to 272); had a marked reduction in the number of cigarettes smoked during the study (from 43 to 11) while the numbers smoked in the placebo group increased; and supporting the validity of this self-report measure the atomoxetine group had a reduction in their cotinine levels (from 4.1 to 2.8). These findings would support the secondary objectives of the study examining the effects of atomoxetine on the symptoms of nicotine withdrawal.

To our knowledge there has been only one prior study of the use of atomoxetine for smoking cessation, and this was carried out among the ADHD population and for one week only. Given that the starting dose of 40 mg is recommended specifically for this treatment population, and the brief study duration, may explain why the drop-out rate (56%) in this other study was a lot less than in the present study. In the ADHD study Ray et al (2009) conducted randomized a placebo controlled study in 50 non-treatment seeking smokers, treated with either atomoxetine or placebo, for seven days. The study used the

Fagerstrom Test for Nicotine Dependence as their primary outcome measure. Mixed-effects model showed that the use of atomoxetine was associated with a decrease in subjective withdrawal symptoms and smoking urges in this population, suggesting that atomoxetine can decrease craving among ADHD smokers, who may use nicotine to increase arousal.

In the Ray study a different measure of withdrawal was also used, the withdrawal symptom checklist (WSC), and the authors reported that placebo groups had significantly higher scores comparing to those in atomoxetine group (Ray et al., 2009). In the present study we used the cigarette withdrawal scale (CWS) that has been shown to be sensitive and reliable, but we found no changes in the treated group, and there were no statistically significant differences between the placebo group and treated group at any o time points (Week 0, Week1, Week2, Week3) with either the treated group nor in the LOCF analysis. Nonetheless, like the Ray study, the scores on the CWS did increase in the placebo group, peaking at the second week. These somewhat different findings can be explained by differences in the measures and the number of items involved in the assessment, there being only three in the WSC versus twenty-one in the CDS.

Another major methodological difference between the present study and the Ray study was we asked participants to stop smoking at baseline and we then monitored their withdrawal symptoms, along with smoking urges, during the following 3 week period (Ray et al., 2009). In contrast, Ray and colleagues did not ask the subjects to stop smoking and observed changes in withdrawal

symptoms while allowing them to continue to smoke. This approach may, in part, explain the differences in the questionnaire for smoking urges (QSU) score (Ray et al., 2009).

Moreover, the type of the questionnaire and response rating scale could also partially explain these differences. In the present study a 10-item version of QSU scale was used, based upon an analysis carried out by Toll and colleagues (Toll et al., 2006). Also, after obtaining permission from the originator of the scale, Dr. Tiffany, we received his original scoring version that was based on 0-to-100 rating scale. In contrast, Ray and colleagues examined the QSU using a 32-item scale with response scale ratings from 1 to 7 (Ray et al., 2009). The problems with this approach were illustrated by Toll and colleagues, who concluded that there was no consistency in terms of the scoring and the structure of this questionnaire (Toll et al., 2006).

A further difference between the present study and that of Ray and colleagues was that subjects in the present study subjects were treated with 40 mg atomoxetine orally per day for 21 continuous days (Ray et al., 2009). Ray and colleagues used an escalating regime titrating atomoxetine dose from 25 mg a day to 1.2 mg per kg within 7 day study period. This would put the dose for an 81 kg subject at 97 mg per day.

Therefore, given the major differences in population, dose, length of treatment, the use of different outcome measures, and the significant limitations in both the present study and the Ray et al study, further comparisons between

these two studies are not terribly informative. Unfortunately, there are no other studies with which we can compare our results.

When considering our results in more detail, because none of the participants discontinued smoking during the study, we were unable to determine if the severity of dependence would be less in those who were treated with atomoxetine. For this reason we were unable to describe either the type of abstinence or the failure rate of those unable to stay abstinent, which have been examined in other studies (Hughes et al., 2003).

If atomoxetine were useful in nicotine withdrawal, as we hypothesized but were unable to conclusively demonstrate, the possible mechanism of action would remain uncertain. As noted in the introduction , preclinical experiments have repeatedly suggested that noradrenaline plays some, as yet undefined, role in nicotine addiction. Animal experiments with atomoxetine have found the reversal of deficits seen during nicotine withdrawal. Similarly, numerous clinical trials on smoking cessation with drugs that possess noradrenaline reuptake qualities have made these drugs the mainstay of smoking cessation therapy. Furthermore, as also discussed in detail in the introduction, atomoxetine has been shown to be effective in stimulant addictions (Safuoglu 2008, 2009; Weinshenker and Schroeder, 2007), although the possible mechanism of action remains uncertain.

One final point to consider was the possible safety of atomoxetine in smoking cessation. This was one of our secondary outcome measures. The adverse events that were reported in the present study are similar in nature to

those reported previously by other researchers and the manufacturer (Elli Lilly). These were detailed in Table 2.1. However, the frequency of the side effects observed in the present study was higher than those reported in some studies, but consistent or even lower than previous findings related to treatment-associated adverse events in adult studies.

The changes we found in both systolic blood pressure and diastolic blood pressure are consistent with previous studies which have examined these physiological parameters in individuals treated with atomoxetine (Adler et al., 2009; Adler, Spencer et al., 2009; Beglinger et al., 2009; Garnock-Jones et al., 2009; Surman et al., 2010; .

With respect to the high dropout rate that occurred in the present study, more than 50% of our sample in 3 weeks, this is notably higher when compared to other studies. The reason for this isn't clear, except that previous studies with this dose have been in those with ADHD, and not in otherwise healthy individuals.

5.4. CONCLUSIONS

The main objective of our study was to determine if more subjects who received atomoxetine were able to be abstinent from cigarette smoking for a twenty-one day period when compared to a matched group who received placebo.

However, we were unable to determine if our initial hypothesis is likely to be correct. The primary reason for this lack of success was due to the inability to recruit enough subjects into the study, despite strenuous efforts to achieve this. Of the 4 individuals who completed 3 weeks of atomoxetine treatment, none were abstinent. However, there were several indications that this small group did have a lowered amount of smoking compared to those who were given placebo, Thus, we found that the number of cigarettes smoked per week by participants who received atomoxetine was relatively stable or even decreased compared to the placebo group. Nonetheless, there was no statistically significant difference between the two treatment arms in terms of the number of cigarettes smoked per week during the study.

The veracity of the self-reported scores was supported by results from the cotinine saliva test, which was an objective measure to quantify tobacco use in the study volunteers. Cotinine measurements were found to be decreased in the atomoxetine group for those who completed the study compared to the placebo completers.

We also had several secondary objectives in our study. First, we wanted to determine if there is a difference in the frequency or severity of withdrawal symptoms in cigarette smokers randomly treated with either atomoxetine or placebo, as well as to assess the effect of atomoxetine on withdrawal symptoms, including craving and smoking urges. Using a mixed effects model we did not find a difference between measurements of the severity of withdrawal symptoms and craving scores, but we did observe the effect of the baseline on both these

scores and there were several suggestions from the completed group that would warrant further study of this drug as a possible treatment for this important condition. It should also be noted that we found no significant differences between the two groups in terms of measurements of either depressed mood or self-esteem.

We had also wanted to determine if there is any correlation between success at stopping smoking during the study and alleviation of withdrawal symptoms observed during treatment period. However, we were not able to draw any conclusions about this point as none of our study participants successfully stopped smoking.

Our final objective was to provide input about the safety of atomoxetine in this study population. Although our findings did not raise significant safety concerns, we did find that the side-effects of atomoxetine in otherwise relatively healthy smokers led to a large number of drop-outs. Only 45% of those randomized to 40 mg atomoxetine could tolerate it for 3 weeks. One question that this raises is the possible effectiveness and/or tolerability of lower doses. Given that we had a single fixed dose we are not able to comment meaningfully about this, but given the suggestive data, this may be something that is worth pursuing in subsequent research.

In conclusion, the data from the present study support suggestions that there may be some useful role for atomoxetine in the treatment of smoking cessation. However, the size of the study and the limitations addressed mean that

further work is required to determine this more definitively. One matter that will need to be addressed in future studies involves the dose and length of treatment.

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6.2. **References – Chapter 2 – Atomoxetine**

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6.3. **References – Chapter 3 – Methodology**

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6.4. **References - Chapter 5 - Discussion, study limitations, and conclusions**

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7.APPEDNICES

7.1. Appendix 1. Strattera Product Monograph (N.B. – first and last pages only of 50 page document shown here).

PRODUCT MONOGRAPH

Pr STRATTERA®

(atomoxetine capsules)

10, 18, 25, 40, 60, 80 and 100 mg

Selective Norepinephrine Reuptake Inhibitor
for Attention-Deficit/Hyperactivity Disorder (ADHD)

© ELI LILLY CANADA INC. 3650 Danforth Avenue Toronto, Ontario, M1N 2E8. 1-888-545-5972 www.lilly.ca	Date of Revision: September 24, 2009

Submission Control № 131306

The following common side effects were reported in clinical trials with STRATTERA:

In teenagers and children over 6:
- upset stomach
- decreased appetite
- nausea or vomiting
- dizziness
- tiredness
- constipation
- low blood pressure

In Adults:
- constipation
- dry mouth
- nausea
- decreased appetite
- dizziness
- problems sleeping
- sexual side effects
- problems urinating
- menstrual cramps
- rapid or irregular heartbeat
- tiredness

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Swelling or hives			√
Dark urine, yellow skin/ eyes, upper right-sided abdominal tenderness, or flu-like symptoms		√	

This is not a complete list of side effects. For any unexpected effects while taking STRATTERA, contact your doctor or pharmacist.

HOW TO STORE IT

STRATTERA should be stored at room temperature (15 to 30°C).

Keep all medicines, including STRATTERA, out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance by:

- **Toll-free telephone: 866-234-2345**
- **Toll-free fax: 866-678-6789**
- **Online : www.healthcanada.gc.ca/medeffect**
- **By email: CanadaVigilance@hc-sc.gc.ca**
- **By regular mail:**
  Canada Vigilance National Office
  Safety and Effectiveness Information Bureau
  Marketed Health Products Directorate,
  Health Products and Food Branch
  Tunney's Pasture, Address Locator: 0701C
  Ottawa, ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc. at: 1-888-545-5972 or visit the website at *www.lilly.ca*.

This leaflet was prepared by Eli Lilly Canada Inc., Toronto, Ontario, M1N 2E8.

Last revised: September 21, 2009.

7.2. Appendix 2. Study Flow Chart

STUDY FLOW CHART					
	Screening	**Baseline**	**Treatment Period**		
Study Week		**WK 0**	**WK 1**	**WK 2**	**WK 3 (or early termination)**
Study Day (days of the visits)	**-7 days**	**Day 1**	**Day 7**	**Day 14**	**Day 21**
Informed Consent	X				
Inclusion/exclusion criteria	X				
Patient Screening Form (Med/Psych History)	X				
Smoking history	X				
Physical exam (vital signs, weight)	X	X	X	X	X
Standardized Scale (MINI)	X				X
Concomitant medications	X	X	X	X	X
Drugs/Alcohol screen (urine)	X				X
Serum Pregnancy Test	X				
Clinical Labs [a]	X				X
Randomization		X			
Efficacy Assessment					
Dependence scale (CDS		X	X	X	X
Withdrawal (CWS)		X	X	X	X
Craving scale (QSU)		X	X	X	X
Depression Scale (MADRS)		X	X	X	X
Rosenberg Self-esteem scale		X	X	X	X
Urine cotinine assay		X	X	X	X
Compliance		X	X	X	X
Self-monitoring Dairy		X	X	X	X
Patient Visit Form					
Safety assessment					
Adverse Events Form			X	X	X
Study drug dispensing and treatments					
Dispense Study Drug		X	X	X	
[a]Clinical labs: (ALT, AST, PT, albumin, bilirubin, ALP with GGT)					

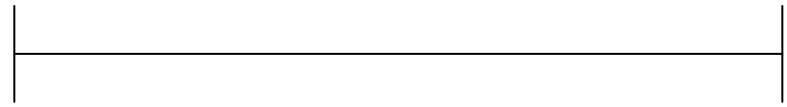
7.3. Appendix 3. Questionnaire for Smoking Urges

QUESTIONNAIRE OF SMOKING URGES (QSU-brief)

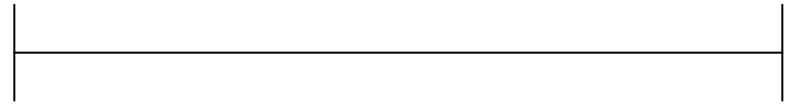
Patient's ID _____ Date_____

INSTRUCTION: Please indicate how much you agree or disagree with each of the following statements by marking your number between 0 and 100 where **0 = STRONGLY DISAGREE** and **100 = STRONGLY AGREE**. Please complete every item. We are interested in how you are thinking or feeling right now, as you are filling out the questionnaire.

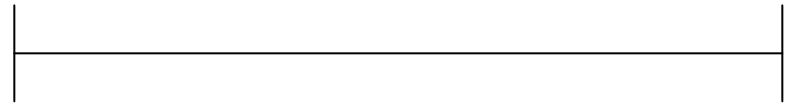
1. I have a strong urge for a cigarette right now



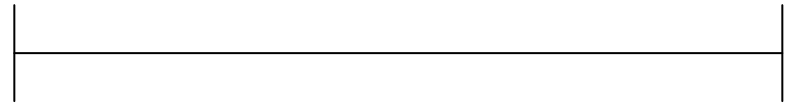
2. Nothing would be better than smoking a cigarette right now.



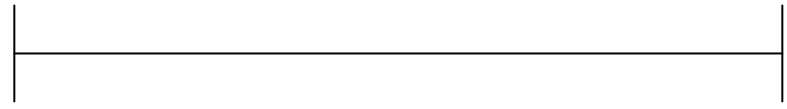
3. If it were possible, I would probably smoke now.



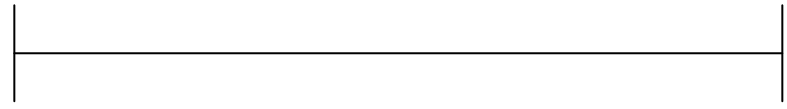
4. I could control things better right now if I could smoke.



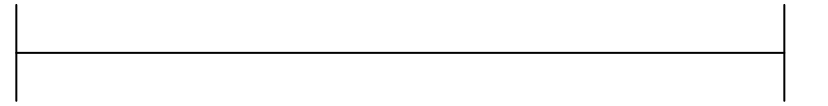
5. All I want right now is a cigarette



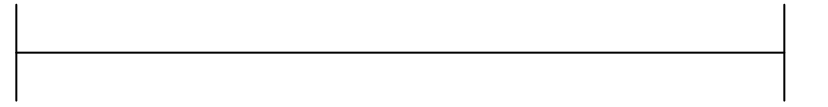
6. I have an urge for a cigarette.



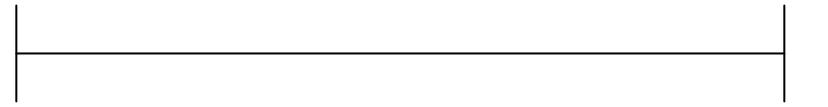
7. A cigarette would taste good now.



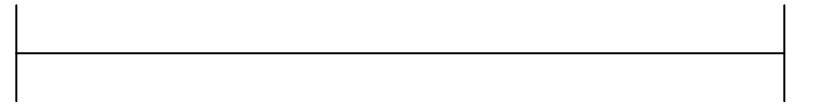
8. I would do almost anything for a cigarette right now.



9. Smoking would make me less depressed.



10. I am going to smoke as soon as possible.



Source: *L.S. Cox; S.T. Tiffany; A.G. Christen. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine and Tobacco Research (2001) 3, 7-16*

7.4. Appendix 4. Montgomery-Åsberg Depression Rating Scale

MONTGOMERY-ÅSBERG DEPRESSION RATING SCALE (MADRS)

Patient's ID_____
Date_____

1. Apparent sadness Representing despondency, gloom and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.	
0. = No sadness.	□
2. = Looks dispirited but does brighten up without difficulty	□
4. = Appears sad and unhappy most of the time.	□
6. = Looks miserable all the time. Extremely despondent.	□

2. Reported sadness Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope.	
0. = Occasional sadness in keeping with the circumstances.	□
2. = Sad or low but brightens up without difficulty.	□
4. = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.	□
6. = Continuous or unvarying sadness, misery or despondency.	□

3. Inner tension Representing feelings or ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.	
0. = Placid. Only fleeting inner tension.	□
2. = Occasional feelings of edginess and ill-defined discomfort.	□
4. = Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.	□
6. = Unrelenting dread or anguish. Overwhelming panic.	□

4. Reduced sleep Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.	
0. = Sleeps as usual.	□
2. = Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.	□
4. = Sleep reduced or broken by at least 2 hours.	□
6. = Less than 2 or 3 hours sleep.	□

5. Reduced appetite Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.	
0. = Normal or increased appetite	□
2. = Slightly reduced appetite.	□
4. = No appetite. Food is tasteless.	□
6. = Needs persuasion to eat at all.	□

6. Concentration difficulties Representing difficulties in collecting one's thoughts mounting to an incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.	
0. = No difficulties in concentrating.	□
2. = Occasional difficulties in collecting one's thoughts.	□
4. = Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.	□
6. = Unable to read or converse without great difficulty.	□

7. Lassitude Representing difficulty in getting started or slowness in initiating and performing everyday activities.	
0. = Hardly any difficulty in getting started. No sluggishness.	□

2. = Difficulties in starting activities.	□
4. = Difficulties in starting simple routine activities, which are carried out with effort.	□
6. = Complete lassitude. Unable to do anything without help.	□

8. Inability to feel Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.	
0. = Normal interest in the surroundings and in other people.	□
2. = Reduced ability to enjoy usual interests.	□
4. = Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.	□
6. = The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.	□

9. Pessimistic thoughts Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.	
0. = No pessimistic thoughts.	□
2. = Fluctuating ideas of failure, self-reproach or self-depreciation.	□
4. = Persistent self-accusation, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.	□
6. = Delusions of ruin, remorse or irredeemable sin. Self-accusations, which are absurd and unshakable.	□

10. Suicidal thoughts Representing the feeling, that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.	
0. = Enjoys life or takes it as it comes.	□
2. = Weary of life. Only fleeting suicidal thoughts.	□
4. = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intension.	□

6. = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.	□

Source: Montgomery SA, Åsberg M: A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979.

7.5. Appendix 5. Self-monitoring diary

Self-Monitoring Dairy: "A wrap-sheet".

Name:

Date:

Week number

Cigarette #	Time of the day	a.m. or p.m.	Craving on the scale from 1 = none to 10 = a lot	Mood on the scale from 1 = very sad to 10 = very happy	Situation or context in which cigarette is smoked
	:				
	:				
	:				
	:				
	:				
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	:				

7.6. Appendix 6. The Mini International Neuropsychiatric Interview

(M.I.N.I.)

M.I.N.I

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

DSV-IV

USA: D.V. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan, E. Knapp, M. Sheehan
University of South Florida – Tampa

FRANCE: Y. Lecrubier, E.Weiller, T. Hergueta, P. Amorim, L.A. Bonora, J.P. Lépine
Hôpital de la Salpètriére - Paris

Patient's ID:		*Protocol Number:*	
Date of Birth:		*Time Interview Began:*	
Interviewer's Name:		*Time Interview Ended:*	
Date of Interview:		*Total Time:*	

MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV	ICD-10
A. MAJOR DEPRESSIVE DISORDER **MDE WITH MELANCHOLIC FEATURES Optional**	Current (2 weeks) Past Current (2 weeks)		296.20-296.26 Single 296.30-296.36 Recurrent 296.20-296.26 Single 296.30-296.36 Recurrent	F32.x F33.x F32.x F33.x
B. DYSTHYMIA	Current (Past 2 years)		300.4	F34.1
C. SUICIDALITY	Current (Past month)			
D. (HYPO)MANIC EPISODE	Current Past		296.00-296.06	F30.x-F31.9
E. PANIC DISORDER	Current (Past Month) Lifetime		300.01/300.21	F40.01-F41.0
F. AGAROPHOBIA	Current		300.22	F40.00
G. SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)		300.23	F40.1
H. OBSESSIVE COMPALSIVE DISORDER	Current (Past Month)		300.3	F42.8
I. POSTTRAUMATIC STRESS DISORDER Optional	Current (Past Month)		309.81	F43.1
J. ALCOHOL DEPENDENCE/ABUSE	Past 12 Months		303.9/305.00	F10.2x/F10.1
K. DRUG DEPENDENCE/ABUSE (Non-alcohol)	Past 12 Months		304.00-.90/305.20-.90	F11.00-F19.1/ F11.2/F19.1
L. PSYCHOTIC DISORDERS	Lifetime Current		295.10-295.90/297.1/ 297.3/293.81/293.82/ 293.89/298.8/298.9	F20.xx-F29
M. ANOREXIA NEVROSA	Current (Past 3 Months)		307.1	F50.0
N.BULIMIA NEVROSA	Current (Past 3 Months)		307.51	F50.2
O.GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)		300.02	F41.1
P.ANTOSOCIAL PERSONALITY DISORDER Optional	Lifetime		301.7	F60.2

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structures interview developed by the World Health Organization for lay interviews for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7±11.6 minutes, median 15 minutes) that the above referred instruments. It can be used by clinicians, after a brief training session. Lay interviews require more extensive training.

INTERVIEW:
In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured that usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:
The M.I.N.I. is divided into modules identifies by letter, each corresponding to a diagnostic category.
At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a gray box.
At the end of each module, diagnostic box(s) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:
Sentences written in "normal font" *should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.*

Sentences written in "CAPITALS" *should not be read to the patient. They are instructions foe the interviewer to assist in the scoring of the diagnostic algorithms.*

Sentences written in "bold" *indicate the time frame being investigated. the interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicate should be considered in scoring the responses.*

Answers with an arrow above them ⟹ *) indicate that one of the criteria necessary for the diagnosis (es) is not met. In this case, the interviewer should go to the end of the module and circle* "NO" *in all the diagnostic boxes and move to the next module.*

When terms are separated by a *slash* (/) the interviewer should read only those symptoms known to be present in the patient (for example, question A5b).

Phrases in (parentheses) are clinical examples if the symptom. These may be read to the patient to clarify the question.

RATING INSTRICTIONS:

All questions must be rated. The rating is done at the right of each question by circling either YES or NO.

The clinician should be sure that each dimension of the questions is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives). Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I.

A. MAJOR DEPERSSIVE EPISODE

(⇨ MEANS: GO TO THE DISGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNSTIC BOXES, AND MOVE TO THE NEXT MOSULE)

A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	NO	YES	1
A2	In the past two weeks, have you been less interested in most things or less able to enjoy the things you used to enjoy most of the time?	NO	YES	2 ⇨
	IS A1OR A2 CODED YES?	NO	YES	
A3	Over the past two weeks, when you felt depressed or uninterested:			
	Was your appetite decreased or increased nearly every day?	NO	YES	3
	Did your weight decreased or increased without trying intentionally (i.e., by ±5% of body weight or ±8 lbs. or ±3.5 kgs, for a 160 lb./70kg. person in a month)? IF YES TO EITHER, CODED YES.	NO	YES	4
	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning waking or sleeping excessively)?	NO	YES	5
	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES	6
		NO	YES	7
	Did you feel tired or without energy almost every day?	NO	YES	8
	Did you feel worthless or guilty almost every day?	NO	YES	9
	Did you have difficulty concentrating or making decisions almost every day?			
	Did you repeatedly consider hurting yourself, feel suicidal, or with you were dead?			
A4	ARE 3 OR MORE A3 ANSWERS CODED YES? (OR 4 A3 ANSWERS IF A1 OR A2 ARE CODED NO)?	NO	YES	***MAJOR DEPRESSIVE EPISODE CURRENT***
IF PATIENT MEETS CRITERIA FOR MAJOR DEPRESSIVE EPISODE CURRENT:				
A5	During your lifetime, did you have other periods of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about?	NO	YES	10 ⇨
	Was there an interval of at least 2 months without depression/loss of interest between your current episode and your last episode of depression?	NO	YES	11

	IS A5b CODED YES?	NO YES ***MAJOR DEPRESSIVE EPISODE PAST***

MAJOR DEPERSSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

(⇨ MEANS: GO TO THE DISGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MOSULE)

IF THE PATIENT CODES POSITIVE FOR A CURRENT MAJOR DEPRESSIVE EPISODE (A4=YES), EXPLORE THE FOLLOWING:

A6	IS A2 CODED YES?	NO	YES	12
	During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up?	NO	YES	13
	IF NO: When something good happens does it fail to make you feel better, even temporarily?	NO	⇨ YES	
	IS EITHER A6a OR A6b CODED YES?			
A7	Over the past two week period, when you felt depressed and uninterested:			
	Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?	NO	YES	14
	Did you feel regular worse in the morning, almost every day?	NO	YES	15
	Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?	NO	YES	16
	IS A3c CODED YES (RETARDATION OR ACTIVATION)?	NO	YES	17
	IS A3c CODED YES (ANOREXIA OR WEIGHT LOSS)?	NO	YES	18
	Did you feel excessive guilt or guilt out of proportion to the reality of the situation?	NO	YES	19
	ARE 3 OR MORE A7 ANSWERS CODED YES?	NO	YES	
		CURRENT MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES		

B. DYSTHYMIA

(⇨ MEANS: GO TO THE DISGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MOSULE)

IF THE PATIENT'S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESSIVE EPISODE, DO NOT EXPLORE THIS MODULE:

B1	Have you felt sad, low or depressed most of the time for the last two years?	NO	⇨ YES	20
B2	Was this period interrupted by your feeling OK for two months or more?	NO	⇨ YES	21
B3	During this period of feeling depressed most of the time: Did your appetite change significantly?	NO	YES	22
	Did you have trouble sleeping or sleeping excessively?	NO	YES	23
	Did you feel tired or without energy?	NO	YES	24
	Did you lose your self-confidence?	NO	YES	25
	Did you have trouble concentrating or making decisions?	NO	YES	26
	Did you feel hopeless?	NO	YES	27
	ARE 2 OR MORE B3 ANSWERS CODED YES?	NO	⇨ YES	
B4	Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?	NO	⇨ YES	28
	IS B4 CODED YES?	NO YES ***DYSTYMIA*** **CURRENT**		

C. SUICIDALITY

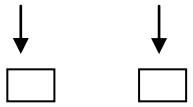
	In the past month did you:			
C1	Think that you would be better off dead or wish you were dead?	NO	YES	1
C2	Want to harm yourself?	NO	YES	2
C3	Think about suicide?	NO	YES	3
C4	Have a suicide plan?	NO	YES	4
C5	Attempt suicide?	NO	YES	5
	In your lifetime:			
C6	Did you ever make a suicide attempt?	NO	YES	6
	IS AT LEAST 1 OF THE ABOVE CODED YES?		NO YES ☐	
	IF YES< SPECIFY THE LEVEL OF SUICIDE RISK AS FOLLOWS:		☐ ***SUICIDE RISK CURRNT***	
	C1 or C2 or C6 =YES: Low		***Low***	
	C3 or (C2 + C6) = YES: Moderate		***Moderate***	
	C4 or C5 or (C3 + C6) = YES: High		***High***	

D. (HYPO) MANIC EPISODE

(⇨ MEANS: GO TO THE DISGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MOSULE)

D 1	Have you ever had a period of time when you were feeling "up" or "high" or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) IF PATIENT IS UZZELED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH', CLARIFY AS FOLLOWS: By 'up' or 'high' I mean: Having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior. IF YES: Are you currently feeling 'up' or 'high' or full of energy?	NO NO	YES YES	1 2
D 2	Have you ever been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? Are you currently feeling persistently irritable? IS D1a or D2a CODED YES?	NO NO NO	YES YES ⇨ YES	3 4
D 3	IF D1b OR D2b = YES: EXPLORE ONLY CURRENT EPISODE IF D1b OR D2b = NO: EXPLORE THE MOST SYMPTOMATIC PAST EPISODE During the times when you felt high, full of energy, or irritable did you: Feel that you could do things others couldn't do, or that you were an especially important person? Need less sleep (for example, feel rested after only a few hours sleep)? Talk too much without stopping, or so fast that people had difficulty understanding? Have racing thoughts? Become easily distracted so that any little interruption could distract you? Become so active or physically restless that others were worried about you?	NO NO NO NO NO NO	YES YES YES YES YES YES	5 6 7 8 9 10 11

	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)? ARE 3 OR MORE D3 ANSWERS CODED YES (OR 4 IF D1a IS NO [PAST EPISODE] OR D1b IS NO [CURRENT EPISODE]?	NO	YES	
D 4	Did these symptoms last as least a week and cause significant problems at home, at work, socially, or at school, or were you hospitalized for these problems? THE EPISODE EXPLORED WAS A:	NO **HYPOMANIC EPISODE**	YES **MANIC EPISODE**	12



ID D4 CODED NO? SPECIFY IF THE EPISODE IS CURRENT OR PAST.	NO ☐ YES ☐ **(HYPO)MANIC EPISODE** CURRENT PAST
ID D4 CODED YES? SPECIFY IF THE EPISODE IS CURRENT OR PAST.	NO ☐ YES ☐ **MANIC EPISODE** CURRENT PAST

E. PANIC DISORDER

(⇨ MEANS: CIRCLE NO IN E5 AMD SKIP TO F1)

E1	Have you, on more, than one occasion, had spells or attacks when you suddenly felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	NO	⇨ YES	1
	Did the spells peak within the 10 minutes?	NO	⇨ YES	2
E2	At any time in the past, did any of these spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	NO	⇨ YES	3
E3	Have you ever had one such attack followed by a month or more of persistent fear of having another attack, or worries about the consequences of the attack?	NO	YES	4
E4	During the worst spell that you can remember: Did you have skipping, racing or pounding of your heart?	NO	YES	5
	Did you have sweaty or clammy hands?	NO	YES	6
	Were you trembling or shaking?	NO	YES	7
	Did you have shortness of breath or difficulty breathing?	NO	YES	8
	Did you have choking sensation or a lump in your throat?	NO	YES	9
	Did you have chest pain, pressure or discomfort?	NO	YES	10
	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES	11
	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES	12
	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES	13
	Did you fear that you were losing control or going crazy?	NO	YES	14
	Did you fear that you were dying?	NO	YES	15
	Did you have tingling or numbness in parts of your body?	NO	YES	16
	Did you have hot flushes or chills?	NO	YES	17
E5	ARE BOTH E3 AND 4 OR MORE E4 ANSWERS CODED YES?	NO	YES ***PD LIFEIME***	
E6	IF E5 = NO, ARE 1,2 or 3 SYMPTOMS IN E4a-m CODED YES? IF YES TO E6, SKIP TO F1.	NO	YES 18 ***LIMITED SYMPTOMS ATTACKS CURRENT***	
E7	In the past months, did you have such attacks repeatedly (2 or more) followed by persistent fear of having another attack?	NO	YES 19 ***PD CURRENT***	

F. AGORAPHOBIA

F1	Do you feel anxious or uneasy in places or situations where you might have a panic attack or the panic–like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crowd standing in a line(queue), when you are alone away at home, or when crossing a bridge, traveling in a bus, train o car?	NO	YES	20
F2	IF F1 = No, CIRCLE No in F2 Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	**NO** **YES** ***AGORAPHOBIA CURRENT***		21

	IS F2 (CURRENT AGORAPHOBIA) CODED NO AND IS E7 (CURRENT AGORAPHOBIA) CODED YES?	**NO YES** ***PANIC DISORDER without Agoraphobia CURRENT***
	IS F2 (CURRENT AGORAPHOBIA) CODED YES AND IS E7 (CURRENT AGORAPHOBIA) CODED NO?	**NO YES** ***PANIC DISORDER with Agoraphobia CURRENT***
	IS F2 (CURRENT AGORAPHOBIA) CODED YES AND IS E5 (PANIC DISORDER LIFETIME) CODED NO?	**NO YES** ***AGORAPHOBIA, CURRENT without history of Panic Disorder***

G. SOCIAL PHOBIA (Social Anxiety Disorder)

(⇨ MEANS: GO TO THE DISGNOSTIC BOX, CIRCLE NO , AND MOVE TO THE NEXT MOSULE)

G1	In the past month, were you fearful or embarrassed being watched, being the focus of attention, fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	NO	YES	1
G2	Is this fear excessive or unreasonable?	NO	YES	2
G3	Do you fear these situations so much that you avoid them or suffer through them?	NO	YES	3
G4	Does this fear disrupt you normal work or social functioning or cause you significant distress?	NO	YES	4
	IS G4 CODED YES?	**NO**	**YES**	
		SOCIAL PHOBIA (Social Anxiety Disorder) CURRENT		

H. OBSESSIVE-COMPULSIVE DISORDER

(⇨ MEANS: GO TO DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

H1.	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive or distressing? (for example, the idea that you were dirty, contaminated, or had germs, or fear of contaminating others, or fear of harming someone even though you did not want to, or fearing you would ask on some impulse, or fear or superstitions you would be responsible for things going wrong, or obsessive with sexual thoughts, images or impulses, or hoarding, collecting, or religious obsessions). (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSSIONS DIRECTLY REALTED TO EATING DISORDERS, SEXUAL DIVIATIONBS, PATHOLOGIC GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM ACTIVITY AND MAY WANT TO RESIST IT ONLY BECASUE ITS NEGATIVE CONSEQUENCES).	NO ⇨ to H4	YES	1
H2.	Did you keep coming back in to your mind even when you tried to ignore or get rid of them?	NO ⇨ toH4	YES	2
H3.	Do you think that these obsessions are the product of your own mind and that they are not impose for the outside? Obsessions	NO	YES	3
H4.	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?	NO	YES	4
	ARE H3 OR H4 CODED YES? Compulsions	⇨ NO	YES	
H5.	Did you recognize that either these obsessive thoughts or these compulsive behaviours were excessive or unreasonable?	⇨ NO	YES	5
H6.	Did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, occupation functioning, usual social activities, or relationships, or did they take more than one hour a day?	NO	YES ***O.C.D. CURRENT***	

I. POSTTRAUMATIC STRESS DISORDER (optional)

(⇨ MEANS: GO TO THE DISGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MOSULE)

I1	Have you ever experienced or witnessed or had to deal with an extremely traumatic even that included actual or threatened death or serious injury to you or someone else? EXAMPLEAS OF TRAUMTIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSALT, OR TERRORIST ATTACK, BEING HELD HOSTIGE, KIDNAPPING, FAIR, DICOVERING A BODY, SUDDEN DEATH OF SOMEONE CLOSE TO YOU, WAR, OR NATURAL DISASTER.	NO	⇨ YES	1
I2	During the past month, have you re-experienced the event in a distressing way (such as, dreams, intense recollections, flashbacks, or physical reactions)?	NO	⇨ YES	2
I3	In the past month: Have you avoided thinking about the event , or have you avoided things that remained you of the event?	NO	YES	3
	Have you had trouble recalling some important part of what happened?	NO	YES	4
	Have you become les interested in hobbies or social activities?	NO	YES	5
	Have you felt detached or estranged from others?	NO	YES	6
	Have you noticed that feelings numb?	NO	YES	7
	Have you felt that your life would be shortened because of this trauma?	NO	YES	8
	ARE 3 OR MORE I3 ANSWERS CODED YES	NO	⇨ YES	
I4	In the past month: Have you had difficulty sleeping?	NO	YES	9
	Where you especially irritable or did you have outbursts of anger?	NO	YES	10
	Have you had difficulty concentrating?	NO	YES	11
	Where you nerves or constantly on your guard?	NO	YES	12
	Where you easily startled?	NO	YES	13
	ARE 2 OR MORE I4 ANSWERS CODED YES?	NO	⇨ YES	
I5	During the past month, have these problem significantly interfered with your work or social activities, or cause significant distress/	NO	YES	14
	IS I4 CODED YES?	**NO**	**YES**	
		PTSD CURRENT		

J. ALCOHOL ABUSE AND DEPENDENCE

(⇨ MEANS GO TO DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

			⇨	
J1	In the past 12 months, have you had 3 or more alcoholic drinks within 3 hour period on 3 or more occasions?	NO	YES	1
J2	In the past 12 months: Did you need to drink more to get the same effect that you got when you first started drinking?	NO	YES	2
	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hangover, for example, "the shakes", sweating or agitated? IF YES TO EITHER, CODE YES.	NO	YES	3
	During the times when you drink alcohol did you end up drinking more than you planned when you started?	NO	YES	4
	Have you tried to reduce drinking or stop drinking alcohol but failed?	NO	YES	5
	On the days that you drank, did you spent substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES	6
	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES	7
	Have you continued to drink even though you knew that the drinking caused you health or mental problems?	NO	YES	8
	ARE 3 OR MORE J2 ANSWERS CODED YES?	**NO**	**YES**	
		ALCOHOL DEPENDENCE **CURRENT**		
J3.	In the past 12 months: Have you been intoxicated, high, or hung-over more than once when you had other responsibilities at school, at work, or at home?	NO	YES	9
	Did this cause any problems? (CODED YES ONLY IF THIS CAUSED PROBLEMS)	NO	YES	10
	Were you intoxicated in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, and est.?	NO	YES	11
	Did you have any legal problems because of your driving, for example, an arrest or disorderly conduct?	NO	YES	12
	Did you continue to drink even though you drinking caused problems with your family or other people?			
	ARE 1 OR MORE J3 ANSWERS CODED YES?	**NO**	**YES**	
		ALCOHOL ABUSE **CURRENT**		

K. NON-ALCOHOLIC PHSYCHOACTIVE SUBSTANCE USE DISORDERS

(⇨ MEANS GO TO DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

K1	Now I am going to show you/ read to you a list of street drugs or medicines In the past 12 month, did you take any of these drugs more than ones, to get high, to feel better, or to change your mood?	NO	YES ⇨

CIRCLE EACH DRUG TAKEN:
Stimulants: amphetamines, "speed", crystal meth, "rush", Dexedrine, Ritalin, diet pills.
Cocaine: snorting, IV, freebase, crack, "speedball".
Narcotics: heroine, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon.
Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("Angel Dust"), ("peace pill"), psilocybin, STP, "mushrooms", ecstasy, MDA, or MDMA.
Inhalants: " glue", ethylene chloride, nitrous oxide, (laughing gas"), amyl or butyl nitrate ("poppers").
Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".
Tranquilizers: quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown.
Miscellaneous: steroids, non-prescriptions sleep or diet pills. Any other?
SPECIFY MOST USED DRUG(S):

_____

SPECIFY WHICH WILL BE EXPLORED IN CRITERISA BELOW:
IF CONCURRECNT OR SEQUENTAL POLYSUBSTANCE USE:

EACH DRUG CALSS USED INDIVIDUALLY. ☐
MOST USED DRUG CLASS ONLY. ☐
ONLY ONE DRUG/ DRUG CLASS BEEN USED. ☐

K2	Considering your use of (NAME THE DRUG/DRUG CLASS SELECTED), in the past 12 months: Have you found that you needed to use more (NAME OF DRUG/DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	NO	YES	1
	When you reduced or stopped using (NAME OF THE DRUG/DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, feeling agitated, anxious, irritable, or depressed)? Did you use any drug (s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better? IF YES TO EITHER, CODED YES	NO	YES	2
		NO	YES	3
	Have you often found that when you used (NAME OF THE DRUG/DRUG CLASS SELECTED), you ended up taking more than you thought you would?	NO	YES	4
	Have you tried to reduce or stop taking (NAME OF THE DRUG/DRUG CLASS SELECTED), but failed?	NO	YES	5
	On the days that you used (NAME OF THE DRUG/DRUG CLASS SELECTED), did you spend substantial time (> 2 hours), obtaining, using or in recovering form then drug, or thinking	NO	YES	6

	about the drug? Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? Have you continue to use (NAME OF THE DRUG/DRUG CLASS SELECTED), even though it caused you health or mental problems?	NO	⇨ YES	7
	ARE 3 OR MORE K2 ANSWERS CODE YES? SPECIFY DRUG(S): _____	**NO**	**YES** ***DRUG DEPENDENCE*** **CURRENT**	

Considering your use (NAME THE DRUG/DRUG CLASS SELECTED), in the past 12 months:

K3	Have you been intoxicated, high, or hung-over from (NAME OF THE DRUG/DRUG CLASS SELECTED) more than ones, when you had other responsibility at school, at work, or at home? Did this cause any problem? (CODE YES ONLY IF THIS CAUSED PROBLEMS.)	NO	YES	8
	Have you been high or intoxicated from (NAME OF THE DRUG/DRUG CLASS SELECTED) in any situation when you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)?	NO	YES	9
	Did you have any legal problems because of your drug use, for example, an arrest or disorderly conduct?	NO	YES	10
	Did you continue to use (NAME OF THE DRUG/DRUG CLASS SELECTED), even though it caused problems with your family or other people?	NO	YES	11
	ARE 1 OR MORE K3 ANSWERS CODED YES? SPECIFY DRUG(S):_____	**NO**	**YES** ***DRUG ABUSE*** **CURRENT**	

L. PSYCHOTIC DISORDERS

ASK FOR AN EXAMPLE OF EACH QUESTION ANSEWERED POSITEVELY. CODE YES ONLY IF EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHTS OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZZZARE".

DELUSIONS ARE "BIZZARE" IF: CLEARILY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDUBLE, AND CAN NOT DERIVE FROM ORDINARY LIFE EXPARIENCE.

HALLUCINATIONS ARE SCORED "BIZZARE" IF : A VOICE COMMENTS ON THE PRESON'S THOUGHTS OR BAHAVIOUR, OR WHEN RWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

Now I going ask you about unusual experience that people have.				BIZZ ARE	
L1	Have you ever believe that people were spying on you m or that someone was plotting against you or tried to heart you? NOTE: ASK FOR EXAMMPLES, TO RULE OUT ACTUAL STALKING. IF YES: do you currently believe these things?	NO NO	YES YES	YES YES ⇨ L6	1 2
L2	Have you ever believe that someone was reading your mind or could hear you thoughts, or that you could actually read someone's mind or hear what another person was thinking? IF YES: do you currently believe these things?	NO NO	YES YES	YES YES ⇨ L6	3 4
L3	Have you ever believe that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC. IF YES: do you currently believe these things?	NO NO	YES YES	YES YES ⇨ L6	5 6
L4	Have you ever believe that you were being sent special messages though the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you? IF YES: do you currently believe these things?	NO NO	YES YES	YES YES ⇨ L6	7 8
L5	Have your relatives or friends ever considered any of your believes strange or unusual? INTERVIEWER: ASK FOR EXAMPLES. ONLY CODED YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS L1 TO L4, FOR EXAMPLE, GRANDIOCITY, HYPOCHONDRIASIS, RUIN, GUILT, ECT. IF YES: do they currently consider your beliefs strange?	NO NO	YES YES	YES YES	9 10

L6	Have you ever heard things other people could not hear, such as voices? HALLUCINATINS ARE SCORD "BIZZARE" ONLY IF PATIENT ANSWERSS YES TO THE FOLLOWING: Did you hear a voice commenting on your thoughts or behaviour or did you hear to or more voices talking to each other? IF YES: Have you heard these things in the past month?	NO NO	YES YES	YES YES YES ⇨ L8b	11 12
L7	Have you ever had visions when you were awake or have you ever seen things other people could not see? CLINICIAN: CKECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE. IF YES: have you seen these things in the past month?	NO NO	YES YES		13 14
	CLINICIAN'S JUDGEMENT				
L8	b. IS THE PATIENT CURRENLY EXIBITING INCOHERENCE, DISORGINIZED SPEECH, OR MAKED LOOSENING OF ASSOCIATIONS?	NO	YES		15
L9	b. IS THE PATIENT CURRENLY EXIBITING DISORGINIZED OR CATATONIC BEHAVIOUR?	NO	YES		16
L10	b. ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, A.G., SIGNIFICANT AFFFECTIVE FLATENING, POVERTY OF SPEECH, (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW?	NO	YES		17
L11	ARE 1 OR MORE "b" QUESTIONS CODED YES BIZZARE? OR ARE 2 OR MORE "a" QUESIONS CODED YES (RATHER THAN YES BIZZARE)?	**NO**	**YES** ***PSYCHOTIC* SYNDROME CURRENT**		
L12	ARE 1 OR MORE "b" QUESTIONS CODED YES BIZZARE? OR ARE 2 OR MORE "a" QUESIONS CODED YES (RATHER THAN YES BIZZARE)? CHECK THAT THE TWO SYMPTOMS OCCURED DURING THE SAME TIME PERIOD. OR IS L11 CODED YES?	**NO**	**YES** ***PSYCHOTIC* SYNDROME LIFETIME**		
L13	IF L12 IS CODED YES AND AT LEAST ONE YES FROM L1 TO L7: DO THE SYMPTOMS CODED YES FOR EITHER MAJOR DEPRESSIVE EPISODE, (CURRENT) OR MANIC EPISODE, (CURRENT OR PAST)?	**NO**	**YES**		

	IF L13 IS CODED YES: You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable). Were the beliefs and experiences you just described (SYMPTOMS CODED YES FROM L1 TO L7) restricted exclusively to times when you were feeling depressed/ high/irritable?	**NO** **YES** **18** ***MOOD DISORDER WITH PSYCHOTIC FEATUES CURRENT***

M. ANOREXIA NERVOSA

(⇨ MEANS GO TO DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

M1	How tall are you? What was your lowest weight in the past 3 months? IS THE PATIENT WEIGHT LOWER THAN THE THRESHOLD CORRESPONDING TO HIS/HER HEIGHT? (SEE TABLE BELOW)	Ft. ☐☐☐ in. ☐☐☐ cm. ☐☐☐ lbs. ☐☐☐ kgs. ⇨ NO	YES	1
M2	In the past 3 months: In spite of this low weight, have you tried not to gain weight?	NO	⇨ YES	2
M3	Have you feared gaining weight or becoming fat, even though you were underweight?	NO	⇨ YES	3
M4	Have you considered yourself fat or that part of your body was too fat? Has your body weight or shape greatly influenced how you felt about yourself? Have you thought your current low body weight was normal or excessive?	NO NO NO	YES YES YES	4 5 6
M5	ARE 1 OR MORE ITEMS FROM M4 CODED YES?	NO	⇨ YES	
M6	FOR FOMEN ONLY: during the last 3 months, did you miss all your menstrual periods, when they were expected to occur (when you were not pregnant)?	NO	⇨ YES	7
	FOR FOMEN: ARE M5 OR M6 CODED YES? FOR MEN: IS M5 CODED YES?	**NO**	**YES**	
		***ANOREXIA NERVOSA* CURRENT**		

TABLE HEIGHT/WEIGHT THRESHOLD (height-without shoes; weight – without clothing)

Female height/weight														
Ft/in	4’9	4’10	4’11	5’0	5’1	5’2	5’3	5’4	5’5	5’6	5’7	5’8	5’9	5’10
Lbs	84	85	86	87	89	92	94	97	99	102	104	107	110	112
Cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs	38	39	39	40	41	42	43	44	45	46	47	49	50	51

Male height/weight															
Ft/in	5’1	5’2	5’3	5’4	5’5	5’6	5’7	5’8	5’9	5’10	5’11	6’0	6’1	6’2	6’3
Lbs	105	106	108	110	111	113	115	116	118	120	122	125	127	130	133
Cm	155	156	160	163	165	168	170	173	175	178	180	183	185	188	191
kgs	47	48	49	50	51	51	52	53	54	55	56	57	58	59	62

The weight thresholds above are calculated as a fifteen percent reduction below the normal range for the patient’s height and gender as required by DSM-IV. This table reflects weights that are 15 % lower than the low end of the normal distribution range in the Metropolitan Life Insurance Table of Weights.

N. BULIMIA NERVOSA

(⇨ MEANS GO TO DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

N1	In the past 3 months, did you have you eating binges or times when you eat a very large amount of food within 2 hours period?	NO	⇨ YES	8
N2	In the last 3 months, did you have eating binges as often as twice a week?	NO	⇨ YES	9
N3	During these binges, did you feel that you eating was out of control?	NO	⇨ YES	10
N4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	NO	⇨ YES	11
N5	Does your body weight or shape greatly influenced how you feel about yourself? IF PATIENT'S SYMPTOMS DO NOT MEET CRITERIA FOR ANOREXIA NEVROSE, SKIP QUESTION N6 AND CODE DIAGNOSTIC BOXES.	NO	⇨ YES	12
N6	DO THE PATIETN'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NEVROSA? IF N6 =NO, SKIP TO N8	NO	YES	13
N7	Do these binges occur only when you are under (_____lbs/kgs)? (INTERVIEWER: WRITE IN THE ABOUVE PARENTHESES THE THRESHOLD WEIHT FOE THIS PATIENT'S HEITH FORN THE HEITH/WEIGHT TABLE IN ANOREXIA NEVROSA MODULE).	NO	YES	14
N8	IS N5 CODED YES AND N7 CODED NO OR SKIPPED?	**NO YES** ***BULIMIA NERVOSA*** **CURRENT**		
	IS N7 CODED YES?	**NO YES** ***BINGE EATING/PURGING TYPE*** **CURRENT**		

O. GENERALIZED ANXIETY DISORDER

(⇨ MEANS GO TO DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

O1	Have you worried excessively or been anxious about several things over the past 6 months? Are these worries present most days?	NO	⇨ YES	1
	ARE BOTH O1a AND O1b CODED YES?	NO	YES	2
	IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PROIOR TO THIS POINT?	NO NO	⇨ YES ⇨ YES	3
O2	Did you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?	NO	⇨ YES	4
O3	FOR THE FOLLWING, CODED NO IF THESE SYMPTOMS CONFINED TO FEATURES OF ANY DISORDER EXPOLORED PRIOR TO THIS POINT. When you were anxious over the past 6 months, did you, most of the time:	NO	YES	5
	Feel restless, keyed up or on edge?	NO	YES	6
	Feel tense?	NO	YES	7
	Feel tired, weak or exhausted easily?	NO	YES	8
	Have difficulty concentrating or find your mind going blank?	NO	YES	9
	Feel irritable?	NO	YES	10
	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning waking, or sleeping excessively)?			
	ARE 3 OR MORE O3 ANSWERS CODED YES?	**NO**	**YES** ***GENERALIZED ANXIETY DISORDER*** **CURRENT**	

P. ANTISOCIAL PERSONALITY DISORDER (optional)

P1	Before you were 15 years old, did you:			
	Repeatedly skip school or run away from home over night?	NO	YES	1
	Repeatedly lie, cheat, "con" others, or steal?	NO	YES	2
	Start fights or bully, threaten, or intimidate others?	NO	YES	3
	Deliberately destroy things or start fires?	NO	YES	4
	Deliberately hurt animals or people?	NO	YES	5
	Force someone to have sex with you?	NO	YES	6
	ARE 2 OR MORE P1 ANSWERS CODED YES? DO NOT CODE YES TO THE BEHAVIOURS BELOW IF THEY ARE EXCLUSIVELY POLITICAL OR RELIGIOUSLY MOTIVATED.	NO	⇨ YES	
P2	Since you were 15 years old have you:			
	Repeatedly behave in a way that others would consider irresponsible, like failing to pay for things you owned, deliberately being impulsive, or deliberately not working to support yourself?	NO	YES	7
	Done things that are illegal even if you did not get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony?	NO	YES	8
	Be in physical fights repeatedly (including physical fights with you spouse or children)?	NO	YES	9
	Often lied or "coned" other to get money or pleasure, or lied just for fun?	NO	YES	10
	Exposed others to danger without caring?	NO	YES	11
	Felt no guild after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES	12
	ARE 3 OR MORE P2 QUESTIONS CODED YES?	**NO**	**YES**	
		ANTISOCIAL PERSONALITY DISORDER **LIFETIME**		

7.7.Appendix 7. Cigarette Dependence Scale

The Cigarette Dependence Scale (CDS)

Patient's ID_____
Date_____

Please mark your answer in appropriate square.

Questions	Variant of answer	Your answer
1. Please rate your addiction to cigarettes on a scale of 0 to 100: 0 = I am NOT addicted to cigarettes at all 100 = I am extremely addicted to cigarettes	0 – 20 21 – 40 41 – 60 51 – 80 80 – 100	□ □ □ □ □
2. On average, how many cigarettes do you smoke per day?	0 – 5 cig/day 6 – 10 11 – 20 21 – 29 30 and +	□ □ □ □ □
3. Usually, how soon after waking up do you smoke your first cigarette?	0 – 5 min 6 – 15 6 – 30 31 – 60 61 and +	□ □ □ □ □

4. For you, quitting smoking for good would be:	Impossible Very difficult Fairly difficult Fairly easy Very easy	□ □ □ □ □

Please indicate whether you agree with each of the following statements:

	Totally disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Fully agree
5. After a few hours without smoking I feel an irresistible urge to smoke	□	□	□	□	□
6. the idea of not having any cigarettes causes me stress	□	□	□	□	□
7. Before going out I always make sure that I have cigarettes with me	□	□	□	□	□
8. I am prisoner of cigarettes	□	□	□	□	□
9. I smoke too much	□	□	□	□	□
10. Sometimes I drop everything to go out and buy cigarettes	□	□	□	□	□
11. I smoke all the time	□	□	□	□	□
12. I smoke despite the risk to my health	□	□	□	□	□

Source: J.-F. Etter; J.Le Houezec; T.P. Perneger. A self-administered questionnaire to measure dependence on cigarettes: The Cigarette Dependence Scale. Neuropsychopharmacology 2003; 28, 359-370

7.8. Appendix 8. Cigarette Withdrawal Scale

The Cigarette Withdrawal Scale (CWS)

Patient's ID_____ Date_____

INSTRUCTION: The following statements describe how you feel today. Please indicate if you agree with each of these statements by circling the appropriate number. Please provide answers all statements.

Item	Totally disagree	Mostly disagree	More or less agree	Mostly agree	Totally agree
Depression–anxiety					
I feel depressed	1	2	3	4	5
My morale is low	1	2	3	4	5
I feel worried	1	2	3	4	5
I feel anxious	1	2	3	4	5
Craving					
The only thing I can think about is smoking a cigarette	1	2	3	4	5
I miss cigarettes terribly	1	2	3	4	5
I feel an irresistible need to smoke	1	2	3	4	5
I would like to hold a cigarette between my fingers	1	2	3	4	5
Irritability–impatience					
I am irritable	1	2	3	4	5
I get angry easily	1	2	3	4	5
I have no patience	1	2	3	4	5
I feel nervous	1	2	3	4	5
Difficulty concentrating					
I find it difficult to think clearly	1	2	3	4	5
I find it hard to concentrate	1	2	3	4	5
I find it hard to focus on the task at hand	1	2	3	4	5
Appetite–weight gain					
I am eating more than usual	1	2	3	4	5
My appetite has increased	1	2	3	4	5
I have put on weight recently	1	2	3	4	5
Insomnia					
I have difficulty sleeping	1	2	3	4	5
I wake up often during the night	1	2	3	4	5
I have trouble falling asleep at night	1	2	3	4	5

Source: J.F. Etter. A self-administered questionnaire to measure cigarette withdrawal symptoms: The Cigarette Withdrawal Scale, Nicotine & Tobacco Research, 2005

7.9.Appendix 9. Rosenberg Self-Esteem Scale

Rosenberg Self-Esteem Scale (SES)

Patient ‘s ID_____ Date_____

Instructions: Below is a list of statements dealing with your general feelings about yourself. Please indicate whether you strongly agree, agree, disagree, or strongly disagree with the statement.

	STATEMENT	Strongly Agree	Agree	Disagree	Strongly Disagree
1.	I feel that I am a person of worth, at least on an equal plane with others.	○	○	○	○
2.	I feel that I have a number of good qualities..	○	○	○	○
3.	All in all, I am inclined to feel that I am a failure.	○	○	○	○
4.	I am able to do things as well as most other people.	○	○	○	○
5.	I feel I do not have much to be proud of.	○	○	○	○
6.	I take a positive attitude toward myself.	○	○	○	○
7.	On the whole, I am satisfied with myself.	○	○	○	◉
8.	I wish I could have more respect for myself.	○	○	○	○
9.	I certainly feel useless at times.	○	○	○	○
10.	At times I think I am no good at all.	○	○	○	○

Source: 1.Rosenberg, M. (1965). Society and the adolescent self-image. Princeton, NJ: Princeton University Press. 2.Crandal, R. (1973). The measurement of self-esteem and related constructs, Pp. 80-82 in J.P. Robinson & P.R. Shaver (Eds), Measures of social psychological attitudes. Revised edition. Ann Arbor: ISR.

7.10.Appendix 10. Patient Visit Form

PATIENT VISIT FORM

Effect of Atomoxetine on nicotine withdrawal: pilot, double-blind, randomized, placebo-controlled study

Primary Investigator Name: Dr. Peter Silverstone
Co-investigator Name: Dr. Rana Dadashova

*Patient ID:*_____ *Date:* _____

*Visit#:*_____ *Week#:*_____

Date when Consent Form signed
dd/mmm/yyyy): _____
Attendance
Did the patient attend the visit? 1. ☐ Yes ☐ Scheduled ☐ Unscheduled 2. ☐ No ☐ Reason: _____
Adverse Event
Since the previous visit, has the patient experienced any adverse events? ☐ No ☐ Yes → adverse event form
Efficasy Assessment
1.Has a Cigarette Dependence Scale been completed? ☐ No ☐ Score: _____ 2. Has a Cigarette Withdrawal Scale been completed? ☐ No ☐ Score: _____ 3.Has a Questionnaire for Smoking Urges been completed? ☐ No ☐ Score: _____ 4.Has a Montgomery-Åsberg Depression Rating Scale been completed? ☐ No ☐ Score: _____ 5.Has a Rosenberg Self-Esteem Scale been completed?

☐ No
☐ Score: _____

6.Has a Self-Monitoring Diary been completed?

☐ No
☐ Score: _____

Cotinine Saliva Assay

Has the assay been performed?

☐ No
☐ Yes, (dd/mmm/yyyy): _____

☐ Saliva cotinine level: _____ ng/mL

Does the cotinine level in saliva changed comparing to baseline or previous assay values?

☐ No
☐ Yes Describe:

_____

Concomitant Mediactions

Were any medications initiated since last visit?

☐ No
☐ Yes
☐ Date of initiation: (dd/mmm/yyyy): _____
☐ Reason for drug initiation:

_____

☐ Name of the drug and dose:_____

_____

_____

Status of Patient During the Study

Is the patient continuing in the study?

☐ Yes
☐ No
☐ Due to adverse event
☐ Death
☐ Drop out
☐ Interruption or discontinuation of medication
☐ Initiation of contraindicated drug(s)
☐ Drug or alcohol abuse
☐ Abnormalities of laboratory data
☐ Abnormal Saliva Cotinine Assay
☐ Lost for follow-up
☐ Other _____

Compliance with the Prescription

Number of tablets dispensed at last visit: _____

(Note: tablets = blisters)

Have all tablets delivered at the previous visit been returned?

☐ Yes → Number of tablets returned:_____ Reason for not taking drug:_____

☐ No → Estimated umber of tablets taken:_____ Reason for not taking drug:_____

Study Medication Dispensation

☐ Yes (dd/mmm/yyyy): _____

☐ No: _____

NUMBER OF DISPENSED STUDY MEDUCATION _____

Signature of Primary Investigator: _____ Signature of Co-investigator Initials: _____

7.11Appendix 11. The Declaration of Helsinki

NB First page only

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

7.12.Appendix 12. The Poster

7.13.Appendix 13. Physical Exam Form

PHYSICAL EXAM FORM

Effect of Atomoxetine on nicotine withdrawal:
pilot, double-blind, randomized, placebo-controlled study

Primary Investigator Name: Dr. Peter Silverstone
Co-investigator Name: Dr. Rana Dadashova

Patient's ID:_____

VITAL SIGNS					
Measurement	Screening visit	Baseline visit (week 0)	Week 1	Week 2	Week 3 (Final visit)
Date (dd/mm/yy)					
Blood pressure (hg/mm)					
Pulse (bpm)					

WEIGHT					
Measurement	Screening visit	Baseline visit (week 0)	Week 1	Week 2	Week 3 (Final visit)
Date (dd/mm/yy)					
Weight (kg)					

7.14.Appendix 14. Concomitant Medications

CONCOMITANT MEDICATION FORM

Effect of Atomoxetine on nicotine withdrawal:
pilot, double-blind, randomized, placebo-controlled study

Primary Investigator Name: Dr. Peter Silverstone
Co-investigator Name: Dr. Rana Dadashova

Patient's ID:_____

Appendix 15. Adverse Event Form 7.15.Appendix 15. Adverse Event Form

Medication Name, Dose, & Route	Start Date	Reason	Stop Date	Reason

ADVERSE EVENT FORM

Effect of Atomoxetine on nicotine withdrawal: pilot, double-blind, randomized, placebo-controlled study

Primary Investigator Name: Dr. Peter Silverstone
Co-investigator Name: Dr. Rana Dadashova

Date:_____ Patient ID_____

Adverse Event	
Date of onset:	**(dd/mmm/yyyy): _____**
Signs & Symptoms:	
Date of termination	**(dd/mmm/yyyy): _____**
Causal relationship with the study drug	☐ **Yes: _____** ☐ **No: Indicate the diagnosis below**
Diagnosis: (if adverse event was not related to use of atomoxetine)	
Action taken due to the adverse event regarding the study drug	☐ No changes in study drug ☐ Drug withdrawn ☐ Withdrawal from study
Has this event required a new treatment	☐ No ☐ Yes _____
Serious Adverse Event	☐ **None** ☐ **Death** Date (dd/mmm/yyyy):_____ Reason:_____ ☐ Sudden ☐ Not sudden ☐ H**ospitalization or Emergency Department Visit** Date: (dd/mmm/yyyy)_____ Reason:_____

	☐ Study Drug Overdose ☐ Other drug overdose ☐ **Disability / Incapacity** ☐ Due to Study Drug Consumption ☐ Other reasons _____ ☐ **Pregnancy**
Re-occurrence of Adverse Event	☐ No ☐ Yes
Outcome	☐ ***Recovered*** ☐ Recovered with sequelae:_____ ☐ Recovering / improving ☐ Not recovered ☐ Fatal

Co-investigator Signature:
_____Date:_____

7.16.Appendix 16. Dispensation/Compliance Form

DISPENSATION/COMPLIANCE FORM

Effect of Atomoxetine on nicotine withdrawal: pilot, double-blind, randomized, placebo-controlled study

Primary Investigator Name: Dr. Peter Silverstone
Co-investigator Name: Dr. Rana Dadashova

Patient's ID:_____

DISPENSATION OF THERAPEUTIC UNIT				
	Baseline visit (week 0)	Week 1	Week 2	Week 3 (Final visit)
Date (dd/mm/yy)				
Number indicated on the bottle				
Number of pills in the botttle				

RETURN OF THERAPEUTIC UNIT				
	Baseline visit (week 0)	Week 1	Week 2	Week 3 (Final visit)
Date (dd/mm/yy)				
Number indicated on the bottle				
Number of pills in the botttle				

7.17.Appendix 17. Cotinine Saliva Test Record Form

COTININE SALIVA TEST RECORD FORM

Effect of Atomoxetine on nicotine withdrawal: pilot, double-blind, randomized, placebo-controlled study

Primary Investigator Name: Dr. Peter Silverstone
Co-investigator Name: Dr. Rana Dadashova
Patient's ID:_____

RESULTS OF COTININE SALIVA TESTS					
Measurements	Screening visit	Week 0 (Baseline visit)	Week 1	Week 2	Week 3 (Final visit)
level 0 - *1-10 ng/ml*, level 1 - *10-30 ng/ml*, level 2 - *30-100 ng/ml*, level 3 - *100-200 ng/ml*, level 4 - *200-500 ng/ml*, level 5 - *500-2000ng/ml*, level 6 - *2000+ ng/ml.*					

7.18.Appendix 18. Patient Baseline Form

PATIENT BASELINE FORM

Effect of Atomoxetine on nicotine withdrawal: pilot, double-blind, randomized, placebo-controlled study

Primary Investigator Name: Dr. Peter Silverstone
Co-investigator Name: Dr. Rana Dadashova

*Patient's ID:*_____ *Date:* _____

Smoking History
Do you smoke cigarettes? ☐ No ☐ Yes
How long have you been smoking?_____
Indicate the age when you started_____
What was/were the reason(s) you strated to smoke? _____
How many cigarettes per day on avearge did you smoke when you started to smoke? ☐ 0-5 ☐ 5-10 ☐ 10-15 ☐ 15-20 ☐ 20-25 ☐ 25-30 ☐ 30+
What is (are) the main reason(s) you continue to smoke? _____
How often do you smoke currently? ☐ every day ☐ twice a week ☐ every 2d days ☐ once a week ☐ every 3d day ☐ on occasions

How many cigarettes per day on avearge do you smoke currently?

☐ 0-5 ☐ 5-10 ☐ 10-15 ☐ 15-20 ☐ 20-25 ☐ 25-30 ☐ 30+

What smoking helping you with?

☐ calm down	☐ relax	☐ suppress appetite/control weight
☐ improve concentration	☐ coop with problems	☐ improve attention
☐ work performance	☐ image	☐ habit
☐ improve mood	☐ just can not quit	☐ prevents withdrawal symptoms
☐ enjoy	☐ free time spending	☐ other

(indicate)_____

What do you dislike about smoking?

☐ health problems	☐ dependence	☐ cost
☐ low energy	☐ smell	☐

other(indicate)_____

Please indicate cigarttes' brand names thath you ussually use starting with one that you prefer and use more often:

a)_____

b)_____

c)_____

After you wake up how long does it ususally take for you to start your first cigarette?

☐ 0-15 minutes ☐ 15-30 minutes ☐ 30 min-1 hour ☐ 1 – 2 hours ☐ >2 hours

How often do you smoke during the day?

☐ every 15 minutes ☐ every 30 minutes ☐ every hour ☐ every 2 hours

☐ every 3 hours ☐ every 4 hours ☐ every 5 hours ☐ every 6 hours ☐ more than 6 hours

In what part of the day do you smoke more?

☐ morning ☐ afternoon ☐ evening

What situsations/activities/emotions provoke more intensive smoking?

☐ stress ☐ use of alcohol ☐ when others smoke around ☐ good mood ☐ anger

☐ craving ☐ relaxation ☐ phone ☐ breaks ☐ TV/computer ☐ partying

☐ boredom ☐ loneliness ☐ sadness ☐ frustration

☐ other_____

In what places do you smoke more often?

_____

Do you smoke when you ill?

☐ No ☐ Yes

Quitting History

Does your smoking worry you?

☐ No ☐ Yes

Have you ever tried to quit smoking?

☐ No ☐ Yes

When did you last time try to quit?

☐ within last month ☐within last 6 months ☐ 1 years ago ☐ over 5 years ago

Did you experience withdrawal (unpleasant symptoms) when you have been trying to quit smoking ?

☐ No ☐ Yes

If Yes please indicated what symptoms did you have and what was intensity of these symptoms form 1 to 10 where 10 is worst one?

☐ Dysphoric mood _____ (from 1-10)
☐ Depressed mood _____ (from 1-10)
☐ Insomnia _____ (from 1-10)
☐ Irritability _____ (from 1-10)
☐ Frustration _____ (from 1-10)
☐ Anger _____ (from 1-10)
☐ Anxiety _____ (from 1-10)
☐ Difficulty concentrating _____ (from 1-10)
☐ Attention problems _____ (from 1-10)
☐ Restlessness _____ (from 1-10)
☐ Increased heart rate _____ (yes/no)
☐ Increase appetite or weight gain _____ (from 1-10)
☐ Weight gain _____ (from 1-10)
☐ Craving _____ (from 1-10)
☐ Respiratory system _____ (from 1-10)
☐ Cardiovascular system _____ (from 1-10)
☐ Gastrointestinal system _____ (from 1-10)
☐ Genitourinary system _____ (from 1-10)
☐ Endocrinology system _____ (from 1-10)
☐ Nervous system _____ (from 1-10)
☐ Dermatologic system _____ (from 1-10)
☐ Musculoskeletal system _____ (from 1-10)
☐ Other

_____
_____
_____
_____

_____

If some one helped you during the quitting process, please indicate:

☐ family member ☐ your family doctor ☐ psychiatrist
☐ therapeutic program ☐ special rehabilitation program ☐ psychologist

☐ religious organization ☐ workmate ☐ other
_____

Have you ever been taking any medications to help with the quitting process?

☐ No ☐ Yes

If yes, please indicate the name of that drugs as many as apply:

☐ Nicotine gum
☐ Nicotine transdermal patch
☐ Nicotine inhaler
☐ Nicotine spray
☐ Nicotine vaccine

☐ Bupropion
☐ Desipramine
☐ Nortryptyline
☐ Amytriptyline
☐ Paxil

☐ Celexa
☐ Propranolol
☐ Clonidine
☐ Naltrexone
☐ Mecamylamine
☐ Moclobomide
☐ Selegiline
☐ Lazabemide
☐ Rimonabat
☐ Varenicline (Champex)
☐ Other
_____

Did the mentioned above medication(s) helped to alleviate your withrawal symptoms?

☐ No ☐ Yes

If Yes, please indicate what symptoms were alleviated and indicate the intensity of these symptoms form 1 to 10 where 10 is worst one after the allevaition?

☐ Dysphoric mood _____ (from 1-10)
☐ Depressed mood _____ (from 1-10)
☐ Insomnia _____ (from 1-10)
☐ Irritability _____ (from 1-10)
☐ Frustration _____ (from 1-10)
☐ Anger _____ (from 1-10)
☐ Anxiety _____ (from 1-10)
☐ Difficulty concentrating _____ (from 1-10)
☐ Attention problems _____ (from 1-10)
☐ Restlessness _____ (from 1-10)
☐ Increased heart rate _____ (yes/no)
☐ Increase appetite or weight gain _____ (from 1-10)
☐ Weight gain _____ (from 1-10)
☐ Craving _____ (from 1-10)
☐ Respiratory system _____ (from 1-10)
☐ Cardiovascular system _____ (from 1-10)
☐ Gastrointestinal system _____ (from 1-10)
☐ Genitourinary system _____ (from 1-10)
☐ Endocrinology system _____ (from 1-10)
☐ Nervous system _____ (from 1-10)
☐ Dermatologic system _____ (from 1-10)

☐ Musculoskeletal system _____ (from 1-10)
☐ Other
_____
_____
_____
_____
_____
_____

Please indicate number of attempts that you made:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ many, do not remember

How long were you able to stay abstinent on average?

☐ several hours _____indicate how many

☐ several days _____indicate how many

☐ several weeks _____indicate how many

☐ several months _____indicate how many

☐ several years _____indicate how many

How would you describe your reason(s) for the relapse (tick if appropriate)?
_____
_____
___

☐ I enjoy smoking too much ☐ no support in family/friends ☐ my motivation was not too strong
☐ I put on weight ☐ all people around me smoke ☐ couldn't resist withdrawal symptoms

☐ I was very stressed ☐ could not resist craving

What reason(s) (if any) can make you to stop smokig?
_____
_____
_____

If you continue to smoke now, please indicate what was a main reason for that?

_____
_____
____

Are you planning to quite smoking within the next month?
☐ No ☐ Yes

Did you participate in other clinical trials related to cigarettes smoking?

☐ No ☐ Yes

Consequences of Cigarette Smoking

Do you know about harm that cigarette smoking causes to your body?
☐ No ☐ Yes

Do you have any problems related to cigarette smoking?
☐ No ☐ Yes

If Yes please indicate:
Respiratory system _____
Cardiovascular system _____
Gastrointestinal system _____
Genitourinary system _____
Endocrinology system _____
Nervous system _____
Dermatologic system _____
Musculoskeletal system _____
Other (accidents) _____

Are you getting any medical help for the mentionaed abouve condition(s)?

☐ No ☐ Yes

Does smoking impacts your social, occupational, educatinal or other activities?

☐ No ☐ Yes

Substance Use History

Do you drink alcohol?
☐ No
☐ Yes

What type of alcohol beverage do you drink?
_____

How much alcohol do you drink per day?_____

How often do you drink?
_____

Do you do drugs?
☐ No
☐ Yes

What type of the drugs do you use? _____

How often do you do drugs? _____

If you do drugs, would you discontinue use of drugs for the period of your participation in our study?
☐ No ☐ Yes

Medical History

Do you have any current medical conditions?

☐ No ☐ Yes

If Yes please indicate:

Respiratory system _____
Cardiovascular system _____
Gastrointestinal system _____
Genitourinary system _____
Endocrinology system _____
Nervous system _____
Dermatologic system _____
Musculoskeletal system _____
Other _____

Are you taking any mediations (prescribed or over-the-counter) or herbs for that?

☐ No ☐ Yes

If Yes please indicate:_____
_____
_____
_____

Have you ever had any liver diseases/problems?

☐ No ☐ Yes

Have you ever had any heart problems?

☐ No ☐ Yes

Do you suffer from high blood pressure?

☐ No ☐ Yes

Have you ever suffer from any mental disorders?

☐ No ☐ Yes

Have you ever had the suicidal ideations, plans or attempts?

☐ No ☐ Yes

Have you taken any medication or herbs in the past 30 days?

☐ No ☐ Yes

If YES , please indicate _____

Have you taken any experimental drugs within the last 30 days?

☐ No ☐ Yes

If YES, please indicate _____

Are you currently pregnant, planning to become pregnant or breast-feeding?

☐ No ☐ Yes

If YES, would you agree to use oracl contaraception while you are in the study and within addictional 30 days after you terminate your particpation?

☐ No ☐ Yes

Second-Hand Smoke

Do you exposed to the second hand smoke?

☐ No ☐ Yes

If yes, where do you get exposed?

☐ home
☐ work
☐ other:_____

How often do you get exposed to second hand smoke?

☐ none ☐ several times a day
☐ every day ☐ every week
☐ once a month ☐ very rare

Family History

Do your family member(s) smoke?

☐ No ☐ Yes

If yes, please indicate?

☐ father ☐ mother ☐ siblings ☐ wife ☐ children ☐ other _____

If Father or Mather, did they smoke when you grow?

☐ No ☐ Yes

Have this person ever tried to quit smoking?

☐ No ☐ Yes

Have you ever tried to help to this person to quit smoking? ☐ No ☐ Yes
Have this person ever had medical problems related to smoking? ☐ No ☐ Yes
Have this person ever helped you to quit smoking? ☐ No ☐ Yes
Does this person aware that his/her smoking afffects your health and health ot others? ☐ No ☐ Yes

Additional Notes:

7.19.Apperndix19. List of CYP2D6 inhibitors and inducers

CYP2D6 Inhibitors

Acebutolol	Dolasetron	Metoclopramide	Quinine
Amiodarone (cordarone)	Doxorubicin	Metoprolol	Rabeprazole
Amitriptyline	Dronedarone	Miconazole	Ranitidine
Amlodipine	Duloxetine	Mifepristone	Ranolazine
Amphetamine	(Cymbalta)	Mibefradil	(antianginal)
Azelastine	Doxepine (TCA)	Midodrine	Risperidone
Bepridil	Entacapone	Moclobemide	Ritonavir
Betaxolol	Escitalopram	MDMA	Ropinirole
Biperiden	Felodipine	Nefazodone	Rosiglitazone
Bortezomib	Fexofenadine	Nelfinavir	Saquinavir
Buprenorphine	Flecainide	Nevirapine	Selegiline
Bupropion (Wellbutrin)	Fluoxetine (Prozac)	Nicardipine	Sertraline
Celecoxib	Fluphenazine	Nifedipine	Serindol
Chloramphenicol	Fluvastatin	Nortriptyline	Sildenafil
(Levomycetine)	Fluvoxamine	Nortuloxeline	Simvastatin
Chloroquine	Gefitinib	Olanzapine	Sulconazole
Chlorphenamine	Halofantrine (Halfan	Omeprazole	Telithromycin
Chlorpheniramine	anti malaria)	Ondansetron	Terbinafine
Chlorpromazine	Haloperidol	Orphenadrine	(Lamizil)
(Thorazine)	(Haldol)	Oxprenolol	Thioridazine
Cholecalciferol/Vitamin	Hydroxyzine	Oxybutynin	Thiothixene
D_3	Hyperforin	Paroxetine (Paxil)	Ticlopidine
Cimetidine	Imatinib (Gleevec)	Pentamidine	Timolol
Cinacalcet (Sensipar)	Imipramine	Pergolide	Tioconazole
Cisapride	Indinavir	Perphenazine	Tranylcypromine
Citalopram	Irbesartan	Pimozide	Trazodone
Clemastine	Isoniazid	Pindolol	Tripelennamine
Clomipramine	Ketoconazole	Pioglitazone	Triprolidine
Clotrimazole	Labetalol	Pravastatin	Valproic acid
Clozapine	Lansoprazole	Praziquantel	Venlafaxine
Cocaine	Levomepromazine	Primaquine	Verapamil
Codeine	Lidocaine	Promethazine	Vinblastine
Delavirdine	Lobeline	Propafenone	Vincristine
Desipramine	Lomustine	(Rhytmol)	Vinorelbine
Dexmedetomidine	Loratadine	Propofol	Yohimbine
Dextromethorphan	Lovastatin	Propoxyphene	Zafirlukast
Dextropropoxiphene	Mefloquine	(Darvon)	Ziprasidone
Dilaverdine	Methadone	Propanolol	
Diltiazem	Methimazole	Pyrimethamine	
Diphenhydramine	Methotrimeprazine	Quinidine	
(Benadril)	Methoxsalen	Quinacrine	
Disulfiram	Methylphenidate		

List of CYP2D6 inducers

Glutethimide (piperidines)
Carbamazepine
Dexamethasone
Rifampin

Source: http://medicine.iupui.edu/flockhart/; Drug bank (www.drugbank.ca/drug/DB00289); http://en.wikipedia.org/wiki/CYP2D6

7.20.Apperndix 20. List of pharmaceutical drugs

- Selective Serotonin Reuptake Inhibitors (SSRIs)
  - citalopram (Celexa, Cipramil, Cipram, Dalsan, Recital, Emocal, Sepram, Seropram, Citox)
  - dapoxetine (Priligy)
  - escitalopram (Lexapro, Cipralex, Esertia)
  - fluoxetine (Prozac, Fontex, Seromex, Seronil, Sarafem, Ladose, Fluctin (EUR), Fluox (NZ), Depress (UZB), Lovan (AUS))
  - fluvoxamine (Luvox, Fevarin, Faverin, Dumyrox, Favoxil, Movox)
  - indalpine (Upstene) (discontinued)
  - paroxetine (Paxil, Seroxat, Sereupin, Aropax, Deroxat, Divarius, Rexetin, Xetanor, Paroxat, Loxamine)
  - sertraline (Zoloft, Lustral, Serlain)
  - zimelidine (Zelmid, Normud) (discontinued)

- Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
  - Desvenlafaxine (Pristiq)
  - Duloxetine (Cymbalta Yentreve)
  - Milnacipran (Dalcipr,an, Ixel, Savella)
  - Venlafaxine (Effexor)
  - Levomilnacipran (F2695) - The levo- isomer of milnacipran. Under development for the treatment of depression in the United States and Canada.
  - Sibutramine (Meridia, Reductil)
  - Bicifadine (DOV-220,075) - By DOV Pharmaceutical, potently inhibits the reuptake of serotonin and norepinephrine (and dopamine to a lesser extent), but rather than being developed for the already crowded antidepressant market, it is being researched as a non-opioid, non-NSAID analgesic.
  - SEP-227162 - An SNRI under development by Sepracor for the treatment of depression.

- Tricyclic Antidepressantss (TCAs)
  - Amitriptyline (Elavil)
  - Butriptyline (Evadyne)
  - Clomipramine (Anafranil)
  - Dibenzepin (Noveril)
  - Dosulepin (Prothiade)
  - Doxepin (Adapin, Sinequan)
  - Imipramine (Tofranil)
  - Lofepramine (Lomont, Gamanil)
  - Nortriptyline (Pamelor, Aventyl)
  - Protriptyline (Vivactil)

- Trimipramine (Surmontil)

- Tetracyclic Antidepressants (TeCAs)
  - Amoxapine (Asendin)

- Opioid Analgesics
  - Meperidine/Pethidine (Demerol)
  - Methadone (Dolophine, Methadose)
  - Propoxyphene (Darvon)

- First-Generation Antihistamines
  - Chlorpheniramine (Chlor-Trimeton, etc)
  - Diphenhydramine (Benadryl, etc)
  - Mepyramine/Pyrilamine (Anthisan, etc)
  - Tripelennamine (Pyribenzamine, etc)

- Selective Norepinephrine Reuptake Inhibitors (NRIs)
  - Atomoxetine/Tomoxetine (Strattera)
  - Mazindol (Mazanor, Sanorex)
  - Reboxetine (Edronax, Vestra)
  - Viloxazine (Vivalan)

- Norepinephrine-Dopamine Reuptake Inhibitors (NDRIs)
  - Amineptine (Survector, Maneon, Directin)
  - Bupropion (Wellbutrin, Zyban)
  - Dexmethylphenidate (Focalin)
  - Fencamfamine (Glucoenergan, Reactivan)
  - Fencamine (Altimina, Sicoclor)
  - Lefetamine (Santenol)
  - Methylphenidate (Ritalin, Concerta, Metadate, Methylin)
  - Pipradrol (Meretran)
  - Prolintane (Promotil, Katovit)
  - Pyrovalerone (Centroton, Thymergix)

- Miscellaneous Agents
  - Cyclobenzaprine (Flexeril)
  - Dextromethorphan (DXM; Robitussin, etc)
  - Dextrorphanol (DXO) (an active metabolite of DXM)
  - Nefazodone (Serzone)
  - Nefopam (Acupan)
  - Sibutramine (Meridia, Reductil)
  - Trazodone (Desyrel)
  - Ziprasidone (Geodon, Zeldox)

Dietary Supplements

- Adhyperforin (found in *Hypericum perforatum* (St. John's Wort))
- Hyperforin (found in *Hypericum perforatum* (St. John's Wort))
- Mesembrine (found in *Sceletium tortuosum* (Kanna))[4]

Research Chemicals

- Alaproclate (GEA-654)
- Bicifadine (DOV-220,075)
- Brasofensine (NS-2214)
- Bromantane (ADK-709)
- Diclofensine (Ro-8-4650)
- DOV-21,947
- DOV-102,677
- DOV-216,303
- Indatraline (Lu-19-005)
- Litoxetine (SL-810,385)
- Lubazodone (YM-992, YM-35,995)
- NS-2359 (GSK-372,475)
- SB-649,915
- SEP-225,289
- SEP-227,162
- Tametraline (CP-24,411)
- Tesofensine (NS-2330)
- Vilazodone (EMD-68,843)
- Viqualine (PK-5078)

- Selective Norepinephrine Reuptake Inhibitors (NRIs)
  - Ciclazindol (Wy-23,409)
  - Esreboxetine
  - Manifaxine (GW-320,659)
  - Nisoxetine (LY-94,939)
  - Radafaxine (GW-353,162)
  - Tandamine (AY-23,946)

- Norepinephrine-Dopamine Reuptake Inhibitors (NDRIs)
  - Difemetorex

- Serotonin-Norepinephrine-Dopamine Reuptake Inhibitors (SNDRIs)
  - Bicifadine (DOV-220,075)
  - Brasofensine (NS-2214)
  - Diclofensine (Ro-8-4650)
  - DOV-21,947
  - DOV-102,677
  - DOV-216,303
  - Indatraline (Lu-19-005)
  - NS-2359 (GSK-372,475)

- Oxaprotiline (CGP-12,103-A)
- SEP-225,289
- SEP-227,162
- Tesofensine (NS-2330)

Street Drugs

- Cocaine (found in *Erythroxylum coca* (Coca))
- Desoxypipradrol (2-DPMP)
- Diphenylprolinol (D2PM)
- Methylenedioxypyrovalerone (MDPV)

Natural Sources

- *Psoralea Corylifolia* (Babchi)[3]

DIRECT-ACTING SYMPATHOMIMETICS

Adrenergic receptor agonists

α_1 agonists

- Methoxamine
- Methylnorepinephrine
- Oxymetazoline
- Phenylephrine
- Tetrahydralazine
- Xylometazoline

α_2 agonists

- Clonidine (mixed alpha2-adrenergic and imidazoline-I1 receptor agonist)
- Guanfacine,[2] (preference for alpha2A-subtype of adrenoceptor)
- Guanabenz (most selective agonist for alpha2-adrenergic as opposed to imidazoline-I1)
- Guanoxabenz (metabolite of guanabenz)
- Guanethidine (peripheral alpha2-receptor agonist)
- Xylazine,[3]
- Methyldopa

Undetermined/unsorted

The following agents are also listed as agonists by MeSH.[4]

- amidephrine
- amitraz
- anisodamine
- apraclonidine
- brimonidine
- cirazoline
- detomidine
- dexmedetomidine
- epinephrine
- ergotamine
- etilefrine
- indanidine
- lofexidine
- medetomidine
- mephentermine
- metaraminol
- methoxamine
- midodrine
- mivazerol
- naphazoline
- norepinephrine
- norfenefrine
- octopamine
- oxymetazoline
- phenylpropanolamine
- rilmenidine
- romifidine
- synephrine
- talipexole
- tizanidine

Beta-1 adrenergic receptor agonists

- Dobutamine
- Dopamine
- Isoproterenol (β_1 and β_2)
- Xamoterol
- epinephrine

Beta$_2$-adrenergic agonist

- salbutamol (albuterol in USA)
- Fenoterol
- Formoterol
- Isoproterenol (β_1 and β_2)
- Metaproterenol

- Salmeterol
- Terbutaline
- Clenbuterol
- Isoetarine
- pirbuterol
- procaterol
- ritodrine
- epinephrine

Undetermined/unsorted

The following agents are also listed as agonists by MeSH.[2]

- arbutamine
- befunolol
- bromoacetylalprenololmenthane
- broxaterol
- cimaterol
- cirazoline
- denopamine
- dopexamine
- etilefrine
- hexoprenaline
- higenamine
- isoxsuprine
- mabuterol
- methoxyphenamine
- nylidrin
- oxyfedrine
- prenalterol
- ractopamine
- reproterol
- rimiterol
- tretoquinol
- tulobuterol
- zilpaterol
- zinterol

Dopaminergic agonists

- fenoldopam (to treat hypertensive crisis).

INDIRECT-ACTING

Norepinephrine transporter blockade

- amphetamines (including MDMA),

- ephedrine
- cocaine

Inhibition of epinephrine and norepinephrine metabolism

- MAOI drugs
- COMT inhibitors
    - entacapone,
    - tolcapone,
    - nitecapone)

MIXED ACTION

- Ephedrine
- Pseudoephedrine

DIGITALIS COMPOUNDS

- Digoxin (Lanoxin)
- Digitoxin
- Ouabain

PHOSPHODIESTERASE INHIBITORS

- PDE3 inhibitors
    - milrinone (Primacor)
    - inamrinone (formerly amrinone) (Inocor)
    - cilostazol (Pletal)

- PDE5 inhibitors
    - sildenafil (Viagra)
    - vardenafil (Levitra)
    - tadalafil (Cialis

VASOPRESSIN

- Arginine vasopressin, AVP;
- antidiuretic hormone, ADH

PROTON PUMP INHIBITORS

- Omeprazole (Losec, Prilosec, Zegerid, ocid, Lomac, Omepral, Omez)
- Lansoprazole (Prevacid, Zoton, Inhibitol, Levant, Lupizole)

- Dexlansoprazole (Kapidex)
- Esomeprazole (Nexium, Esotrex)
- Pantoprazole (Protonix, Somac, Pantoloc, Pantozol, Zurcal, Pan)
- Rabeprazole (Zechin, Rabecid, Aciphex, Pariet, Rabeloc, Dorafem)

ANTACIDS

- Aluminium hydroxide (Amphojel, AlternaGEL)
- Magnesium hydroxide (Phillips' Milk of Magnesia)
- Aluminum hydroxide with magnesium hydroxide (Maalox, Mylanta, Diovol)
- Aluminum carbonate gel (Basaljel)
- Calcium carbonate (Alcalak, TUMS, Quick-Eze, Rennie, Titralac, Rolaids)
- Sodium bicarbonate (Bicarbonate of soda $NaHCO_3$ and/or $KHCO_3$, Alka-Seltzer)
- Hydrotalcite ($Mg_6Al_2(CO_3)(OH)_{16} \cdot 4(H_2O)$; Talcid)
- Bismuth subsalicylate (Pepto-Bismol)
- Magaldrate with Simethicone (Pepsil)

- Equate – $Al(OH)_3$ and $Mg(OH)_2$
- Gaviscon – $Al(OH)_3$
- Rolaids – $CaCO_3$ and $Mg(OH)_2$
- Tums – $CaCO_3$
- Mylanta
- Eno