

# Cluster Headache: Conventional Pharmacological Management

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Cluster headache pain is very intense, usually increases in intensity very rapidly from onset, and attacks are often frequent. These clinical features result in significant therapeutic challenges. The most effective pharmacological treatment options for acute cluster attack include subcutaneous sumatriptan, 100% oxygen, and intranasal zolmitriptan. Subcutaneous or intramuscular dihydroergotamine and intranasal sumatriptan are additional options. Transitional therapy is applicable mainly for patients with high-frequency (>2 attacks per day) episodic cluster headache, and options include short courses of high-dose oral corticosteroids, dihydroergotamine, and occipital nerve blocks with local anesthetic and steroids. Prophylactic therapy is important both for episodic and chronic cluster headache, and the main options are verapamil and lithium. Verapamil is drug of first choice but may cause cardiac arrhythmias, and periodic electrocardiograms (EKGs) during dose escalation are important. Many other drugs are also in current use, but there is an insufficient evidence base to recommend them.

*Key words: cluster headache, prophylactic medication, transitional medications*

Because the pain of cluster headache is one of the most severe that humans experience, the treatment of cluster headache often becomes almost an emergency as patients seek relief. Fortunately, effective pharmacological options are available to help the great majority of patients with cluster headache, although a sizeable minority is not responsive to conventional pharmacological therapy. For these patients, several surgical options have become available, and these are discussed elsewhere in this issue of *Headache Currents*.

The treatment of cluster headache is primarily pharmacological, although anecdotally, some success has been reported for thermal biofeedback<sup>1</sup> and for blood volume pulse biofeedback.<sup>2</sup> Other behavioral approaches that might be expected to be of some benefit would include cognitive behavioral therapy to improve patient pain coping skills and headache trigger avoidance (eg, avoiding alcohol during a cluster). For the most part, however, the severe pain attacks demand acute pharmacological intervention and, because the attacks are frequent, also pharmacological prophylaxis.

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## GENERAL PRINCIPLES OF PHARMACOLOGICAL MANAGEMENT

Pharmacological approaches can be divided into acute, transitional, and prophylactic components.

Acute therapy, as for migraine, involves the treatment of individual headache attacks. The pain of cluster attacks builds up in intensity very rapidly, however, so only rapidly acting medications are helpful. Patients may also experience several attacks per day so repeated dosing may be necessary.

The transitional medications are useful primarily in high-frequency episodic cluster headache and play an important role in stopping the headache cluster quickly, while prophylactic medication dosages are being increased to therapeutic levels. They are generally used for 1-3 weeks depending on the medication chosen. An exception is occipital nerve blockade with local anesthetics and steroids where only one dose may be necessary, although multiple doses may also be used.

Prophylactic therapy is perhaps the most important component of pharmacological cluster headache treatment and often becomes effective quite rapidly. Although there is some overlap with the drugs used in migraine prophylaxis, there are important differences, and many proven migraine prophylactic drugs appear ineffective in cluster. Patients with chronic cluster headache may require prophylaxis indefinitely. In episodic cluster headache, an important issue is how long prophylaxis should be continued once the cluster has stopped. There are no firm guidelines, but usually, prophylaxis is continued for a month or 2 after the patient becomes asymptomatic and is then stopped. The length of the patient's previous clusters may serve to some extent as a guide. If the patient normally has quite prolonged clusters lasting 3 months or longer, prophylaxis may need to be continued for at least that long, whereas a patient with clusters that usually last only 3-4 weeks may do well with a shorter duration of prophylaxis. These are clinical decisions that must be made without an adequate evidence base.

Several guidelines have been published that address the pharmacological treatment of cluster headache. The European Federation of Neurological Societies (EFNS) published a comprehensive guideline in 2006.<sup>3</sup> Several countries have produced guidelines either focused on cluster headache treatment (Taiwan,<sup>4</sup> Germany<sup>5</sup>), or which have included cluster treatment in a more general headache treatment guidelines (Scottish Intercollegiate Guidelines Network,<sup>6</sup> Croatia,<sup>7</sup> and Italy<sup>8</sup>). Recent publications also include a systematic review and meta-

Conflict of Interest: None.

**Table.—Pharmacological Cluster Headache Management: Usual Medications Used**

Acute medications		
Medication	Dose	Comment
Subcutaneous sumatriptan	6 mg	May be used up to 2 times a day†, fast-acting, treatment of choice
Oxygen	100% oxygen	Use a flow rate of 12 L/minute, for 15 minutes, non-rebreathing mask
Intranasal zolmitriptan	5 mg	May be used up to 2 times a day†
Subcutaneous or intramuscular DHE	1 mg	May be used up to 3 times daily
Intranasal sumatriptan	20 mg	May be used up to 2 times a day†, more evidence is available for zolmitriptan nasal spray
Transitional medications		
Prednisone	60-80 mg daily (starting dose)	One paradigm: 70 mg daily for 4 days, then reduce daily dose by 5 mg everyday (17 days course)
Subcutaneous or intramuscular DHE	1 mg	Is often used 2 or 3 times a day for a week if tolerated and may be continued once or twice a day for another week – longer if necessary and tolerated. Note contraindications, watch for vasoconstriction-related side effects
Occipital nerve block with steroids	Methylprednisolone (slow release) 40-80 mg (or equivalent)	Is usually done in combination with lidocaine, repeated injections can be used, role of systemic absorption in therapeutic response is unclear
Prophylactic medications		
Verapamil	80 mg 3 times a day (starting dose)	Increase dose by 80 mg every week up to 480 mg daily, then increase more slowly if needed by 80 mg every 2 weeks (other dose escalation paradigms have also been recommended, some faster, some slower), baseline and periodic EKGs should be considered (see text)
Lithium	300 mg twice a day (starting dose)	Increase to 300 mg 3 times a day after 1 week if no response, do lithium blood levels and increase further if necessary (usual therapeutic range 0.4-0.8 mEq/L)

†Maximum daily dosage limits from the product monographs are shown in this table. These should be used as a guide, although clinical experience indicates that somewhat more frequent dosing may be tolerated safely by some patients, particularly over short periods of time. Clinical judgment with consideration of risks and benefits is advised.

For references, see text.

DHE = dihydroergotamine; EKG = electrocardiogram.

analysis of cluster headache treatment,<sup>9</sup> and a comprehensive general review.<sup>10</sup> These should be consulted for a more detailed discussion of relevant clinical trials and references.

## ACUTE THERAPY

The main options for acute therapy are shown in the Table.

The 5HT<sub>1b/1d</sub> agonists, in particular the triptans, are the most effective acute medications for cluster headache. Because a rapid onset of action is essential, only injectable and intranasal formulations should be considered for most patients.

### Subcutaneous Sumatriptan

Subcutaneous (SC) sumatriptan 6 mg is the acute treatment of choice for most patients with cluster headache. It has been shown to be effective in well-done clinical trials,<sup>11</sup> with 36% of patients pain-free within 10 minutes and 46% within 15 minutes. It is a short-acting drug and is only approved for up to 2 doses per day. Patients with a high frequency of cluster headache attacks (more than 2 per day) may tend to exceed this amount. It is important therefore to start a transitional therapy quickly in such patients.

### Intranasal Zolmitriptan

Intranasal zolmitriptan 5 mg is a good alternative<sup>12,13</sup> for patients who cannot tolerate self-injection or if the cost of SC sumatriptan

is an issue. It often provides good relief, although it is slower than SC sumatriptan. The proportion of patients with a pain-free response was superior to placebo at 15 minutes after dosing, and pain-free rates at 30 minutes were found to be 38.5% with the 5 mg dose.<sup>12</sup> The 10 mg nasal spray dose is more effective but not generally available.

### Oxygen

Breathing 100% oxygen through a non-rebreathing mask is effective for many patients, although in some, it seems to simply postpone the attack rather than truly aborting it. High flow rates may be required. It would seem prudent to use the flow rates and duration of therapy used in the largest randomized, placebo-controlled trial that showed oxygen to be effective.<sup>14</sup> The dose of oxygen used was 100% oxygen with a flow rate of 12 L/minute for 15 minutes.

### Dihydroergotamine

Dihydroergotamine (DHE) is another injectable alternative for the acute treatment of cluster headache, but one for which there is little formal evidence for efficacy. In a retrospective study, intravenous DHE was found to render most patients headache-free within 2 days, and 16% became headache-free after the first

dose.<sup>15</sup> DHE can be self-administered subcutaneously or intramuscularly at home and as an injectable medication has the potential for a rapid onset of action. As a result of its long half-life, it may protect patients with frequent attacks from further attacks for as long as 12 hours, for example overnight. For routine use for individual attacks, SC sumatriptan is a more evidence-based and faster agent.

### Others

Among other options, intranasal sumatriptan has the most evidence for efficacy. Intranasal zolmitriptan has stronger evidence for efficacy, however, and also stronger evidence for substantial direct absorption through the nasal mucosa<sup>16</sup> that would be expected to allow for a faster onset of action. There is also some evidence for efficacy of oral zolmitriptan in acute cluster headache treatment, and some patients, particularly those with longer attacks, find oral triptans helpful. They can be expected to be slower than intranasal zolmitriptan, and their evidence for efficacy is less strong. They are therefore not recommended for routine use. There is little evidence for efficacy of DHE nasal spray in cluster headache, and in clinical use, the intranasal triptans are generally superior.

Non-steroidal anti-inflammatory drugs are not usually helpful for cluster attacks, and the usefulness of opiate analgesics is very limited. Neither is recommended for routine use. SC octreotide has some evidence for efficacy,<sup>9</sup> but we have no experience with its use. Intranasal lidocaine has minimal evidence for use,<sup>10</sup> and we have little experience with it.

### TRANSITIONAL THERAPIES

The main options for transitional therapy are shown in the Table. Transitional therapies are indicated primarily in high-frequency (>2 attacks/day) episodic cluster headache.

Agents used for transitional therapy have been referred to as transitional prophylactics,<sup>10</sup> as opposed to the maintenance prophylactics that are for more long-term use. Transitional therapies are needed primarily in patients with relatively frequent attacks (more than 2 attacks per day). Their role is to stop the cluster headache attacks quickly both to prevent pain and disability, and to reduce the patient's requirements for acute medication so that the frequency of use of acute medications remains within acceptable limits. Most transitional medications cannot be used longer term without risk of major side effects.

#### Oral Corticosteroids

Oral corticosteroids, usually prednisone, have been used for many years to stop clusters quickly, usually in a matter of a few days. One small double-blind controlled cross-over study is available to confirm prednisone efficacy,<sup>17</sup> and there seems little doubt, based also on clinical experience and open-label trials, that they are very effective.<sup>18</sup> An adequate dose must be used, and this should be at least 40 mg. A commonly used paradigm is to use

60 mg daily for 3 days, and then to reduce the daily dose by 10 mg every 3 days.<sup>19</sup> This provides a treatment course of 18 days, which should provide time to increase the dose of verapamil (or another prophylactic drug) to therapeutic levels. If the steroid course is used without a concomitant long-term prophylactic drug, the cluster headache is very likely to relapse as the steroid dose is reduced.<sup>18</sup> Higher initial steroid doses can also be used and may well be more effective. Raskin<sup>20</sup> recommended prednisone 80 mg for 7 days, followed by a rapid taper over 6 days. We use prednisone 70 mg for 4 days, and the dose is then tapered by 5 mg every day (total treatment time 17 days) to achieve both a high initial dose but to limit the time on the high dose to a relatively short period. In one small open-label study, a single dose of high-dose intravenous methylprednisolone (30 mg/kg) temporarily abolished cluster headache attacks in all patients, although they recurred within a few days in most.<sup>21</sup> **If prednisone doses greater than 60 mg are used, a more rapid taper should be considered so that the course of steroid therapy is not prolonged much beyond 18 days to avoid steroid-related adverse effects.**

#### DHE

As might be expected, even though controlled trial data is lacking, many cluster headache patients will respond to DHE, at least when it is given intravenously.<sup>15</sup> With its long half-life, DHE can be used as a transitional therapy, with dosing 2 or 3 times a day for several days and up to a week if well tolerated. For most patients on repetitive doses of DHE, attacks stop within 2 days of initiating therapy.<sup>15,22</sup> The most reliable method of administration for use at home is by SC or intramuscular self-injection using a dose of 1 mg. If patients suffer from nocturnal attacks, a dose at bedtime may protect them from attacks during the night. DHE nasal spray could theoretically also be used, but the dose would need to be 2 mg as not all the medication is absorbed. We have no experience with intranasal DHE used in this way.

DHE given subcutaneously at lower doses (eg, 1 mg twice a day or just 1 mg at bedtime) can be continued beyond 1 week.<sup>22</sup> Although the DHE product monograph lists 6 mg per week as the maximum dose, these dosages are often exceeded in the setting of transitional therapy for cluster headache. As DHE is a vasoconstrictor, drug contraindications should be carefully observed, and **the patient should be instructed to watch for vasoconstriction-related side effects (leg cramps, cold numb hands and feet, and chest pain).**

#### Occipital Nerve Block With Corticosteroids

Greater occipital nerve block with local anesthetic and corticosteroid, or with corticosteroid alone, has been shown to be helpful in patients with cluster headache in randomized, controlled trials. It is unclear what mechanisms lead to this efficacy and what role systemic absorption of steroids might play. Peres et al<sup>23</sup> reported that lidocaine in combination with triamcinolone 40 mg provided some benefit in a small open-label trial, although

this benefit was far from universal. In a placebo-controlled trial, Ambrosini et al<sup>24</sup> found that a single suboccipital injection of steroid (a mixture of short- and long-acting betamethasone: total dose 17.72 mg) with lidocaine completely suppressed cluster attacks in more than 80% of patients, and that this effect was maintained for at least 4 weeks in the majority. Leroux et al found that 3 suboccipital injections of cortivazol (without local anesthetic) given 48-72 hours apart reduced the number of cluster headache attacks as compared with placebo during the first 15 days after the first injections,<sup>25</sup> again indicating that suboccipital steroid injections can be a helpful transitional treatment in cluster headache.

The ideal injection regimen for steroids by suboccipital injection for cluster headache transitional therapy has not been established. It would appear that a long-acting preparation is appropriate, and based on the 2 controlled trials, a relatively high dose should be used. Betamethasone has potency approximately 5 times that of methylprednisolone, so a dose equivalent of 90 mg of methylprednisolone was used in one trial in a single injection.<sup>24</sup> In the other, the equivalent of 150 mg of methylprednisolone was given in 3 injections over approximately 6 days.<sup>25</sup> It would appear then that methylprednisolone dosages of between 40 and 80 mg in a slow release preparation would be appropriate and that several repeated injections can be utilized. Based on the study by Ambrosini et al cited earlier,<sup>24</sup> if only a single injection is planned, 80 mg of methylprednisolone might be more appropriate than 40 mg. It has been suggested that triamcinolone should be avoided because of risk of cutaneous atrophy and localized alopecia.<sup>26</sup> Avoidance of superficial injection of steroid may also be helpful in avoiding this complication.

The use of suboccipital steroid injections for cluster headache has been exhaustively reviewed by Leroux and Ducros.<sup>27</sup>

### Others

Ergotamine tartrate has been used as transitional prophylaxis,<sup>10</sup> but we have little experience with this approach and consider DHE as a similar but safer option.

## PROPHYLACTIC THERAPY

The main options for prophylactic therapy are shown in the Table.

In some patients, cluster headache may not recur in the short term after some of the transitional therapies listed earlier. However, most patients do require longer term prophylaxis, and this is best started at the same time as the transitional therapy, as most prophylactics do require some time for dosage escalation, and also for the prophylactic drug to become adequately effective.

The first-line prophylactic medication for cluster headache is verapamil, and very high doses may be required. Second choice is lithium. Methysergide is an effective prophylactic drug that was commonly used in the past, but it is used much less now because

of concerns over side effects (fibrotic complications) and concerns over the safety of simultaneous use with the triptans.

### Verapamil

Verapamil is considered the first-line prophylactic drug for cluster headache. It is usually well tolerated, although side effects include constipation and occasionally leg edema. It can be effective quite quickly. In a double-blind placebo-controlled trial, half of responders had improvement in the first week, and the rest responded in the second week of therapy.<sup>28</sup>

The usual starting dose is 80 mg 3 times a day, and the short-acting preparation is usually used. Verapamil has a short half-life (3-7 hours, although half-life may be up to 5-12 hours with chronic dosing) so dosing 3 times a day is necessary. Regular release verapamil tablets are usually used, as the slow release preparations do not seem to be reliable in terms of maintaining blood levels with longer dosing intervals. A concern with verapamil is its effects on atrioventricular conduction. It has been shown that approximately 19% of patients receiving verapamil for cluster headache develop electrocardiogram (EKG) abnormalities, although the great majority of these consist only of prolonged PR intervals, or right bundle branch blocks. However, about 4% can develop complete heart block with junctional rhythms.<sup>29</sup> Because of this, a slow increase in verapamil dosage has been recommended, with the dosage increased from the starting dose of 80 mg 3 times a day by 80 mg every 2 weeks. With this regimen, it takes 6 weeks to reach a dose of 480 mg daily. Although some patients will achieve effective prophylaxis at lower doses, patients with cluster headache may require verapamil doses in excess of this, and these are usually tolerated. Doses up to 640 mg daily are not uncommonly used, and higher doses have been reported to be effective and tolerated. A slow dosage increase is problematic, in that cluster headache attacks are usually very severe and most bridging medications would also pose significant risks if used for more than several weeks. Faster dosage escalation for verapamil in cluster has been recommended (increased by 80-160 mg every 2 or 3 days, starting from 80 mg 3 times a day)<sup>30</sup> and also used by other authors (dose increased by up to 120 mg every 2 days).<sup>25</sup>

A reasonable compromise, therefore, would be to start verapamil at 80 mg 3 times a day and to increase the verapamil dosage by 80 mg every week up to a dose of 480 mg daily. Above 480 mg, dosage increases of 80 mg every 2 weeks should be considered in order to ensure that the dosage is not higher than necessary to control the headaches. Although EKG changes can occur at lower doses, an EKG should certainly be done once a daily dose of 400 mg has been reached, and a week after each dosage increase above this level. A baseline EKG has also been recommended and periodic follow-up EKGs in patients on maintenance doses of verapamil, as arrhythmias may develop over time on stable verapamil doses.<sup>29</sup> However, it needs to be emphasized that most patients tolerate even high-dose verapamil well. In a study that reviewed 29 patients with cluster headache who

were taking 720 mg or more of verapamil daily, 11 were found to have EKG abnormalities. However, 7 had only bradycardia, and 2 additional patients had only a prolonged PR interval. One patient had a second-degree heart block, and one had a third-degree heart block.<sup>31</sup> In total, 2 patients required discontinuation of verapamil, and one needed a dose reduction. Periodic EKGs are therefore important in patients on verapamil, particularly if they are taking a dose of over 480 mg. Given the efficacy of high-dose verapamil in cluster headache, however, it is an important option to consider in patients who do not respond to lower doses.

Patients on verapamil should be cautioned to avoid grapefruit including grapefruit juice. Grapefruit and some related fruit (limes and pomelos) contain furanocoumarins that cause irreversible inactivation of CYP3A4.<sup>32</sup> This can result in increased verapamil levels, and a case of complete heart block presumably resulting from this interaction has been reported.<sup>33</sup> However, the effect of moderate amounts of grapefruit on verapamil levels does not appear to be as great as for some other drugs.

### Lithium

Lithium should be the next prophylactic drug considered if verapamil is not tolerated or ineffective. In a comparison study, lithium appeared to have similar efficacy as verapamil but worked more slowly and had more side effects.<sup>34</sup> Although a placebo-controlled, double-blind trial of lithium use in cluster headache<sup>35</sup> was negative, this trial used too low a dose (800 mg) and too short a treatment period (1 week) to assess lithium efficacy adequately. Lithium is used more in patients with chronic cluster headache but can also be effective in patients with episodic cluster. If patients on verapamil are not achieving sufficient relief, lithium can be added to the verapamil, and if a favorable response is achieved, the verapamil can then be slowly tapered to see if lithium alone or lithium in combination with a lower dose of verapamil can control the headaches. We usually start lithium at 300 mg twice a day and increase to 300 mg 3 times a day after 1 week. In some patients, 1200 mg a day may be necessary, but the dose likely should not be increased until lithium levels have been checked while the patient is on 900 mg daily. Baseline thyroid function and renal function tests should be done prior to starting lithium and periodically thereafter. Lithium levels should also be used to monitor therapy and to avoid unnecessary toxicity. The serum level required for therapeutic response is usually 0.4-0.8 mEq/L.<sup>10</sup> Higher levels may be tolerated but should be maintained below 1.2 mEq/L.<sup>20</sup> If the patient responds at relatively low lithium doses and levels, there is no need to increase the dose further.

Lithium, especially in high doses, can cause nausea, diarrhea, and a plethora of central nervous system (CNS) side effects, including tremor, confusion, lethargy, and ataxia. Patients do require clinical follow-up and monitoring. If patients are taking relatively high doses of verapamil (over 560 mg daily), we recommend reducing the dose as lithium is started to avoid possible drug interactions.

### Others

Methysergide is probably effective, although there is a lack of controlled trials in cluster headache. It is used much less now for cluster headache because of concerns with concomitant triptan use, and long-term therapy is difficult because of the potential fibrotic complications. Other options are sodium valproate, melatonin, and topiramate, although evidence for efficacy is minimal. In a recent systematic review, based on the evidence, divalproex sodium was not recommended. Melatonin received a level C recommendation for use based on 1 randomized, controlled trial.<sup>9</sup> The single randomized, controlled trial with melatonin showed a modest positive result with a 10-mg dose using regular release tablets.<sup>36</sup> Another study that used a 2-mg slow-release tablet and a placebo control failed to show benefit.<sup>37</sup> Data to date would suggest that if cluster patients respond to melatonin, this appears limited to episodic cluster patients. It appears that many issues related to dose, tablet formulations and timing of administration need to be resolved with regard to testing melatonin therapy. A dose of 10 mg, titrated quickly to 25 mg, given in the late evening before going to bed has been advocated.<sup>30</sup> Although topiramate has been recommended for cluster therapy as a second-line drug<sup>10</sup> and listed as “probably effective” by the EFNS guidelines,<sup>3</sup> it has only open-label evidence for efficacy. Despite some earlier more positive studies,<sup>10</sup> in 1 open-label study, only 7 (6 of whom had episodic cluster) of 33 patients had a headache reduction of 50% or more.<sup>38</sup> Interestingly, in a randomized, placebo-controlled cross-over trial in patients with refractory chronic cluster headache, low-intensity anticoagulation with warfarin was associated with a significantly higher incidence of remission and less impact of headache on patients’ lives compared with placebo.<sup>39</sup> These observations require confirmation through more research.

### CONCLUSION

Cluster headache is relatively uncommon, and pharmacological management is complex. Most patients with cluster headache require specialist referral. Conventional pharmacological therapy, as described earlier, can be successful in the majority of patients with cluster headache. In general, pharmacological therapy of the patient with episodic cluster headache is more likely to be successful than therapy of the patient with chronic cluster headache. Although the medications used for both are similar, for patients with chronic cluster, prophylactic options will need to be maximized, and invasive surgical options may need to be considered. For both episodic and chronic cluster, however, experience and therapeutic expertise are required for success. Acute, transitional, and prophylactic therapies need to be expertly applied as appropriate based on the clinical features of the patient.

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