NCT Study Title: Inflammation and Daily Life Study

Grant Study Title: Can an anti-inflammatory medication reduce loneliness?

NCT: NCT03771612

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Study Protocol

Due to the relationships between loneliness and a variety of poor health outcomes and mortality, loneliness is increasingly being recognized as an important public health issue. Despite the relevance of loneliness for health, including evidence suggesting the effects may be particularly pronounced for middle-aged adults, loneliness is a highly understudied topic in mid-life in need of further research. One potential mechanism for the effect of loneliness on health is inflammation. Lonely individuals have heightened inflammation, and inflammation can increase feelings of loneliness. Furthermore, loneliness and inflammation share similar psychological states, both marked by hypersensitivity to the social world, including increased sensitivity to both negative and positive social cues (i.e., social threat and social reward). Thus, by breaking the cycle between inflammation and loneliness, and altering the underlying hypersensitive psychological state, it is possible that an anti-inflammatory drug may lead to improvements in loneliness. However, to our knowledge, no studies have explicitly tested this. The objective of this study is to address this gap in the literature and test the effect of an anti-inflammatory medication on loneliness in a sample of middle-aged adults and to examine the social psychological mechanisms that may underlie any benefits.

This randomized double-blind placebo-controlled study will test the effect of an NSAID (naproxen) on loneliness and explore which psychological mechanisms are best targeted by an NSAID. Participants, all middle-aged adults screened for high levels of loneliness, will be randomized into a 2-week naproxen or placebo intervention. All participants will complete pre- and post-intervention sessions online to assess self-report psychological outcomes, inflammatory activity, and performance on behavioral tasks.

Participants will be men and women, ages 45-59, who all have high levels of loneliness. High loneliness scores will be assessed using the UCLA Loneliness Scale, with eligible subjects having a score of 41 or greater (approximately 20-25% of middle-aged adults), which has been previously used by our group to define a high loneliness group.

Participants will be recruited from the greater Los Angeles community using advertisements. All interested participants will first complete a structured telephone interview in order to assess eligibility; prospective participants with co-morbid medical conditions or characteristics known to affect inflammation or put them at undue risk will be ineligible to participate. Notably, participants with current Major Depressive Disorder will be excluded. However, we will control for depressive symptoms in analyses examining effects on loneliness to test whether the effect of NSAIDs on loneliness hold over and above effects on depression.

At baseline, participants will complete their first session online with an experimenter. Here, they will provide blood spots, complete self-report measures as well as several psychological tasks. Psychological tasks will include a task in which participants view negative social images and make ratings of their affective responses. Participants will also include a social/monetary reward task (revised Monetary Incentive Delay Task; Knutson et al., 1999) in which they will press a button once a target flashes on the screen in order to win money or see a close other or smiling stranger. Reaction times will be assessed, with faster reaction times indicating greater reward anticipation. We are

particularly interested in the difference in reaction times to close others vs. control targets.

They will be mailed their pill packs for the intervention. Following the baseline assessment, participants will take one 200 mg pill immediately after waking up each day, and another 200 mg pill an hour before going to sleep, daily for 2 weeks. By random assignment, half of the participants will take naproxen and half will take the same dose of placebo. The random allocation sequence will be generated by a statistical consultant who was will not be involved in running participants and will be kept by the UCLA Pharmacy to ensure proper drug preparation for each participant. Randomization will be done using a computerized uniform random number generator; males and females will be randomized separately in permuted blocks of 4.

Naproxen was chosen as it is available as a generic (and thus low-cost) drug, has a less frequent dosing schedule (i.e., twice daily) than some other NSAIDs (e.g., ibuprofen, taken every 4-6 hours), and has been associated with lower risk for adverse cardiovascular side effects compared to others NSAIDs. Furthermore, naproxen can reduce depressive symptoms in both animals and humans, providing evidence that it can affect psychological states. Additionally, the effect of NSAIDs on circulating levels of inflammation are inconsistent, but there is some meta-analytic evidence to suggest that naproxen specifically may lead to significant decreases in C-reactive protein, suggesting naproxen may be one of the best NSAIDs for reducing circulating levels of inflammation. The dosing of 400 mg/daily was chosen based on maximum over-the-counter recommendations.

Over the 2-week period, subjects will complete daily and weekly (online) measures of loneliness, other social psychological outcomes, and any side effects. Additionally, participants will receive text message reminders to take their pills, and report on symptoms, adherence, and any side effects (monitored by study staff). Participants will be asked to report on a full range of symptoms (mild, moderate, severe) in both a checklist and an open-ended fashion. Adverse events will be reported to the study physician, who will not be blinded to condition. If, at any point in the study, participants report mild side effects (e.g., diarrhea, heartburn for 2 consecutive days or more), their dose will be reduced by half to 200 mg each day. If participants report moderate to severe side effects (e.g., stomach pain, shortness of breath or trouble breathing), they will be removed from the study. At the end of the 2-week intervention, participants will get online again with an experimenter to provide another blood sample (to be mailed back) as well as to complete self-report measures and behavioral tasks, similar to the baseline assessment. In addition, participants will be contacted again 2 weeks later to assess measures of loneliness.

IRB amendment (5/2021):

Major changes to study protocol for COVID and financial reasons

<u>Minor Amendment - Types of change(s) proposed.</u>

Check all that apply:

- Clarification or technical change
- **Minor increase/decrease in number of Study participants**
- Narrowing of the inclusion criteria

- Broadening of the exclusion criteria
- **Changes in the dosage or form (e.g., tablet to liquid) but not the route of administration of an approved drug**
- **Increase or decrease in the number of safety monitoring visits provided that there is no impact on subject safety.**
- Addition or deletion of study sites
- **Change in payments to study participants**
- **Minor changes to recruitment materials**
- **Minor changes to screening procedures**
- **Change in funding (for example, addition of new funding or completion of grant) – Please describe below AND update the funding status in section 6.2 in the main application**
- **Other**

Major Amendment - Types of change(s) proposed.

Check all that apply:

- **Change in study design of a protocol approved by the full board of the IRB**
- Change in status of study participants (e.g., study participant becomes prisoner, ward, or pregnant in a protocol not approved for these populations (Note: This primarily applies to medical or treatment studies.)
- Addition of a procedure not approvable using expedited review procedures (e.g., ionizing radiation)
- Changes that increase risk or discomfort to study participants
- **Substantive changes to a consent form or other study documents distributed to subjects.**
- **Other**

Numerous reasons have converged and required us to change this study protocol drastically. First, because of the COVID-19 pandemic, we want to minimize all in-person contact as much as possible for participants and staff. Second, the budget/finances available to run this study have been drastically reduced because the pandemic as well. As such we are proposing the following changes to the study:

- Instead of n=100, we will have a final sample of n=50 (necessary for cost-saving)
- As the inflammatory markers were only an exploratory aim of the study, we will be eliminating all inflammatory markers / blood draws from the study for cost-saving reasons, as well as to be able to allow participants to complete the study entirely from their own homes for COVID safety reasons. All references to blood draws, inflammatory markers, gene expression analyses, medical records, medical tests, UCLA health phlebotomy, etc. have been removed from all materials/throughout the IRB.
- As such, all study procedures (consent, all questionnaires, tasks, drugs will be mailed to participants' homes, etc.) will take place from the participant's own homes. Participants will complete all questionnaires on their own online via Qualtrics. Tasks that would have been done at UCLA with study staff will now be done in a virtual session with study staff. All relevant sections/materials of the IRB have been updated to reflect this.

- Instead of participants taking naproxen/placebo twice daily for 4 weeks, they will take it twice daily for 2 weeks, for both cost-saving and safety reasons.
- As the over the counter indication for naproxen/Aleve is 10 days, and we are proposing 14 days, this will also eliminate the need to have any safety blood panels completed prior to starting the study. As noted above, all blood draws previously done for scientific reasons have been eliminated from this study. As such, the safety blood draws are not feasible for this study, for cost reasons. If the IRB would be more amenable to 10 days for safety reasons to drop these blood draws, we are willing to go down to 10 days as well.
- Relatedly, we have re-classified this study as minimal risk. We have greatly reduced the risks associated with this study by cutting down the time of the drug in half from 4 weeks to 2 weeks. We are also removing all blood draws associated with the study. We believe it is fair to classify this study as minimal risk now.
- As the study is considerably safer for participants, with this reduced dosage, and that all study procedures will be taking place online, we have changed the consent form to be done online by study staff, not just the study physician. Participants will be emailed a copy of the consent form to review at their convenience. They will be encouraged to ask the study staff any questions they have, including the study physician, in advance of signing the consent form. Prior to the participant's signing of the consent form, a member of the study team will contact the participant and go over and confirm that the participant has understood the form and has no remaining questions. Once they are comfortable, participants will sign the consent form virtually by completing a Qualtrics form. All relevant sections of the IRB have been updated to reflect this change.
- We have shortened the 2-week follow-up online questionnaires to a shorter session (30 minutes) and dropped the 4-week survey altogether, for cost-saving reasons
- All participant payments and time required has also been updated to reflect the shortened study design

IRB amendment (7/2021):

Study amended to include blood spot collection for inflammatory assessment. Blood spot collection devices will be mailed to participants and sent back to us for analysis.

Statistical Analysis Plan

Primary:

To examine whether naproxen reduces feelings of loneliness, we will use repeated measures analyses to examine time (pre- vs. post-intervention) by condition (naproxen vs. placebo) interactions on loneliness.

To examine whether naproxen reduces sensitivity to social threat, we will use repeated measures analyses to examine time (pre- vs. post-intervention) by condition (naproxen vs. placebo) interactions on self-reported ratings to negative social images. We anticipate that subjects in the naproxen (vs. control) condition will rate negative images as less negative from pre-to-post intervention.

To examine whether naproxen reduces sensitivity to social reward, we will use repeated measures analyses to examine time (pre- vs. post-intervention) by condition (naproxen vs. placebo) interactions on reaction times to social reward (with faster reactions times indicative of greater reward). Specifically, we expect that subjects in the naproxen (vs. placebo) condition will show less of a difference in reaction times to viewing close others vs. control targets from pre- to post-intervention.

Secondary:

To examine whether naproxen reduces inflammatory gene expression, we will use repeated measures to examine time (pre- vs. post-intervention) by condition (naproxen vs. placebo) interactions on the inflammatory gene composite measure.

To examine whether naproxen reduces feelings of loneliness at follow-up (2 weeks post-intervention), we will use repeated measures analyses to examine time (pre- vs. post- vs. follow-up intervention) by condition (naproxen vs. placebo) interactions on loneliness.