

Novel Therapies in Trigeminal Neuralgia: A Narrative Review

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Abstract

Background: Trigeminal neuralgia (TN) is a severe neuropathic pain disorder for which treatment remains largely dependent on sodium-channel blockers. Although carbamazepine and oxcarbazepine are effective initially, adverse effects and treatment failure drive the search for novel therapies.

Objective: To review emerging therapies for TN according to their level of clinical evidence and identify barriers to translation.

Methods: PubMed, Embase, the Cochrane Library and ClinicalTrials.gov were searched for literature on emerging pharmacological, neuromodulatory and molecular therapies in TN and trigeminal neuropathic pain.

Findings: Botulinum toxin type A has the strongest clinical evidence among novel therapies, with randomized trials demonstrating pain reduction. Sodium-channel approaches have produced mixed results, with vixotrigine failing its phase 2a endpoint, while the selective Nav1.8 inhibitor suzetrigine has not been studied in TN. A randomized trial of erenumab targeting CGRP was negative. Neuromodulation, including transcranial magnetic stimulation, peripheral stimulation and deep brain stimulation, remains supported mainly by small studies. Cannabinoid, gene-transfer and glial-directed therapies remain largely preclinical.

Conclusion: Despite expanding understanding of TN pathophysiology, translation into effective novel treatments remains limited. Diagnostic heterogeneity and methodological challenges continue to impede progress. Future research should prioritize mechanism-based trials and better patient stratification.

Keywords: trigeminal neuralgia; neuropathic pain; sodium channels; botulinum toxin; neuromodulation; emerging therapies.

Introduction

Trigeminal neuralgia is defined by recurrent, unilateral, electric shock-like pain confined to one or more divisions of the trigeminal nerve, abrupt in onset and termination and frequently provoked by innocuous stimuli such as light touch, chewing or a draught of cold air. The third edition of the International Classification of Headache Disorders distinguishes classical TN, attributable to morphological change in the trigeminal root from neurovascular compression, from secondary TN due to an identifiable neurological disease, and from idiopathic TN in which no cause is demonstrable.^{1,2}

Few conditions carry a comparable burden. Patients describe interference with eating, speaking, oral hygiene and social contact, and the disorder is associated with substantial reductions in quality of life and with psychiatric comorbidity.³ Against this, the therapeutic armamentarium is narrow. European Academy of Neurology guidance recommends carbamazepine or oxcarbazepine as first-line long-term treatment, with lamotrigine, gabapentin, botulinum toxin type A, pregabalin, baclofen and phenytoin available alone or as add-on therapy, and surgery offered when pain is not sufficiently controlled.⁴ Both first-line agents predate the modern understanding of the disorder, require slow titration, interact widely and are limited by sedation, ataxia, hyponatraemia and haematological monitoring requirements.^{5,6}

The last decade has produced a substantial body of work on new molecular targets and delivery strategies: subtype-selective sodium channel inhibitors, glutamatergic modulators, neuropeptide-directed biologics, cannabinoid receptor ligands, viral vector gene transfer to the trigeminal ganglion, glial modulation and several forms of central and peripheral neuromodulation. Reviews of this literature typically organise it by mechanism, which has the effect of presenting approaches supported by a single rodent study alongside those with replicated randomised evidence. This review takes a different organising principle. Emerging therapies are grouped by the level of evidence they have actually attained in human TN, from replicated randomised data through active clinical programmes to preclinical proof of concept. The purpose is to make explicit where translation has succeeded, where it has failed, and what the failures suggest about the design of future trials.

Methods

PubMed, Embase, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov were searched from database inception to the date of writing. Search terms combined “trigeminal neuralgia”, “trigeminal neuropathic pain” and “orofacial pain” with “sodium channel”, “Nav1.7”, “Nav1.8”, “botulinum toxin”, “cannabinoid”, “gene therapy”, “transcranial magnetic stimulation”, “deep brain stimulation”, “peripheral nerve stimulation”, “monoclonal antibody”, “CGRP”, “microglia” and “neuroinflammation”.

English-language randomised controlled trials, systematic reviews, meta-analyses, observational cohorts, case series, preclinical studies and registered protocols were eligible. Reference lists of retrieved articles and relevant guidelines were hand-searched. Where a therapy had been evaluated in trigeminal neuropathic pain or in mixed facial pain populations rather than in classical TN, this is stated explicitly in the text, because the distinction materially affects how the evidence should be read. Selection of studies for discussion was purposive rather than exhaustive, prioritising the highest available level of evidence for each therapeutic class.

Pathophysiological basis for new targets

Contemporary models of classical TN centre on focal demyelination of the trigeminal root entry zone, most often produced by pulsatile arterial compression. Demyelination permits ephaptic transmission between adjacent axons and generates hyperexcitable membranes capable of high-frequency afterdischarge. A light tactile stimulus carried by large myelinated fibres can therefore cross into nociceptive afferents and trigger a paroxysm, which accounts for the characteristic trigger phenomenon and for the refractory period that follows an attack.^{2,4}

Voltage-gated sodium channels are central to this account, which explains both the efficacy of carbamazepine and the persistent interest in subtype-selective blockade. Nav1.7, Nav1.8 and Nav1.3 are upregulated after trigeminal nerve injury, and the channels responsible for pathological high-frequency firing are in principle separable from those sustaining normal low-frequency signalling.^{2,12}

Figure 1 sets out the principal anatomical loci at which TN pain signalling is generated and relayed, together with the sites at which each class of emerging therapy is proposed to act.

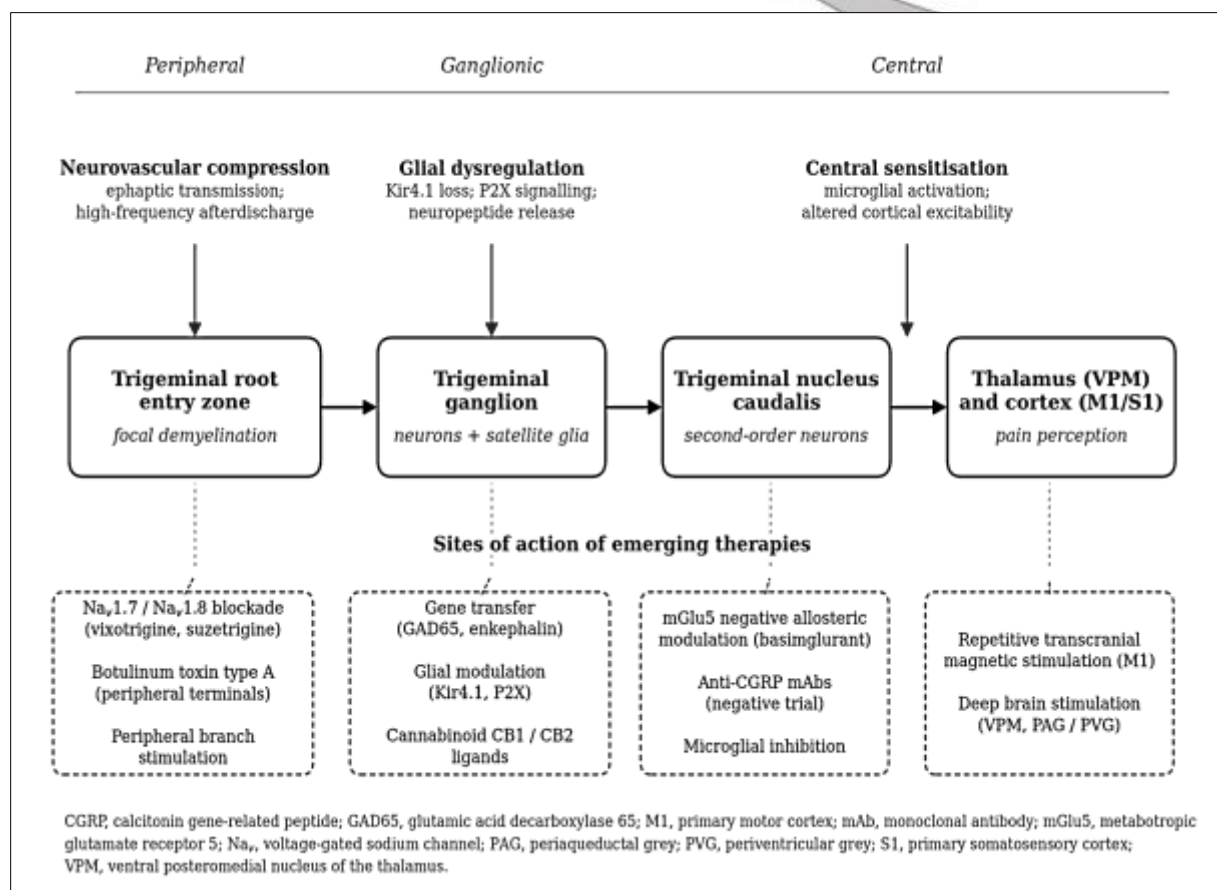


Figure 1: Anatomical loci of trigeminal pain signalling and the proposed sites of action of emerging therapies. The upper annotations indicate the principal pathological processes at each level; the lower boxes indicate the therapeutic classes discussed in this review. Placement reflects the proposed primary site of action and does not imply demonstrated clinical efficacy at that site.

Peripheral events do not exhaust the pathophysiology. Nerve injury within the trigeminal ganglion disturbs satellite glial cell homeostasis, with loss of Kir4.1 potassium channels and a shift toward purinergic P2X receptor signalling; centrally, microglial activation in the trigeminal nucleus caudalis and in cortical territories contributes to sensitisation.^{7,8} This neuro-immune dimension has provided the rationale for glial-directed and cytokine-directed strategies. Endocannabinoid signalling,⁹ glutamatergic transmission through metabotropic receptors, and the release of neuropeptides including substance P and calcitonin gene-related peptide from trigeminal afferents supply further candidate targets.² Each of these is biologically defensible; as the following sections show, biological plausibility has proved a poor predictor of clinical benefit.

Emerging pharmacological approaches

1. Botulinum toxin type A: the current benchmark

Botulinum toxin type A (BTX-A) occupies an unusual position. It is frequently described as an emerging therapy, yet it is the only novel agent in TN supported by replicated randomised evidence and incorporated into guidelines,⁴ and it is therefore better treated as the standard against which newer candidates should be measured.

Its analgesic action is not attributable to muscle relaxation. BTX-A cleaves SNARE proteins and thereby inhibits the release of substance P, CGRP and glutamate from peripheral nociceptors, and downregulates TRPV1 expression at the nociceptor surface.^{10,11} A systematic review and meta-analysis of four randomised controlled trials including 178 patients found the proportion of responders significantly favoured BTX-A over placebo, with a risk ratio of 2.87 (95% CI 1.76 to 4.69).¹⁰ A later meta-analysis of ten randomised trials in TN and peripheral neuropathic pain, comprising

391 patients, reported standardised mean differences in pain intensity of -0.58 (95% CI -0.91 to -0.24) at two months and -0.55 (95% CI -0.87 to -0.22) at three months.¹¹

The limitations are equally clear. Individual trials are small, most carry a high risk of bias, injection protocols and doses differ substantially between centres, and blinding is compromised by the visible effects of the toxin.^{10,11}

Transient facial asymmetry and injection-site oedema are common but self-limiting. The EAN guideline lists BTX-A among agents that may be used alone or as add-on therapy,⁴ a position that reflects both genuine efficacy and the modest quality of the underlying evidence.

2. Nav1.7-preferring blockade: the vixotrigine experience

Vixotrigine (BIIB074, formerly CNV1014802) was designed for TN and offered the clearest test to date of subtype-selective sodium channel blockade in this disorder. It is a voltage- and use-dependent blocker that preferentially binds the inactivated channel state, conferring selectivity for channels engaged in high-frequency pathological firing over those carrying normal low-frequency traffic.^{12,13}

The phase 2a study used an enriched enrolment randomised withdrawal design, adopted because prolonged placebo exposure in TN raises evident ethical difficulty and because carbamazepine is unsuitable as an active comparator given its pharmacokinetic interactions.¹² The primary endpoint, treatment failure, was not met.¹⁴ Secondary data did favour active treatment, notably a significant reduction in the number of daily paroxysms, and on this basis two phase 3 randomised withdrawal studies were initiated.^{13,14,15} Neither reported a positive outcome, and the programme was discontinued in 2023.

This sequence deserves more attention than it usually receives. Vixotrigine had a coherent mechanism, a purpose-built trial design and a favourable tolerability profile, and it still failed. Whether the failure reflects insufficient subtype selectivity, an inadequate therapeutic window, the statistical fragility of randomised withdrawal designs in small populations, or a genuine limit to what peripheral sodium channel blockade can achieve in a disorder with a central component, remains unresolved. Any review presenting selective sodium channel modulation as a promising direction has an obligation to state that the field's most advanced attempt did not succeed.

3. Nav1.8 inhibition: relevance by extrapolation

Nav1.8 is selectively expressed in peripheral nociceptors and dorsal root ganglion neurons and is absent from the brain, a distribution that predicts analgesia without central adverse effects or abuse liability.^{16,17} Suzetrigine (VX-548), a selective Nav1.8 inhibitor, was approved by the United States Food and Drug Administration in January 2025 for moderate to severe acute pain, the first non-opioid analgesic of a new class to be approved in over two decades.¹⁷ A phase 2 randomised, active-controlled study in painful diabetic peripheral neuropathy, enrolling 192 patients with pregabalin as an active reference, met its primary endpoint of change in the numeric pain rating scale.¹⁶

It must be stated plainly that no trial of suzetrigine or of any other selective Nav1.8 inhibitor has been conducted in trigeminal neuralgia. Peripheral neuropathic pain has been identified as a development priority and TN is named among the conditions within that category, but the current evidence base permits only extrapolation. Given that TN differs from length-dependent polyneuropathy in mechanism, in the paroxysmal character of the pain and in its response to sodium channel blockade, and given the vixotrigine outcome, that extrapolation should be made cautiously.

4. Metabotropic glutamate receptor modulation

Metabotropic glutamate receptor 5 (mGlu5) regulates neurotransmitter release and postsynaptic responsiveness in both central and peripheral nervous systems, and mGlu5 activity potentiates NMDA receptor currents. Negative allosteric modulation of mGlu5 therefore offers a route to attenuating excitatory transmission without direct NMDA receptor blockade.

Basimglurant (NOE-101), an orally bioavailable mGlu5 negative allosteric modulator with a long half-life supporting once-daily dosing, was previously investigated in major depressive disorder and fragile X syndrome and received FDA Fast Track designation for TN in 2022. It is currently the most advanced dedicated TN drug programme. The phase 2/3 LIBRA study uses an enriched randomised withdrawal design in adults meeting ICHD-3 criteria for primary TN with at least three moderate to severe paroxysms daily, with time to loss of efficacy as the primary outcome, an eight-week open-label run-in, an enrolment target of approximately 200 patients yielding around 70 randomised responders, and a 52-week open-label extension. Secondary measures include paroxysm severity, continuous pain, the Penn Facial Pain Scale-Revised and the Patient Global Impression of Change.¹⁸

Results are not yet available. The programme is nonetheless notable for adopting an outcome measure, durability of response, that addresses the clinically salient problem of waning efficacy rather than short-term pain reduction alone.

5. Neuropeptide- and cytokine-directed biologics

CGRP is released from trigeminal afferents, is implicated in trigeminal sensitisation and has been reported at altered concentrations in TN. Open-label reports and a retrospective case series suggested benefit from erenumab, a monoclonal antibody against the CGRP receptor with established efficacy in migraine, and the mechanistic case appeared strong.¹⁹

A randomised, double-blind, placebo-controlled trial conducted at the Danish Headache Centre tested this directly in adults with classical or idiopathic TN. There was no difference between groups in responder rate at four weeks: 14 of 40 patients (35%) receiving erenumab versus 18 of 40 (45%) receiving placebo, an estimated effect size of -10% (95% CI -31 to 11; $p=0.36$). Adverse events occurred in 20 of 40 patients in each group. The investigators concluded that erenumab did not reduce pain intensity relative to placebo and that CGRP probably does not have an important role in the transmission of paroxysmal pain in TN.²⁰

This is a clearly negative result and should be reported as such. It also carries a methodological lesson, since the open-label and retrospective data that preceded the trial pointed in the opposite direction,¹⁹ illustrating how readily uncontrolled observation misleads in a condition with a fluctuating natural history and a substantial placebo response.

Tumour necrosis factor alpha (TNF-alpha) has been proposed as an alternative biologic target. Endoneural injection of TNF-alpha into the rat trigeminal nerve produces mechanical and thermal allodynia and is used as a model of TN, and cytokine-directed intervention attenuates neuroinflammatory signalling in rodent orofacial pain models.⁷ No trial of a TNF-alpha directed biologic has been performed in human TN, and the evidence remains entirely preclinical.

6. Cannabinoid-based therapies

Cannabinoid CB1 and CB2 receptors are expressed in the periaqueductal grey and rostral ventromedial medulla, structures central to descending pain modulation, and in immune cells including microglia. Synthetic cannabinoids inhibit allodynia and hyperalgesia in the rat infraorbital nerve constriction model, and inhibition of monoacylglycerol lipase, which degrades the endocannabinoid 2-arachidonoylglycerol, attenuates neuropathic orofacial pain following trigeminal nerve injury in mice. Strategies targeting CB2 receptors or peripherally restricted CB1 receptors have been developed specifically to avoid the sedation, cognitive impairment and dependence liability associated with central CB1 activation.⁹

Human evidence in TN is limited to observational reports and case-level documentation. No randomised controlled trial of a cannabinoid has been completed in TN. The class is therefore best characterised as mechanistically supported and clinically untested, and the regulatory and formulation heterogeneity of cannabis-derived products further complicates interpretation of the observational literature.

Neuromodulation

Neuromodulation for TN presents a recurring interpretive difficulty. Most published series pool classical TN with trigeminal neuropathic pain, post-herpetic neuralgia, anaesthesia dolorosa, post-traumatic facial pain and persistent idiopathic facial pain.²³⁻²⁵ These entities differ in mechanism and in expected response, and classical TN is usually a minority of the sample. Reported outcomes should not be read as applying straightforwardly to classical TN.

1. Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) delivered to the primary motor cortex (M1) contralateral to the pain is the best-established non-invasive approach for neuropathic pain, although benefits are variable and frequently short-lived. In facial pain specifically, a randomised sham-controlled cross-over study compared MRI-guided rTMS delivered to the M1 representation of the painful face against the adjacent hand area and against sham, addressing the question of optimal target within M1.²¹

Longer-term application has been documented in a patient with TN refractory to microvascular decompression who underwent 73 sessions of 10 Hz rTMS over 23 months, with 70.89% overall pain reduction, progressive dose reduction and eventual discontinuation of medication, and no serious adverse events.²²

The technique is safe and non-invasive, which lowers the threshold for trial. Against this, sample sizes are small, stimulation parameters and targets are not standardised, the durability of effect is uncertain, and blinding is difficult because active stimulation produces distinctive scalp sensation. Evidence that rTMS modifies cortical network dynamics does not by itself establish clinical benefit.

2. Peripheral trigeminal branch stimulation

Implanted stimulation of the supraorbital and infraorbital nerves is technically straightforward, reversible and generally well tolerated, and it is most often applied when microvascular decompression is unsuitable or has failed.

In a single-centre series of 15 patients undergoing supraorbital and/or infraorbital stimulation for facial pain of post-herpetic, traumatic or idiopathic origin, 12 (80%) reported more than 50% pain relief during the trial stimulation period and median visual analogue scores fell from 7 preoperatively to 1.8 postoperatively; over a median 5.8 months following permanent implantation, one patient experienced lead erosion with generator migration, two developed lead infections and one had wound dehiscence.²³

A further single-institution series reported 19 patients undergoing trial electrode placement with 15 proceeding to permanent implantation, the commonest diagnoses being idiopathic TN type 2 and trigeminal neuropathic pain; at a median follow-up of 14 months, 12 of 15 implanted patients (80%) remained on stimulation with mean pain reduction of 52.3%, although infection and revision rates were high.²⁴ Peripheral nerve field stimulation has similarly been reported in a mixed series in which four patients had recurrent classical TN, with mean visual analogue scores falling from 9.3 preoperatively to 0.75 postoperatively.²⁵ A systematic review and meta-analysis of 13 studies including 221 participants estimated a pooled response rate of 61.3% (95% CI 44.4 to 75.9) at last follow-up, with substantial heterogeneity.²⁶

These results are encouraging but derive predominantly from retrospective, unblinded, single-centre experience in small and diagnostically heterogeneous cohorts, with classical TN consistently in the minority. Hardware complications including lead migration, erosion and infection are not rare.

3. Deep brain stimulation

Deep brain stimulation of the ventral posteromedial nucleus of the thalamus, generally combined with periaqueductal or periventricular grey stimulation, has the longest history of any approach considered here, dating to work on facial anaesthesia dolorosa in the 1970s. It remains an off-label, investigational indication, principally because two randomised trials conducted in 1976 and 1990 failed to demonstrate efficacy.²⁷

Contemporary series are small and report mixed outcomes. Seven consecutive patients with unilateral intractable neuropathic facial pain treated with VPM and periaqueductal grey stimulation showed approximately 70% pain reduction, with maximal benefit up to nine months postoperatively.²⁷ A separate series of nine patients with post-stroke, post-traumatic, post-herpetic or atypical facial pain reported eight permanent implantations, with mean visual analogue scores falling from 9.4 to 6.1 over a mean 40.3 months in the seven with adequate follow-up.²⁸

The relevance of these data to classical TN is limited. The patients in these series predominantly had deafferentation or post-stroke facial pain rather than classical paroxysmal TN, and classical TN in any case has effective and less invasive surgical options in microvascular decompression, percutaneous procedures and stereotactic radiosurgery.⁴ Deep brain stimulation is best regarded as a consideration for trigeminal deafferentation pain and anaesthesia dolorosa, not as an emerging therapy for classical TN. Advances in sensing-capable devices, which permit longitudinal recording of local field potentials and the identification of candidate electrophysiological biomarkers in the VPM, may improve patient selection and stimulation programming.

Preclinical and molecular frontiers

The approaches in this section have not entered human testing in TN. They are included because they define plausible future directions, and they are separated from the preceding sections to avoid conveying a level of readiness that the evidence does not support.

1. Gene therapy

The trigeminal ganglion is comparatively accessible and anatomically circumscribed, which makes it an attractive target for local vector delivery. Two rodent strategies are established. Injection of a serotype 5 adenoviral vector encoding glutamic acid decarboxylase 65 into the rat trigeminal ganglion produced sustained GAD65 expression in satellite glial cells over four weeks with local GABA synthesis; treated animals showed significantly reduced pain behaviour in the orofacial formalin test, an effect abolished by the GABA-A antagonist bicuculline but not by a GABA-B antagonist, and absent in animals receiving control vectors.²⁹ Separately, viral-driven enkephalin overproduction in trigeminal ganglion neurons attenuated pain-related behaviour in a rat model of trigeminal neuropathic pain.³⁰ Optogenetic inhibition of the trigeminal ganglion has provided further proof that local intervention at this site can relieve pain behaviour in a TN model.³¹

These findings establish that local vector delivery can produce target engagement and antinociception in the trigeminal system. They do not establish clinical readiness. No first-in-human gene therapy trial has been undertaken in TN. Vector immunogenicity, durability and reversibility of expression, the consequences of irreversible modification of a sensory ganglion, and the regulatory pathway for an intraganglionic vector in a non-fatal condition

all remain unaddressed. The correct description of gene therapy in TN is preclinical proof of concept, and characterisations suggesting that clinical trials are under way are not accurate.

2. Neuro-glial interaction therapies

Glial cells are now recognised as active participants in chronic orofacial pain rather than passive bystanders. A systematic review of animal models found that activation of satellite glial cells, microglia and astrocytes was consistently associated with increased neuroinflammatory signalling and enhanced neuronal excitability within trigeminal pathways, involving both peripheral and central compartments, and that pharmacological modulation of glial activity reduced pain-related behaviour.⁷

Pharmacological support comes largely from minocycline, a non-selective microglial inhibitor. In a mouse model of trigeminal neuropathic pain, microglia in the primary somatosensory barrel cortex were activated with changes in density and morphology, and intraperitoneal minocycline attenuated pain sensitisation and reduced glutamatergic neuronal activity; chemogenetic inhibition of the same neuronal population relieved mechanical allodynia, while chemogenetic activation in naive animals induced pain sensitisation.⁸

The limitation is the absence of selective, clinically usable agents. Minocycline is a research tool with multiple actions and an unfavourable profile for chronic administration, and glial activation is a general feature of neuropathic pain rather than a TN-specific mechanism. Advancing this area requires targeted compounds acting on defined glial pathways, such as Kir4.1 restoration or selective P2X antagonism, and a demonstration that the target is engaged in human disease.

Synthesis

Table 1 summarises the therapies considered, the target of each, the highest level of evidence attained in TN and the principal limitation.

Table 1: Emerging therapies in trigeminal neuralgia by target, evidence level and principal limitation.

THERAPY	MOLECULAR / ANATOMICAL TARGET	HIGHEST LEVEL OF EVIDENCE IN TN	PRINCIPAL LIMITATION
Botulinum toxin type A	SNARE-mediated release of substance P, CGRP, glutamate; TRPV1	Multiple RCTs; two meta-analyses; EAN add-on recommendation ^{4,10,11}	Small trials, high risk of bias, transient facial asymmetry
Vixotrigine (BIIB074)	State- and use-dependent Nav blockade (Nav1.7-preferring)	Phase 2a primary endpoint not met; phase 3 discontinued 2023 ¹²⁻¹⁵	Programme terminated; no marketing authorisation
Suzetrigine (VX-548)	Selective Nav1.8 inhibition in peripheral nociceptors	Approved for acute pain; phase 2 in diabetic neuropathy; no TN trial ^{16,17}	No TN-specific efficacy data; extrapolation only
Basimglurant (NOE-101)	mGlu5 negative allosteric modulation	Phase 2/3 randomised withdrawal trial (LIBRA) in progress ¹⁸	Results not yet reported
Anti-CGRP mAbs (erenumab)	CGRP receptor	Negative randomised placebo-controlled trial ²⁰	No benefit over placebo; mechanism appears not to apply
TNF-alpha directed biologics	TNF-alpha signalling in trigeminal ganglion	Rodent models only ⁷	No human TN data; systemic immunosuppression risk
Repetitive TMS	Contralateral primary motor cortex (M1)	Small randomised sham-controlled studies; case reports ^{21,22}	Short-lived effect; heterogeneous protocols; sham blinding

THERAPY	MOLECULAR / ANATOMICAL TARGET	HIGHEST LEVEL OF EVIDENCE IN TN	PRINCIPAL LIMITATION
Peripheral trigeminal branch stimulation	Supraorbital / infraorbital nerves	Retrospective series; one meta-analysis of mixed cohorts ²³⁻²⁶	Mostly TN type 2 and neuropathic pain, not classical TN; hardware complications
Deep brain stimulation	VPM thalamus; PAG / PVG	Small retrospective series; two historical negative RCTs ^{27,28}	Off-label; predominantly deafferentation pain, not classical TN
Cannabinoid-based therapy	CB1 and CB2 receptors; endocannabinoid-degrading enzymes	Rodent models; observational reports only ⁹	No completed RCT in TN; product and dose heterogeneity
Gene therapy (GAD65, enkephalin)	Trigeminal ganglion neurons and satellite glia	Rodent models only ^{29,30}	No first-in-human trial; vector safety and durability unresolved
Glial modulation (e.g. minocycline)	Microglia, satellite glial cells, Kir4.1, P2X receptors	Rodent models only ^{7,8}	Non-specific agents; no TN-specific human trial

CGRP, calcitonin gene-related peptide; EAN, European Academy of Neurology; mAb, monoclonal antibody; mGlu5, metabotropic glutamate receptor 5; Nav, voltage-gated sodium channel; PAG, periaqueductal grey; PVG, periventricular grey; RCT, randomised controlled trial; TMS, transcranial magnetic stimulation; TN, trigeminal neuralgia; VPM, ventral posteromedial nucleus of the thalamus.

Figure 2 presents the same information as a translational readiness map, plotting each therapy against the furthest stage of evaluation it has reached in TN specifically and indicating the direction of the result where one exists.

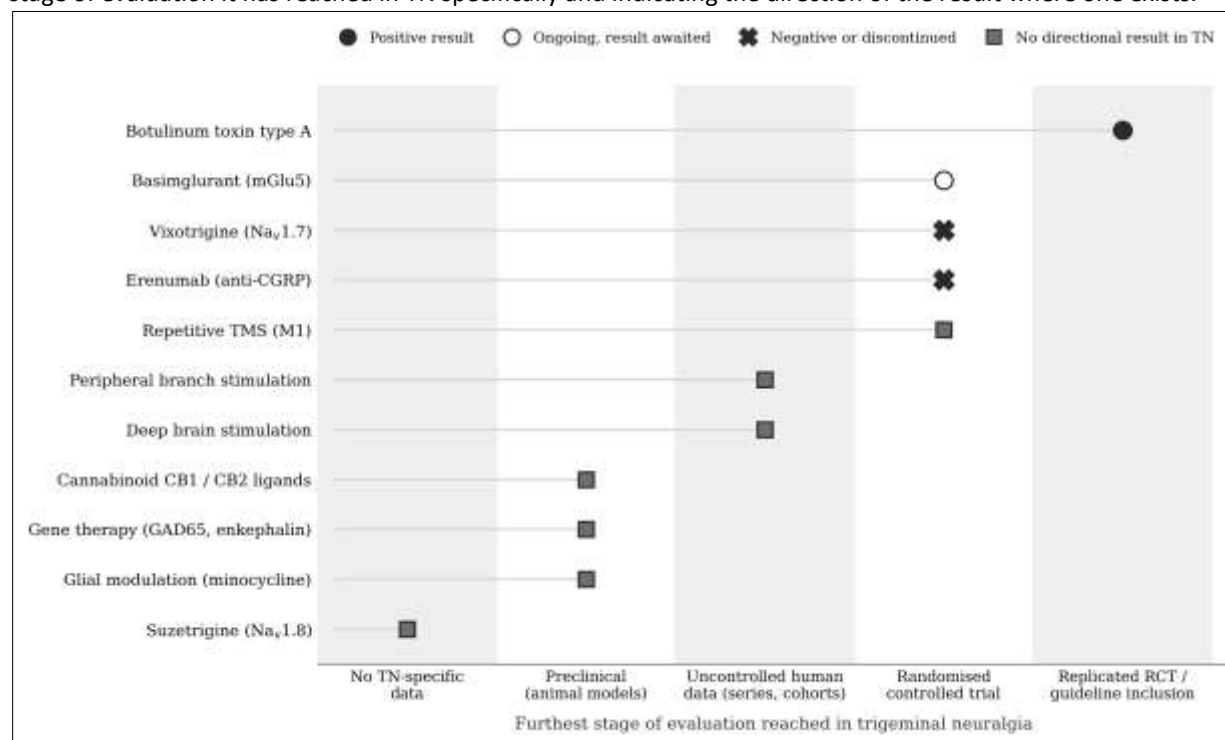


Figure 2: Translational readiness of emerging therapies in trigeminal neuralgia. Each therapy is plotted at the furthest stage of evaluation reached in TN specifically; suzetrigine appears in the leftmost category because, despite an

extensive clinical programme in other pain conditions, it has not been studied in TN. Deep brain stimulation is plotted at uncontrolled human data because the two historical randomised trials were conducted in chronic pain broadly rather than in TN, and contemporary evidence in facial pain is limited to small retrospective series. Marker position reflects evidential stage, not relative clinical value.

Read together, three observations follow. First, the distribution of evidence is heavily skewed: one therapy has replicated randomised support, one is in an active late-phase programme, and the remainder are preclinical or supported only by small uncontrolled series. Second, two well-founded mechanistic hypotheses have been tested rigorously and rejected, in the case of CGRP receptor blockade, or have failed to demonstrate benefit, in the case of Nav1.7-preferring blockade. Third, the neuromodulation literature systematically conflates classical TN with other facial pain syndromes, so that apparently favourable response rates cannot be assumed to apply to classical TN.

The obstacle is therefore not a shortage of candidate mechanisms. It lies in the conditions under which those mechanisms can be tested. Trigeminal neuralgia is uncommon, which constrains recruitment; the pain is severe enough that prolonged placebo exposure is ethically problematic; carbamazepine is unsuitable as an active comparator because of its pharmacokinetic complexity; and the natural history is fluctuating, with spontaneous remissions that inflate apparent response in uncontrolled studies.¹² Enriched enrolment randomised withdrawal designs were adopted to address these constraints, but they are statistically demanding in small samples and carry their own carry-over and unblinding vulnerabilities.

Limitations

This review is narrative rather than systematic. The search was not registered, study selection was purposive, no formal risk-of-bias instrument was applied and no quantitative synthesis was performed; selection bias in the choice of studies discussed cannot be excluded. Restriction to English-language publications may have omitted relevant work, particularly from centres where botulinum toxin and radiofrequency techniques are extensively used.

Several therapies are supported principally by conference abstracts, protocol publications or registry entries rather than by peer-reviewed outcome reports, and negative or discontinued programmes are systematically under-reported in the published literature, so the true picture may be less favourable than the one presented here. Where evidence derives from mixed facial pain cohorts this is stated, but residual uncertainty about applicability to classical TN remains. Finally, the field is moving quickly and readers should verify the status of ongoing trials at the time of reading.

Future directions

Four priorities emerge from this synthesis. First, trial populations should be defined by ICHD-3 criteria and reported separately for classical, idiopathic and secondary TN, and for purely paroxysmal TN versus TN with concomitant continuous pain, since these subtypes plausibly differ in their response to peripherally and centrally acting agents.¹ The pooling of classical TN with trigeminal neuropathic pain in the neuromodulation literature is the single most correctable weakness in the current evidence base.

Second, outcome measures should reflect what matters clinically. Durability of response, rather than short-term pain intensity, is the relevant endpoint in a disorder where initial efficacy is common and loss of efficacy is the usual reason for treatment failure; the LIBRA design reflects this shift.¹⁸

Third, multicentre collaboration is necessary. Single centres cannot recruit adequately powered samples in a disorder of this incidence, and the recurring pattern of underpowered single-centre series contributes directly to the uncertainty documented above.

Fourth, biomarker development deserves investment. Candidate approaches include quantitative sensory testing, trigeminal reflex testing, advanced imaging of the root entry zone, cerebrospinal fluid neuropeptide profiling and, in implanted patients, thalamic local field potential recording. Stratification by mechanism would allow trials to enrol patients in whom a given target is plausibly operative, rather than testing every agent against an undifferentiated population.

Conclusion

Emerging therapies for trigeminal neuralgia span a wide mechanistic range, but the evidence supporting them is far more uneven than mechanism-organised reviews tend to convey. Botulinum toxin type A is the only novel agent with replicated randomised support and guideline endorsement. The metabotropic glutamate receptor 5 programme is the most advanced dedicated development effort and its results are awaited. Against these, the discontinuation of the vixotrigine phase 3 programme and the clearly negative erenumab trial demonstrate that mechanistic plausibility in trigeminal pain does not reliably predict clinical benefit.

Neuromodulation retains a place in carefully selected refractory patients, with the important qualification that most supporting evidence derives from trigeminal neuropathic pain rather than classical TN. Cannabinoid, gene-transfer and glial-directed strategies remain preclinical and should be described as such.

Progress will depend less on identifying further targets than on improving the conditions under which they are evaluated: precise diagnostic classification, adequately powered multicentre trials, endpoints that capture durability, and biomarkers that permit mechanistic stratification. Until these are in place, patients with trigeminal neuralgia will continue to depend on drugs introduced before the pathophysiology of their disorder was understood.

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