Comparing Effectiveness of Duloxetine and Desipramine in Patients with Chronic Pain: A Pragmatic Trial Using Point of Care Randomization

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1. PURPOSE OF THE STUDY

a. Brief Summary

The purpose of this study is to compare effectiveness of duloxetine and desipramine in (1) decreasing pain, (2) improving function, (3) improving depression and (4) decreasing pain interference in patients with chronic pain. We will also compare compliance of patients with these two medications. We will apply a novel point of care randomization method which allows integration of randomized comparative effectiveness research with patient care.

b. Objectives

The importance of the proposed research has two aspects: 1) it establishes how pragmatic clinical trials can be integrated with patient care. This will lead to numerous more trials in future that can generate more evidence and direction for medical practice in perioperative and pain medicine; 2) it will determine if either a tricyclic antidepressant or a serotonin norepinephrine reuptake inhibitor is superior in treating patients with chronic pain. The subgroup analysis proposed will provide information about characteristics of patients who respond to these medications differently.

c. Rationale for Research in Humans

The study is comparing effectiveness of duloxetine and desipramine in patients with chronic pain. Administration of these medications to human subjects is necessary for the purpose of the study.

2. STUDY PROCEDURES

a. Procedures

Study Design: We will conduct a prospective open label randomized trial comparing effectiveness of duloxetine and desipramine.

Randomization (research): After obtaining research informed consent, the participants are going to be randomized by the treating pain provider using point of care randomization during the clinic visit. Point of care randomization will be done through Collaborative

Health Outcomes Information Registry (CHOIR) using computer generated random numbers.

Intervention: (standard of care) The participants are going to receive either duloxetine or desipramine. Duloxetine will be started at 20 mg per day. It will be increased to 40 mg per day at the beginning of week two, and then to 60 mg per day at the beginning of week three. Desipramine will be started at 25 mg per day. It will be increased to 50 mg per day at the beginning of week two, and then to 75 mg per day at the beginning of week three. These treatments will be continued for at least 6 months provided that the patients can tolerate the side effects and are willing to continue the treatment. Further titration of doses based on participants' tolerance and response is allowed based on clinical decision of the treating pain provider. Concomitant use of other analgesics or pain medications as well as pain interventions are also allowed.

Data collection: (standard of care and research) The participants are going to receive monthly electronic surveys which are already part of their routine clinical care. These surveys are going to be abbreviated to include average and worst Numerical Rating Scale (NRS) of pain; National Institute of Health (NIH) Patient Reported Outcomes Measurement Information System (PROMIS) measures for function, depression and pain interference; and questions about medication compliance, dose and adverse events. Data about use of other analgesics and medications, and pain interventions will also be recorded at these intervals from participants' electronic health records. If the participants do not complete the surveys within five days of receipt of the survey link, they will be contacted to be reminded of the survey. We will also record participants' baseline characteristics including age, sex, main pain diagnosis, other pain diagnoses, psychological comorbidities, medical comorbidities, medication use, and education.

b. Procedure Risks

The medications studied are both commonly used medications for patients with chronic pain. There is no additional risk with participation in the study.

c. Use of Deception in the Study

Deception will not be used.

d. Use of Audio and Video Recordings

Audio or video recording will not occur.

e. Alternative Procedures or Courses of Treatment

No alternative treatment is withheld from the patients.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Participant will continue to receive their usual care from Stanford Pain Management Center after completion of the study. If one medication is proven to be superior, then the participants' physicians will be notified.

g. Study Endpoint(s)

We will not have any interim analysis; thus, we will be able to assess the superiority of one treatment at conclusion of the study.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Chronic pain is a major healthcare problem affecting more than 100 million Americans. Chronic pain is a disease that can significantly compromise patients' quality of life and cause disability. It bears annual cost of around 635 billion Dollars on United States Healthcare System. The number of treatment modalities available for this condition is disproportionately low; moreover, the quality of data available for these modalities is not optimal either.(1) Pain medicine literature like other specialties faces problems with reproducibility and generalizability. In an attempt to test reproducibility of present literature, investigators could reproduce the results of only six (11%) out of 53 hematology-oncology trials. Interestingly, all these manuscripts had been published in reputable peer-reviewed journals with impact factors of above five.(2) We do not expect perioperative and pain medicine literature to be remarkably different.

The other problem with current literature is generalizability of the data. Large clinical trials usually have stringent inclusion and exclusion criteria. By restricting enrollment of patients with more serious comorbidities and psychological conditions, the observed differences can be attributed to interventions studied. By decreasing variability, statistical power to detect a treatment effect can be increased with the same number of patients. The disadvantage of this approach is that the results cannot easily be generalized to a large population of patients with more serious comorbidities and psychological conditions. This cohort of the patient is usually more difficult to treat.(3,4) Our current literature lacks high quality data to guide clinicians providing care to these patients. A simple example is implant to trial ration in patients undergoing trial of spinal cord stimulation. Most large clinical trials show that around 90% of patients have a successful trial of spinal cord stimulation and proceed with implantation.(5) However, case series published by large academic centers report that around 70% of the patients undergoing trial of spinal cord stimulation proceed to receiving an implanted device. (6,7) Comparative effectiveness research integrated with patient care can be one of the solutions to the current problem. These trials have a less stringent inclusion and exclusion criteria targeting patients who routinely receive clinical care. Therefore, the patients enrolled in these studies will better represent patients with chronic pain. Integration of research into patient care will allow enrollment of larger number of patients. This will enable the researchers to analyze known and unknown effects of treatments in the whole sample as well as in specific subgroups.3,4 Outcomes Research Consortium has already shown the benefits of this approach in perioperative medicine.(8) Comparative effectiveness trials focus more on effectiveness rather than efficacy. A specific treatment might be efficacious but not effective, especially in long term administration. In addition to efficacy, there are other factors than can affect effectiveness of a treatment including compliance, accessibility, ease of administration, etc. In chronic conditions, it is essential

to study long term effectiveness of a treatment modality in order to achieve meaningful sustainable improvement for patients.

We will leverage the advantages of a comparative effectiveness trial to answer an important question in pain medicine. Antidepressants are widely used to treat patients with chronic pain. Initial choice of antidepressant is usually based on clinical judgement of the clinician considering potential benefits versus risks of individual medications. Two most important classes of antidepressants used in patients with chronic pain are tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Duloxetine is an SNRI that is approved by United States Food and Drug Administration for treatment of fibromyalgia, painful diabetic neuropathy and chronic musculoskeletal pain. Two previous small size trials compared the efficacy of duloxetine with TCAs after a short course of treatment (4-6 weeks). The investigators could not find a difference between duloxetine and amitriptyline.(9,10) Moreover, meta-analysis of studies that compared these two groups of medications with placebo could not find any difference between these medications. However, none of the initial trials included in the meta-analysis compared these TCAs and SNRIs directly.(11) One retrospective study showed decreased healthcare utilization in patients prescribed duloxetine compared to patients taking amitriptyline, pregabalin or gabapentin.(12,13)

While most TCAs share the side effect of drowsiness, desipramine can be a better comparison for duloxetine. Like duloxetine, desipramine does usually not cause sleepiness or drowsiness. To the best of our knowledge, there has not been any clinical trials comparing long-term efficacy or effectiveness of duloxetine and desipramine.

b. Findings from Past Animal Experiments

Not applicable

4. Drugs, Biologics, Reagents, or Chemicals Used in the Study

a. Investigational Drugs, Biologics, Reagents, or Chemicals

N/A

b. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1	
Name:	Duloxetine
Dosage:	20-120 mg per day
Administration Route	Oral, Capsule
New and different use? (Y/N)	No
Commercial Product 2	
Name:	Desipramine
Dosage:	25-150 mg per day
Administration Route	Oral, Tablet
New and different use? (Y/N)	Yes

5. Disinfection Procedures for Medical Equipment Used on Both Humans and Animals

N/A

6. PARTICIPANT POPULATION

a. Planned Enrollment

Accepting type I error of 0.05 with 90% power, we will require 107 participants per group to detect one unit between-group difference in NRS pain scale. We are proposing a more conservative (larger) sample size to: (1) preserve power if the effect size is underestimated secondary to low medication adherence; and (2) preserve power for our subgroup analyses. We will therefore add 50% to our sample size to a total of 160 patients in each arm. Correlation between repeated measure will decrease variance and increase the power of the proposed study.

b. Age, Gender, and Ethnic Background

Men and women of any ethnic background who are 18 years old or above will be enrolled.

c. Vulnerable Populations

We will not enroll potentially vulnerable subjects.

d. Rationale for Exclusion of Certain Populations

We are studying the comparative effectiveness of these two medications in adults. Study of chronic pain in children is beyond the scope of our study.

e. Stanford Populations

Not applicable

f. Healthy Volunteers

Not applicable

g. Recruitment Details

All adult patients with chronic pain receiving care from Stanford Pain Management Center will be assessed for eligibility by their treating pain physician during each clinical visit. If eligible, the treating pain physician will go through the oral consent script. If the patient consents to participate, he/she will be randomized to receiving either duloxetine or desipramine. Open label prescription will be then sent to participants' pharmacy.

h. Eligibility Criteria

i. Inclusion Criteria

1. Age of 18 years old or above
2. Persistent pain for more than 3 months
3. Candidate for treatment by anti-depressant based on treating pain provider

ii. Exclusion Criteria

1. Prior failure of duloxetine and/or desipramine (patients who have failed other TCAs or SNRIs can be considered for the trial based on the reason for previous medication failure)
2. Contraindication to taking duloxetine or desipramine
3. Patient refusal

i. Screening Procedures

We do not collect any PHI prior to enrollment.

j. Participation in Multiple Protocols

Participants will be asked if they are enrolled in any other research study.

k. Payments to Participants

Participants will not receive any payment for taking part in this study.

l. Costs to Participants

Cost of the study medication will be borne by the participants and/or insurance company as part of standard of care. The study itself does not incur any cost in addition to standard of care.

m. Planned Duration of the Study

We estimate the study to be completed in 5 years as below:
1. Enrollment: 48 months
2. Follow up for last enrolled patient: 6 months
3. Data analysis and reporting the results: 6 months

7. RISKS

a. Potential Risks

i. Investigational devices

None

ii. Investigational drugs

None

iii. Commercially available drugs, biologics, reagents or chemicals

Potential adverse events are based on package insert approved by United States Food and Drug Administration:

Duloxetine
Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent

adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

Cardiac Disorders — Frequent: palpitations; Infrequent: myocardial infarction and tachycardia.

Ear and Labyrinth Disorders — Frequent: vertigo; Infrequent: ear pain and tinnitus.

Endocrine Disorders — Infrequent: hypothyroidism.

Eye Disorders — Frequent: vision blurred; Infrequent: diplopia and visual disturbance.

Gastrointestinal Disorders — Frequent: flatulence; Infrequent: eructation, gastritis, halitosis, and stomatitis; Rare: gastric ulcer, hematochezia, and melena.

General Disorders and Administration Site Conditions — Frequent: chills/rigors;

Infrequent: feeling abnormal, feeling hot and/or cold, malaise, and thirst; Rare: gait disturbance.

Infections and Infestations — Infrequent: gastroenteritis and laryngitis.

Investigations — Frequent: weight increased; Infrequent: blood cholesterol increased.

Metabolism and Nutrition Disorders — Infrequent: dehydration and hyperlipidemia; Rare: dyslipidemia.

Musculoskeletal and Connective Tissue Disorders — Frequent: musculoskeletal pain; Infrequent: muscle tightness and muscle twitching.

Nervous System Disorders — Frequent: dysgeusia, lethargy, and parasthesia/ hypoesthesia; Infrequent: disturbance in attention, dyskinesia, myoclonus, and poor quality sleep; Rare: dysarthria.

Psychiatric Disorders — Frequent: abnormal dreams and sleep disorder; Infrequent: apathy, bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt; Rare: completed suicide.

Renal and Urinary Disorders — Infrequent: dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal.

Reproductive System and Breast Disorders — Frequent: anorgasmia/orgasm abnormal;

Infrequent: menopausal symptoms, and sexual dysfunction.

Respiratory, Thoracic and Mediastinal Disorders — Frequent: yawning; Infrequent: throat tightness.

Skin and Subcutaneous Tissue Disorders — Infrequent: cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, and photosensitivity reaction; Rare: ecchymosis.

Vascular Disorders — Frequent: hot flush; Infrequent: flushing, orthostatic hypotension, and peripheral coldness."

Desipramine
"ADVERSE REACTIONS
Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when NORPRAMIN is given.

Cardiovascular: Hypotension, hypertension, palpitations, heart block, myocardial infarction, stroke, arrhythmias, premature ventricular contractions, tachycardia, ventricular tachycardia, ventricular fibrillation, sudden death

There has been a report of an "acute collapse" and "sudden death" in an 8-year-old (18 kg) male, treated for 2 years for hyperactivity.

There have been additional reports of sudden death in children. (See PRECAUTIONS-Pediatric Use)

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis

Neurologic: Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alterations in EEG patterns; tinnitus

Symptoms attributed to Neuroleptic Malignant Syndrome have been reported during desipramine use with and without concomitant neuroleptic therapy.

Anticholinergic: Dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of urinary tract

Allergic: Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross-sensitivity with other tricyclic drugs Hematologic: Bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia

Gastrointestinal: Anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue, hepatitis, jaundice (simulating obstructive), altered liver function, elevated liver function tests, increased pancreatic enzymes

Endocrine: Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Other: Weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, proneness to falling, weakness and fatigue, headache; fever; alopecia; elevated alkaline phosphatase"

iv. Procedures

None

v. Radioisotopes/radiation-producing machines

None

vi. Physical well-being

Not applicable

vii. Psychological well-being

Not applicable

viii. Economic well-being

Not applicable

ix. Social well-being

Not applicable

x. Overall evaluation of risk

Low

b. International Research Risk Procedures

Not applicable

c. Procedures to Minimize Risk

Study medications will be administered as open label prescription. Both duloxetine and desipramine are commercially used medications at Stanford Pain Management Center; hence, all our clinicians have extensive experience in prescribing these medications and monitoring participants afterwards. We will continue safety monitoring procedure of Stanford Pain Management Center for these medications which includes regular follow-up visits as well as an open line of communication with nurses and physicians of our clinic. Moreover, the participants will have the contact information of the protocol directors and can consult them with any further questions or concerns.

d. Study Conclusion

The study will terminate at the completion of follow-up for last patient enrolled. Study medication will be stopped if the participant decides to discontinue the medication. Since the medications used are part of standard clinical care that the patients receive in our clinic, the participants can continue the medication after the completion of the study if they would like to.

e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

The treatments in the study are not different from routine clinical practice; therefore, adverse events will be monitored as a part of participants' clinical care by their clinic providers. Protocol Director (PD) will monitor for protocol deviations.

ii. Person(s) responsible for Data and Safety Monitoring

Data and safety will be monitored by investigators and PD.

iii. Frequency of DSMB meetings

N/A

iv. Specific triggers or stopping rules

N/A

v. Will the Protocol Director be the only monitoring entity? (Y/N)

Yes

f. Risks to Special Populations

N/A

8. BENEFITS

There is no potential benefit related to participation in the study. Any benefit can be attributed to clinical administration of these two medications that are commonly used in adult patients with chronic pain.

9. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.