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Healthcare costs of post-traumatic trigeminal neuropathy in Belgium - A retrospective analysis

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ABSTRACT

The present aim was to estimate direct health care costs of patients suffering from post-traumatic trigeminal neuropathy (PTTN) and to compare the use of health care services, medications, and costs between temporary and persistent (>3 months) PTTN cohorts.

A pre-existing clinical dataset of PTTN patients visiting a tertiary orofacial pain clinic in Belgium was utilized, including symptoms and quality of life measurements. Cost and resource utilization data were obtained by Belgium's largest health insurance provider for a period of 5 years after onset.

Data from 158 patients was analyzed. The average cost per patient in the first year after injury was €2353 (IQR 1426–4499) with an out-of-pocket expense of 25% of the total cost. Hospitalization and technical interventions were the main drivers of cumulative costs, followed by consultation costs. For each cost category, expenditure was significantly higher in patients with persistent PTTN than in those with temporary PTTN (median 5-year total costs in persistent PTTN patients yielded €8866 (IQR 4368 −18191) versus €4432 (IQR 2156–9032) in temporary PTTN, p <0.001) PTTN patients received repeated and frequent head and neck imaging (mean number of imaging investigations per patient was 10 ± 12). Medication consumption was high, with an unwarranted higher use of opioids and antibiotics in persistent PTTN patients.

Within the limitations of this study, it seems there is a need for informing patients in detail on the inherent risks of nerve damage during dental and oromaxillofacial procedures. Every surgery should be preceded by a risk-benefit assessment in order to avoid unnecessary nerve damage.

1. Introduction

Post-traumatic trigeminal neuropathy (PTTN) is defined by a painful or non-painful lesion of the trigeminal nerve, caused by trauma with symptoms and/or clinical signs of trigeminal nerve dysfunction. In the case of painful PTTN, the term post-traumatic trigeminal neuropathic pain is currently used as defined by the recently introduced International Classification of Orofacial Pain (ICOP) (International Classification of Orofacial Pain, 1st edition (ICOP) 2020).

PTTN is a well-known complication in the field of oral and maxillofacial surgery and dentistry. A previous study, on which this one builds, has already shown that about half of the cases are caused by dentists, and the other half by oral and maxillofacial surgeons (Van der Cruyssen et al., 2020). Because the trigeminal nerve supplies most of the face and mouth with sensory and partly motor innervation, damage can occur during numerous procedures in this region. The most common cause of PTTN is the removal of

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wisdom teeth, a frequently performed procedure. In the United States ten million third molars are removed each year (Friedman, 2007). Other causes of PTTN may include tooth extractions, endodontic treatment, administration of local anesthetics, orthognathic surgery, placement of dental implants, and maxillofacial trauma (Klazen et al., 2018; Schenkel et al., 2016). The true incidence of PTTN is not well known but it is estimated that 1% of dental, oral or maxillofacial procedures result in persistent PTTN (Baad-Hansen and Benoliel, 2017; Politis et al., 2014).

Symptoms of PTTN are considered very disabling for the patient (Smith et al., 2013; Van der Cruyssen et al., 2020). They range from numbness in one part of the face to severe electrical or burning pain radiating to various orofacial regions. When the symptoms persist for more than three months, the condition is known as persistent PTTN (Schug et al., 2019). Diagnosing and managing PTTN can be challenging, and long referral delays to specialist centers, medical shopping, overtreatment, and legal claims are often a consequence of this (Klazen et al., 2018; Politis et al., 2014; Van der Cruyssen et al., 2020). Treatment of PTTN remains cumbersome and may include surgical intervention or a pharmacological approach (Biglioli et al., 2015; Renton and Van der Cruyssen, 2019). Recent animal studies show promise for the use of low-level laser or ozone treatment and more disease-specific treatments are on the way (Yuca et al., 2020; Finnerup et al., 2021).

To date, no data exist on the specific resource utilization pattern of patients with PTTN as well as its estimated costs to patients, health systems and society. A single study from the UK by Durham et al. in patients with persistent orofacial pain, not limited to PTTN, shows a per annum overall direct cost per patient of 362£ at 2012 prices (i.e., €478 in Belgian 2019 prices (Shemilt et al., 2010)). However, no stratification according to the cause of orofacial pain was made. Another study shows the cost of neuropathic pain conditions in five European countries (Liedgens et al., 2016). Annual direct costs per patient ranged from €1939 to €3131 (i.e., €2335–€4158 in Belgian 2019 prices (Shemilt et al., 2010)) and were highest for diabetic peripheral neuropathy, radiculopathy, and neuropathic back pain. Total annual costs were mainly driven by indirect costs of productivity loss and varied from €9305 to €14446 per patient (€11207–€17168) in Belgian 2019 prices (Shemilt et al., 2010).

The present aim of the present study is to estimate direct health care costs of patients suffering from temporary and persistent postraumatic trigeminal neurpathy (PTTN).

2. Materials and methods

2.1. Source of data

The study protocol was approved by the institute's ethical committee (S62333, ClinicalTrials.gov identifier NCT04612855). For the identification of PTTN patients a hybrid bottom-up and top-down method was used. A clinical dataset from the orofacial pain clinic at the university hospitals of Leuven with confirmed PTTN patients was linked to financial and healthcare resource utilization data of Belgium's largest health care insurance provider, the Christian Health Insurance (CM). The latter also stores data on prescribed medications, dosages, medical-technical services performed and work incapacity. They also keep a registry of the patient's share of costs (out-of-pocket expenses) and amounts reimbursed by the provider.

The clinical data used in this study originated from the TrigNerveBeUK (TNVBUK) registry (Van der Cruyssen et al., 2020). The study protocol was approved by the institute's ethical committee (S62333, ClinicalTrials.gov identifier NCT04612855). The study was conducted according to the STROBE guidelines. Data retrieved from the charts of patients visiting the Department of Oral and Maxillofacial Surgery and the orofacial pain clinic (University Hospitals Leuven, Leuven, Belgium) were collected between October 2018 and January 2019 after informing all patients. Next, a data team from CM retrieved financial and health care services data (resource use data) for each individual patient. Finally, clinical and resource use data were matched, pseudonymised and analyzed by the CM team. All data extractions and analyses that used or included CM data were performed under supervision of the Chief Medical Officer and Chief Scientific Officer of CM. The other research partners received no personally identifiable information (including small cells) from CM. The CM gathers all resource use information of its members.

2.2. Patient selection

Patients were included in the TrigNerveBeUK registry if they presented with post-traumatic or iatrogenic injury of the trigeminal nerve or its branches (e.g., inferior alveolar nerve, lingual nerve) and met the recent ICOP criteria for PTTN (International Classification of Orofacial Pain, 1st edition (ICOP) 2020). No restriction was made on age. Patients were excluded if the pain presented in a region other than the trigeminal nerve or the injury was not caused by an oromaxillofacial or dental procedure. Traumatic events that were considered were: facial trauma, local anesthesia administration, tooth extraction, wisdom tooth surgery, endodontic treatment, and dental implant placement.

After pseudonymization and selection of CM-affiliated patients, the dataframe was further completed by the CM data team. The study flow chart is summarized in Fig. 1.

After grouping all data, two patient cohorts were constructed: temporary PTTN and persistent PTTN. Persistent PTTN was defined if the symptoms persisted for more than 3 months after trauma. This is according to the definition put forward by the International Association for the Study of Pain for chronicity after trauma or surgery (Schug et al., 2019).

2.3. Measures and instruments

Initial data collection included demographic data, time and cause of trauma, location of complaints, persistence of symptoms, and health related quality-of-life (HRQoL) using the visual analog scale (VAS) of the EQ5D-5L questionnaire (Herdman et al., 2011). The EQ5D-5L assesses five domains including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression on a five-point ordinal scale (0: no problems; 1: slight problems; 2: moderate problems; 3: severe problems; 4: extreme problems). Patients also indicated their self-rated health on a VAS, ranging from 0 (worst) to 100 (best imaginable health state). The EQ5D-5L scores from the last clinical report were used.

The resource and cost data were collected starting from the date of trauma up to the five consecutive years. The CM also added data on employment status, assigned preferential payer rate, and whether the patient had a registered chronic pain status. The preferential rate in Belgium exists for people with a lower income, orphans, or people with a disability, to keep health care costs affordable.

Direct total costs recorded at the CM were further stratified into consultation costs, technical costs, imaging costs, and medication-related costs. All healthcare utilization costs are shown in Euro and represent Belgian rates in 2019.

Total costs, out-of-pocket (patient) expenses, and health care provider expenses were identified. Consultations were reviewed and divided into primary medical care versus secondary (specialist) medical care visits. Dental visits were not listed separately as dental

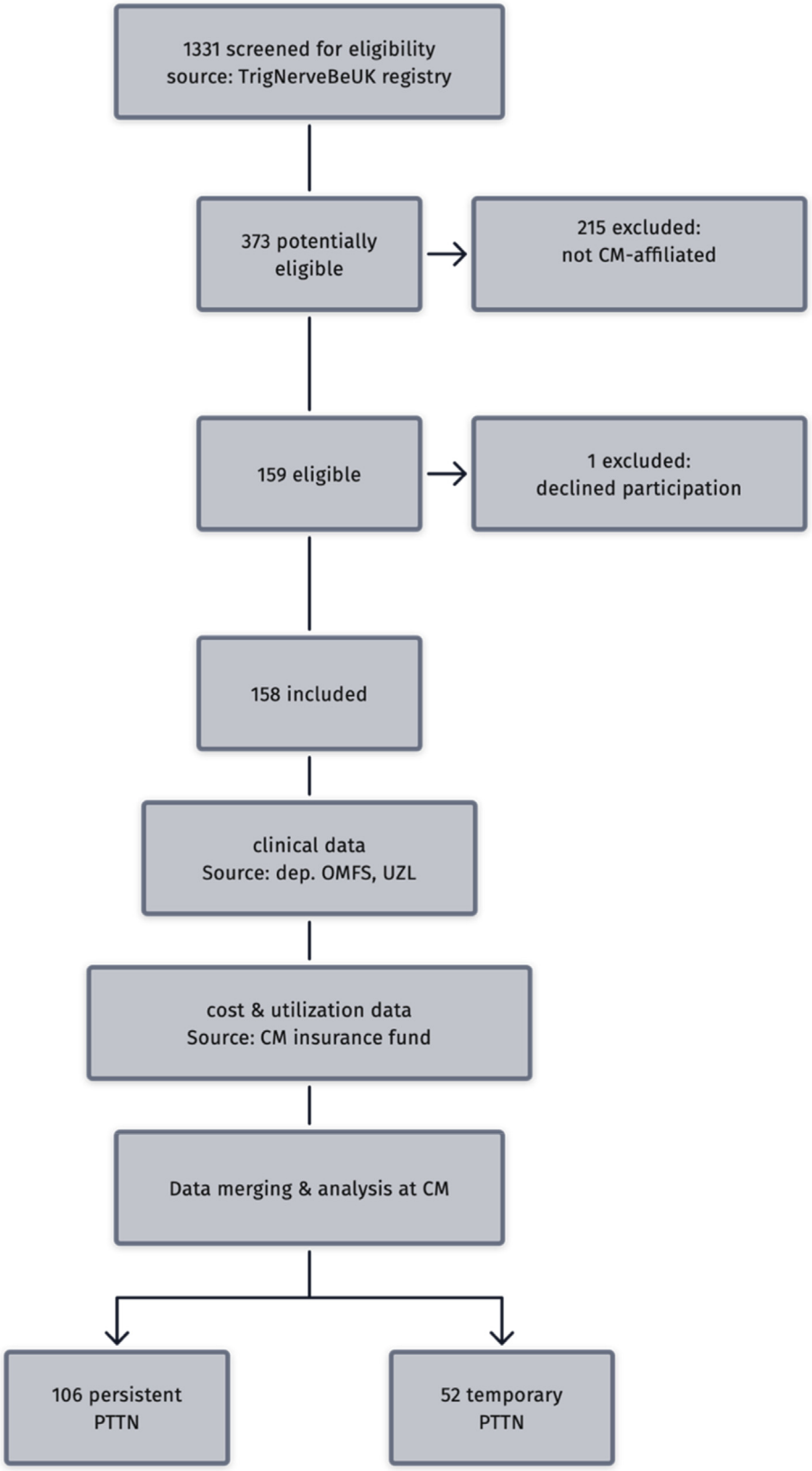

Fig. 1. Study flowchart.

consultations in Belgium are coded in combination with technical interventions.

All head and neck or oral imaging modalities were reviewed and summarized. Technical interventions were checked and stratified according to the performing physician's specialty code. After consultation with all authors, it was decided to focus on the PTTN-relevant specialties: primary care, dentistry, maxillofacial surgery, neurosurgery, neurology, and psychiatry. Finally, medication consumption was analyzed by summarizing costs and the defined daily dose (DDD). We applied the World Health Organization's anatomical therapeutic chemical (ATC)/DDD system to analyze consumption of paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, antidepressants, antiepileptics, antipsychotics, corticosteroids, and antibacterials per patient.

In Belgium, work incapacity is registered by health insurance providers as soon as it exceeds 30 days. Consequently, any episode of work incapacity lasting longer than 30 days was reviewed.

2.4. Data analysis and statistical procedures

RStudio (version 1.4.1103, PBC, Boston, MA, USA) and SAS software (SAS Institute Inc 2013; Cary, NC, USA) were used for all analyses. Sample size was determined for a moderate effect ($d = 0.4$) with alpha of 0.05 and beta of 0.80 at 114 patients. Standard descriptive statistics were calculated followed by non-parametric testing to compare group differences. Data are mean ± standard deviation or median (interquartile range (IQR)) unless otherwise stated.

EQ5D-5L index values were calculated based on the Flemish index values for the EQ-5D-3L from Cleemput (2010) and mapped for the EQ5D-5L according to the crosswalk function proposed by van Hout et al. (van Hout et al., 2012).

Mean differences between temporary and persistent PTTN were compared using a Mann-Whitney *U* test. Ratios between cohorts were calculated and compared using a Chi square or Fisher's exact test.

A time-series analysis was done comparing total direct health care costs between temporary and persistent PTTN cohorts in the 5 years following the onset of PTTN. A multiple linear regression with stepwise selection model was calculated to determine if age, EQ5D, gender, affected nerve and cause of trauma could predict total cost.

Finally, an outlier analysis was performed based on boxplot inspection and the Rosner test of total costs over a 5-year period to identify and further characterize potential risk populations. The cumulative total costs of this subgroup were compared with the cumulative total cost of the overall sample.

There were no missing data in the final sample.

3. Results

3.1. Study sample

The final study population consisted of 158 (or 43%) patients with a female predominance of 66% and mean age of 52 years. There were no statistical differences between the final study sample and the non-cm affiliated, excluded, patients (**Supplementary table**). The main cause of PTTN in this sample was third molar surgery (21%), followed by non-third molar extraction (19%). Most patients reported symptoms in the lower jaw (51%) and 67% had persistent PTTN. The average QoL index value was 0.70 ± 0.20. Patient characteristics are presented in Table 1.

Seventy-five percent of patients were employed at the time of data collection, 10% were self-employed, and 15% were retired. No patients in this sample were unemployed. However, 14% received a preferential rate and 13% had a registered chronic pain status. The mean QoL score was 71 ± 26 out of 100 (100 indicating best QoL). Twenty-one percent indicated no problems on EQ-5D dimensions.

3.2. Overall costs and health care utilization

Table 2 summarizes average and median costs and health care use for the total study population since the complaint began. Hospitalization and technical interventions were the main drivers of cumulative costs, followed by consultation costs. The total average cost per patient in the first year was €2353 (1426–4499). Of this, the patient paid an average of €587 (303–982) out-of-pocket (i.e., 25% of total costs). In a period of 5 years after PTTN diagnosis, the average cumulative cost per patient was €6978 (3473–15338) with a mean out-of-pocket expense of €1802 (651–3658), i.e., 26%. The multiple regression model could not significantly predict total cost ($F(18, 80) = 0.8385$, $p < 0.6508$, adj. $R2 = -0.03057$. None of the variables added significantly to the prediction.

The number of doctor visits in this population was high, with a mean of 27 primary care visits and 47 specialist visits over a 5-year period per patient amounting to a total annual mean cost of €133 and €211, respectively. When assessing median visiting numbers mainly primary care physicians were visited.

In the 5-year period after the onset of PTTN, 97% of patients received at least one head and neck imaging exam. The mean number of imaging investigations per patient was 10 ± 12, with one patient receiving up to 94 investigations (mainly intra-oral radiographs). On average, patients received one computed tomography (CT) head and several intraoral and panoramic radiographs in the 5 years following the occurrence of PTTN. Thirty-seven percent of patients underwent magnetic resonance imaging (MRI) of the brain and 70% had cone-beam computed tomography (CBCT) or a CT of the head. Eleven percent of patients underwent at least two MRIs of the brain in the first 5 years and 36% of patients had two or more CTs or CBCTs of the head taken. Costs of technical interventions mainly cumulated in the dental and maxillofacial disciplines, but also a considerable share of interventions were registered by the primary care giver. On an annual basis, maxillofacial surgery costs were the highest with a median cost of €183 (52–362), followed by dental procedures amounting to €158 (71–323).

We observed a high level of medication consumption in this population as illustrated in Table 2. The cumulative costs were the highest for antibacterials, NSAIDs and antidepressants after PTTN was diagnosed.

3.3. Comparing temporary versus persistent PTTN cohorts

When comparing temporary and persistent PTTN cohorts, the persistent PTTN cohort comprised relatively more women than the temporary PTTN cohort (72% versus 54%, $p = 0.026$). The median age was significantly higher in the persistent PTTN group (54 versus 46 years, $p = 0.003$). We observed a disproportionate localization of nerve damage: persistent nerve damage was more commonly associated with localization in the upper jaw (Table 3). No significant differences were noted in the cause of injury between both cohorts. Quality of life was significantly lower in patients with persistent PTTN (0.60 ± 0.24 versus 0.92 ± 0.15, $p < 0.001$)

Health care expenditure was highest in the persistent PTTN cohort with a median 5-year total expense of €8866 (4368–18191) versus €4432 (2156–9032) in patients suffering from temporary PTTN ($p < 0.001$). This corresponds to a ratio of 2. Furthermore, the median 5-year out-of-pocket expense for a patient with persistent PTTN was €2084 (1088–3989) (i.e., 24% of the total health care expenditure) versus €1294 (446–2754) (i.e., 29% of the total health care expenditure) with a ratio of 1.6. Hospitalization and technical

Table 1
Patient characteristics of the study sample.

Characteristic (N)	N	Count (%)	Mean (SD)	Median (IQR)
Age	158		52 (17)	52 (36–64)
Gender	158			
Male		54 (34)		
Female		104 (66)		
Cause of injury - count (%)	158			
Local anesthesia		2 (1.3)		
Third molar surgery		33 (20.9)		
Tooth extraction		30 (19.0)		
Endodontic treatment		15 (9.5)		
Dental implant placement		20 (12.7)		
Maxillofacial trauma		21 (13.3)		
Other		37 (23.0)		
Location of complaints	158			
Lower jaw		80 (50.6)		
Tongue		22 (13.9)		
Upper jaw		56 (35.4)		
Persistency of symptoms	158			
Temporary (<3 months after injury)		52 (32.9)		
Persistent (>3 months after injury)		106 (67.1)		
Employment status	175			
Employee		131 (75)		
Self-employed		17 (10)		
Retired		27 (15)		
Work incapacity >30 days				
Number of patients		52 (33)		
Days			264 (749)	0 (0–55)
Preferential rate	175	25 (14)		
Chronic pain status	158	21 (13)		
Quality of Life (EQ5D-5L)	100			
Dimensions				
No problems		21 (21)		
Any problem		79 (79)		
Index			0.70 (0.26)	0.76 (0.62–0.81)
Health state			71 (26)	75 (65–90)

interventions yielded the highest costs for both cohorts. For each cost category, the expenditure of patients with persistent PTTN was statistically significantly higher than that of patients with temporary PTTN.

Medication consumption measured by the defined daily dose (DDD) was high in both cohorts. The amount of prescribed NSAIDS, opioids, antibiotics, and corticosteroids was significantly higher in patients with persistent PTTN. The DDD of typical pain medications (paracetamol, NSAIDs, opioids) and atypical pain medications (antidepressants, antiepileptics, antipsychotics) was particularly high for both cohorts. For instance, the maximum DDDs reported for paracetamol and opioids per annum were 2203 and 3543, respectively.

There were no statistically significant differences in work incapacity between the two cohorts. A significantly higher proportion of persistent PTTN patients had a registered chronic pain status (19% versus 1.9%, $p = 0.003$) and their QoL scores were lower (66 ± 29 versus 82 ± 9, $p = 0.002$).

We performed a longitudinal analysis of annual mean costs in the first 5 years after occurrence of PTTN between the two cohorts. Total costs were higher for persistent PTTN versus temporary PTTN at every time point. Furthermore, a steady increase in costs was seen in patients with persistent PTTN versus a decrease in the temporary PTTN group (Fig. 2). This translated into a cost ratio of 1.4 at the start of symptoms, increasing to 2.4 after 5 years.

3.4. Outlier analysis

Outlier analysis revealed that eight patients (5% of the study population) had particularly high direct health care costs. The cumulative cost of these eight patients was €533526 with an average of €66691 per patient, over the 5-year period following the onset of PTTN. Together this represented 28% of the overall direct costs of the entire study population. Further exploratory analysis showed that these were seven women and one man with a mean age of 70 ± 13 years. These patients all belonged to the persistent PTTN cohort. The mean QoL index value was 0.40 ± 0.40 with a self-perceived HRQoL score of 48 ± 17.

4. Discussion

This study demonstrates that PTTN patients represent a high economic burden, with a median annual direct cost of €1396 per patient. Patients with persistent PTTN incurred significantly higher direct costs (annual median cost of €1773 versus €886 in temporary PTTN) which further increased in the years after the onset of PTTN. The identified direct costs incurred by PTTN patients are considerably higher than the previously reported annual direct costs of 362£ at 2012 prices (i.e., €478 in Belgian 2019 prices (Shemilt et al., 2010)) in persistent orofacial pain patients, published by Dubner et al. (2016). The annual direct total costs reported in this study are comparable to the costs of postsurgical neuropathy reported by Liedgens et al. (2016). To put this further into perspective, other analyses of national health insurance data, which applied a methodology similar to that of this study, show that the average annual health care expenditure of dental patients without a chronic condition in Belgium is €980 versus €5076 when a chronic condition is present (Brenez, 2013). For reference, we mention that OECD figures of 2019 state an average overall health care expenditure of €3679 per capita in Belgium (OECD & European Union, 2020). However, the methodology behind these figures is different and does not allow for an unequivocal comparison.

Table 2
Direct health care costs and resource utilization of the study sample.

Characteristic (N)	Year 1				5-year-average per annum				5-year-total			
	Mean frequency (SD)	Median frequency (IQR)	Mean cost (SD)	Median cost (IQR)	Mean frequency (SD)	Median frequency (IQR	Mean cost (SD)	Median cost (IQR)	Mean frequency (SD)	Median frequency (IQR	Mean cost (SD)	Median cost (IQR)
Consultations												
Primary medical care	7 (9)	6 (3–10)	179 (235)	147 (78–229)	5 (6)	4 (1–7)	133 (170)	87 (30–178)	27 (15)	18 (6–36)	663 (380)	436 (149–890)
Secondary medical care	17 (16)	14 (9–19)	352 (393)	296 (182–458)	9 (11)	0 (0–2)	211 (256)	0 (0–33)	47 (24)	0 (0–8)	1055(573)	0 (0–167)
Hospitalization												
Duration (in days)	1.7 (5.6)	2 (1–4)	612 (779)	2418 (1537–3777)	2.0 (14.0)	0 (0.0–0.4)	508 (2273)	0 (0–315)	9.9 (31.4)	0 (0–2)	2542 (5095)	0 (0–1573)
Imaging												
Intra-oral	1.5 (3.7)	1 (0–2)	15 (30.8)	12 (0–26)	0.9 (2.7)	0.4 (0.0–1.0)	10.3 (38.1)	4 (0–11)	4.6 (6.0)	2.0 (0.0–5.0)	51.3 (85.5)	20 (0–57)
Panoramic	1.4 (2.3)	1 (0–2)	43.2 (63.3)	42 (0–111)	0.6 (1.3)	0.3 (0–0.8)	18.3 (36.4)	9 (0–24)	3.0 (3.0)	1.5 (0.2–4.0)	91.3 (81.5)	44 (0–119)
Lateral head	0.2 (0.4)	0 (0–0)	4.4 (10.0)	0 (0–0)	0.1 (0.3)	0 (0–0)	2.26 (10.2)	0 (0–0)	0.4 (0.7)	0 (0–0)	11.3 (22.8)	0 (0–0)
Conebeam CT	0.2 (0.2)	0 (0–0)	12.2 (12.3)	0 (0–0)	0.1 (0.1)	0 (0.0–0.2)	4.80 (7.48)	0 (0–12)	0.4 (0.3)	0 (0.0–1.0)	24.0 (16.8)	0 (0–60)
Head CT	0.4 (0.2)	0 (0–1)	26.2 (31.5)	0 (0–60)	0.2 (0.3)	0.2 (0.0–0.2)	12.2 (21.7)	0 (0–18)	1 (0.6)	1.0 0.0–1.0)	60.9 (48.7)	0 (0–88)
MRI head-brain	0.3 (0.4)	0 (0–1)	20.7 (28.1)	0 (0–0)	0.1 (0.2)	0 (0.0–0.2)	8.22 (14.0)	0 (0–18)	0.5 (0.4)	0 (0–1)	41.1 (31.4)	0 (0–92)
Technical interventions												
Primary medical			226 (266)	160 (74–273)			169 (199)	126 (43–223)			846 (446)	630 (216–1117)
Dental			557 (1252)	228 (86–580)			1306 (1587)	158 (71–323)			261 (708)	790 (353–1616)
Maxillofacial surgery			1090 (1427)	573 (68–1369)			323 (852)	183 (52–362)			1613 (1909)	913 (260–1810)
Neurosurgery			22.8 (154)	0 (0–0)			15.6 (159)	0 (0–0)			78.2 (356)	0 (0–0)
Neurology			31.4 (58.7)	0 (0–0)			29.6 (74.3)	0 (0–23)			148 (167)	0 (0–113)
Psychiatry			48.3 (292)	0 (0–0)			31.9 (174)	0 (0–0)			160 (390)	0 (0–0)
Medications	DDD (SD)				DDD (SD)				DDD (SD)			
Paracetamol	34.7 (196)	0 (0–1)	2.30 (4.83)	0 (0–2.5)	45.1 (414)	0 (0–5)	1.85 (8.34)	0.5 (0–1.2)	226 (928)	1 (0–24)	9.26 (18.7)	2 (0–6)
NSAID's	27.2 (32.8)	15 (0–35)	12.8 (17.2)	7 (0–16)	12.4 (23.3)	6 (3–16)	5.39 (9.86)	3 (1.3–6.6)	62.0 (52.2)	30 (15–80)	26.9 (22.1)	15 (7–33)
Opioids	22.2 (74.9)	0 (0–5)	29 (198)	0 (0–9)	26.4 (205)	3 (0–27)	24.4 (180)	0 (0–5)	132 (460)	1 (0–5)	122 (404)	1 (0–27)
Antidepressants	57.4 (105)	0 (0–42)	42.8 (103)	0 (0–28)	53.5 (98.2)	5 (0–54)	45.1 (125)	3 (0–28)	267 (220)	27 (0–272)	226 (280)	13 (0–140)
Antiepileptics	17.0 (53.0)	0 (0–0)	19.3 (52.6)	0 (0–0)	17.6 (46.8)	0 (0–5)	23.8 (104)	0 (0–3)	88.0 (105)	0 (0–24)	119 (233)	0 (0–17)
Antipsychotics	5.52 (30.2)	0 (0–0)	9.63 (58.2)	0 (0–0)	4.40 (20.2)	0 (0–1)	6.78 (41.8)	0 (0–0)	22.0 (45.3)	0 (0–5)	33.9 (93.7)	0 (0–0)
Corticosteroids	9.49 (16.5)	2 (0–6)	5.22 (6.77)	0 (0–8.6)	7.91 (35.3)	1 (0–6)	3.48 (13.2)	1.7 (0–3.46)	39.6 (79.1)	6 (0–30)	17.4 (29.5)	8 (0–17)
Antibacterials	30.0 (28.6)	19 (2–43)	43.9 (53.3)	22 (6–55)	16.4 (22.1)	10 (4–21)	22.5 (37.5)	11 (4–31)	82.2 (49.5)	48 (18–103)	112 (84.1)	57 (19–155)
Total			3577 (3457)	2353 (1426–4499)			2400 (4156)	1396 (695–3068)			12002 (9317)	6978 (3473–15338)

The present study suggests high out-of-pocket rates nearly of up to 30% for patients suffering from PTTN. Other studies have already shown that inequality occurs in chronic conditions (McRae et al., 2013; Paez et al., 2009). Out-of-pocket spending generally increases with increasing age, multimorbidity, and chronicity (Paez et al., 2009). The persistent PTTN cohort in this study consisted of significantly older people, which may explain why the out-of-pocket expenses are higher in this group. This study adds to the evidence base that those out-of-pocket costs are relatively high in the presence of a neuropathic condition.

Health care resource utilization was significantly higher in patients with persistent PTTN. A high frequency of primary care visits was seen in this cohort. On average, there were five general practitioner (GP) visits per year and nine visits to specialists. Figures from Liedgens' study show that here too, the economic impact of PTTN is higher than the mean of three GP visits and five specialist consultations reported in their study on a large population of neuropathic pain patients in Europe (Liedgens et al., 2016). The annual average number of hospitalization days in this study of two days per patient is lower than reported figures for patients with chronic conditions in Belgium, which is estimated to be 13 days per year (Brenez, 2013), and the reported OECD average length of stay of 7.2 days (OECD & European Union, 2020).

Table 3
Comparison of patient characteristics and health care expenditure between persistent and temporary PTTN. Prices are given in 2019 € for Belgium. SD: standard deviation.

Characteristic	Persistent PTTN (N = 106)	Temporary PTTN (N = 52)	p-value
Age - mean (SD)	55 (15)	46 (18)	0.003
Gender - count (%)			0.026
Female	76 (72)	28 (54)	
Male	30 (28)	24 (46)	
Cause of injury - count (%)			>0.05
Local anesthesia	1 (0.9)	1 (0.9)	
Third molar surgery	15 (14.0)	18 (35.0)	
Tooth extraction	19 (18.0)	11 (21.0)	
Endodontic treatment	11 (10.0)	4 (7.7)	
Dental implant placement	15 (14.0)	5 (9.6)	
Maxillofacial trauma	14 (13.0)	7 (13.0)	
Other	31 (29.0)	6 (12.0)	
Location of complaints - count (%)			
Lower jaw	49 (46)	31 (60)	0.034
Tongue	14 (13)	8 (15)	
Upper jaw	43 (41)	13 (25)	
Employment status - count (%)			0.064
Employee	85 (71)	45 (82)	
Self-employed	24 (20)	3 (5.5)	
Retired	10 (8.4)	7 (13)	
Work incapacity >30 days			
Patients - count (%)	40 (38)	12 (23)	0.065
Days - mean (SD)	304 (800)	175 (619)	0.2
Preferential rate - count (%)	19 (16)	6 (11)	0.6
Chronic pain status - count (%)	20 (19)	1 (1.9)	0.003
Quality of Life (EQ5D-5L)			
Dimensions - count (%)			<0.001
No problems	1 (1)	20 (20)	
Any problems	71 (71)	8 (8)	
Index	0.61 (0.24)	0.92 (0.15)	<0.001
Health state - mean (SD)	66 (29)	82 (9)	0.002
Health care expenditure in € - median (IQR)			
Patient expenditure (out-of-pocket) year 1	618 (398–1130)	441 (198–793)	0.029
Health insurance provider expenditure year 1	1912 (946–4273)	1393 (1043–2040)	0.017
Total healthcare expenditure year 1	2535 (1584–5478)	1946 (1299–3228)	0.021
Patient expenditure (out-of-pocket) first five years	2084 (1088–3989)	1294 (446–2754)	0.005
Health insurance provider expenditure first five years	6716 (2713–13569)	3202 (1665–5876)	<0.001
Total healthcare expenditure first five years	8866 (4368–18191)	4432 (2156–9032)	<0.001
Patient expenditure (out-of-pocket) 5-year-average per annum	417 (218–798)	259 (89–551)	0.005
Health insurance provider expenditure 5-year-average per annum	1343 (543–2714)	640 (333–1175)	<0.001
Total expenditure 5-year-average per annum	1773 (874–3638)	886 (431–1806)	<0.001

From a 2018 Belgian population-wide study we learn that the overall HRQoL was 0.79 for Belgians with age of 15 years or more (Van der Heyden et al., 2019). The HRQoL for men in age group 45–54 was 0.81 and for women 0.75. This suggest a lower HRQoL in patients with PTTN and even more so when patients suffer from persistent PTTN.

It is striking in this study that the average number of examinations and repetitive imaging per patient is very high. This might indicate that both practitioners and patients refuse to accept or recognize the diagnosis, therapy, and prognosis of a PTTN-condition. This hypothesis is strengthened since costs seem to decrease over time for patients with temporary PTTN.

Technical services proved to be one of the main drivers of total costs. Of the disciplines investigated, the cumulative intervention cost was highest in the fields of maxillofacial surgery, primary care, and dentistry. However, there was a slight but significant difference in cumulative costs between the persistent and temporary PTTN cohorts. Contrary to expectations, there thus appears to be no imbalance in the costs of delivered technical services between these cohorts.

Medications were prescribed more often for patients with persistent PTTN, who recorded significantly higher use of NSAIDs, opioids, and corticosteroids. There was a wide range in the DDDs with some extremely high outliers (Table 4). This is a disturbing finding, especially because we also found these extreme values for opioids and antibiotics. Both have no or only a limited place in the treatment of PTTN. This indicates that this population may be at particular risk of wrongful prescribing and overprescribing (Finnerup et al., 2015). Currently and to the best of our knowledge, no data are available on the DDD for the investigated medication classes in comparable populations. Additionally, care should be taken when using the DDD metric because the actual DDD of different opioid derivatives and the WHO-reported DDD can differ significantly (Nielsen et al., 2017).

A small number of patients (5%) contributed to almost 30% of total costs in this study population. This suggests a subpopulation with particularly high economic and psychosocial impact. Early identification and adequate support of these patients should therefore be high on the agenda.

The strengths of this study are that the analysis was based on real-world data and could be traced back to the individual level to identify clinically relevant subpopulations. Without a national registry or universal coding of these patients, it would not be possible to obtain these data.

Study limitations include a potential selection bias as all patients were drawn from a tertiary center clinical dataset. No detailed information was available as to who caused the injuries, their experience or training. Also, compared to other health insurance companies, within the CM membership, there is a slight bias towards older age groups (mean age CM members = 44, versus mean

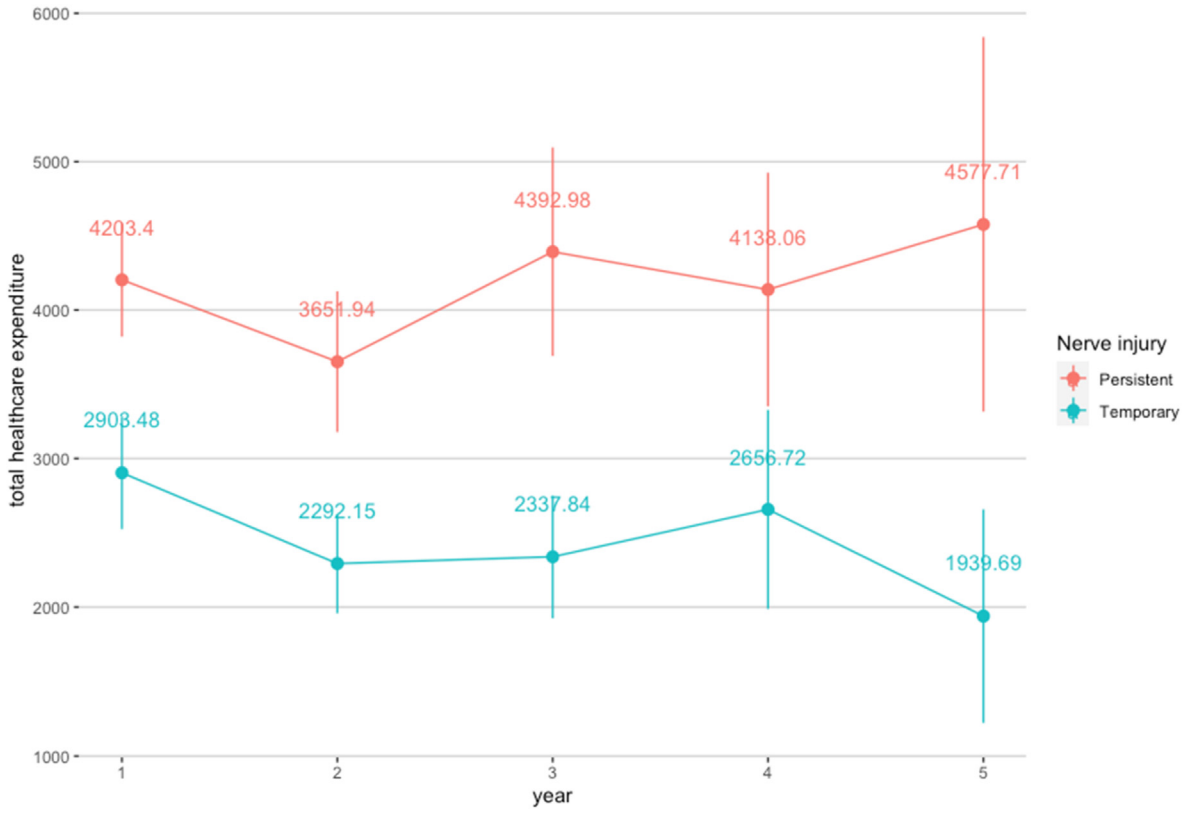

Fig. 2. Time series analysis of total health care expenditure between temporary and persistent PTTN cohorts in the first five years after onset of PTTN. Mean prices ± standard deviations are given. Prices are given in 2019 € for Belgium.

Table 4
Comparison of medication use between persistent and temporary PTTN patients. Per annum and per day defined daily dose (DDD) of frequently used medication classes.

DDD per annum per patient during first five years	Persistent PTTN				Temporary PTTN				p-value
	Mean (SD)	Median (IQR)	Min	Max	Mean (SD)	Median (IQR)	Min	Max	
Paracetamol	94 (378)	4 (1–16)	0	2203	12 (25)	2 (1–11)	0	140	0.2
NSAIDS	25 (34)	14 (7–30)	0	240	15 (16)	9 (6–19)	3	97	0.023
Antidepressants	158 (226)	41 (11–219)	2	964	78 (86)	40 (7–108)	3	286	0.4
Antiepileptics	129 (207)	25 (5–162)	1	993	36 (37)	28 (15–36)	4	106	0.9
Antipsychotics	40 (71)	5 (2–45)	0	257	36 (37)	28 (15–36)	4	106	0.7
Opioids	98 (452)	10 (3–28)	0	3543	10 (27)	3 (0–6)	0	140	<0.001
Antibacterials	52 (59)	38 (14–71)	1	418	19 (17)	14 (8–27)	0	72	<0.001
Corticosteroids	21 (51)	7 (3–15)	0	322	6 (7)	4 (3–8)	1	30	0.010
DDD per day per patient during first five years	Persistent PTTN				Temporary PTTN				p-value
	Mean (SD)	Median (IQR)	Min	Max	Mean (SD)	Median (IQR)	Min	Max	
Paracetamol	0.26 (1.04)	0.01 (0.00–0.04)	0.00	6.03	0.03 (0.07)	0.01 (0.00–0.03)	0.00	0.38	0.2
NSAIDS	0.07 (0.09)	0.04 (0.02–0.08)	0.00	0.66	0.04 (0.04)	0.02 (0.02–0.05)	0.01	0.26	0.023
Antidepressants	0.43 (0.62)	0.11 (0.03–0.60)	0.01	2.64	0.21 (0.24)	0.11 (0.02–0.30)	0.01	0.78	0.4
Antiepileptics	0.35 (0.57)	0.07 (0.01–0.44)	0.00	2.71	0.10 (0.10)	0.08 (0.04–0.10)	0.01	0.29	0.9
Antipsychotics	0.11 (0.19)	0.01 (0.01–0.12)	0.00	0.71	0.11 (0.24)	0.01 (0.01–0.08)	0.01	0.27	0.7
Opioids	0.27 (1.24)	0.03 (0.01–0.08)	0.00	9.71	0.03 (0.07)	0.01 (0.00–0.02)	0.00	0.38	<0.001
Antibacterials	0.14 (0.16)	0.10 (0.04–0.19)	0.00	1.15	0.05 (0.05)	0.04 (0.02–0.07)	0.00	0.20	<0.001
Corticosteroids	0.06 (0.14)	0.02 (0.01–0.04)	0.00	0.88	0.02 (0.02)	0.01 (0.01–0.02)	0.00	0.08	0.010

SD: standard deviation.

age Belgian population = 41) and the unemployed are slightly underrepresented (40.6% of the unemployed are members vs. an expected 43.7%) (Beutels et al., 2006). Only, direct costs were investigated, and all financial data were taken into account—not only those attributable to PTTN. However, we did prove that e.g. age and gender did not explain the total cost. This indicates that these populations do indeed differ in terms of disease phenotype and thus total cost. A future study that also identifies the indirect costs of these patients based on structured interviews could be a logical next step. Finally, we note that the current dataset did not allow us to map all out-of-pocket expenses. Particularly in the ambulant care setting in Belgium, additional supplements as well as the system of an out-of-pocket maximum can influence the patient contribution, which was not accounted for here.

5. Implications and future opportunities

The presented results highlight the importance of first and foremost preventing nerve injuries from happening. Trigeminal nerve injuries are largely preventable by careful patient selection and treatment planning. 3D virtual planning is routinely applied in both dental and maxillofacial surgery specialties. These new tools already implement nerve tracing tools to avoid these structures being injured during surgery (Kuntz and Schulze, 2021).

But, even in the best hands and with the most minimal invasive techniques, nerve injuries can still occur. This is where current evidence stops. Both patients and specialists languish into ignorance. There is a risk misdiagnosing and mistreating the nerve injury patient. Patients may steer towards medical shopping or medicolegal action. Some will end up with lifelong neuropathic pain resulting in a detrimental QoL. Secondary prevention is currently lacking. This is illustrated by studies showing large variation in referral delays, diagnostic measures and treatment options. Unfortunately no gold standard or internationally accepted guidelines exist (Klazen et al., 2018; Renton and Van der Cruyssen, 2019).

Future studies should focus on developing diagnostic and treatment guidelines. In parallel, both patients and clinicians should be made aware of the risk of trigeminal nerve injuries, how they can be avoided and treated. Expert talks at conferences and in patient support groups could be a good starting point to increase this awareness.

Finally, we hypothesize that centralization of these patients may aid in a faster and more cost-effective approach. This could be evaluated in a future cost-effectiveness study.

6. Conclusion

Within the limitations of this study, it seems there is a need for informing patients in detail on the inherent risks of nerve damage after dental and oromaxillofacial procedures. Every surgery should be preceded by a risk-benefit assessment in order to avoid unnecessary nerve damage.

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Availability of data and material

Raw data were generated at the Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, and the Christian Sickness Fund. Derived data supporting the findings of this study are available from the corresponding author (FVDC) on request.

Code availability

Not applicable.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Dr. Fréderic Van der Cruyssen and Dr. Margaux Nys. The first draft of the manuscript was written by Dr. Fréderic Van der Cruyssen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

The study protocol was approved by the institute's ethical committee (S62333, ClinicalTrials.gov identifier NCT04612855).

Consent for publication

Not applicable.

Précis

PTTN is an avoidable, debilitating condition that is costly for both patients and society.

Declaration of competing interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2022.07.002.

References

Baad-Hansen, L., Benoliel, R., 2017. Neuropathic orofacial pain: facts and fiction. Cephalalgia 37 (7), 670–679.
Beutels, P., Van Damme, P., Oosterhuis-Kafeja, F., 2006. Effecten en kosten van de vaccinatie van Belgische kinderen met geconjugeerd pneumococcenvaccin. 33A. Federaal Kenniscentrum voor de gezondheidszorg (KCE), Brussels.
Biglioli, F., Allevi, F., Lozza, A., 2015. Surgical treatment of painful lesions of the inferior alveolar nerve. J. Cranio-Maxillo-Fac. Surg. 43, 1541–1545.
Brenez, X., 2013. Uitgaven gezondheidszorg: meer aandacht voor chronische ziektes. Healthc. Forum 36.
Cleemput, I., 2010. A social preference valuations set for EQ-5D health states in Flanders, Belgium. Eur. J. Health Econ. 11 (2), 205–213.
Dubner, R., Durham, J., Shen, J., Breckons, M., Steele, J.G.G., Araujo-Soares, V., Exley, C., Vale, L., 2016. Healthcare cost and impact of persistent orofacial pain. J Dent Research 95 (10), 1147–1154.
Finnerup, N.B., Attal, N., Haroutounian, S., McNicol, E., Baron, R., Dworkin, R.H., Gilron, I., Haanpaa, M., Hansson, P., Jensen, T.S., Kamerman, P.R., Lund, K., Moore, A., Raja, S.N., Rice, A.S.C., Rowbotham, M., Sena, E., Siddall, P., Smith, B.H., Wallace, M., 2015. Pharmacotherapy for neuropathic pain in adults: systematic review, meta-analysis and updated NeuPSIG recommendations. Lancet Neurol. 14 (2), 162–173.
Finnerup, N., Kuner, R., Jensen, T., 2021. Neuropathic pain: from mechanisms to treatment. Physiol. Rev. 101, 259–301.
Friedman, J.W., 2007. The prophylactic extraction of third molars: a public health hazard. Am. J. Publ. Health 97 (9), 6.
Herdman, M., Gudex, C., Lloyd, A., Janssen, M.F., Kind, P., Parkin, D., Bonsel, G., Badia, X., 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual. Life Res. 20 (10), 1727–1736.
International Classification of Orofacial Pain, , 1stvol. 40, 2020. ICOP, Cephalalgia, pp. 129–221. 2.
Klazen, Y., Van der Cruyssen, F., Vranckx, M., Van Vlierberghe, M., Politis, C., Renton, T., Jacobs, R., 2018. Iatrogenic trigeminal post-traumatic neuropathy: a retrospective two-year cohort study. Int. J. Oral Maxillofac. Surg. 47 (6), 789–793.
Kuntz, N.M., Schulze, R., 2021. 3D classification of lower third molars and their relationship to the mandibular canal. J. Oral Maxillofac. Surg. 79 (8), 1611–1620.
Liedgens, H., Obradovic, M., De Courcy, J., Holbrook, T., Jakubanis, R., 2016. A burden of illness study for neuropathic pain in Europe. Clinicoecon Outcomes Res 8 (113–26).
McRae, I., Yen, L., Jeon, Y.-H., Herath, P.M., Essue, B., 2013. Multimorbidity is associated with higher out-of-pocket spending: a study of older Australians with multiple chronic conditions. Aust. J. Prim. Health 19 (2), 144–149.
Nielsen, S., Gisev, N., Bruno, R., Hall, W., Cohen, M., Lrance, B., Campbell, G., Shanahan, M., Blyth, F., Lintzeris, N., Pearson, S., Mattick, R., Degenhardt, L., 2017. Defined daily doses (DDD) do not accurately reflect opioid doses used in

contemporary chronic pain treatment: defined daily doses for opioids in chronic pain. Pharmacoepidemiol. Drug Saf. 26 (5), 587–591.
Paez, K.A., Zhao, L., Hwang, W., 2009. Rising out-of-pocket spending for chronic conditions: a ten-year trend. Health Aff. 28 (1), 15–25.
Politis, C., Lambrichts, I., Agbaje, J.O., 2014. Neuropathic pain after orthognathic surgery. Oral Surg Oral Med Oral Pathol Oral Radiol 117 (2) e102–7.
Renton, T., Van der Cruyssen, F., 2019. Diagnosis, pathophysiology, management and future issues of trigeminal surgical nerve injuries. Oral Surg 13 (4), 389–403.
Schenkel, J.M., Jacobsen, C., Rostetter, C., Gratz, K.Z., Rukcer, M., Gander, T., 2016. Inferior alveolar nerve function after open reduction and internal fixation of mandibular fractures. J. Cranio-Maxillo-Fac. Surg. 44, 743–748.
Schug, S.A., Lavand'homme, P., Barke, A., Korwisi, B., Rief, W., et al., 2019. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. Pain 160 (1), 45–52.
Shemilt, I., Thomas, J., Morciano, M., 2010. A web-based tool for adjusting costs to a specific target currency and price year. Evid Policy 6 (1), 51–59.
Smith, J.G., Elias, L.-A., Yilmaz, Z., Barker, S., Shah, K., Shah, S., Renton, T., 2013. The psychosocial and affective burden of posttraumatic neuropathy following injuries to the trigeminal nerve. J. Orofac. Pain 27 (4), 293–303.
OECD, Union, European, 2020. Health at a Glance: Europe 2020: State of Health in the EU Cycle. OECD.
Van der Cruyssen, F., Peeters, F., Gill, T., De Laat, A., Jacobs, R., Politis, C., Renton, T., 2020. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. J. Oral Rehabil. 47 (10), 1212–1221.
Van der Heyden, J., Nguyen, D., Renard, F., Scohy, A., Demarest, S., 2019. Belgisch Gezondheidsonderzoek 2018. Sciensano, Brussels.
van Hout, B., Janssen, M.F., Feng, Y.-S., Kohlmann, T., 2012. Busschbach: interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 15 (5), 708–715.
Yuca, Y., Yucesoy, T., Tok, O.E., Alkan, A., 2020. The efficiency of ozone therapy and low-level laser therapy in rat facial nerve injury. J. Cranio-Maxillo-Fac. Surg. 48, 308–314.