Consent

Title: A randomized, double-blind, placebo-controlled, parallel-group study of adjunctive mixed salts amphetamine in adult outpatients with major depressive disorder responding inadequately to current antidepressant therapy

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Title of Study: A randomized, double-blind, placebo-controlled, parallel-group study of flexible dose mixed salts amphetamine (5-60 mg) adjunctive to antidepressant therapy among adult outpatients with major depressive disorder responding inadequately to current antidepressant therapy

Sponsor: Cheryl T. Herman Foundation

RUSH

Subject Information Sheet and Consent Document

Introduction

This form provides you with information so you can understand the possible risks and benefits of participating in this study; so that you can decide whether or not you want to be a part of this research study. Before deciding whether to participate in this study, you should read the information provided on this document and ask questions regarding this study. Once the study has been explained and you have had all your questions answered to your satisfaction, you will be asked to sign this form if you wish to participate.

Why are you invited to participate in this study?

You are being asked to take part in this study because you have major depressive disorder that has not responded adequately to prior antidepressant therapy.

Research studies include only people who choose to take part. Please take your time to make your decision and discuss it with your friends, family and/or physician. Remember that your participation is completely voluntary. There is no penalty if you decide not to take part in this study or decide later that you want to stop participating in this research study. Your care at Rush University Medical Center will not be affected if you decide not to participate.

What is the purpose of this study?

The purpose of this study is to find out if adding a mixed salts amphetamine (Adderall®), a stimulant medication, to current treatment with an antidepressant provides better response than remaining on the antidepressant alone. Mixed salts amphetamine is approved by the U.S. Food and Drug Administration (FDA) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), but is not approved for the treatment of depression, as being used in this study, either as a single treatment or as a combination treatment.

How many people are expected to take part in the study?

We expect to enroll 60 subjects in this study at Rush University Medical Center. This is the only site participating in this study.

What will you be asked to do?

If you meet criteria to enter the study, you will come to the research center for a total of 9 study visits. Before we perform any study procedures, you must sign this consent document.

In order for us to determine if this study is appropriate for you, we will ask you to sign an authorization that will allow previous treatment records to be released to us so that we can review your treatment history.

Visit 1 - Screen visit

The screen visit is expected to last approximately 2 hours. Study procedures performed at this visit will include:

- Demographic information: The study doctor or study staff will collect information about your date of birth, gender, race, and ethnicity (family background).
- Medical and psychiatric history: The study doctor or study staff will ask about your health, and any illnesses or medications you are taking (including over-the-counter medications, vitamins, or herbal treatments). You may have to stop taking some of these medications or over-the-counter medications in order to participate in this study. You will also be asked about your emotional and psychiatric history and symptoms and about your method of birth control if you are a woman who can have children.
- Physical examination: You will receive a physical examination, which will include assessment of the head, eyes, ears, nose, throat, skin, thyroid, neurological (checking things like your reflexes and the reaction of your eyes to light, for example), lungs, heart, abdomen (liver and spleen), lymph nodes (feeling for swelling or lumps in areas such as your neck and under your arms) and extremities (arms, hands, legs, feet, etc.). Height and weight will also be measured and recorded.
- Vital signs: Your blood pressure, heart rate and temperature will be measured and recorded.
- Blood tests: You will have blood drawn (approximately 1-2 tablespoons) for routine blood tests to assess things like your blood sugar and blood minerals (for example, sodium and potassium). If you have had these same lab tests performed within 3 months prior to study enrollment and can provide us with a copy of the results, these tests may not need to be repeated at this time.
- Electrocardiogram (ECG): a test of the heart's electrical activity.
- Urine tests: You will provide a urine sample (about 1-2 ounces) to test for pregnancy (in women of childbearing potential only) and drugs of abuse. Results of both of these tests must be negative for you to participate in the study. You will be notified if your test results are positive. These results will remain confidential.
- Interviews and Questionnaires: You will be asked questions by the study doctor and study staff and asked to fill out questionnaires about your symptoms of depression and how your quality of life is affected.

Visit 2 - Baseline visit

Approximately 1 week following the Screen visit, you will return for a Baseline visit. This visit is expected to last approximately 1 hour. The study entry criteria will be reviewed to be sure you still meet the study criteria. Study procedures will include:

- Medical/psychiatric history and medications: You will be asked about any changes since the last visit.
- Side effects and other medications, vitamins or herbal treatments: You will be asked about any problems you have had since the last visit. You will also be asked if you have taken any other medications (including over-the-counter), vitamins or herbal treatments.
- Vital signs: Your blood pressure, weight, heart rate and temperature will be measured and recorded.
- Interviews and Questionnaires: You will be asked questions by the study doctor and study staff and asked to fill out questionnaires about your symptoms of depression and how your quality of life is affected.
- Study medication: The study medication you will receive will be decided by chance (like a flip of a coin). You will have a 3 out of 4 chance of receiving MSA at some point in the study and a 1 out of 4 chance of receiving placebo at some point. This is called a double-blind study, meaning neither you nor the study staff will know which treatment you are receiving, because all packaging will look the same. In case of an emergency, however, the study staff can find out your assigned treatment if needed. Placebo is an inactive "sugar pill" made to look like the active medication, but it does not have any active medication in it. Placebo is used in research studies to help us tell whether the medication being tested is effective.

  You will be given a supply of study medication (mixed salts amphetamine or placebo) to take until your next study visit along with instructions for how to take the medication (quantity to take and how often to take it). You will be asked to return all unused study medication and containers (even if empty) at each visit.

  Neither you nor the study staff will know which group you are assigned to. This is known as double-blind.

Visits 3-5 - Phase 1

After the baseline visit, you will return each week for 6 more study visits. Each of these visits is expected to last approximately 1 hour. Study procedures will include:

- Side effects and other medications, vitamins or herbal treatments: You will be asked about any problems you have had since the last visit. You will also be asked if you have taken any other medications (including over-the-counter), vitamins or herbal treatments.
- Vital signs: Your blood pressure, weight, heart rate and temperature will be measured and recorded.
- Interviews and Questionnaires: You will be asked questions by the study doctor and study staff and asked to fill out questionnaires about your symptoms of depression and how your quality of life is affected.
- Study medication: At each visit, you will be given a supply of study medication to take until your next study visit along with instructions for how to take the medication (quantity to take and how often to take it). You will be asked to return all unused study medication and containers (even if empty) at each visit.

Visits 6-8 - Phase 2

You will return each week for 3 more study visits. Each of these visits is expected to last approximately 1 hour. Study procedures will include:

- Side effects and other medications, vitamins or herbal treatments: You will be asked about any problems you have had since the last visit. You will also be asked if you have taken any other medication (including over-the-counter), vitamins or herbal treatments.
- Vital signs: Your blood pressure, weight, heart rate and temperature will be measured and recorded.
- Interviews and Questionnaires: You will be asked questions by the study doctor and study staff and asked to fill out questionnaires about your symptoms of depression and how your quality of life is affected.
- Study medication: At each visit, you will be given a supply of study medication to take until your next study visit along with instructions for how to take the medication (quantity to take and how often to take it). At visit 8, you will receive specific instructions for discontinuing the study medication. You should follow these instructions carefully, as it may not be advisable to stop taking the study medication abruptly. You will be asked to return all unused study medication and containers (even if empty) at each visit.

Visit 9 – 2-week follow-up visit

Approximately 2 weeks following the last study visit, you will return for a 2-week follow-up visit. At this visit, the following procedures will be performed:

- Side effects and other medications, vitamins or herbal treatments: You will be asked about any problems you have had since the last visit. You will also be asked if you have taken any other medication (including over-the-counter), vitamins or herbal treatments.
- Vital signs: Your blood pressure, weight, heart rate and temperature will be measured and recorded.
- Interviews and Questionnaires: You will be asked questions by the study doctor and study staff and asked to fill out questionnaires about your symptoms of depression and how your quality of life is affected.
- Study medication: Any unused study medication and containers (even if empty) will be collected.
- Electrocardiogram (ECG): a test of the heart's functioning.
- Blood tests: You will have blood drawn (approximately 1-2 tablespoons) for routine blood tests to assess things like your blood sugar and blood minerals (for example, sodium and potassium).
- Urine tests: You will provide a urine sample (about 1-2 ounces) to test for pregnancy (in women of childbearing potential only) and drugs of abuse.

"After-Study Care"

If you complete the study, or if it is determined that it is not in your best interests to continue in the study at any point following Visit 2, we will attempt to provide adequate treatment for a limited time through the research center while you transition to the care of a doctor outside of the study. You will be responsible for the cost of medication or other treatment prescribed during this transition period. Whether you submit these costs to your health insurance company is your decision. We are not able to submit insurance claims. There will be no charge for the office visits during this transition. This transition period and referral to a doctor outside of the study (if needed) will be addressed individually and will occur as quickly as possible in order for you to secure follow-up care. The study doctor and study staff will remain medically available during the transition. If your new doctor requires information from your participation in the study, the

study staff will provide it upon your authorization to do so.

How long will you be in the study?

If you remain in the study for all of the visits, your participation will last approximately 9 weeks.

You may be removed from this study without your consent for any of the following reasons: the study doctor decides that continued participation in the study will be harmful to you, you will need a treatment not allowed on the study, your disease becomes worse, you are unable to take the treatment as indicated, or the study is canceled.

What are the possible risks of the study?

It is possible that you may experience side effects from the study medication. It is also possible that the study medication may have no beneficial effect and as a result you may feel that your condition is getting worse. Inform your study doctor immediately if this occurs, and he/she will assess your condition and make changes to your treatment if it is required.

Patients taking mixed salts amphetamine may experience the following side effects: general asthenia (weakness), headache, loss of appetite, diarrhea, dry mouth, nausea, agitation, anxiety, dizziness, insomnia (inability to sleep), tachycardia (rapid heartbeat), weight loss and urinary tract infection.

Please contact the study doctor if you experience any of these side effects or any other side effects during the study.

Sudden deaths, stroke, and myocardial infarction (heart attack) have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is unknown, adults have a greater likelihood than children of having serious heart problems, including serious heart rhythm abnormalities, coronary artery disease and other serious heart problems. Adults with such abnormalities should generally not consume stimulant drugs.

Stimulant medications can cause a modest increase in average blood pressure and average heart rate, and some individuals may have larger increases. Your blood pressure is checked at every visit to monitor for significant changes in heart rate and blood pressure.

Taking stimulants may exacerbate (make worse) behavior problems and thought disorders in patients with a pre-existing psychotic disorder. If you experience any signs or symptoms of bipolar illness (such as elevated mood or aggressive behavior), or symptoms of psychotic illness (e.g., hallucinations, delusional [thinking things that are not true or real] thinking) you should discuss these experiences with your study doctor promptly.

Do not take your study medication other than as directed by your study doctor. Amphetamines have the potential for abuse. Tolerance (needing higher doses to achieve a result), extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to levels many times higher than recommended. Abrupt cessation (stopping suddenly) following prolonged high dosage administration results in extreme fatigue (tiredness) and mental depression. Signs of taking too much amphetamine may include severe skin conditions, severe inability to sleep, irritability, hyperactivity, and personality

changes. The most severe sign of taking too much is psychosis (described in the paragraph above).

Toxic symptoms may occur unexplainably at low doses. Symptoms may include restlessness, tremor (shakiness), hyperreflexia (reduced muscular reflexes), rapid breathing, confusion, assaultiveness (hostility), hallucinations (seeing or hearing things that are not real), panic states, hyperpyrexia (high fever) and rhabdomyolysis (sometimes fatal disease of the skeletal muscle). Cardiovascular effects include arrhythmias (irregular heartbeat), hypertension (high blood pressure) or hypotension (low blood pressure) and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually occurs before convulsions (seizures) and coma.

If you believe you have overdosed on your study medication please call 911, or contact your study doctor immediately using the provided 24-hour hotline phone number (312-980-0585).

Other risk information
The risks of taking blood may include pain, discomfort, bleeding, bruising, a small blood clot or infection at the site the needle enters the body. In rare cases, fainting may occur.

You may find it uncomfortable answering questions that are included in the questionnaires. Some of these questions may ask about difficulties and symptoms you have experienced and difficulties you have dealt with in your life, including thoughts or attempts of suicide.

There may be risk of allergy to the study medication used in this study. Signs of an allergic reaction may include redness, itching, swelling or (in rare cases) difficulty with breathing, and lightheadedness. Severe allergic reactions may result in death. If you feel that you are experiencing a severe allergic reaction, first seek treatment and then call your study doctor at 312-942-5592 or 312-980-0585 (this number is available 24 hours a day).

All medications have side effects, and with research medications some of these can be unexpected. Therefore, other possible side effects may occur in addition to those listed above. You will be given any new information that may affect your willingness to start or continue in the study. You will be monitored throughout the study in order to minimize risks.

Only you may take the study medication. The study medication must be kept out of the reach of children or persons of limited capacity to read or understand.

Use of alcohol and recreational drugs must be avoided while you are in this study because of potential interference with the study medication.

Are there any anticipated pregnancy risks?

Women

The effect of the study medication on an unborn child or nursing infant is unknown.

If you are pregnant or breastfeeding, you cannot take part in this study. A urine pregnancy test is required and will be given before you start taking the study medication and at the Visit 9 study visit. Results of the pregnancy test must be negative for you to participate in the study. You are responsible for using an effective birth control method such as birth control pills, barrier method (such as condoms or diaphragms), intrauterine device (IUD), hormone implants or surgical sterility while you are taking part in this study. Once you have completed treatment, you may discontinue the use of birth control. If you become pregnant while on the study, you must notify the study doctor immediately.

Men

You are responsible for using an effective birth control method, such as the ones listed above. If you are a male and your female partner becomes pregnant while you are on the study, you must notify your study doctor immediately. Once you have completed treatment, you may discontinue the use of birth control.

Are there benefits to taking part in the study?

You may not benefit from participating in this study; however, you may experience relief or improvement of your depressive symptoms. You will have the benefit of the psychiatric evaluation prior to entering the study, physical examination, laboratory evaluations and general health information from your discussions with the study doctor.

Your participation may provide information about the study treatment that may benefit others in the future.

What other options are there?

Instead of participating in this study, you may choose to receive another treatment (including the amphetamines) from a doctor outside of this study. Alternative treatments include antidepressants, talk therapy and vagus nerve stimulation.

What about confidentiality of your information?

Records of participation in this research study will be maintained and kept confidential as required by law. Information gathered during your participation in this study will be coded with a number.

The United States Food and Drug Administration (FDA) will be able to inspect and copy confidential study-related records which identify you by name. Therefore, absolute confidentiality cannot be guaranteed. The Rush Institutional Review Board (IRB) will have access to your files as they pertain to this research study. The IRB is a special committee that reviews human research to check that the rules and regulations are followed.

If the results of this study are published or presented at meetings, you will not be identified.

In order to conduct the study, the study doctor, John Zajecka, M.D., will use and share personal health information about you. This includes information already in your medical record, as well as information created or collected during the study. Examples of the information that may be shared include your medical history, physical exam and laboratory test results. The study doctor will use this information about you to complete this research.

Confidentiality and disclosure of your personal information is further described in the attachment to this form. The attachment is entitled HIPAA Authorization to Share Personal Health Information in Research (2 pages).

What are the costs of your participation in this study?

There is no charge to you for the study medication, study procedures (such as lab tests required for this study) and study clinic visits. You will continue to be responsible for the cost of the antidepressant you were taking when you entered the study.

Parking in the Rush parking lots will be provided at no cost. Limited assistance may be available for travel to and from the study site for study visits. Please discuss these arrangements with the study staff.

This study is supported by a financial grant from the Cheryl Herman Charitable Trust. This financial support covers a portion of study staff salary, supplies, tests and medication needed for the study, and other research related costs. A portion of this money will go to Rush University Medical Center to compensate for other institutional research related costs.

Will you be paid?

You will not be paid for your participation in this study.

What happens if you experience a research related injury?

If you experience any injury or illness as a direct result of your participation in this research study, immediate treatment will be provided. However, the cost of that treatment will be billed to you or your insurance company.

If you have any medical problems during the study, please contact the study doctor, they will explain your treatment options to you or tell you where you can get treatment.

Rush University Medical Center has no program for financial compensation or other forms of compensation for injuries which you may incur as a result of participation in this study.

What happens if you need emergency care?

If you need emergency care while you are participating in this study, it is important that you inform emergency personnel of your participation in this study.

Whom do you call if you have questions or problems?

Questions are encouraged. If there are any questions about this research study or if you experience a research related injury, please contact Dr. Corey Goldstein at 312-942-5592 or 312-980-0585 (outside of usual business hours). Questions about the rights of research subjects may

be addressed to the Rush Research & Clinical Trials Administration Office at 312-942-5498.

By signing below, you are consenting to participate in this research study. You have read the information given or someone has read it to you. You have had the opportunity to ask questions, which have been answered satisfactorily to you by the study personnel. You do not waive any of your legal rights by signing this consent document. You will be given a copy of the signed and dated consent document for your records.

SIGNATURE BY THE SUBJECT:

Name of Subject	Signature of Subject	Date of Signature

SIGNATURE BY THE WITNESS:
I observed the signing of this consent document.

Signature of Witness	Date of Signature

SIGNATURE BY THE INVESTIGATOR/INDIVIDUAL OBTAINING CONSENT:
I attest that all the elements of informed consent described in this document have been discussed fully in non-technical terms with the subject. I further attest that all questions asked by the subject were answered to the best of my knowledge.

Signature of Individual Obtaining Consent	Date of Signature
Signature of the Investigator	Date of Signature