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Neurological Effects of Therapeutic Laser

The rehabilitative possibilities of therapeutic laser are encouraging and continuing studies of the underlying mechanism of action and biologic effects will likely result in improved outcomes for the neurologic patient.

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Mar 7, 2011 **William J. Kneebone, CRNA, DC, CNC, DIHom**

One of the areas of laser therapy that is rather interesting and promises significant potential for healing is application of therapeutic laser to neurological conditions. In this article, I will present a review of scientific studies relative to neurological effects of laser and discuss some of the more promising applications.

Therapeutic laser has been studied for numerous neurological conditions that include:

- Stroke (including acute embolic stroke, ischemic stroke)
- Traumatic brain injury
- Neurodegenerative diseases such as Parkinson's Disease
- Trigeminal neuralgia
- Post-herpetic neuralgia (PHN)
- Cerebral palsy
- Spinal cord injuries
- Peripheral nerve regeneration
- Major depression

Stroke

Lapchak et al applied infrared light therapy to rabbits that suffered acute embolic stroke. Light therapy was applied transcranially 6 to 12 hours post embol-ization with continuous wave and pulsed waves. Behavior analysis was performed 48 hours after ischemic stroke. The results demonstrated that the pulsed mode IR light therapy resulted in significant clinical improvement when administered 6 hours following embolic strokes in rabbits.[1]

Oron et al studied the effects of GaAs laser irradiation on adenosine triphosphate (ATP) production in normal human neural progenitor cells. Tissue cultures were treated with the GaAs laser and ATP levels were determined at 10 minutes post laser application. The quantity of ATP in the treated cells was significantly higher than the non-treated group. The application of laser to normal human neuronal progenitor (NHNP) cells significantly increases ATP production. This may explain the beneficial effects of LLLT in stroked rats.[2]

Naeser studied the effect of laser acupuncture to treat paralysis in stroke patients and to examine the relationship between anatomical lesion sites on CT scan and the potential for improvement following laser acupuncture treatments. Seven stroke patients (five men and two women; aged 48 to 71) were admitted to the study. Five cases had a single left hemisphere stroke and two cases had a single right hemisphere. Five patients were treated for residual arm or leg paralysis. They exhibited greatly reduced arm and leg power with greatly reduced or absent voluntary isolated finger movement. Two cases, with good arm and leg power but exhibiting mildly reduced isolated finger movement, were treated only for hand paresis.

CT scans were obtained on all patient at least three months post stroke. Six patients began receiving the laser acupuncture treatments during the chronic phase post stroke (10 months to 6.5 years). These intervals are beyond the spontaneous recovery period of up to six months post stroke.[3,4] One hand paresis case began receiving treatments during the acute phase post stroke (one month post stroke). Because all but one patient were beyond the spontaneous recovery period, each patient served as his/her own control. No sham laser treatments were administered. None of the stroke patients was receiving physical therapy or occupational therapy treatments during the course of the laser acupuncture treatments. The use of low-level laser for long-term treatment is especially desirable for chronic stroke patients with hand paresis. The patient can be trained to treat him/herself at home, using an inexpensive 5mW red-beam diode laser pointer and a microamps TENS device.

This is the first study to examine the effect of low-level laser therapy on acupuncture points to treat paralysis in stroke patients where the lesion location was known for each patient. Results suggest that low-level laser therapy on acupuncture points is effective to help reduce the severity of paralysis in stroke patients—especially those with mild-to-moderate paralysis. The treatments should be initiated as soon as possible post stroke, even within 24 hours post stroke. A comprehensive rehabilitation program of physical therapy, occupational therapy, plus needle and/or laser acupuncture is recommended.[5]

Lampi et al conducted a prospective, intention-to-treat, multicenter, international, double-blind trial (Neurothera® Effectiveness and Safety Trial-1; NEST-1) involving 120 ischemic stroke patients treated, randomized in a 2:1 ratio, with 79 patients in the active treatment group and 41 in the sham (placebo) control group. Only patients with baseline stroke severity scores of 7 to 22 were included, as measured by the National Institutes of Health Stroke Scale (NIHSS). Patients who received tissue plasminogen activator were excluded. Outcome measures were the patients' scores on the NIHSS, modified Rankin Scale (mRS), Barthel Index, and Glasgow Outcome Scale at 90 days after treatment.

The primary outcome measure, prospectively identified, was successful treatment as documented by NIHSS. This was defined as a complete recovery at day 90 (NIHSS 0 to 1), or a decrease in NIHSS score of at least 9 points (day 90 versus baseline) and was tested as a binary measure (bNIH). Secondary outcome measures included mRS, Barthel Index, and Glasgow Outcome Scale. Primary statistical analyses were performed with the Cochran-Mantel-Haenszel rank test, stratified by baseline NIHSS score or by time to treatment for the bNIH and mRS. Logistic regression analyses were conducted to confirm the results.

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Mean time to treatment was >16 hours (median time to treatment 18 hours for active and 17 hours for control). Time to treatment ranged from 2 to 24 hours. More patients (70%) in the active treatment group had successful outcomes than did controls (51%) as measured prospectively on the bNIH (P=0.035 stratified by severity and time to treatment; P=0.048 stratified only by severity). Similarly, more patients (59%) had successful outcomes than did controls (44%) as measured at 90 days with a binary mRS score of 0 to 2 (P=0.034 stratified by severity and time to treatment; P=0.043 stratified only by severity). Also, more patients in the active treatment group had successful outcomes than controls as measured by the change in mean NIHSS score from baseline to 90 days (P=0.021 stratified by time to treatment) and the full mRS ("shift in Rankin") score (P=0.020 stratified by severity and time to treatment; P=0.026 stratified only by severity). The prevalence odds ratio for bNIH was 1.40 (95% CI, 1.01 to 1.93) and for binary mRS was 1.38 (95% CI, 1.03 to 1.83), controlling for baseline severity. Similar results held for the Barthel Index and Glasgow Outcome Scale. Mortality rates and serious adverse events (SAEs) did not differ significantly (8.9% and 25.3% for active 9.8% and 36.6% for control, respectively, for mortality and SAEs).[6]

The NEST-1 study indicates that infrared laser therapy has shown initial safety and effectiveness for the treatment of ischemic stroke in humans when initiated within 24 hours of stroke onset. A larger confirmatory trial to demonstrate safety and effectiveness is warranted.

Zivin et al performed a double-blind, sham-controlled (placebo) trial (NEST-2) which enrolled 660 patients. Patients were eligible for inclusion in the study if they were 40-90 years of age, had moderate to severe strokes, and had not received tissue plasminogen activator (tPA). Initiation of treatment had to occur within 24 hours after stroke onset.

In NEST-2, TLT achieved a favorable outcome in 36.3% of patients compared to only 30.9% of patients in the sham group (p-value 0.094). The primary efficacy endpoint was a favorable 90-day score of 0-2 using the modified Rankin Scale (mRS). Mortality rates and serious adverse events (SAEs) did not differ between groups, providing further evidence of the safety of TLT.

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"TLT is one of the most promising new therapies that we've seen in a long time, especially as it may expand the treatment window for ischemic stroke to 24 hours. We look forward to commencing NEST-3 to further investigate TLT," stated Professor Werner Hacke, MD, PhD, Chairman of Neurology at the University of Heidelberg, who will join Professor Zivin as Co-Chairman of the NEST-3 Steering Committee.[7]

Traumatic Brain Injury

Oron et al, in another study, evaluated the use of LLLT as a potential therapy for traumatic brain injury (TBI) utilizing a rat model. TBI was induced by a weight–drop device. Motor function was assessed one hour post trauma using a neurological severity score (NSS). The mice were divided into three groups of eight each: a control, and two laser groups, one receiving 10 mW/cm2 and one receiving 20 mW/cm2 transcranially. A GaAs laser was used four hours post trauma to illuminate the entire cortical area of the brain. No significant changes were seen in the neurological soft signs (NSS) from 24 to 48 hours. There were significantly lower scores in the laser treated groups from days 5 to 28. The results suggest that a non-invasive transcranial application of laser therapy given four hours post TBI provides significant long-term neurological benefit.[8]

Rockhind et al performed a study on the effect of 780 nm laser irradiation on the growth of embryonic rat brain cultures embedded in NVR-Gel (cross-linked hyaluronic acid with adhesive molecule laminin and several growth factors). Dissociated neuronal cells were first grown in suspension attached to cylindrical micro-carriers (MCs). The formed floating cell-MC aggregates were subsequently transferred into stationary cultures in gel and then laser treated. The response of neuronal growth following laser irradiation was investigated. The 780 nm laser irradiation accelerated fiber sprouting and neuronal cell migration from the aggregates. Furthermore, unlike control

cultures, the irradiated cultures (mainly after a one minute irradiation of 50 mW) were already established after a short time of cultivation. They contained a much higher number of large size neurons ($P<0.01$), which formed dense branched interconnected networks of thick neuronal fibers.

They concluded that 780 nm laser phototherapy of embryonic rat brains cultures, embedded in hyaluronic acid-laminin gel and attached to positively charged cylindrical MCs, stimulated migration and fiber sprouting of neuronal cells aggregates and developed large size neurons with dense branched interconnected network of neuronal fibers. This modality can therefore be considered as potential procedure for cell therapy of neuronal injury or disease.[9]

Parkinson's Disease

Trimmer et al performed an in vitro study that showed a single, brief treatment with a GaAlAs laser increased the velocity of mitrochondrial movement for two hours in cells taken from patients with sporadic Parkinson's Disease (PD). This accelerated the velocity up to levels approximating those of disease free age-matched cells. Their findings provide early stage confirmation that laser therapy has the potential to improve neuronal function in many patients with PD and other neurodegenerative diseases.[3]

Trigeminal Neuralgia

Eckerdal and Lehmann performed a double-blind, placebo controlled study with low intensity laser therapy on patients with trigeminal neuralgia. Two groups of patients, one with 14 subjects and the other with 16 subjects, were studied. The results showed that in the active laser treatment group of 16, ten were completely pain free, two had less pain, and four had little or no change in pain. Six of these patients had continued relief at one year post treatment.

The placebo-treated group had one person who was pain free, four had less pain and the remaining nine had little or no relief. After one year only one person was pain free. The researchers concluded that the study demonstrated that LLLT treatment is an effective method and excellent supplement to conventional therapies used in the treatment of trigeminal neuralgia.[4]

Post-Herpetic Neuralgia

Kemmotsu et al performed a double blind study utilizing low-level laser therapy (LLLT) for the treatment of post-herpetic neuralgia (PHN). Sixty-three patients were evaluated (25 males and 38 females with an average age of 69 years). A double blind assessment of LLLT was also performed in 12 PHN patients. A GaAlAs laser with a continuous output of 60 mW was used. Pain scores were obtained via the visual analogue scale (VAS). There was very good ($VAS<3$) immediate pain reduction after the first treatment in 26 and good relief (VAS 7-4) in 30 patients. The long term effects of LLLT was no pain (VAS 0) in 12 patients and slight pain (VAS 1-4) in 46 patients. The researchers concluded that LLLT is a useful modality for pain attenuation in PHN patients and, because LLLT is non-invasive, painless and safe.[10]

Toshikazu et al performed a study to evaluate the effects of laser irradiation (LLLT) in the area near the stellate ganglion on regional skin temperature and pain intensity in patients with postherpetic neuralgia. A double blind, crossover and placebo-controlled study was de-signed. Eight inpatients (six male, two female) receiving laser therapy for pain attenuation were enrolled in the study after institutional approval and informed consent. Each patient received three treatment sessions on separate days in a randomized fashion. Three minutes irradiation with a 150 mW laser (session one), three minutes irradiation with a 60 mW laser (session two), and three minutes placebo treatment without laser irradiation.

Neither the patient nor the therapist was aware which session type was being applied until the end of the study. Regional skin temperature was evaluated by thermography of the forehead and pain intensity was recorded using a visual analogue scale (VAS). Measurements were performed before treatment, immediately after then at 5, 10, 15, and 30 minutes after treatment. Regional skin temperature increased following both 150 mW and 60mW laser irradiation, whereas no changes were obtained by placebo treatment. VAS decreased following both 150 mW and 60 mW laser treatments, but no changes in VAS were obtained by placebo treatment. These changes in the temperature and VAS were further dependent on the energy density (i.e., the dose).

Results demonstrate that laser irradiation near the stellate ganglion produces effects similar to a stellate ganglion block. The results clearly indicate that they were not placebo effects but true effects of laser irradiation.[11]

Cerebral Palsy

Anwar et al conducted a study at Anwar Shah's First Cerebral Palsey and Paralysis Clinic and Research Center in collaboration with the Departments of Neurology and Neurosurgery, Children Hospital Lahore, Pakistan, to evaluate the effects of aculaser therapy (laserpuncture) in children suffering from cerebral palsy and associated neurological disorders like epilepsy, cortical blindness, spasticity, hemiplegia, paraplegia, quadriplegia, paraplegia, monoplegia, sensory-neural deafness and speech disorders. One hundred children were treated and the data were gathered during a period of 18 months from December 2003 till June 2005. The treatment of the children lasted a minimum of six weeks and a minimum of ten treatment sessions. Those children who were given a break from treatment for 4 to 12 weeks did not show any reversal of symptom relief.

Analysis of the data showed the following results12:

- 69 out of 81 children with spasticity and stiffness (85%) showed a marked improvement.
- Significant reduction in intensity, frequency, and duration of epileptic activity was observed in 34 out of 54 children (63%).
- There was improvement in 13 out of 18 children with cortical blindness (72%).
- 31 out of the 45 children with hearing difficulties marked improvement (69%).
- 67 out of 100 children with speech disorders showed improvement (67%).
- 32 out of 46 children with hemiplegia showed improvement in movement, muscle tone, and power (69%).
- 25 out of 36 children with quadriplegia showed improvement in gross and fine muscle function (69%).
- 12 out of 18 children with lower body paraplegia showed improvement in weight bearing capabilities, standing, and movement (67%).

Spinal Cord Injuries

Wu et al performed a study on rats utilizing a 810 nm GaAlAs laser with a 150 mW output to treat spinal cord injuries (SCI) following creation of a contusion model and a dorsal hemi-section model. Light was applied transcutaneously at the lesion site immediately after injury and daily for 14 consecutive days. The daily dose at the skin overlying the lesion was 1589 J/cm2 (0.3 cm2 spot area for 2997 seconds). Mini-ruby was used to label corticospinal tract axons. These were counted and measured from the lesion site distally. Functional recovery was assessed by footprint test for the hemi-section model and open-field test for the contusion model. The rats were euthanized three weeks after injury. The average length of axonal regrowth in the group of rats treated with the laser was 6.89 +/- 0.96 in the hemi-section group and

7.04 +/- 0.76 in the contusion group as compared with the untreated control group of 3.66 +/- 0.26 in the hemi-section group and 2.89 +/- 0.84 in the contusion group.

The total axon number in the LT groups was significantly higher compared to the untreated groups for both injury models (P<0.05). For the hemi-section model, the LT group had a statistically significant lower angle of rotation (P<0.05) compared to the controls. For contusion model, there was statistically significant functional recovery (P<0.05) in the LT group compared to untreated control. It is concluded that light therapy, applied non-invasively, promotes axonal regeneration and functional recovery in acute SCI caused by different types of trauma. These results suggest that light is a promising therapy for human SCI.[13]

> "Rochkind...study shows that low power laser irradiation can progressively improve peripheral nerve function in long-term peripheral nerve injured patients, leading to significant functional recovery."[17]

Byrnes et al performed a study aiming to demonstrate the photobiomodulation (PBM) effects of 810 nm GaAlAs laser as a potential therapy for the treatment of spinal cord injuries (SCI). They aimed at demonstrating that the laser could penetrate deeply into the body and promote neuronal regeneration and functional recovery. Adult rats underwent a T9 dorsal hemisection followed by treatment with an 810 nm, 150 mW diode laser (dosage = 1,589 J/cm^2). Axonal regeneration and functional recovery were assessed using single and double label tract tracing and various locomotor tasks. The immune response within the spinal cord was also assessed. PBM, with a 6% power penetration to the spinal cord depth, significantly increased axonal number and distance of regrowth (P < 0.01). PBM also returned aspects of function to baseline levels and significantly suppressed immune cell activation and cytokine/chemokine expression. The authors concluded that their results demonstrate that light, delivered transcutaneously, improves recovery after injury and suggests that light will be a useful treatment for human SCI.[14]

Byrnes et al studied secondary injury in the spinal cord which results in axonal degeneration, scar and cavity formation and cell death around the site of initial trauma and is a primary cause for the lack of the axonal regeneration observed after spinal cord injury (SCI). The immune response after SCI is under investigation as a potential mediator of secondary injury. Treatment of SCI with 810 nm LLLT suppresses the immune response and improves axonal regeneration. This study demonstrated that LLLT has an anti-inflammatory effect on the injured spinal cord, and may reduce secondary injury, thus providing a possible mechanism by which light therapy may result in axonal regeneration.[15]

Peripheral Nerve Regeneration

Midamba and Haanaes performed a study on peripheral nerve regeneration in humans. Forty patients with short and long term neuro-sensory impairment following perioral nerve injuries were chosen for the study. Assessment of their sensory level was undertaken using a variety of nerve tests. One of them was a visual analogue scale (VAS) for registration of sensitivity level prior to and after 10 treatment sessions and additionally for 21 of the 40 patients after 20 treatment sessions. Low level laser therapy (LLLT) was applied using GaAlAs 830 nm, 70 mW continuous wave. A dose of 6.0 J/cm^2 was standardized for all patients. Improvement of the eight patients with clinical symptoms of less than one year was between 40-90% (average 51.9%) after 10 treatments and between 50-80% (average 66.7%) after 20 treatments for the three patients who continued with the treatment. In 32 of the 40 patients with clinical symptoms of more than one year duration, their improvement was estimated at between 40 and 80% (average 54.8%). Of the 21 patients who completed 20 treatment sessions, the end results were between 60% and 90% (average 71.1%). This was an uncontrolled clinical study of LLLT on perioral nerve injuries and demonstrated the effectiveness of GaAlAs laser when applied to the nerve trunk and terminal endings. Although controlled research into actual mechanisms and pathways is needed, the preliminary findings are very promising.[16]

Rochkind performed a clinical, double-blind, placebo-controlled randomized study to measure the effectiveness of laser phototherapy on patients who have been suffering from incomplete peripheral nerve and brachial plexus injuries for six months up to several years. This study shows that low power laser irradiation can progressively improve peripheral nerve function in long-term peripheral nerve injured patients, leading to significant functional recovery. Recently, biodegradable composite transplants—based on cell tissue-engineering technology—were used for the treatment of complete peripheral nerve and spinal cord injury in rats. The laser phototherapy was applied as a supportive factor for accelerating and enhancing axonal growth and regeneration after reconstructive peripheral nerve and spinal cord procedures. The significance of this innovative methodology will be the provision of a new nerve tissue-engineering modality and laser technology for treatment of complete peripheral nerve and spinal cord injury.[17]

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Rockhind et al also performed a series of experimental studies to evaluate the efficacy of low power laser irradiation as a supportive factor for accelerating and enhancing axonal growth and regeneration after reconstructive peripheral nerve and spinal cord procedures. In these procedures, regenerative and reparative biotechnological sources were used for the microsurgical reconstruction. These re-search projects are an interdisciplinary effort of a novel therapeutic strategy where a biodegradable nerve tube was used for peripheral nerve reconstruction and composite implants of cultured embryonal nerve cells were applied for a transected spinal cord followed by post-operative laser treatment.

In addition, the studies investigated the role of low power laser irradiation in accelerating and enhancing axonal growth in a nerve cell culture model and primary repair of injured peripheral nerve. The significance of these approaches will be the provision of new nerve tissue-engineering modality and laser technology for treatment of severe peripheral nerve and spinal cord injury.[18]

Anders and Backs have previously shown that LLLT increases the rate of facial nerve regeneration and alters choline acetyltransferase immunoreactivity during regeneration of crushed rat facial nerves and increases mRNA for a calcitonin gene-related peptide after facial nerve transection. These findings indicate that LLLT optimizes nerve regeneration. The purpose of this study was to quantitatively determine if LLLT can rescue motoneurons after transection of the facial nerve. A 633 nm laser 8.5 mW laser was used for 90 minutes for 14 days. This was done six to nine months after the nerve injury. The frequency of facial motoneurons that died after axotomy was decreased significantly from 36.45% to 13.30% when the axotomized facial nerves were treated with LLLT. These results suggest that LLLT is a non-invasive therapy for rescue of axotomized neurons and may afford a promising treatment for devastating spinal cord injuries.[19]

Datsenko studied twenty-three patients aged 23-75 who had ischemic stroke in the carotid basin (up to two years after the acute period of the stroke). The course of magneto-laser therapy (MLT) lasted 15 days. The author carried out neurological examination, determined the state of psycho-emotional activity, cerebral hemodynamics, and frequency amplitude indices of the brain to assess the mechanisms of MLT effect on the CNS functional state in patients during a rehabilitative period after ischemic stroke. The course of MLT was found to improve cerebral hemodynamics and increase the level of bioelectrical activity in the brain. Based on the results, we can recommend that MLT be included in the rehabilitation program in patients that have had ischemic stroke.[20]

Major Depression

Schiffer et al performed a study with 10 patients (five male, five female) with major depression, including nine with anxiety, seven with a past history of substance abuse (six with an opiate abuse and one with an alcohol abuse history), and three with post traumatic stress disorder. The study participants were given a baseline standard diagnostic interview, a Hamilton Depression Rating Scale (HAM-D), a Hamilton Anxiety Rating Scale (HAM-A), and a Positive and Negative Affect Scale (PANAS). They were then given four 4-minute treatments in a random order: Near Infrared Light Radiation (NIR) to left forehead at F3, to right forehead at F4, and placebo treatments (light off) at the same sites. Immediately following each treatment, the PANAS was repeated. At two weeks and at four weeks post treatment, all 3 rating scales were repeated. During all treatments, total hemoglobin (cHb) as a measure of rCBF was recorded with a commercial NIR spectroscopy device over the left and the right frontal poles of the brain. At two weeks post treatment, 6 of 10 patients had a remission (a score < 10) on the HAM-D and 7 of 10 achieved a score less than or equal to 10 on the HAM-A. Patients experienced highly significant reductions in both HAM-D and HAM-A scores following treatment, with the greatest reductions occurring at two weeks.

Mean rCBF across hemispheres increased from 0.011 units in the ‘off’ condition to 0.043 units in the ‘on’ condition, for a difference of 0.032 (95% CI: -0.016, 0.080) units, though this result did not reach statistical significance. Immediately after treatment, the PANAS improved to a significantly greater extent with NIR ‘on’ relative to NIR ‘off’ when a hemisphere with more positive HEV was treated than when one with more negative HEV was treated. No side effects were observed. This small feasibility study suggests that NIR-PBM may have utility for the treatment of depression and other psychiatric disorders and that double blind randomized placebo-controlled trials are indicated.[21]

Conclusion

We can see from the referenced studies that there are a number of beneficial neurological effects arising from the application of therapeutic laser and point to significant implications for therapeutic applications in potentially serious neurological conditions such as stroke, Parkinson's Disease and cerebral palsy, to name a few. The rehabilitative possibilities are encouraging and should cause us to adjust our concepts and explanation of the mechanisms of many of these neurological conditions including axonal degeneration following spinal cord injury. Therapeutic laser is a low risk clinical approach that could benefit countless numbers of neurological patients. It is expected that as research continues and understanding of the underlying mechanisms improves, we will be able to apply laser therapy more effectively to the neurological patient.

SEE OUR REFERENCES

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Mar 7, 2011 **Lawrence Robbins, MD,** Neurologist, Director

A preventive is chosen with regard to the type of headache and presenting comorbidities—e.g., anxiety, depression, GI upset, medication sensitivities, etc.—and is individualized toward the patient's needs. In using such medication, a realistic goal is to decrease the tension headache severity by 70%, not to completely eliminate the headaches. It is wonderful when the headaches are 90% improved, but the idea is to keep the medication and any side effects to a minimum. Trial and error is often used to find the best preventive approach for a person and preventive medications may take weeks to become effective. The doses often need to be adjusted and thus patience is necessary with these medications. The physician needs to be available for phone consultations pertaining to the patient's headaches and medicine. In the long run, preventive medications are effective for approximately 50% of patients.

What Patients Need to Know Prior to Starting a Preventive

Most patients need to be willing to settle for moderate improvement in their head-aches. Preventives may take three to six weeks to work, and there may be only a 50% improvement. The patient must accept this, and be willing to tolerate the possible side effects. Further, patients must be willing to change medications when necessary. They need to be aware that what is effective for someone else may not work for them. Most preventive medications are utilized in medicine for another purpose. Patients should be informed that amitriptyline (Elavil®), for instance, is also used for depression, usually in much higher doses. Patients using Elavil should be told why and be reassured that it is not because they are depressed.

Side effects are possible with any medication. A patient has to be prepared to endure mild side effects in order to achieve results. We cannot stop one medication and switch to another because of very mild side effects. Most patients are usually willing to put up with mildly annoying side effects. Fatigue, however, is a major reason for patients abandoning a preventive medication. Headache patients commonly complain of fatigue, and tend to give up on medications that increase tiredness.

Natural Supplements and Herbs for Headache

Feverfew, Petadolex® (butterbur), and magnesium oxide have all proven effective in double-blind studies as migraine preventives. Of these, Petadolex has been the most effective. Omega-3 fatty acids may help headaches, and are an excellent supplement for general good health.

- Petadolex is commonly used in Europe, and this herbal preparation has been successful in preventing migraines in several well-designed blind studies. The usual dose is 50 mg., twice a day. Earlier concerns about carcinogenesis with this family of herbs have decreased with Petadolex, which is a purified form of the herb butterbur. Patients have occasionally experienced GI upset or a bad taste in the mouth, but Petadolex is usually well tolerated. It is prudent to stop it every three months or so. Petadolex is available by calling 1-888-301-1084 or through www.petadolex.com.
- Magnesium is a naturally occurring mineral that helps many systems in the body to function, especially the muscles and nerves. It has been shown that magnesium levels in the brain of migraine patients tend to be lower than normal. Magnesium oxide is used as a supplement to maintain adequate magnesium in the body. A dose of 400 or 500 mg. per day can be used as a preventive; tablets are found in most pharmacies. However, mild GI side effects may limit use. There are also complications from drug interactions, and kidney and other diseases.
- Feverfew has been demonstrated to be mildly effective in some patients for prevention of migraine headache. Feverfew can cause a mild increased tendency toward bleeding, and should be discontinued two weeks prior to any surgery. The problem with many herbal supplements is quality control. The amount of parthenolide (the active ingredient in feverfew) varies widely from farm to farm; certain farms consistently have better quality than others. Eclectic Institute uses a process that freeze-

active ingredient in feverfew) varies widely from farm to farm, certain farms consistently have better quality than others. Eclectic Institute uses a process that freeze dries the herbs, making the product highly reliable. It is available in health food stores and at Whole Foods. The usual dose is two capsules each morning. Patients occasionally will be allergic to feverfew, and it should not be used during pregnancy.

- Long Chain Fatty Acids (omega-3 fatty acids) may play a role in headache prevention, and possibly be useful against anxiety, hypertension, arthritis, high lipids, depression and heart disease. We usually recommend fish oil or flaxseed oil, 1000 mg. capsules, two to four per day. In studies on depression, as many as eight capsules per day have been utilized. Fish oil capsules may be more effective than flaxseed oil. Fatty fishes such as salmon and tuna contain more oil than others. Look for the brands with the highest amounts of EPA/DHA listed on the label.

First Line Preventive Medications for Migraine

- Topamax® (topiramate). Topamax is FDA approved as a migraine preventive. A generic is available, but is not always as effective. This anti-seizure medication is utilized for migraine, CDH, and cluster headache. It does not irritate the liver. Sedation and cognitive side effects (such as confusion or memory problems) may limit its use. Topamax often decreases appetite, which leads to weight loss; this is unusual among headache preventives. The starting dose is 25 mg. once or twice daily; this may be pushed to 100 mg. once or twice per day. 100 mg. daily is the usual dose. It is usually well-tolerated in lower doses and may be effective as a mood stabilizer for some milder bipolar patients. GI upset may occur. Acute glaucoma has been a rare side effect. The risk of forming kidney stones is increased by the use of Topamax. Bicarbonate levels should be monitored, as Topamax may cause a dose-related metabolic acidosis.
- Depakote® (Valproate). This seizure medication is a long time staple, popular for migraine prevention. It is usually well tolerated in the lower doses utilized for headaches. The generic may not be as effective. Liver functions need to be monitored in the beginning of treatment. Side effects include lethargy, GI upset, depression, memory difficulties, weight gain and alopecia. Dosage ranges from 250 to 1500 mg. per day, in divided doses. The average dose is 500 to 1000 mg. per day. Levels need to be checked for toxicity on the higher doses. Depakote is also one of the primary “mood stabilizers” for bipolar. Available in 125, 250 and 500 mg. tablets. Depakote ER, 500 mg., is an excellent long-acting tablet that may be dosed at once daily. Depakote 250 ER is also available. As with most preventives, Depakote needs four to six weeks to become effective. It is FDA-approved for migraine prevention. Depakote should not be used during pregnancy.
- Beta Blockers. Effective for migraine. Long-acting (LA) Inderal® (propano-lol) capsules may be dosed once per day. Occasionally effective as a preventive for daily headaches. Sedation, diarrhea, lower GI upset and weight gain are common. Very useful in combination with amitriptyline. Dosage begins with the long-acting at 60 mg., and is usually kept between 60 and 160 mg. per day. Lower doses are sometimes effective, such as 20 mg. of propranolol twice a day. Other beta-blockers are also effective, such as metoprolol (Toprol® XL) and atenolol. Some of these are easier to work with than propranolol because they are scored tablets, and metoprolol and atenolol have fewer respiratory effects. Depression may occur. Beta blockers are useful for those with concurrent hypertension, tachycardia, panic, anxiety, and mitral valve prolapse. A new beta-blocker, nebivolol (Bystolic®), may be helpful, and has fewer side effects.
- Amitriptyline (Elavil® and other tricyclics). Effective, inexpensive and also useful for daily headaches and insomnia. Use in low doses at night. Sedation, weight gain, dry mouth and constipation are common. Starting dose is 10 mg., and titrated up to 25 or 50 mg.; can be pushed up to 150 mg. or decreased to 5 mg. Other tricyclic antidepressants such as doxepin and protriptyline can be effective for migraine. Nortriptyline is similar to amitriptyline, with somewhat fewer side effects. These are also used for daily tension-type headaches. Pro-triptyline is one of the few older antidepressants that does not cause weight gain. However, anticholinergic side effects are increased with protriptyline. While the SSRIs are utilized, they are more effective for anxiety and depression than for migraine. Tricyclics are more effective for pain than are the SSRIs.
- Naproxen (Naprosyn®, Naprelan®, Anaprox®, Aleve®, and other NSAIDs). Useful in younger patients; once a day dosing. Sometimes helpful for daily headaches, but particularly useful for menstrual migraine. Non-sedating, but frequently causes GI upset. Effective as an abortive and may be combined with other first line preventive medications. The usual dose is 500 or 550 mg., once a day, but this may be pushed to twice a day. Other anti-inflammatories can be utilized for prevention of migraine. As with all anti-inflammatories, GI side effects increase as people age, and so these are used much more in the younger population. With daily NSAIDs, blood tests are needed to monitor liver and kidney function.
- Verapamil. Reasonably effective for migraine; once a day dosing with the slow release (ER) tablets. Usually non-sedating, and weight gain is uncommon. Occasionally

- Verapamil. Reasonably effective for migraine, once a day dosing with the slow release (ER) tablets. Usually non-sedating, and weight gain is uncommon. Occasionally helpful for daily headaches. May be combined with other first line medications, particularly amitriptyline or naproxen. Con-stipation is common. Starting dose is 1/2 of a 240 mg. ER tablet, increasing quickly to one 240 mg. tablet per day. May be pushed to 240 mg. twice a day, or decreased to 120mg. or 180 mg. per day. With doses higher than 240 mg. daily, an EKG needs to be done.
- Natural Supplements and Herbs. Many patients prefer to start with the natural preventives. Petadolex, a safer form of the herb butterbur, has been the most effective natural preventive. It has held up well in multiple trials. It is widely used in our office and effective for all ages. See previous section titled "Natural Supplements and Herbs for Headache."

Second Line Migraine Preventive Therapy

- Botulinum Toxin Injections. Botulinum Toxin A (Botox®, Dysport®) has been studied extensively in migraineurs. Approximately 50% to 60% of patients have significant relief after botulinum injections. Low doses are usually used (50 to 100 units total per patient, in 8 to 12 injections) primarily in the frontal and temporal areas. While it is expensive, Botox is relatively safe and only takes a few minutes to inject. One set of injections can decrease the head-aches for 1 to 3 months. Posterior (occipital) or upper cervical injections are starting to be investigated and appear to have some utility. Botul-inum toxin may be safer than many of the medications that are utilized for headache.
- Gabapentin (Neurontin®; generic available). Neurontin is an anti-seizure medication that has been de-monstrated to be useful in migraine and tension headache prophylaxis. Tablets are available in 100, 300, 400, 600 and 800 mg. sizes. The usual dose for headache prevention is 600 to 2400 mg. per day. In a large study on migraine, doses averaged around 2,300 mg. per day, but lower doses are usually prescribed. Some patients do well with very low doses (200 or 300 mg. per day). Sedation and dizziness may be a problem. However, Neurontin does not appear to cause end-organ damage, and weight gain is relatively minimal. Neurontin can be used as an adjunct to other first line preventive medications. The generic, gabapentin, is now widely in use. A newer drug, Lyrica® (pregabalin), has a similar mechanism of action to gabapentin. Lyrica is an anti-seizure drug, but is useful for preventing pain. Side effects are similar to those of gabapentin. The dose of Lyrica varies from 25 mg BID to 150 mg TID.
- Polypharmacy. Two first line medications are used together. The combination of two preventives is more effective than one drug alone. Depakote is often combined with an antidepressant. Amitriptyline may be combined with propranolol, particularly if the tachycardia of the amitriptyline needs to be offset by a beta-blocker; this combination is commonly used for "mixed" headaches (migraine plus chronic daily headache.)
- The NSAIDs may be combined with most of the other first line preventive medications. Thus, naproxen is often given with amitriptyline, propranolol or verapamil. Naproxen is employed simultaneously as a preventive and abortive medication. Poly-pharmacy is commonly employed when significant comorbidities (anxiety, depression, hypertension, etc.) are present.
- Tizanidine and Cyclobenzaprine. A safe, non-addicting muscle relaxant, tizanidine is useful for migraine and CDH. The usual dose is one or two 4 mg. tablets qhs; the 4 mg. tablets are double-scored, so that patients may begin with 1/4 or 1/2 tablet. Sedation and dry mouth are common. Tizani-dine may be used on as needed basis for milder headaches, or for neck or back pain. A 2 mg. tablet is also available. Cyclobenzaprine (10mg) is helpful for sleeping, and helps some with migraine and chronic daily headache. A half- tablet maybe used. Sedation is a common side effect.
- Ace inhibitors and ARBs. There have been a number of studies on this category of blood pressure meds; ARBs are preferred due to the minimal side effects. Examples include Cozaar® (losartan), Benicar®, and Atacand®. For the patient with hypertension and migraine, these may be useful. Side effects include dizziness, among others, but they are usually well tolerated, with no sedation/ weight gain.
- Antidepressants (Effexor® XR, Cym-balta®, Pristiq®). Effexor XR is an excellent antidepressant; used primarily as a SSRI at lower doses, and at 100 to 150 mg., norepinephrine is also increased. The generic form of Effexor may not be as effective. The antidepressants with dual mechanisms (serotonin and norepinephrine are more effective for pain and headache. Doses vary from 75mg to 225mg, and Effexor XR is particularly useful for anxiety with depression. Pristiq is an excellent newer version of Effexor. Duloxetine (Cymbalta) also has a dual mechanism of action, and has been useful for pain.

When to Proceed Quickly to Two Simultaneous Preventives

With most patients, we utilize one preventive medication at a time, beginning with low doses and slowly raising the dose as needed. Most patients appreciate the approach, and are willing to wait for the medication to work.

At times, patients can become ex-tremely frustrated with their headaches, and desire quick results. When these patients suffer from moderate or severe chronic daily headache, or with severe migraines, pushing ahead at a faster rate with a preventive approach is justified. For instance, amitriptyline and verapamil, or amitriptyline and propranolol may be initiated at the same time. Alternatively, doses of a single medication may be increased rapidly. The initial amount of preventive medication utilized for a patient depends upon the severity of the headaches and the frustration level of the patient.

Patients with new onset of severe headaches, typically daily headaches plus migraine, are often extremely upset and frustrated with the pain. In this situation, pushing preventive medication at a faster pace is justified. Of course, patients need to be willing to put up with certain side effects.

Third Line Migraine Prevention for Refractory Patients

In my practice, long-acting opioids are the most commonly utilized approach for refractory chronic migraine. They include:

- Methadone
- Oxycontin®
- Kadian®
- MS-Contin®
- Avinza®
- Duragesic®

In a small, select group of severe headache patients, particularly those with severe, chronic daily headaches and migraines, long-acting opioids have some demonstrated utility. The best candidate for long-acting opioids (LAOs) is the person who has done well on short-acting opioids (SAOs) and who does not have characteristics of a personality disorder and has not been addicted in the past.

The advantages of long-acting opioids include:

- avoidance of mini-withdrawals through-out the day and the “end-of-the-dose” phenomenon,
- consistent dosing of one or two times daily decreases the obsession with the next dose,
- maintenance of stable blood levels,
- avoidance of the acetaminophen, aspirin and NSAIDs that are components of many short-acting preparations,
- probable diminished risk of significant abuse,
- better compliance, with less psychological dependency on the drug.

- Disadvantages of the long-acting opioids include:
- social stigma,
- fatigue and constipation,
- difficulty in obtaining scripts, with no refills available,
- need for frequent office visits and monitoring,
- risk of opioid-induced hyperalgesia,
- risk of abuse, although probably less than the SAOs,
- interactions with other sedating drugs and alcohol risk of overdose.

Using higher doses of the opioid rarely works in the long term, in my experience. It places the patient at increased risk of addiction and abuse, and complicates withdrawal. Given the great variation in individual responses, it may be thought that the opioid should be increased or "pushed" to whatever level is beneficial to the patient. However, medical and regulatory considerations should be limiting factors in keeping the opioid dose at a low level. The choice of opioid may be a key factor; some have been shown to have less abuse potential. The long-acting fentanyl patch is subject to less abuse than Oxycodone CR. Taken once or twice daily, the long-acting morphine preparations such as Kadian, Embeda® or MS-Contin have not been subjected to widespread abuse. Methadone may be more effective than some of the other medications, but has a litany of problems associated with it. Besides the social stigma, high protein binding is a risk, which may lead to irregular drug levels, difficulty with withdrawal, and an increased risk for sudden death. If methadone is used, it should be started at a very low dose of no more than 5-10 mg. a day and titrated slowly. Patients placed on methadone require close monitoring and other sedatives must be reduced or discontinued.

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The usual dosing range in my practice is: methadone, 5 to 40 mg. per day; morphine, 20 to 90 mg. per day; oxycodone, 20 to 60 mg. per day; fentanyl patch, 12.5 to 50 mcg. per day. Opioids may be combined in low doses with stimulants. Stimulants may help the pain and also offset fatigue. Patients must be aware of, and accept, the risks of these medications.

Daily or Frequent Triptans

Some patients respond only to triptan medications (sumatriptan, naratriptan, rizatriptan, almotriptan, zolmitriptan, frovatriptan, eletriptan). Short-lasting adverse events are often encountered with triptan use. These include paresthesias, fatigue, chest heaviness, jaw or neck discomfort, etc. Chest symptoms are, with rare exceptions, not of cardiovascular origin. Cardiac ischemia due to triptan use is rare. Triptans do constrict coronary vessels, but it is a mild and short-lived effect. Despite widespread triptan use, the number of adverse cardiac events has been limited. Echocardiography and electrocardiography generally are normal after triptan use, even in the presence of chest symptoms.

The primary issue with frequent triptan use, assuming rebound headache is not present, is long-term adverse events. The cardiovascular system would be the most likely for possible long-term sequelae. Chronic ischemic changes, valvular abnormalities, or fibrosis are theoretical considerations. To date, there is no evidence of long-term triptan use producing any of these adverse events. This has not been systematically studied, however. The number of patients throughout the world who have utilized triptans on a near-daily basis is unknown. Until these patients have been studied, it is reasonable and prudent to do cardiac monitoring, as well as hematologic tests.

Stimulants

When prescribed for headache patients, stimulants (dextroamphetamine, meth-ylphenidate, phentermine, Adderall®, Vyvanse®) may be beneficial for various comorbidities, such as attention deficit hyperactivity disorder (ADHD), depression, and fatigue. In addition, stimulants do not cause the weight gain that is seen with a number of other current headache preventives. Amphetamines have been shown to possess intrinsic analgesic properties, primarily through brain catecholamine activity. They also intensify the analgesic effects of certain opioids. Stimulants have been utilized to counteract the sedation encountered by opioids. An excellent review article on stimulants as adjuncts for opioids concluded that, "The evidence suggests that amphetamine drugs may enhance the effect of opioids and, at the same time, decrease somnolence and increase cognitive performance."

Advantages of stimulants include enhanced cognition and alertness, with no weight gain.

Disadvantages primarily revolve around the side effects, such as anxiety or insomnia. Abuse may certainly occur, but it is uncommon in adults. Stimulants should be considered in patients with certain comorbidities. The few studies to date have indicated a positive role for stimulants, but further studies on stimulants for headache would help to clarify that role.

Monoamine Oxidase Inhibitors (MAOIs)

For those with refractory chronic mi-graine and unipolar depression, MAOIs may be of help. MAOIs are sometimes effective for treatment-resistant depression. They are also effective for alleviating anxiety. MAOIs were commonly prescribed in the 1980s but, with the advent of SSRIs and triptans, they fell out of favor. Careful patient selection is crucial when using the MAOIs. Patients need to strictly observe the restrictions on diet and medications. I usually prescribe low doses of phenelzine (Nardil®) 15 mg. tablets, starting with one tablet at night and increasing after a week to two tablets at night. If no response is noted after three to four weeks, I usually push the dose to three tablets. Five tablets a day (75 mg.) is the usual maximum. By always using the MAOI at night, the patient is less likely to encounter a food interaction. Side effects include insomnia, weight gain, sedation, and orthostatic hypotension.

The MAOIs have a reputation as being somewhat dangerous and difficult to use. Despite this reputation, MAOIs are usually well-tolerated. The hypertensive crisis that may occur with a food interaction is due to a number of factors, primarily the amount of tyramine, an amino acid, absorbed into the bloodstream. The tyramine content of food has been difficult to accurately establish, but there are lists of tyramine-rich foods to avoid. Look online or ask a dietician for the MAOI diet." When patients consume low doses of phenelzine at night, while avoiding the major tyramine-rich foods, interactions are less likely.

Repetitive IV DHE Therapy

Treatment with intravenous dihydroergotamine (IV DHE®) is helpful for patients with frequent migraine, severe daily headache, and status migraine. DHE has a long track record with a good safety profile. Weeks of headache improvement are often seen. IV DHE is useful in patients who are withdrawing from analgesics. The protocol can be done in the office or hospital. In the office, the first dose of 1/3 mg. is given and, if it is well tolerated, the subsequent doses are 1/2 or 1 mg. Oral Reglan® is usually given prior to the DHE to combat nausea. Three or four doses are given over two days in the office, and up to nine may be given in the hospital. The IV DHE is usually well tolerated and effective. Side effects include nausea, heat flashes, muscle contraction headache, leg cramps, diarrhea, and GI pain. After the DHE, patients are continued on prevention medication. Occasionally, Migranal® (DHE) nasal spray, used daily for several weeks, is effective.

Levadex®, the newer form of inhaled DHE, is awaiting approval by the FDA. In recent trials, patients with allodynia, menstrual migraine, migraine with nausea and vomiting, severe migraine and those treating late in their migraine cycle responded well to Levadex.

First Line Chronic Daily Headache Preventive Medications

- Valproate (Depakote), Amitriptyline (Elavil), Topamax. See section titled “First Line Preventive Medications for Migraine.”
- SSRIs (Cymbalta, Pristiq and Effexor). Fewer side effects than amitriptyline, but are not as effective. More effective for anxiety and de-pression than for headache. Nausea, anxiety, sexual dysfunction, fatigue, and insomnia are common; weight gain is relatively common. SSRIs are helpful for migraine in some patients. Begin with low doses. All of the SSRIs have been somewhat useful for preventing chronic daily headache, and for migraine, to a lesser extent. The dose for headache is usually lower than that for depression. Considering tolerability, these are often the best choice for chronic daily headache. Any of these may also exacerbate headaches. See section on SSRIs. For Cymbalta, Pristiq and Effexor, see the section on antidepressants titled “Second Line Migraine Preventive Therapy.”
- Protriptyline (Vivactil®). Effective and non-sedating. While weight gain does not occur, dry mouth, constipation, and dizziness are common. Commonly used in the morning, as insomnia may be a side effect. May be used in the morning with a sedating tricyclic used at night. Usual dose is 5 to 15 mg. per day (lower than the dose for depression). This is the only tricyclic that tends not to cause weight gain. It increases norepinephrine, not serotonin.
- Nortriptyline (Pamelor®). A metabolite of amitriptyline, nortriptyline is better tolerated than amitriptyline, but less effective. Side effects are similar to amitriptyline, but less severe. Nortriptyline is useful in children, adolescents and the elderly and is occasionally helpful in migraine. Usual dose is 25 to 75 mg. per day; some patients do well on one 10 mg. capsule daily.
- Doxepin (Sinequan®). Very similar to amitriptyline. Begin with very low doses (10 mg. each night), as many patients cannot tolerate more than this amount. Usual dose is 25 to 75 mg. per day. Doxepin has the same side effects as amitriptyline, but is generally better tolerated. It primarily increases norepinephrine.
- NSAIDs. These are not as effective as the antidepressants for chronic daily headache but do not have the cognitive side effects. GI side effects are common, however. Hepatic and renal blood tests need to be monitored. NSAIDs are used more frequently in younger patients. Ibuprofen is available over the counter, but is short-acting. Naproxen (Naprosyn®, Napre-lan®, Aleve®, Anaprox®) is more effective than ibuprofen. Flurbiprofen (Ansaid®) and diclofenac sodium (Vol-taren®) are also utilized. As always, we attempt to use the minimum effective dose.
- Gabapentin (Neurontin®). See section titled “Second Line Migraine Preventive Therapy.” The newer Lyrica (pregabalin) may also be effective.
- Tizanidine (Zanaflex®) and cyclo-benzaprine. These are muscle relaxants. See section titled “Second Line Migraine Preventive Therapy.”

Conclusion

Patients with chronic daily headache, or those having more than three migraines per month that are not well-controlled, may be candidates for preventives. A preventive is chosen with regard to the type of headache and presenting comorbidities while keeping the medication dose and any side-effects to a minimum. Medication selection and dosing may require significant trial and error since what may work in one individual may not work in another. In using such medication, a realistic goal is to decrease the tension headache severity by 70%, not to completely eliminate it. This guide presents the author’s opinion and clinical experience but is not a prescription and does not represent a standard consensus of treatment.

SEE OUR REFERENCES

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