

D2d Ancillary Study Letter of Intent



Office Use

Ancillary Study Number _____

Date Submitted (MM/DD/YYYY) _____

To: D2d Ancillary Studies Subcommittee

Re: D2d Ancillary Study Preliminary Concept Proposal

Title of Proposal
(81 character limit)

Effects of Vitamin D Supplementation on Depression and Mood

Principal Investigator Patrick O'Neil, PhD
Institutional Affiliation Medical University of South Carolina
Street Address 1 67 President St.
Street Address 2 Suite 410S
City Charleston State SC Zip Code 29425
Phone (843) 792-2273 Fax (843) 792-5432 Email oneilp@musc.edu

If Principal Investigator is not a member of the D2d study group, please specify:

D2d Co-Investigator Robert Malcolm, MD
Institutional Affiliation Medical University of South Carolina

Significance, Brief Background, Proposed Central Hypothesis and Specific Aims

Depression is widely prevalent in the general population; overweight and obesity increase the risk of developing depression by more than 50%.(1) Therefore depression and depressed mood are expected to be prevalent in the D2d sample. Depression and depressed mood have been reported to be associated with decreased Vitamin D levels.(2-4) Vitamin D supplementation has been shown to decrease depressive symptoms and improve mood, acutely (5 days) among healthy college students (5) and over one year among overweight and obese Norwegian adults, using weekly administered supplements of 20,000 or 40,000 IU.(3)

One form of depression of particular relevance is Seasonal Affective Disorder (SAD), which is characterized by seasonally recurring (fall and winter) periods of depressed mood, lethargy, hypersomnia, hyperphagia and carbohydrate craving.(6) Winter SAD is linked to shortened photoperiod and is more prevalent at more northern latitudes; prevalence was estimated at 9.7% among New Hampshire respondents, 6.3% among Maryland respondents, and only 1.4% among Sarasota, Florida respondents.(6,7) SAD patients frequently experience weight gain during episodes, which often is not subsequently lost, leading to a pattern of cumulative weight gain.(8) As is well known, weight gain in adulthood strongly increases the risk of developing Type 2 diabetes.(9,10)

SAD has been inconsistently linked to lowered Vitamin D levels.(11,12) A small study showed that acute Vitamin D supplementation of patients with active SAD led to significant improvement in general and SAD-specific measures of depression, relative to the standard phototherapy treatment.(11) Further, level of improvement in SAD was positively related to amount of increase in serum 25-OHD levels(11) (A larger study purporting to assess seasonal depression examined effects of 800 mg Vitamin D plus calcium among UK women aged 70 and over, and found no differences between summer and winter assessments of mental health, but the measure (mental component score of SF-12) was not specific to SAD or even depression).(13)

The D2d study provides a unique opportunity to determine whether Vitamin D supplementation at 4,000 IU/day will have beneficial effects on mood and reduce the incidence of depression, including SAD, over a 3-year follow-up. Identification of such an effect would have substantial public health implications for prevention or management of depression.

The Proposed Central Hypothesis and Specific Aims are included in the Study Design section below.

Study Design

Please address study type (e.g. intervention or observational); population and setting (inclusion/exclusion); study design (e.g. study procedures, outcomes assessment and time-points, confounders); analytical methods (e.g. preliminary sample size/power calculations and assumptions).

SPECIFIC AIMS:

1. To measure the effects of Vitamin D supplementation mood and incidence of depression
 - 1.1. Hypothesis: Participants receiving Vitamin D supplementation, compared to participants receiving placebo, will show improved mood and a lower incidence of depression.
2. To measure the effects of Vitamin D supplementation on the incidence of winter SAD (full and subsyndromal) and seasonal alteration in mood
 - 2.1. Hypothesis: Participants receiving Vitamin D supplementation, compared to participants receiving placebo, will have lower incidence of winter SAD (full and subsyndromal) and reduced seasonal alteration in mood.
 - 2.1.1. Sub-hypothesis: This effect will be more pronounced at more northerly latitudes.

DESIGN:

Brief questionnaires assessing mood, depression and SAD symptoms will be administered to all subjects at Baseline and at Months 6, 12, 18 and 24. The mid-year assessments (Months 6 and 18) will permit capture of seasonal shifts in mood.

The following questionnaires will be administered:

- 1) PHQ-9 Questionnaire. This is a 9-item questionnaire designed for screening for depression in primary care settings. The participant's timeline for recall is 2 weeks.
- 2) Positive and Negative Affect Schedule (PANAS). As opposed to screening for symptoms of major depression (PHQ-9), this questionnaire assesses positive and negative moods within the normal range of variation. Respondents simply indicate the extent (1-5 scale) to which each of 20 mood descriptors applies currently (i.e., past week).
- 3) Hamilton Depression Rating Scale – Seasonal Affective Disorders Version (Self-Rating Format) (SIGH-SAD-SR). This is a 29-item questionnaire assessing current symptoms of seasonal affective disorder.

DATA ANALYSIS:

A specific plan for statistical analyses will be provided in the full application if we are invited to submit one. In general, analyses will compare Vitamin D and placebo groups on a) cumulative incidence of major depression according to PHQ-9 criteria; b) cumulative incidence of SAD based on SIGH-SAD-SR criteria; c) positive and negative mood (PANAS) scores at the four post-baseline; d) level of fluctuation in PANAS scores reflective of sub-syndromal seasonal changes. Analyses will control for gender, race-ethnicity, and because of its relation to seasonal mood changes, latitude of the study site.

Innovation and Impact

Depression and overweight/obesity are strongly interrelated. Vitamin D levels have been implicated in general depression and SAD. This will be the largest study to assess the impact of Vitamin D supplementation on depression, SAD and mood among a sample of pre-diabetic overweight and obese adults. If beneficial effects are noted, the public health implications may be substantial; Vitamin D supplementation may represent an extremely accessible and affordable means of reducing the incidence of depression and/or SAD. Further, the large variation among sites in latitude will permit determining whether such recommendations may be most useful in certain geographic regions.

Subject Burden and Potential Risks

Please describe (1) additional procedures that will be required of participants; (2) risks to participants from the proposed procedures; (3) ways to minimize burden and risk

Participants will simply be asked to complete 3 short questionnaires at each of 5 visits. Completion of the 3 instruments should require no more than 15 minutes of subject time per visit. Staff will only have to provide very brief instructions when handing the questionnaires to the participant. The questionnaires are very easily and quickly scored, and produce a small number of scores to be entered into the data capture system. Therefore, the added burden on site staff should be minimal.

There are no foreseeable risks to participants from completing these measures.

Use of Stored Specimens

Please select all specimens required for the ancillary study.

- Checkboxes for DNA, Plasma, Serum, and Urine, each with associated 'Amount needed' and 'Time point(s)' fields.

Funding

Anticipated Funding Source We are requesting that these questionnaires be added to the general study protocol, therefore no separate budget should be required for this proposed study.

Anticipated Date of Submission to Funding Agency

Acknowledgement of D2d Ancillary Studies Policies & Procedures

I have read and agree to abide by the policies and procedures for D2d Ancillary Studies as described in the document titled: D2d Ancillary Studies Policies and Procedures & Instructions for Submission of Proposals, and specifically regarding the presentation and publication of ancillary study results and data sharing policies.

Principal Investigator Signature [Signature] Date 05/01/2013

D2d Co-Investigator Signature [Signature] Date 05/01/2013

Final steps to submission:

Save a copy of this form to your computer. Click on the "Submit" button and follow the directions to submit electronically. Alternatively, you may attach the file manually to an email and send to: D2d@TuftsMedicalCenter.org.

Submit button

WORKS CITED:

1. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Archives of general psychiatry*. Mar 2010;67(3):220-229.
2. Berk M, Sanders KM, Pasco JA, et al. Vitamin D deficiency may play a role in depression. *Medical hypotheses*. 2007;69(6):1316-1319.
3. Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *Journal of internal medicine*. Dec 2008;264(6):599-609.
4. Murphy PK, Wagner CL. Vitamin D and Mood Disorders Among Women: An Integrative Review.
5. Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. *Psychopharmacology (Berl)*. Feb 1998;135(4):319-323.
6. Rosenthal NE, Sack DA, Gillin JC, et al. Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. *Archives of general psychiatry*. Jan 1984;41(1):72-80.
7. Rosen LN, Targum SD, Terman M, et al. Prevalence of seasonal affective disorder at four latitudes. *Psychiatry research*. Feb 1990;31(2):131-144.
8. Rosenthal NE, Genhart M, Jacobsen FM, Skwerer RG, Wehr TA. Disturbances of appetite and weight regulation in seasonal affective disorder. *Annals of the New York Academy of Sciences*. 1987;499:216-230.
9. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med*. Apr 1 1995;122(7):481-486.
10. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care*. Sep 1994;17(9):961-969.
11. Gloth FM, 3rd, Alam W, Hollis B. Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. *The journal of nutrition, health & aging*. 1999;3(1):5-7.
12. Oren DA, Schulkin J, Rosenthal NE. 1,25 (OH)₂ vitamin D3 levels in seasonal affective disorder: Effects of light. *Psychopharmacology* 1994;116:515-516.
13. Dumville JC, Miles JN, Porthouse J, Cockayne S, Saxon L, King C. Can vitamin D supplementation prevent winter-time blues? A randomised trial among older women. *The journal of nutrition, health & aging*. Mar-Apr 2006;10(2):151-153.