



Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk

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Abstract

Surgical and medical procedures, mainly those associated with nerve injuries, may lead to chronic persistent pain. Currently, one cannot predict which patients undergoing such procedures are 'at risk' to develop chronic pain. We hypothesized that the endogenous analgesia system is key to determining the pattern of handling noxious events, and therefore testing diffuse noxious inhibitory control (DNIC) will predict susceptibility to develop chronic post-thoracotomy pain (CPTP). Pre-operative psychophysical tests, including DNIC assessment (pain reduction during exposure to another noxious stimulus at remote body area), were conducted in 62 patients, who were followed 29.0 ± 16.9 weeks after thoracotomy. Logistic regression revealed that pre-operatively assessed DNIC efficiency and acute post-operative pain intensity were two independent predictors for CPTP. Efficient DNIC predicted lower risk of CPTP, with OR 0.52 (0.33–0.77 95% CI, $p = 0.0024$), i.e., a 10-point numerical pain scale (NPS) reduction halves the chance to develop chronic pain. Higher acute pain intensity indicated OR of 1.80 (1.28–2.77, $p = 0.0024$) predicting nearly a double chance to develop chronic pain for each 10-point increase. The other psychophysical measures, pain thresholds and supra-threshold pain magnitudes, did not predict CPTP. For prediction of acute post-operative pain intensity, DNIC efficiency was not found significant. Effectiveness of the endogenous analgesia system obtained at a pain-free state, therefore, seems to reflect the individual's ability to tackle noxious events, identifying patients 'at risk' to develop post-intervention chronic pain. Applying this diagnostic approach before procedures that might generate pain may allow individually tailored pain prevention and management, which may substantially reduce suffering.

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1. Introduction

The prediction of susceptibility for future development of chronic pain presents an ongoing challenge

to the medical community and has immediate relevance for pain patients. Clinical observations indicate that diseases or injuries of similar severity can cause a wide range of pain experience, despite corresponding peripheral tissue damage. This variability is likely a consequence of differences in the central processing of the peripherally generated pain data. Neural messages evoked by noxious stimulation ascend along peripheral nerves, spinal cord, brainstem and then rise

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to the cortex, where they reach consciousness. These messages can be modulated along this pathway at several points, such that the same experimental peripheral stimulation given in the laboratory can generate different percepts in different healthy people. Such inter-personal variability also occurs in the clinical pain field, where pain induced by a seemingly similar severity of pathology can be perceived much differently by different people [7,23].

A key mechanism of central pain modulation is the endogenous analgesia (EA) system, commonly evaluated by the diffuse noxious inhibitory control (DNIC) test paradigm [17,18]. Recent evidence indicates that patients with idiopathic pain disorders, such as temporomandibular disorders, fibromyalgia, tension headache, migraine and irritable bowel syndrome, demonstrate lower DNIC efficiency [12,16,20,25,30]. This suggests that altered DNIC might be relevant in the pathogenesis of these pain disorders. Along this line, less efficient DNIC was found to be associated with an increased history of pain among healthy subjects [5].

Based on this understanding, we hypothesized that DNIC efficiency would be significant in the prediction of chronic pain development. Thus, patients with less efficient DNIC would be expected to be ‘at risk’ for pain disorders when exposed to pain-generating perturbations. To investigate this assertion, we chose the model of post-operative chronic pain, as patients can be assessed at a pain-free stage before surgery, with a ‘naive’ pain modulation system not yet affected by the presence of induced clinical pain. We specifically explored thoracotomy-induced chronic pain due to (i) its relatively high frequency, affecting nearly half of post-thoracotomy patients and (ii) its relatively high severity, therapy resistance and association with significant disability. A third advantage was the attribution of the post-thoracotomy pain to a uniform surgical procedure rather than to diverse underlying pulmonary diseases, such that all patients had a common pain-generating mechanism.

The aim of the present study is exploring whether the innate pain modulation property represented by DNIC efficiency before surgery predicted a risk for development of chronic post-thoracotomy pain.

2. Methods

The local Institutional Review Board approved the study before it began, and all participating patients signed an informed consent form. In this interim analysis of a larger study, we report the effects of DNIC, pain thresholds and supra-threshold magnitude estimation of pain on acute and chronic post-operative pain. All pain evaluation procedures were performed 1–3 days before surgery in pain-free patients by a single examiner (YC).

2.1. Pre-operative psychophysical assessment

2.1.1. DNIC paradigm

DNIC was calculated as the difference in pain rating between two identical noxious ‘test stimuli’, applied first at baseline and then concomitantly with another ‘conditioning’ remote noxious stimulus. A decrease in the ‘test stimulus’ pain scores from the baseline indicates efficient pain inhibition, expressed as a positive DNIC value. The ‘test’ stimulus was a 30-s contact heat stimulus (TSA-2001, Medoc, Israel) applied to the volar aspect of the dominant forearm. The intensity of this stimulus was determined first for each individual using a short series of ascending and descending thermal stimuli, culminating in identification of the temperature that induced a pain experience score of 60 on a 0–100 numerical pain scale (NPS) (for more details, see Granot et al. [10]). The pain magnitude of the 30-s ‘test stimulus’ was the mean of 3 estimations, given every 10 s during stimulation.

The ‘conditioning stimulus’ was delivered by immersion of the other hand in a hot water bath (46.5 °C) (Heto Cooling Bath, Jouan Nordic A/S, Allerød, Denmark) for 1 min. The mean of three pain ratings during the first 30 s of conditioning stimulus (hot water) was used as the measure of the conditioning pain score. After 15 min break, a second assessment of the ‘test stimulus’ was performed during the last 30 s of the immersion time, and patients were asked to report pain magnitude three times during this repeated test stimulus.

2.1.2. Heat pain threshold

The heat pain threshold was assessed by TSA (Medoc, Ramat Yishay, Israel) using the Method of Limits [37]. Heat stimuli were delivered on the thenar part of the right forearm using a 30 × 30 mm contact thermode. The adaptation temperature was set at 32 °C, and was increased at 1 °C/s and decreased at 8 °C/s. The mean of responses to 3 stimuli for which the standard deviation was less than 0.5 °C was taken as thermal pain threshold.

2.1.3. Supra-threshold pain magnitude

The pain ratings assessed in response to the pre-conditioning ‘test stimulus’ were taken as the supra-threshold pain magnitude. Patients were asked to report the level of pain intensity three times during the 30-s contact heat stimulus (before they were exposed to the conditioning stimulus). The mean of three pain ratings was taken as the supra-threshold heat pain rating.

2.2. Surgical procedure

Thoracotomy was performed by one of two types of surgical procedures. Thirty-four patients underwent postero-lateral thoracotomy. In short, a curvilinear incision was made between a point midway between the spine and the posterior border of the scapula and a point one fingerbreadth below the inferior tip of the scapula. The incision was extended anteriorly and postero-superiorly as needed. The latissimus dorsi and serratus anterior muscles were divided, the rib cage was exposed, and the chest cavity was entered above the 6th rib, with a fracture of the posterior part of this rib. The other 28

patients underwent muscle-sparing lateral thoracotomy. A 10–15 cm incision was made on the lateral aspect of the chest between the posterior and the anterior axillary lines, and latissimus dorsi and serratus anterior were mobilized, without rib fracture. All surgeries were performed under general anaesthesia using double lumen endotracheal intubation, by balanced anaesthesia, and by regional anaesthesia with continuous thoracic epidural catheter using local anaesthetics and opioids. Mean time of surgery was roughly 100 min (skin to skin), and no difference was found in surgery duration for the two types of procedures.

2.3. Post-operative pain management

All patients received a routine acute post-operative pain management protocol, consisting of continuous thoracic epidural analgesia for the first 3 days after surgery (marcaine 7 mg and fentanyl 0.03 mg in 6 ml saline per hour). Patients were offered additional analgesia upon request, including morphine, tramadex, diclofenac, etodolac or dipirone.

2.4. Post-operative pain assessment

Acute pain scores were obtained during hospitalization by a single observer (YC) who was blind to the type of surgery. Patients were asked to report the level of pain at rest, in response to arm elevation ipsilateral to surgery, and while deliberately coughing. These scores were obtained twice, on the mornings of the 2nd and 5th days after surgery, the latter being at least 24 h after removal of the epidural catheter (inserted at a level between T5 and T10). The parameter of acute pain as used for analysis was the mean of 4 pain ratings in response to the two manoeuvres in the 2 days.

Chronic post-thoracotomy pain intensity was assessed during the follow-up visit to the clinic or during a special home visit for patients unable to be assessed in hospital. Patients were asked to report the level of mean spontaneous pain at the area of the scar during the week prior to the visit. They were also asked to report whether they consumed analgesics on a regular basis. Treatment for pain control was provided at the discretion of the primary care physician only.

2.5. Statistical analysis

The simple pairwise relationships of DNIC, acute pain, and chronic pain were assessed by Pearson correlation. DNIC was defined as the negative difference between post- and pre-conditioning NPS, i.e., $-(NPS_{\text{post}} - NPS_{\text{pre}})$, such that a positive score represents increased DNIC efficiency. Determination of whether development of chronic pain could be predicted by DNIC, 'test stimulus' pain, pain threshold, type of surgery, daily opiate dosage at the chronic stage, gender and age was made by logistic regression analyses. Odds ratios, with 95% confidence limits, were determined based on the logistic regression analyses and appropriate logistic plots or nomograms were prepared to aid in interpretation of the logistic models. JMP (SAS Institute, Cary, NC, USA) and the R statistical software environment (<http://www.ron-breaking-project.org>) were employed in statistical analyses.

3. Results

Sixty-two patients (38 men and 24 women) who consented to the study and underwent thoracotomy during 2006 and the beginning of 2007 were available for post-operative follow-up of chronic pain. Mean age of patients was 61.76 (SD 13.7) years (range = 19–86) and mean level of education 11.36 (SD 4.3) years. Mean time of the chronic pain follow-up assessment was at 29.0 (SD 16.9) weeks after surgery.

Mean acute post-operative pain scores were 49.03 (SD 20.6), with scores of 37.97 (SD 25.4) at rest, and 48.10 (SD 21.3) after provocation. Chronic pain scores were 55.2 (SD 26.8). Chronic post-operative pain (pain scores greater than 20 in 0–100 NPS) was found in 36 patients. No effect of surgery type (with and without 6th rib fracture) was observed for the acute or for the chronic pain scores; acute pain during rest was 36.94 (SD 26.3) for those with rib fracture and 41.06 (SD 24.7) for those without rib fracture ($p = 0.536$). Provoked acute pain scores were 50.34 (SD 19.6) and 47.76 (SD 22.3), respectively ($p = 0.653$) for those without rib fracture. Similarly, chronic pain scores were 34.58 (SD 29.7) for those with rib fracture, and 31.92 (SD 32.2) ($p = 0.734$). Mean opioid-equivalent consumption additional to the epidural analgesia, along the 6 post-operative days, was 194.14 ± 135.93 mg, and was not correlated with scores of acute or chronic pain.

In agreement with the literature, positive correlation was found between scores of acute and chronic post-operative pain intensity (Table 1). The intensity of chronic pain was not associated with time elapsed from surgery ($r = -0.164$, $p = 0.263$). Only 11 patients (15%) used opioid analgesics on a regular basis at the chronic stage; mean equivalent opioid dose was 40 mg morphine/day. Chronic pain scores were independent of opioid consumption at the chronic stage ($r = 0.13$, $p = 0.667$).

A significant DNIC effect was demonstrated prior to surgery, with scores for the contact heat 'test stimulus' decreasing from 58.33 (SD 16.4) at baseline to 43.95 (SD 17.3) ($p < 0.001$) when given concomitantly with the painful hot water immersion. Pain scores reported for the conditioning hot water immersion were 66.58 (SD 23.0) and were not correlated with the extent of DNIC ($r = -.093$, $p = 0.474$).

Table 1
Correlation of DNIC, acute and chronic post-operative pain scores

Variable	By variable	Correlation	<i>p</i>
Acute pain	DNIC	0.1469	0.2546
Chronic pain	DNIC	0.3684	0.0032
Chronic pain	Acute pain	0.5947	<0.0001

Pre-operative DNIC extent was negatively correlated with chronic post-operative pain scores ($r = -0.368$, $p = 0.003$), such that patients with more efficient DNIC before surgery reported less intense chronic post-operative pain. DNIC extent, however, was not associated with the acute post-operative pain intensity (Table 1). In line with this finding, scores of test stimulus were not correlated with acute post-operative pain scores ($r = 0.036$, $p = 0.783$). Pain induced by water immersion showed a correlation trend with acute pain ($r = 0.237$, $p = 0.064$), but not with chronic pain scores ($r = 0.013$, $p = 0.919$).

To determine which factors were significant in pain prediction, an overall logistic regression analysis was performed, using DNIC, ‘conditioning pain’ scores, pain threshold, type of surgery, daily opiate dosage at chronic stage, gender and age as predictors, and the development of chronic pain as the binary outcome, where chronic pain was defined as present when the pain score was >20 . The results of this analysis are provided in Table 2. The whole model test was significant, $p = 0.0003$. It is noted that only DNIC and acute pain served as significant predictors of chronic pain ($p = 0.0065$ and $p = 0.0038$, respectively). A reduced model based on these results was fit, with only DNIC and acute pain as predictors; results are shown in Table 3, where we see that the whole model test was significant, $p < 0.0001$, and that DNIC and acute pain served as significant predictors of chronic pain (both $p = 0.0024$). The odds ratios (OR) were determined based on the probability change for development of chronic pain for each 10-point increase in DNIC or increase in acute pain. Thus, the chance of a patient who reported a decrease of ‘test stimulus’ scores from 50 at baseline to 40 during immersion to develop chronic post-operative pain was about one-half that of a patient who reported unchanged scores. A practical tool allowing easy prediction of the probability to develop chronic pain for the individual patient, based on both DNIC and acute pain scores, is provided as a nomogram in Fig. 1.

Because, prior to surgery, the clinician will have neither a post-surgical acute pain estimate nor knowledge

Table 2
Overall logistic regression analysis with eight prospective predictors of chronic pain

Term	Chi-square	<i>p</i>
Intercept	0.13	0.72
DNIC	7.42	0.0065
Acute pain	8.36	0.0038
Supra-threshold pain scores	0.22	0.64
Pain threshold	0.18	0.67
Surgery type	1.52	0.22
Gender	1.30	0.25
Age	0.17	0.68
Opiate dosage during the chronic pain stage	0.00	0.95

Table 3
Reduced model based on only DNIC and acute pain as predictors of chronic pain

Term	Chi-square	<i>p</i>	Odds ratio	OR lower 95% CI	OR upper 95% CI
Intercept	2.47	0.12			
DNIC	9.20	0.0024	0.52	0.33	0.77
Acute pain	9.20	0.0024	1.80	1.28	2.77

The odds ratios are based on changes of 10 U for both DNIC and acute pain, i.e., 10-point changes on scales ranging from -100 to 100 and 0 to 100 , respectively.

of the daily opioid dosage at the chronic stage, logistic models were also fit without those post-surgical parameters. Table 4 depicts the results of that analysis; the whole model test was significant, $p = 0.0092$, in which DNIC was the only significant predictor ($p = 0.0035$). Again, we fit a reduced model, this time using only DNIC as the predictor; the overall model was significant, $p = 0.0003$, and DNIC was a significant predictor, $p = 0.0016$ (Table 5). A logistic plot allowing easy prediction of the probability of developing chronic pain as a function of DNIC is provided as Fig. 2.

4. Discussion

The major finding of this study is that incidence and severity of chronic post-operative pain can be predicted by experimental pain assessment, obtained before surgery in pain-free patients. The dynamic parameter of DNIC efficiency, representing pain modulation, and not the static parameters of pain thresholds or magnitude estimation of supra-threshold noxious stimuli, determines risk for chronic post-operative pain. Thus, the ability to modulate experimental pain in the laboratory setting translates, in the clinical setting, to the susceptibility of developing future pain.

There are several points of strength to this study, despite the relatively small sample size. Firstly, the utilization of dynamic psychophysical parameters, reflecting pain modulation processing, has the potential to uncover susceptibility to develop pain in the future. We assume then that pain modulation capabilities will protect or unprotect the patient regardless of the specific pain-generating procedure, allowing generalization of the concept to other surgical and medical interventions beyond thoracotomy. Secondly, the prospective design, with special emphasis on the initial assessment held at a pain-free state, allows characterization of the naive pain-modulating system, free of potential neuroplastic changes due to the presence of induced clinical pain. Thirdly, the selection of thoracotomy as the surgical procedure allows the investigation of chronic post-operative pain of relatively (i) high intensity, avoiding a floor effect and (ii) high incidence, generating valid comparison of painful and pain-free patients. Fourthly, the use

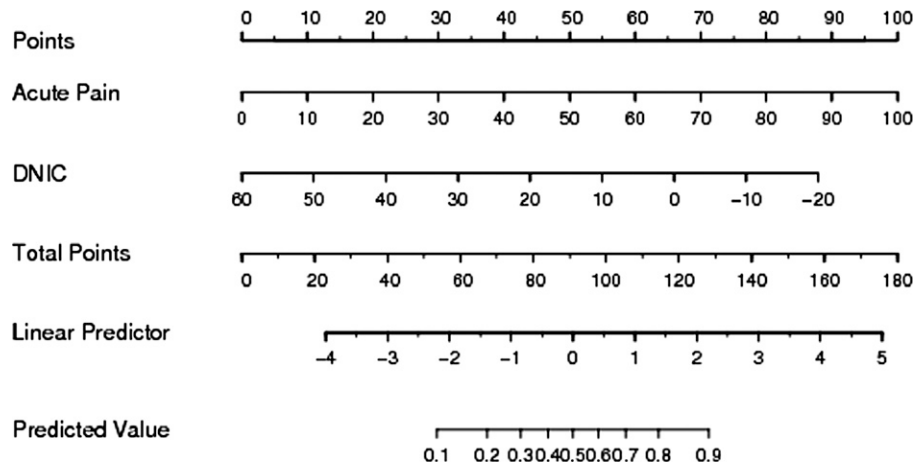


Fig. 1. Nomogram to predict the probability of developing chronic pain following thoracotomy surgery. To use the nomogram, locate the scores for DNIC and acute pain on the appropriate axes, then draw a line up to the Points axis to determine the number of points due to each predictive factor. Sum these values and locate the sum on the Total Points axis. Draw a line directly down to the Predicted Value axis – this will be the predicted probability of developing Chronic Pain. The score on the Linear Predictor scale is the value used by the logistic model to directly determine the predicted probability, and is provided to assist those readers who may be interested in utilizing or testing the elements of the underlying statistical model.

of uniform anaesthesia and a uniform acute pain management protocol decreased the possible effect of intervening factors other than innate pain processing itself.

To date only a handful of studies have explored the predictive value of pre-surgical psychophysical pain assessment for several surgical interventions, revealing mixed results [3,9,11,24,26,34–36]. These studies focused on the prediction of post-operative pain during the immediate phase after surgery via pre-operative psychophysical tests. While several reports have shown that pain threshold obtained via various stimuli modalities were correlated with the acute PO pain intensity [24,26,34,35], others did not [9,11,36]. Some of the above studies also demonstrated the association between the acute PO pain and the scoring of supra-threshold noxious stimuli [3,9,11,26,34,36].

The common feature of these studies, which paved the way for experimentally based pain prediction, is the exploration of acute post-operative pain only. We assume that the pain experience in the acute post-operative phase is affected by many peri-operative factors such as hospitalization stress, sleep, bowel movements, breathing, mobilization, etc. These factors may mask

individual susceptibility to pain and blur predictive ability based on this susceptibility. Indeed, we found that of all the psychophysical measures only the magnitude estimation of the pain induced by water immersion had a correlation trend with acute pain, while pain thresholds, supra-threshold magnitude estimation of the test stimulus, or DNIC, did not. The complexity of pain processing at such different stages, at a pain-free stage in the

Table 4
Overall logistic regression analysis with six predictors of chronic pain

Term	Chi-square	<i>p</i>
Intercept	1.10	0.2940
DNIC	8.52	0.0035
Pre-conditioned pain	0.01	0.9124
Pain threshold	0.22	0.6423
Surgery type	1.61	0.2043
Gender	0.69	0.4073
Age	0.79	0.3754

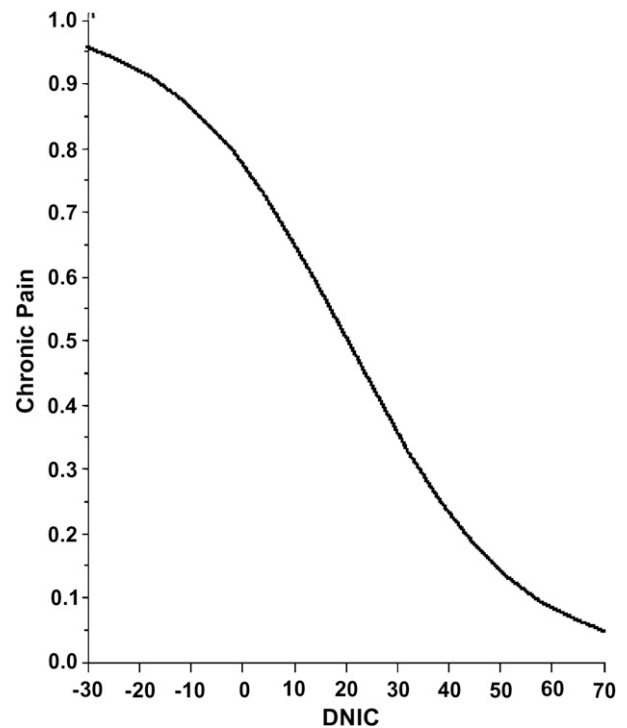


Fig. 2. Logistic regression probability plot relating DNIC to the probability of development of chronic pain.

Table 5
Reduced model based on only DNIC as predictor of chronic pain

Term	Chi-square	<i>p</i>	Odds ratio	Odds lower	Odds upper
Intercept	9.20	0.0024			
DNIC	9.97	0.0016	0.55	0.36	0.77

The odds ratios are based on changes of 10 U for DNIC, i.e., 10-point changes on a scale ranging from –100 to 100.

laboratory, before surgery, during acute post-operative pain, and at chronic stage prohibits simple minded interpretation of interrelations between the relevant factors. Thus, additional factors, such as personality and cognition probably also play an important role in such prediction, and need to be further explored. Our understanding is that the pain processing system at the chronic stage is relatively free of the peri-operative intervening factors and expresses uncontaminated innate pain modulation. Thus, the same pain modulation properties that were evaluated at the pre-surgical assessment prevail at the chronic stage and allow the association between the two. It seems that these modulation properties are much less expressed during the acute pain phase, whose intensity is mostly determined by the surgical procedure itself, and therefore, the acute pain is weakly correlated with the pre-operative factors compared to the chronic pain.

Additionally, these studies were based on more classical ‘static’ psychophysical pain parameters, such as pain threshold and tolerance. The basic assumption of the present study is that a dynamic pain test is required in order to uncover the pain modulation capability of the individual [1]. Pain thresholds, however, mainly reflect discrimination between noxious and innocuous sensations and are mainly sensitive to identification of sensory alteration, positive or negative, in neuropathic situations, rather than characterizing the general pain sensitivity of the individual. Pain tolerance is mainly affected by motivation and culture and, therefore, is less relevant for our purpose [4,6,21,33]. Moreover, thresholds, supra-thresholds and tolerance all reflect a single point on a continuum of pain experience and are affected only to a slight extent by processes of pain modulation [22]. In line with this, the present study shows that neither pain threshold nor supra-threshold magnitude estimates were correlated with the chronic post-operative pain, whereas DNIC was.

Interestingly, and in agreement with the literature, acute post-operative pain was strongly correlated with chronic post-operative pain [13,14,28,29,31,32]. The lack of correlation between DNIC and acute pain indicates that the two are independent predictors of chronic pain, probably representing two different mechanisms affecting pain perception. While the first reflects the pain modulation capabilities of the patient, the latter represents the tissue injury and inflammation induced by the surgical

intervention [15]. We constructed a nomogram that combines the data of these two factors into a graphic prediction model of the ensuing chronic pain (Fig. 1).

On practical grounds, while our findings are derived from the specific conditions of this study, we believe that this concept will prevail for other medical and surgical interventions characterized by the subsequent development of chronic pain. This is because of the convincing evidence for association between (i) non-efficient DNIC response and many clinical chronic pain conditions as well as the greater pain experience in healthy subjects [5,12,16,20,25,30] and (ii) acute and chronic post-operative pain intensity [15]. The meaningful ORs derived here position DNIC as a very powerful predictive tool with pertinent clinical application. Needless to say that, as opposed to the predictive factor of acute post-operative pain, the major advantage of DNIC efficiency is that one does not need to go through surgery in order to obtain it.

What are the clinical implications of these findings? Chronic pain generally and chronic post-operative pain specifically are currently accepted as diseases on their own merit, being relatively common and often resistant to therapy [1,8,15,19,27]. Thus, like every other disease, they should be investigated with the goal of clarification of relevant risk factors, consequent preventive measures and therapeutically pertinent actions. Testing for DNIC efficiency clearly identifies patients ‘at risk’ for development of chronic pain. The identification of patients ‘at risk’ to develop pain should render the medical system more aware of these patients and special precautions should be taken to minimize the pain risk. Procedures and surgeries of lower pain-generating potential should be planned when possible for these patients. For thoracotomy specifically, Kehlet et al. pointed to such procedures including minimally invasive thoracoscopy [15], muscle-sparing thoracotomy [2], and intercostal suturing technique.

As a long-term vision, we foresee a pain susceptibility profile based on DNIC and/or other psychophysical tests yet to be developed being applied routinely as part of a comprehensive health care system, enabling the implementation of an evidence-based and effective pain management strategy tailored for each individual.

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