Chapter 21. Mood Disorders

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I. INTRODUCTORY REMARKS

The mood disorders that have been most extensively examined in epidemiological studies are major depressive disorder (MDD), dysthymia, and bipolar I disorder (BDI) (1). MDD is the most prevalent of the other disorders. The lifetime prevalence rates of MDD show that 5%-12% of men will experience depression at some point in their lifetime while that rate is higher in women accounting for 10%-25% (2). The diagnostic criteria of MDD according to the DSM-IV (American Psychiatric Association, 1994) are the feeling of sadness and/or loss of pleasure present most of the day, everyday, for at least two weeks (anhedonia). During this period, at least five other symptoms must be present including appetite disturbances, weight disturbances, sleep disturbances, activity disturbances, fatigue, inappropriate guilt, and thoughts of death (3). The lifetime prevalence rate of Bipolar I Disorder is much less than the prevalence of MDD accounting for only 1 to 2% (2). However, individuals exhibiting BDI experience more depressive episodes than those with MDD do (2). The diagnostic criteria for BDI according to the DSM-IV are the occurrence of one or more manic episodes or mixed episodes. Often individuals have also had one or more Major Depressive Episodes. Pharmacotherapy for BDI includes mood stabilizers, such as lithium and valproate, as first line of treatment and mood stablizers with other medications for people unresponsive to first line treatments (1). During a manic episode, individuals experience hyperactivity, hallucinations, and paranoia (2). These symptoms usually cause problems to the diagnosed patients with the law, at work, and with other individuals. Because of the nature of the disorder, clinical studies aimed at investigating treatments for BDI are difficult to establish because of the lack of compliance and the large dropout rate.

Choices of pharmacological therapy for the treatment of depression include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and newer agents such as selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRI) (1). TCAs and MOAIs have been associated with severe adverse effects, drug interactions, and toxicities. Side effects of TCAs administration include dry mouth, constipation, blurred vision, sedation, weight gain, and sexual dysfunction while the most frequent adverse effects of MAOIs are similar to TCAs and also include orthostatic hypertension, palpitations, tachycardia, peripheral edema, and muscle cramps (2). Depressed patients usually terminate the drug therapy due to the side effects before the full course of the treatment is achieved, which leads to reccurrence of symptoms. SSRIs and SNRIs have a better profile of adverse effects. They are less sedating, and have no cardiac effects. However, they still cause nausea, headaches, insomnia, sexual dysfunction, tremors, and CYP 450 inhibition (2). If lower doses of the drugs are used to minimize adverse effects, the efficacy of the drugs will be negatively affected and full recovery will not be achieved. In addition, approximately 5 weeks are required for the onset of action of SSRIs, and sometimes about 1 week for the onset of action of SNRIs (2). As a result, there is a need for newer antidepressant agents that have great efficacy for moderate to severe depression, better profile of adverse effects, fewer drug interactions, and a faster onset of action.

In this chapter, a double-blind, placebo-controlled, parallel-group study design will be used to test the efficacy and safety of investigational drug XOXO for patients with moderate to severe depression. Previous clinical studies have shown that drug XOXO is a highly selective serotonin reuptake inhibitor, is linear and dose-proportional, has a half-life of 27-32 hrs which accounts for its once daily dosing, its onset of action occurs within one week, and is eliminated by biotransformation. In addition, drug XOXO has a low potential for drug-drug interactions since its effect on CYP 450 is negligible, and has a favorable profile of adverse effects. 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 antidepressants intended to be used in patients as first line of treatment.

II. PHASE II STUDIES FOR REGISTRATION OF NEW ANTIDEPRESSANT DRUGS

II.1. Outline of a typical development plan

This study will examine the efficacy and safety of drug XOXO in men and women experiencing moderate to severe depression. 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 XOXO or placebo for 12 weeks. Efficacy and safety measures are going to be performed at weekly intervals up to the end of week 12. 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

a. To compare the efficacy of drug XOXO treatment versus placebo in reducing the symptoms of MDD
b. To compare the safety of drug XOXO treatment versus placebo

Secondary Objectives

a. To determine the onset of the antidepressant action of drug XOXO
b. To determine the duration of the antidepressant effect of drug XOXO
c. To determine the peak antidepressant effects of drug XOXO

II.2.b. Primary Endpoints

The efficacy of antidepressant drugs in clinical trials is measured using a wide variety of assessment tools, which include clinical observations, interviews, and self-reports. Currently, a number of rating scales exists that provide a standardized approach to evaluate the severity of mental disorders and the treatment outcomes. Scales are designed to measure either general symptoms or disease-specific symptoms. Some scales have to be rated by psychiatrists; nurses or research assistants can rate others, and yet other scales are self-evaluated. The choice of the appropriate scales for the diagnosis of specific mental disorder and the evaluation of the efficacy of investigational drugs depends on the specificity, sensitivity, and simplicity of the scales in question. The assessment tools have been extensively researched and evaluated for their specificity and sensitivity for each of the mental disorders that are going to be discussed in this chapter.

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

a. Structured Clinical Interview for DSM-IV to diagnose patients with major depressive disorder
b. The Montgomery Asberg Depression Scale, MADRS, (Score $\geq$ 30 for severely depressed patients) and The Beck Depression Inventory, BDI, (Score $\geq$ 16 for severely depressed patients) to assess current level of depression (4).
c. The Hamilton Depression Scale, HAM-D to asses severity of depressed mood (score $\geq$ 17 for severely depressed patients), which contains 17 items to assess depressed mood, suicidal ideation, somatic symptoms, and loss of interest. Four additional items are included (i.e. diurnal variation, derealization, paranoid symptoms and obsessional symptoms), making the total questionnaire 21 questions in length (4).
d. The Beck Anxiety Inventory and/ Stait-Trait Anxiety, STA-IX, to exclude patients with comorbid depression and anxiety, which is composed of 21 questions and evaluates the current level of depression (4).

Responders to the antidepressant drug XOXO versus placebo, where a response is defined as:

a. R = a reduction from baseline (weeks 1) on weeks 2, 4, 6, 8, 10, 12 during and post treatment as measured by the HAM-D.
b. R = a reduction from baseline (week 1) on weeks 2, 4, 6, 8, 10, 12 during and post treatment as measured by the BDI.
c. R < 2 on weeks 2,4,6,8,10,12 during and post treatment, as measured by the Snaith-Hamilton Pleasure Scale (SHAPS), which is a validated self-assessment scale estimating the degree to which a person is able to experience pleasure or the anticipation of a pleasurable event (i.e. hedonic tone). A score of 2 or more "disagree/definitely disagree" is considered to be indicative of an anhedonic state (4).
d. R = a reduction in the score, on weeks 2,4,6,8,10,12 during and post treatment, as measured by the Addiction Research Center Inventory (ARCI), which is a 77-item questionnaire that measures subjective effects of drugs' positive/reinforcing (e.g. euphoria, stimulation) and negative or dysphoric (e.g. sedation, confusion). This inventory allows the quantification of subjective drug effects with scales sensitive to the effects of specific drugs and drug classes (4).
e. R = a reduction in the score, on weeks 2,4,6,8,10,12 during and post treatment, as measured by the Profile of Mood States (POMS), which is commonly used for assessing drug-induced changes in mood, the POMS consists of a series of 72 adjectives. With respect to each adjective, subjects respond how they feel using a five-point scale ranging from "extremely" to "not at all". Tension-Anxiety, Anger-Hostility, Depression-Dejection, Friendliness, Fatigue, Confusion, Vigor, Elation, Arousal, and Positive Mood are the 10 scales covered in the POMS (4).

II.2.c. Secondary Endpoints

a. The time of onset of a consistent decrease in depressed mood as measured by the Visual Analogue Scale (VAS) compared to baseline. The VAS is often used in the assessment of momentary changes in affect. They consist of a selection of visual analog rating scales (100mm lines) anchored at each end by opposing adjectives to evaluate drug "liking", drug effect and desire to experience the drug effects again. Subjects are instructed to rate how they feel by making a mark anywhere along the line (4).
b. The treatment day during which the greatest reduction in mood is present as measured by the HAM-D.
c. The number of patients that achieve HAM-D ≤ 7.
d. 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. There will be 2 groups in this study, a moderate to severely depressed group, and a healthy control group. Patients in each group will receive either a single dose of drug XOXO or a single dose of placebo randomly once daily for 12 weeks. The number of patients receiving drug XOXO will equal the number of patients receiving placebo within each group. The antidepressant effects of drug XOXO 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, Week 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 depression (Hamilton Depression Scale (HAM-D), Montgomery Asberg Depression Scale (MADRS), and Beck Depression Inventory (BDI)), and anxiety (Beck Anxiety Inventory and/ State-Trait Anxiety (STA-IX)). 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 2-12)

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, increases in severity of depressive symptomatology).
f. Review Daily Diary forms on which patients record compliance with medication.
g. At each visit, the MADRS, BDI, HAM-D, SHAPS, ARCI, POMS, 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 3, 5 and 7 (4, 8 and 12 weeks after commencing medication).
j. Blood and urine will also be collected at visits 4, 6 and 8 for drug screen, complete biochemistry and hematology analysis.
k. 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.
l. Individuals who do not respond to drug XOXO 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 depressed symptoms, interview patients for concomitant illness and examine potential adverse reactions.
d. Complete questionnaires: MADRS, BDI, STAI-XI, HAM-D, SHAPS, ARCI, POMS, and VAS.
e. Blood and urine collection for drug screen, complete biochemistry, and hematology analyses.

II.2.e. Planned Sample

Flemming's Single Stage Procedure will be used in calculating the sample size in the demonstrated phase II study (5). The procedure depends on the assumption that investigators usually have some knowledge of the activity of drugs similar to the one being studied. Therefore, in this study, researchers will compare the anticipated response of drug XOXO to other observed responses of similar drugs with the same

therapeutic indication. Researchers will then specify a probability of a response, which could then be compared to the actual responses to standard treatments. If the response exceeds that of standard treatments, then it can be concluded that Drug XOXO exhibits efficacy (5).

Therefore, assume:
Largest response proportion = Ro
Smallest response proportion = Ra
Hypothesis:
$R \leq Ro$
$R \geq Ra$
α_1, probability of rejecting the hypothesis of $R \leq Ro$
β_1, probability of rejecting the hypothesis of $R \geq Ra$
For N patients recruited for phase II trial, the observed number of patient responses r has a binomial distribution with parameter π.
Therefore, the sample size required for Flemming's Single Stage Procedure is approximately,
$N = [Z_{1-\alpha}\sqrt{\{Ro(1-R0)\}} + Z_{1-\beta}\sqrt{\{Ra(1-Ra)\}}]^2 / [Ra-Ro]^2$

A treatment regimen using SSRIs indicated in the treatment of MDD in phase II studies is expected to yield a response in at least 35% of the patients being tested to show efficacy. Previous phase I trials have shown that Drug XOXO exhibits a higher safety profile than standard treatments indicated for MDD. A one-sided test size is set at 5% and the power at 80%. Since the new investigational drug is shown to be safer than the standard treatments, the values of Ro and Ra will be set at 0.6 and 0.5 respectively with $\alpha = 0.05$ and $1-\beta = 0.8$. Therefore, from Table 12.1 in the "Statistical Tables for the Design of Clinical trials" handbook, or from calculating the equation, the sample size N will equal 16 (5). Therefore, at least 16 patients are needed in each group (16 in the MDD group and 16 in the healthy control group) to detect significance in efficacy for this trial. Therefore, a total of 38 patients are going to be enrolled for the successful completion of this study.

II.2.f. Study Population

Male or Female over 18 years of age meeting DSM-IV criteria for MDD and who exhibit moderate to severe depression or a Ham-D score of ≥ 17.

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 major depressive disorder.
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, 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. If meet criteria for Bipolar Disorder, schizophrenia, schizo-affective or other substance abuse/dependence.
b. Evidence of medical or surgical illness requiring treatment.
c. History of psychoactive drug dependence or a positive urine test for psychoactive drugs.
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. Active suicidal ideation.
g. Receiving or will receive other investigational drug during the study.
h. Pregnant or lactating females.

II.2.i. Tools to assess endpoints
Efficacy should be evaluated using the tools depicted in the following table:

Variable	Assessment Tools to Measure Variable	Time of Assessment
MDD diagnosis	DSM-IV, HAM-D	Visit 1, Week 1
Level and severity of depression	HAM-D, MADRS, BDI	Visit 1, Week 1
Excluding patients with concomitant anxiety	STA-XI	Visit 1, Week 1
Reduction in depressed mood	HAM-D, POMS	Visits 2 - 9
Reduction in loss of interest (ability to experience pleasure)	HAM-D, SHAPS	Visits 2 - 9
Increase in Euphoria	HAM-D, ARCI	Visits 2 - 9
Decrease in dysphoria	ARCI	Visits 2 - 9
Increase/decrease in hostility, fatigue, and confusion	POMS	Visits 2 - 9
Time of onset of consistent decrease in depressed mood	VAS, HAM-D	Visits 2 - 9
Time of greatest reduction in depressed mood	HAM-D	Visits 2 - 9
Number of patients achieving HAM-D ≤ 7 after end of study	HAM-D	Visits 2 - 9
Drug Compliance	Daily Diary and returned pills	Visits 2 - 7

Tools to assess safety
Adverse events such as GI abnormalities, blood pressure and heart rate changes, and blood biochemistry and hematology changes will be assessed in this study.

a. A complete medical examination will be performed, by a physician, at baseline (visit 1) as well as during all visit days. Any changes in blood pressure, heart rate, GI motility, and other complaints made by the patient will be recorded and compared to baseline. In the case of a patient developing any kind of adverse reaction, the subject will be immediately asked to return all medications and withdraw from the study. The patient will then be referred to his/her family doctor to avoid further complications.
b. Urine and blood tests will be performed on visits 2, 4, 6, 8, and 9. Any changes will also be reported and the patient will be asked to withdraw from the study.
c. The daily diaries are provided for the patients to record their feelings, drug compliance, and the occurrence of any adverse effects daily. The diaries will then be reviewed by the psychiatrist and their contents discussed by the patients.
d. If a serious side effect develops in a patient, a full analysis will be made to ensure that the adverse effect is from the investigational drug and not caused by other drugs that the patient may have taken, drug interaction, or a disease.
e. The adverse effects caused by the investigational drug XOXO and those developing from placebo will be compared to determine if a significant difference exists in order to identify the safety profile of drug XOXO.

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

Subjects are allowed to withdraw from the study at any time. Subjects must leave the study if one of these conditions holds:

a. Occurrence of serious side effects
b. Pregnancy
c. Non-compliance
d. Development of a medical condition
e. Use of other medication
f. Violation of the protocol
g. Withdrawal of consent

Subjects that terminate their involvement in the study because of the occurrence of side effects will be considered as having completed the study. Blood tests, urine tests and a complete medical exam should be performed on these patients. The results should determine whether the patients need to be placed on therapy to eliminate the side effects or whether the side effects will resolve on their own. In addition, these patients will be referred to their family physician and an assessment session should be performed after 3 months of withdrawal. Subjects that withdraw because of use of other medications, non-compliance, violation of the protocol, pregnancy, or development of a medical condition will be considered as having not completed the study and will be replaced by new participants. Subjects that terminate the study after drug administration should be contacted and followed-up to ensure that no severe side effects or worsening of the condition takes place. These subjects should also be referred to their family physician and called for a follow-up assessment after 3 months.

II.2.k. Data Analysis Method

For each visit, subject group (ex. Depressed vs. Controls) and dependent variables (e.g. HAM-D scores), parameters such as the mean, maximum, minimum change from baseline will be calculated and analyzed for the effects of drug XOXO. An analysis of variance will be conducted to compare all groups in order to determine if there is a significant difference in the way the groups responded to drug XOXO challenge. These data will also be entered into an ANOVA in order to evaluate the role of depression on the effect of drug XOXO. Together, these analyses should provide information on the efficacy and safety of drug XOXO on patients with MDD.

III. REFERENCES

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