Research – Treatment of Chronic Migraine

Brief	AAT Matter (Access) A summary of best practice treatment interventions for chronic migraines
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Delegates have access to a wide variety of comprehensive guidance material. If Delegates require further information on access or planning matters they are to call the TAPS line for advice.

The Research Team are unable to ensure that the information listed below provides an accurate & up-to-date snapshot of these matters.

1 Contents

2 Summary

- Literature sourced indicates there are several options available for the treatment of chronic migraine which include:
    - Acute medication
    - Preventive medication
    - Complementary treatments
    - Neuro stimulation devices
    - Procedures
    - Psychological / Behavioural Treatments

- Research indicates that:
    - The first line approach to treatment is **medication** where there are two categories of medication: Acute and Preventative
    - **Preventive / Prophylactic medication** appears to be underutilised in Australia with general practitioners restricting their choice, in most cases, to pizotifen or propranolol
    - New **CGRP antibodies** medication for migraine may offer an new approach in the treatment and prevention of migraine
    - **Acupuncture** can be an effective treatment for migraine
    - There is insufficient evidence that **nutraceuticals** is as an effective treatment for migraine
    - There is insufficient evidence that **psychological therapies** are an effective treatment for migraine
    - **Botox injections** can effectively reduce the duration and severity of migraine
    - There is insufficient evidence that the currently available **neuro stimulation treatment devices** are effective treatment for migraine. However, the Cefaly device (Transcranial supraorbital stimulation) appears to show some benefit in managing migraine

3 Treatment

The Royal Australian College of General Practitioners (RAZCGP) recommends a pharmacological treatment approach [1]. Although they mention a number of important issues to consider regarding non-pharmacological treatment, they do not advocate the use of any specific treatments [1].

Migraine and Headache Australia recommend medication as the first line treatment option, however, they also suggest are other treatment options which are reflective of much of the other non-peer reviewed literature, and include [2]:

- Acute Medication [3]
- Preventive Medication [4]
- Complementary treatments [4]
- Neuro stimulation devices [4, 5]
- Procedures [6]
- Psychological / Behavioural Treatments [4]

3.1 Medications

3.1.1 Acute medications

Acute medications are treatments taken at the onset of a migraine attack to reduce the symptoms associated with migraine. There are a variety of medications available for the acute treatment of migraines, depending upon the severity of the attack [3].

Medications used at the onset of migraines include [3]:

- Aspirin or other nonsteroidal anti-inflammatory drugs
- Paracetamol
- Ergotamine
- Anti-nausea drugs (e.g. domperidone, metoclopramide, prochlorperazine)
- Triptans (e.g. sumatriptan, naratriptan, zolmitriptan)

3.1.2 Preventive / Prophylactic medications

Prophylactic medication appears to be underutilised, especially in patients with frequent migraine. A report in the Australian Medical Journal by Stark, Valenti [7] has suggested that Australian General Practitioners (GPs) appear to select from a limited range of therapeutic options for migraine prophylaxis, despite the availability of several other well documented efficacious agents, and some use inappropriate drugs for migraine prevention.

Australian Therapeutic Guidelines recommend regular preventive treatment for patients who continue to experience more than two or three acute attacks of migraine per month [8, 9]. Influential evidence-based reviews of migraine treatment have been published by both the American

Academy of Neurology [8, 10] and the European Federation of Neurological Societies [8, 11]. Although there are many prophylactic agents with established efficacy, Australian GP's restrict their choice, in most cases, to pizotifen or propranolol [7, 8].

Conventional preventative medications include [4]:

- Blood pressure medications
  - Beta-blockers – propranolol, metoprolol
  - Calcium channel blockers – verapamil
- Antidepressants
  - Tricyclic antidepressants – amitriptyline, nortriptyline
  - SNRIs – venlafaxine, duloxetine
- Antiepileptics
  - Topiramate
  - Sodium valproate
  - Gabapentin
- Other
  - Pizotifen
  - Cyproheptadine

3.1.2.1 Calcitonin Gene-related Peptide Treatments

Anti-Calcitonin Gene-related Peptide (CGRP) monoclonal antibodies have recently become available [4]. Phase 3 clinical research studies are showing that CGRP antibodies for migraine may offer an entirely new approach in the treatment and prevention of migraine. Most treatments for migraine were originally designed for other conditions such as epilepsy, hypertension or depression. This class of CGRP treatments are the first preventative treatment designed specifically for migraine [12].

3.2 Complementary and alternative therapies

3.2.1 Nutraceuticals

Migraine & Headache Australia suggest that there is evidence to support that the following nutraceuticals and supplements for migraine, in particular magnesium, riboflavin and CoQ10. All of these have been shown in small studies to reduce migraine frequency when used as a daily preventative [4].

- Magnesium
- Riboflavin (Vitamin B2)
- Coenzyme Q10 (CoQ10)
- Melatonin

Two studies [13, 14] were sourced both of which suggested the need for investigation of nutraceuticals as a result of greater use by patients concerned with the lack of efficacy, cost, and side effects of conventional pharmacologic medications.

A 2016 study reviewed the guidelines from the American Academy of Neurology/American Headache Society, Canadian Headache Society, and European Federation of Neurological Societies in

the use of nutraceuticals including riboflavin, coenzyme Q10, magnesium, butterbur, feverfew, and omega-3 polyunsaturated fatty acids [14]. The authors concluded that there is a *limited number of studies of sufficient quality available in favour of or against their use in migraine prophylaxis*. Further well designed, randomized controlled trials (RCT) on nutraceuticals are require so that clinicians can offer evidence based recommendations to patients with migraine who are significantly affected by migraines.

A 2014 literature review identified both observational studies and RCTs on the use of nutraceuticals for the prophylaxis of paediatric and adult migraine [13]. Thirty studies were reviewed on six different nutraceuticals: butterbur, riboflavin, ginkgolide B, magnesium, coenzyme Q10 and polyunsaturated fatty acids. The study concluded that the *quality of the evidence for the use of nutraceuticals in paediatric migraine prophylaxis is poor*, and that further research is needed in order to study the efficacy of nutraceuticals for the prophylaxis of paediatric migraine [13].

3.2.2 Acupuncture

Migraine & Headache Australia, suggest that acupuncture has been shown to be beneficial. Initially there was some suggestion that sham acupuncture is just as effective as true acupuncture, but more recent studies indicate that true acupuncture is more effective than sham acupuncture. Findings suggest that many patients respond well to this, particularly when treatment occurs over a duration of at least a few months [4].

A systematic review conduced in 2008 evaluated the efficacy of acupuncture for treatment of chronic headache [15]. Databases searches were conducted to locate RCTs investigating the use of acupuncture for chronic headache. Studies were included in which adults with chronic headache, including migraine, tension-type headache or both, were randomized to receive needling acupuncture treatment or control consisting of sham acupuncture, medication therapy, and other non-pharmacological treatments. Data was extracted on headache intensity, headache frequency, and response rate assessed at early and late follow-up periods.

Thirty-one studies were included in the review. The majority of included trials comparing true acupuncture and sham acupuncture showed a trend in favour of acupuncture. The study concluded that needling acupuncture is superior to sham acupuncture and medication therapy in improving headache intensity, frequency, and response rate [15]. (NOTE: Sham acupuncture (SA), also called placebo acupuncture (PA), performed away from the acupuncture points established by TCM or without stimulation and manipulation to avoid eliciting “De Qi” sensations or using a non-penetrating technique, is used as control in scientific studies to determine the efficacy of acupuncture [16])

A recent 2019 systematic review compared the effectiveness of acupuncture treatment with conventional migraine preventative medications [17]. Randomized trials and RCTs with adult patients that compared the clinical effects of acupuncture with a standard migraine preventive medication in patients with a diagnosis of chronic or episodic migraine with or without aura were included. Seven clinical trials (n = 1430) met the inclusion criteria. Although a meta-analysis could not be performed due to methodological heterogeneity, several of the studies did show that acupuncture can be more effective than standard pharmacological treatments for migraine prevention. The study concluded that there is growing evidence that acupuncture is just as effective

and has fewer side effects than many of the standard pharmaceutical agents that are currently used. However, the heterogeneity of the existing studies limits effective comparison and analysis [17].

3.2.3 Psychological / Behavioural treatment

Migraine and Headache Australia, and other non-peered reviewed information websites suggest that behavioural treatments are alternative and helpful options for the management of migraine, which include [4]:

- Cognitive Behavioural Therapy (CBT)
- Relaxation Therapy
- Mindfulness Meditation
- Biofeedback

Research indicates that there is an absence of high-quality evidence to determine whether psychological interventions are effective in managing migraine.

A recent 2019 Cochrane review aimed to evaluate the efficacy and adverse events of psychological therapies for the prevention of migraine in adults [18].

Database searches were conducted to identify RCTs of any psychological intervention for adults with migraine chronic or episodic migraine, with or without aura. Interventions could be compared to another active treatment (psychological or medical), an attention-placebo (e.g. supportive counselling) or other placebo, routine care, or waiting-list control. Studies were excluded if fewer than 15 participants completed each arm [18].

Twenty one RCTs with 2,482 participants with migraine were included. Data from 14 studies were extracted for meta-analysis. Most intervention arms were a form of behavioural or CBT. Interventions varied from one 20-minute session to 14 hours of intervention [18].

The review concluded that [18]:

- There was an absence of good-quality evidence that psychological therapy was effective or harmful in managing frequent migraine immediately following treatment or in the longer term
- There was no evidence that psychological treatments resulted in less migraine frequency in the four weeks following treatment
- There was no evidence that psychological treatments affected migraine intensity, medication use for migraine, mood or quality of life
- Follow-up data was rarely found, and there was no evidence to support or refute any long-term effects of psychological treatment
- Funding of high-quality studies is needed and additional studies may change the conclusions of the review.

3.3 Neuro stimulation Devices

Neuro stimulation treatment has recently emerged in the last few years as a potential option for migraine sufferers. Neuro stimulators target certain nerves or parts of the brain that we think are involved in migraine. They act by modulating or modifying the pain system through electrical currents or magnetic impulses. Currently there are three options that have been developed and are available to varying degrees [4].

- Transcranial supraorbital stimulation – Cefaly
- Non-invasive vagal nerve stimulation – gammaCore
- Transcranial magnetic stimulation

3.3.1 Cefaly

CEFALY sends tiny electrical impulses through a self-adhesive electrode placed on the forehead to stimulate the trigeminal nerve, reducing the frequency and intensity of migraine attacks [19]. The device has American Food and Drug Administration (FDA) approval for the prevention of episodic migraine [20]. Two research studies were sourced on the efficacy of Cafaly and concluded with positive results [20, 21]

A 2015 research paper [20] reviewed in detail the available data for Cefaly device as a migraine treatment including technical aspects, effect size, and safety, as well as possible explanations for its mode of action. The paper is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors. The study found that the device [20]:

- Was shown to be efficient by decreasing migraine and headache days significantly more than sham stimulation
- Reduced the number of migraine attacks
- Could be proposed to patients who prefer non-pharmacologic treatments, or who have contraindications to the usual preventive anti-migraine drugs or do not tolerate them
- Allows to significantly reduce acute anti-migraine medication use and therefore reduces the risk for chronification of migraine by acute medication overuse, which represents a pharmaco-economical advantage

A 2017 prospective, multi-center clinical study was performed in patients diagnosed with episodic or chronic migraine with a previous failure to topiramate treatment requiring prevention with Cefaly® according to the treating physician's suggestion [21]. A one-month period of baseline observation was followed by a 3-month period of observation during the use of transcutaneous supraorbital nerve stimulation (t-SNS) with Cefaly® as the only preventive treatment.

A small but statistically significant decline was shown over time in the number of days with headache (HA), the number of days with HA with intensity ≥5/10, and the number of days with use of acute medication after 3 months ($p < 0.001$ for all of the three changes). Twenty-three patients (65.7%) expressed their satisfaction and intent to continue treatment with Cefaly®. Compliance was higher among satisfied subjects compared to non-satisfied subjects. None of the explored factors were significantly associated with the reason for the failure of topiramate [21].

The study concluded that the three-months of preventive treatment for episodic or chronic migraine with t-SNS proved to be an effective, safe and well tolerated option for the treatment of patients with migraine who were intolerant or did not respond to topiramate [21].

3.3.2 gammaCore

gammaCore (nVNS) activates the vagus nerve with patented, gentle electrical stimulation [22]. The device is cleared by the FDA for acute and preventive treatment of cluster headache and the acute treatment of migraine in adults [23].

There is little research on the efficacy of the gammaCore. Following FDA approval of gammaCore in April 2017 and its subsequent launch in the United States, the gammaCore Patient Registry (GPR) was designed to provide a platform for patients receiving therapy to voluntarily provide information that could help provide a deeper understanding of gammaCore usage and improve patient care. GPR was a prospective observational program designed to enable patients with episodic cluster headache who were prescribed gammaCore to voluntarily enrol and submit information on their experiences between July 2017 and June 2018 [23].

Of the 182 participants who provided baseline data, 152 participants provided complete EuroQol Health Index tool, 5-level format (EQ5D-5L) baseline data, and 17 provided documentation of a total of 192 cluster headache attacks. The mean number of months of known diagnosis of cluster headache was 57. The mean number of patients reporting attacks in their respective previous cluster headache cycle was 14 per month with the mean pain score of 3.67 (0-4 scale), while the mean duration of attacks was 74 minutes [23].

The study suggests that [23]:

- The gammaCore significantly adds a valuable therapeutic option for patients who suffer from episodic attacks of cluster headaches, based on patient-documented attacks
- The successful use of gammaCore in the real-world setting provides evidence to support the need to redefine gammaCore as no longer investigational or experimental treatment, as well as for consideration for reimbursement by policy makers
- Evidence shows gammaCore is more cost-effective than the treatments that were standard of care (including sumatriptan and oxygen) prior to gammaCore introduction

3.3.3 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) works by possibly decreasing a process called cortical spreading depression which is believed to be the mechanism behind migraine with aura. This potentially has a role in migraine prevention as well as possibly acute treatment for migraine with aura [4]. Research on the subject was minimal and provided little evidence of efficacy.

A recent 2019 systematic review was performed on the use of TMS and transcranial direct current stimulation (tDCS) for the treatment of specific headache disorders (i.e., migraine, tension, cluster, posttraumatic) [24]. Inclusion criteria of studies were:

- Adults aged 18-65 with primary or secondary headaches
- Interventions including TMS and tDCS
- Comparators such as sham or alternative standard of care
- Study type of case control, cohort or RCT

A structured synthesis was performed due to heterogeneity of participants and methods. The study concluded that [24]:

- Of all TMS and tDCS modalities, rTMS is most promising with moderate evidence that it contributes to reductions in headache frequency, duration, intensity, abortive medication use, depression, and functional impairment. However, only few studies reported changes greater than sham treatment.

- Further high-quality RCTs with standardized protocols are required for each specific headache disorder to validate a treatment effect.

3.4 Procedures

3.4.1 Botox injections

In Australia, Botox has commonly been used for migraine for several years with good results and received coverage on the PBS a few years ago. Usage of Botox for migraine has increased and has now become a standard of care for people with chronic migraine who have not responded to three or more traditional preventive migraine treatments. While Botox is on the PBS for chronic migraine, there are still criteria to be fulfilled. Patients need to have tried or have contraindications to three of the standard preventives first [4].

A recent 2019 Cochrane review and meta-analysis, aimed to assess the effects of Botox for prevention of migraine in adults [25]. Included were RCTs of Botox compared with placebo, active treatment or clinically relevant different dose for adults with chronic or episodic migraine, with or without the additional diagnosis of medication overuse headache.

Cochrane methods were used to review double-blind RCTs. Twelve week post treatment time-point data was analysed. Twenty-eight trials (n=4190) were included. Trial quality was mixed. Botox treatment resulted in reduced frequency of −2.0 migraine days/month (95% CI −2.8 to −1.1, n=1384) in chronic migraineurs compared with placebo. An improvement was seen in migraine severity, measured on a numerical rating scale 0 to 10 with 10 being maximal pain, of −2.70 cm (95% CI −3.31 to −2.09, n=75) and −4.9 cm (95% CI −6.56 to −3.24, n=32) for chronic and episodic migraine

respectively. Botox had a relative risk of treatment related adverse events twice that of placebo, but a reduced risk compared with active comparators (relative risk 0.76, 95% CI 0.59 to 0.98) and a low withdrawal rate (3%). Although individual trials reported non-inferiority to oral treatments, insufficient data were available for meta-analysis of effectiveness outcomes [25].

The study concluded that the data suggests that Botox effectively reduces the duration and severity of migraines in sufferers [25].

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