Study Title: Epidural Steroid Injection with Supplemental Oral Eplerenone for Low Back Pain: A Prospective, Double Blind Randomized Trial.

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1. **Length of time for research**
   a. data collection completion: two years
   b. data analysis and report writing/publication: two years

2. **Research Location(s):**

UCHealth Pain Medicine Center - chronic pain outpatient clinics associated with University of Cincinnati College of Medicine Department of Anesthesiology at West Chester and Midtown locations.

3. **Abstract/Brief Overview:**

Low back pain is a leading cause of disability and health care costs in the United States, and treatments are ineffective for many patients. Epidural steroid injections are a common treatment, but their efficacy has been questioned and for many patients they do not provide complete relief. We hypothesize, based on preclinical studies, that lack of complete efficacy may be due to the fact that clinically used steroids activate not only the intended drug target, the glucocorticoid receptor, but also the pro-inflammatory mineralocorticoid receptor. To test this hypothesis, the pilot study will recruit patients scheduled for lumbar epidural steroid injections for degenerative disc disease, and randomize them to receive a concurrent treatment with oral eplerenone (a clinically approved antagonist of the mineralocorticoid receptor) or placebo for 10 days starting just after the epidural injection. The primary outcome will be improvement in treatment outcome as measured by the Oswestry Low Back Pain Questionnaire, a validated research instrument that investigates both pain and functional outcomes. Subjects will be followed for one year. Secondary outcomes include the clinical course, in particular, whether the patient requires additional injections or not as part of their routine clinical care.

4. **Purpose of Study:**

Lumbar epidural steroid injections are commonly used for the management of low back and lower extremity pain, including lumbar disc herniation causing radiculopathy. The variability of response to epidural steroid injections has resulted in questions regarding technique, disease diagnosis, and medications administered. Preclinical research suggests that the anti-inflammatory corticosteroids often used in epidural steroid injections have activity at the glucocorticoid receptor (GR), its primary target, but also some activity at the mineralocorticoid receptor (MR))[1,2]. Activation of the MR, in many tissues, promotes the production of pro-inflammatory cytokines [3,4]. Our primary hypothesis is that treatment of low back pain with corticosteroids is not maximally effective because the steroids used clinically activate the pro-inflammatory MR in addition to the drug's primary target, the GR. By blocking the MR with the orally

administered steroid antagonist, eplerenone, pro-inflammatory effects of corticosteroid administration will be reduced, promoting the anti-inflammatory effect of GR activation. To test this hypothesis we propose the following specific aims:

1. Recruit patients who meet study criteria and conduct a double-blind trial by providing eplerenone or placebo in conjunction with lumbar epidural steroid injection.
2. Utilize the Oswestry Low Pain Questionnaire (version 2) prior to and following treatment up to one year to monitor treatment effectiveness.

5. Background:

Low back pain is a leading cause of disability and health care costs in the United States, and treatments are ineffective for many patients[5,6]. Lumbar epidural injections remain one of the most commonly performed procedures for treatment of lumbar radiculopathy[7]. Despite widespread use of epidurals, clinical effectiveness and cost effectiveness have been challenged. Multiple randomized control trials evaluating the efficacy of epidural injections for pain, resulted in conflicting conclusions [8]. The variability of response has been attributed to approach, technique, indication, and medications used. Initially performed with local anesthetic alone, steroids were added to epidural injections in the 1950s and used regularly since then [9]. While often used, the mechanism by which injected steroids provide reduction in pain from lumbar radiculopathy is still being elucidated and the cause for inconsistent results is unclear.

Local inflammation in the region of the lumbar sensory ganglia plays a role in many forms of low back pain, including those forms involving pathology of the intervertebral discs [10,11]. A common treatment for some forms of low back pain is local injection of corticosteroids. Randomized clinical trials of such treatments have often suggested that steroid injections are effective only in the short term[12,13]. The nominal target of anti-inflammatory corticosteroid drugs is the glucocorticoid receptor (GR). However, recent in vitro studies show that many clinically used steroids (including those commonly used for back pain, e.g. 6-α methylprednisolone and triamcinolone) can also activate the mineralocorticoid receptor (MR) with similar potency [1,2]. The MR was originally viewed only as the target of aldosterone, promoting sodium reabsorption in the kidney. However, this receptor has been detected in other cell types including peripheral sensory neurons[14]. In many tissues, MR activation is pro-inflammatory [3,4]. Some pro-inflammatory effects may be due to receptors in macrophages, where MR activation promotes production of pro-inflammatory cytokines and tissue destruction, while GR activation promotes tissue remodeling and wound repair [15]. We hypothesize that adding an oral MR blocker, eplerenone, at the time of steroid epidural injections for low back

pain due to lumbar degenerative disc disease, will improve response to the injected corticosteroids.

Eplerenone is chosen as a more specific MR blocker than its predecessor, spironolactone [16], avoiding side effects such as gynecomastia and sexual dysfunction. It is currently approved for use in the US as a therapy for high blood pressure and for heart failure. Its effectiveness in heart failure is thought to be due in part to anti-inflammatory effects in cardiac tissue[15].

In preclinical models of back pain, several of which were developed in our laboratories[17], we have observed that pain behaviors and abnormal sensory neuron hyper-excitability induced by the models are reduced by local application of clinically used corticosteroids. Consistent with our hypothesis, highly selective GR agonists are more effective than clinically used steroids that activate both GR and MR, and oral or local EPL can improve the effectiveness of the latter[14,18]. Although some highly GR-selective steroids are in clinical use (e.g., fluticasone), they are used primarily for topical or asthma indications and are not formulated for epidural injection. It should also be noted that in preclinical back pain models the model itself may locally activate the MR[14]; if this occurs in patients then even a highly selective epidural glucocorticoid steroid might be more effective with added MR blockers.

6. **Study design:**

The Department of Anesthesia has two suburban pain clinics that will serve as sources for recruiting subjects, UC Health Pain Medicine Center (Midtown) and UC Health Pain Medicine Center (West Chester). In the past year, 675 unique patients with the diagnosis of lumbar degenerative disc disease were evaluated between the two clinics. Our target number for study enrollment is 40 subjects (20 per group). We are requesting authorization for 60 subjects, in order to allow for subjects who drop out. Patients evaluated for degenerative disc disease are routinely given an epidural steroid injection as part of their treatment regimen. Often this is the preferred treatment; if there is no clear indication for surgical intervention, a more conservative approach is sought prior to considering surgery.

Eplerenone and placebo pills with blinded labels will be provided by Investigational Drug Pharmacy. We will use a block-stratified randomization schedule with blocks of sizes 2 and 4. The West Chester and Uptown locations will have separate randomization schedules. Patients will be randomized to receive either eplerenone or placebo, which will be taken for 10 days starting two days after the epidural injection. This timing is based on the pharmacokinetic profile of eplerenone, and on the time window in which the steroid injection is usually expected to begin having an effect (requiring a minimum

of 72 hours, and up to a week, to take effect). Studies show that eplerenone is well absorbed orally with a variable half-life of 2.2-9.4 hours [19]. The dose of eplerenone will be 50 mg PO daily. This is a commonly used starting dose for eplerenone's FDA-approved and indicated use in the treatment of hypertension and heart failure. Eplerenone is extensively metabolized with less than 5% excreted unchanged in the urine. Thus, renal dysfunction has little effect on eplerenone pharmacokinetics. However, patients with compromised renal function may be at greater risk for hyperkalemia when taking eplerenone. For this reason, a blood sample will be obtained from each participant to verify inclusion criteria related to kidney function (see below) based on a basic metabolic panel performed the day of the procedure. Subjects with elevated potassium or creatinine will not be included in the study. The blood sample will be obtained just prior to the epidural injection, at the clinical laboratories located within (West Chester site) or adjacent to (Midtown clinic) the participating pain clinics. This will allow the results (metabolic panel including K^+ and creatinine level) to be available by the following day. In order to avoid having subjects make an additional trip to the clinic, subjects will receive their study medications via overnight delivery service, once their blood test results have been reviewed. Alternatively, subjects who prefer may return to the clinic to pick up their medications. A single take-home sheet of information about the study medication will be given to each patient along with the medication, to help reinforce these directions (included in IRB submission). We anticipate that few subjects will be excluded on the basis of their blood test. Such subjects will still receive the $35 incentive payment for completing their first Oswestry questionnaire, however, their data will not be included in the study. Patients will be offered access to their blood test results, and given the option of having their primary care physicians notified of any abnormal findings.

Patients are normally seen for follow-up approximately one month after an epidural injection. Subjects who are recommended to have a second epidural injection at this follow-up visit will receive a second dose of the same study medication they received after their first injection. The same protocol will be followed: such subjects will have a repeat blood draw and re-confirmation of inclusion parameters prior to restarting the medication. Subjects who become ineligible at the time of the second injection will not receive a second round of study medication, but will continue to complete questionnaires and their data will be retained for analysis.

All patients will receive the same epidural steroid and approach (interlaminar injection of Kenalog (triamcinolone) and saline) as part of their standard care. Triamcinolone has a substantial potency for the MR in addition to the GR; all of the steroids commonly used for epidural injections show some activity at the MR [2]. The procedures and drug are routinely used at the participating clinics for treatment of degenerative disc disorders. We will use the REDCap (Research Electronic Data Capture) system for secure web based capture of questionnaire data, which is required in order to protect the

confidentiality of the subjects' data. This is provided by the Center for Clinical and Translational Science and Training. We already use this system for another project.

7. Research data collection/study procedures:

Patients meeting criteria will be invited to participate in the study prior to their first epidural steroid injection. If they consent, they will complete the Oswestry Low Back Pain Questionnaire (version 2) just prior to their first injection. This instrument is commonly used for research and is well-validated [20]. It is completed by the patient and captures the functional effects of back pain on various activities, providing a more meaningful picture than a simple static pain rating.

The patients will complete the Oswestry Low Back Pain Questionnaire again four weeks after their first injection, a time point at which patients routinely have a follow-up visit. Patients referred for a second injection at this time will complete an additional Oswestry just prior to that injection. The research nurse will contact the patients for additional follow-up at 3 months, 6 months, 1 year after their epidural injection (or after their second epidural injection if this is recommended).

Follow-up contacts will be made via email, text message, or phone, based on the subject's preference. For patients opting to have a link to the Oswestry sent to their cell phones, the REDCap-Twillio integration platform will be used. The follow-up will be used to direct the patients to an online version of the Oswestry Questionnaire or a mailed in or telephone version, as per the subject's preference. Subjects will receive a $35 gift card for each completed follow-up, to improve the response rate. Patients will also be informed of potential eplerenone side effects, including but not limited to dizziness, fatigue, abdominal pain, and diarrhea. Patients will be instructed to discontinue the medications and contact the on-call physician should they experience an adverse reaction. Patients referred for a second injection will receive a second round of the same drug (eplerenone or placebo) to which they were first randomized. Currently approximately 30% of the patients seen at the clinic receive a second injection.

8. Specimen collection:

Study participants will consent to providing a blood sample for performing a basic metabolic panel. Safety parameters related to kidney function will be confirmed prior to the start of the blinded medication. Both participating clinics have immediate proximity to Lab Corp facilities where the samples will be collected and analyzed. One sample collection tube (approximately 5 mL) prior to each epidural steroid injection is all that will be required from each subject.

9. **Potential Benefits:**

Anticipated contributions from the proposed research include an improved method for the treatment of radicular low back pain, a growing healthcare concern. Application of an existing medication to a different problem allows widespread accessibility and ease of further evaluation through multicenter trials. In addition, this study will provide a better understanding of the mechanism of steroid use in the treatment of low back pain, and provide an avenue for translation of the department's basic science findings.

10. Potential Risks, Discomforts, and inconveniences:

Potential risks include those associated with, administration of the study drug, and collection of the blood sample. Based on study design, the epidural steroid lumbar injection procedure performed will be indicated by clinical criteria and is standard of care, so risks of these procedures are not related to participation in the study. Eplerenone is a highly selective aldosterone receptor antagonist significantly reducing progesterone and antiandrogen activity seen in other aldosterone antagonists, such as spironolactone. It is well absorbed and extensively metabolized to inactive metabolites[19]. Associated risks with the study medication are expected to be small; the primary warnings and precautions relate to hyperkalemia, as eplerenone is potassium sparing. A blood sample will be collected and a basic metabolic panel performed to ensure normal serum potassium level and normal creatinine level prior to the study. In the context of normal kidney function there is expected little risk of developing hyperkalemia. Phlebotomy is associated with a very small risk of infection, bleeding, hematoma, and pain. Subsequent follow up will be in the form of a questionnaire, expected to take a few minutes to complete. Patients will be compensated with a $35 gift card at every subsequent follow up as a token of appreciation.

Risks of adverse reactions were obtained from the FDA drug information sheet; however, note that some of these numbers were probably obtained from longer term use or higher doses than we propose:

- Hyperkalemia (3 – 4%)
- Diarrhea (1 – 2%)
- Abdominal pain (1%)
- Coughing (1 – 2%)
- Dizziness (1 – 3%)
- Fatigue (1 – 2%)
- Influenza-like symptoms (1 – 2%)

Criteria for having a subject stop the study medication early: any adverse reaction to the medication concerning enough to the subject to have them call the researchers, or any adverse reaction deemed possibly study related during follow-up phone calls that will be made to the subjects 4 – 7 days after starting the study medication. Such subjects would continue to complete questionnaires and that data would be retained in the study. They would not receive a second round of study medication if referred for a second epidural steroid injection.

Criteria for stopping the study early: Any single instance of hospitalization or emergency room visit deemed likely related to the study medication, or two instances of subjects discontinuing the study medication early due to reported side effects requiring a doctor visit deemed likely related to the study medication

11. Data Safety monitoring plan and/or DSMB:

Patients recruited to participate will undergo the clinically indicated lumbar epidural steroid injection as part of their treatment regimen, considered standard of care. Additionally, they will concurrently receive the study drug or placebo for ten days. Patients who have met all inclusion criteria, including a basic metabolic panel with potassium and creatinine within normal limits, are expected to have low risk of adverse effects from the study drug - eplerenone. However, participants will be informed of potential side effects, including but not limited to dizziness, fatigue, abdominal pain, and diarrhea, and instructed to call study physician to discuss evaluation and/or discontinuation.
An interim analysis will be conducted halfway through the study (after 20 subjects are enrolled) to ensure there are no unexpected adverse responses to eplerenone. Dr. William Hurford, a department physician not involved with the study, will review subjects' records for safety issues on an ongoing basis.

12. Data Analysis:

The primary analysis will be to compare the change (difference score) in the Oswestry Disability Index between the placebo and eplerenone groups at each time point. Scores on this instrument range from 0 to 100%. With 20 subjects per group, a difference of 9 points in score can be detected with 80% power and $\alpha = 5\%$, assuming a standard deviation of 10. This value of standard deviation has been observed in similar studies [20]. Some studies have considered a difference of 4 points to be clinically significant while others have used higher values, up to 15 (the value used by the FDA in evaluating one back pain procedure). Average differences of 15 have been reported in studies of sciatica and chronic back pain[20]. Thus although the sample size is small it should be large enough to detect large or moderately sized clinically significant differences

between the groups. The Mann-Whitney test will be used to evaluate the significance of differences between the two groups, as the Oswestry is an ordinal scale.

Primary outcome measure: The change from the pre-injection Oswestry Disability Index scores for low back pain and disability at the selected time points.

Secondary outcome measures*:* We will also classify the clinical course following the first steroid injection, grouping patients into 3 groups as normally done by the participating clinics: 1) Pain relief deemed adequate and no further treatment recommended; 2) partial pain relief obtained and a second injection recommended (this usually occurs about 4-6 weeks after the first); 3) no pain relief obtained and alternative treatments pursued. Additional demographic data routinely collected for clinical purposes will also be analyzed (e.g. age, sex, weight/BMI, subtype of disc degeneration, duration and history of low back pain symptoms). As this is a small pilot study we do not anticipate having enough subjects to do a detailed analysis of interactions between the treatment and these other variables, but we will determine whether the two groups differ from one another on these secondary variables despite randomization.

13. Data storage and confidentiality

The signed consent forms will be stored in locked cabinets at the 2 participating clinics accessible only to the research nurse. The research nurse who consents the patients and administers the inventories, and the team member who mails out the medications after blood test results are obtained, will be the only members of the research team other than clinical providers who have access to the names of the patients. Original paper copies of the Brief Pain Inventories will be stored in the locked research laboratory in a locked cabinet accessible only to members of the research team. The names of the subjects will only be on the consent forms, and all other data including the inventories will be identified only by subject code numbers. The research nurse will enter the inventory scores and demographic data into a project database that will be stored in the Redcap server. The database will be designed with dropdown entries so that invalid values for the pain ratings cannot be entered. The Redcap data is encrypted and password protected so that only study members have access to it. A different researcher will verify the accuracy of data entry in a random 15% subset of the brief pain inventories that are manually entered. One member of the research team has already completed Redcap training. The Redcap project design has been completed. The deidentified data extracted from Redcap, and computer files generated from analysis of the data, will be stored on the research server. This server is password protected so that only members of the Co-investigator's laboratory can have access, and the directory containing study data will be further restricted so only the researchers

directly involved in the study have access. The server contents are automatically backed up several times per day and retained off-site for 30 days.
Paper copies of subject surveys will be destroyed when the study has been completed and the IRB protocol has been closed.

14. Study Population

Inclusion criteria: We are requesting authorization to recruit up to 60 subjects to allow for dropouts, with a goal of recruiting 40 subjects (20 per group). Subject must meet the following inclusion criteria:

- Adult patients of either sex, age 18 to 65
- Scheduled for lumbar epidural steroid injection as part of routine clinical care
- Have a diagnosis of lumbar degenerative disc disease demonstrated on either lumbar X-Ray or lumbar MRI.
- Have unilateral radicular symptoms or EMG consistent with radiculopathy and exam findings corresponding to this diagnosis: with symptoms reflecting a dermatomal distribution of pain and positive response to straight leg raise test, which is known to be a sensitive, but not specific test for nerve root irritation.

Exclusion criteria: Excluded from the study will be patients with medical contraindications, including specifically those related to use of eplerenone:

- Unable to complete questionnaires or give informed consent in English
- Unavailable for follow-up contacts to complete questionnaires
- Renal impairment (estimated GFR <50 mL/min or serum creatinine >1.8mg/dL) on metabolic panel obtained just prior to epidural injections.
- Elevated serum potassium (>5.5 mEq/L) on metabolic panel obtained just prior to epidural injections.
- Have undergone previous lumbar surgery.
- Treated with oral steroids or injectable steroid within the past year.
- Diabetic
- Systolic blood pressure reading less than 100 mm Hg at most recent clinic visit.
- Prescribed protease inhibitors, a class of antiviral drugs widely used to treat HIV/AIDS and Hepatitis C (included in list below and in the prescreening document to be used by the study nurse). This exclusion is based on the unpredictable metabolism of steroid observed with concurrent administration and such patients are also excluded from receiving epidural injections.
- Taking strong CYP3A4 inhibitors (included in detailed list given below and in the prescreening document to be used by the study nurse)

- Taking potassium supplements or potassium-sparing diuretics (amiloride, spironolactone, or triamterene) or using salt substitutes that contain potassium (examples given below and in the prescreening document to be used by the study nurse).
- Lactating.
- Patients receiving epidural steroid injections are already required to sign a pregnancy waiver, because the steroid is FDA pregnancy category C and involves fluoroscopy exposure. Patients with childbearing potential will be given a urine pregnancy test. Patients without a pregnancy waiver or negative urine test will also be excluded from the study. Eplerenone is a category B medication.

By limiting the study to patients with pain due to degenerative disc disease we aim to have a more defined population; different types of low back pain may have different etiologies, different degrees of local inflammation, and different sensitivity to epidural steroid. Clinical trials of epidural steroids in which multiple types of patients are lumped together have been criticized as difficult to interpret [12,13].

Drugs that if being taken by the patient will exclude them from the study (both generic and brand names are given):

Aldactone
amiloride
Aptivus
atazanavir
Biaxin
Bunavail
clarithromycin
Crixivan
Crixivan
darunavir
darunavir/cobicistat
Dyrenium
Evotaz
Fortovase
fosamprenavir
indinavir
indinavir
Invirase
Invirase
itraconazole
Kaletra
Ketek
Ketek

ketoconazole
Lexiva
lopinavir/ritonavir
Midamor
nefazodone
nelfinavir
nelfinavir
Nizoral
Norvir
Norvir
Pak
Potassium supplements
Prezcobix
Prezista
Reyataz
ritonavir
ritonavir
saquinavir
saquinavir
Serzone
spironolactone
Sporanox
suboxone
Suboxone
Tao
tazanavir/cobicistat
telithromycin
tipranavir
triamterene
troleandomycin
Viracept
Viracept
Zubsolv

Examples of salt substitutes containing potassium that patient cannot be using

Morton Salt Substitute
NoSalt
Nu-Salt
Morton Lite Salt
(Herb blends such as Mrs. Dash are OK, not based on potassium substitution.)

15. Consenting process and plan

In normal practice, patients are evaluated for low back pain. The formulation of a treatment plan may involve administration of a lumbar epidural steroid injection. Providers at the aforementioned clinics have agreed to allow recruitment of patients and will identify eligible subjects during the course of clinic visits. A one page summary of the study for providers will be made available at the clinics. Study personnel will also review the clinic schedule to identify additional potential subjects who have been scheduled to have an epidural steroid injection. The study nurse will contact these potential subjects by phone to inform them of the study. We have applied for an IRB waiver to do a preliminary research screening in the medical record, to avoid approaching potential subjects outside the age range or excluded conditions. The research will not alter the standard of care related to low back pain.

A one page invitation to participate in the study will be available for patients referred for epidural steroid injections. If patients are interested in participating, the research nurse will contact them to obtain consent, review risks and benefits, administer the pain inventory assessment. This process will be initiated during the initial evaluation appointment, or by phone (during the interval between evaluation/referral and the actual epidural injection), and consenting will be completed at the time of procedure and blood draw. A prescreening document will be used to note the information obtained from patients approached in the study, to document the reasons for screening failures. These documents will be stored with the consent documents.

16. Compensation:

Participants will be compensated with a $35 gift card for every questionnaire completed – at 4 weeks, 3 months, 6 months, and one year following. Patients who are referred for a second epidural injection (typically 4 – 6 weeks after the first) will complete an additional questionnaire at the time of the second injection and receive an additional $35 gift card. Payments will be made using the Greenphire system.

17. Subject costs:

There is no additional cost expected from the subjects. No extra clinic visits outside the standard of care are required.

18. Literature cited

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