DGIM Project Summary

Name of Project: "Neurosteroid Metabolism and the Antidepressant Effects of Serotonin Specific Reuptake Inhibitors (SSRI's)."
Nickname: "BRAIN, BIOLOGY AND MOOD STUDY". CHR Approval # 10-00825, Approval Expires 01/14/2014

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Research question(s): Patients with major depressive disorder (MDD) have a higher likelihood of developing serious medical conditions, e.g., cardiovascular disease, stroke, dementia, diabetes, etc. Depressed individuals, especially untreated ones, may have accelerated cellular aging, at least in their immune cells, as demonstrated by shortened leukocyte telomeres. Our goals in the current study are to determine whether:

1. Un-medicated depressed individuals have shorter leukocyte telomeres than matched healthy controls;
2. Leukocyte telomere length is inversely correlated with inflammatory cytokines and measures of oxidative stress.
3. Leukocyte telomere length is inversely correlated with severity and duration of depression.

The above "Baseline" hypotheses will be tested in a single outpatient visit on the UCSF GCRC (CTSI). If depressed subjects and their DGIM physicians wish, and if it is clinically warranted, UCSF psychiatry faculty will also offer optional 8-weeks of standard clinical SSRI antidepressant treatment at no charge to the subject (CHR approval pending). In such cases, three additional hypotheses will be examined:

1. Baseline markers of cell aging predict response to antidepressants
2. Antidepressant treatment normalizes cell aging markers and their putative mediators (inflammation and oxidation)
3. Antidepressant-associated clinical improvement is directly correlated with normalization of cell aging markers and putative mediators.

Brief Background/Significance:
This study will help determine if un-medicated patients with MDD have an accelerated biological aging phenotype and if this is linked to over-activation of inflammatory cytokines and oxidative stress. This will be assessed in blood, urine and saliva samples (although participants may elect not to collect saliva or urine samples) and a low dose dexamethasone suppression test. The results may help explain the high medical co-morbidity in depressed patients and may identify new biological treatment targets.

INCLUSION CRITERIA (Study staff will review these criteria with subjects to minimize burden to the DGIM referring clinician):

- Age 18-70 y.o.; Good general medical health (No current severe unstable medical illness.)
- Clinical labs (electrolytes, liver function test, CBC) with no clinically significant abnormalities (Testing will performed at no-charge by the study);
- Negative urine toxicology (drugs of abuse) screen. Not pregnant.
- Taking no drugs likely to interfere with the study objectives (including birth control pills). Taking no antidepressant, mood-stabilizing or anti-anxiety medication for a minimum of 4 weeks (with the exception of prn benzodiazepines)

Additional criteria for Depressed Participants:

- Current DSM-IV diagnosis of Major Depressive Disorder, unipolar, without psychotic features (co-morbid anxiety diagnoses are permitted)
- At least mild-moderate severity depression
- Not actively suicidal.

Additional criteria for Normal Controls:

- No DSM-IV Axis I diagnoses

Method of contact/ recruitment

1. We will provide brochures and flyers for the waiting area of DGIM
2. We will provide PCPs with a detailed description of the study and our inclusion/ exclusion criteria with a request that they consider suggesting the study to potentially eligible patients in their care.

Benefits/burden for participants

1. Antidepressant Treatment (optional): We are using drugs from the antidepressant class called Serotonin Selective Reuptake Inhibitors (SSRIs). The specific drugs we will use are: fluoxetine (Prozac®), sertraline (Zoloft®), paroxetine (Paxil®), citalopram (Celexa®) or escitalopram (Lexapro®). These drugs are among the most commonly prescribed antidepressants in the United States and worldwide. Each of these drugs is FDA-approved for treating depression in the doses we will use in this study. This class of drugs generally has a benign side effect profile, and most side effects dissipate within 2-3 weeks (e.g., GI side effects, activation, sedation, etc.), although side effects of sexual dysfunction (e.g., low libido, anorgasmia, delayed orgasm, difficulty achieving arousal) and weight gain may persist until the drug is stopped. The placebo-adjusted rates of side effects with these five SSRI’s are presented in the Table. Other potential side effects are pharmacokinetic interactions with other drugs the individual may be taking. The physician-investigator of this study, who will be prescribing and monitoring the SSRI, is familiar with these interactions, and the potential for drug-drug interactions will weigh into the decision as to which antidepressant to select. Abrupt antidepressant discontinuation may result in transient, mild withdrawal symptoms, e.g., “flu-like” feelings or dizziness or paraesthesias. Subjects will be advised against discontinuing their antidepressant abruptly. If subjects do experience withdrawal symptoms after stopping the antidepressant, they will be offered a brief course (up to two-four weeks) of open-label, gradually tapered antidepressant to facilitate their withdrawal. The FDA placed a “black box” warning on the labeling of all antidepressants, including SSRI’s, noting that antidepressant use may be associated with an increased risk of suicidal thinking in children and adolescents. In pre-marketing studies, 4% of depressed child and adolescent and young adult patients treated with antidepressants...
exhibited suicidal thinking or behavior compared to 2% of patients treated with placebo. The increased risk was not seen in adults over 24 years old, in whom the risk of suicidality was unchanged or less than with placebo. Real-world risk of this occurrence has been debated within the psychiatric profession, but there is no doubt that these medications effectively treat depression and suicidality in the majority of patients taking them (Boerner and Moller 1999; Mendlewicz and Lecrubier 2000). We carefully screen out participants with current suicidality, and the development of suicidality would be cause for terminating a participant’s participation in the study and referring the participant to standard clinical care. We follow participants closely during this study, with mandatory psychiatric evaluations at Baseline and at Weeks 1, 2, 3, 4, and 8 of treatment, plus additional clinical contact as clinically determined. We feel this risk: benefit ratio is warranted, since these depressed participants would generally be candidates for such clinical intervention regardless of their participation in this study. If participants experience objectionable side effects, the investigators may lower the drug dose or discontinue it. Participants are free to withdraw from the study at any time.

TABLE: Placebo-adjusted incidence of side effects with SSRI’s (%)

2. Venipuncture. Standard venipuncture risks are pain, possible infection and fainting. The total amount of blood to be drawn during the Baseline and Week 8 visits will be approximately 190cc per visit. Saliva collection: This is without risk except for the mild inconvenience some participants may experience. 24 hour urine collection: This is without risk except for inconvenience. Dexamethasone Suppression Test: This very low dose of dexamethasone (one oral dose of 0.25 mg.) has no known risks. Behavioral ratings: These are generally without risk except for the inconvenience and time required. Confidentiality: Participation in research may involve a loss of privacy, but information will be handled as confidentially as possible.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Citalopram</th>
<th>Escitalopram</th>
<th>Fluoxetine</th>
<th>Paroxetine</th>
<th>Sertraline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gi</td>
<td>7</td>
<td>8</td>
<td>12</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Sexual</td>
<td>5</td>
<td>7</td>
<td>2</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>N/A</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Sedation</td>
<td>8</td>
<td>5</td>
<td>7</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Appetite change</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Sweating</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>AVERAGE</td>
<td>11.2</td>
<td>6.8</td>
<td>4.3</td>
<td>5.4</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Any benefits or burden to DGIM practitioners?
The possible benefits to DGIM practitioners include: (1) psychiatric assessment of their patients’ depression by a UCSF faculty psychiatrist; (2) a no-cost 8-week clinical SSRI antidepressant trial for their patients with a report of their patients’ response to treatment at the end of the 8 weeks (with patients’ consent). (3) With the patients’ consent, reports of all clinical laboratory tests (performed at no charge) will be sent to the DGIM physician.

The possible burden to DGIM practitioners is minimal. They will receive only one letter from us, providing information about the study and offering to provide brochures that they can pass along to their depressed patients.

Timeline for recruitment (projected start and stop dates)
For our DGIM recruitment, we would like to start sometime in June OR July 2013. The study will continue into 2015.

Funding source
NIH: National Institute of Mental Health, Award # A114651

Potential for DGIM collaborators?
At the moment, we are collaborating with Dr. Mitchell Feldman. However, we are open to collaborating with other DGIM physicians (and residents) if they have an interest.

Do you agree to notify us when recruitment is completed? Yes.

Date form completed: Form completed 06/04/13 by Laura Mahan. Updated 6/12/13 by Laura Mahan.
Please note: A prior version of this study, shown on the following pages, was already approved by the DGIM. The present version has several changes (e.g., no MRI scan)
PREVIOUSLY APPROVED PROJECT FOR DGIM:

DGIM Project Summary  Name of Project: “Neurosteroid Metabolism and the Antidepressant Effects of Serotonin Specific Reuptake Inhibitors (SSRI’s).” Nickname: “MDD STUDY”. CHR Approval # 10-00825, Approval Expires 01/14/2012

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Research question(s):
We are seeking to test the following hypotheses.

PRIMARY HYPOTHESES: 1. Neuroprotective factors are deficient in depression, and antidepressant treatment stimulates these factors. 2. Depression is a chronic stress syndrome which results in accelerated cellular aging and a higher oxidative stress index. 3. Genetic abnormalities interact with early trauma history to increase the vulnerability to depression.

SECONDARY HYPOTHESES 1. Specific memory functions are disturbed in depression, and these are related to deficient neuroprotective factors. 2. Depression is associated with chronic changes in appetitive behavior with resultant physiological and metabolic disturbances

Brief Background/Significance:
It has been demonstrated that chronic stress results in a shortening of telomeres. It is possible that major depression, as a form of chronic stress, also results in shortening of telomeres. There may also be interactions between the action of SSRI's and telomere length, as well as levels of telomerase.

Inclusion/exclusion criteria (list)
INCLUSION CRITERIA
All participants must meet the following criteria: Age 18-70 y.o.; Good general medical health: Clinical labs (electrolytes, liver function test, CBC) with no clinically significant abnormalities; Negative urine toxicology (drugs of abuse) screen; Taking no medication or drugs likely to interfere with the study objectives (including birth control pills), except as allowed by protocol; Free of any antidepressant, mood-stabilizing or anti-anxiety medication for a minimum of 6 weeks before entry into the study (with the exception of prn benzodiazepine, anxiolytic or sedative-hypnotic use, < 3 nights per week); No current diagnosis of PTSD; No history of angina or known coronary artery disease.; Lab results demonstrate an Hct of 36-48 for females and 38-54 for males, or a Hgb of between 12.5-20, for all participants regardless of an age.

Additional criteria for Depressed Participants: Current DSM-IV Axis I diagnosis of Major Depressive Disorder, unipolar, without psychotic features (co-morbid diagnoses of Panic, Generalized Anxiety Disorder, or Phobias are permitted.); Baseline 17-item Hamilton Depression Rating Scale (HDRS) rating of > 17; Baseline HDRS item #3 (“suicidality”) rating of < 1, and clinician’s determination of absence of active suicidal intent.; No anticipated changes in psychotherapeutic interventions during the study. Additional criteria for Normal Controls: No DSM-IV Axis I diagnoses.

Method of contact/recruitment (be specific)
1. We will have an assistant do a STOR search for patients who are diagnosed with depression and who are not currently on antidepressants. We will then send a letter to their primary physician describing the study and expressing our interest in the patient. Instead of sending one letter per patient, we will send each physician one letter

inquiring about all of his or her patients that are of interest to us. They physician will have an opportunity to decline on behalf of the patient. Then, we will send a letter to the patient, describing the study and giving them an opportunity to decline participation. Then we will call them and screen them by phone. Then we will invite them
for an in-person screening visit. 2. We will also be recruiting participants through ads on Craigslist, and flyers, but those methods do not specifically involve DGIM.

**Benefits/burden for participants (clearly identify potential for harm)**

1. Sertraline Treatment: We are using sertraline (Zoloft), which is a highly selective SSRI shown to be effective in treatment of major depression. Sertraline is the most commonly prescribed FDA-approved antidepressant in the US. In the doses used in this study, it is considered very safe. We screen out participants with current suicidality, and development of suicidality would be cause for terminating participation and referring the participant to standard clinical care. We follow participants closely, with mandatory clinical evaluations at Baseline and at Weeks 1, 2, 3, 4, and 8 of treatment, plus additional clinical contact as needed. Significant clinical deterioration (judged by the investigators or by the subject) will lead to discontinuation and referral to clinical care.

2. Limitation on Other Treatments: Participants are only eligible to participate in this study if they have not been taking psychotropic medications for six weeks prior to beginning the study, and no new non-study related psychotropic medications may begin during the course of the study. No new courses of psychotherapy may begin during the study.

3. Venipuncture. Standard venipuncture risks are pain, possible infection and fainting. The total amount of blood to be drawn during the Baseline visit and during the Week 8 visit will be approximately 190cc per visit. Thus, the healthy controls have approximately 190 cc of blood drawn, and the depressed participants have approximately 380 cc of blood drawn over an 8-week period.

4. Saliva collection: This is without risk except for the mild inconvenience some participants may experience. 5. 24 hour urine collection: This is without risk except for inconvenience. 6. Dexamethasone Suppression Test: The dexamethasone (up to 0.5 mg.) has no known risks associated with it, because it is a very low dose and single administration of synthetic glucocorticoid. 7. Body measurements: There is no except possible embarrassment. 8. Behavioral ratings: These are generally without risk except for the inconvenience and time required. 9. Genetic Studies: Donating genetic material could result in a loss of confidentiality. We make every effort to preserve the confidentiality of genetic ands well as complete health information. 10. Confidentiality: Participation in research may involve a loss of privacy, but information will be handled as confidentially as possible. 11. MRI: The MR apparatus attracts certain metals so there is the small possibility that magnetic objects will accidentally fly into the magnet. This risk is greater at 4.0 Tesla field strength. Subjects who have metal in their bodies that may interfere with the magnet may not be admitted to the study. This will be determined on a case-by-case basis. Clothing (including undergarments that contain metal) may not be allowed in the 4.0 Tesla MR unit. Instead, we provide subjects with a hospital garment to wear for the MR procedure. NOTE: The MRI is currently removed from our study due to lack of funding, but it may return in the future if and when more funding becomes available. 12. Actigraphy: This may produce slight discomfort from prolonged wear. That is the only known risk. 13. BIA (bioelectric impedance analysis): May involve slight social discomfort. That is the only known risk.

**Any benefits or burden to DGIM practitioners?**
The possible benefit or burden to DGIM practitioners is minimal. They will receive only one letter from us, which they only need to respond to if they object to us contacting their patient.

**Timeline for recruitment (projected start and stop dates)**
For our DGIM recruitment, we would like to start sometime in May 2011. Then, we may do it again once every 3-6 months for approximately the next 5 years.

**Funding source**
NIH: National Institute of Mental Health, Award # A114651

**Potential for DGIM collaborators?**
At the moment, we are only planning on collaborating with Mitch Feldman and the administrative assistant whom we will hire. However, we are open to collaborating with other DGIM physicians (and residents) if they have an interest.

**Do you agree to notify us when recruitment is completed?** Yes.

**Date form completed:**
Form completed 04/18/11 by John Coetzee. Updated 07/10/11 by John Coetzee.