Detoxification of neuromodulation eligible patients by a standardised protocol: a retrospective pilot study

Running title: detoxification before neuromodulation

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Financial support: None.

Authorship statement:
Conceptualization: all authors
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Formal analysis: LG, ADS, MM
Investigation: all authors
Methodology: all authors
Writing – review & editing: all authors
Final approval manuscript: all authors

Conflict of interest: Jean-Pierre Van Buyten and Iris Smet serve as consultants for Medtronic, Abbott, Nevro, Mainstay Medical and Boston Scientific. Maarten Moens has received speaker fees from Medtronic and Nevro. There are no other conflicts of interests to declare.

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Abstract

Objectives. Patients eligible for Spinal Cord Stimulation (SCS) generally experience excruciating pain, requiring more opioid consumption, which is usually an indication for SCS implantation. After final implantation, SCS has the ability to stabilize or decrease opioid usage in half of the patients. In this study, opioids were actively eliminated prior to implantation of any neuromodulation device with a standardized detoxification protocol. This pilot study aims to explore the feasibility, effectiveness and safety of this opioid detoxification protocol prior to neuromodulation techniques.

Materials & Methods. In this retrospective pilot study, 70 patients who were taking opioids and who were eligible for neuromodulation techniques, underwent the detoxification program. A combined in- and out-patient clinic protocol was applied, whereby clonidine was the main component of both parts of the program. A multidisciplinary team with pain physicians and psychologists was responsible for performing this detoxification program. Safety and feasibility were systematically recorded during the hospitalization.

Results. No serious safety issues were reported. At the start of the program, patients reported a mild sedative effect of clonidine. Additionally, most patients presented mild symptoms of opioid withdrawal, which were partially countered by the sedative effect of clonidine. Both patients and the medical staff found this protocol feasible in clinical practice. Concerning the effectiveness, a statistically significant decrease in median morphine milligram equivalents (MME) was found with a MME of 175 (Q1-Q3: 118.1 – 240) at baseline and at the last available follow-up visit the MME was 0 (Q1-Q3: 0 – 16.88).

Conclusions. This standardised detoxification program has proven its effectiveness, safety and feasibility in this single-center experience pilot study in patients eligible for neuromodulation techniques.

Keywords: clonidine; detoxification; neuromodulation; opioids; pilot study.
Introduction

New insights have led to the awareness of the danger of narcotics, coming from a total denial of addiction to the current opioid crisis with an increasing number of narcotics’ related deaths\textsuperscript{1-3}. Additionally, there is no proven long-term efficacy of opioids in the treatment of chronic pain, with even strong evidence of harm, especially at high doses\textsuperscript{4}. When patients move from occasional use to continuous use of opioids, each dose (instead of providing euphoria) is needed to avoid dysphoria\textsuperscript{5}. A similar mechanism is proposed for analgesia whereby each dose is needed to avoid hyperalgesia, instead of producing analgesia. This leads to the hypothesis that patients who are taking opioids are in a continuous state of withdrawal\textsuperscript{5}.

Patients eligible for Spinal Cord Stimulation (SCS) generally experience excruciating pain, requiring more opioid consumption, which is usually an indication for SCS implantation \textsuperscript{6}. After implant, SCS can stabilize or decrease opioid usage\textsuperscript{6, 7}. However, the hypothesis raised by many researchers, is to consider SCS before escalated opioid usage to improve outcome in complex chronic pain\textsuperscript{7}. In a big data report, pre-SCS implant opioid use was found to be the most significant risk factor for prolonged postoperative opioid use. Additionally, preoperative anxiolytic and muscle relaxant use was found to be significantly associated with prolonged postoperative opioid use\textsuperscript{8}.

This encouraged the idea to eliminate actively the opioid use prior to initiating a neuromodulation trajectory by a standardized protocol. A good opioid detoxification protocol should accomplish many important goals in a patient’s recovery. Firstly, eliminate the physical dependence on opioid drugs; secondly, lessen or relieve the pain of withdrawal, thirdly address any other medical problem and finally prevent relapse\textsuperscript{9, 10}.

The introduction of opioid-free patients eligible to neuromodulation might improve the effectiveness of these techniques. The aim of the current pilot study was to investigate the
feasibility and safety of a standardized opioid detoxification protocol prior to neuromodulation.

Materials and Methods

Study protocol

In this retrospective study, data from a single-centre pilot study towards detoxification prior to neuromodulation was used. In this centre, all patients who were using opioids (regardless of the type of opioids) and who were eligible to neuromodulation first underwent a detoxification program. Data from these patients (between July 2016 and November 2019) was extracted for this retrospective study.

For all patients the baseline measurements (pain intensity at predominant pain location and pain medication intake) were recorded during a steady state prior to detoxification and at the last routine care visit after neuromodulation. The ethics committee of AZ Nikolaas approved the use of anonymized data from 2016 for research purposes. According to the GDPR regulation from 2018 onwards, patients additionally provided written informed consent to grant permission for the use of anonymized medical data for research (EC19006).

Protocol for the detoxification program

All chronic pain patients with (high) intake of opioids were informed about the detoxification protocol, including the advantages and disadvantages of such a detoxification. Concerning the disadvantages, all patients were informed about the withdrawal symptoms that would occur, the temporary increase in pain intensity, the hospitalization of 8 days, the psychological confrontation during the detoxification and not a direct satisfactory clinical effect, before initiating the detoxification protocol. All patients underwent the detoxification protocol voluntarily and were intrinsically motivated (figure 1).
In hospital part of the protocol

At admission, all opioids and benzodiazepines were stopped and a continuous infusion with normal saline (NaCl 0.9%) at a rate of 20 ml/h was administered. A drip of clonidine (1200 µg/48 ml) started at a rate of 2 ml/h with a daily dose decrease of 150 µg a day until stop hospitalization after 8 days. All patients received 4 daily doses of paracetamol 15 mg/kg with a maximum of 1 gram per dose and 2 daily doses of diclofenac 1 mg/kg with a maximum administration of 75 mg, if no contra-indications (e.g. gastric ulcer in the history) were present. Patients who had contra-indications for NSAID use only received per protocol paracetamol (15 mg/kg 4dd) and additional psychological support. In case patients suffered from restless legs syndrome, clonazepam 1 to 2 mg a day in one or two gifts was prescribed. Patients with high doses of benzodiazepines received clorazepate 15 mg, if needed.

Blood pressure and heart rate were monitored. Per protocol the drip of clonidine was temporarily lowered to a rate of 1 ml/h in case of a heart rate between 40 and 45 bpm. In case of symptomatic hypotension or a heart rate lower than 40 bpm, the drip was stopped. In the case of a symptomatic hypotension without bradycardia a fluid challenge bolus of 250 ml was administered, with the possibility of an additional 250 ml of saline.

A daily follow-up by a dedicated pain psychologist was a prerequisite. Before the detoxification program, a session was scheduled focusing on motivational and coaching techniques. Also, patients’ expectations and goalsetting were embedded in this first session. Subsequently, an educational session about withdrawal symptoms, side effects of medication, the principles of opioid-induced hyperalgesia and the possibility of having a rebound of pain intensity was performed. During hospitalization, the daily sessions were focused on these educational topics and the out-clinic situation was discussed. The cornerstone of dealing with the out-clinic situation was based on identification and interpretation of triggers and alternatives. Recovery strategies concerning relapse and failures were also discussed during these sessions.

Out-patients clinic part of the protocol

After 8 days of intravenous administered clonidine, a substitution of oral clonidine was prescribed with a compounded preparation of 25 µg per capsule 3 times daily, continued for 2 days until the patient left the hospital at day 10. This regime of oral clonidine persisted for
3 consecutive weeks and a follow-up appointment every 2 weeks prior to scheduled neuromodulation implantation was scheduled.

A zero tolerance of opioids was maintained prior to neuromodulation. All patients were asked to reliably report whether they completely omitted all opioids (self-reporting). Only in case of serious doubt, a urine sample screening was performed, to prove this prerequisite. The decision to perform a urine screening was made by the physician of the pain clinic, in collaboration with the general practitioner. Tapering of gabapentinoids started after implantation of a neuromodulation device with a gradual decrease of 10% per two weeks until patients reported a neuropathic component in their pain experience.

**Outcome measurements**

The main goal of this pilot study was to evaluate the feasibility and safety of a standardized opioid detoxification protocol prior to neuromodulation. To evaluate feasibility and safety, the treating physician systematically recorded all side effects and possible complications related to the detoxification protocol, (severe) adverse events and patient reported perceptions on a daily basis. Moreover, these were regularly updated by the medical staff, psychological and nursing team. Additionally, the effectiveness of this program was explored based on a dataset of 70 patients who underwent the detoxification program.

**Statistical analysis**

All analyses were performed in R Studio version 1.2.5019 (R version 3.6). Normality was controlled with the Shapiro Wilk test and QQ-plots and equality of variances by Levene’s tests. Descriptive statistics are provided as mean (±SD) or as median (interquartile range). In all analyses, p-values of 0.05 or less were considered statistically significant. There was no imputation for missing data. Differences in pain intensity scores and MME scores between the baseline visit and the last available follow-up visit (allocated as last visit) were calculated with paired Wilcoxon tests. Additionally, the same tests were performed separately for patients who were scheduled to receive SCS and Intrathecal Drug Delivery (ITDD) after the detox program. For a subset of patients, pain intensity scores immediately after the detox program
were available as well, wherefore paired Wilcoxon tests were used to compare the pain intensity score before and after the detox program.

Results

Between July 2016 and November 2019, in total 70 patients eligible for neuromodulation underwent this detoxification program. Twenty-six male patients (37.14%) and 44 female patients (62.86%) underwent this detoxification program with a mean age of 49 years (SD: 10.73 years). Before the detoxification protocol, 30% of the patients was taking oxycodone, 22.8% fentanyl, 17.1% oxycodone in combination with fentanyl, 5.7% tramadol, 5.7% morphine, 4.3% fentanyl in combination with morphine, 2.8% oxycodone in combination with morphine, 2.8% fentanyl in combination with tramadol, 2.8% a combination of oxycodone, fentanyl and tramadol, 1.4% hydromorphone, 1.4% oxycodone in combination with tramadol and 1.4% codeine in combination with tramadol. For 1 patient, the exact type of opioids was not recorded.

Safety

From the point of view of side effects from clonidine, the researchers did not witness serious hemodynamic adverse events, needing cardiovascular supporting inotropic or vasoconstriction medication. At the start of the detoxification program, a mild sedative effect of the clonidine was reported, with a maximum at the third day, despite lowering the dose on a daily base. From day 5, patients experienced loss of appetite and mild nausea. Mild nausea was counter counted by anti-emetics. Due to the possibility of orthostatic hypotension, patients were instructed to stay in their rooms. None of the patients fell due to orthostatic hypotension.

Mild symptoms of opioid withdrawal such as a bad/metal taste, diarrhea, feeling cold, sweating and shivering were reported by most of the patients from the third day on. Tolerable withdrawal symptoms were reported in both parts (in- and out clinic) of the protocol.
The psychological team noticed ruminations as the narcotic effect of the opioids began to wear off (from day 5 of the program). No serious neurologic symptoms, like delirium, were noted.

**Feasibility & tolerability**

Patients admitted to the hospital for the in-hospital part of the detoxification protocol stayed at a non-continuous monitoring ward. In total, 64/70 (91.4%) patients tolerated the program without any complaints or remarks and executed the post protocol follow-ups dedicatedly. Six patients did not completely finish the detoxification protocol due to mental and psychological aspects (limited internal motivation, increased stress levels and increased anxiety). The detoxification protocol (figure 1) was clear and well received by the medical staff and nurses. A 24/7 support team with senior staff members was available if needed.

**Pilot effectiveness data**

Baseline MME scores were available for 68 patients and baseline pain intensity scores for 62 patients. Additionally, MME scores from the last visit, meaning the most recent patient visit in clinical routine care after detox and after initiating the neuromodulation trajectory, were also extracted. The mean time duration between the baseline visit and the last visit was 13 months, ranging from 1 month to 38 months. At the last visit, MME and pain intensity scores were available for 64 and 52 patients, respectively. Most of the patients suffered from Failed Back Surgery Syndrome (N=48, 68.57%). Other indications can be found in Table 1. The following treatment modalities were proposed to patients: SCS (N=42, 60%), ITDD (N=19, 27.14%), dorsal root ganglion stimulation (N=4, 5.71%), occipital nerve stimulation (N=2, 2.86%), peripheral nerve stimulation (N=1, 1.43%), trigeminal stimulation (N=1, 1.43%), and repetitive transcranial magnetic stimulation (N=1, 1.43%). For three patients, urine sample screening was performed to objectify whether they completely omitted opioid use before neuromodulation.

At baseline, the median MME score was 175 (Q1-Q3: 118.1 – 240) and at the last available follow-up visit the median MME was 0 (Q1-Q3: 0 – 16.88) (V=1822, p<0.001) (Figure 2). A median relative percentage decrease of 100% (Q1-Q3: 86.65 – 100) was found for MME.
scores. When specifically focusing on patients who received the detox program in preparation for SCS, a significant reduction in MME score (baseline 154.5 (Q1-Q3: 94.5 – 209.0), last visit 0 (Q1-Q3: 0 – 26.56), V=661, p<0.001) was found between baseline and last visit. For patients scheduled for ITDD, a significant reduction in MME score (baseline 202.5 (Q1-Q3: 150 – 292.5), last visit 0 (Q1-Q3: 0 - 5), V=153, p<0.001) was found between baseline and last visit. For a subset of patients (N=14) who received ITDD, more details concerning the IT therapy were available; nine patients had morphine monotherapy with a median daily dose of 0.90 (Q1-Q3: 0.72 – 1.40 mg) mg, one patient received hydromorphone monotherapy and four patients received polytherapy.

The median pain intensity score was 8.5 (Q1-Q3: 7.6 – 9) at baseline and 5.35 (Q1-Q3: 3.75 – 7.78) at the last follow-up visit. The median pain intensity score was significantly decreased at the last follow-up visit compared to the baseline pain intensity score (V=993, p<0.001). For a subset of 10 patients, a pain intensity score immediately after the detox program (i.e. before neuromodulation) was available. For those 10 patients, the median pain intensity at baseline was 8 (Q1-Q3: 7.275 – 8.375) and 8.4 (Q1-Q3: 8 – 8.98) after the detox program. There was no significant difference between both pain intensity scores (V=15.5, p=0.24). This means that the pain intensity score before and after the detoxification program was not statistically significantly different. The median time between the end of the detox and the start of a neuromodulation trajectory was 37 (Q1-Q3: 25.5-71) days.

Additionally, for 12 SCS patients, the total score on the Oswestry Disability Index was available with median values of 67 (Q1-Q3: 65 – 74.5) at baseline and 57 (Q1-Q3: 47 – 68.5) at the last follow-up, indicating a statistically significant improvement in disability (V=77, p=0.003).

Discussion

Since a decade, the awareness about prescription opioids as the devastating primary driver of opioid-related deaths is increased. The numbers of deaths by overdose and opioid use disorder (OUD) increased since 2016 in the USA\(^1\). According to the DSM-5, OUD is defined as “a problematic pattern of opioid use leading to clinically significant impairment or distress” and strongly involves dependency and addiction\(^12\)\(^\text{--}^\text{14}\).
Besides OUD, a recent systematic review also indicated the importance of cognitive and neuropsychological effects of long-term use of opioids in patients with chronic non-cancer pain\textsuperscript{15}, with a significant attention reduction especially in combination with antidepressants and/or anticonvulsants\textsuperscript{16, 17}. These neuropsychological effects impairing the daily life of patients, might be related to the fact that many brain areas involved in cognitive functions have opioid receptors\textsuperscript{18, 19}. A review concerning the role of the opioid system in cognitive control concluded that the mu-opioid system can influence higher-level cognitive function in orbitofrontal cortex, basal ganglia, amygdalae, anterior cingulate cortex, and prefrontal cortex\textsuperscript{20}. For antidepressants, alterations in neural activity are previously revealed in dorsolateral prefrontal cortex, ventrolateral prefrontal cortex and several limbic regions among which hippocampus, amygdala, insula, ventral part of anterior cingulate cortex, and orbitofrontal cortex\textsuperscript{21}. In comparison with the general population, patients with OUD have worse physical and mental quality of life\textsuperscript{22}. In addition to the potential danger of opioid (ab)use, the effects of prescribed opioids are controversial and opioids are currently recommended for only a short period of time \textsuperscript{23}.

Given the devastating effects on quality of life and the controversial effects in chronic pain, SCS, i.e. a non-pharmacologic treatment, has proven to be the treatment choice above opioids to alleviate chronic pain and to reduce opioid use \textsuperscript{24}. Recently, a combined systematic review and meta-analysis was conducted to evaluate the effect of SCS on opioid and pain medication reduction in patients with intractable spine or limb pain \textsuperscript{25}. The authors reported that the odds of reducing opioid consumption were significantly increased when being treated with SCS compared to medical care. New stimulation waveforms such as high frequency SCS at 10 kHz and burst SCS already demonstrated the opioid-sparing effects of SCS \textsuperscript{24, 26-28}. A similar idea prior to administering low doses of morphine intrathecally, is the microdose method\textsuperscript{29}. Complete cessation of systemic opioids followed by a period of abstinence is essential before initiating low doses of intrathecal morphine\textsuperscript{30}. These findings hypothesized the need to detox patients from opioids prior to implantation of any neuromodulation device\textsuperscript{31, 32}. Neuromodulation is not used as a replacement therapy for opioids, but rather as a method to reduce or eliminate opioids in the treatment of chronic pain\textsuperscript{33}.  

10
We investigated for the first time the feasibility and safety of a standardised detoxification protocol prior to minimally invasive neuromodulation therapies. A combination of an in-hospital and out-patient clinic part for the detoxification protocol has been presented. During the detoxification process, no major side effects of clonidine were registered, and minimal withdrawal signs were reported. Clonidine commonly causes dizziness, drowsiness, slight vision disturbances and general weakness. According to the *Diagnostic and Statistical Manual of Mental Disorders (DSM–5)* criteria, signs and symptoms of opioid withdrawal include lacrimation or rhinorrhea, piloerection "goose flesh," myalgia, diarrhea, nausea/vomiting, pupillary dilation and photophobia, insomnia, autonomic hyperactivity (tachypnea, hyperreflexia, tachycardia, sweating, hypertension, hyperthermia), and yawning. The majority of the patients experienced some signs of withdrawal due to the abrupt elimination of the opioids after long usage, but administering clonidine countered some of those symptoms (insomnia and autonomic hyperactivity) and tempered the others because of its sedative effect. In line with the “microdosing experience” in intrathecal drug delivery therapy, patients experienced no clinical important increase of pain intensity during the detoxification period. For the concern of feasibility, the majority of patients (91.43%) successfully completed the protocol and did not raised any concerns of feasibility. The medical, psychological and nursing staff did not experience any difficulties with implementing the detoxification protocol into daily practice. The authors would like to stress out the importance of mental well-being during the whole period of detoxification and therefore emphasize the psychological necessity for individual coaching of every patient.

After initiating neuromodulation, patients were instructed to downsize gabapentinoids use with 10% every two weeks. In 2016, an extensive analysis was performed to identify and assess cases of gabapentinoid misuse or dependence as reported to the European Medicines Agency's EudraVigilance database, whereby all spontaneous reports of both gabapentin and pregabalin related misuse/abuse/dependence were retrieved. Around 6.6% cases of misuse and dependence on a total of 115,616 adverse drug reaction reports on pregabalin and 4.8% cases on a total of 90,166 reports on gabapentin were revealed. A total of 27 and 86 fatalities were identified, associated with pregabalin and gabapentin respectively, and mostly in combination with opioids. Therefore, we strived towards a limited use of gabapentinoids after initiating neuromodulation.
In this study, an in-hospital detoxification protocol of 8 days was used, which is in contrast to the slow forms of tapering, typically applying a tapering of 5-20% every four weeks\textsuperscript{38}. Since the majority of patients eligible to SCS generally requires high opioid consumption due to high pain intensity scores and since SCS is able to stabilize or decrease opioid usage (but not always completely omit opioid use)\textsuperscript{6, 7, 39}, the risks of continuing the opioid outweigh the risks of a rapid taper wherefore the choice was made to use a faster tapering protocol. The disadvantage of this protocol is that clonidine was needed for withdrawal symptoms, which might have been omitted if a slower tapering protocol was used\textsuperscript{38}.

One of the limitations of this study is the presence of selection bias since this study is only conducted at one hospital, which is specialized in this detoxification program. Due to the retrospective design of this study, information bias is almost inevitably present under the form of variables that were not systematically recorded in the patient files, leading to missing observations afterwards. Additionally, a pilot study is not a hypothesis testing study and therefore efficacy (for example compared to a group of patients who did not underwent the detoxification program by means of a randomized controlled trial) of the detoxification program cannot be evaluated by this study. Another limitation is that all patients were asked to reliably report whether they completely omitted all opioids before neuromodulation, instead of systematically objectifying this statement with a urine sample screening.

By this specific opioid detoxification protocol prior to neuromodulation for chronic pain, the classical goals of detoxification are fulfilled\textsuperscript{9}. The physical dependence on opioid drugs was reduced to a strict minimum and the pain of withdrawals was relieved. Via specific psychological sessions including education, goalsetting, coping strategies to triggers and failure, patients were empowered to prevent of a relapse. Based on the results from this pilot study, traditional studies investigating the effectiveness and/or efficacy of neuromodulation as monotherapy for chronic pain disorders are within reach.
Conclusion

Detoxification from opioids can be safely achieved via a standardized detoxification protocol in patients eligible to neuromodulation techniques. Detoxification of opioids prior to neuromodulation is achievable via a protocol combining an in-hospital and out-clinic part.

Acknowledgments

Financial support: None.

Conflict of interest: Jean-Pierre Van Buyten and Iris Smet serve as consultants for Medtronic, Abbott, Nevro, Mainstay Medical and Boston Scientific. Maarten Moens has received speaker fees from Medtronic and Nevro. There are no other conflicts of interests to declare.

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## Tables

<table>
<thead>
<tr>
<th>Main Indication</th>
<th>Number of patients (%)</th>
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<tr>
<td>Post-surgical/traumatic neuropathic pain</td>
<td>5 (7.14%)</td>
</tr>
<tr>
<td>FBSS</td>
<td>48 (68.57%)</td>
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<tr>
<td>FBSS + FNSS</td>
<td>2 (2.86%)</td>
</tr>
<tr>
<td>CRPS</td>
<td>3 (4.29%)</td>
</tr>
<tr>
<td>Failed knee surgery syndrome</td>
<td>3 (4.29%)</td>
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<tr>
<td>Degenerative back pain</td>
<td>3 (4.29%)</td>
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<tr>
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<tr>
<td>Pancreatitis</td>
<td>2 (2.86%)</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>1 (1.43%)</td>
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<tr>
<td>FNSS / Cervicogenic headache</td>
<td>1 (1.43%)</td>
</tr>
<tr>
<td>Trigeminal neuropathy</td>
<td>1 (1.43%)</td>
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</table>

**Table 1. Main indications for treatment with neuromodulation techniques (N=70).** Abbreviations. ACNES: Anterior Cutaneous Nerve Entrapment Syndrome; CRPS: Complex Regional Pain Syndrome; FBSS: Failed Back Surgery Syndrome; FNSS: Failed Neck Surgery Syndrome.
Figure legends

**Figure 1.** Detoxification protocol. Abbreviations. Bpm: beats per minute; dd: daily dose; HR: heart rate; IV: intravenous; PO: per os.

**Figure 2.** The difference in MME scores between baseline and the last follow-up visit. (*** p<0.001)