

## Chapter 22. Anxiety Disorders

**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**

Anxiety Disorders are the most common forms of mental illness (1). The National Comorbidity Survey indicated that about 48% of the US population of Americans aged 15 to 54 years had at least one mental illness in their lifetime. Of these, 24.9% reported having an anxiety disorder in their lifetime (1). Anxiety disorders include general anxiety disorder (GAD), panic disorder (PD), and obsessive compulsive disorder (OBC) (2). Of the three disorders, GAD has been shown to be the most prevalent in a population. Patients are required to exhibit at least six symptoms of hyperarousal, vigilance, motor tension, and autonomic hypersensitivity to fit the criteria of GAD in the DSM-IV (2). Pharmacotherapies of anxiety disorders include treatment with benzodiazepines, buspirone, and antidepressants (3). Benzodiazepines have been known for their high efficacy and their fast onset of action. However, they are only recommended for treatment of acute anxiety as long term use of benzodiazepines leads to a wide range of adverse effects including sedation, improper coordination, memory loss, depression, dependence, and potential for abuse (3). The use of antidepressants, venlafaxine, imipramine, and paroxetine, in the treatment of anxiety has been shown to be efficacious; however, these drugs exhibit a delayed onset of action and various adverse effects including nausea, insomnia, jitteriness, restlessness and agitation. As a result, patients on antidepressants usually terminate the treatment before full recovery from anxiety is accomplished (3). The use of TCAs, such as clomipramine, is also efficacious; however, its anticholinergic side effects are so severe that patients also tend to end the treatment before full recovery is reached (1). Studies with buspirone have showed that it also exhibits a more gradual onset of action and may have a lower efficacy than benzodiazepines. Its adverse effects include GI symptoms and dizziness (3).

As a result, a newer anxiolytic agent is required that has similar or better characteristics of efficacy and onset of action as benzodiazepines, exhibits a better profile of safety and no dependence, and indicated for long term treatment of anxiety.

In this chapter, a double blind, placebo controlled, parallel-group study design will be used to test the efficacy and safety of investigational drug XXX versus placebo in patients diagnosed with moderate to severe anxiety. Previous clinical studies have shown that drug XXX is a highly potent serotonin 1A receptor agonist, is not structurally or chemically related to benzodiazepines, has no sedative effect, does not lead to dependence, has a fast onset of action, requires once daily dosing and is eliminated by biotransformation. In this study design, these properties of the drug will be better characterized and its efficacy will be determined. The example of the study design illustrated in this chapter is most applicable to trials for evaluating anxiolytic drugs intended to be used in patients with moderate to severe anxiety as the first line of treatment.

## **II. PHASE II STUDIES FOR REGISTRATION OF NEW ANXIOLYTIC DRUGS**

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

This study will examine the efficacy and safety of drug XXX in men and women experiencing moderate to severe anxiety. All patients enrolled in the study meeting inclusion/exclusion criteria and that give consent will be randomly assigned to receive one oral daily dose of drug XXX or placebo for 6 months. Efficacy and safety measures are going to be performed at weekly intervals up to week 4, then at 2-week intervals up to week 12, and then at 4-week intervals up to the end of the 6 months. The study will be randomized, double blind, placebo-controlled and patients will come back for two follow-up assessments.

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

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

##### Primary Objectives

- a. To compare the efficacy of drug XXX treatment versus placebo in reducing the symptoms of anxiety.
- b. To compare the safety of drug XXX treatment versus placebo

## Secondary Objectives

- a. To determine the onset of the anxiolytic action of drug XXX
- b. To determine the duration of the anxiolytic effect of drug XXX
- c. To determine the peak anxiolytic effects of drug XXX

### II.2.b. Primary Endpoints

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

- a. Structured Clinical Interview for DSM-IV to diagnose patients with Generalized Anxiety Disorder
- b. The Hamilton Rating Scale for Anxiety, HAM-A to assess severity of anxiety (score  $\geq 18$  for patients with severe anxiety and a score of  $\geq 2$  on the HAM-A item 1 (anxious mood) and item 2 (tension)). It is a simple 14-item five step rating scale. Each item is a group of symptoms that represents one general criterion associated with the disorder. For example, the combination of worries, anticipation of the worst, apprehension, and irritability determine anxious mood. This scale is simple, specific for anxiety measurement, and sensitive to drug effects (4).
- c. The State-Trait Anxiety, STA-IX to measure subject selection (the Trait) and treatment effects (the State). It is a self-evaluation scale that consists of 20 items with a four step severity scale. The Questionnaire asks the patient to indicate how he/she feels at the moment (state) or in general (trait) by selecting “not at all”, “somewhat”, “moderately so”, or “very much so”, with the latter indicating high anxiety (4).

Responders to the anxiolytic drug XXX versus placebo, where a response is defined as:

R = a reduction from baseline (week 1) to week 8 and a similar or a further reduction from baseline to the end of month 6 as measured by the HAM-A, in order to determine the differences in efficacy and safety between the short-term outcome (by week 8) and the long-term outcome (by the end of month 6).

R = a reduction in anxiety measures from baseline to week 8 and a similar or further reduction from baseline to the end of month 6 as measured by the STA-IX scale.

### II.2.c. Secondary Endpoints

- a. The time of onset of a consistent decrease in anxious mood as measured by the Visual Analogue Anxiety Scale (VAAS) compared to baseline (4).
- b. The day during which the greatest reduction in anxious mood is present as measured by the HAM-A.
- c. The number of patients that achieve HAM-A  $\leq 10$  or full recovery.

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

This is a double blind, randomized, placebo-controlled, parallel-group study. The subjects will be administered either a single oral dose of drug XXX or a single oral dose of placebo daily for 6 months. The number of patients receiving drug XXX will equal the number of patients receiving placebo within each group. The anxiolytic effects of drug XXX 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 psychiatric status and to rule out dependence on psychoactive substances.
- c. Current level of anxiety (Hamilton Depression Scale (HAM-A), State-Trait Anxiety (STA-IX)). This is the baseline measure 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 1-10, Months 1-6)*

- a. Eligible subjects will attend 11 treatment sessions (weekly intervals up to week 4, then at 2-week intervals up to week 12, and then at 4-week intervals up to the end of the 6 months).
- b. Medical examination.
- c. Medication will be dispensed (enough pills to last for the next visit at once daily dosing).
- d. Treatment will consist 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, increases in severity of anxious symptomatology).
- f. Review Daily Diary forms on which patients record compliance with medication and any side effects that the patient may be experiencing.
- g. At each visit, the HAM-A and the STA-IX, and VAS will be completed and subjects will be interviewed regarding concomitant illness and medication use.
- h. Ask patients to return any unused medication in the vial.
- i. Blood will be drawn for trough drug concentrations at visits 2, 4, 6, 8, 9, 10, and 11 (weeks 2, 4, 8, 12, 16, 20, 24 after commencing medication).
- j. Blood and urine will also be collected at visits 2, 4, 6, 8, 9, 10, and 11 for drug screen, complete biochemistry and hematology analysis.
- k. Subjects will be referred to their family physicians either at the end of the 6 months or if a subject decides to terminate participation in the study.
- l. Individuals who do not respond to drug XXX will be referred to alternate psychiatric treatment or to their family physicians.

*Follow-up visits 11 and 12 (at 8 months and at the 12 months after treatment)*

- a. Review daily diary.
- b. Medical examination.
- c. Psychiatrist: examine any increased anxious symptoms, interview patients for concomitant illness, and examine potential adverse reactions.
- d. Complete questionnaires: HAM-A, STAI-XI, VAS.
- e. Blood and urine collection for drug screen, complete biochemistry, and hematology analyses.

**II.2.f. Planned Sample**

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

### II.2.f. Study Population

Male or Female over 18 years of age meeting DSM-IV criteria for GAD and who exhibit moderate to severe anxiety or a Ham-A score of  $\geq 18$ , and a score of  $\geq 2$  on the HAM-A item 1 (anxious mood) and item 2 (tension).

### II.2.g. Specific Inclusion Criteria

A subject will be eligible for inclusion in the study 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 general anxiety disease.
- d. In-patients or out-patients.
- e. Non smokers.

### 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 any of the following criteria apply:

- a. If they meet criteria for comorbid anxiety and MDD, or Panic disorder, or Obsessive compulsive disorder.
- b. Active suicidal ideation.
- c. If they meet criteria for Bipolar Disorder, schizophrenia, schizo-affective or other substance abuse/dependence.
- d. Evidence of medical or surgical illness requiring treatment.
- e. History of psychoactive drug dependence or a positive urine test for psychoactive drugs
- f. Use of medications which may interfere with the study procedures (e.g. SSRIs).
- g. Any clinically significant abnormality evident in biochemistry or hematology test results or in urine analysis requiring further investigation.
- h. Receiving or will receive other investigational drug during the study.
- i. Pregnant or lactating females.

### II.2.i. Tools to Assess Endpoints

The tools used to assess efficacy are shown in the following table.

Variable	Assessment Tools to Measure Variable	Time of Assessment
Diagnosis of Anxiety	DSM-IV, HAM-A	Visit 1 (baseline)
Level and Severity of Anxiety	HAM-A, VAAS	Visit 1 (baseline)
Reduction in symptoms of anxiety	HAM-A, Sta-IX, VAAS	Visits 1-12
Reduction in Trait Effects	Sta-IX	Visits 1-12
Reduction in Treatment Effects	Sta-IX	Visits 1-12
Time of onset of a consistent decrease in anxiety symptoms	HAM-A, VAAS	Visits 1-12
Time of greatest reduction in symptoms of anxiety	HAM-A	Visits 1-10
Number of patients achieving HAM-A < 10	HAM-A	Visits 1-10
Drug Compliance	Patient Daily Diaries and Returned Medication	Visits 1-8

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.

**III. REFERENCES**

1. Gray J. 2003. Therapeutic Choices. 4<sup>th</sup> edition. Canadian Pharmacist Association. Ottawa, Canada. Pp: 8-19, 42-53, 63-99.
2. American Psychiatric Association. 2000. Diagnostic Criteria From DSM-IV-TR. Washington, DC, USA. Pp: 105-209.
3. Montgomery SA, Mahe V, Haudiquet V, Hackett D. Effectiveness of venlafaxine, extended release formulation, in the short-term and long-term treatment of generalized anxiety disorder: results of a survival analysis. J Clin Psychopharmacol 2002;22:561-567.
4. Riezen HV, Segal M. 1988. Comparative Evaluation of Rating Scales for Clinical Psychopharmacology. New York, Amsterdam, Oxford. Pp:123-334, 483-458.