Rationale and design of a multicenter randomized clinical trial with memantine and dextromethorphan in ketamine-responder patients

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The N-methyl-D-aspartate receptor plays an important role in central sensitization of neuropathic pain and N-methyl-D-aspartate receptor antagonists, such as ketamine, memantine and dextromethorphan may be used for persistent pain. However, ketamine cannot be repeated too often because of its adverse events. A drug relay would be helpful in the outpatient to postpone or even cancel the next ketamine infusion. This clinical trial evaluates if memantine and/or dextromethorphan given as a relay to ketamine responders may maintain or induce a decrease of pain intensity and have a beneficial impact on cognition and quality of life. This trial is a multi-center, randomized, controlled and single-blind clinical study (NCT01602185). It includes 60 ketamine responder patients suffering from neuropathic pain. They are randomly allocated to memantine, dextromethorphan or placebo. After ketamine infusion, 60 patients received either memantine (maximal dose 20 mg/day), or dextromethorphan (maximal dose 90 mg/day), or placebo for 12 weeks. The primary endpoint is pain measured on a (0–10) Numeric Rating Scale 1 month after inclusion. Secondary outcomes include assessment of neuropathic pain, sleep, quality of life, anxiety/depression and cognitive function at 2 and 3 months. Data analysis is performed using mixed models and the tests are two-sided, with a type I error set at α = 0.05. This study will explore if oral memantine and/or dextromethorphan may be a beneficial relay in ketamine responders and may diminish ketamine infusion frequency. Preservation of cognitive function and quality of life is also a central issue that will be analyzed in these vulnerable patients.

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Abbreviations:
ANOVA, Analysis of variance; BPI, Brief Pain Inventory; BLC, Big/Little Circle; DN4, Neuropathic pain in 4 questions; DX, Dextromethorphan; GNT, Graded Naming Test; HAD, Hospital Anxiety and Depression scales; IST, Information Sampling Task; LSEQ, Leeds Sleep Evaluation Questionnaire; M, Memantine; MAOIs, Monoamine oxidase inhibitors; NP, Neuropathic pain; NMDA, N-methyl-D-aspartate; NPRS, Numeric Pain Rating Scale; NPSI, Neuropathic Pain Symptom Inventory; NSAIDs, Non-steroidal anti-inflammatory drugs; PGIC, Patient Global Impression of change; RTI, Reaction Time; SF 36, Short Form 36 Health Survey; SOC, Stockings of Cambridge.

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1. Introduction

The International Association for the Study of Pain defines neuropathic pain (NP) as “pain caused by a lesion or disease of the somatosensory system” [1]. Despite the large literature on NP treatment over the last decade, medical treatment of NP is still far from being satisfactory, with less than half of the patients achieving significant benefit with any pharmacological drug [2,3]. A number of guidelines [4,5] for NP treatment have been published, with antidepressants and antiepileptics as first-line drugs. N-Methyl-D-Aspartate receptor (NMDAR) antagonists, such as ketamine, dextromethorphan (DX) and memantine (M) are possible drugs after therapeutic failure with recommended guidelines, and could prevent or treat painful symptoms [6]. In NP, an excessive release of glutamate and substance P has been described, leading to a constant opening and activation of the NMDAR, with a massive calcium entry and an amplified trafficking of pain signals to central sites [7,8]. NMDAR belongs to the family of ionotropic glutamate receptors that mediate a slow, Ca\(^{2+}\) permeable component of excitatory synaptic transmission in the Central Nervous System. Following channel opening, membrane depolarization, mediated by glutamate binding to AMPA and NMDA receptors, is required to relieve the voltage-dependent Mg\(^{2+}\) block before ions can permeate the channel pore [9-11].

The hyperexcitability state described in NP as central sensitization, is associated with abnormalities in the sensory peripheral and central systems, resulting in neuronal excitation and abnormal pain manifestations such as spontaneous pain, allodynia and hyperalgesia [10]. The blockade of these receptors by NMDAR antagonists causes a decrease in the release of neurotransmitters into the synapse, inhibits the propagation of nociceptive input to central sites [7] and may lead to a reduction of pain [6,10].

However, data concerning the efficacy of NMDAR antagonists in NP are controversial. Ketamine has shown an efficacy in NP [12-19], in post-operative pain [20,21] and in phantom limb pain [16,22] but other trials showed a limited analgesic effect on surgery-induced NP [23,24]. Overall, ketamine is efficacious in 65% of patients [25,26] but this alleviation of pain lessens after a few weeks or months [27,28], requiring a new hospital admission for intravenous (iv) ketamine infusion. But because of its possible psychodyseleptic, cardiovascular and hepatic severe adverse events (AEs) [29,30], ketamine cannot be safely administered too frequently. M and DX are also NMDAR antagonists but have lesser AEs than ketamine [31,32].

M is described as a noncompetitive NMDAR antagonist with moderate affinity, strong voltage-dependency and rapid unblocking kinetics [33,34]. It is used in Alzheimer’s disease to prevent cognitive deterioration. DX is a low affinity noncompetitive NMDAR antagonist [35] and is prescribed for its antitussive properties. M and DX show controversial results concerning their impact on NP. It has been reported that M is effective in complex regional pain syndrome [36] and in phantom limb pain [37,38]. No efficacy was obtained in post-herpetic NP [39,40], after amputation [41], in phantom limb pain [42,43] or in NP associated with diabetes [40]. Concerning DX, it is effective in diabetes [40,44-46] and trauma-induced NP [31], but is not effective in postherpetic [40,44], and trauma-induced [31] NP, in phantom limb pain, in amputation associated with cancer [47,48], or in facial neuralgia [49]. All these studies display a number of methodological differences and a recent review of the literature including 28 randomized clinical trials [50] highlights the need to develop further clinical trials of good methodological quality with NMDAR antagonists. Recently, we showed an efficacy of M in patients with NP induced by surgery and chemotherapy (unpublished results) and of M and DX in alleviating animal induced chronic pain [51,52]. The effect of M or DX as a therapeutic relay of ketamine has never been studied and this challenging issue is explored in our study.

We hypothesize that pain relief induced by ketamine – this being reported in 65% of patients – “the ketamine responders” [25,26] could be maintained with oral M or DX, used as relay drugs, with less adverse events. M or DX could be a therapeutic option for ketamine responder patients suffering from NP, in order to postpone or even cancel a new ketamine infusion and next hospital admission.

Another important point in pain is the observation that a link between pain, impaired cognition and diminished quality of life has also been shown in the literature. In NP animals with chronic pain [52], DX but not M administered post-surgically has been shown to improve cognitive impairment. Cognition and quality of life will also be evaluated in the present study in order to estimate the global impact of both treatments in the patients.

In order to test our hypothesis that consists of maintaining ketamine-induced pain relief with oral M or DX, as relay drugs to ketamine, this randomized controlled trial in ketamine-responder NP patients aims to assess pain intensity after one month treatment. In addition, the impact of these drugs on cognition, sleep, anxiety, depression and quality of life will be analyzed.

2. Materials and methods

2.1. Study design

The study is designed as a prospective, randomized, controlled, single-blind, multi-center clinical trial in a parallel design including a M group, a DX group and a placebo group. The French Research Ethics Committee gave a positive approval on July 5, 2011 (leading ethics committee number AU 895). The trial is registered in ClinicalTrials.gov (trial number NCT01602185). Patients meeting inclusion criteria sign a consent form after receiving oral and written information about the study. At baseline they complete tests including: pain assessment with Numeric Pain Rating Scale (NPRS), Neuropathic pain in 4 questions (DN4) [53], Neuropathic Pain Symptom Inventory (NPSI) [54], Brief Pain Inventory (BPI) [55], and McGill pain questionnaire [56,57]. Other tests include: Hospital Anxiety and Depression scale (HAD) [58], Patient Global Impression of change (PGIC) [59], Leeds Sleep Evaluation Questionnaire (LSEQ) [60], Short Form 36 Health Survey (SF 36) [61], and cognition Cantab® tests. All patients receive ketamine infusion. Responders to ketamine (defined as a decrease of 1.5 point on the NPRS or a one positive unit difference of the PGIC on the 3rd day after the infusion) continue the trial for a study period of three months. They are randomly assigned to a study group: M (n = 20) or DX (n = 20) or placebo (n = 20) and complete a pain diary (mean daily pain and maximum pain using NPRS, number of paroxysms, concomitant analgesic treatment). M or DX or placebo (lactose) is given orally for 12 weeks. M and DX
are given in increasing doses with the following dosing schedule: M: week 1: 5 mg/day; week 2: 10 mg/day; week 3: 15 mg/day; and weeks 4 to 12: 20 mg/day. DX: week 1: 30 mg/day; week 2: 60 mg/day; and weeks 3 to 12: 90 mg/day. Evaluations and tests are repeated at 1, 2 and 3 months. In order to maintain a good compliance and to verify that patients do not develop adverse events, these are called by phone once a week. Fig. 1 summarizes the flowchart of the study.

2.2. Objectives

The primary objective of this study is to assess if oral M or DX, given as a relay after ketamine infusion, in ketamine responder patients, may maintain or even induce a decrease of pain intensity in NP patients 1 month after the end of ketamine infusion.

The secondary objectives are to evaluate the pain intensity, the concomitant analgesic treatments and the impact of treatments (M or DX or placebo) on cognitive parameters, sleep, anxiety, depression and quality of life at 2 and 3 months after the end of ketamine infusion.

2.3. Participants and setting

2.3.1. Inclusion criteria

Patients must fulfill the following criteria: have chronic NP excluding central or diabetic origin, be a responder to ketamine (defined as a decrease of 1.5 point on the NPRS or a one positive unit difference of the PGIC scale), be ≥18 years, have completed the battery of tests before and after the ketamine infusion, be affiliated to the French Social Security, and have given informed consent.

2.3.2. Exclusion criteria

Patients will not be accepted if they meet any of the following exclusion criteria: have a contraindication to M or DX (hypersensitivity to the active substance or the excipients, hypertension, history of stroke, severe heart failure or diabetes Types I and II), medical and/or surgical history not compatible with the study, progressive disease at the inclusion time, alcohol addiction and treatment with specific drugs (amantadine, memantine, ketamine, dextromethorphan, L-Dopa, dopaminergic agonists, anticholinergic, barbituric, neuroleptic, IMAO, antispastic agents, dantrolene or baclofen, phenytoin, cimetidine, ranitidine, procainamide, quinidine, quinine, nicotine, hydrochlorothiazide, warfarin). Will also be excluded women of childbearing potential not using an effective contraceptive, pregnant or breastfeeding, taking part in any other interventional trial, and inability to understand patients’ information and informed consent form.

2.4. Eligibility and randomization

Patients are recruited from eight Pain Clinics in France, and the Clinical Investigation Center University Hospital of Clermont-Ferrand, France is the coordinating center. Patients with severe chronic NP responding to ketamine treatment are included. Before enrollment, an informed consent is obtained from each patient. The treatment allocation follows a predefined randomization plan and is conducted by a person independent from the protocol. The randomization sequence is generated using random blocks.

Fig. 1. Flowchart of the study design.
2.5. Primary and secondary outcomes

The primary outcome measure is the average intensity of pain measured by Numeric Pain Rating Scale in the past 24 h, one month after inclusion. Patients verbally rate the intensity of pain on a scale form “0” (no pain) to “10” (worst pain). This measure will be repeated at Months 2 and 3.

Secondary outcome measures are the evaluation of pain at Months 1, 2 and 3 after inclusion (Numeric Pain Rating Scale, Neuropathic Pain in 4 questions, Neuropathic pain Symptom Inventory, Brief Pain Inventory, McGill Pain Questionnaire), anxiety and depression (Hospital Anxiety and Depression scale), quality of life (Patient Global Impression of Change, Leeds Sleep Evaluation Questionnaire, Short Form 36 Health Survey), cognition (Cantab® Tests), and concomitant analgesic treatments (Pain diary). The summary of the different evaluations and questionnaire is reported in Table 1.

2.5.1. Outcome measures

2.5.1.1. Numeric pain rating scale. The primary outcome will be the rating of global pain measured by the Numeric Pain Rating scale. This scale is an 11-point scale for patient self-reporting of pain. Patients verbally rate the intensity of pain on a scale from “0” (no pain) to “10” (worst pain possible).

2.5.1.2. Neuropathic pain in 4 questions (DN4). DN4 [53] is a clinical tool for the diagnosis of NP. This questionnaire included a series of four questions consisting of both sensory descriptors and signs related to bedside sensory examination. Two questions (I and II) are based on the interview of the patient and two questions (III and IV) are based on a standardized clinical examination. A score of 1 is given to each positive item and a score of 0 to each negative item. The total score is calculated as the sum of the 10 items and the cut-off value for the diagnosis of NP is a total score of 4/10.

2.5.1.3. Neuropathic pain symptom inventory. This questionnaire [54] includes 12 items: 10 descriptors of the different symptoms of NP and 2 items for assessing the duration of spontaneous ongoing and paroxysmal pain. A total intensity score can be calculated as the sum of the scores of the 10 descriptors. In addition, five subscores ( Burning spontaneous pain; Pressing spontaneous pain; Paroxysmal pain; Evoked pain; Paresthesia/dysesthesia) corresponding to the mean scores of the items belonging to each of the five factors can be identified.

2.5.1.4. Brief pain inventory. This questionnaire [55] assesses the severity of pain and the impact of pain on daily function according to mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. It also assesses location of pain, pain medications and amount of pain relief in the past 24 h.

2.5.1.5. McGill pain questionnaire. This self-report questionnaire [56,57] is used to evaluate a person experiencing significant pain. It can be used to monitor the pain over time and to determine the effectiveness of any treatment or intervention.

2.5.1.6. Hospital anxiety and depression scale. This 14-item scale [58] is used to determine the levels of anxiety and depression that a patient is experiencing. Seven of the items relate to anxiety and seven relate to depression.

2.5.1.7. Patient global impression of change. This is a 7-point numerical scale [59] used to assess from patients what the change in their condition following treatment meant to them.

2.5.1.8. Leeds sleep evaluation questionnaire. This 10-item, subjective self-report measure [60] is used to assess changes in sleep quality over the course of a treatment intervention. The scale evaluates four domains: ease of initiating sleep, quality of sleep, ease of waking, and behavior following wakefulness. The

Table 1
Summary of evaluations for a patient.

<table>
<thead>
<tr>
<th>Visits</th>
<th>Inclusion</th>
<th>Post ketamine infusion</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical interviews</td>
<td></td>
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<tr>
<td>Verification of inclusion and exclusion criteria</td>
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<td>X</td>
<td></td>
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<tr>
<td>Informed consent</td>
<td>X</td>
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<tr>
<td>Measures</td>
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<tr>
<td>Numeric Pain Rating Scale (NPRS)</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Neuropathic pain four questions (DN4)</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Neuropathic Pain Symptom Inventory (NPSI)</td>
<td>X</td>
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<tr>
<td>Brief Pain Inventory (BPI)</td>
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<tr>
<td>McGill pain questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Hospital Anxiety and Depression scale (HAD)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Patient Global Impression of Change (PGIC)</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Leeds Sleep Evaluation Questionnaire (LSEQ)</td>
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<tr>
<td>SF36 Health Survey (SF36)</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Cantab® Tests</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Treatments</td>
<td></td>
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<tr>
<td>Return of therapeutic units</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Return of pain diary</td>
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<tr>
<td>Reports of adverse effects and concomitant analgesic treatments</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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</tr>
</tbody>
</table>
patient has to indicate whether these 4 aspects of sleep are improved or impaired in comparison to usual.

2.5.1.9. Short form 36 health survey. This questionnaire [61] is a measure of health status and quality of life of patient. This questionnaire includes eight health concepts divided into two categories, Physical Health and Mental Health. Physical health category includes general health perception, physical functioning, role limitations due to physical health problems and bodily pain. Mental health category includes role limitations due to emotional problems, social functioning, mental health and vitality. It also includes a single item that provides an indication of perceived change in health.

2.5.1.10. Cantab® tests. The Cambridge Neuropsychological Test Automated Battery (Cantab®, Cambridge, U.K.) [62] is a battery of twenty two neuropsychological tests, administered to subjects using a touch screen computer and a press-pad.

The selected tests are: Reaction Time (RTI), Information Sampling Task (IST), Big/Little Circle (BLC), Stockings of Cambridge (SOC) and Graded Naming Test (GNT).

- Reaction Time (RTI) is a latency task used to distinguish reaction time from movement time. The task is divided into five stages and in each case, the participant must react as soon as a yellow dot appears. In some stages the dot may appear in one of five locations, and the participant must sometimes respond by using the press-pad, sometimes by touching the screen, and sometimes both.

- The Information Sampling Task (IST) tests impulsivity and decision making. The participant is presented with gray boxes on the screen, and two colored panels below these boxes. The aim of this task is making a correct decision about which color is in the majority. For that, the participant must touch the gray boxes one at a time, which reveal one of the two colors. When the participant has made his decision about which color is in the majority, he must touch the panel of that color to indicate his choice. After that, all the boxes reveal their colors and a message is displayed to inform if the decision was correct or not.

- Big/Little Circle (BLC) assesses comprehension, learning, speed of response and ability to touch the correct circle. Participants must first touch the smaller of the two circles displayed, then, after 20 trials, touch the larger circle for 20 further trials.

- Stockings of Cambridge (SOC) is a spatial planning test which provides information about executive function. The participant is shown two displays containing three colored balls. The participant must move the balls one at a time in the lower display to copy the pattern shown in the upper display. The participant’s planning ability is measured thanks to the time taken to complete the pattern and the number of moves.

- Graded Naming Test (GNT) assesses object-naming ability. Patients have to name drawings of objects in ascending difficulty.

2.5.1.11. Pain diary. This will be kept daily during the three months after randomization. The pain diary includes assessment of mean daily pain using NPRS, maximum pain, number of paroxysms, and reports of concomitant analgesic treatments.

2.6. Data handling and record keeping

All original records such as consent forms, CRFs are anonymized and maintained also for 15 years.

2.7. Sample size calculation

The number of subjects required is 60 patients with NP (20 in each group) (\(\alpha = 0.05\) bilateral situation; \(\beta = 0.20,\) minimum \(\delta\) difference estimated at 1.4, \(\sigma\) standard deviation at 1.5 from the published literature [63,64] and considering drop-outs of patients [40] for adverse events or premature withdrawal from the study, we plan to screen 80 subjects.

2.8. Statistical analysis

The primary analysis will be carried out in intention-to-treat and all statistical tests (except multiple tests) will be done with \(\alpha\) risk = 5% (two-sided). Concerning the primary objective, comparison between the three randomized groups at 1 month will be made using ANOVA or Kruskal–Wallis test (homo- 
escasticity studied by Bartlett test) followed by appropriate post-hoc test: Tukey–Kramer test or Dunn test. Comparisons between treatment groups will be done systematically without adjustment and by adjusting other factors whose distribution could be, despite randomization, unbalanced between treatment groups. If factor adjustments are needed, a linear regression model could be developed.

The analysis of secondary endpoints shall be identical as above: intergroup comparisons for cognitive parameters and scales of quality of life. Comparisons concerning qualitative criteria between the three groups will use the chi-squared test or Fisher’s exact test (if validity conditions not met). The percentage of patients responding to treatment with a decrease of \(\geq 30\%\) on the Numeric Pain Rating Scale and a decrease of at least 2 points on the Numeric Pain Rating Scale will be presented with confidence interval 95%. To measure the evolution of various parameters collected during the 4 visits (NPRS, PGIC, DN4, NPSI, QCD, QDSA, HAD anxiety and depression, LSEQ, SF36, Cantab®), a longitudinal data analysis was considered by mixed models (or random effects models) that will measure between and within subject variability (“random intercept” and “slope”) and study the (fixed) effects group, time and interaction time \(\times\) group. The impact of covariates (e.g. etiology and ketamine response) will be explored to assess the impact of treatments on cognitive parameters and quality of life of patients.

A sensitivity analysis of missing data will be performed, to ensure the pertinence of the longitudinal data (MAR or MCAR). In order to assess the problem caused by missing longitudinal data at 6 months, estimation methods developed by Verbeke and Molenberghs [65] should be proposed.
3. Discussion

Ketamine is often prescribed in patients with persistent NP. However, a drawback with ketamine is that its beneficial effect on pain decreases with time. Other marketed NMDAR antagonists, M and DX, have a mechanism of action similar to ketamine’s, but with lesser AEs and, display also some degree of efficacy in a number of studies. Our hypothesis is that ketamine responders may also be M and/or DX responders and that a drug relay with these drugs in ketamine responders may maintain the pain relief obtained with ketamine. Furthermore an additive action of M or DX on ketamine pain alleviation may also be envisaged although such a result has not been obtained so far in preclinical and clinical literature. If such effects of M and DX were demonstrated, these findings would open a very interesting avenue for patients and clinicians [27,28]. It is also widely reported that chronic pain affects cognition, quality of life and is generally associated with psychological discomfort such as anxiety and/or depression in a large number of patients [66,67] and a lesser pain report might also improve the life of the patients.

In conclusion, a beneficial effect of M or DX in ketamine responders would suggest prescribing the drugs to out-patients. It would offer the clinician a therapeutic alternative after ketamine infusion, and help to maintain the autonomy of these vulnerable patients with sometimes intractable pain.

References


