The University of New Mexico Health Sciences Center
Consent to Participate in Research

Non-opioid pramipexole suppresses immune NLRP3 reactivity for pain control

Nov 9, 2018

Purpose and General Information

You are being asked to participate in a research study that is being done by Dr. Eugen Koshkin, MD., and Dr. Erin Milligan, PhD., who is the Principal Investigator. This research is being done to evaluate and characterize the pro- and anti-inflammatory cytokine profile, and the immune cell phenotype collected from your serum prior to the initiation and at the termination of the study. You are being asked to participate because you have agreed to receive pramipexole from Dr.Koshkin. Approximately 45 people will take part in this study at the University of New Mexico Health Sciences Center (UNMHSC). This is not yet a multi-institutional study. There is currently no sponsor funding this study.

This form will explain the study to you, including the possible risks as well as the possible benefits of participating. This is so you can make an informed choice about whether or not to participate in this study. Please read this Consent Form carefully. Ask the investigators or study staff to explain any words or information that you do not clearly understand.

What will happen if I participate?

If you agree to be in this study, you will be asked to read and sign this Consent Form. After you sign the Consent Form, the following things will happen:

The purpose of this study is to characterize the pro- and anti-inflammatory cytokine profile and the immune cell phenotype collected from your blood prior and following initiation of pramipexole treatment. *Food and Drug Administration* (FDA) approved drugs that demonstrate an excellent safety profile in humans while also demonstrating the above-noted anti-inflammatory profile could be explored **as repurposed drugs for non-opioid pain therapeutics**. One such compound that satisfies this profile is pramipexole, which is now documented to reduce inflammation in several preclinical animal models of peripheral inflammatory pain (Sadeghi, H., et al., *Pramipexole reduces inflammation in the experimental animal models of inflammation.* Immunopharmacol Immunotoxicol, 2017. **39**(2): p. 80-86). While this study did not examine rodent pain behaviors, the classic hallmarks of hindpaw edema and neutrophil accumulation were assessed, with pramipexole significantly blunting these inflammatory processes. In a separate study examining brain inflammatory cytokines in mice following low-dose LPS inflammation, IL-1β mRNA levels were blunted following treatment with pramipexole (Lieberknecht, V., et al., *Pramipexole, a Dopamine D2/D3 Receptor-Preferring Agonist, Prevents Experimental Autoimmune Encephalomyelitis Development in Mice.* Mol Neurobiol, 2017. **54**(2): p. 1033-1045). Pramipexole is well-documented as a preferred dopamine-2/3 (D2/D3) receptor agonist that is a FDA approved for alleviating movement disorders in Parkinson Disease and for treating restless leg syndrome, with modest therapeutic outcomes. Therefore, based on the documented safety profile of pramipexole, we propose to explore whether it exerts anti-inflammatory (anti- IL-1β actions) resulting in therapeutic pain suppression in people.

The purpose of this study is to determine if pramipexole will control clinical pain by suppressing the activation of the IL-1β, and me be a new approach to treat pain.

Participation in this study will take a total of approximately one hour, during which your procedure will be performed and a small portion of your blood will be collected for analysis at a later date.

What are the possible risks or discomforts of being in this study?
Pramipexole (a.k.a. Mirapex) vs. Placebo: will be taken orally by capsule (2-3 hours before bedtime, with an initial starting dose of 0.125 mg /day for 1 week, and increased to 0.25 mg/day beginning the second week if pain relief remains suboptimal. Maximal doses of up to 0.5 mg/day for weeks 3 and/or 4 will be taken as needed to achieve maximal pain relief. The recommended doses and titration steps are derived from the manufacturer (Boehringer Ingelheim Pharmaceuticals, Inc) for treating Restless Legs Syndrome. Pramipexole is predicted to be well tolerated in the current pilot study because the dose range is much lower (by 60%) than documented doses noted as well-tolerated (1.5 to 4.5 mg/day).

Adverse reactions occur at doses greater than 0.5 mg/day. However, patients may have the potential to develop drowsiness and an increased risk for somnolence with Pramipexole capsules, which may occur when also using sedating medications or alcohol, or if there is the presence of sleep disorders.

However, every effort will be made to protect the information you give us. However, there is a small risk of loss of privacy and/or confidentiality. Although a breach in patient confidentiality is unlikely to occur and should not negatively impact your health or overall well-being, the necessary precautions will be taken to minimize this risk. Otherwise, we foresee no other direct risks of participating in the study. There are some risks of the pramipexole, which are explained by your doctor prior to you electing to receive pramipexole as an addition to your pain treatment.

How will my information be kept confidential?
Your name and other identifying information will be maintained in locked files, available only to authorized members of the research team, for the duration of the study. For any information entered into a computer, the only identifier will be a unique study identification (ID) number. Any personal identifying information and any record linking that information to study ID numbers will be destroyed when the study is completed. Information resulting from this study will be used for research purposes and may be published; however, you will not be identified by name in any publications.

Information from your participation in this study may be reviewed by the investigators only, and by the UNM Human Research Review Committee (HRRC), which provides regulatory and ethical oversight of human research. There may be times when we are required by law to share your information. However, your name will not be used in any published reports about this study.

What are the benefits to being in this study?
Your participation may lead to improved pain control and any help discover an immune signaling profile of chronic pain patients. It will help the investigators determine what leads to the therapeutic efficacy of the product, and will provide clinical evidence for insurance companies to ascertain the benefits of this therapy.

What other choices do I have if I don't participate?
Taking part in this study is voluntary so you can choose not to participate.

Will I be paid for taking part in this study?
Yes, you will be compensated $15 per visit.

What will happen if I am injured or become sick because I took part in this study?
If you are injured or become sick as a result of this study, UNMHSC will provide you with emergency treatment, at your cost.

No commitment is made by the University of New Mexico Health Sciences Center (UNMHSC) to provide free medical care or money for injuries to participants in this study.

In the event that you have an injury or illness that is caused by your participation in this study, reimbursement for all related costs of care will be sought from your insurer, managed care plan, or other

benefits program. If you do not have insurance, you may be responsible for these costs. You will also be responsible for any associated co-payments or deductibles required by your insurance.

It is important for you to tell the investigator immediately if you have been injured or become sick because of taking part in this study. If you have any questions about these issues, or believe that you have been treated carelessly in the study, please contact the Human Research Review Committee (HRRC) at the (505) 272-1129 for more information.

How will I know if you learn something new that may change my mind about participating?
You will be informed of any significant new findings that become available during the course of the study, such as changes in the risks or benefits resulting from participating in the research or new alternatives to participation that might change your mind about participating.

Can I stop being in the study once I begin?
Yes. You can withdraw from this study at any time without affecting your access to healthcare.
The investigators have the right to end your participation in this study if they determine that you no longer qualify to take part, if you do not follow study procedures, or if it is in your best interest or the study's best interest to stop your participation.

HIPAA Authorization for Use and Disclosure within the Research Team, of Your Protected Health Information (HIPAA)
As part of the patient treatment , we will be collecting health information about you, and only sharing it with members of the research team. This information is "protected" because it is identifiable or "linked" to you.

Protected Health Information (PHI)
By signing this Consent Document, you are allowing the investigators to use your de-identified protected health information for the purposes of this study. This information may include: medical exam information, sex, age, co-morbidities, and other possible pre-existing conditions.

In addition to researchers and staff at UNMHSC listed in this form, there is a chance that your health information may be shared (re-disclosed) outside of the research study and no longer be protected by federal privacy laws. Examples of this include disclosures for law enforcement, judicial proceeding, health oversight activities and public health measures.

Right to Withdraw Your Authorization
Your authorization for the use and disclosure, within the research team, of your health information for this study shall not expire unless you cancel this authorization. Your health information will be used or disclosed within the research team as long as it is needed for this study. However, you may withdraw your authorization at any time provided you notify the UNM investigators in writing. To do this, please send a letter notifying them of your withdrawal to either:

Dr.Eugene Koshkin, MD.
MSC 10 6000
1 University of New Mexico
Albuquerque, New Mexico, 87131-0001

Dr. Erin Milligan, PhD.
MSC 08 4740
1 University of New Mexico
Albuquerque, New Mexico, 87131-0001

Please be aware that the research team will not be required to destroy or retrieve any of your health information that has already been used or shared before your withdrawal is received.

Refusal to Sign
If you choose not to sign this consent form and authorization for the use, and disclosure within the research team, of your PHI and sample, you will not be allowed to take part in the research study.

What if I have questions or complaints about this study?
If you have any questions, concerns or complaints at any time about the research study, Dr.Koshkin, MD. or his associates will be glad to answer them at (505) 272-2610, Monday - Friday, 8 am - 5 pm. If you would like to speak with someone other than the research team, you may call the Human Research Review Committee (HRRC) at (505) 272-1129. The HRRC is a group of people from UNMHSC and the community who provide independent oversight of safety and ethical issues related to research involving human participants.

What are my rights as a research participant?
If you have questions regarding your rights as a research participant, you may call the Human Research Protections Office (HRPO) at (505) 272-1129 or visit the HRPO website at http://hsc.unm.edu/som/research/hrrc/.

ClinicalTrials.gov
A description of this study clinical trial will be available on http://www.ClinicalTrials.gov , as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of results. You can search this website at any time.

Consent and Authorization

You are making a decision whether to participate in this study. Your signature below indicates that you read the information provided (or the information was read to you). By signing this Consent Form, you are not waiving any of your legal rights as a research participant.

I have had an opportunity to ask questions and all questions have been answered to my satisfaction. By signing this Consent Form, I agree to participate in this study and give permission for my health information to be used or disclosed as described in this Consent Form. A copy of this Consent Form will be provided to me.

Name of Adult Participant (print)	Signature of Adult Participant	Date /

I have explained the research to the participant and answered all of his/her questions. I believe that he/she understands the information in this consent form and freely consents to participate.

Name of Research Team Member	Signature of Research Team Member	Date /