

AAN-EFNS guidelines on trigeminal neuralgia management

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Several issues regarding diagnosis, pharmacological treatment, and surgical treatment of trigeminal neuralgia (TN) are still unsettled. The American Academy of Neurology and the European Federation of Neurological Societies launched a joint Task Force to prepare general guidelines for the management of this condition. After systematic review of the literature the Task Force came to a series of evidence-based recommendations. In patients with TN MRI may be considered to identify patients with structural causes. The presence of trigeminal sensory deficits, bilateral involvement, and abnormal trigeminal reflexes should be considered useful to disclose symptomatic TN, whereas younger age of onset, involvement of the first division, unresponsiveness to treatment and abnormal trigeminal evoked potentials are not useful in distinguishing symptomatic from classic TN. Carbamazepine (stronger evidence) or oxcarbazepine (better tolerability) should be offered as first-line treatment for pain control. For patients with TN refractory to medical therapy early surgical therapy may be considered. Gasserian ganglion percutaneous techniques, gamma knife and microvascular decompression may be considered. Microvascular decompression may be considered over other surgical techniques to provide the longest duration of pain freedom. The role of surgery versus pharmacotherapy in the management of TN in patients with multiple sclerosis remains uncertain.

Introduction

The American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) decided to develop scientifically sound, clinically relevant guidelines to aid specialists and non-specialists in the management of trigeminal neuralgia (TN), by addressing its diagnosis, pharmacological treatment, and surgical treatment.

The International Association for the Study of Pain (IASP) defines TN as sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve.[54] The annual incidence of TN is 4 to 5/100,000.[34] TN is the most common neuralgia. In the

latest classification of the International Headache Society,[29] a distinction is made between *classical* and *symptomatic* TN: classical TN (CTN) includes all cases without an established etiology, i.e. idiopathic, as well as those with potential vascular compression of the fifth cranial nerve, whereas the diagnosis of symptomatic TN (STN) is made in cases secondary to tumour, MS, structural abnormalities of the skull base, and the like. It should be noted that categorization of TN into *typical* and *atypical* forms is based on symptom constellation, and not etiology, and will not be discussed further in this review.

The first issue facing the clinician caring for a patient with TN is accurately distinguishing symptomatic from classical TN. The diagnostic portion of this parameter addresses the following questions:

1. How often does routine neuroimaging (CT, MRI) identify a cause (excluding vascular contact) of TN?
2. Which clinical or laboratory features accurately identify patients with STN?
3. For patients with classical TN does high resolution MRI accurately identify patients with neurovascular compression?

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This is a Continuing Medical Education article and can be found with corresponding questions on the internet at <http://www.efns.org/content.php?pid=132>. Certificates for correctly answering the questions will be issued by the EFNS.

The first line therapy of trigeminal neuralgia is pharmacological, if for no other reason than in most cases it is immediately available and usually effective. Introduction of phenytoin in the 1940s and carbamazepine in the 1960s changed the management of TN considerably, which previously had been almost exclusively surgical. The pharmacological portion of this parameter addresses the following questions:

4. Which drugs have shown efficacy in the treatment of CTN?
5. Which drugs have shown efficacy in the treatment of STN?
6. Is there evidence of efficacy of intravenous drugs in acute exacerbations of TN?

When medical treatment fails either due to poor pain control or because of intolerable side effects surgery is often considered the next option. The timing of surgery and choice of surgery then becomes the next issue to face the patient. Surgical interventions are varied and are best classified according to the principal target: peripheral techniques targeting portions of the trigeminal nerve distal to the Gasserian ganglion; percutaneous Gasserian ganglion techniques targeting the ganglion itself; gamma knife radiosurgery targeting the trigeminal root, and posterior fossa vascular decompression techniques.

7. When should surgery be offered?
8. Which surgical technique gives the longest pain free period with fewest complications and good quality of life?
9. Which surgical techniques should be used in patients with multiple sclerosis?

Search Methods

The AAN and EFNS identified an expert panel of TN experts and general neurologists with methodological

expertise. Conflicts of interest were disclosed. Panelists were not compensated.

We searched MEDLINE, EMBASE and the Cochrane library. Searches extended from the time of database inception to 2006. All searches used the following synonyms for TN: trigeminal neuralgia, tic douloureux, facial pain or trigeminal neuropathy. Search terms were used as text words or MESH headings as appropriate. The primary search was supplemented by a secondary search using the bibliography of retrieved articles and knowledge from the expert panel. Only full original communications were accepted. Panel members reviewed abstracts and titles for relevance. Then, at least two panel members reviewed papers meeting inclusion criteria. An additional panel member arbitrated disagreements.

The methods of classifying evidence adopted by AAN and EFNS are very similar, those of grading the recommendations—though largely compatible—differ in a few points. A detailed comparison of the two methods of classification and grading can be found in Appendix 1 (supplementary material). The classification of the identified studies was agreed by American and European authors (details can be found in the evidence Tables 1–9). This was not possible for the grading of recommendations. The present article, meant for the *European Journal of Neurology*, used the EFNS grading of recommendations.[10]

Results

1. Diagnosis

Question 1

For patients with trigeminal neuralgia without non-trigeminal neurological symptoms or signs, how often does neuroimaging (CT, MRI) identify a cause (excluding vascular contact)?

Table 1 Diagnosis: frequency at which neuroimaging identified patients with symptomatic TN

First Author Year	Class	Sampling	Population	Data collection	TN criteria	Modality	Total TN Patients	STN Patients (CI)
Crucca 2006 [16]	III	Consecutive pts with TN	Referral centre	prospective	IHS	MRI	120	16 MS 6 tumours
Sato 2004 [69]	III	Consecutive patients with TN	University	retrospective	IASP	MRI or CT	61	7 tumours
Goh 2001 [27]	III	Consecutive patients with TN and MRI	National dental centre	retrospective	Not stated	MRI	40 ^a	4 masses
Majoie 1998 [50]	III	Consecutive patients with TN and MRI	University	retrospective	Not stated	MRI	22	3 tumours 1 aneurysm
Nomura 1994 [59]	IV	Consecutive patients with TN	University	retrospective	Not stated (non-TN neurological signs)	MRI or CT	164	22 masses
Pooled Class III							37/243 Yield	15% (11 to 20)

^aPatients with non-trigeminal symptoms or signs eliminated. CI: 95% confidence interval.

Table 2 Diagnostic accuracy of clinical features for distinguishing symptomatic TN from classic TN

First Author Year	Class	Design	Spectrum	CTN/ STN	Number	Age mean \pm SD	Sensory Deficits	First division	Bilateral	Poor rx response
Crucchu 2006 [16]	I	CO P	Broad	CTN	96	62 \pm 12	0/96	28/136	0/96	–
				STN	24 (mixed)	51 \pm 10	2/24	9/33	0/24	–
De Simone 2005 [19]	III	CC P	Narrow	CTN	13	60 \pm 12	4/13	8/25	0/13	–
				STN	15 (MS)	43 \pm 11	10/15	3/23	0/15	–
Sato 2004 [69]	II	CO R	Broad	CTN	43					3/43
				STN	7 (tumours)					2/7
Ogutcen-Toller 2004 [62]	II	CO R	Broad	CTN	31				0/31	
				STN	7 (masses)					1/7
Goh 2001 [27]	II	CO R	Broad	CTN	36	60 \pm 13	0/36		0/36	10/35
				STN	6 (masses)	54 \pm 11	2/6		0/6	3/6
Hooge 1995 [31]	IV	CS R	Narrow	CTN	0	–	–	–	–	–
				STN	35 (MS)	51	3/35		5/35	2/20
Nomura 1994 [59]	II	CO R	Broad	CTN	142	47 \pm 13 (<i>n</i> = 58)	1/142	11/58	0/58	
				STN	22 (masses)	48 \pm 16	11/22	6/22	0/22	
Pooled Classes I-III				P assoc		<0.0001	<0.001	NS	<0.001	NS
				Sen% (CI)		–	37 (27 to 49)	23 (15 to 34)	1.4 (0 to 7)	39 (18 to 65)
				Spe% (CI)		–	98 (96 to 99)	79 (73 to 84)	100 (98 to 100)	83 (74 to 9)
				Pos LR		–	18.5	1.1	Large	2.3

CO: cohort survey. CC: case control. CS: Case series. P: Prospective data collection. R: Retrospective or not described data collection. CI: 95% confidence intervals. P assoc: probability of statistically significant association between the presence of the characteristic and the presence of symptomatic STN. Sen: sensitivity. Spe: specificity. Sensitivities calculated for presence of characteristic in symptomatic TN. Specificities calculated for absence of characteristic in classical TN. Pos LR: positive likelihood ratio.

Table 3 Diagnostic accuracy of trigeminal reflex testing for distinguishing symptomatic TN from classic TN

First Author Year	Class	Design	Spectrum	Ref. Standard	STN A/T	CTN A/T	P assoc	Spe (CI)	Sen (CI)
Kimura 1970 [38]	III	CC P	narrow	Clinical	1/1	1/14	NS	93%	100%
Ongerboer de Visser 1974 [63]	III	CC R	narrow	Clinical	16/16	0/11	<0.0001	100%	100%
Kimura 1983 [37]	II	CC P	broad	Clinical	10/17	4/93	<0.0001	96%	59%
Crucchu 1990 [17]	II	CC P	broad	Clinical imaging	4/4	2/30	<0.0003	93%	100%
Crucchu 2006 [16]	I	CO P	broad	Clinical MRI	23/24	7/96	<0.0001	93%	96%
Pooled Classes I-III					54/62	14/244	<0.0001	94% (91 to 97)	87% (77 to 93)

Trigeminal reflex testing: R1 early blink reflex after supraorbital stimulation (for ophthalmic division), SP1 early masseter inhibitory reflex after infraorbital stimulation (for maxillary division), and SP1 early masseter inhibitory reflex after mental stimulation or mandibular tendon reflex (for mandibular division). A/T: abnormal/total. CO: cohort survey. CC: case control. P: Prospective data collection. R: Retrospective or not described data collection. CI: 95% confidence intervals. P assoc: probability of statistically significant association between the presence of the characteristic and the presence of symptomatic STN. Sen: sensitivity. Spe: specificity. Sensitivities calculated for presence of abnormal trigeminal reflexes in symptomatic TN. Specificities calculated for absence of abnormal trigeminal reflexes in classical TN.

Table 4 Diagnostic accuracy of evoked potentials for distinguishing symptomatic TN from classic TN

Author year	Class	Method	Design	Spectrum	Ref. Standard	STN A/T	CTN A/T	P assoc	Sen (CI)	Spe (CI)
Leandri 1988 [43]	III	electrical-TEPs	CC P	narrow	imaging	18/23	9/38	<0.0001	78%	76%
Crucchu 1990 [17]	III	electrical-TEPs	CC P	broad	imaging	4/4	9/30	<0.05	100%	70%
Crucchu 2001 [18]	II	laser-EPs	CC P	broad	MRI	20/20	24/47	<0.0001	100%	49%
Mursch 2002 [57]	II	electrical-TEPs	CO R	broad	Not stated	6/10	13/37	NS	60%	65%
Pooled II-III						48/57	55/152	<0.0001	84% (73 to 92)	64% (56 to 71)

TEPs, trigeminal evoked potentials; A/T, abnormal/total; CO, cohort survey; CC, case control; P, prospective data collection; R, retrospective or not described data collection; CI, 95% confidence intervals; P assoc, probability of statistically significant association between the presence of the characteristic and the presence of symptomatic STN; Sen, sensitivity; Spe, specificity. Sensitivities calculated for presence of abnormal evoked potentials in symptomatic TN. Specificities calculated for absence of abnormal evoked potentials in classical TN.

Table 5 Diagnostic accuracy of MRI for identifying abnormal vascular contact in classic TN

Author year	Class	Method	Design	Spectrum	Masked	Ref. Standard	Symptomatic NVC/T	Asymptomatic NVC/T	P assoc	Sen (CI)	Spe (CI)
Korogi 1995 [40]	I	3D-TOF	CO P	broad	yes	Symptomatic side	12/16	4/16	< 0.012	75%	75%
Masur 1995 [52]	I	3D-FLASH	CO P	broad	yes	Symptomatic side	12/18	10/18	NS	67%	44%
Majoie 1997 [51]	III	3D-FISP MP-RAGE	CC P	narrow	yes	clinical	10/13	8/113	< 0.0001	77%	93%
Yamakami 2000 [79]	I	CISS-3D-TOF	CO P	broad	yes	Symptomatic side	14/14	7/30	< 0.0001	100%	77%
Benes 2005 [6]	I	3D-Fiesta 3D-FSPGR	CO P	broad	yes	Symptomatic side	11/21	10/21	NS	52%	52%
Anderson 2006 [1]	I	3D-TOF 3D-Gad	CO P	broad	yes	Symptomatic side	42/48	34/48	NS	88%	29%
Erbay 2006 [23]	III	CISS-MPR	CO R	broad	yes	Symptomatic side	30/40	10/40	< 0.0001	75%	75%
Pooled	I-III						131/170	83/286	< 0.0001	77% (70–83)	71% (65–76)

NVC/T: neurovascular contact/total. CO: cohort survey. CC: case control. P: Prospective data collection. R: Retrospective or not described data collection. CI: 95% confidence intervals. P assoc: probability of statistically significant association between the presence of the characteristic and the presence of TN. Sen: sensitivity. Spe: specificity. Sensitivities calculated for presence of neurovascular contact on the symptomatic side. Specificities calculated for absence of neurovascular contact on the asymptomatic side.

Evidence. Five articles (one graded Class IV) reported the results of head imaging on consecutive patients diagnosed with TN (Table 1). Four studies included cohorts of TN patients assembled at University and tertiary centres with a presumed interest in TN. Because more complicated and potentially less representative TN patients get treated at such centres, these studies were judged to be at risk for referral bias and thus graded Class III.[16,27,50,69] Yields of brain imaging ranged from 10 to 18%. Combining Class III studies results in pooled estimate of yield of 15% (95% CI, 11 to 20).

Conclusions. For patients with trigeminal neuralgia without non-trigeminal neurological symptoms, routine neuroimaging possibly identifies a cause in up to 15% of patients. (Four Class III studies.)

Question 2

For patients with trigeminal neuralgia, which clinical or laboratory features accurately identify patients with STN?

Evidence. We found seven papers (one graded Class IV) studying the diagnostic accuracy of clinical characteristics for distinguishing STN from CTN (Table 2). Potential clinical characteristics studies included: the presence of sensory deficits, age of onset, first division of trigeminal nerve affected, bilateral trigeminal involvement, and unresponsiveness to treatment.

One study was graded Class III because of a case control design with a narrow spectrum of patients (De

Simone *et al.* 2005).[19] Four studies were judged to have a moderately low risk of bias because of a cohort design with a broad spectrum of patients. However, these studies collected data retrospectively and were thus graded Class II.[27,59,62,69] We found one prospective Class I study.[16] In these studies involvement of the first trigeminal division and unresponsiveness to treatment were not associated with a significant increase in the risk of STN. Younger age was significantly associated with increased risk of STN. However, in these studies there was considerable overlap in the age ranges of patients with CTN and STN. Thus, although younger age increases the risk of finding STN, the diagnostic accuracy of age as a predictor of STN was too low to be clinically useful. The presence of trigeminal sensory deficits and bilateral involvement was significantly more common in patients with STN. However, many patients with normal sensation and unilateral involvement of the trigeminal nerve were found to have a cause of their TN (Figure 1).

Nine studies looked at the diagnostic accuracy of electrophysiological testing in distinguishing STN from CTN patients. Five studies addressed the accuracy of trigeminal reflex testing (Table 3); one study used a prospective design and was graded Class I:[16] the remaining studies, either using a case control design with a narrow spectrum of patients or retrospective data collection, were graded Class II or III.[17,37,38,63] The diagnostic accuracy of trigeminal reflexes for identifying STN patients in most studies was relatively high (sensitivity 59 to 100%, specificity 93 to 100%).

Table 6 Medical treatment. Placebo controlled trials

Author/year	Class	No patients	Intervention	Design	Allocation conceal	No. drop outs	Outcomes	Improved on active	Improved on placebo	Duration of treatment arm & long-term Follow up
Campbell <i>et al.</i> 1966 [14]	I	70 (77 patients recruited); age range 20–84	CBZ 300–800 mg/d	R, D-B, double C-O	Not stated	Not stated, possibly none	Severity of pain, No paroxysms, Trigger inactive	58% 68% 68%	26% 26% 40%	4 weeks No F/U
Killian & Fromm 1968 [36]	II	24 (30 patients recruited); age range 36–83	CBZ 400–1000 mg/d	R, D-B, initially C-O, followed by closed label extension	Not stated	3 on active, placebo not stated	Global pain response	24/24 (complete or v.good)	0/24 (“response in all minimal or absent”)	C-O, 5 days Extension, 2 weeks to 36 months
Nicol 1969 [58]	II	44 (of 54 entered)	CBZ 100–2400 mg/d	R, D-B, modified C-O, followed by closed label extension	Not stated	10 insufficient follow up	Global pain response	15/20 (good or excellent)	6/7 (good or excellent)	C-O, 2 weeks F/U up to 46 months
Rockcliff & Davis, 1966 [68]	II	9; age range 37–81	CBZ 600 mg/d	R, D-B, C-O, sequential design	Independent pharmacist	No drop outs	Patient preference	8/9	0/9	3 days F/U 7–10 months, median 9 months
Fromm <i>et al.</i> 1984 [26]	II	10; age range 59–78	Baclofen 40–80 mg/d	Randomization unclear, D-B, C-O	Not stated	No drop outs	No. paroxysms	7/10 reduction	1/10 reduction	1 week No F/U
Zakrzewska <i>et al.</i> 1997 [81]	II	14; age range 44–75	Lamotrigine 400 mg/d	R, D-B, C-O, add on	Not stated	1 on placebo	Composite index, global response	7/13	1/14	2 weeks No F/U
Fromm 1993 [25]	III	11, age range 41–83; most pts had undergone surgery or were on concurrent medications	Tizamide 12 mg/d	Randomization unclear, D-B, C-O	Not stated	1 on placebo	Frequency of paroxysms	8/10 reduction	4/10 reduction	1 week F/U 6 patients (effect lost 1–3 months)
Kondziolka <i>et al.</i> 1994 [39]	I	47; age range 26–82	Proparacaine 0.5% eyedrops	R, D-B, C-O	Not stated	No drop outs	Pain score, frequency	6/25	5/25	30 days No F/U

R, randomized; D-B, double-blind; C-O, cross-over; PG, parallel group, CBZ, carbamazepine; NK, not known

Table 7 Medical treatment. Comparator studies against carbamazepine

Author/year	Class	No patients	Intervention	Design	Allocation concealment	No. drop outs	Outcomes	Improved on study drug	Improved on comparator	Duration of treatment arm & long-term Follow up
Lindstrom & Lindblom 1987 [46]	III	12; age range 41–78	Tocamide 20 mg/kg/d	R, D-B, C-O	Not stated	TOC 0	Global pain	9/12	10/12	2 weeks
Lechin <i>et al.</i> 1989 [44]	II	48; age range 48–68	Pimozide 4–12 mg/d vs. CBZ 0.3–1.2g/d	R, D-B, C-O	Not stated	PMZ 0 CBZ not stated	Composite “TN score”	48/48	27/48	No F/U 8 weeks Duration of F/U not stated
Liebel 2001 [45]	II	48; age range 38–83	OXC 600 mg/d increased to “optimal” vs. CBZ 400 mg/d to “optimal”	R, D-B, PG	Not stated	OXC 0 CBZ 2	50% reduction in TN attacks	24/24	19/20	6–32 weeks
Beydoun <i>et al.</i> 2000, 2002 [7,8]	II	130 (meta-analysis of 3 studies)	OXC 700–900 mg/d vs. CBZ 500–1200 mg/d	R, D-B, PG	Not stated		No. weekly attacks, (evoked pain global efficacy)	63/69	54/61	6–8 weeks

R, randomized; D-B, double-blind; C-O, cross-over; PG, parallel group, CBZ, carbamazepine; OXC, oxcarbazepine; PMZ, pimozide; TOC, tocamide; NK, not known;

Pooled sensitivity 94% (95% CI, 91 to 97); pooled specificity 87% (95% CI, 77 to 93). Four studies addressed the accuracy of evoked potential (Table 4), two attaining a grade of Class II and two Class III.[17,18,41,58] The diagnostic accuracy of evoked potentials for identifying STN patients was moderate (sensitivity 60 to 100%, specificity 49 to 76%). Pooled sensitivity 84% (95% CI, 73 to 92); pooled specificity 64% (95% CI, 56 to 71).

Conclusions. For patients with TN, involvement of the first division of the trigeminal nerve and unresponsiveness to treatment are probably not associated with an increased risk of STN. (One Class I, two Class II). Younger age (one Class I, three Class II studies) and abnormal trigeminal nerve evoked potentials (two class II and two Class III studies) are probably associated with an increased risk of STN. However, there is too much overlap in patients with CTN and STN for these predictors to be considered clinically useful. The presence of trigeminal sensory deficits or bilateral involvement of the trigeminal nerves probably increases the risk of STN. However, the absence of these features does not “rule out” STN. (One Class I, two Class II). Because of a high specificity (94%) and sensitivity (87%) abnormal trigeminal reflexes are probably useful in distinguishing STN from CTN (one Class I and two Class II studies).

Question 3

For patients with classical TN, does high resolution MRI accurately identify patients with neurovascular compression?

Evidence. Sixteen papers studied TN patients with high resolution MRI, usually prior to microvascular decompression. Nine studies were graded Class IV because they relied on the unmasked findings of the operating surgeon to determine the presence of vascular contact; in these studies, the surgeon always found a blood vessel contacting the trigeminal nerve. Table 5 lists the seven higher-quality studies and their methodological characteristics. One study employed a case control design with a narrow spectrum of patients and another was retrospective (Class III).[23,50] Five studies were masked cohort surveys with prospective data collection (Class I).[1,6,40,52,79] The most common reference standard in these Class I studies was the masked comparison of the MRI of the symptomatic side to the asymptomatic side.

Pooled data showed a highly significant association between the presence of a MRI-identified vascular contact and the presence of TN ($P < 0.0001$). But sensitivities and specificities in the Class I-III studies

Table 8 Surgical treatment: demographics of patients in the Class-III studies

	Mittal <i>et al.</i> 1986 [55]	Zakrzewska <i>et al.</i> 1999 [84]	North <i>et al.</i> 1990 [60]	de Siqueira 2006 [20]	Barker <i>et al.</i> 1996 [4]	Broggi <i>et al.</i> 2000 [11]	Piatt <i>et al.</i> 1984 [65]	Zakrzewska <i>et al.</i> 1993 [85]	Zakrzewska <i>et al.</i> 2005 [82]	Maesawa <i>et al.</i> 2001 [49]	Petit <i>et al.</i> 2003 [64]	Regis <i>et al.</i> 2006 [67]
Technique	RFT	RFT	GR	BC	MVD	MVD	MVD	MVD	MVD	GKS	GKS	GKS
No. of patients	229	48	85	105	1185	250	104	65	245	220	112	110
No. of interventions	280	48	109	105	1204	105	105	66	245			
Male %	42.9	40		42	40	48.6	42	37.0	34	42.0	37.5	57
Female %	57.1	60		57	60	51.4	63	63.0	66	66.0	62.5	43
Right side %	57	58	59	69	61	54.7	60	65.0		60.9	48	53
Left side %	43	38	41	29	37	45.3	43	33.0		39.1	49	47
Bilateral %	2.8	4	0	1	2	1.4	1	2.0			3	0
mean duration (yrs)	7.5		9.2	9.5	8	8.5	4		6.7	8.0		6
duration 1–5 yrs %	50	65										
duration > 6 yrs %	50	35										
range duration (yrs)	0.4–32		1–50	.05–30	1–44	1–44	1–44			0.4–47	0.2–40	0.7–44
Mean/median age op	60.5		62	61	57	56.7	56.7	54	59	70	64	68
age range at op	18–91		30–89	35–85	5–87	20–74	25–78	21–75		26–92	24–95	29–90
Atypical %	0	35.4	12.9		0	4	0	0	ns	7.3	30	
MS %	5.6	0	4.7		0	4	0	0	0			7
symptomatic %	5	0			0			6		0		
previous surgery %	ns	0	39		28	45	32	ns	20	61.4	31	44
pre-op sensory changes %	ns	ns			37			ns	ns	37.8		64
mean/median follow up (months)	44	30	36	7	74	48.3	48.3	45	5.3	22	30	
range of follow up months	4–96	7–55	0.5–4.5	0–7	26–246	12–94	37–53	6–240	6–78	8–66	8–66	12–?
lost to follow up %	7	10	ns	10	10	4.8	8	5	10	0	14	8
data collection	question.	question.	interview	question.	question.	telephone	question.	question.	question.	telephone	telephone	question.
			interview	interview	question.	telephone	question.	question.	question.	telephone	telephone	exam

Table 9 Surgical treatment: complications

Reference	Procedure	no.	mor- tality	peri- operative	cerebellar oedema or haema- toma	sinus throm- bosis	CSF leak	reoperation for CSF leak	aseptic menin- gitis	bacterial menin- gitis	4th nerve	6th nerve	7th nerve	8th perm.	8th sensory	dyses- thesia	5th ad	corneal bumb- ness	eye pain	other facial	other minor compli- cation	
Mital Thomas 1985 [55]	RFT	265	1	1							2		1	1	135	15	22	2	16	10	28	
Zakrzewska <i>et al.</i> 1999 [84]	RFT	31	0										2	2	24	2	0	2	0	2	3	
Zakrzewska <i>et al.</i> 1999 [84]	RFT	17	0										1	1	14	4	0	4	0	4	12	
North <i>et al.</i> 1990 [60]	GR	85	0	4							1				3	3	0	5		33		
de Siqueira <i>et al.</i> 2006 [20]	BC	105	0	1	0	0	0	0	1	0	0	0	0	3	?	5	0	2		3	?	
<i>total</i> <i>percent</i>	PGL	503	1	5	0	0	0	0	1	0	2	1	1	3	11	178	29	22	10	21	19	34
		0.2	1	0	0	0	0	0	0.2	0	0.5	0.2	0.2	0.6	2	45	5.8	4.4	2	4.2	3.8	6.8
Barker 1996 [4]	MVD	1185	2	31	8	0	17		198	4	13	2	6	1	15	7	0					
Barker 1997 [5]	MVD															78	48				39	
Broggi <i>et al.</i> 1999 [11]	MVD	250	0	14	1	1	12	5			6		3	1	8	16	0	2			?	
Piatt & Wilkins 1984 [65]	MVD	104	1	13	2	2	2		3	0	0	0	2	4	15	9	2	0	0	0	?	1
Zakrzewska 1993 [85]	MVD	66	0											6	12	3	0	4	0	2	7	25
Zakrzewska 2005 [82]	MVD	245	0										24	9	10	10	0	5	0	10	57	
<i>total</i> <i>percent</i>	MVD	1850	3	58	11	3	31	5	201	4	13	2	6	68	124	70	2	9	0	12	46	83
		0.2	3.1	0.6	0.6	0.2	1.7	0.3	10.9	0.2	0.7	0.1	0.3	0.6	3.7	3.8	0.1	0.5	0	0.6	3.1	4.5
Maesawa <i>et al.</i> 2001 [49]	GKS	220	0												17	1	0	0				
Petit 2003 [64]	GKS	112													7							
Regis 2006 [67]	GKS	100	0	0											6	4	0	0				
<i>total</i> <i>percent</i>	GKS	432	0	0											30	5	0	0				
		0	0	0											6.9	0.3	0	0				

BC: balloon compression; GKS: gamma knife surgery; GR: glycerol rhizolysis; MVD: microvascular decompression; PGL: percutaneous Gasserian lesions; RFT: radiofrequency thermocoagulation; ad: anaesthesia dolorosa; perioperative complications include: pneumonia, deep vein thrombosis, GI bleed, those expected after any surgery not specific to this surgery; box with number 0 indicates that the text specifically reports absence of that kind of complication; empty box indicates that the complication is not mentioned; we assumed that the Authors would have reported all complications, i.e. in calculating percentages we considered empty boxes equal 0; box with question mark indicates that we did not consider it in calculating percentages because the text left some doubt.

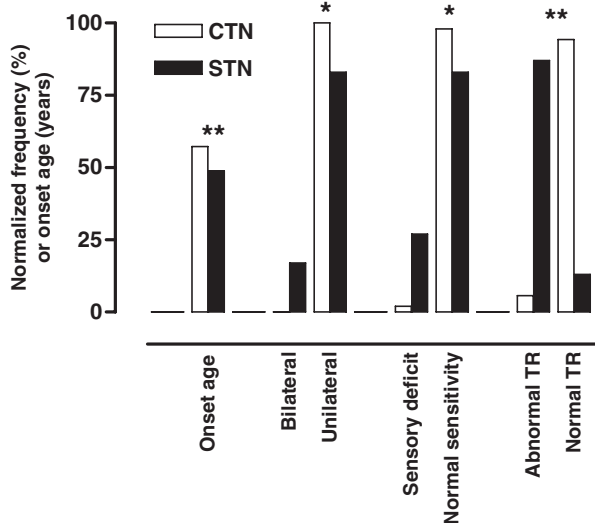


Figure 1 Differential diagnosis between classical (CTN) and symptomatic trigeminal neuralgia (STN). Response to treatment and involvement of first trigeminal division are similar in the two populations. Onset age is lower in CTN than STN (** $P < 0.0001$). Bilateral neuralgia and sensory deficits only occur in STN (* $P < 0.001$). Trigeminal reflexes (TR) are abnormal in STN (87%) and normal in CTN (94%) (** $P < 0.0001$). Data from 10 trials (Class I-III) in 628 patients, detailed in Tables 2 and 3.

varied widely (sensitivity 52 to 100%; specificity 29 to 93%) and in three Class-I studies the association was not significant. The heterogeneity in results may result from differences in the various MRI techniques employed. Currently it is not possible to establish which MRI technique is most reliable.

Conclusions. Because of inconsistency of results, there is insufficient evidence to support or refute the usefulness of MRI to identify vascular contact in CTN or to indicate the most reliable technique. Given the significance of pooled data, however, we suggest patients considered suitable for MVD undergo high-resolution MRI.

Recommendations on diagnosis

For patients with TN without non-trigeminal neurological symptoms, routine imaging may be considered to identify STN (Level C). Younger age of onset, involvement of the first division of the trigeminal nerve, unresponsiveness to treatment, and abnormal trigeminal evoked potentials should be disregarded as useful for disclosing STN (Level B). Determining the presence of trigeminal sensory deficits or bilateral involvement of the trigeminal nerves should be considered useful to distinguish STN from CTN. However, the absence of these features should be disregarded as useful for distinguishing STN from CTN. (Level B). Measuring

trigeminal reflexes in a qualified electrophysiological laboratory should be considered useful for distinguishing STN from CTN (Level B). There is insufficient evidence to support or refute the usefulness of MRI to identify CTN patients who are more likely to respond to MVD.

2. Pharmacological Treatment

Question 4

Which drugs have shown efficacy in the treatment of classical trigeminal neuralgia (CTN) in general?

Evidence. Our search strategy identified 15 randomized controlled trials studying the effectiveness of various medications for TN. In three of these the number of patients (from 3 to 6) was too small. Of the remaining 12, eight were placebo controlled trials and four used carbamazepine as the comparator (Tables 6,7).

Phenytoin was the first drug to be used for CTN with positive effects, but no randomized controlled trials have ever been published (four class III open studies, cf. Sindrup and Jensen[71]).

Four placebo-controlled studies (Class I or II) totalling 147 patients demonstrated efficacy of carbamazepine (CBZ).[14,36,58,68] The treatment response in these trials was robust with the number needed to treat (NNT) to attain important pain relief being 1.7–1.8.[71,77,78] CBZ reduced both the frequency and intensity of painful paroxysms and was equally efficacious on spontaneous and trigger-evoked attacks.[14] The efficacy of CBZ is compromised by poor tolerability with numbers-needed-to-harm (NNHs) of 3.4 for minor and of 24 for severe adverse events.[53,77,78] The use of older antiepileptic drugs such as CBZ is often complicated by pharmacokinetic factors and frequent adverse events.[77,78] The issue of balance between effect and adverse reactions is particularly important in elderly patients with TN.

Oxcarbazepine (OXC) is often used as initial treatment for TN.[32] Its preference over CBZ is mainly related to its documented efficacy in epilepsy and accepted greater tolerability and decreased potential for drug interactions (Class I).[41] Three randomised controlled trials (RCTs) using a double blind design including a total of 130 patients compared oxcarbazepine (OXC) 600–1800 mg/day to CBZ in CTN patients (Class II and meta-analysis).[7,8,45] The reduction in number of attacks and global pain assessments were equally good for both CBZ and OXC (88% of patients achieving a reduction of attacks by > 50%). These studies used as comparator CBZ rather than placebo, disallowing calculations for NNT values for OXC.

Other drugs have each been studied in single trials: baclofen was superior to placebo in reducing the number of painful paroxysms (Class II);[26] lamotrigine (400 mg/day) was effective as add-on therapy on a composite index of efficacy (Class II);[81] pimoziide was more effective than CBZ (Class II);[44] tocainide was as effective as CBZ (Class III).[46] Tizanidine, in a small group of patients (most having already undergone trigeminal surgery or taking concurrent medications) was better than placebo but its effect decayed within 1–3 months (Class III).[25]

Small open label studies (Class IV) have suggested therapeutic benefit from other antiepileptic drugs (clonazepam, gabapentin, valproate); but in general the proportion of patients improving was lower than that yielded by CBZ.

Topical ophthalmic anesthesia was ineffective in a Class I placebo-controlled RCT.[39]

Conclusions. Carbamazepine is established as effective for controlling pain in patients with TN (multiple Class I and II). Oxcarbazepine (one meta-analysis and one Class II) is probably effective, and baclofen, lamotrigine, and pimoziide are possibly effective for controlling pain in patients with TN (single Class II). Topical ophthalmic anesthesia is probably ineffective for controlling pain in patients with TN (single Class I). There is insufficient evidence to support or refute the efficacy of clonazepam, gabapentin, phenytoin, tizanidine, topical capsaicin, and valproate for controlling pain in patients with TN.

Considering the relatively narrow mechanism of action of the available drugs, *combination treatments* might be useful. However, there are no published studies directly comparing polytherapy with monotherapy.[61]

Question 5

Which drugs have shown efficacy in the treatment of STN?

Evidence. There are no placebo-controlled studies in patients with STN. The existing studies all deal with TN associated to multiple sclerosis and are small open label trials (class IV). Lamotrigine has been reported to be more effective than CBZ in 18 patients.[43] Three trials including a total of 19 patients have reported an effect of gabapentin alone or associated with CBZ.[35,72,73] One study reported efficacy of topiramate in six patients.[86] Finally two Class-IV studies reported efficacy of misoprostol (a prostaglandin-E₁-analogue) in a total of 25 patients.[21,66]

Conclusion. There is insufficient evidence to support or refute the effectiveness of gabapentin, lamotrigine, mi-

soprostol, and topiramate in treating pain in symptomatic TN (Class IV studies).

Question 6

Is there evidence of efficacy of intravenous administration of drugs in acute exacerbations of TN?

Evidence. We were unable to find published RCTs on the use of intravenous opioids, TCAs, benzodiazepines, antiepileptic drugs or non-opioid analgesics. Textbooks make a passing remark on the use of i.v. antiepileptic drugs in the emergency management of TN, and Cheshire[15] has reported three patients who responded quickly to i.v. fosphenytoin (class IV).

Conclusion. There is insufficient evidence to support or refute the efficacy of i.v. fosphenytoin or other i.v. medications for the acute treatment of pain form TN (Class IV).

Recommendations on pharmacological treatment

Carbamazepine is established as effective (level A) and oxcarbazepine is probably effective (level B) for controlling pain in CTN. Baclofen, lamotrigine, and pimoziide may be considered to control pain in patients with CTN (level C). Topical ophthalmic anesthesia is probably ineffective in controlling pain in patients with CTN (Level B). There is insufficient evidence to support or refute the efficacy of other medications in CTN, of any medication in STN, and of any intravenous medication for the acute treatment of pain form TN.

Evidence translated in a clinical context. In line with the recent EFNS Guidelines,[3] the two drugs to consider as first-line therapy in CTN are CBZ (200–1200 mg/day) and OXC (600–1800 mg/day). Although the evidence for CBZ is stronger than for OXC, the latter may pose fewer safety concerns. If any of these sodium-channel blockers is ineffective, referral for a surgical consultation would be a reasonable next step. In cases where surgical intervention is unlikely, e.g. because of the frailty of the patient, there are insufficient data to recommend the next step. Limited evidence supports add-on therapy with lamotrigine or a switch to baclofen (pimoziide being no longer in use). The effect of other drugs commonly used in neuropathic pain, such as gabapentin, pregabalin, serotonin-noradrenaline reuptake inhibitors, or tricyclic antidepressants is unknown.

Because spontaneous recovery in typical CTN is rare and the condition is cyclical with periods of partial or complete remission and recurrence, it is reasonable to encourage patients to adjust the dosage to the frequency of attacks.

3. Surgical Treatment

Our literature search on surgical procedures revealed three Class I prospective RCTs, one Class II prospective cohort study, and a handful of Class III studies where the outcome was independently assessed (explicitly stated). The vast majority of the evidence was Class IV.

Question 7

When should surgery be offered?

Evidence. There are no studies dealing specifically with this issue. Some guidance can be found in two studies (Class III) that specifically asked patients after surgery whether they would have preferred the surgical option.[82,83] Zakrzewska and Patsalos[83] followed up a cohort of 15 patients for over 15 years who were initially treated medically and then where offered surgery when medical management failed to control their pain. Twelve patients underwent a variety of surgical procedures and eight of these stated that they should have had surgery earlier. In a large study of patients who underwent posterior fossa surgery, over 70% of 245 patients treated with microvascular decompression would have preferred to have treatment earlier.[82]

Conclusion. Patients with TN refractory to medical therapy possibly prefer a surgical option early (two Class III).

Question 8

Which surgical technique gives the longest pain free period with fewest complications and good quality of life?

Evidence. The evidence from direct comparisons between different surgical procedures is insufficient.[2,13,30] Demographics of the patients included in our analysis can be found in Table 8 and complications in Table 9 and Figure 2.

Peripheral techniques. These techniques involve block or destruction of portions of the trigeminal nerve distal to the Gasserian ganglia. Two small RCTs (Class I) on the use of streptomycin and lidocaine compared with lidocaine on its own showed no effect on pain.[9,74] Other peripheral lesions (including cryotherapy, neurectomies, alcohol injection, phenol injection, peripheral acupuncture, radiofrequency thermocoagulation) have all been reported as case series with no independent outcome assessment (Class IV). These studies showed that 50% of patients had a recurrence of pain after one year. The morbidity

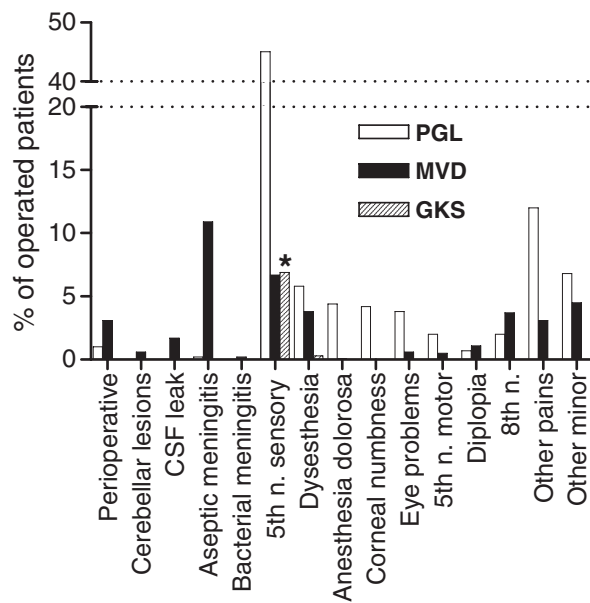


Figure 2 Complications of surgery. Frequency (%) of complications with surgical procedures for trigeminal neuralgia. PGL: Percutaneous Gasserian Lesions (includes radiofrequency thermocoagulation, glycerol rhizotomy, balloon compression). MVD: Microvascular Decompression. GKS: Gamma Knife Surgery. Data from 14 trials (Class III) in 2785 operated patients, detailed in Table 9. *: many Class IV studies on GKS report trigeminal sensory disturbances in 9–37% of patients.

associated with the peripheral procedures was low. There is no data on quality of life.

Percutaneous procedures on the Gasserian ganglion. These techniques [48] (also called percutaneous rhizotomies) involve penetration of the foramen ovale with a cannula and then controlled lesion of the trigeminal ganglion or root by various means: thermal (radiofrequency thermocoagulation, RFT),[75] chemical (injection of glycerol)[28] or mechanical (compression by a balloon inflated into Meckel's cave).[56] Notwithstanding the thousands of patients who underwent and currently undergo these percutaneous procedures, we only found uncontrolled case series. Only two reports on RFT, one on glycerol injection and one on balloon compression employed independent outcome assessors (Class III).[20,55,60,84] Ninety percent of patients attain pain relief from the procedures. Failure is often due to technical difficulties. At one year 68–85% of patients will be pain free but by three years this has dropped to 54–64%. At five years, around 50% of patients undergoing RFT are still pain free. Sensory loss after these percutaneous procedures is present in almost half of patients (Figure 2). Less than 6% develop troublesome dysesthesias. The incidence of anesthesia dolorosa is

around 4%. Post operatively 12% of patients report a discomfort described as burning, heavy, aching or tiring. Corneal numbness, with the risk of keratitis, occurs in 4% of patients. Problems with other cranial nerves are low, and the major peri-operative complication is meningitis, mainly aseptic (0.2%). Up to 50% of patients undergoing balloon compression suffer temporary and rarely chronic masticatory problems.[20] Mortality is extremely low.[80]

Gamma knife surgery. This is the only non-invasive technique, which aims a focused beam of radiation at the trigeminal root in the posterior fossa. There is one Class-I RCT comparing two different regimes.[24] This study showed no major differences between the gamma-knife techniques used. Additionally we found three case series (Class III) which used independent outcome assessment and provided long term follow-up.[49,64,67] At one year after gamma knife therapy complete pain relief with no medication occurs in up to 69% of patients. This falls to 52% at three years. Pain relief can be delayed for a mean of one month.[47] In the Class-III studies sensory complications average 6% only. But in large Class-IV series facial numbness is reported in 9–37% of patients (though it tends to improve with time) and troublesome sensory loss and/or paresthesias are reported in 6–13% (whereas anesthesia dolorosa is practically absent).[30,47,70,76] No complications outside the trigeminal nerve have been reported. Quality of life improves and 88% are satisfied with outcome.[67]

Microvascular decompression. This is a major neurosurgical procedure that entails craniotomy to reach the trigeminal nerve in the posterior fossa. Vessels compressing the nerve are identified and moved out of contact. The procedure aims to preserve trigeminal nerve function. Five reports were identified which used independent outcome assessment (Class III).[4,11,65,82,85] Ninety percent of patients obtain pain relief. Over 80% will still be pain free at one year, 75% at three years and 73% at five years. The average mortality associated with the operation is 0.2% though it may raise to 0.5% in some reports.[33,80] Postoperative morbidity is lowest in high volume units.[33] Up to 4% of patients incur major problems such as CSF leaks, infarcts or hematomas. Aseptic meningitis is the commonest complication (11%). Diplopia due to 4th or 6th nerve damage is often transient and 7th nerve palsy is rare. Sensory loss occurs in 7% of patients.[5] The major long term complication is ipsilateral hearing loss which can be as high as 10% depending on how it is evaluated (audiometry or subjective reports) (Figure 2).

Recurrences of pain after surgery. Recurrence of pain after surgical intervention, particularly ablative procedures, is common occurring in up to 50% of patients after 5 years. A few studies were identified that dealt with recurrences but their quality was poor and there were no studies that used independent observers.[80]

Conclusions. Percutaneous procedures on the Gasserian ganglion, gamma knife and microvascular decompression are possibly effective in the treatment of TN (multiple Class III studies). Microvascular decompression possibly provides the longest duration of pain freedom as compared to other surgical techniques. (multiple Class III studies). The evidence about peripheral techniques either is negative (two Class I about streptomycin/lidocaine) or is insufficient. (Class IV studies for all the other peripheral techniques).

Question 9

Which surgical techniques should be used in patients with multiple sclerosis?

Evidence. There are only small case series reporting treatment outcomes in patients with multiple sclerosis, with a general tendency toward lesser efficacy in this population. Most authors recommend the use of Gasserian ganglion procedures unless a definitive vascular compression of the trigeminal nerve is identified on MRI. Case reports of benefit of microvascular decompression in patients with MS suggest less efficacy than in non-MS patients.[12,22]

Conclusion. There is insufficient evidence to support or refute the effectiveness of the surgical management of TN in patients with MS. Due to uncertainty of surgical outcome, we believe that in this patients population pharmacotherapy should be carefully assessed and only patients with compelling evidence of drug resistant TN be considered for surgical procedures.

Recommendations on surgical treatment

For patients with TN refractory to medical therapy early surgical therapy may be considered (Level C). Percutaneous procedures on the Gasserian ganglion, gamma knife and microvascular decompression may be considered (Level C). Microvascular decompression may be considered over other surgical techniques to provide the longest duration of pain freedom (Level C). Although the evidence regarding the surgical management of TN in patients with MS is insufficient, we recommend that before surgical intervention pharmacological avenues be thoroughly explored (Clinical good practice point).

Conclusion and recommendations for future research

Regarding diagnosis, we conclude that the presence of trigeminal sensory deficits, bilateral involvement, or abnormal trigeminal reflexes are useful indicators of symptomatic TN, whereas younger age of onset, involvement of the first division, unresponsiveness to treatment, and abnormal trigeminal evoked potentials are not. We recommend the use of carbamazepine or oxcarbazepine as first choice pharmacological treatment in classical TN, and baclofen or lamotrigine as second choice. Although all the surgical procedures are inherently supported by low-level evidence, the results in thousands of patients indicates that the surgical treatments for trigeminal neuralgia are efficacious and acceptably safe. An evidence-based direct comparison between the different surgical procedures is so far impossible. To briefly differentiate them, however, we may summarise that the percutaneous Gasserian lesions can be safely performed in the elderly but often engender facial numbness, microvascular decompression provides the longest-lasting pain relief but involves some risk of major neurological complications, gamma-knife is the least invasive and safest procedure but pain relief may take one month to develop.

To improve the management of TN, a number of studies would be useful: population-based studies of TN patients to determine true prevalence of STN in TN patients without non-trigeminal symptoms; more prospective cohort surveys of TN patients to determine which clinical characteristics and electrophysiological studies identify STN patients; cohort surveys of CTN patients planning MVD, all having high resolution preop MRI with characterization of vascular contact, if any; RCTs of newer drugs compared to carbamazepine with adequate assay sensitivity and focus on all relevant outcomes including tolerability, safety and quality of life; studies directly addressing the definition of pharmacoresistance and the appropriateness of referral to surgery; RCTs in symptomatic TN patients; RCTs comparing different surgical techniques; long term cohort studies to determine how quickly medical management fails.

Finally, we regard this first attempt to produce joint AAN-EFNS guidelines largely successful. All the specific problems of trigeminal neuralgia and the search results that are reported here, were fully agreed by American and European authors. Difficulties only arose with the grading of recommendations that eventually led to two slightly different documents. We feel that AAN and EFNS should make further efforts to overcome the remaining problems.

Declaration of conflict of interest

The following authors (initials) gave lectures or participated in advisory boards for the following pharmaceutical companies: GC: Lundbeck, Novartis, Pfizer; GG: Böhringer, GlaxoSmithKline, Pfizer; TN: Allergan, Astra-Zeneca, GlaxoSmithKline, GWPharma, Napp, Novartis, Pfizer, Renovis, SchwarzPharma, Wyeth; JMZ: UCB Pharma.

The authors have no other conflicts to declare.

Supplementary material

The following supplementary material is available for this article online:

Appendix S1. Comparison of the AAN and EFNS methods of classifying evidence and grading recommendations.

Appendix S2. Extended list of references.

The material is available as part of the online article from: <http://www.blackwell-synergy.com/doi/abs/10.1111/j.1468-1331.2008.02185.x>

(This link will take you to the article abstract).

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