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

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ABSTRACT

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 $\alpha = 0.05$. 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.

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 psychodysleptic, 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