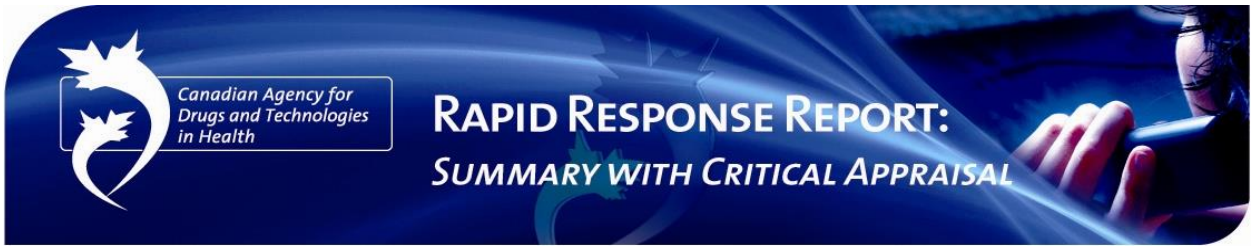

TITLE: Surgical Interventions for Trigeminal Neuralgia: A Review of Clinical and Cost-Effectiveness

DATE: 06 April 2016

CONTEXT AND POLICY ISSUES

Trigeminal neuralgia is a debilitating ailment characterized by sudden and severe unilateral facial pain described as stabbing, electrical, or bursts of shock-like pain, which can be triggered by simple activities like brushing teeth, eating, drinking, or talking.[1-3] The condition can be classified as idiopathic or secondary. The current hypothesis is that idiopathic trigeminal neuralgia is caused by neurovascular contact between an aberrant vein or artery and the fifth cranial nerve at the root entry zone.[4] Secondary trigeminal neuralgia is caused by other factors such as tumors, infarction, and demyelination in multiple sclerosis (MS) and vascular disorders.[4,5] Globally, the annual incidence of trigeminal neuralgia is estimated to be 12.6 per 100,000 person-years.[4] In Canada, about five out of every 100,000 people are diagnosed with trigeminal neuralgia each year.[3]

Pharmacotherapy is first-line treatment for the management of trigeminal neuralgia, with about 75% of patients responding well to medication.[2,6] In Canada, medications used to treat trigeminal neuralgia include carbamazepine, oxcarbazepine, gabapentin, phenytoin and baclofen.[3] However, pharmacotherapy is ineffective in some patients, and in others, the pain becomes either refractory to medication with time, or the patients are intolerant of the side effects of the medications.[1] Surgical intervention may be appropriate for patients whose trigeminal neuralgia pain is intractable to medical therapy, and those who are intolerant to the adverse effects of the medications. Surgical interventions may also be appropriate for patients in whom previous procedures failed, or those having recurrent pain after previous successful surgery.[3,7]

Surgical interventions for trigeminal neuralgia aim to either relieve compression that causes abnormal nerve activity leading to pain (nerve preserving), or destroy selective pain fibers (nerve damaging). Currently, microvascular decompression (MVD), which involves placing a patch of Teflon between the vascular structure and the offending nerve root, is the only nerve preserving surgical procedure for trigeminal neuralgia. Destructive procedures either apply radiation on the nerve root (as in Gamma knife surgery), or involve percutaneous application of

chemicals (glycerol or alcohol), balloon compression, or electricity induced by radiofrequency to damage the offending nerve.[3,7]

The aim of this review is to summarize evidence of the clinical effectiveness and cost-effectiveness of surgical interventions for trigeminal neuralgia to support treatment decisions.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of surgical interventions for adult patients with trigeminal neuralgia?

2. What is the cost-effectiveness of surgical interventions for adult patients with trigeminal neuralgia?

KEY FINDINGS

In general, surgical interventions that were compared in each study had comparable clinical effectiveness to relieve symptoms of trigeminal neuralgia. In one study[8] percutaneous radiofrequency thermocoagulation (PRFT) showed a significantly higher rate of pain relief than percutaneous retrogasserian glycerol rhizolysis (PRGR). One study reported that whereas pain relief was immediate with PRGR, pain relieve with gamma knife radiosurgery (GKRS) was achieved over a median of six months. A conclusive determination could not be made about the comparative clinical effectiveness of the surgical interventions due to the differences in study designs, populations, settings, interventions that were compared, and the outcomes of interest of each study. Both radiofrequency rhizotomy (RFR) and partial sensory rhizotomy (PSR) were found to be more cost-effective than microvascular decompression (MVD) and stereotactic radiosurgery (SRS).

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1 2011 and March 8 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adult patients with trigeminal neuralgia requiring surgical intervention
Intervention	Surgical interventions for trigeminal neuralgia, including: • Microvascular decompression (MVD) • Partial sensory rhizotomy (also known as Dandy procedure) • Percutaneous rhizotomy (e.g., glycerol injection, balloon compression, radiofrequency thermocoagulation) • Rhizotomy with stereotactic radiosurgery (e.g., LINAC-based, gamma knife) • Peripheral procedures (e.g., neurectomy, cryotherapy, peripheral injections)
Comparator	Surgical interventions compared with each other
Outcomes	*For research question 1:* Clinical benefit (e.g., pain relief) or harms (e.g., adverse events of surgical procedures, including: dysesthesia, paresthesia, hypoesthesia, anesthesia dolorosa, masseter dysfunction) *For research question 2:* Cost-effectiveness (e.g., ICER, cost-benefit ratios) and budget impact analysis outcomes
Study Designs	Health Technology Assessments /Systematic Reviews/Meta-Analyses, Randomized Controlled Trials, Non-Randomized Studies, Economic Evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Studies were also excluded if they had non-comparative designs, were presented as narrative reviews, assessed different techniques of the same surgical intervention without comparison to any other surgical modality, or used a design not permitting a direct comparison between individual modalities.

Critical Appraisal of Individual Studies

The included non-randomized studies were critically appraised using Downs and Black checklist, [9] while economic analyses were assessed using the Drummond checklist.[10] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 601 citations were identified in the literature search. Following screening of titles and abstracts, 572 citations were excluded and 29 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of these 31 potentially relevant articles, 22 publications were excluded for various reasons, while nine publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study Design

A total of nine non-randomized studies were included in this review.[2,4-6,8,11-14] Seven studies,[4-6,8,11,13,14] reported clinical effectiveness outcomes and two studies[2,12] reported cost-effectiveness outcomes.

Each of three studies[5,11,14] retrospectively analyzed medical records of patients treated for trigeminal neuralgia from single centers. One study[4] analyzed a nationwide database of hospital records while another study[6] conducted telephone interviews to collect data from patients who had previously undergone surgical interventions for trigeminal neuralgia. It was not specified in the latter study[6] whether the patients interviewed were from a single-center or multiple centers. The two prospective studies[8,13] were single-center studies.

One economic study[2] retrospectively reviewed data spanning a ten-year period (2003 to 2013) to determine the cost-effectiveness of the surgical interventions used to treat trigeminal neuralgia in patients of a single provider at a single academic institution. Another economic study[12] analyzed a sample of the USA national Medicare claims data for 2011 in conjunction with a literature review to assess the usage, effectiveness, and cost-effectiveness of three different surgical interventions for trigeminal neuralgia.

Country of Origin

The clinical outcome studies were conducted in Brazil,[13] Canada,[14] China,[5] India,[8] The Netherlands,[4] Sweden,[11] and the United States of America (USA).[6] Both economic studies were conducted in the USA.[2,12]

Patient Population

Six clinical outcome studies [4-6,8,11,14] limited participation to patients who underwent first-time surgical intervention for trigeminal neuralgia. The other clinical outcome study[13] did not include previous surgical intervention as an exclusion criteria and did not report whether any of the patients had previously been surgically treated for trigeminal neuralgia.

Clinical outcome studies

One study,[11] included 206 patients with a mean age in treatment groups ranging from 68.7 to 71.5 years. Fifteen percent (15%) of the patients had secondary trigeminal neuralgia due to MS. The duration of their trigeminal neuralgia symptoms was not reported. Another study[5] included 105 patients with idiopathic trigeminal neuralgia. They ranged in age from 34 to 73 years, and the median duration of symptoms was 5.8 years (range 1 to14 years). In one study,[13] 78 patients with idiopathic trigeminal neuralgia with a mean age in treatment groups ranging from 49.17 to 61.97 years were included. The mean duration of the disease was 6.0 years. Thirty healthy controls, matched by age and sex, were included to assess discrete sensory deficits which can occur in the natural history of trigeminal neuralgia even in patients who do not undergo surgery. One study[6] included 49 patients with mean ages for the intervention groups ranging from 61.3 to 63.9 years. The duration of disease symptoms prior to study was not reported. In another study,[14] 45 patients with MS-related trigeminal neuralgia, ranging in age

from 41 to 79 years were included. The duration of disease symptoms ranged from a year to 14.7 years (range 12 to 276 months). One study[8] included 79 patients , three of whom had trigeminal neuralgia secondary to MS.[8] The age of the patients ranged from 28 to 83 years, with duration of disease symptoms ranging from 61.4 to 64.0 months. One study,[4] involved 672 patients with average age of 65.8 years. No details of disease symptom duration were reported.

Economic study

One study,[2] included data from a total of 89 patients with mean age of patients for each procedure ranging from 53.9 to 76.2 years. Another study[12] analyzed data from 94 patients who underwent surgical intervention. For this study[12] age was reported by age groups and presented. In the MVD group, 58.3% of the patients were between 65 and 69 years. Most patients (92.3%) in the SRS group of were ≥75 years, while 57.1% of patients in the PSR group were >74 years. None of the economic studies[2,12] reported on duration of disease symptoms.

Interventions and Comparators

Clinical outcome studies

In one study,[11] patients underwent treatment with percutaneous balloon compression (PBC) (n=82) or percutaneous retrogasserian glycerol rhizolysis (PRGR) (n=126). In the PBC procedure, a balloon catheter was inserted into the oval foramen and inflated with 0.3 to 0.8 mL iohexol to 300 mg/mL pressure, which was sustained for 1.5 to 3 minutes before being released. In the PRGR group, 0.20 to 0.35 mL anhydrous glycerol was injected within the Meckel cave, while the patients were awake and in a sitting position which they maintained for an hour. Patients in each intervention group received a follow-up evaluation 1 to 3 days after surgery and at an outpatient visit 3 to 6 months after surgery.

In another study,[5] patients were assigned to a nerve combing (NC) (n=50) or percutaneous radiofrequency thermocoagulation (PRFT) (n=55) procedure. The NC procedure involved longitudinally splitting the branches of trigeminal nerve according to preoperative pain locations and intraoperative findings using a special fiber knife. The PRFT procedure involved introducing a special needle into the foramen ovale to heat the trigeminal ganglion with a radiofrequency probe for 70 to 100 seconds to produce a partial lesion.

The patients in one study[13] underwent treatment with microvascular decompression (MVD) (n=18), PBC (n=30), or carbamazepine (n=30). To address the specific question of the review, this report has been limited to issues related to the surgical interventions only. All patients had been treated with anticonvulsants and had been receiving between 600 and 1200 mg/day of carbamazepine in the prior 6 months. In the MVD procedure, the blood vessel in the vicinity of the offending trigeminal nerve was mobilized and the nerve decompressed. The PBC procedure was performed by introducing a balloon through the foramen ovale to the trigeminal ganglion and inflating it to apply pressure for a minute before removing it. Follow-up evaluations were conducted immediately (mean 7 days) after treatment, 30 days (± 7 days) after the treatment, and 6 months (± 14 days) after the treatment.

One study[6] treated patients with gamma knife radiosurgery (GKRS) (n=49) or MVD (n=20). No details were provided about the procedures. The median duration of follow up was 5.3 years.

In another study,[14] patients underwent treatment with GKRS (n=27) or percutaneous retrogasserian glycerol rhizotomy (PRGR) (n=18). In the GKRS procedure, the trigeminal nerve was irradiated with a maximum radiation dose of 80 to 90 Gy after which the patients were

observed for 30 minutes and then discharged on the same day.[14] In the PRGR procedure, between 0.4 and 1.0 ml of 99% pure glycerol was slowly injected into the Meckel cave, and the patients were kept in the sitting position for 2 hours. Patients were discharged from the hospital on the following day. The median follow-up time after GKRS was 39 months (range 13 to 69 months) and the median follow-up time after PRGR was 38 months (range 2 to 75 months).

In another study,[8] patients underwent treatment with either PRGR (n=40) or PRFT (n=39). In the PRGR procedure, 0.3 mL of freshly prepared anhydrous glycerol was deposited into the trigeminal cistern while the patient was in a sitting position. In the PRFT procedure, radio-frequency induced heat of 60 ^{o}C to 80 ^{o}C was administered to the offending trigeminal nerve for 60 seconds with the patients in supine position. All patients in both intervention groups were discharged on the same day. The median duration of follow-up was 30 months (range, 3 to 54 months) in the PRGR group and 24 months in the PRFT group (range, 3 to 60 months).

In one study,[4] patients underwent treatment with either PRFT, MVD, or partial sensory rhizotomy (PSR). Patients were followed-up for a 1-year period, or until they were readmitted for a complication or repeat procedure involving any of the 3 modalities, whichever came first.

Economic study

One study[2] assessed the cost-effectiveness of MVD (n=27), PRFR(n=23), and SRS(n=39) to treat trigeminal neuralgia. Patients treated with PRFR and SRS were discharged the same day, whereas patients who underwent MVD were discharged the following day. Another study[12] evaluated the cost-effectiveness of MVD (n=48), PSR (n=39), and SRS (n=7). In each of the economic studies,[2,12] actual cost considerations were assessed up to the time patients were discharged from hospital. However, recurrence of pain requiring further treatment was considered in the overall cost-effectiveness assessment.

Outcomes

Clinical outcome studies

The most commonly reported outcome measure was pain relief which was reported by five studies.[5,6,8,11,14] One study[11] only reported a pain-free outcome, which was defined as the patient being completely free, without medication, from trigeminal pain. Two studies[6,14] reported a pain outcome assessed with the Barrow Neurological Institute (BNI) Pain Scale, in which the following scores apply: I, no trigeminal pain with no medication; II, occasional pain that requires no medication; IIIa, no pain and medication is used; IIIb some pain, which is adequately controlled using medication; IV, some pain, which is not adequately controlled using medication; and V, severe pain that has no relief even with medication.[14] One study[5] assessed pain relief according to a tool based on the criteria established by the University of California at San Francisco and graded outcomes as “satisfactory”; “pain free, recurrence”; and “poor”. “Satisfactory” referred to when patients reported complete pain relief without the need for medication or intermittently needing medication for pain. “Pain free, recurrence” referred to if patients first experienced complete pain relief for at least one month after operation, but subsequently had a recurrence of pain. Pain relief was designated as poor if patients reported little or no pain relief, or experienced persistent pain despite medication. In one study[8] pain relief after the procedure was graded as “excellent, complete pain relief and no medications required”; “good, medications needed at a reduced dose for adequate pain relief”; and “poor, when pain persisted despite full pre-procedure medications”.

One study[13] reported sensory thresholds and masticatory function outcomes as determined by Helkimo indices, and a quantitative sensory-testing protocol. The Helkimo index is a validated tool consisting of a questionnaire that rates the dental occlusion, mandibular movements and their limitations, and clinical dysfunction of and complaints about the masticatory function.[13] The study[13] also reported quality of life outcomes using Research Diagnostic Criteria for temporomandibular disorders (RDC/TMD Axis II). The RDC/TMD Axis II tool consists of a protocol for the evaluation of associated emotional and functional aspects including depression, anxiety symptoms, and mandibular limitations.[13] Another study[4] reported complications and treatment failure leading to hospital readmission within one year of the initial admission. Complications included hospitalizations for hearing loss, dysesthesia, persistent neurological deficit, death, cerebrospinal fluid leakage, facial hypoesthesia, facial asymmetry among many others.[4] Appendix 4 Table A5 provides a summary of the main outcomes of the individual studies.[4-6,8,11,13,14]

Economic study

Cost-effectiveness was the outcome of interest in all three economic studies.[2,12,15] In one study,[2] this was calculated by dividing the average total costs of the operation, including hospital fees, surgeon fees, fees surrounding complications, and cost of secondary procedures, by the quality adjusted pain-free years (QAPFY). The QAPFY was calculated by multiplying the length of last known follow-up or time to next surgical intervention by an outcome-based adjustment factor defined as follows: excellent (1.0), good (0.7), fair (0.5), or poor (0.1). In another study,[12] the cost-effectiveness was defined as the ratio of weighted cost per procedure to quality-adjusted life years (QALYs). The QALY is a measure of health care outcomes reported as a value from 0 to 1, where 0 corresponds to death and 1 corresponds to a year of life lived in perfect health, defined in this study[12] as the time when a patient is pain-free without medication or equivalent to the BNI pain scale score of 1.

Summary of Critical Appraisal

All the included studies[2,4-6,8,11-14] had clearly defined objectives, inclusion and exclusion criteria, and the details of the intervention being compared. In addition, the outcomes of interest and the main findings of the study were clearly described. The authors in each study[2,4-6,8,11-14] declared that they had no conflicts of interest in relation to the research and/or its publication. One prospective study[13] reported that all patients completed the 6-month study period and participated in the end-of-study evaluation period. Thus, there was a high potential for complete data to permit rigorous analyses. In addition, the entire evaluation in this study[13] was performed by the same examiner to minimize the potential for bias. In another study[14] data were collected by a physician who was not directly involved in the patients' care, thus reducing the potential for bias.

The two economic studies[2,12] considered both cost and effects of the alternative surgical interventions. They described the competing interventions clearly alone with clinical outcome measures of interest. One cost study[12] used a healthcare system perspective, whereas the perspective of the other study[2] was not specified.

All the studies used a non-randomized design and the potential for incomplete availability of data, misclassification, recall bias, and other confounding factors to influence the reported findings was high. For instance, the protocol for allocating patients to particular interventions was not reported in many studies. Where it was reported, three studies[5,8,14] stated that allocation was based on clinician and/or patients' preference, while two studies[4,13] reported a tendency to

assign statistically significantly younger patients to one intervention (MVD). Therefore, there were selection biases that may have influenced the outcomes reported for the interventions that were investigated.

One study[11] analyzed two consecutive cohorts with data collected from 1986 to 2000 for the first and 2000 to 2013 for the second. Thus the potential for variability in techniques, settings, and general patient care to influence the results cannot be ruled out. Further, none of the studies[2,4,5,8,11-14] performed any calculation to determine the appropriate sample size for their investigations. Therefore, it is unknown if any of the included studies[2,4-6,8,11-14] was sufficiently powered to detect relevant difference between the interventions which were compared.

None of the economic studies[2,12] adjusted (discounted) cost values for different time horizons, and no sensitivity analyses were conducted to assess the robustness of the findings reported by any of the studies.[2,6]

Only one of the included studies was conducted in Canada,[14] with the rest performed in Brazil,[13] China,[5] Europe,[4,11] India,[8] and the USA.[2,6,12] Therefore, for the majority of studies it is unknown if their findings are generalizable to the Canadian population. Moreover, the study conducted in Canada[14] was a single-center study with only 45 patients, all of whom had trigeminal neuralgia secondary to multiple sclerosis and unlikely to be representative of the general population of patients who suffer from trigeminal neuralgia. Thus the generalizability of the study findings beyond the study population is uncertain.

Summary of Findings

1. *What is the clinical effectiveness of surgical interventions for adult patients with trigeminal neuralgia?*

Seven studies[4-6,8,11,13,14] reported clinical outcomes for a total of seven surgical interventions for trigeminal neuralgia; namely, microvascular decompression (MVD), percutaneous balloon compression (PBC), percutaneous retrogasserian glycerol rhizolysis (PRGR), percutaneous radiofrequency thermocoagulation (PRFT), gamma knife radiosurgery (GKRS), partial sensory rhizotomy (PSR), and nerve combing (NC) procedure.

Clinical benefits

One study[11] found no significant difference between the effectiveness of PBC and PRGR to relieve trigeminal neuralgia pain. The initial pain relief rate was 82% for PBC and 85 % for PRGR, with median duration of pain relief of 20 months and 21 months after PBC and PRGR procedures, respectively. In one study,[13] a visual analog scale (VAS) evaluation of pain intensity after six months following surgical intervention showed that all patients who underwent PBC had complete pain relief whereas those treated with MVD had VAS pain intensity reduced from 7.22 ± 2.86 at baseline to 2.4 ± 4.06. There were no significant differences in emotional and quality of life, as measured by RDC indices, between the PBC and MVD groups, with both groups showing significant reduction from baseline in the degree of pain severity ($P < 0.001$), depression trait ($P = 0.006$), and mean of mandibular limitations ($P < 0.001$).

One study[6] compared MVD to GKRS and found that although the trend favored MVD, there was no significant difference between the two procedures with regards to initial pain relief and recurrence of pain after initial relief. All the patients (100%) who underwent MVD had initial pain

relief compared with 84% of patients who underwent GKRS (*P* = 0.055), and recurrence of pain after initial relief occurred in 20% of patients in the MVD group compared with 38.8% in the GKRS group (*P* = 0.133). However, at last the follow-up (median follow up of 5.3 years), a significantly greater proportion of patients in the MVD group (85%) had total pain relief (BNI scale I) compared with 44.9% of patients in the GKRS group (*P* = 0.002). There was no significant difference in patients' satisfaction with the two procedures, with 90% and 69.4% in the MVD and GKRS, respectively, indicating they would undergo the same procedure again (*P* = 0.19), while 95% and 83.7%, respectively, would recommend the procedure to family members (*P* = 0.205).

One study[14] compared GKRS and PRGR and found that 81.5% of patients who underwent GKRS achieved reasonable pain control (defined as BNI pain scale scores of I to IIIb) compared 100% of those who underwent PRGR. Pain relief was immediate with PRGR procedure, but was achieved over a median of 6 months for patients who underwent GKRS. As of the last follow-up, 85.2% of patients who underwent GKRS had achieved complete or reasonable pain control compared with 88.9% of those who were treated with the PRGR procedure. The statistical significance of this difference was not reported.

One study[8] compared PRGR with PRFT and found a significantly higher proportion of patients who underwent PRFT experienced "excellent" pain relief compared with those who underwent PRGR (84.6% versus 58.9%, *P* < 0.05). However, there was no significant difference between the two treatments with regards to proportion of patients who did not require any medication until the end of the study period (35% in the PRGR group and 41% in the PRFT group, *P* > 0.05). The mean duration of "excellent" pain relief in the PRGR (24 ± 15 months) was comparable to the duration in the PRFT groups (28.7 ± 18.7 months). At the end of the first year, significantly greater proportion of patients in the PRFT group had excellent pain relief compared with those in PRGR group (78.8% versus 65%; *P* < 0.05). However, recurrence of pain after initial relief was higher among patients treated with PRFT (51.5%) compared with those who underwent PRGR (39.1%).

One study[5] compared PRFT and NC and reported that both were effective at relieving trigeminal neuralgia symptoms without statistically significant differences in measured outcomes between the two procedures. Satisfactory symptom relief was achieved in 82% of patients who underwent NC compared 76.4% of patients who underwent PRFT (*P* > 0.05). Initial pain relief with recurrence occurred in 10% of patients in the NC group compared with 4.5% of patients in the PRFT group (*P* > 0.05).

Complications and adverse events

Five studies[4,5,8,11,14] reported harms outcomes. One study[4] compared MVD, PSR and PRFT for the risk of readmission for repeat procedure or complication. The overall relative risk (RR) of readmission in one year was lowest with MVD (RR = 0.09; 95% CI: 0.03, 0.15) and highest for PRFT (RR = 0.38; 95% CI: 0.34, 0.42). The PSR procedure had a relative risk of 0.15 (95% CI: 0.04, 0.47) for readmission after surgery. The risk of readmission for complication was lowest with PRFT (RR = 0.02; 95% CI: 0.01, 0.03) followed by MVD (RR = 0.06, 95% CI: 0.01, 0.11) and PSR (RR = 0.08; 95% CI: 0.0, 0.16). The significance of these differences was not reported.

One study[5] reported that overall, there were no significant differences in surgery-related complications between the PRFT procedure than NC (*P* > 0.05). Observed postoperative

morbidity included dysesthesia, diplopia, and partial facial nerve palsy, hearing loss, tinnitus, cerebrospinal fluid leak, meningitis and mortality. Dysesthesia and facial nerve palsy was reported to have occurred significantly more frequently with the PRFT procedure than NC ($P < 0.05$). One study[8] reported that the most common side effect observed after treatment with PRFT and PRGR was minor hypesthesia which occurred in 79% and 75% of patients in the two groups, respectively, and did not require any treatment. No major complications were observed during the study period in any group, and there was no significant difference in proportion of patients who underwent a second procedure (20.5% in PRFT versus 22.5% in PRGR; $P > 0.05$).[8]

One study[14] reported higher rate of complications with PRGR (66.7%) compared with GKRS (22.2%). All the complications in the GKRS group were due to sensory loss and paresthesia, whereas in the PRGR group, complications were mostly due to hypalgesia, with corneal reflex loss reported in two patients (11%) while one patient (5.6%) suffered meningitis due to infection. Dysesthesia was significantly more common after PRGR than after PBC (23% versus 4%; $P < 0.001$), and decreased corneal sensibility was common after PRGR but not after PBC ($P < 0.001$).

2. *What is the cost-effectiveness of surgical interventions for adult patients with trigeminal neuralgia?*

One study,[2] found that compared with MVD and SRS, radiofrequency rhizotomy (RFR) was the most cost-effective procedure tor trigeminal neuralgia. The procedure had the lowest average total costs (US$4,700 ± 2,200), the highest, mean quality adjusted pain-free years (QAPFY; 2.28), and the longest average time to secondary procedure(59 ± 76 months). The cost-effectiveness in this study calculated as the ratio of the average total costs of the operation to QAPFY, was US$2100 for RFR compared with US$31,800 for MVD and US$39,600 for SRS ($P < 0.001$). One study[12] found that PSR had the lowest (US$3,911) average weighted cost compared with MVD (US$40,434.95) and SRS (US$38,062). Although the MVD procedure had the highest QALYs of 8.2 followed by PSR (6.5) and SRS (4.9), PSR was the most cost-effective procedure (cost per QALY) at U$602 compared with MVD (US$4,931), and SRS (US$7,768).

Limitations

The literature search did not retrieve any systematic reviews/meta-analysis or randomized studies that met the inclusion criteria for this review. Thus, with all the included studies[2,4-6,8,11-14] having non-randomized designs, the potential for bias due to lack of relevant data, misclassification, recall bias, and other confounding factors is high. Three studies[5,8,14] reported that treatment allocation was based on clinician and/or patients' preference, while three studies[2,4,13] reported a tendency to assign statistically significantly younger patients to one intervention (MVD). These were sources of selection bias that may have influenced the outcomes reported for the interventions that were investigated. Treatment allocation in the other studies was not adequately reported. For one study,[11] the period (1986 to 2000) over which data were collected for analysis was very long; suggesting a high potential for variability in techniques, settings, and general patient care, which could influence the reported outcomes. However there was no adjustment for these potential confounding factors. Further, since none of the studies[2,4,5,8,11-14] provided any *a priori* justification of the sample sizes used, it is unknown if any were sufficiently powered to detect relevant differences between the interventions they compared. Finally, the generalizability of the findings from these studies in Canada is unknown

since only one study[14] was conducted in Canada. Even so, this study was a single-center study involving only 45 patients with secondary trigeminal neuralgia due to multiple sclerosis. Therefore, the study population was unlikely to be representative of the general trigeminal neuralgia patient population, and thus may not be generalizable beyond the study sample. None of the economic studies[2,12] adjusted (discounted) cost values for different time horizons, and no sensitivity analyses were conducted to assess the robustness of the findings reported by any of the studies.[2,6]

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Three studies[4,6,13] compared microvascular decompression (MVD) with other surgical interventions for trigeminal neuralgia. In one study,[6] there were no significant differences in pain and patient satisfaction when MVD was compared with GKRS. In another study,[13] there was no significant difference in pain when MVD was compared with PBC. Although each of the two surgical procedures reduced myofascial and jaw articular complaints, and caused an increase in thermal thresholds, PBC decreased masticatory function and mobility to a greater extent than MVD. One study[4] found that MVD was associated with the lowest risk of readmission for lower risk of repeat procedure compared with partial sensory rhizotomy (PSR) and percutaneous radiofrequency thermocoagulation (PRFT). However, PRFT had the lowest risk of complications requiring hospital readmission compared with MVD and PSR. One study[5] demonstrated that both PRFT and a nerve combing (NC) procedure had similar pain relief rates, recurrent rates and complications. Although the overall surgery-related complications were similar between PRFT and NC, dysesthesia and facial nerve palsy were reported significantly more frequently with PRFT than NC, and the incidences of sensory and facial palsy morbidity were significantly higher with NC than PRFT ($P < 0.05$). Another study[8] showed that a significantly higher proportion of patients treated with PRFT experienced excellent pain relief compared with those who were treated with percutaneous retrogasserian glycerol rhizolysis (PRGR). However, the mean duration of pain relief was similar among all patients in the study, and the rates of pain recurrence after two years were not statistically significantly different between PRFT and PRGR. Incidence of adverse events was comparable between the two procedures, with minor hypesthesia which did not require any treatment being the most common. One study[11] reported similar effectiveness of PBC and PRGR to achieve complete pain relief associated with trigeminal neuralgia. The risk of dysesthesia and decreased corneal was significantly more common after PRGR than after PBC ($P < 0.001$ for both comparisons). One study[14] showed both PRGR and GKRS were effective procedures to achieve reasonable pain control (defined as BNI pain scale scores of I to IIIb) in trigeminal neuralgia patients, with PRGR resulting in immediate pain relief while GKRS achieved pain relieve over a median of six months. Although the statistical significance in the difference was not reported, there was a trend towards a higher proportion of pain relief among patients who underwent GKRS, and a higher rate of complications was reported with PRGR than GKRS.

With regards cost-effectiveness of surgical interventions for trigeminal neuralgia, one study,[2] found radiofrequency rhizotomy (RFR) to be the most cost-effective compared with MVD and SRS while one study[12] found that PSR was the most cost-effective procedure compared with MVD and stereotactic radiosurgery (SRS).

Therefore, in general, the clinical effectiveness of the various surgical interventions to relief symptoms of trigeminal neuralgia seemed to be similar in the included studies, with the exception being one study[8] in which a significantly higher proportion of patients who underwent PRFT experienced greater pain relief than those who underwent PRGR. However, given the

differences in study designs, populations, settings, interventions that were compared, and the outcomes of interest of each study, it is difficult to determine conclusively from this review whether one surgical procedure has a better comparative clinical effectiveness than any other. No major adverse events or complications were reported in any of the studies. In terms of cost-effectiveness, both RFR and PSR were found to be more cost-effective than MVD and SRS.

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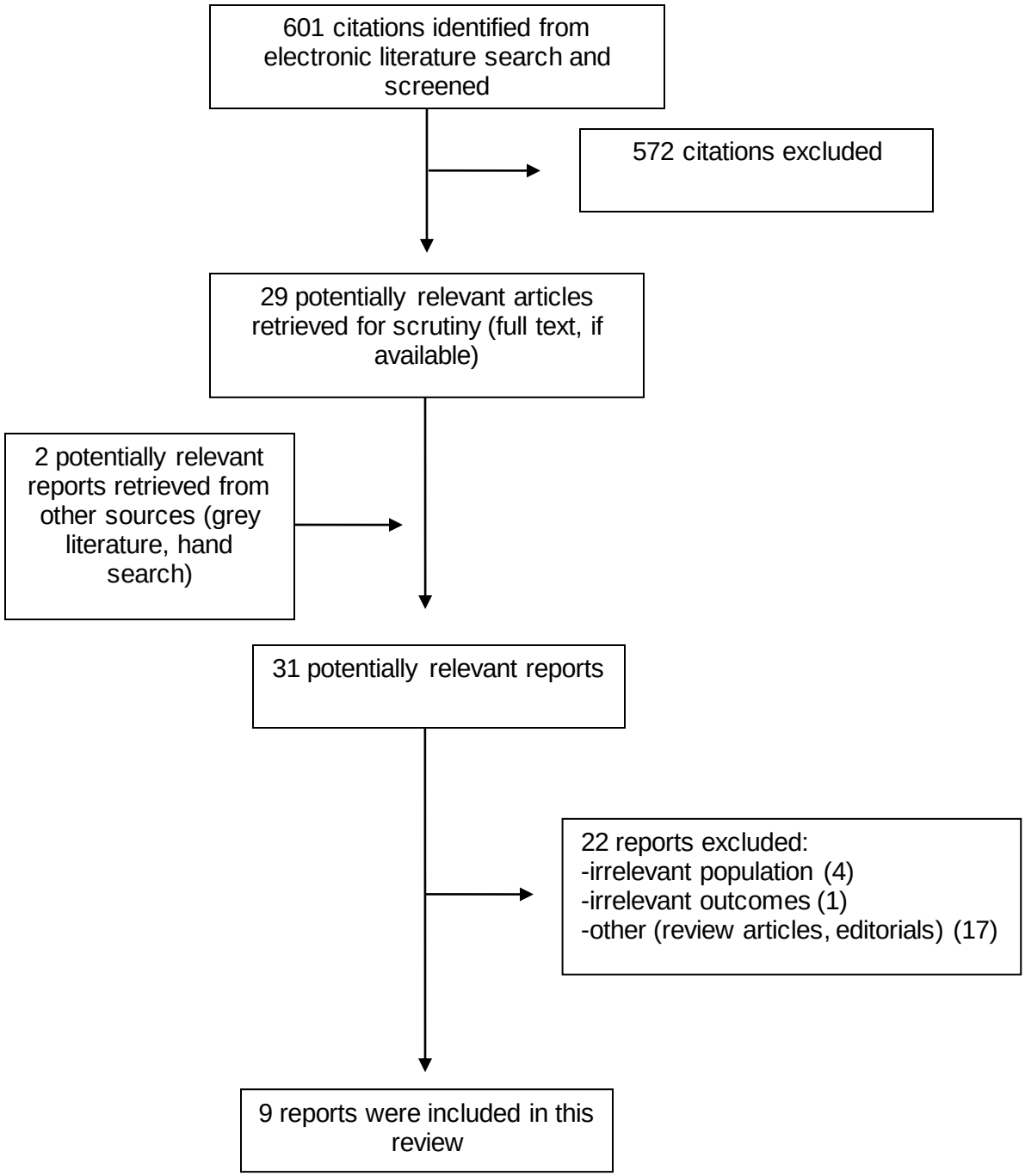
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Asplund, 2016[11] Sweden	A retrospective cohort comparison study	A total of 206 TN patient in two consecutive cohorts who underwent surgical treatment from 1986 to The mean age ranged from 68.7 years to 71.5 years across the intervention groups	Percutaneous balloon compression	Percutaneous retrogasserian glycerol rhizolysis	Duration of pain relief, frequency of sensory disturbances, and side effects.
Zhou, 2016[5] China	Retrospective study	A total of 105 patients with iTN which had failed to respond adequately to treatment with medication (carbamazepine). The median age ranged from 48.9 ± 8.6 years to 49.3 ± 8.7 years across the intervention groups. The median duration of symptoms was 5.8 years (range 1 to 14 years).	Percutaneous radiofrequency thermocoagulation	Nerve combing	Pain relief, recurrence, complication and need for additional treatment
			The follow-up period ranged from 48 to 168 months with a median duration of 90 months in both groups		
Ichida, 2015[13] Brazil	Prospective study/ case-controlled longitudinal study	A total of 78 patients with iTN. The mean age ranged from 49.17 ± 13.16 years to 61.97 ± 10.98 years across intervention groups. The mean duration of the symptoms was 6.0 ± 5.4 years. The mean pain intensity on a VAS scale ranged from 7.22 ± 2.86 to 8.12 ± 1.9 across intervention groups.	Microvascular decompression [a]	Balloon compression [a]	Sensory thresholds and masticatory function

Table A1: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Nanda, 2015[6] USA	Retrospective study	A total of 69 patients who had previously undergone surgical procedure to treat TN were included in the study. The median age ranged from 61.3 years to 63.9 years across intervention groups.	Microvascular decompression	Gamma knife radiosurgery	Pain relief status and patient satisfaction rates as measure by likelihood to: • Elect to undergo the same procedure again, • Recommend the procedure to family and friends
			The median follow up was 5.3 years.		
Mathieu, 2012[14] Canada	Retrospective study	A total of 45 patients with MS-related TN. Age of ranged from 41 years to 79 years and the duration of disease symptoms ranged from 12 months to 276 months.	Gamma Knife surgery The median duration of follow-up was 39 months (range: 13 to 69 months).	Percutaneous retrogasserian glycerol rhizotomy. The median duration of follow-up was 38 months (range: 2 to 75 months)	Pain relief (on BNI Pain Scale), procedure-related morbidity, time to pain relief and recurrence, and subsequent procedures that were performed
Udupi, 2012[8] India	Prospective study	A total of 79 TN patients including 76 with iTN as well as those with TN secondary to MS (n-1) and brain tumor (n=2) were included in the study. Age ranged from 28 years to 83 years and the majority (56.9%) was men. The duration of TN symptoms ranged from 64.0 ± 51.5 to 61.4 ± 61.3 months.	Percutaneous anhydrous glycerol rhizolysis. The median duration of follow-up was 30 months (range, 3 to 54 months)	Radiofrequency (RF) thermocoagulation. The median duration of follow-up was 24 months (range, 3 to 60 months).	Pain relief, duration of pain relief, and side effects.

Table A1: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Koopman 2011[4] The Netherlands	A retrospective analysis of a national registry database	672 patients treated surgically for TN. The mean age was 65.8 ± 13.4 years,	Percutaneous radiofrequency thermocoagulation	Partial sensory rhizotomy (PSR), and microvascular decompression	Primary outcome was readmission for repeat procedures for TN or known complications within 1 year

BNI = Barrow Neurological Institute; GKS= Gamma Knife surgery; iTN =idiopathic trigeminal neuralgia; MS = multiple sclerosis; PBC = percutaneous balloon compression; PRGR = percutaneous retrogasserian glycerol rhizolysis; QALYs = quality adjusted life years; TN = trigeminal neuralgia; USA United States of America.

[a] Although the study compared the outcomes from these surgical intervention with outcome from treatment with carbamazepine, data reporting and discussion have been limited to outcomes of surgical procedures to answer the specifics questions of this review.

Table A2: Characteristics of Included Cost Studies

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Holland, 2015[2] USA	Cost-effectiveness analysis (ratio of average total cost per procedure to QAPF). The perspective was not specified.	Microvascular decompression, percutaneous radiofrequency rhizotomy, and stereotactic radiosurgery compared to each other	89 surgically naïve patients with TN. The majority (62%) was female and the average age of patients ranged from 53.9 ± 16 to 76.2 ± 16 years, with patients who underwent MVD being significantly younger (P < 0.001 MVD vs. other modalities)	At least two years	QAPF is a product of last known follow-up or time to next surgical intervention and an outcome-based adjustment factor, which can range from 0.1 to 1.0 depending on the level of pain-relief
Sivakanthan, 2014[12] USA	Cost-effectiveness analysis (ratio of weighted cost per procedure to QALY). Healthcare perspective	Microvascular decompression, stereotaxic radiosurgery, and percutaneous stereotaxic rhizotomy compared with each other	Ninety-four patients who underwent surgical intervention for TN.	One year	The value QALY assumes a range from 0 to 1, where 1 is a year of life lived in perfect health and 0 is death.

BNI = Barrow Neurological Institute; GKS= Gamma Knife surgery; MS = multiple sclerosis; PBC = percutaneous balloon compression; PRGR = percutaneous retrogasserian glycerol rhizolysis; QALY = quality adjusted life years; QAPF = quality adjusted pain-free years. TN = trigeminal neuralgia; USA United States of America.

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Non-Randomized Trials using Downs and Black [9]

Strengths	Limitations
Asplund, 2016[11]	
• The objectives of the study and the details of the intervention were clearly defined • Inclusion and exclusion criteria were defined. • The main findings of the study were clearly described and probability values were properly reported. • The authors had no personal, financial, or institutional interest in drugs, materials, or devices described in this article.	• A sample size determination was not made. Therefore, it is unknown if the study was sufficiently powered to detect relevant difference between the compared intervention. • Data for the study were collected from 1986 to 2013. Thus the potential for variability in techniques, settings, and general patient care to influence the results cannot be ruled out. • Patients' medical history, such as duration of disease and length of follow-up, was not adequately reported. Differences in such parameters could be sources of bias. • The study was conducted in a University hospital in Sweden. Therefore, the generalizability of the study findings to other settings, especially in Canada is unknown.
Zhou, 2016[5]	
• The objectives of the study the inclusion and exclusion criteria, and the details of the intervention being compared were clearly defined • The main findings of the study were clearly described with estimates of variability for outcomes, where applicable. • Patients' characteristics including sex, median age, median duration of symptoms, and affected side are similar between the groups. • The authors declare no conflicts of interest.	• The retrospective nature of the study and use of questionnaires makes it subject to a recall bias and potential for incomplete availability of data from the patient charts is high. • It is unknown if the study was sufficiently powered to detect relevant difference between the compared intervention. • The treatment allocation to groups was based on clinician and patients' preference, which increased the potential of selection bias that could influence the reported outcomes for the two interventions. • The "special knife" used in the NC procedure was manufactured in-house. Couple with the fact that the study was conducted in China, it is unknown if its findings will be generalizable in Canada.
Ichida, 2015[13]	
• The objectives of the study the inclusion and exclusion criteria, and the details of the intervention being compared were clearly defined • The main findings of the study were clearly described	• There were statistically significant differences in ages with the patients in the MVD group being younger than in the PBC group • All patients were being treated with medication, which could have partially or completely alleviated the symptoms and interfered with

Table A3: Strengths and Limitations of Non-Randomized Trials using Downs and Black [9]	
Strengths	**Limitations**
with estimates of variability for outcomes, where applicable, and probability values were properly reported • All patients completed study (6 months duration) and participated in the end-of- study evaluation, with the same examiner who had been previously trained to use testing tools calibrated by the Orofacial Pain Group of the hospital conducting the entire evaluation.	the measured outcomes. • It is unknown if the study was sufficiently powered to detect relevant difference between the compared intervention. • The study was conducted in Brazil. Thus, it is unknown if its findings will be generalizable in Canada.
Nanda, 2015[6]	
• The objectives of the study and the main outcome measures were clearly described. • Patients' characteristics were similar across intervention groups, thus minimizing the potential for biases due to differences in groups. • The interventions in the study as well as the main findings were clearly described. • The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.	• No details were provided about how patients were recruited and selected for the telephone interviews of this study, and it is unknown how patients were assigned to the interventions. Therefore, the potential for selection bias and reporting bias cannot be ruled out. • In the absence of a sample size calculation, it is unknown whether the study was sufficiently powered to detect relevant difference in outcomes between the two interventions. • The findings are subjective because they are based on patient-reported outcomes obtained through telephone interviews. • Although, 121 patients of the patients who underwent the two surgical modalities for TN were alive, the investigators reported successful telephone interview was obtained with only 69. The criterial for selecting these patients as well as the extent to which they differ from the non-patients are unknown. Thus, there is uncertainty about the representativeness of the reported findings to the entire group of patients treated with the interventions. • This was a single-center study from the USA. Therefore, it is unknown whether the study findings will be applicable in other health institutions, especially in Canada.
Mathieu, 2012[14]	
• The objectives of the study the inclusion and exclusion criteria, and the details of the intervention being compared were clearly defined	• There was a high potential for selection bias because treatment was assigned according to patient and physician preference as well as the severity of the patients' pain.

Table A3: Strengths and Limitations of Non-Randomized Trials using Downs and Black [9]	
Strengths	**Limitations**
• The main findings of the study were clearly described • Data were collected by a physician who was not directly involved in the patients' care, thus reducing the potential for performance bias. • The authors reported no conflict of interest regarding the materials or methods used in this study or the specified findings.	• Data for analysis were collected by reviewing patient medical records and by phone interviews with patients. Thus potential for error and incomplete information cannot be ruled. Furthermore, patient-reported outcomes are subject to recall bias and are hence unreliable. • Neither estimates of variability for outcomes nor probability values were reported in this study • It is unknown if the study was sufficiently powered to detect relevant difference between the compared intervention.
Udupi, 2012[8]	
• The objectives of the study the inclusion and exclusion criteria, and the details of the intervention being compared were clearly defined • The main findings of the study were clearly described. • The authors had no personal, financial, or institutional interest in drugs, materials, or devices described in this article.	• The treatment was chosen by the patient therefore there is a high potential for selection bias. • Patients' data was derived from medical charts, thus the potential for errors, and incomplete availability of data was high. • It is unknown if the study was sufficiently powered to detect relevant difference between the compared intervention. • Probability values and the levels of significance were inadequately reported, with p-values stated as <0.05 or > 0.05 instead of the actual. • The study was conducted in India. Therefore, it is unknown whether the study findings will be applicable in Canada.
Koopman 2011[4]	
• The objectives of the study and the details of the intervention were clearly defined • Inclusion and exclusion criteria were defined. • The main findings of the study were clearly described with estimates of variability for outcomes, where applicable. In addition, probability values were properly reported • The authors declared no conflict of interest.	• The outcome measure was readmission for repeat procedure or complications. Therefore, treatment failures which were addressed in an outpatient setting were not captured. It was also not known whether there was a mechanism in place to follow patients who could access a second procedure in another facility besides where the primary surgery was conducted. • Patients who underwent MVD were younger than those treated with PRFT or PSR. It is unknown whether this affected the reported outcomes. • Patients' characteristics were not adequately reported and it is

Table A3: Strengths and Limitations of Non-Randomized Trials using Downs and Black [9]	
Strengths	**Limitations**
	unknown whether the lack of specific prognostic factors such as disease severity, and duration of symptoms affected the outcomes. • The study was conducted in The Netherlands. Therefore, it is unknown whether the findings will be applicable in Canada.

PBC = percutaneous balloon compression; PRGR = percutaneous retrogasserian glycerol rhizolysis; TN = trigeminal neuralgia;

Table A4: Strengths and Limitations of Economic Studies using Drummond[10]	
Strengths	**Limitations**
Holland, 2015[2]	
• The objective of the study was well-defined, and the analysis considered the both cost and effects of the alternative surgical interventions. • Description of the competing interventions was clearly provided, alone with clinical outcome measures of interest. • The authors declared no conflict of interest with regards to the content of their manuscript.	• Although the average total costs of the alternative procedures were calculated by summing the average physician fee and the average hospital fee, the viewpoint adopted for this calculation was not specified, and it is unknown whether the capital costs were factored in the fees. • The sources of the values used in costing were not specified. Thus it is unknown whether they reflect market value, patients', health professionals' or policy-makers' views. • It was not specified whether the cost were adjusted for different time horizons at all, and if so how the adjustment was done. • No sensitivity analysis was conducted to assess the robustness of the reported findings. • The generalizability of the reported findings to Canada is unknown since the study was conducted in the USA
Sivakanthan, 2014[12]	
• The objective of the study was well-defined, and the analysis considered the both cost and effects of the alternative surgical interventions. • Description of the competing interventions was clearly provided, alone with clinical outcome measures of interest. • The weighted total costs per competing	• Further, the database did not distinguish between patients who were undergoing surgical operation for the first time and those who were having repeat operation. • The data for analysis in this study was derived from 5% of the data sets for 2011, and covered a relatively small number (n=89) of patients. Therefore, the study is supposed to be based on a national database, it is uncertain whether it is truly representative of the national trigeminal neuralgia population. • Values were based on the 2011 estimates without adjustment for any other

Table A4: Strengths and Limitations of Economic Studies using Drummond[10]	
Strengths	**Limitations**
procedures were calculated from the US Medicare claims database and does assumes a healthcare perspective. • The authors declared no conflict of interest with regards to the content of their manuscript	time period. Thus it is unknown whether the reported findings are still valid in the current economy. • The QALY used in this study was retroactively calculated for each intervention based on historical case series, and did not take into consideration facial numbness. Therefore, it is uncertain whether it reflects the actual patients whose data were used in the study. • No sensitivity analysis was conducted to assess the robustness of the reported findings. The generalizability of the reported findings to Canada is unknown since the study was conducted in the USA

PBC = percutaneous balloon compression; PRGR = percutaneous retrogasserian glycerol rhizolysis; TN = trigeminal neuralgia;

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Asplund, 2016[11]	
• The initial success rate was 82% for PBC and 85 % for PRGR. The median pain-free time was 20 months. • The Median duration of pain relief was 20 months after PBC and 21 months after PRGR. • At the last follow-up, 30 patients (37%) in the PCB group and 47 patients (38%) were pain-free. • Both methods carried a high risk of hypesthesia/hypalgesia ($P < 0.001$) that was partly reversed with time. • Decreased corneal sensibility was common after PRGR ($P < 0.001$) but not after PBC. • Dysesthesia was more common after PRGR (23%) compared after PBC (4%; $P < 0.001$). Other side effects were noted but uncommon.	• "PBC and PRGR are both effective as primary surgical treatment of trigeminal neuralgia. Both carry a risk of postoperative hypesthesia, but in this series, the side effect profile favored PBC. Furthermore, PBC is technically less challenging, whereas PRGR requires fewer resources. Between these 2 techniques, we propose PBC as the primary surgical technique for percutaneous treatment of trigeminal neuralgia on the basis of its lower incidence of dysesthesia, corneal hypesthesia, and technical failures."[11] page 421
Zhou, 2016[5]	
• Both NC and RF were effective at relieving TN symptoms without statistically significant differences between treatment outcomes of the two procedures ($P > 0.05$ for all comparisons). • Among patients who underwent NC, 41 (82%) had satisfactory relief compared with 42 patients (76.4%) among patients who underwent RF. • Five patients (10%) in the NC group experienced initial pain relief with recurrence compared with eight (14.5%) of patients in the RF group. • Postoperative morbidity included dysesthesia, diplopia, and partial facial nerve palsy, hearing loss, tinnitus, cerebrospinal fluid leak, meningitis and mortality. • Dysesthesia and facial nerve palsy was reported to have occurred significantly more frequently with the RF procedure than NC ($P < 0.05$). However, with regards the surgery-related	• "Nerve combing and RF are both satisfactory treatment strategies for patients with ITN. From our analysis above, both NC and RF have similar pain relief rates, recurrent rates and complications. But NC carries higher sensory and facial palsy morbidity than RF ($p < 0.05$). In addition, NC is an open retrogasserian surgery with much higher surgical risk, com-pared to minimally invasive RF. Some elderly patients may be not suitable for this type of surgical intervention. Therefore, RF is preferable to NC in patients with ITN."[5] page 6

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
complications, there were no significant differences between the patients in the 2 groups were observed ($P > 0.05$). Details were not provided.	
Ichida, 2015[13]	
• Both MVD and PBC were effective at reducing pain intensity. Six months after procedures, patients in the MVD group had VAS pain intensity reduced from 7.22 ± 2.86 at baseline to 2.4 ± 4.06 while in the PBC group pain was completely relieved (VAS intensity 0.0) at six months compared to 8.22 ± 2.86 at baseline. • Myofascial pain, decreased from 38.9% before surgery to 22.2% after MVD and from 20% to 10% after PBC. • Patients in the MVD group showed significant post-surgery improvement as assessed with Helkimo indices ($P < 0.003$), as well as increased sweet ($P = 0.014$) and salty ($P = 0.003$) thresholds. • Although both MVD and PBC resulted in decreased sour threshold ($P = 0.003$) and increased cold and warm thresholds ($P < 0.001$), only the patients who underwent PBC had an increase in touch threshold ($P < 0.001$). • Differences between the MVD and PBC groups in emotional and quality of life indices were not statistically significant, with both groups showing significant reductions in the degree of pain severity ($P < 0.001$), depression trait ($P = 0.006$), and mean of mandibular limitations ($P < 0.001$).	• "Microvascular decompression and BC resulted in a reduction in myofascial and jaw articular complaints, and the impact on masticatory function according to Helkimo indices was greater after BC than MVD. MVD resulted in more gustative alterations, and both procedures caused impairment in thermal thresholds (warm and cold). However, only BC also affected touch perception. The sensorial and motor deficits after BC need to be included as targets directly associated with the success of the surgery and need to be assessed and relieved as goals in the treatment of iTN."[13] Page 1315 • "MVD and BC resulted in a decrease in myofascial and jaw articular complaints, and the impact on the masticatory function and mobility was greater after BC than MVD. Myofascial pain relief with a surgical procedure should indicate that this pain could be an effect of central sensitization by chronic pain and iTN. On the other hand, MVD resulted in more gustative alterations, and both procedures caused an increase in thermal thresholds (warm and cold), although only BC also affected touch perception. The numbness complaint of patients who underwent BC is more likely associated with abnormal touch perception, but MVD can also affect small fibers related to temperature and therefore also causes sensory disturbance. Despite the fact that none of the patients in the BC group experienced pain again after 6 months, 2 patients had pain recurrence after MVD, but this was not a statistically significant difference. The sensorial and motor deficits after BC need to be included as targets directly

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
	associated with the success of the surgery and need to be assessed and relieved as a goal in the treatment of iTN."[13] Page 1322
Nanda, 2015[6]	
• Initial assessment showed that all 20 patients (100%) who underwent MVD had pain relief compared with 41 (84%) of patients who underwent GKRS. The difference was not statistically significant (*P*=0.055). • Recurrence of pain after initial relief occurred in four (20%) patients in the MVD group compared with 19 patients (38.8)% in the GKRS. The difference was not statistically significant (*P*=0.133). • At last follow up (median follow up was 5.3 years), a significantly greater proportion of patients in the MVD group (85%) had total pain relief (BNI scale I) compared with 44.9% of patients in the GKRS group (*P*=0.002). • There was no significant difference in the patient satisfaction rate between the two groups. 90% and 69.4% of patients indicated they would undergo the same procedure again in the MVD and GKRS, respectively *(P*=0.19); and 95% and 83.7% in the MVD and GKRS groups, respectively, would recommend the procedure to family members (*P*=0.205).	• "From our study, MVD offered total pain relief in significantly higher number of patients than GKRS. There was no significant difference in the rates of patient satisfaction between the two groups although there was a trend for greater satisfaction after MVD. Our observations regarding long term efficacy of MVD are similar to those published in the literature, but there is a lack of high quality evidence to support the clinical practice. Properly matched prospective studies or randomized controlled trials are needed to help clinicians in selecting the appropriate mode of treatment and improving the patient outcomes."[6] Page 821
Mathieu, 2012[14]	
• Twenty-two patients (81.5%) who underwent GKS achieved reasonable pain control compared with 18 patients (100%) who underwent PRGR. Reasonable pain control was defined as BNI Pain Scale Scores of I to IIIb). • Whereas pain relief was immediate for patients who underwent PRGR, the median time to pain relief was 6 months for patients who underwent GKS. • Twelve patients in the GKS required subsequent procedures compared with six patients in the PRGR group. Subsequent	• "Both GKS and PRGR are satisfactory strategies for treating MS-related TN. Gamma Knife surgery has a lower rate of sensory and overall morbidity than PRGR, but requires a delay before pain relief occurs. The authors propose that patients with extreme pain in need of fast relief should undergo PRGR. For other patients, both management strategies can lead to satisfactory pain relief, and the choice should be made based on patient preference and expectations."[14] Page 175

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
procedures were for absence of response (n=3) and pain recurrence (n=9) in the GKS group, whereas in the PRGR all subsequent procedures were for pain recurrence. • As of the last follow-up, the number of patients who had achieved complete or reasonable pain control was 23 (85.2%) and 16 (88.9%) in the GKS and the PRGR groups, respectively. • The rate of complications was 22.2% in the GKS group compared with 66.7% in the PRGR group. All the complication in the GKS group was due to sensory loss and paresthesia, whereas in the PRGR group complications were mostly due to hypalgesia, with 2 patients having corneal reflex loss and 1 patient suffering from meningitis. • The authors reported no conflict of interest regarding the materials, methods used or the findings reported in the study.	• Gamma Knife surgery and PRGR are both satisfactory treatment strategies for patients with MS who suffer from intractable TN. Most patients treated with GKS will obtain pain relief after a latency period, which can last many months. Glycerol rhizotomy achieves pain relief faster and more efficiently than GKS, but carries higher overall risks and sensory morbidity. We propose that patients with MS-related TN who are in acute pain undergo PRGR first to produce fast pain relief. For other patients, the choice of treatment should be made based on patient preference and expectations. In the long term, it is possible to achieve satisfactory pain relief for most patients independent of the original surgical strategy, by repetition of treatment or by switching to the other procedure as needed."[14] Page 179
Udupi, 2012[8]	
• Patients who underwent PRFT had significantly higher rates of excellent pain relief than those who underwent PRGR (84.61% versus 58.97%; $P < 0.05$). • The mean duration of excellent pain relief was 24 ± 15 months with PRGR and 28.7 ± 18.7 months with PRFT, and the proportion of patients who did not require any medication until the end of the study period was 35% with PRGR and 41% with PRFT. The differences were not statistically significant ($P > 0.05$ for both comparisons). • At the end of the first year, the rate of excellent pain relief was significantly higher with PRFT than with PRGR (78.8% versus 65%; $P < 0.05$). However, by the end of 2 years, there was no significant difference in the two procedures with regards to recurrence of pain 9 patients (42.42% versus 39.13% for PRFT and PRGR, respectively, $P > 0.05$). • Survival probability [a] was not statistically significantly different	• "Both PRGR and RF techniques can achieve acceptable pain relief with minimal side effects."[8] Page 407 • "No single, standard method for the treatment of trigeminal neuralgia exists. Our experience indicates that both PRGR and RF thermocoagulation are minimally invasive, and either of these techniques can achieve acceptable pain relief with minimal side effects. Both PRGR and RF are safe and well tolerated."[8] Page 412

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
between PRFT and PRGR group was (60.9% versus 45.3%, respectively, *P* = 0.51). • Nine patients (22.5%) in the PRGR group and 8 (20.5%) in the PRFT group underwent a second procedure (*P* > 0.05). • No major complications were observed during the study period in both groups. The most common side effect observed was minor hypesthesia (75%) in patients receiving PRGR compared with 79% of patients undergoing PRFT, which did not require any treatment.	
Koopman, 2011[4]	
• The overall one-year risk of readmission for complications or repeat procedure was lowest with MVD (RR = 0.09; 95% CI: 0.03, 0.15) compared with PSR (RR = 0.15; 95% CI: 0.04, 0.27) and PRFT (RR = 0.38; 95% CI: 0.34, 0.42) • The one-year risk of readmission for repeat procedure was lowest with MVD (RR = 0.05; 95% CI: 0.00, 0.09) compared with PSR (RR = 0.08; 95% CI: 0.00, 0.17) and PRFT (RR = 0.37; 95% CI: 0.33, 0.41) • The one-year risk of readmission for complications was lowest with PRFT (RR = 0.02; 95% CI: 0.01, 0.03) compared with MVD (RR = 0.06; 95% CI: 0.01, 0.11) and PSR (RR = 0.08; 95% CI: 0.00, 0.16).	• "In conclusion, although PSR and MVD are associated with a lower risk of repeat procedure than PRT, they seem to be more prone to complications requiring hospital readmission."[4] Page 507 • "Despite its limitations, the results of our study are unique in that they capture a large nationwide study sample that provides a comprehensive overview of the application of invasive procedures for trigeminal neuralgia in daily practice. The study further gives a valid estimate of the absolute and relative risks (complications requiring admission) and effectiveness (readmission for repeat procedure) of individual surgical procedures in patients with trigeminal neuralgia. Previous reports showing a higher success rate of MVD compared with PRT have now been confirmed in a single data source. Finally, we have shown that the choice for a certain treatment modality is, at least in The Netherlands, a largely institutionalized practice and not based on a nationwide consensus." [4] Page 513
Economic Studies,[2,12,15]	
Holland, 2015[2]	
• MVD had significantly higher physician and hospital costs, as well as average total fess, compared with SRS and RFR (*P* <	• "There are significant cost differences among the three most common surgical procedures for TN. MVD was the

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
0.001). The average total charges were US$50,100 ± 9,600, US$39,300 ± 6,000, and US$4,700 ± 2,200 for the MVD, SRS, and RFR procedures, respectively; (*P* < 0.001). • The mean QAPFY was highest with RFR (2.28) followed by MVD (1.58), and SRS (0.99). • Overall, the most cost-effective procedure was RFR at US$2100 followed by MVD at US$31,800, and SRS at US$39,600 (*P* < 0.001). • Post-procedure facial numbness was significantly higher with RFR (52%) compared with MVD and SRS, with rates of 11% and 28% respectively (*P* < 0.01). • At two years, the rates of recurrence requiring a second procedure were significantly higher with RFR (74%) compared with MVD (22%) or SRS (31%) (p < 0.01). However, the average time to secondary procedure was longer with RFR (59 ± 76 months) compared with MVD (26 ± 29 months) SRS (35 ± 25 months).	most expensive procedure, was more likely to be performed on younger patients, had the lowest rate of facial numbness, and had the lowest rate of recurrence requiring a secondary procedure. SRS was slightly less costly, more likely to be performed on an older population, and had a rate of recurrence similar to MVD. RFR was the least expensive procedure, provided immediate relief, but was associated with the highest rates of facial numbness and recurrence. Based on cost-effectiveness, considering both cost and outcome, RFR was the most cost-effective, followed by MVD, and finally SRS."[2] Page 34
Sivakanthan, 2014[12]	
• Analysis indicated that in 2011, MVD was the most frequently utilized surgical treatment for TN (51.1%) followed by SRS (41.5%), while PSR was used in 7.4% of the patients. • The MVD procedure had the highest average weighted cost (US$40,435) followed by SRS (US$38,062) and PSR (US$3,911). • The MVD procedure had the highest QALYs of 8.2 followed by PSR (6.5) and SRS (4.9). • Overall, PSR was the most cost-effective procedure (cost per QALY) at US$602 followed by MVD at US$4,931, and SRS at US$7,768	• "Our study is a preliminary attempt at addressing the difficult question of cost-effectiveness in the care we offer to TN patients. Analysis of the Medicare claims data has demonstrated that, in 2011, MVD was the most widely used surgical treatment modality for TN, followed closely by SRS. Our calculations also revealed that, albeit PSRs are on average 11.5 times more cost-effective than either of the other 2 interventions, they are by far the least utilized of all surgical modalities. Although these results need to be examined with some level of critique, this article provides the best assessment to date of the relative utilization and cost-effectiveness of the 3 surgical modalities used for the management of TN in the United States."[12] Page 224

BC = balloon compression; GKRS = gamma knife radiosurgery; CI = confidence interval; iTN = idiopathic trigeminal neuralgia; MVD = microvascular decompression; NC = nerve combing; PBC = percutaneous balloon compression; PRGR = percutaneous retrogasserian glycerol rhizolysis; QAPFY = quality adjusted pain-free years; RF = radiofrequency; RFR = radiofrequency rhizotomy; SRS = stereotactic radiosurgery; TN = trigeminal neuralgia; VAS = visual analog scale

[a] The survival probability refers to the pain-free survival in the Kaplan-Meier curve at 54 months

APPENDIX 5: Additional References of Potential Interest

Systematic review – Based on three studies, which compared different techniques of performing some surgical procedures for TN without comparing the index modalities.

1. Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. Cochrane Database Syst Rev. 2011;(9).[16]

A retrospective study – Intervention groups (MVD alone versus MVD+PSR in a series) do not permit a definitive conclusion about the comparative efficacy of the individual modalities.

2. Zhang L, Zhang Y, Li C, Zhu S. Surgical treatment of primary trigeminal neuralgia: comparison of the effectiveness between MVD and MVD+PSR in a series of 210 patients. Turk Neurosurgery. 2012;22(1):32-8.[17]

A narrative review – Does not meet inclusion criteria of studies for this review

3. Parmar M, Sharma N, Modgill V, Naidu P. Comparative evaluation of surgical procedures for trigeminal neuralgia. J Maxillofac Oral Surg. 2013 Dec;12(4):400-9.[1]

Cost effectiveness study –Lacks details to permit critical appraisal

4. Fransen P. Cost-effectiveness in the surgical treatments for trigeminal neuralgia. Acta Neurol Belg. 2012 Sep;112(3):245-7.[15]