

## Chapter 24. Alcohol and Nicotine Addiction

**Claudio A. Naranjo, M.D.** <sup>1</sup>

**Lara Chayab** <sup>2</sup>

<sup>1</sup> Professor  
Department of Pharmacology  
Psychiatry and Medicine  
University of Toronto  
Toronto, Ontario  
CANADA  
and  
Head  
Neuropsychopharmacology Research Program  
Sunnybrook & Women's College Health Science Centre  
Toronto, Ontario  
CANADA

<sup>2</sup> M.Sc. Candidate  
Department of Pharmacology  
University of Toronto  
Toronto, Ontario  
CANADA  
and  
Researcher  
Neuropsychopharmacology Research Program  
Sunnybrook & Women's College Health Science Centre  
Toronto, Ontario  
CANADA

## **I. INTRODUCTORY REMARKS**

Alcohol, opioids, nicotine, and psychostimulants have different chemical structures; however, they seem to exert their actions via similar neurochemical pathways in the brain, which lead to addiction. Current pharmacotherapy approaches available for the treatment of alcohol and drug addiction aim at minimizing symptoms of acute abstinence and the risk of relapse. Alcoholism is a complex disorder exhibiting multiple symptoms. It is often co-morbid with Major Depressive Disorders, antisocial personality, or anxiety. According to the American Psychiatric Association (DSM-IV), individuals must meet three of the following criteria during a 12-month period for a diagnosis of alcohol dependence: a) Tolerance to alcohol, increase amounts of alcohol consumption to achieve same effects, b) Signs or symptoms of alcohol withdrawal, c) Attempts to cut down are unsuccessful, d) Long periods of time spent in obtaining alcohol, alcohol consumption, and hangovers, e) Impaired social and work activities due to alcohol consumption, and f) Alcohol consumption is not decreased even if it leads to adverse effects physically and psychologically (1).

Pharmacological treatment of alcohol dependence include agents that minimize the positive reinforcing effects of alcohol (such as naltrexone) and other agents used to relieve withdrawal symptoms and promote abstinence (such as Sedatives and Disulfiram) (2). Naltrexone is a mu-opioid and a delta-opioid receptor antagonist. It functions by blocking the binding of the endogenous opioid, beta-endorphin, to the mu-opioid receptor, which leads to the alleviation of positive effects (euphoria) induced by alcohol intake (3). It is administered orally, and taken 3 times/week at 100-150mg. It is generally safe, with no known interactions caused by alcohol intake and no withdrawal symptoms after drug discontinuation (3). Studies have shown that naltrexone does not lead to complete abstinence from drinking, however, it may cause a reduction in the amount of alcohol intake and a better control over drinking behaviors (4). Acamprosate exhibits a structure similar to the neurotransmitters GABA and glutamate (5). It is thought to work by stabilizing the neurotransmitter balance seen in alcohol dependent people (5). Several trials have shown that acamprosate is efficacious in the treatment of alcohol dependence and is well tolerated (5). However, approval of acamprosate is still pending in many countries. As a result, there is a need for pharmacological agents that treat alcohol dependence, maintain abstinence from alcohol, and do not exhibit adverse effects.

Persistence of cigarette smoking leads to nicotine addiction. Smoking is the leading cause of death in North America, implicated in one of every five deaths (4). Unaided attempts of smoking cessation are successful in only 5% of people who attempt to quit (4). Most pharmacological agents that are available for smoking cessation are nicotine replacement agents such as nicorette (a chewing gum formulation that contains 2 mg of nicotine), and nicotine patch (6). In addition, some investigational drugs for smoking cessation include nicotine inhalers, mecamylamine, a nicotine receptor antagonist, antidepressants, clonidine, and airway sensory replacement (6). Nicorette produces adverse effects that include bad taste, difficulty with chewing, and stomach upset (6). The nicotine patch is better tolerated; however, it may lead to skin irritation and allergies in patients (6). As a result, a pharmacological agent is required that functions to cease cigarette smoking in individuals that are mild to heavy smokers, decreases craving, has no side effects and prevents relapse.

In this chapter, two separate double blind, placebo-controlled, parallel-group study designs will be carried out to test the efficacy and safety of investigational drug AAA (in study-1 for patients with moderate to severe depression, and investigational drug SSS (in study-2 for patients with nicotine addiction. Previous clinical studies have shown that drug AAA is a highly purely selective mu-opioid receptor antagonist, has a half-life of 24 hrs, and is administered 3 times/week. In addition, drug AAA has no potential for alcohol interactions, has mild adverse effects, and has no potential for withdrawal symptoms after drug discontinuation. With the design of the present study, the properties of drug AAA will be better characterized and its efficacy will be determined. Drug SSS is a highly selective nicotine receptor

antagonist that blocks the physiological, behavioral, and reinforcing effects of nicotine. It has a half-life of 12 hours, which accounts for its twice daily dosing, and it is well tolerated due to its mild adverse effects. The properties of Drug SSS will be further investigated and its efficacy will be determined with the present experimental design. The experimental design of both study is most applicable to trials intended to be used in patients as a first line of treatment.

## **II. PHASE II STUDIES FOR REGISTRATION OF NEW DRUGS FOR THE TREATMENT OF ALCOHOL AND NICOTINE DEPENDENCE**

### **II.1 Outline of a typical development plan**

The two studies will examine the efficacy and safety of drug AAA in men and women experiencing moderate to severe alcohol dependence and drug SSS in men and women experiencing moderate to severe nicotine addiction. All patients enrolled in study 1 meeting inclusion/exclusion criteria for alcohol dependence and that give consent will be randomly assigned to receive one oral dose of drug AAA 3 times/week or placebo for 3 months. In addition, patients enrolled in study 2 meeting inclusion/exclusion criteria for nicotine addiction will be randomly assigned two oral daily doses (every 12 hours) of drug SSS or placebo for 3 months. Efficacy and safety measures are going to be performed at weekly intervals up to the end of the third month. The study will be a randomized, double blind, placebo-controlled and patients will come back for two follow-up assessments.

### **II.2. Short-term studies**

#### **II.2.a. Study Objectives**

Primary objectives of study 1

- a. To compare the efficacy of drug AAA treatment versus placebo in the abstinence from alcohol in alcohol dependent patients.
- b. To compare the safety of drug AAA treatment versus placebo.

Secondary objectives for study 1

- a. To determine the onset of a decrease in alcohol intake by drug AAA.
- b. To determine the duration of the decrease in alcohol intake by drug AAA.
- c. To determine the time at which a complete abstinence from alcohol takes place.
- d. To determine the time at which a consistent abstinence from alcohol takes place.
- e. To determine if patients will relapse after abstinence.
- f. The time at which patients start drinking again if relapse took place.

Primary objectives of study 2

- a. To compare the efficacy of drug SSS treatment versus placebo in the abstinence from cigarette smoking in patients with nicotine addiction.
- b. To compare the safety of drug SSS treatment versus placebo.

Secondary objectives for study 2

- a. To determine the onset of a decrease in cigarette smoking by drug AAA.
- b. To determine the duration of the decrease in cigarette smoking by drug AAA.
- c. To determine the time at which a complete abstinence from cigarette smoking takes place.
- d. To determine the time at which a consistent abstinence from cigarette smoking takes place.
- e. To determine if patients will relapse after abstinence.
- f. The time at which patients start drinking again if relapse took place.

## II.2.b. Primary Endpoints

### Primary endpoints of study 1

Rating scales will be administered to assess the following dependent variables:

- a. Structured Clinical Interview for DSM-IV to diagnose patients with alcohol dependence
- b. Alcohol Dependence Scale (ADS): The ADS provides a quantitative measure of the severity of alcohol dependence consistent with the concept of the alcohol dependence syndrome. Its 25 items cover alcohol withdrawal symptoms, impaired control over drinking, awareness of a compulsion to drink, increased tolerance to alcohol, and salience of drink-seeking behaviour. Alcohol dependent patients entering the study must score  $\geq 22$  on the ADS, while healthy individuals must score  $\leq 2$  (7).
- c. Michigan Alcohol Screening Test (MAST): Consisting of 25 questions, the MAST serves to uncover the problems the individual is experiencing as a result of his/her alcohol dependence. Because of the seemingly neutrality of some of the questions, it is easier to extract pertinent information about one's affliction which that person might have been otherwise reluctant to admit. Alcoholic dependent patients entering the study must score  $\geq 6$  while healthy patients in the control group must score  $\leq 2$  (7).
- d. Clinical Institute Withdrawal Assessment for Alcohol (revised) (CIWA): This 10-item scale is used to measure the severity of alcohol withdrawal symptoms. It is important for our results that subjects are not undergoing withdrawal while being tested. All patients entering the study must score  $\leq 15$  for no signs of withdrawal symptoms (7).

Responders to drug AAA versus placebo, where a response is defined as:

- a. R = a reduction from baseline (visit 1) on weeks 1-12 during and post treatment as measured by the ADS.
- b. R = a score of  $\leq 2$  as measured by the MAST during (weeks 1-12) and post treatment (follow-up sessions) with drug AAA.
- c. R  $\leq 15$  on the CIWA for no signs of withdrawal detected.

### Primary endpoints of study 2

Rating scales will be administered to assess the following dependent variables:

- a. Structured Clinical Interview for DSM-IV to diagnose patients with nicotine dependence.
- b. Fagerstrom Test for Nicotine Dependence (FTND) is used to assess tobacco dependence. The questionnaire contains items that determine the number of cigarettes smoked per day, the time to the first cigarette after awakening, and the difficulty of restraining from smoking when strongly advised to (ill). Patients with moderate to severe nicotine dependence typically score  $\geq 6$ . Non-smokers (in the control group) should have 0 points (7).

Responders to drug SSS versus placebo, where a response is defined as:

- a. R = any reduction from baseline (visit 1) on weeks 1-12 during and post treatment as measured by the FTND.

## II.2.c. Secondary endpoints

### Secondary endpoints for study 1

- a. The first day during which a reduction in alcohol intake is seen as measured by ADS and as reported by the patient daily diaries.
- b. The treatment day during which the greatest reduction in alcohol intake is present as measured by the ADS.
- c. The day at which a complete abstinence from alcohol takes place as measured by the ADS and as reported by the daily diaries.
- d. The amount of days during which a consistent abstinence from alcohol takes place.

- e. The number of patients that achieve  $ADS \leq 2$ .
- f. The day at which patients start drinking alcohol again if relapse occurs.

Secondary endpoints for study 2

- a. The first day during which a reduction in cigarette smoking is seen as measured by FTND and as reported by the patient daily diaries.
- b. The treatment day during which the greatest reduction in cigarette smoking is present as measured by the FTND.
- c. The day at which a complete abstinence from cigarette smoking takes place as measured by the FTND and as reported by the daily diaries.
- d. The amount of days during which a consistent abstinence from cigarette smoking takes place.
- e. The number of patients that achieve  $FTND = 0$ .
- f. The day at which patients start smoking again if relapse occurs.

Adverse effects are measured by changes in blood pressure, heart rate, GI motility, and abnormal laboratory tests (blood and liver).

**II.2.d. Study Design**

Both studies are double blind, randomized, placebo-controlled, parallel-group study. There will be 2 groups in study 1, a moderate to severely alcohol dependent group, and a healthy control group. Patients in each group will receive either a single dose of drug AAA or a single dose of placebo randomly once daily, 3 times/week, for 12 weeks. In addition, there will also be 2 groups in study 2, a moderate to severely nicotine dependent group, and a healthy (non-smokers) control group. Patients in each group will receive either drug SSS or placebo twice a day for 12 weeks. The number of patients receiving drug AAA/SSS will equal the number of patients receiving placebo within each group. The effects of drug AAA/SSS will be measured using various questionnaires (discussed below). Objective measures, such as blood pressure, will also be obtained. The results will be compared and analyzed between and within groups.

*Screening for Eligibility (Visit 1)*

Subjects will be interviewed to ensure suitability for study participation a week before the commencement of the study. The following will be required to assess eligibility:

- a. Written informed consent.
- b. Structured Clinical Interview for DSM-IV to assess dependence on psychoactive substances (alcohol or nicotine).
- c. Current level of alcohol dependence (moderate to severe alcohol dependent patients must have a score of  $\geq 22$  on the ADS while healthy patients in the control group must score  $ADS \leq 2$ ). Current level of nicotine dependence (moderate to severe nicotine dependent patients must score  $\geq 3$  on the FTND while non-smokers in the control group must have no FTND score. This is the baseline measure to which all upcoming results will be compared against.
- d. Brief medical examination (heart rate, blood pressure).
- e. Medical history.
- f. Review of inclusion/exclusion criteria.
- g. Pregnancy test for women.
- h. Blood and urine samples to assess liver function, hematology, biochemistry, and to detect the presence of other psychoactive drugs.
- i. Participants will be provided with a pager number to be used if they experience any serious side effects and a wallet card containing information about participation in this study.
- j. Patients are also given a diary in which they record drug compliance and any side effects that they may experience on a daily basis.

*Treatment Phase (Visits 2 -7, Weeks 1-12)*

- a. Eligible subjects will attend six treatment sessions (one every two weeks).
- b. Medical examination.
- c. Medication will be dispensed (enough pills for two weeks).
- d. Treatment will take place at 2-week intervals consisting of 30 to 45 minute sessions with the research assistant.
- e. A psychiatrist will be available for consultation, assessment, and treatment, as needed (i.e. adverse drug reaction, any withdrawal symptoms).
- f. Review Daily Diary forms on which patients record compliance with medication.
- g. Study 1: At each visit, the ADS, MAST, and CIWA will be completed and subjects will be interviewed regarding concomitant illness and medication use.
- h. Study 2: At each visit, the FTND will be completed and subjects will be interviewed regarding concomitant illness and medication use.
- i. Ask patients to return any unused medication in the vial.
- j. Blood will be drawn for trough drug concentrations at visits 3, 5 and 7 (4, 8 and 12 weeks after commencing medication).
- k. Blood and urine will also be collected at visits 4, 6 and 8 for drug screen, complete biochemistry and hematology analyses.
- l. Subjects will be referred to their family physicians either at the end of the 12 week study or if a subject decides to terminate participation in the study.
- m. Individuals who do not respond to drug AAA/SSS will be referred to alternate psychiatric treatment or to their family physicians.

*Follow-up visits (Visits 8-9, at 3 months and 6 months after treatment)*

- a. Review daily diary.
- b. Medical examination.
- c. Psychiatrist: examine any increased alcohol/nicotine dependence, interview patients for concomitant illness, and examine potential adverse reactions.
- d. Study 1: Complete questionnaires: ADS, MAST, and CIWA to check for increase/decrease/relapse to alcohol dependence.
- e. Study 2: Complete questionnaires: FTND to check for increase/decrease/ relapse to nicotine dependence.
- f. Blood and urine collection for drug screen, complete biochemistry, and hematology analyses.

**II.2.e. Planned Sample**

Refer to Flemming's Single Stage Procedure Subsection II.2.e. (planned sample) of the Mood disorders Section in Chapter 20.

**II.2.f. Study Population**

Males or Females over 18 years of age meeting DSM-IV criteria for alcohol/nicotine dependence and exhibit moderate to severe alcohol dependence or an ADS score of  $\geq 22$ / moderate to severe nicotine dependence or an FTND  $\geq 3$ .

**II.2.g. Specific Inclusion Criteria**

A subject will be eligible for inclusion in both studies only if all of the following criteria apply:

- a. Males or females between 19 to 50 years of age.
- b. Socially stable.
- c. Meet DSM-IV criteria for alcohol/nicotine dependence.
- d. In-patients or out-patients.
- e. Non-smokers for study 1.

### II.2.h. Specific Exclusion Criteria

Exclusion criteria must take into account the characteristics of the drug (pharmacokinetics, and pharmacodynamics, drug-drug interactions, and adverse effects). Patients will not be eligible to participate in the study if one of the following criteria apply:

- a. Meet criteria for MDD, Anxiety, Bipolar disorder, Schizophrenia, Schizo-affective or other substance abuse/dependence (other than alcohol and nicotine).
- b. Evidence of medical or surgical illness requiring treatment.
- c. History of psychoactive drug dependence (other than alcohol and nicotine) or a positive urine test for psychoactive drugs (other than alcohol and nicotine).
- d. Use of medications which may interfere with the study procedures (e.g. SSRIs).
- e. Any clinically significant abnormality evident in biochemistry or hematology test results or in urine analysis requiring further investigation.
- f. Receiving or will receive other investigational drug during the study.
- g. Pregnant or lactating females.

### II.2.i. Tools to assess

Tools to assess efficacy in alcohol and nicotine dependence are shown in tables 1 and 2.

<b>Table 1. Alcohol Dependence</b>		
<b>Variable</b>	<b>Assessment Tools to Measure Variable</b>	<b>Time of Assessment</b>
Diagnosis of Alcohol Dependence (AD)	DSM-IV	Visit 1 (baseline)
Level and Severity of AD	ADS	Visit 1 (baseline)
Reduction in AD	ADS, MAST	Visits 2-9
Reduction in impaired control over drinking	ADS, MAST	Visits 2-9
Reduction in drinking-seeking behavior	ADS, MAST	Visits 2-9
Increase in tolerance to drinking	ADS, MAST	Visits 2-9
Severity of Alcohol Withdrawal	CIWA	Visits 2-9
Time of onset of a consistent decrease in AD	ADS	Visits 2-9
Time of greatest reduction of AD	ADS	Visits 2-9
Number of patients achieving ADS < 2	ADS	Visits 2-9
Number of patients achieving MAST < 2	MAST	Visits 2-9
Drug Compliance	Patient Daily Diaries and Returned Medication	Visits 2-7

The tools to assess safety are described in Subsection II.2.i. (Tools to Assess Safety) of the Mood Disorders Section of Chapter 20.

### II.2.j. Specific criteria for early withdrawal and discontinuation

Refer to Subsection II.2.j. (Specific criteria for early withdrawal and discontinuation) of the Mood Disorders Section of Chapter 20.

### II.2.k. Data Analysis Method

Refer to Subsection II.2.k. (Data Analysis Method) of the Mood Disorders Section of Chapter 20.

<b>Table 2. Nicotine Dependence</b>		
<b>Variable</b>	<b>Assessment Tools to Measure Variable</b>	<b>Time of Assessment</b>
Diagnosis of Nicotine Dependence (ND)	DSM-IV	Visit 1 (baseline)
Level and Severity of ND	FTND	Visit 1 (baseline)
Reduction in ND	FTND	Visits 2-9
Reduction in the number of cigarettes smoked per day	FTND	Visits 2-9
Reduction in the time to first cigarette after awakening	FTND	Visits 2-9
Time of onset of a consistent decrease in ND	FTND	Visits 2-9
Time of greatest reduction in ND	FTND	Visits 2-9
Number of Patients achieving FTND = 0	FTND	Visits 2-9
Drug Compliance	Patient's Daily Diaries and Returned Medication	Visits 2-7

### **III. REFERENCES**

1. American Psychiatric Association. 2000. Diagnostic Criteria From DSM-IV-TR. Washington, DC, USA. Pp: 105-209.
2. Gray J. 2003. Therapeutic Choices. 4<sup>th</sup> edition. Canadian Pharmacist Association. Ottawa, Canada. Pp: 8-19, 42-53, 63-99.
3. Bisaga A, Popik P. In search of a new pharmacological treatment for drug and alcohol addiction: N-methyl-D-aspartate (NMDA) antagonists. *Drug Alcohol Depend* 2000;59:1-15.
4. Rose JE. Nicotine Addiction and Treatment. *Ann Rev Med* 1996;47:493-507.
5. Jones DL, Mobley CC. Treatment of Nicotine Addiction. *Text Dent J* 2000;117:26-32.
6. Naranjo CA, Chu AY, Tremblay LK. Neurodevelopmental liabilities in alcohol dependence: central serotonin and dopamine dysfunction. *Neurotox Res* 2002;4:343-361.
7. Riesen HV, Segal M. 1988. Comparative Evaluation of Rating Scales for Clinical Psychopharmacology. New York, Amsterdam, Oxford. Pp:123-334, 483-458.