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Protocol Title: The effects of antipsychotic drugs on brain metabolism in healthy individuals

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PROTOCOL TITLE

The effects of antipsychotic drugs on brain metabolism in healthy individuals.

BACKGROUND

Schizophrenia is a complex psychiatric disorder characterized by alterations in brain structure. It remains unclear yet whether some of these alterations may be related to pathophysiology of illness per se, or are the consequence of brain exposure to the effects of psychotropic drugs. In recent years evidence suggests that exposure to the effects of psychotropic drugs may contribute to some structural and other changes in brain. In this study, we aim to evaluate the effects of short-term antipsychotic medication use in healthy subjects on neuroimaging markers. We will also examine effects of antipsychotic exposure on neurocognitive performance.

The primary aim of this study is to investigate antipsychotic drug effects on brain energy metabolism in 30 healthy people by administering olanzapine over 15 days and using 31P MRS imaging at 4 Tesla. Secondary aims include studying the effects of olanzapine on other neuroimaging markers collected using MRI approaches and cognition.

We plan to study the levels of chemicals associated with cellular energy metabolism: kinetics of enzymes involved in cellular energy metabolisms in brains of healthy people before and after use of antipsychotic drug olanzapine for 15 days. In addition, we will also collect data on the structure of the gray matter and white matter; resting state functional brain activity; levels of brain chemicals including glutamate and GABA; white matter integrity; and neurocognition. We will collect whole brain data where possible and focus on the medial prefrontal cortex and parietal cortex as two regions of interest whenever whole-brain data collection is not possible due to technical limitations.

RESEARCH DESIGN AND METHODS

Enrollment: The study will enroll up to 30 healthy people with no history of psychiatric illness or family history of psychosis.

There are no restrictions on subject recruitment based on sex, ethnic background or health status other than those mentioned below. Individuals who do not speak English will be excluded.

Inclusion Criteria

1. Age: 21-50 years old.
2. Male or female.
3. Without psychiatric diagnosis according to a structured psychiatric interview (SCID; First et al 1994).
4. Without history of a psychotic disorder among parents, siblings, or children.

Exclusion Criteria

1. Significant medical or neurological illness.
2. Unstable/active disease or potential contraindications.
3. Body mass index (BMI) greater than or equal to 30.
4. Taking any other medications, including over the counter supplements, with the exception of oral contraceptives for women.
5. Pregnancy. Females of child-bearing age must be using an effective contraceptive method.
6. History of smoking, substance abuse or dependence.
7. Contraindication to MR scan,
8. Medical condition that would prevent blood draws.

This study will be comprised of three main parts. The subject is free to withdraw from the study at any time. Similarly, the investigators may decide to stop the study if the purposes of the study cannot be met. All participants will be asked not to use alcohol or any other substances and drugs during the study period.

1. **Baseline Assessments**: The first part of the study will be carried out within 10 days of study entrance and consists of 3 separate visits which will take about 8 hours in total. This part of the study will consist of the following procedures:
    a. Consenting procedures (20 minutes)
    b. Clinical evaluation (120 minutes)
    c. Urine toxicology screen (5 minutes) and blood pregnancy test (5 minutes)
    d. MRI procedure:
        i. Common Anatomic Protocol (CAP) at 3T (MR Scan at 3T – 1) (45 minutes)
        ii. MRS protocol at 3T (MR Scan at 3T – 2) (30 minutes)
        iii. Phosphorous MRS/MT at 4T (MR Scan at 4T – 1) (90 minutes)
        iv. Diffusion Tensor Spectroscopy (DTS) at 4T (MR Scan at 4T – 2) (90 minutes)
    e. Fasting (12 hours) blood draw of 20 mL (10 minutes)
    f. Assessment of vital signs, weight, height, waist and hip circumference (5 minutes)
    g. ECG (10 minutes)
    h. Neuropsychiatric assessment (60-90 minutes)
        i. MATRICS Consensus
    i. 24-Hour food recall (Total Dietary Intake ASA24)

2. **Study Visits**: The second part of the study in which participants will take daily antipsychotic medication will be carried out within 15 days. There will be 5 separate visits on 1st, 2nd, 5th, 10th, and 14th days of medication and each visit will take about thirty to sixty minutes.

    Participants will take daily olanzapine as the antipsychotic medication, Zyprexa Zydis.
    On the first day of medication each participant will take Zyprexa Zydis 2.5 mg/day PO. Dose will be increased in the second day and participants will be taking Zyprexa Zydis 5 mg/day, PO, for the following days.

The medication will always begin on weekdays except Friday. On the 1st and 2nd day of the medication, participants will be asked to take the medication at McLean Hospital. After they take the medication we will monitor them closely for 1 hour to observe any side effects.
If the participants do not have any unacceptable side effects in the first two days, then they will be able to take the 13 remaining doses at home starting from the third day

On the 2nd, 5th, and 10th days of medication we will administer LUNSERS (Liverpool University Neuroleptic Side Effect Rating Scale), ESRS (Extrapyramidal Symptom Rating Scale) and the Columbia Suicide Severity Rating Scale to assess potential side effects better. Weight and vital signs assessment, random blood glucose test will be done and ECG will be taken in these visits. On 5th, 10th, and 14th days all participants will have blood drawn for assessment of olanzapine plasma levels. Each visit will take about 30 minutes to an hour.

Participants' dietary intake will be assessed throughout the study using the 24-Hour Food Recall ASA24 at visits 3 and 8, and with the Food Craving Questionnaire-Trait-reduced (FCQ-T-r) at the 1st, 7th and 9th visits.

We will still complete the study with participants who miss up to 3 days of medication administration and qualify those participants as having received the intended course of medication (while recording their degree of noncompliance). Participants who miss more than 3 days of medication will be discontinued from the study.

3. **Endpoint Assessments**: All participants will undergo final investigations on the 15th and 16th days of the medication follow up period. The participants will take their last olanzapine dose on the evening of the 15th day. They will not be asked to take it on the 16th day as we plan to finish all final assessments during daytime and they take their medications in the evening. Participants will undergo 4T MR scan and neurocognitive testing on the 16th day. All other assessment and 3T MR scans will be done on the 15th day. The third part of the study will consist of the following procedures:
    a. Clinical evaluation (60 minutes)
    b. Urine toxicology screen (5 minutes) and pregnancy test (5 minutes)
    c. MRI procedure:
        i. Common Anatomic Protocol (CAP) at 3T
        ii. MRS protocol to quantify Glu and GABA at 3T
        iii. Phosphorous MRS/MT at 4T
        iv. Diffusion Tensor Spectroscopy (DTS) at 4T
    d. Fasting (12 hours) blood draw of 20 mL (10 minutes)
    e. Assessment of vital signs, weight, height, waist, and hip circumference (5 minutes)
    f. ECG (10 minutes)
    g. Neuropsychological Assessment (60-90 minutes)
        i. MATRICS Consensus Cognitive Battery
    h. 24-Hour food recall (Total Dietary Intake ASA24)

Medication: The half-life of olanzapine is 30 hours and one week would be sufficient to reach steady state. However, we decided to give medication longer than 1 week as we know that drug-induced adaptive changes take time to occur. Up until now, the longest duration of olanzapine use in healthy

volunteers has been 15 days. It is a randomized, PBO controlled, two- treatment (OLZ and PBO), crossover study in which the metabolic effects of olanzapine were investigated. 30 healthy men aged between 18-49 years underwent 10 mg/d olanzapine treatment for 15 days (5 mg/d for 3 days, then 10 mg/d for 12 days) in this study [15]. There are also some other multiple-dose studies in which the participants were given daily olanzapine to investigate metabolic effects up to 15 days [16, 17, 18 19]. None of the participants in these studies had major, severe side effects of olanzapine. Based on these studies we determined the duration of medication as 15 days in this study. We determined the daily olanzapine dosage as 5 mg in this study. We aimed to give healthy subjects only 5 mg/d olanzapine, the lower limit of the optimal dose range (5 mg ± 2.5 mg/d), to mimic the therapeutic effect but also protect the participants from adverse effects of treatment.

To assess the potential side effects of olanzapine, we set up 5 separate visits on the 1st, 2nd, 5th, 10th, 14th days of medication period. A physician will be present to monitor all participants' reactions to the medication and stop the medication if they are affected adversely.

MRI/MRS Scan: We have found that most subjects find that remaining in the scanner is somewhat uncomfortable but acceptable. An MRI technologist will be able to communicate with subjects at all times via intercom. Subjects are informed that they are free to stop at any point. Padding around the head will protect subjects from minor mechanical injuries and reduce head motion. Earplugs will be used to minimize the scanning noise of MR scanner. Women of childbearing potential must undergo a negative urine pregnancy test prior to completing the MR procedure on each day of MR scanning.

Women of childbearing age: Pregnant women and nursing mothers cannot participate to this study. If the participant is a woman of childbearing potential, she must be using a metal-free IUD, oral contraceptive, or barrier methods (*for at least 3 months*) or must be abstinent (*for at least 1 month: time to get the most reliable result with pregnancy test*) prior to this study. In addition, they must have a negative blood pregnancy test (*instead of urine pregnancy test*) at the beginning of the study.

Blood Draw: Subjects will be monitored for 15 minutes following the blood draw to ensure they are doing well. To minimize the possibility of bruising and infection from the blood draw, proper sterile phlebotomy techniques will be used.

Psychiatric Evaluation: Some subjects might feel uncomfortable answering questions during the psychiatric evaluation. They will not be forced to answer if they do not wish to answer any particular question.

Neuropsychiatric Assessment: Fatigue, frustration, or boredom may occur during the assessment; however, participants will be offered the option to discontinue testing or training sessions and resume at a later time in order to minimize these effects.

To minimize potential breach of confidentiality, subject data are coded with unique research numbers. The code linking the research number with personal identifiers is kept in binders separate from both clinical and imaging data and also in password- protected computer files on computers in a locked office at McLean. Subject interview records and imaging data are identified by research numbers and will be collected and stored via the secure web-based application REDCap. The application complies

with HIPAA regulations and will store the information securely, protected by web authentication, and Secure Sockets Layer (SSL) encryption. Dietary information captured from the ASA24 is stored in an NIH-designed database that is completely deidentified. The only document linking the participant's username and study number will be kept in a password-protected computer file in a locked office at McLean.

Statistical Analysis: There is no published literature on the effects of olanzapine on the brain measures we plan to study. Therefore, it is not possible to calculate a sample size that would detect a given between-group difference in this study. In fact, our hypothesis is that olanzapine administration does not cause significant abnormalities in brain metabolism. Therefore, we plan to recruit a sample that is large enough to establish the absence of a moderate or large effect. Our proposed sample size of 30 subjects will allow us to detect a difference with effect sizes of 0.45 or greater as significant at the $p<0.05$ level with 80% power. Note that effect sizes of 0.5 are generally considered moderate and 0.8 considered large. Therefore, a non-statistically significant finding with our sample size will suggest that any effects of olanzapine on brain metabolism are at best small. We will examine deviations induced by the study drug on brain metabolism using paired t-tests for before and after measurements.

FORESEEABLE RISKS AND DISCOMFORTS

In terms of olanzapine treatment, the medication may be unsafe for some people and cause some unwanted side effects (*neurological, gastrointestinal, dermatological, ocular, musculoskeletal, hematologic, endocrine, metabolic, psychiatric*).

Nervous system side effects have frequently included somnolence, tremor, insomnia, dizziness, speech disorder, abnormal gait, amnesia, paresthesia, apathy, confusion, tremor, akathisia, hypertonia, articulation impairment, incoordination, abnormal dreams, emotional lability, agitation, nervousness, and hostility. Akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, and withdrawal syndrome have also been reported. Circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse, and sleep related eating disorder have been reported rarely [22, 23, 24, 25, 26]. Almost all antipsychotics have been associated with a risk of epileptic seizure provocation. Olanzapine can lower seizure threshold. However, in patients on olanzapine for the treatment of a primary psychiatric disorder, clinical seizure is a rare occurrence. In most of these cases, a history of seizure or risk factors for seizures were reported.

All antipsychotics have been associated with the risk of sudden cardiac death due to an arrhythmia. In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] $\geq$ 500 milliseconds [msec] at any time post-baseline in patients with baseline QTcF $<$ 500 msec) were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo.

Metabolic side effects have frequently included weight gain. Binge eating and increases in food craving have been associated with olanzapine. Additional studies have confirmed that patients receiving atypical antipsychotics are at an increased risk of developing hyperglycemia and/or diabetes mellitus.

Hepatic side effects have rarely included hepatitis, liver fatty deposit, and cholestatic or mixed liver injury. Transient and moderate, asymptomatic elevations in liver function tests have been reported.

Gastrointestinal side effects have frequently included dry mouth, increased appetite, thirst, constipation, dyspepsia, increased salivation, vomiting, and flatulence. Dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, taste perversion, and tooth caries have also been reported. Isolated cases of olanzapine-induced acute pancreatitis have been reported during post marketing use [33].

Musculoskeletal side effects have included extremity pain (other than joint pain) and joint pain in 5% of patients. Joint stiffness and twitching have been reported frequently. Arthritis, arthrosis, leg cramps, and myasthenia have also been reported. Bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis, and rhabdomyolysis have been reported rarely [34].

Hematologic side effects have rarely included anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia, normocytic anemia, neutropenia, leukopenia, agranulocytosis, eosinophilia, agranulocytosis, and thrombocythemia[35, 36, 37, 38].

Ocular side effects have frequently included amblyopia, abnormal vision, and conjunctivitis. Abnormality of accommodation, blepharitis, cataract, diplopia, dry eyes, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality have also been reported. Glaucoma, corneal lesion, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, esotropia, and pigment deposits in the lens have been reported rarely [39, 40, 41].

Psychiatric side effects have frequently included depression, euphoria, delusions, manic, and psychotic symptoms. Obsessive-compulsive symptoms and suicide attempts have also been reported [42]. One of the important side effects of antipsychotic drugs is neuroleptic malignant syndrome. Neuroleptic malignant syndrome (NMS) is a rare (incidence rates; range from 0.02 to 3 percent among patients taking neuroleptic agents) but life-threatening, idiosyncratic reaction to neuroleptic medications.

Olanzapine, like all other drugs, can cause hypersensitivity syndrome which is seen very rarely. Drug Hypersensitivity Syndrome (DHS) is unpredictable but potentially life- threatening with significant morbidity. This syndrome is a severe, idiosyncratic multi- system reaction defined by the clinical triad of fever, rash and internal organ involvement (e.g., hepatitis, myocarditis, nephritis or pneumonitis), which may occur 1 - 8 weeks after medicine exposure. Fever is a common early feature, usually preceding a widespread and long-lasting papulopustular or erythematous skin eruption, which often progresses to exfoliative dermatitis. The severity of the skin-related changes does not correlate with the extent of internal organ involvement, which may remain asymptomatic or be life- threatening. Treatment consists of immediate withdrawal of all suspect medicines, followed by supportive care of symptoms. Hospitalization may be required. The mortality from drug hypersensitivity syndrome is estimated at around 8% [51].

In terms of the MRI and MRS scans, unlike X-rays or CAT scans, magnetic resonance (MR) technology does not use ionizing radiation. The MR system requires the use of rapidly varying magnetic gradient fields and strong radio frequency fields, which conform to the guidelines established

by the US FDA for time varying magnetic fields in MR devices. This study uses a standard clinical MRI scanner (3 Tesla or 3T), as well as a high field (4 Tesla or 4T) MRI scanner. The 4T scanner is not used for routine clinical studies in children or adults, but the FDA has determined (July 14, 2003) that scanners with magnetic field strengths of less than 8 Tesla (double this scanner) or less do not represent a significant risk to adults, children, or infants aged more than 1 month. There could be adverse effects that are delayed or very mild, such that they have not yet been recognized. Most people experience no ill effects from 3T or 4T scans, but some people do report claustrophobia dizziness, mild nausea, headaches, a metallic taste in their mouth, double vision, or sensation of flashing lights. These symptoms, if present, disappear shortly after leaving the scanner. No serious adverse effects have been reported to date at any site operating at 3T or 4T field strength.

Blood draw may lead to a small arm bruise and, in rare cases clot or infection at the site the blood was drawn. Some people become light-headed during or immediately after a blood draw. These are rare occurrences, and, in our experience, the vast majority of subjects tolerate blood draws well.

In terms of the psychiatric evaluation, some subjects might feel uncomfortable answering questions, but they will not be forced to answer if they do not wish to do so.

In terms of the neuropsychiatric assessment, some participants may experience fatigue, frustration, or boredom; however, participants will be offered the option to discontinue testing or training sessions and resume at a later time in order to minimize these effects.

To minimize potential breach of confidentiality, subject data are coded with unique research numbers. The code linking the research number with personal identifiers is separate from both clinical and imaging data and also in password- protected computer files on computers in a locked office at McLean. Subject interview records and imaging data are identified by research numbers and will be collected and stored via the secure web-based application REDCap. The application complies with HIPAA regulations and will store the information securely, protected by web authentication, and Secure Sockets Layer (SSL) encryption. Dietary information captured from the ASA24 is stored in an NIH-designed database that is completely deidentified.

RECRUITMENT PROCEDURES

For subject recruitment, the research coordinators/assistants will post online advertisements and flyers around the McLean campus and local universities describing the study and the procedures involved. The participants will come in and go through the consent process and be administered the Informed Consent by a licensed physician investigator. The subject is then provided with a copy of their signed consent form to review and keep.

Subjects will be compensated by check for the procedures that they complete. If the subject does not complete the entire study, he/she will be compensated for the procedures that were completed. The subjects will be compensated a total of up to $680 for all study procedures. Travel costs above $5, as authenticated by a receipt, will be reimbursed up to $25 per visit.

CONSENT PROCEDURES

For participants, consent is obtained in a private interview room. The physician and a research assistant will thoroughly review the consent form with the participant. Subjects are given as much time as they need to look over the consent for before signing it.

DATA AND SAFETY MONITORING

Subjects are thoroughly screened by a research assistant and a qualified physician prior to their enrollment in the study to ensure subject safety. The physician closely monitors the participants during the medication period. Subjects are carefully assessed before, during, and after the MRI scans by the research assistant and MR technologist or authorized personnel to ensure that they suffer no adverse reactions. The physician will be present in all phases of the screening process. The PI closely oversees all of the study activities and intervenes wherever necessary.