STUDY QUESTIONNAIRE

A. PARTICIPANT’S DATA

GENDER ( ) Men ( ) Women

Age: _____ years

WORKING PLACE ________________________________

CITY: ________________________________________

PROVINCE: ________________________________

1. Where do you practice your professional activity?
   o In a public center.
   o In a private center.
   o Mixed.

2. Years of professional practice __________ years (excluding years of fellowship).
   o < 5 years.
   o 5 – 10 years.
   o > 10 years.

3. What clinical specialty do you practice at the present time?
   o Traumatology
   o Rehabilitation.
   o Anesthesiology / Pain management specialist.
   o Primary Care.
   o Geriatrics.
   o Rheumatology.
   o Another. Which? ___________________

4. Regarding to the concept of central sensitization:
   o I know the electrophysiological findings, its clinical consequences (hyperalgesia), and the basic neurobiology involved.
   o I have only a conceptual knowledge of this phenomenon.
   o I do not know this concept.

4. In your opinion, which of the following definitions of osteoarthrosis of the knee is more correct?
   o A clinical concept that involves painful knee and clinical history compatible with joint wear.
   o It is a radiological concept, being necessary a MRI scan to establish the diagnosis and the actual repercussion.
   o It is a radiological concept, being necessary 2 orthogonal radiographs for the diagnosis and assessment.
B. DATA RELATED TO CENTRAL SENSITIZATION

6. In the case of pain secondary to osteoarthritis of the knee, when do you consider that the pain can be classified as chronic?
   - > 1 month.
   - > 3 months.
   - > 6 months.

7. How many patients with chronic pain related to knee osteoarthritis, in total, did you treat over the last month?
   - 0-10 patients.
   - 11-20 patients.
   - 21-30 patients.
   - > 30 patients.

8. According to your usual clinical practice and experience, what are the age ranges in which pain secondary to osteoarthritis of the knee is more prevalent?
   - 30 – 54 years.
   - 55 – 74 years.
   - 74 – 84 years.
   - > 85 years.

9. Which is the percentage according to gender?
   - Men ___ \%.
   - Women ___ \%.

10. According to your experience, what would be the distribution in percentages, according to the intensity of the pain, in patients with osteoarthritis of the knee?
    - No pain: ___ \%.
    - Mild pain: ___ \%.
    - Moderate pain: ___ \%.
    - Severe pain: ___ \%.

11. According to your usual clinical practice and experience, what are the age ranges in which painful symptoms secondary to osteoarthritis of the knee are more severe and limiting?
    - 30 – 54 years.
    - 55 – 74 years.
    - 74 – 84 years.
    - > 85 years.

12. Which do you consider, according to your clinical experience that are the main challenges in the management of patients with pain secondary to osteoarthritis of the knee?
    CHALLENGE 1: _______________________________________________________
    CHALLENGE 2: _______________________________________________________
    CHALLENGE 3: _______________________________________________________
    CHALLENGE 4: _______________________________________________________
    CHALLENGE 5: _______________________________________________________
13. Some patients with osteoarthritis of the knee have a characteristic central sensitization phenotype that includes (please check all that apply):

- Pain at rest.
- Long lasting disease.
- History of inadequate response to multiple analgesics and conservative treatments.
- Progressive increase of the painful area.
- Mirror pain in the contralateral knee.
- Appearance of multiple painful sites during treatment.
- Poor acceptance of the disease.
- Insomnia.
- Depression and/or anxiety.
- Levels of pain and disability not proportional to the degree of the joint lesion.

14. What percentage of patients attended in a week, with osteoarthritis of the knee, presents, at least, one of the characteristics listed in the previous question?

- < 10%.
- 10-30%.
- 31-50%.
- 51-70%.
- > 70%.

C. IMPACT OF CENTRAL SENSITIZATION IN THE PATIENTS WITH PAIN SECONDARY TO KNEE OSTEOARTHRITIS

C.1. Impact on the course of the disease.

15. Please, indicate your level of agreement with the following statements

| Patients with knee osteoarthritis and central sensitization... | 0 | 1 | 2 | 3 | 4 |
|---------------------------------------------------------------|---|---|---|---|---|
| ... present an analgesic control difficult to manage, since they usually show a poor response to conventional analgesics. |   |   |   |   |   |
| ... are prone to suffer a higher pain intensity than patients without central sensitization. |   |   |   |   |   |
| ... suffer from a higher degree of functional limitation and loss of quality of life during the course of treatment of their disease as compared to those without central sensitization. |   |   |   |   |   |
... they have a higher risk for not responding adequately to knee arthroplasty and to suffer from chronic pain after replacement surgery,

... are more prone to suffer from psychological comorbidities, such as anxiety and depression during the course of treatment.

... show a poor prognosis regarding the results of medical, surgical, and rehabilitation treatment.

### C.2. Impact on the non-pharmacological treatment.

16. Please, indicate your level of agreement with the following statements

| Patients with arthrosis of the knee and central sensitization ... |
|---------------------------------------------------------------|
| ... they respond to a lesser extent to non-pharmacological treatment (immobilization, rest, exercises, etc.), decreasing the impact of these measures on the total result of treatment. |
| ... present a lower degree of achievement of goals of physical rehabilitation therapy. |

### C.3. Impact on the pharmacological treatment.

17. Please, indicate your level of agreement with the following statements

| 0 | Strongly disagree | 1 | Somewhat agree | 2 | Agree but not determinant for the prognosis of treatment | 3 | Agree and determinant for the prognosis of treatment | 4 | Strongly agree and very determinant for the prognosis of treatment |
|---|-------------------|---|----------------|---|------------------------|---|-----------------------------|---|-----------------------------|

There is a great lack of knowledge about the mechanisms involved in the pathophysiology of pain due to osteoarthritis of the knee, and therefore in its correct taxonomy and treatment.

Patients with knee osteoarthritis and central sensitization responded to a lesser extent to conventional analgesics.

Most patients with pain due to osteoarthritis of the knee are treated with analgesics whose mechanism of action is not adequate to counteract the mechanisms involved in the pathophysiology of pain.

C.4. Impact on the surgical treatment.

18. Please, indicate your level of agreement with the following statements

| 0 | Strongly disagree | 1 | Somewhat agree | 2 | Agree but not determinant for the prognosis of treatment | 3 | Agree and determinant for the prognosis of treatment | 4 | Strongly agree and very determinant for the prognosis of treatment |
|---|-------------------|---|----------------|---|-----------------------------------------------|---|-----------------------------------------------|---|-----------------------------------------------|
| The presence of central sensitization in patients with osteoarthritis of the knee... |
| ... is an important predictor of the time needed for functional recovery after knee replacement surgery. |
| ... is an important predictor of results of the physical rehabilitation therapy after knee replacement surgery. |
| ... it implies a higher level of pain and functional limitation in the early postoperative period after knee replacement surgery, and, in general, a higher consumption of analgesics as compared to patients without central sensitization. |
C.5. Impact on the general results of treatment.

19. Please, indicate your level of agreement with the following statements

| The presence of central sensitization may be an important prognostic factor for the success of treatment of patients with knee osteoarthritis. | 0  | 1 | 2 | 3 | 4 |
| A better knowledge of the mechanisms involved in the physiopathology of pain due to knee osteoarthritis may improve the general prognosis of treatment of patients with knee osteoarthritis. | 0  | 1 | 2 | 3 | 4 |
| To date, there are no therapeutic guidelines or adequate treatment algorithms easily applicable to routine daily practice for the treatment of central sensitization in patients with osteoarthritis of the knee | 0  | 1 | 2 | 3 | 4 |
| Early recognition of the central sensitization phenotype in patients with osteoarthritis of the knee could improve treatment outcomes. | 0  | 1 | 2 | 3 | 4 |

D. DIAGNOSTIC CRITERIA OF CENTRAL SENSITIZATION

D.1. Data of the clinical history.

20. Please select the 3 criteria/symptoms that according to your clinical practice consider most important for the diagnosis of the central sensitization and indicate your level of agreement with the use of the following data from the patient's clinical history for the diagnosis of the central sensitivity.
| 0 | Strongly disagree |
|---|------------------|
| 1 | Somewhat agree |
| 2 | Agree but not determinant for the prognosis of treatment |
| 3 | Agree and determinant for the prognosis of treatment |
| 4 | Strongly agree and very determinant for the prognosis of treatment |

- Catastrophism and preoperative anxiety and depression.
- The presence of joint pain at rest.
- Pain of disproportionate intensity for the degree of radiological lesion of the joint.
- Frequency of appearance of pain (0 never, 10 very frequently) and its intensity (numeric rating scale 0-11) permanently, during movement, when loading weights, incidental.
- Mirror pain in the contralateral joint.
- Constant pain associated with levels of disability.
- Progression of pain outside of the original site of the lesion.
- Progressive appearance of multiple pain sites.
- Concomitant fatigue and/or sleep disturbances.
- Pain that accompanies long-standing osteoarthritis.
- Poor acceptance of the current condition.
- Concomitant anxiety and/or depression.
- Generalized pain.
- Cramps and/or parenthesis in the extremities.
- Feeling of swelling in the extremities.
- Poor response to regular analgesics.
- Poor response to non-pharmacological treatments.
The appearance or coexistence of the following associated physical symptoms:

- Bruxism / headache.
- Alternating diarrhea / constipation without data of an organic cause.
- Mandibular pain.
- Tension pain in the neck and/or shoulders.
- Frequent micturition / painful urination.
- Pelvic pain.
- Skin problems.
- Restless legs syndrome.
- Hypersensitivity to light.
- Hypersensitivity to certain smells.
- Hypersensitivity to noise.
- Hypersensitivity to pesticides.
- Hypersensitivity to touch.
- Hypersensitivity to mechanical pressure.
- Hypersensitivity to drugs.
- Hypersensitivity to temperature (hot / cold).

Presence of the following comorbidities:

- Chronic lumbar pain.
- Whiplash-associated disorders
- Disorders of the temporomandibular joint.
- Myofascial pain syndrome.
- Rheumatoid arthritis.
- Arthrosis in other joints.
- Fibromyalgia.
- Chronic fatigue syndrome.
- Irritable colon syndrome.
- Post-surgical persistent pain.
D.2. **Tests to be performed during physical examination.**

21. Please, indicate your level of agreement regarding performance of the following tests for the diagnosis of central sensitization

| Test Description                                                                 | 0            | 1            | 2            | 3            | 4            |
|----------------------------------------------------------------------------------|--------------|--------------|--------------|--------------|--------------|
| Assessment of pressure pain thresholds in the most affected joint area.          |              |              |              |              |              |
| Assessment of pressure pain thresholds 10 cm above the affected joint.           |              |              |              |              |              |
| Assessment of pressure pain thresholds in the forearm.                          |              |              |              |              |              |
| Assessment of touch sensitivity in the most affected joint area.                 |              |              |              |              |              |
| Assessment of touch sensitivity 10 cm above the affected joint.                  |              |              |              |              |              |
| Assessment of touch sensitivity in the forearm.                                  |              |              |              |              |              |
| Assessment of vibration sensitivity in the most affected joint area.             |              |              |              |              |              |
| Assessment of vibration sensitivity 10 cm above the affected joint.              |              |              |              |              |              |
| Assessment of vibration sensitivity in the forearm.                              |              |              |              |              |              |
| Assessment of heat pain sensitivity in the most affected joint area.             |              |              |              |              |              |
| Assessment of heat pain sensitivity 10 cm above the affected joint.              |              |              |              |              |              |
| Assessment of heat pain sensitivity in the forearm.                              |              |              |              |              |              |
| Assessment of cold pain sensitivity in the most affected joint area.             |              |              |              |              |              |
| Assessment of cold pain sensitivity 10 cm above the affected area.               |              |              |              |              |              |
| Assessment of cold pain sensitivity in the forearm.                              |              |              |              |              |              |
| Assessment of touch sensitivity (pinprick hyperalgesia) in the most affected joint area. |              |              |              |              |              |
| Assessment of sensitivity (pinprick hyperalgesia) 10 cm above the affected joint. |              |              |              |              |              |
| Assessment of sensitivity (pinprick hyperalgesia) in the forearm.                |              |              |              |              |              |
| Assessment of temporal summation to touch in the most affected joint area.       |              |              |              |              |              |
| Assessment of temporal summation to touch 10 cm above the affected joint.        |              |              |              |              |              |
| Assessment of temporal summation to touch in the forearm.                        |              |              |              |              |              |
| Assessment of dynamic mechanical allodynia triggered by touch in the most affected joint area. |   |   |   |
| Assessment of dynamic mechanical allodynia 10 m above the affected joint. |   |   |   |
| Assessment of dynamic mechanical allodynia in the forearm. |   |   |   |
| Assessment of deep somatic hyperalgesia to touch in the most affected joint area. |   |   |   |
| Assessment of deep somatic hyperalgesia 10 cm above the affected joint. |   |   |   |
| Assessment of deep somatic hyperalgesia in the forearm. |   |   |   |
| Assessment of the descending inhibitory pathway in the most affected joint area. |   |   |   |
| Assessment of the descending inhibitory pathway 10 m above the affected joint. |   |   |   |
| Assessment of the descending inhibitory pathway in the forearm. |   |   |   |
| Assessment of pressure thresholds during and after exercise in the most affected joint area. |   |   |   |

### D.3. Data of physical examination

22. Please, indicate your level of agreement with the use of the following data from physical examination for the diagnosis of central sensitization

| Decrease of pressure pain thresholds in the most affected joint area. | 0 | 1 | 2 | 3 | 4 |
| Decrease of pressure pain thresholds 10 above the affected joint. |   |   |   |   |   |
| Decrease of pressure pain thresholds in the forearm. |   |   |   |   |   |
| Touch hypersensitivity in the most affected joint area. |   |   |   |   |   |
| Touch hypersensitivity 10 cm above the affected joint. |   |   |   |   |   |
| Touch hypersensitivity in the forearm. |   |   |   |   |   |
| Vibratory hypersensitivity in the most affected joint area. |   |   |   |   |   |
| Vibratory hypersensitivity 10 cm above the affected joint. |   |   |   |   |   |
| Vibratory hypersensitivity in the forearm. |   |   |   |   |   |
| Heat hypersensitivity in the most affected joint area. |   |   |   |   |   |
| Heat hypersensitivity 10 cm above the affected joint. |   |   |   |   |   |
| Heat hypersensitivity in the forearm. |   |   |   |   |   |
Cold hypersensitivity in the most affected joint area.
Cold hypersensitivity 10 cm above the affected joint.
Cold hypersensitivity in the forearm.
Tactile pinpick hyperalgesia in the most affected joint area.
Pinpick hyperalgesia 10 cm above the affected joint.
Pinpick hyperalgesia in the forearm
Temporal summation to touch in the most affected joint area.
Temporal summation 10 cm above the affected joint.
Temporal summation in the forearm.
Dynamic mechanical allodynia triggered by touch in the most affected joint area.
Dynamic mechanical allodynia 10 cm above the affected joint.
Dynamic mechanical allodynia in the forearm.
Deep somatic hyperalgesia to touch in the most affected joint area.
Deep somatic hyperalgesia 10 cm above the affected joint.
Deep somatic hyperalgesia in the forearm.
Altered descending inhibitory pathway in the most affected joint area.
Altered descending inhibitory pathway 10 cm above the affected joint.
Altered descending inhibitory pathway in the forearm
Low pressure thresholds during and after exercise in the most affected joint area.
D.4. Complementary tests.

23. Please, indicate your level of agreement with the use of the following complementary tests for the diagnosis of central sensitization.

| Level | Description |
|-------|-------------|
| 0     | Strongly disagree |
| 1     | Somewhat agree |
| 2     | Agree but not determinant for the prognosis of treatment |
| 3     | Agree and determinant for the prognosis of treatment |
| 4     | Strongly agree and very determinant for the prognosis of treatment |

The following questionnaires may be useful in the diagnostic process of central sensitization:

- Visual analogue scale.
- Drawings of the painful area.
- Central Sensitization Inventory (CSI).
- Brief pain inventory (BPI).
- Western Ontario and McMaster (WOMAC) osteoarthritis index.
- PainDETECT questionnaire (PDQ).
- Modified PainDETECT questionnaire for osteoarthritis.
- Pain Quality Assessment Scale (PQAS).
- Health-related quality of life questionnaires (SF-12, EQ-5D).
- Quality of sleep questionnaires (Medical Outcomes Study Sleep Scale (MOS-Sleep)).
- Anxiety scales [Hospital Anxiety and Depression Scale – (HAD)].
- Pain catastrophizing scale.
- The Doleur Neuropathique 4 questionnaire(DN4).
- The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale.

The following complementary tests may be useful in the diagnostic process of central sensitization:

- Nociceptive withdrawal reflex (NWR).
- Quantitative sensory testing (QST).
- Cortical event-related potential amplitudes.
- Functional nuclear magnetic resonance imaging.
- Radiological assessment (anteroposterior and lateral) of the affected joint.
- The finding of discrepancy between pain intensity, the degree of disability and the degree of joint lesion in the diagnostic images is a good indicator of the presence of central sensitization in patients with knee osteoarthritis.
E. TREATMENT OF CENTRAL SENSITIZATION

E.1. Pharmacological treatment.

24. Please, indicate your level of agreement:

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Strongly disagree | Somewhat agree | Agree but not determinant for the prognosis of treatment | Agree and determinant for the prognosis of treatment | Strongly agree and very determinant for the prognosis of treatment |

**Analgesic drugs that would act specifically on central sensitization in patients with knee osteoarthritis would be:**

- Dual reuptake inhibitors of epinephrine and serotonin (duloxetine, venlafaxine, amitriptyline)
- A2delta calcium channel ligands (gabapentin, pregabalin)
- Tramadol.
- Tapentadol.
- NMDA receptor antagonists (ketamine, dextromethorphan).
- Serotonin reuptake inhibitors.
- Calcium channel blockers.
- Some drugs may have some value in the treatment of patients with pain due to knee osteoarthritis and central sensitization.
- Classical opioids (oxycodeone, oxycodone-naloxone, morphine, fentanyl, etc.).
- Paracetamol.
- Non-steroidal anti-inflammatory drugs (NSAIDs).

Tramadol, although it has a double mechanism of action (serotonin and epinephrine reuptake inhibition) is not recommendable for prolonged treatment.

The most important mechanism in the treatment of central sensitization is to reestablish the normal function of the epinephrine descending inhibitory pathway.

The most important mechanism in the treatment of central sensitization is to reduce hyperexcitability of the ascending pain pathway.

Classical opioids (oxycodeone, oxycodone-naloxone, morphine, fentanyl, etc.) are considered second-line treatments, only indicated when analgesics of central action have not been effective.

Pharmacological treatment should be guided by the...
mechanisms involved in the physiopathology of pain.
Pharmacological treatment should be guided by the intensity of pain, both at rest and on movement.
The use of WHO analgesic step ladder is not an adequate reference framework for the selection of the adequate analgesic drug in patients with knee osteoarthritis and central sensitization.

E.2. Non-pharmacological treatment.

25. Please, indicate your level of agreement:

| 0  | Strongly disagree | 1 | Somewhat agree | 2 | Agree but not determinant for the prognosis of treatment | 3 | Agree and determinant for the prognosis of treatment | 4 | Strongly agree and very determinant for the prognosis of treatment |
|----|-------------------|---|----------------|---|---------------------------------|---|---------------------------------|---|-------------------------------------------------|

The following non-pharmacological treatments would be useful in the management of the patient with knee osteoarthritis and central sensitization
Conductual cognitive therapy.
Exercise.
Manual therapy.
Education of the patient on chronic pain.
Mindfulness.
Management of stress.
Neurofeedback.
Transcutaneous electrical nerve stimulation.
Non-invasive cerebral stimulation.
F. USEFULNESS OF THE CONCEPT OF CENTRAL SENSITIZATION IN THE INTEGRAL MANAGEMENT OF THE PATIENTS WITH KNEE OSTEOARTHRITIS.

26. Please, indicate your level of agreement:

| Early diagnosis and treatment of central sensitization may improve the results of conservative management strategies in patients with knee osteoarthritis. | 0 Strongly disagree | 1 Somewhat agree | 2 Agree but not determinant for the prognosis of treatment | 3 Agree and determinant for the prognosis of treatment | 4 Strongly agree and very determinant for the prognosis of treatment |
| --- | --- | --- | --- | --- | --- |
| Early diagnosis and treatment of central sensitization may preserve functionality and quality of life of patients with knee osteoarthritis during all phases of treatment. |  |  |  |  |  |
| Early diagnosis and treatment of central sensitization may shorten the referral healthcare route of the patient with knee osteoarthritis. |  |  |  |  |  |
| Early diagnosis and treatment of central sensitization may improve results of total knee replacement surgery in patients with knee osteoarthritis. |  |  |  |  |  |
| Early diagnosis and treatment of central sensitization may reduce the use of analgesics in the immediate postoperative period. |  |  |  |  |  |
| Early diagnosis and treatment of central sensitization may reduce the length of hospital stay in patients undergoing total knee replacement surgery. |  |  |  |  |  |
| Early diagnosis and treatment of central sensitization may facilitate early ambulation in the postoperative period of patients undergoing total knee replacement surgery. |  |  |  |  |  |
| Early diagnosis and treatment of central sensitization may reduce the rate of adverse events caused by analgesic medications used for pain treatment in the course of the disease. |  |  |  |  |  |
### Pain treatment during the course of the disease

Early diagnosis and treatment of central sensitization may reduce direct and indirect costs related to the treatment of the patient with knee osteoarthritis.

Early diagnosis and treatment of central sensitization may facilitate physical rehabilitation therapy of the patient with knee osteoarthritis.

Early diagnosis and treatment of central sensitization may facilitate physical rehabilitation therapy of the patient with knee osteoarthritis after total knee replacement surgery.

### Early diagnosis and treatment of pain sensitization by the primary care physician...

... once joint symptoms have appeared, may preserve functionality and quality of life of patients with knee osteoarthritis during all phases of treatment.

... once joint symptoms have appeared, may improve general results of treatment of patients with knee osteoarthritis.

... once joint symptoms have appeared, may reduce the incidence of persistent pain after total knee replacement surgery.

... once joint symptoms have appeared may delay the time to total knee replacement surgery.

... once joint symptoms have appeared, may reduce costs derived from visits and procedures of specialized medicine.

### Early diagnosis and treatment of pain sensitization by the reference specialist (traumatologist, rehabilitator, anesthetist, etc.)

... may improve general results of treatment of patients with knee osteoarthritis.

... may preserve functionality and quality of life of patients with knee osteoarthritis during all phases of treatment.

... may reduce the incidence of persistent pain after total knee replacement surgery.

... may reduce the number of patients requesting a knee prosthesis as a solution for his/her joint pain.

... may improve analgesic control during the whole process, including the perioperative period, even reducing the length of hospital stay.

... may facilitate physical rehabilitation therapy of the patient in the immediate postoperative period after total knee replacement surgery.

... may decrease the percentage of patients with persistent intense pain after total knee replacement surgery.

... may reduce overall direct and indirect costs involved in the treatment of the patients with knee osteoarthritis.