Dorsal root ganglion stimulation for pain relief in painful polyneuropathy

Chapter 8

Valorization Addendum

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In this addendum, we will attempt to translate the findings of this thesis in terms of 'knowledge valorization'. Knowledge valorization of research refers to the process of creating value from knowledge, by making it available for social and or societal utilization. Diseases associated with chronic pain are increasing in prevalence and are a global cause of disability in both the developed and developing countries.[1,2] Chronic pain is associated with a lowered quality of life (QoL),[3,4] and can have an important impact upon mood, cognition and emotional functioning,[5] leading to restrictions upon functioning during daily activities and work.[6] Amongst all causes of chronic pain, neuropathic pain is particularly cumbersome.[7] Additionally, neuropathic pain is widely recognized as one of the most difficult pain syndromes to manage.[8]

One of the most common causes of neuropathic pain is polyneuropathy, which is typically characterized by symmetrical sensory symptoms in the distal parts of the limbs.[9] The overall prevalence of polyneuropathy in the general population ranges from 1 to 3% and rises to 7% in the elderly.[10] In developing countries the prevalence is lower, possibly explained by a smaller proportion of elderly and by differences in the prevalence of polyneuropathy risk factors.[10] In the last decades, the prevalence of polyneuropathy is increasing due to an aging population and the increasing prevalence of risk factors like diabetes mellitus (DM) and obesity.[10,11] The prevalence of neuropathic pain in diabetic polyneuropathy in people with DM ranges from 6 to 34%,[12] and this symptom is its most costly complication.[13–15]Other causes of polyneuropathy include toxic agents, such as chemotherapeutic drugs, nutritional deficiencies, autoimmune-mediated causes and hereditary factors.[9,10] Polyneuropathy is furthermore reported to be present in 13–66 % of chronic alcoholics,[16,17] and in up to 50% an underlying cause cannot be identified.[18]

In this chapter, we will address the social and economic relevance of our research results. For this purpose, will we first present the impact of pain on patients with polyneuropathy and its impact on society.

What is the impact of pain on patients with polyneuropathy?

Painful polyneuropathy has a huge impact on patients. Despite other symptoms like paresthesias and dysesthesias, pain is a primary indicator for worsening QoL and diminished overall wellbeing in patients with polyneuropathy.[19] A study regarding PDPN patients showed that PDPN patients had a significantly worse QoL compared with DM patients without pain and DM patients with non-neuropathic pain.[20] QoL is inversely associated with neuropathic pain severity and pain duration in patients with painful polyneuropathy.[21] The etiology of polyneuropathy does not influence levels of neuropathic pain-related compromise of QoL.[19]

Painful polyneuropathy is a disabling disease and is related to poor sleep and symptoms of anxiety and depression.[19,20,22] Pain intensity in polyneuropathy patients is positively associated with disability.[22] Pain in these patients can considerably affect daily life by reducing the ability to walk and perform general everyday activities.[12] It can have a major impact on recreational activities, work, social activities, mobility, and experienced stress.[23,24] Studies have demonstrated that PDPN patients score 4.8 for overall pain interference on the brief pain inventory (BPI) (0 is no interference and 10 is complete interference).[12] The subscales for general activity and walking ability were generally most affected.[12,25] However, the subscales for sleep, mood and enjoyment of life were almost equally highly impaired.[25] Painful polyneuropathy is often associated with sleep disturbance due to the fact that most patients have nocturnal pain. Studies of PDPN patients report that 72–96% of the patients are moderately to severely affected in their sleep.,[26] Higher pain severity is significantly correlated with higher interference of sleep.[12,27] In addition, studies have shown that 24.5–72.1% of PDPN patients have symptoms of depression and/or anxiety pain,[12] and PDPN has been shown to be a greater determinant of depression than other DM-related complications and comorbidities.[28]

Despite this great patient burden of pain caused by polyneuropathy, pain in polyneuropathy patients is often not well recognized and treated.[29] The effectiveness of pharmacological treatment is often minor and frequently accompanied by unacceptable side effects.[30] In addition, patients with painful polyneuropathy are more likely to have medication incompliance, like inappropriate polypharmacy and misuse of prescribed medications.[19] Many patients require pain treatment with more than one medication, which increases the risk of additional adverse events and incorrect use of medication.[31] Furthermore, concomitant medication use is high in these patients. For instance, a patient survey has shown that 43% of PDPN patients received prescription medications for sleep disturbance, anxiety and/or depression.[32]

What is the impact of pain in patients with polyneuropathy on society?

Painful polyneuropathy is associated with greater health care utilization in comparison to not painful polyneuropathy. Examples of health care utilization are outpatient clinic visitations, overnight hospitalizations, and the use of a nursing or rehabilitation home.[19] To give an example, the resource use of PDPN patients results in mean annual per patient UK health care costs of €2,963.[33] Of these costs, 41% is accounted for inpatient care. The annual costs found in the UK were comparable to those found in Spain.[34] The costs of medications account for approximately 30% of the healthcare costs.[33,34] In addition, in patients with painful polyneuropathy a large number

of hospital admissions are related to medication side effects.[19] Higher pain severity in PDPN patients is significantly correlated with higher resource use and direct costs.[25,33,35]

Painful polyneuropathy can result in additional costs for society because it can lead to absence from work or reduced functionality at work.[12] In a European study regarding 634 PDPN patients, disturbance in employment status resulted in productivity losses of €10,484 per patient per year.[36] PDPN severity was significantly associated with lost productivity, which was higher with increasing severity, and resulted in significantly higher costs. Productivity losses were similar among the countries France, Germany, Italy, and the UK, and were primarily driven by presenteism (impairment while working). In a UK study, 35% of the PDPN patients reported disruption in employment status due to pain, and 59% of the working patients was less productive at work.[25]

Generally, neuropathic pain reduction, as a result of treatment, is related to improvement in QoL.[37]

The humanistic and economic burden from painful polyneuropathy appears to be higher with increasing pain severity. Therefore, it is of particular importance to recognize painful polyneuropathy in patients and to optimize pain treatment.[19] Emerging neuromodulation options for painful polyneuropathy are spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRGS),[38–42] being a last resort treatment method when conventional therapies have failed.[38,39,43,44] SCS has been shown to be effective in PDPN.[38,45–49] Treatment with SCS has also been shown to be effective in intractable painful polyneuropathy due to other causes, like HIV infection and chemotherapy.[43,44] Slangen et al. performed an economic evaluation comparing SCS with best medical treatment (BMT) in PDPN patients.[50] Incremental cost-effectiveness ratios were based on: 1) societal costs and quality-adjusted life years, and 2) direct health care costs and the number of successfully treated patients, respectively. Although SCS was considerably more effective compared with BMT, Slangen et al. concluded from the results of their study that SCS was not cost effective compared with BMT at the 12-month follow-up, mainly because of the substantial initial investment costs of SCS. However, secondary analyses showed that the incremental cost effectiveness ratios decreased considerably when correcting for baseline differences in costs, and extending the depreciation period of the SCS material to 4 years.[50]

There are limits to the effectiveness of conventional SCS in the treatment of painful polyneuropathy. To illustrate, this treatment is known to provide approximately 50% pain reduction to only 60% of PDPN patients.[38,45,46,49] Forty percent of the patients is therefore not responding to this therapy. Furthermore, the analgesic effect of SCS treatment is known to decrease over time,[51] and SCS is often unable to cover the pain in the so-called "difficult-to-reach areas", like the feet.[52,53] In view of these limitations, optimization of neurostimulation therapy is needed and the new location of stimulation at the DRG (dorsal root ganglion stimulation, DRGS) is shown to be a promising new option for treatment of PDPN. Early findings from one retrospective case series in painful diabetic polyneuropathy patients suggested that DRGS is an effective neuromodulation modality

to improve painful symptoms.[41] Furthermore, the results of another small retrospective case series suggest that DRGS may be an effective treatment option for painful hereditary and idiopathic axonal polyneuropathy.[42] Except the fact that DRGS seems provide a better coverage of the difficult-to-reach areas, it offers several other potential benefits over SCS systems like lack of positional and movement effects on stimulation and reduced migration rate, because of better lead stability.[52,54] Additionally, as the anatomical location of the DRG offers a closer proximity to the electrodes compared to the spinal cord and its dorsal columns, reduced power is required.[52,54] Nevertheless, more clinical evidence is warranted to confirm the efficacy of this treatment for painful polyneuropathy.

What is the social and economic relevance of our research results?

If DRGS can effectively reduce pain in intractable painful polyneuropathy, not only the individual patient would benefit, but also the burden on medical care systems would be lessened. Hence, the research described in this thesis focused upon establishment and optimization of treatment with DRGS in painful polyneuropathy patients, and further understanding the underlying mechanism.

A major conclusion of the results in this thesis is that DRGS seems to be established for pain relief in painful polyneuropathy in humans and in a PDPN animal model (Chapter 2, 3 and 4). Our results furthermore showed that effectiveness for pain relief is similar with DRGS and SCS in PDPN animals (Chapter 4).

To further optimize effectiveness of DRGS in the treatment of pain in painful polyneuropathy, we explored and compared the effectiveness of different DRGS frequencies and concluded that DRGS is equally effective when applied at low-, mid- and high-frequency, at least in an animal model of PDPN (Chapter 5). Nevertheless, as low-frequency DRGS resulted in a delayed wash-out effect, this frequency might be the most optimal setting in DRGS for PDPN as compared to mid frequency and high frequency. Moreover, the use of LF-DRGS will lead to a prolonged battery life as compared to MF- and HF-DRGS and thus has important consequences for costs-effectiveness of this treatment.

Lastly, understanding of the working mechanism underlying SCS- and DRGS-induced pain relief may enable optimization of treatment and result in better treatment outcomes. In relation to this, another key finding of this thesis is that DRGS, in contrast to SCS, does not induce γ-aminobutyric acid (GABA) release in spinal dorsal horn of PDPN rats (Chapter 6). With this observation we suggest that the mechanism underlying DRGS-induced pain relief is different from that of dorsal column SCS and the modulation of a GABA mediated “Gate Control” in the DRG, functioning as a prime Gate of nociception, is

suggested. Further research is warranted to elucidate the mechanism underlying DRGS in pain relief.

To conclude, painful polyneuropathy patients are subjected to a significant physiological, psychological and functional burden. It is essential to raise awareness of painful polyneuropathy and to encourage healthcare providers to better identify patients with painful polyneuropathy to, as this condition deeply affects patients's quality of life and disability. If new treatment options like DRGS can effectively reduce pain in painful polyneuropathy patient, the humanistic and economic burden of painful polyneuropathy would be lessened. With the research of this thesis, we established and tried to optimize DRGS in the treatment of painful polyneuropathy patients. Furthermore, our research let us a little bit closer to understanding the underlying mechanism of DRGS, hopefully enabling future optimization of treatment, resulting in better outcomes.

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