Appendix Document 1

What are the device-related treatment options for migraine?

Neuromodulation devices apply an external stimulus over a peripheral nerve or cortical brain region to exert a modulating effect on central structures involved in migraine genesis and propagation (1,2). They are non-invasive, have minimal side effects and are safe for use in pregnancy (1,2). There are four FDA-approved devices**,** only two of which are available in Canada: External trigeminal nerve stimulation (eTNS; Cefaly) and non-invasive vagal nerve stimulation (nVNS; gammaCore) (1,2). Both can be used alone or together with pharmacotherapy for the acute or preventive treatment of migraine. Unlike less expensive transcutaneous electrical nerve stimulation (TENS) machines, the safety and efficacy of their use in migraine treatment (at a prescribed dose/frequency/location) have been specifically evaluated in prospective, double-blind, randomized, sham-controlled studies**.** However, they are not covered by public or private plans, and they are expensive.

Both randomized controlled trials (RCTs) assessing eTNS (Cefaly) met their primary endpoints. The ACME trial (n=106) showed that acute use of eTNS during a migraine attack reduced mean pain scores by 59% after 1 hour (sham 30%, $p<0.0001$; primary endpoint), with 29% of patients being pain-freedom after 1 hour (sham 6%, $p=0.0016$; secondary endpoint) (3). In the PREMICE trial (n=67), prophylactic use of eTNS over 3 months reduced mean monthly migraine days by 2.08 days ($p=0.023$) with 38.1% of patients achieving ≥50% reduction in monthly migraine days (sham 12.1%, $p=0.023$) (4). Significant reduction in monthly migraine attacks, headache days, and acute medication use were also observed. In comparison, RCTs assessing nVNS have failed to meet their primary endpoints. The PRESTO trial (n=248) found that acute use of nVNS was

not superior to sham in achieving pain-freedom at 2 hours (30.4% vs. 19.7%, p=0.067; primary endpoint), although the effect was statistically significant at 1 hour (21.0% vs. 10%, p=0.023) and it was associated with a reduction in acute medication use (5). Similarly, the PREMIUM trial (n=332) failed to show that preventive use of nVNS was superior to sham in reducing mean monthly migraine days (primary outcome); however, post hoc analysis revealed a statistically significant effect among patients with adherence ≥67% (6). The safety and efficacy of nVNS was also evaluated for prevention of chronic migraine in a pilot RCT (n=59), which did not demonstrate a statistically significant effect.

Overall, there is a paucity of strong evidence for neuromodulation devices. Most trials excluded patients with chronic migraine and medication overuse, decreasing the external validity of the results. Nevertheless, neuromodulation devices may be a reasonable option in people who are pregnant, for patients who wish to avoid or are intolerant to medications, or as an adjunct treatment for patients with medication overuse.

eTNS: For acute treatment, apply for 1 hour during a migraine attack. For prevention, apply for 20 minutes daily. VNS: For acute treatment, apply 2 times for 120 seconds each time within 20 minutes of attack onset and repeat once after 15 minutes. For prevention, apply 2 times for 120 each time, 3 times daily.

What are the procedural treatment options for migraine?

Peripheral nerve block using local anesthetic (such as bupivacaine or lidocaine) is a safe, fast-

acting, and cost-effective treatment option for migraine. While the mechanism by which nerve blocks work is not completely understood, it is known that afferent nociceptive signals from trigeminal and cervical nerve branches converge at the TNC, where activation of secondary neurons leads to central transmission of pain (7). Due to this convergence mechanism, it is believed that blocking afferent signaling in one component of the trigeminocervical system can have a modulating effect on other parts of the system, by increasing the threshold required for pain transmission and reducing sensitization of central pain structures (7).

Peripheral nerve blockade can be performed at various nerve branches of the trigeminocervical system, including the greater occipital, lesser occipital, auriculotemporal, supraorbital, supratrochlear, and infraorbital nerves and the sphenopalatine ganglion. Greater occipital nerve (GON) blockade is the most widely used and has the most evidence supporting its efficacy in the treatment of migraine. In a RCT, GON blockade administered weekly or monthly was superior to placebo in reducing headache severity, duration and frequency in patients with chronic migraine (8), with the clinical effect exceeding the short duration of the local anesthetic effect. Similarly, another RCT in patients with chronic migraine showed that GON blockade significantly reduced the number of days per week with moderate-to-severe headache (-2 days; 95% CI -2.7, -1.3) compared to placebo (-0.4 days; 95% CI -1.4, 0.5, p=0.027) in the week following administration, with 55.6% of patients achieving a ≥50% response (placebo 27.8%; OR 2.92, 95% CI 1.19, 7.15, p=0.019) (9). GON blockade was not associated with any severe adverse events; the most commonly observed side effects are injection site pain, vertigo and nausea (8).

Peripheral nerve block is covered by most public provincial health plans. Patients can be referred to trained providers (e.g. pain and headache specialists) for a trial of GON blockade as a transitional therapy in patients with chronic migraine while they wait for preventive treatment to take effect or when other preventive treatments may be temporarily contraindicated (pregnancy, breastfeeding). GON block can also be used acutely in the setting of status migrainosus to break the pain cycle when other acute treatments are ineffective.

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