EUROPEAN HEADACHE SCHOOL
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Pharmacological treatment of TACs

Srdjan Lj Sretenović

Headache and Migraine Centre
University Hospital KBC Zvezdara
Belgrade

The IHS summarizes the TAC category:

- Cluster headache
  - Episodic cluster headache
  - Chronic cluster headache
- Paroxysmal hemicrania
  - Episodic paroxysmal hemicrania
  - Chronic paroxysmal hemicrania (CPH)
- Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
- Probable trigeminal autonomic cephalalgia
  - Probable cluster headache
  - Probable paroxysmal hemicrania
  - Probable SUNCT

The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004, 24 Suppl 1:9-160.

Treating cluster headaches

- All cluster headache patients require treatment.
- Other headache syndromes can sometimes be managed non-medicinally but in regard to cluster headache, medication, sometimes even multiple medications at one time, are indicated.

Red Flags for symptomatic CH

- First episode
- Unilateral pain attacks lasting more than 3-4 hours
- Absence of autonomic features
- Unusual pain location
- Unresponsive to drugs
- Unusual age onset
- Abnormal neurological examination

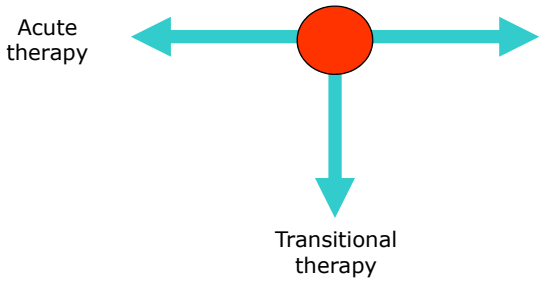
Secondary causes of cluster headache

- **Vascular**
  - Carotid artery dissection or aneurysm
  - Vertebral artery dissection or aneurysm
  - Pseuroaneurysm of intracavernous carotid artery
  - Anterior communicating artery aneurysm
  - Occipital lobe AVM
  - Middle cerebral artery territory AVM
  - AVM in self tissue of scalo above ear
  - Frontal lobe and corpus callosum AVM
  - Cervical cord infarction
  - Lateral medullary infarction
  - Frontotemporal subdural haematoma
- **Tumor**
  - Prolactinoma
  - Pituitary adenoma
  - Parasellar meningeoma
  - Sphenoidal meningenoma
  - Epidermoid tumor in the prepontine (behind dorsum sella turcica)
  - Tentorial meningeoma
  - High cervical meningeoma
  - Nasopharyngeal carcinoma
- **Infection**
  - Maxillary sinusitis
  - Orbito-sphenoidal aspergillosis
  - Herpes Zoster ophtalmicus
  - Postr-traumatic or surgery
  - Facial trauma
  - Following eye enucleation
- **Dental**
  - Inpacted wisdom tooth
  - Following dental extraction
- **Secondary headache syndromes**
  - Tolosa-Hunt syndrome
  - Temporal Arteritis
  - Reader's paratrigeminal neuralgia

Modified from Goadsby, Drug 2003;63:1637-1677

Treating cluster headaches

- Cluster headache treatment can be divided into three classes:
  1) abortive or acute therapy (treatment given at the time of an attack);
  2) transitional therapy, which can be considered intermittent or short-term preventive treatment;
  3) preventive therapy which consists of daily medication aimed at decreasing the frequency, intensity, and duration of cluster headache attacks.



Triggers to be avoided

- Alcohol
- Napping
- Vasodilatators
  - Nitroglycerin
  - Various antihypertensive preparations
- Prolonged exposure to volatile substances, such as solvents and oil-based paints
- A small percentage of cluster patients do much better when they stop smoking

Abortive therapy

- The goal of abortive therapy for cluster headache is fast, effective and consistent relief. Because a cluster headache is relatively short in duration, the abortives should work within 10-15 minutes to be considered adequate therapy.

Cluster headache
Evidence-Based Treatment

Substance	*Evidence based efficacy*
Sumatriptan 6mg sc	++++
Oxygen 100% 7-12 l/min.	+++
Dihydroergotamine im or iv	+++
Ergotamine supp	++
Indomethacine 50mg supp	++
Sumatriptan 20mg nasal spray	++
Zolmitriptan nasal spray	+
Dihydroergotamine nasal spray (puff 0.5mg)	+/-
Zolmitriptan 10mg oral	+/-

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Abortive therapy

- ***Oxygen***
  - Excellent abortive for cluster
  - Shown to work in up to 70% of cluster patients
  - Safe and easy to use
  - Typical dosing — 100% oxygen given via face mask (nasal cannula not effective) at 10-15 liters/minute for 20 minutes. Pain relief typically occurs after 10-20 minutes
  - 15 L/min may be effective in those not responding to lower rates (e.g., chronic smokers)

    Kudrow et al.,1981

Potential problem:

Bulky equipment

Abortive therapy Triptans

- ***Sumatriptan 6mg sc***
  - Injectable — most effective, often giving complete relief within 15 minutes after injection
  - Nasal spray formulation is not as effective as injectable
  - Oral tablets are not effective in cluster due to the 1-2 hours it takes for the medication to produce relief; the individual cluster headache is over by then

    Ekbom et all., 1993
- ***Zolmitriptan 10mg***
  - First **oral** triptan effective in cluster
  - Doses for cluster are higher than that used for migraine
  - Response — not as good as with oxygen therapy or injectable sumatriptan but an option in patients who cannot tolerate injections and have either failed oxygen therapy or find it difficult to use in certain situations *Bahra et all., 2001*

Contraindications

Ischemic coronary, cerebral or peripheral vascular disease, uncontrolled arterial hypertension, severe liver or kidney disease

Abortive therapy

- ***Ergot derivative***
  - ***Dihydroergotamine (DHE)***
    - Available in injectable and nasal spray preparations
    - Nasal spray (1-2mg)
    - Most cluster patients experience relief within 15 minutes when DHE is given intravenously; relief is slower with intramuscular or subcutaneous formulations

      Anderson, Jespersen.,1986
  - ***Ergotamine (ergotamine tartarat 1mg+caffeine 100mg)***
    - Available in supp, subligual and tablets
    - To slow in onset to provide meaningful relief in a timely manner

      Kudrow, 1981

Contraindications:

Coronary, cerebral or peripheral vascular disease, arterial hypertension, severe liver or kidney disease

Abortive therapy
Other potential drugs

- ***Lidocaine***
  - ***Lidocaine solution***
    - Available in nasal drops
    - Applied in the region of the pterygopalatine fossa

Kitrelle et al., 1985; Costa et., 2000

- ***Olanzapine (from 2mg-10mg)***
  - Effective and safe to use in patients unable to take sumatriptan or oxygen
  - In one study, typically alleviated pain within 20 minutes after oral treatment
  - May induce sleepiness, but most cluster patients prefer sedation to agitation
  - Needs further study to ascertain effective dose

Rosen, 2001

- ***Hyperbaric Oxigen, Somatostatin receptor agonist, Analgesics ?***

Transitional therapy

- Transitional therapy is a short-term preventive treatment that bridges the time between cluster diagnosis and when a true preventive agent becomes effective.
- Transitional preventives are started at the same time the true preventive is begun
- The transitional preventive should provide the cluster patient with almost immediate pain relief and allow the patient to be headache-free or near headache-free while the maintenance preventive medication is being tapered up to an effective level.
- When the transitional agent is tapered off (typically in one to two weeks) the maintenance preventive will have kicked in, thus the patient will have no gap in headache prevention.

Transitional therapy to stop attacks:

- ***Steroids (e.g., prednisone, dexamethasone)***

  Dexamethasone i.v. 12mg (3 days); 8mg (3 days); 4mg (3 days)
  Dexamethasone i.m. 8mg (4/7 days); 4mg (4/7 days)

  - Best transitional therapy for cluster
  - Typically effective within 24 to 48 hours of administration
  - Usually discontinued after 8-10 days of treatment when main preventive agent has started to become effective
  - Long-term use not recommended because of very severe side effects with extended usage

- ***Dihydroergotamine (DHE)***
  - Can be used as either abortive or transitional therapy
  - Best given intravenously in a hospital or outpatient infusion setting
  - Typically relieves pain in 1-2 days of repetitive treatment; pain may not return for days to months which allows time for a preventive(s) to become effective

Transitional therapy

- ***Naratriptan***
  - Dose — 7 days at 2.5 mg twice daily while transitioning to a preventive program
  - Drawback — if an attack occurs when a cluster patient is on naratriptan, sumatriptan cannot be used as an abortive; however, oxygen therapy can be used in this case

- ***Occipital nerve blockade***
  - Injection of anesthetic agent and a small dose of steroid into the region of the greater occipital nerve (base of skull) can provide relief averaging 13 days
  - Can be performed in an outpatient setting with minimal discomfort for the patient
  - Comparable to getting Novocain at the dentist
  - More studies are necessary to establish this as a legitimate transitional treatment for cluster headache

Preventive therapy

FACTS AND SUGGESTIONS:

- The main goal of cluster headache preventive therapy is to make a patient cluster-free on preventives even though they are still in a cluster cycle.
- Preventive agents are absolutely necessary in cluster headache.
- The maintenance preventive should be started at the time a transitional agent is given.
- Sometimes very large dosages, much higher than that suggested in the literature, are necessary when treating cluster headache. A well-recognized trait of cluster patients is that they can tolerate medications much better than non-cluster patients.
- It is not uncommon for cluster patients to require several preventive medications at once to get better results.
- Most physicians treating cluster will increase the dosages of the preventive agents very quickly to get a desired response.
- Preventive medications are only used while the patient is in cycle and then are tapered off once a cluster period has ended.
- If a patient decides to remain on a preventive agent even after their cluster cycle has ended, it does not appear to prevent a subsequent cluster period from starting.

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Preventive therapy
Facts and suggestion:

- Monotherapy
- Start as soon as possible, above all in episodic forms
- Continue for at least 10-14 days after attacks cease
- Taper slowly
- Attack reappearance back to minimum effective dosage
- For the cluster period: use previously effective drug

Preventive therapy Medications:

Monotherapies	***Combinations***
Verapamil	***Verapamil+prednisone***
Lithium	***Verapamil+ergotamine***
Methysergide	***Verapamil+lithium***
Topiramate	***Lithium+prednisone***
Valproate	***Topiramate+methysergide***
Ergotamine	
Pizotifen	
Gabapentin	
Corticosteroids (prednisone)	

Preventive therapy

Verapamil

Dose: min 240mg/day; max 960mg/day; mean 360mg/day

- May be best first-line therapy for both episodic and chronic cluster
- Useful with hypertension or tachycardia
- Can be used in conjunction with sumatriptan, ergotamine, corticosteroids, and other preventive agents
- Non-sustained-release formulation appears to work better than sustained release preparation
- EKG is necessary before starting, before each dose change, and during long/term treatment, thereafter to guard against heart block

Meyer et al., 1983, Bussone et al., 1990

Contraindications: Hearth bloct
AEs: constipation, dizzines, distal edema, nausea, fatigue, hypotension, bradycardia
β-Blockers must not be given concurrently

Preventive therapy

Corticosteroids

Prednison dose: min 5mg/day; max 100mg/day; mean 30-60mg/day

- Preventiv therapy:
  - Start: Prednisolone tbl 1mg/kg daily for 5 days, and decrease the dose by 10mg every 3 days
- Transitional therapy to stop attacks:
  - Dexamethasone i.v. 12mg (3 days); 8mg (3 days); 4mg (3 days)
  - Dexamethasone i.m. 8mg (4/7 days); 4mg (4/7 days)

Kudrow, 1980; Couch and Ziegler, 1978

Contraindications: tuberculosis, psychotic symptoms, GT ulcer
Causion: uncontrolled diabetes, hypertension, glaucoma
AEs: diabetes, arterial hypertension, GT ulcer, increased weight, fluid retention, cardiac failure, bone fracture (vertebral body), osteonecrosis of femoral head, erythematous skin lesion, severe paroxismal myopathy, glaucoma, agitation, insomnia, psychotic symptoms

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Preventive therapy

Topiramate

Dose: min 25mg/day; max 300mg/day;mean 75-100mg/day
Start: at low dosages (15-25mg daily), and increase 25-50mg every 10 days

- Effective in both migraine and cluster headaches prevention
- Effective for both episodic and chronic cluster sufferers
- Topiramate in fairly low dosages can turn off cluster headaches on average within 1-2 weeks after starting the medication
- To do!: Periodic blood check (Na, Cl, K, Ca) renal and liver function, urin analysis

Lainez et al., 2003, Rapoport et al., 2003

Contraindications: anorexia, lowered body mass/weight
AEs: Paresthesia at extremities, somnolence, dizzibes, cognitive symptoms, disturbances of balance, and ataxia are common. Mood changes, psychosis, and weight loss may occur, glaucoma and nephrolithiasis are much less common

Preventive therapy

Lithium carbonate

Dose: min 600mg/day; max 1200mg/day; mean 900mg/day

- First choise if depression is present
- Effective but narrow therapeutic window and high side effect profile make it less desirable than newer preventives
- Effective in both episodic and chronic cluster headaches
- Drug withdrawal at least once annually to detect patients who have transition from chronic to episodic cluster headache
- Serum lithium concentrations should be checked during initial treatment stages to guard against toxicity; renal and thyroid functions need to be checked prior to starting lithium, and periodic check

Lieb, Zeff., 1978, Ekbom, Solomon., 2000

Contraindications: hypothyroidism, renal insufficiency
Concomitant use of NSAIDs, diuretics and Carbamazepine is contraindicated

AEs: agitation, postural tremor of hands, insomnia, weakness, nausea, slurred speach, blurred vision, leukocytosis.
Toxicity: signaled by vomiting, anorexia, diarrhea, confusion, nystagmus, ataxia, extrapyramidal signs, seizures
Hypothyroidism and polyuria in long-term course

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Preventive therapy

Methysergide

Dose: 3-12mg/day

- Role as a preventive is limited since it can potentially cause fibrotic complications
- Patients should not remain on methysergide more than 6 months at a time
- Ergotamine od DHE should not be taken concomitantly with methysergide (ergot derivate)

Berde, Schild., 1978; Garrison., 1990

Contraindication: pregnancy, peripheral vascular disorders, severe atherosclerosis, coronary artery desease, severe hypertension, peptic ulcer disease, fibrotic disorders, lung diseases, colagen disease, liver or renal function impairment, valvular hearth disease

Valproic acid

Dose: 600-2000mg/day

- No valid conclusion about the efficacy of sodium valšproate in prophylaxis of episodic and chronic cluster headache

Amrani et al., 2002

- May be more effective in patients whose cluster headaches are accompanied by migraine-type features, such as nausea, vomiting, photophobia, and phonophobia

Preventive therapy

Naratriptan
Dose: 2.5mg, 2tbl/day

- Remains effective in the body for a longer period of time than other available triptans
- Drawback — if breakthrough attack occurs, sumatriptan (another triptan) cannot be used as abortive; however, oxygen therapy can be used in this case
- Preventive use of triptans increase cluster headache frequency!
- Caution is urged when using a daily triptan in a patient who smokes

Loder., 2002, Rossi et al., 2004

Melatonin
Dose: 6 to 9 mg at bedtime

- Natural sleep hormone that is not produced in normal amounts by cluster patients. This may be an inciting factor in cluster headaches that occur in the night
- Can be used along with other cluster medications; may be able to use a lower dose of other medications when used with melatonin
- Trials have shown that fairly large doses can stop cluster attacks.
- Purchased over-the-counter and appears to have minimal side effects. No current governmental regulation; therefore, if one brand does not help, trying another brand of melatonin may be worthwhile
- Should consult physician before starting

Leone et al., 1996, Peres, Rosen., 2001

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Preventive therapy

- ***Ergot derivative***
  - ***Ergotamine (ergotamine tartarat 1mg+caffeine 100mg)***
    - Was widely used as the first-choice prophylaxis until the efficacy of lithium and verapamil became evident.
    - If the patterm of attacks is predictible, the dose can be given 30-60min before the expected attacks
    - If the pacient hac nocturnal attacks, 1 to 2mg may be given at night in the form of tablets or suppositories

Symond., 1956, Lance & Goadsby., 2005

  - ***Dihydroergotamine (DHE)***
    - Repetitive IV Dihidroegotamine administration over 3 days (episodic and chronic cluster headaches)

Mather et al., 1991

Contraindications:
Coronary, cerebral or peripheral vascular disease, arterial hypertension, severe liver or kidney disease

Preventive therapy

Other possible preventives

- A small number of case reports suggest the use of transdermal Clonidine, Baclofen, Tizanidine, nasal Capsaicin, Pizotifen, Leuprolide and Thorazine for cluster prevention
- These preventives should only be tried when other well-recognized preventives have failed and if there is no contraindication for their use

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New types of surgical treatment for cluster headache

- ***Radiofrequency thermocoagulation***
- ***Glycerol trigeminal rhizotomy***
- ***Trigeminal nerve root section***
- ***Microvascular decompression***
- ***Gamma knife radiosurgery***
- ***Deep brain / hypothalamic stimulation***

Short Lasting Unilateral Neuralgiform Headache Attacks with Conjuctival Injection and Tearing (SUNCT Syndrome)

- Several categories of drugs have proved to be ineffectual: NSAID-s, Paracetamol, Triptans, Egrgotamine, DHE, Beta-blockers, tricyclic antidepressants, calcium channel antagonist (verapamile and nifedipine). Methysergide, Lithium, Prednisolone, Phenytoin and Baclofen

  Pareja et al., 1995
- ***Lidocaine*** by infusion (1.3-3.3 mg kg(-1) h(-1))

  Treatment with lidocaine can be considered when acute intervention is required to suppress a severe exacerbation of SUNCT, and further broaden the therapeutic and clinical background of this syndrome.

  Matharu, Cohen & Goasdsby., 2004
- ***Lamotrigine*** 100-300mg daily

  Induced a complete remission in more than 80% of patients

  D Andrea et al., 1999, Piovesan et al., 2003

Paroxismal Hemicrania Treatment

- **Indometacin**
  - 25mg tid with meals, 150mg often required
  - Dose can be lowered to find lowest effective dose
  - Complete resolution of the headache is prompt, usually occuring within 1 to 2 days of initiating the effective disage
  - Intermittent discontinuation useful as remissins occur
  - EPH: should be given for slightly longer than the tipical headache bout, an then gradually tapered
  - CPH: long-term treatment is usually necessary
- **Other treatments reported effective (anectodal cases)**
  - (COX-2 inhibitors, other NSAID-s, AED-s /gabapentin, topiramate/, acetazolamide,verapamil)