Chapter 12
Treatment of Trigeminal Autonomic Cephalalgias and Other Primary Headaches

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Introduction

This chapter is the bookend to Chap. 2, "Diagnosis of the Trigeminal Autonomic Cephalalgias" and Chap. 3, "Diagnosis of Other Primary Headaches." Because Trigeminal Autonomic Cephalalgias (TACs) are so severe, treatment must be very aggressive. Treatment comprises acute treatment, preventive treatment, and, in the case of cluster headaches (CH), transitional or "bridge" therapy.

Acute treatment is of the essence, as attacks peak in seconds to minutes. Prevention is mandatory for TACs as well, when feasible. Transitional therapy is a bridge between abortive therapy and the (successful) establishment of preventive therapy and plays an important role in managing CH. Because cluster attacks are so terrible, transitional therapy is a compassionate act in between acute and preventive treatment.

Treatment of the Trigeminal Autonomic Cephalalgias

Cluster Headache

The treatment goals for cluster are (1) to terminate an attack within 15 min or less acutely, (2) to induce remission with preventive treatment, and (3) to offer a transitional treatment to buy headache freedom long enough to get the effective preventive treatment in place (Table 12.1).

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S. J. Tepper, D. E. Tepper (eds.), *The Cleveland Clinic Manual of Headache Therapy, Second Edition,* DOI 10.1007/978-3-319-04072-1_12,

Table 12.1 Goals for treatment of cluster headache

- To abort a cluster headache (CH) as quickly as possible (within 15 min or less). This is the *acute or abortive therapy*
- To induce a remission, preferably a lasting remission. This is the *preventive therapy,* and it may take weeks to induce
- Initiate *transitional* or *bridge therapy* that "buys" headache freedom and enough time for the preventive therapy to work

Table 12.2 Level A-recommended acute treatment of cluster headache attacks

Level A-recommended abortive measures for acute cluster headache attack on the basis of Class 1 studies

- Sumatriptan 6 mg subcutaneously → headache relief[a] in 15 min (FDA approved)
- Sumatriptan 20 mg nasal spray → headache relief in 30 min
- Zolmitriptan 5 mg nasal spray → headache relief in 30 min
- Oxygen 100 % (high-flow mask)
  - 12 L/min → pain-free[b] at 15 min

[a] Headache relief is defined as the transition of a moderate or severe headache to a mild or no headache at the measured time point

[b] Headache- or pain-free indicates the complete termination of pain in a moderate or severe headache at the measured time point

Acute or Abortive Therapy of Cluster Headache

To the patient in the throes of a CH attack, the most important goal is to abort the unrelenting pain. For most patients, the interictal period between attacks is pain-free or only mildly uncomfortable, but the seasoned cluster veteran fears that the headaches, brief though they may be, will return, recur, and persist. Many patients will voice their trepidation about falling asleep at night, as headaches commonly "crash" into the rapid eye movement (REM) sleep onset. Because alcohol triggers CH, I have seen a male patient with well-entrenched alcoholism opt to suffer delirium tremens rather than *look* at a bottle of gin, much less take a drink from it, during a cluster period!

This section will discuss treatments that are effective and safe, using the principles of evidence-based medicine (EBM), in which prospective, randomized, controlled trials with clearly defined outcomes and inclusion/exclusion criteria (i.e., Class 1 studies) are included, and treatment groups are large and similar enough in clinical characteristics to allow a comparison of effects. In certain situations, agents will be recommended based not on controlled studies, but on a long history of clinical experience by established clinics in the field of headache medicine.

The following acute cluster medications, listed in Table 12.2, are supported by at least two Class 1 studies with end points of either pain freedom or pain relief (≥ 50 % pain reduction from baseline) at either 15 or 30 min, depending on the study. They are granted a Level A recommendation ("Established as effective…or established as

Table 12.3 Other acute treatments of cluster headache attacks

Abortive medications that do not meet Level A (due to inadequate studies or only one Class 1 study)
• Zolmitriptan 5 mg or 10 mg oral tablet → headache relief in 30 min
• Nasal cocaine
• Nasal lidocaine
• Octreotide subcutaneously
• Intravenous (IV) somatostatin
• Nasal dihydroergotamine (DHE; DHE is FDA approved for cluster)
• Parenteral DHE
• Intravenous magnesium sulfate 1–2 gm
• Intravenous valproate 500–1,000 mg
• Quetiapine 25–50 mg

Table 12.4 Clinical pearls on acute treatment of cluster

• Acute treatment must be very fast, as cluster attacks peak rapidly. Never prescribe tablets for acute treatment of cluster! Do not overlook the efficacy of parenteral dihydroergotamine (DHE)
• Oxygen is the first-line acute treatment. Give the patient a nonrebreathing mask, deliver 100% oxygen at a rate of 10–15 L/min, and have them take the oxygen in a sitting position like Rodin's "The Thinker," while holding the mask loosely. Never resort to nasal cannula!
• Nonoral home acute treatments for cluster include sumatriptan subcutaneous (FDA approved), nasal zolmitriptan, DHE self-administered (FDA approved), and, last, nasal sumatriptan
• A useful rescue, which puts the patient to sleep and may not necessarily abort the pain, includes oral atypical neuroleptics such as olanzapine or quetiapine

useful/predictive…for the given condition in the specified population") and are derived from the American Academy of Neurology Practice Guidelines for treatment of CH. Other treatments for acute treatment of cluster are included in Table 12.3.

Comments on Acute Treatment of Cluster Headache

The emergent nature of a CH attack necessitates rapid therapy, and often calls for *combination therapy*. Acute treatment must demonstrate rapid onset, as cluster attacks peak very fast (Table 12.4). Never prescribe a tablet for acute treatment of cluster, even zolmitriptan (see above)!

If this is new-onset CH, and the patient has never tried oxygen therapy, high-flow oxygen at the onset of an attack should be attempted first line, either in the office or at home. The oxygen is given by a high-flow mask—not nasal cannula—and provided at a flow rate of 10–15 L/min for 20 min, barring any medical contraindications. Have the patient sit in a position similar to Rodin's The Thinker, holding the mask loosely over the face.

Some form of parenteral therapy should be available should oxygen prove ineffective or too slow, or the situation warrants it: subcutaneous or nasal sumatriptan;

nasal, intravenous (IV), subcutaneous, or intramuscular dihydroergotamine (DHE); nasal zolmitriptan; and/or IV valproate and/or magnesium sulfate (barring any medical contraindications). Our experience is that injectable sumatriptan is optimal, using either the generic Statdose or other needle-free (but not pain-free) injection SUMAVEL system. The latter is marketed in boxes of six, which may be of greater convenience for cluster patients while prevention is adjusted. In addition, the simplicity of the needle-free system is useful for cluster patients during the agitation of an attack, when loading the Statdose device can be challenging.

In our hands, nasal zolmitriptan is next on the utility list, then self-administered DHE, with nasal sumatriptan dead last (after oxygen, sumatriptan subcutaneously, zolmitriptan nasal, and DHE). There are no comparative studies.

For rescue of patients, instead of using opioids orally or parenterally, we resort to atypical neuroleptics in the form of oral quetiapine (25–100 mg with repeat dose, as needed) or olanzapine (5–10 mg with a repeat 5-mg dose, as needed). These medications induce sleep and sedation.

Just because a medication has failed to achieve a Level A recommendation does not mean it is ineffective. DHE remains one of the most versatile medications available for aborting and preemptively treating future attacks, and is, in fact, Food and Drug Administration (FDA) approved for cluster. IV DHE, in experienced hands, is as fast as parenteral sumatriptan and has a long duration of action. The metabolites of DHE, like the parent drug, are believed to be active and lipophilic and to readily penetrate brain substance where they bind to serotonin and dopamine receptors. The development of orally inhaled DHE may revolutionize the treatment of cluster, as it promises an effective, more patient-friendly, nonoral route for this drug.

The treating clinician should not overlook the opportunity to initiate bridge or transitional therapy and preventive therapy at the earliest opportunity.

The future holds promise of new therapies in the next few years. As discussed below, occipital nerve stimulators, sphenopalatine ganglion stimulators, handheld vagal nerve stimulators, and deep brain stimulation are being studied for the treatment of refractory and chronic CH. One controlled study demonstrated that high-frequency stimulation of the sphenopalatine ganglion can terminate an acute attack, and further studies are under way.

Transitional or Bridge Therapy for Cluster Headache

Transitional or bridge therapy is an attempt to prevent cluster attacks while awaiting onset of (successful) prevention. The purpose of transitional therapy is to buy time, since preventive medication often takes weeks for titration to optimal dose (Table 12.5). Without transitional therapy, the patient is likely to use injectable sumatriptan daily and run out of insurance allotments, even with oxygen provided.

Transitional therapy of cluster is the most poorly understood and studied phase of treatment, and the majority of the approaches involve the use of steroids, either

Table 12.5 Transitional treatment of cluster headache

- The purpose of transitional treatment in cluster headache is to buy time while waiting for the preventive medications to kick in
- Barring medical contraindications, these are three options:

  Option 1. *Ipsilateral greater occipital nerve (GON) block/suboccipital steroid injections:* In patients with tenderness in the GON region ipsilateral to the CH, inject 40 mg triamcinolone or equipotent injectable glucocorticoid mixed with 3 ml of 0.5 % bupivicaine. Leroux and colleagues published a double-blind randomized controlled study demonstrating the efficacy of 3 days of consecutive GON blocks with betamethasone and lidocaine in inducing remission of CH attacks that occur two or more times/day

  Option 2. *Systemic steroids:* Give a high dose of methylprednisolone, dexamethasone, or prednisone daily for 10 days to 2 weeks as preventive medications are adjusted. Do not use MEDROL dose packs (dose too low)

  Option 3. *DHE:* Have the patient inject DHE 1mg subcutaneously nightly, until the patient is headache-free for 2 weeks, whereupon the patient may skip the injection for a day to see if he is in remission. An alternative is nightly oral ergotamine tartrate

injected into the greater occipital nerve (GON) vicinity ipsilateral to the headache or taken systemically. Three approaches and their rationales will be discussed below.

1. Ipsilateral GON block/suboccipital steroid injections

Small studies have demonstrated induction of remissions in episodic and a few chronic CH patients within 1 week of a GON injection of lidocaine and betamethasone. None of the placebo group, injected with just lidocaine, achieved pain freedom. More than 50 % of the steroid-injected patients achieved a 4-week or greater remission. Another retrospective study also demonstrated greater than 50 % of CH patients achieving a complete or partial response lasting for a median of 17 days (for the partial response).

A predictor for a successful response was tenderness in the region of the GON on the side ipsilateral to the CH. No relationship was shown between the response and the level of induced dermatomal anesthesia from the injection.

Recommendation: Barring medical contraindications, in patients with tenderness in the GON region ipsilateral to the CH, inject 40 mg triamcinolone or equipotent injectable glucocorticoid mixed with 3 ml of 0.5 % bupivicaine.

2. Systemic steroids

Years of anecdotal experience support the use of oral prednisone or equivalent steroid in an attempt to "buy enough time" for the preventive therapy to work or the patient to spontaneously remit. We know of no studies that support the assertion that this is effective. However, in patients who can tolerate the innumerable possible adverse effects of glucocorticoid therapy over a period of 2 weeks, or who are not candidates for GON blocks or for whom GON blocks were ineffective, we utilize systemic steroids.

The dose and route of steroids are both empirical: pulse methylprednisolone as in an exacerbation of multiple sclerosis, IV dexamethasone 8 mg for 1–3 days, or oral dexamethasone, prednisone, or methylprednisolone. The commercially marketed

methylprednisolone oral dose pack, commonly utilized to treat poison ivy-induced dermatitis, is too low a dose to be effective in both CH and status migrainosus.

Recommendation: Barring medical contraindications, a trial of oral prednisone, starting at 60 mg daily and tapering off over a period of 2 weeks.

3. Daily preemptive DHE injections at bedtime

As mentioned above, DHE, the progenitor of the triptans, is as effective in aborting CH as subcutaneous sumatriptan and perhaps is more durable. In our clinic, we utilize a modified Raskin protocol (see Chapter 14, Table 14.13 for details) to treat a cluster period.

The patient will come in for a DHE infusion, and if successful, can be sent home with 8-hourly DHE self-injections or with a continuous subcutaneous DHE pump until 24 h of being headache-free. We will then initiate *preemptive* subcutaneous DHE injections 1 mg at bedtime since REM-onset cluster attacks are so predictable. We continue this until the patient is completely headache-free for at least 2 weeks, whereupon the patient will skip a day of self-injection to see if he is in remission.

If a headache breaks through, the patient will use the DHE injections every 8 h as needed to abort the headache. If the patient enters remission, he or she can continue the prevention for a certain amount of time and eventually taper off the preventives.

DHE has replaced nighttime doses of ergotamine tartrate preventively, which can also be used in this manner. A disadvantage is that the use of the ergots means the patient cannot treat breakthrough attacks with a triptan. However, there is always an extra DHE dose or oxygen for this need.

Recommendation: Barring medical contraindications with DHE, have the patient inject DHE 1mg subcutaneously nightly, until the patient is headache-free for 2 weeks, whereupon the patient may skip the injection for a day to see if he is in remission. When orally inhaled DHE becomes available, self-injected DHE may no longer be necessary.

Preventive Therapy of Cluster Headache

Considering that CH periods last weeks to months, the institution of preventive therapy is usually indicated. For the lucky ones who respond to GON blocks or who have short cluster periods, prophylaxis may not be necessary. For the chronic CH sufferer, tolerable preventive therapy must be fashioned over a period of years or indefinitely. Unfortunately, there are little data to support any specific protocol; again, this does not mean none exists. In addition, novel approaches are currently being studied, and they make use of a better understanding of pathophysiology of CH.

As noted above, the American Academy of Neurology Practice Guidelines did a very thorough review of all treatments for CH in the literature. Table 12.6, adapted from these guidelines, lists the oral medications utilized for preventive therapy. Few studies deemed Class 1 succeeded in providing evidence of efficacy, and many of

Table 12.6 Preventive therapies for cluster headaches. (Adapted from Francis et al. 2010)

Treatment	Efficacy	Level of evidence	Comment
Civamide	One small randomized controlled trial (RCT) of intranasal therapy demonstrated efficacy	Class 1	100 μl intranasal for prevention of CH/induction of remission; not available yet in the US
GON injections—steroids	Demonstrated efficacy in one study	Class 1	For the prevention/induction of remission
Sodium valproate	500 mg did not prevent CH	Class 1	Not recommended
Sumatriptan	Studies did not confirm role in prevention	Class 1	Not recommended for prevention or preemptive therapy
Melatonin	Evidence that doses greater than 10 mg may help induce remission when added to verapamil	Class 2	May be used in conjunction with other preventives, especially verapamil
Verapamil	Evidence that doses of 360 mg were effective in improving headache response	Two studies: Classes 2 and 3	May cause bradycardia and heart block in doses higher than 240 mg/day. Follow ECG; constipating
Lithium	Dose of 900 mg a day effective in CH prevention	Two trials Class 2 evidence	Side effects include CNS toxicity with therapeutic levels, hypothyroidism, and polyuria
Oxygen 100%	Hyperbaric oxygen not effective	Class 2 evidence	In contrast to evidence supporting its use for aborting acute cluster headaches
Capsaicin nasal	Insufficient evidence	Class 3 trial	Insufficient evidence. Painful to the nasal mucosa
Prednisone 20 mg qod	Insufficient evidence	Class 3 trial	In contradistinction to its efficacy for transition or bridge therapy
Ergot therapy	Insufficient evidence	None	While used by experienced clinicians as DHE subcutaneously or ergotamine tartrate rectally once or twice a day, this has not been studied

CH cluster headache, *CNS* central nervous system, *DHE* dihydroergotamine, *ECG* electrocardiogram, *qod* every other day

the medications presently used are Level B or C and derive from experience and consensus.

Only civamide, an intranasal analogue of capsaicin not available yet in the US, and GON injections with steroids were Class 1 and recommended (Table 12.7). Conventionally, many medications not recommended or with poor evidence, are widely used clinically: verapamil, lithium, melatonin, valproate, and topiramate.

Table 12.7 Clinical recommendations for cluster prevention

- Institute prevention utilizing rational polypharmacy, and start with the least toxic approach
- While the evidence for verapamil fails to meet Class 1 evidence, start with immediate- release verapamil provided on a three times daily basis: 80 mg orally TID, and increase by 80–160 mg from every 2 or 3 days to every 2 weeks
  1. Have a baseline ECG, and check for first degree (and complete) AV block during titration of verapamil above 240 mg a day. Titrate verapamil as high as 1,000 mg if needed and tolerated in terms of adverse events
  2. Addition of magnesium oxide 400–1,000 mg a day to offset constipation. Any absorbed magnesium may, in theory, suppress trigeminal nucleus caudalis nociceptive activity. There are almost no data on its use in CH
  3. Addition of melatonin, for which data are also limited. Given in the late evening before bed, doses may be titrated quickly as high as 25 mg, starting with a minimum of 10 mg. During a cluster period, both ictally and interictally, cluster sufferers have measurably low cerebrospinal levels of melatonin. For more details, see suggested reading on the neuroendocrinology of cluster headaches
- If no remission or reduction in the frequency of the headaches ensues in 2 or more weeks after institution of the highest tolerated doses, add another medication(s):
  1. Divalproex sodium 500–1,500 mg per day, and/or
  2. Topiramate 100–200 mg at night (titrate up by 15–25 mg every week), and/or
  3. Lithium carbonate in doses to build a therapeutic blood level
- In our clinic, I routinely investigate the hormonal levels of all chronic CH patients, as I have been surprised to find low bioavailable testosterone levels in these seemingly hyperandrogenized men. If there are no contraindications (i.e., prostate disease, lipid disorders), I provide testosterone replacement therapy for hypogonadal individuals and have been able to induce complete remission or a reversion to an episodic CH pattern (see references below) in a number of them
- Anecdotal reports of the herb kudzu suggest doses of 1,500 mg TID may reduce the frequency and severity of the attacks. This is an otherwise harmless over-the-counter approach

TID three times a day

Treatment of Refractory Cluster Headaches

Refractory CH occur in either (a) episodic CH patients who fail to respond to any abortive therapies or (b) chronic CH patients who cannot revert to an episodic pattern or who have never been able to go into remission despite concerted medication trials. Until recently, there were few options other than chronic opioid therapy or a destructive neurosurgical procedure. Multiple surgical and pain anesthesia procedures have been described for CH and are listed in Table 12.8.

None of these therapies offers more than modest results; none has met the rigors of randomized controlled trials, and all carry risk of failure of response and delayed deafferentation pain syndromes. Recent knowledge culled from functional neuroimaging combined with advances in neurostimulatory procedures promise chances for new therapies. For refractory CH patients, *after expending all attempts at medical management,* we consider the patient for sphenopalatine block, then nondestructive neurostimulatory (neuromodulatory) procedures (Table 12.9). These await the studies needed for FDA approval.

Because CH patients are so desperate, numerous unusual approaches to treatment have been tried or championed. We summarized some of these approaches in

Table 12.8 Surgical procedures for refractory cluster

- Radiofrequency ablation of the trigeminal nerve
- Glycerol trigeminal rhizotomy
- Trigeminal nerve sectioning
- Balloon compression of the trigeminal ganglion
- Microvascular decompression of the trigeminal nerve
- Sphenopalatine gangliolysis
- Superficial petrosal neurectomy
- Sectioning of the nervus intermedius
- Gamma Knife radiosurgery of the trigeminal ganglion

Table 12.9 Last-resort options for refractory cluster

- Sphenopalatine (SPG) block followed by radiofrequency ablation was effective in an open study of intractable chronic cluster headache patients followed for more than 18 months. Note that this is an ablative procedure of a parasympathetic ganglion and is not reversible, although clinical response was generally transient
- SPG stimulation was effective in a European study for aborting and preventing acute CH attacks. An implantable SPG stimulator is now approved in Europe for chronic CH, and studies are planned in the USA
- Occipital nerve stimulation (ONS) is frequently successful in CH. Clinical response often takes months to reach full effect, and technical difficulties (lead migration, infection, battery failure) can plague this approach. For more information, please see reference below on potential options in CH for medically refractory patients
- A non-invasive, hand-held vagal nerve stimulator is being currently studied for acute treatment of cluster attacks
- Deep brain stimulation (DBS) of the posterior hypothalamus has been in use for more than 10 years to prevent CH attacks. Serious adverse effects can include intracranial bleeding, stroke, infection, vertigo, and syncope, and there was one death reported, making DBS the very last resort

Table 12.10 Diagnostic and therapeutic trial of indomethacin for paroxysmal hemicrania

- Start with 25 mg of indomethacin TID for 48 h to 1 week
- Place the patient on a proton pump inhibitor and have the indomethacin taken with meals
- Increase to 50 mg TID for 48 h to 1 week
- If there is no response, the dose is then increased to 75 mg TID and maintain for 72 h to 2 weeks
- If there is a partial response, increase to 100 mg TID if the patient can tolerate it
- If there is no response or if the patient has intolerable adverse effects, stop indomethacin

a review entitled “Cluster Headache: Potential Options for Medically RefractoryPatients (When All Else Fails)”, and the reference is included in the suggested reading.

The Paroxysmal Hemicranias

The paroxysmal hemicranias (PH) are defined by an absolute responsiveness to indomethacin. The approach is similar to that used for hemicrania continua (HC) and is repeated here in Table 12.10.

Table 12.11 Other treatment for indomethacin-intolerant patients with paroxysmal hemicrania or hemicrania continua

• Celecoxib or another NSAID (e.g., piroxicam, diclofenac, etc.)
• Melatonin, which is structurally similar to indomethacin
• Topiramate or gabapentin in escalating doses, as used for migraine prophylaxis
• Greater Occipital Nerve block with 'caine + steroid' as described above for CH. Currently, I approach all patients with any form of TAC with this approach initially, and, when necessary, will provide 3 consecutive days of blocks, as described by Leroux et al. in 2011 (see references)
• A trial of deep brain stimulation of the ipsilateral posterior hypothalamus.

Alternatives for patients intolerant to indomethacin or for whom it is contraindicated are listed in Table 12.11. These generally include other nonsteroidal anti-inflammatory drugs (NSAIDs) or anticonvulsants.

Short-Lasting Unilateral Neuralgiform Headache Attacks (SUNHA) with Conjunctival Injection and Tearing (SUNCT)/ Short-Lasting Unilateral Neuralgiform Headache Attacks with Cranial Autonomic Symptoms (SUNA)

These rare, short-lasting headaches with prominent cranial autonomic symptoms can deceive the clinician because, as with trigeminal neuralgia, they can be triggered by cutaneous stimuli. Unlike trigeminal neuralgia, however, they are recognized by the autonomic features and by the location of pain around the eye in V1. They present with single stabs, many (more than a hundred) separate single stabs anywhere in the head, or groups of stabs (sawtooth pattern) separated by complete or partial resolution of the pain (see Chap. 2).

SUNCT and SUNA do not respond to indomethacin in any dose—eliminating PH from the differential diagnosis—nor do they respond to high-flow 100% oxygen, or serotonin agonists (DHE or triptans), eliminating the diagnosis of CH. Oxcarbazepine and carbamazepine may be effective, further complicating differential diagnosis from trigeminal neuralgia. However, unlike in trigeminal neuralgia ablative neurosurgical procedures generally have poor outcomes.

Treatment described as useful in SUNCT and SUNA, listed in Table 12.12, relies on anticonvulsant therapy. Note that these options actually include lidocaine, which was used by neurologists to treat refractory status epilepticus in a time before the introduction of newer parenteral anticonvulsants and before attempting a trial of general anesthesia.

For patients refractory to the above, there are few options. One patient responded in an on–off fashion to ipsilateral posterior inferior hypothalamic deep brain stimulation, parallel to the turning on and turning off of the stimulator. Occipital nerve stimulation is an option that could be pursued, as it is obviously less dangerous.

Table 12.12 Treatments for SUNHA (SUNCT and SUNA)

- Lamotrigine (100–400 mg/day) → relief in up to 2/3 of patients (drug of choice for SUNCT)
- Topiramate (50–400 mg/day) → response in ~50% of patients
- Gabapentin (600–3,600 mg/day) → response in ~45% of patients (drug of choice for SUNA)
- Oxcarbazepine and carbamazepine may be effective, complicating differential diagnosis from trigeminal neuralgia
- IV lidocaine 1.3–3.3 mg/kg/h. Lidocaine infusion will require cardiac monitoring and drug levels should be followed. No trials of mexiletine or tocainide have been reported, but doses of 400–600 mg of mexiletine have been given in two to three divided doses a day. Levels of mexiletine also should be measured to avoid potential toxicity
- GON steroid block may abort attacks in up to 2/3 of all patients

Table 12.13 One indomethacin titration schedule for hemicrania continua

- Start with 25 mg of indomethacin TID for 48 h to 1 week
- Place the patient on a proton pump inhibitor and have the indomethacin doses taken with meals
- Increase to 50 mg TID for 48 h to 1 week
- If there is no response, the dose is then increased to 75 mg TID and maintained for up to 2 weeks
- May increase to 100 mg TID if the patient can tolerate it
- If no response, and the clinician really thinks this is HC, consider increasing the dose to 450–500 mg over 1–2 weeks and maintain the patient on this for an additional 1–2 weeks
- If the patient has intolerable adverse effects, stop trial

Finally, one additional word on SUNHA. There are a number of case series showing that SUNHA can be associated with pituitary lesions, specifically pituitary adenomas. There are also descriptions of SUNCT cured by surgical extirpation of these tumors. A careful MRI search for lesions of the adenohypophysis is in order for SUNHA. When medical therapy is ineffective in a SUNHA patient with one of these tumors, a surgical approach should probably be considered.

Hemicrania Continua

The diagnosis of Hemicrania Continua (HC) is made by a combination of the clinical headache features *plus a complete* therapeutic response to indomethacin at pharmacological doses. There is debate about how long to wait before abandoning indomethacin. Some studies suggest the response should be complete and rapid within 48 h of reaching the therapeutic dose of indomethacin, but other researchers feel that the trial of large doses (doses as high as 500 mg/day; see Cittadini et al.) should be extended a full 2 weeks before abandoning the drug. Fortunately, for many patients, when HC remits once the therapeutic dose is reached, the dose of indomethacin can be tapered down to a lower dose that is maintained indefinitely (Table 12.13).

Clearly, some patients cannot tolerate the central nervous, gastric, or renal side effects of this harsh drug; additionally, there are patients, such as those with diabe-

tes, renal, and/or hepatic dysfunction, or those with bleeding issues, who will never be able to take the medication. For these patients, there are rays of hope in the case reports showing benefit from large doses of melatonin or trials of gabapentin, topiramate, and celecoxib.

As mentioned above with other TACs, there is usually no harm in initiating therapy with an ipsilateral local anesthetic/steroid GON block(s) and waiting expectantly 72–96 h before starting indomethacin therapy. Some patients—particularly those with tenderness over the site—will respond to this approach, at least temporarily. Ipsilateral occipital nerve stimulation and GON blocks are other approaches that can be utilized.

Treatment of Other Primary Headaches

Some of the Other Primary Headaches are not well studied and, after preliminary comments, will allow a summary in the form of a table. Not surprisingly, the recommendations summarized in this table will be an amalgam of recommendations and time-tested therapies. There are no data remotely approaching Class 1 status.

The first and foremost therapeutic approach to these headaches—particularly, cough headache, exercise headache, headache associated with sexual activity, and thunderclap headaches—is to investigate and rule out causation. Similar to primary stabbing headaches, if deemed "primary," these headaches are best treated by prevention of the inciting cause (of course, with the exception of thunderclap and sex headaches).

As expected, a recommendation to patients to modify behavior drastically often does not sit well. In such cases, after an appropriate workup, reassurance that a short-lived but severe headache is primary, and thus benign, might suffice.

Primary thunderclap headache necessarily distinguishes itself from the rest of other headaches, due to its random and unexpected presentation. As expected, treatment is palliative while a workup ensues to rule out an ominous cause.

Table 12.14 summarizes the treatment of the listed Other Primary Headaches. Hypnic headache is discussed below separately. Primary thunderclap headache is not listed, as explained above. Treatment of new daily persistent headache is discussed in Chap. 14.

Hypnic Headache

Treatment of hypnic headache is as unusual as the headache itself and is listed in Table 12.15. The most important three treatments are caffeine, lithium, and indomethacin.

It seems counterintuitive to recommend caffeine before a patient goes to sleep or takes a nap, but remember the English traditionally have a cup of tea before bed-

Table 12.14 Treatment of Other Primary Headaches

Headache	Therapy	Comments
Primary stabbing	– Indomethacin: 25–250 mg/day in divided doses – Celecoxib 100–400 mg/day in divided doses – Melatonin 3 mg at night; titrate to higher dose – Nifedipine or verapamil	– Sharp stabs of pain last 1–10 seconds and cannot be effectively treated once they occur – Indomethacin is most commonly used when the stabs occur in volleys – Celecoxib is used in indomethacin intolerance – Calcium channel blockers can be used as well (anecdotal)
Cough headache	– Indomethacin: 25–250 mg/day in divided doses – Acetazolamide 250–500 mg twice daily	– Lasts seconds to minutes after Valsalva – Primary form not commonly seen in patients under 40 – Not usually seen with nausea and vomiting – Up to 40% of patients have a secondary cause (Chiari, posterior fossa lesion) – Responds to indomethacin or high-volume CSF removal
Exercise headache	– Indomethacin: 25–250 mg/day in divided doses – Beta blocker: proprano-lol 40–240 mg/day or equivalent	– May last minutes to 2 days – Unlike primary cough headache, more common in young adults and in those with migraine – May masquerade as cardiac ischemia – Try tapering therapy after several months
Headache associated with sexual activity	– Indomethacin: 25–250 mg/day in divided doses – Beta blocker: proprano-lol 40–240 mg/day or equivalent – Diltiazem 180 mg/day for beta blocker intolerance	– Advising the patient to be more passive during intercourse may help prevent the headache – Try tapering therapy after several months to test for recurrence
Cold-stimulus headache		– Advise the patient to avoid rapid ingestion of cold drinks or solids
External-pressure headache		– No specific therapy other than avoidance and treatment similar to early migraine treatment (indomethacin or some other NSAID) – Migraine prevention may work for this type of headache as the pain is reminiscent of allodynia and hyperpathia seen in migraine
Nummular headache	– Carbamazepine or gabapentin have been used in anecdotal reports – OnabotulinumtoxinA has been used successfully in a few patients – There are reports of an occasional patient who responds to local anesthetic injection	– Reassurance after a negative exam and workup may be all that is needed

Table 12.15 Medications for the treatment of hypnic headache

Medication	Dose	Comments
Caffeine	40–60 mg as tablet or coffee at hour of sleep	First and easiest approach
Lithium carbonate	300–600 mg at bedtime	Watch for toxicity: tremors, chorea, ataxia, hyperthyroidism, electrolyte disorders
Indomethacin	25–75 mg at bedtime	May be more effective if the headache is unilateral and side-locked

time. The fact that this simple, inexpensive treatment frequently works should make clinicians pine for the days when Britannia ruled the seas.

Lithium has been most studied for this disorder, but comes with an assortment of toxicities, some of which do not correlate with toxic blood levels, such as renal and thyroid abnormalities. Recent case reports suggest potential benefit with indomethacin. There are no randomized controlled trials.

Conclusions on Treatment of TACs and other Primary Headaches

- For the TACs and Other Primary Headaches, the correct diagnosis is vital to choosing proper therapy. Proper treatments are often disorder specific
- New insights into the pathophysiology of these headaches has opened the door to novel treatment approaches including neuromodulation such as deep brain, occipital nerve, non-invasive hand-held vagal nerve, and implantable sphenopalatine ganglion stimulation
- Several of the headaches discussed are so uncommon or so unpredictable in onset, no evidence-based recommendations exist for treatment

Suggested Reading

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