The Serotonin Syndrome, Triptans, and the Potential for Drug–Drug Interactions.

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The serotonin syndrome is an acute adverse reaction to medications that enhance serotonergic activity. The severity of cases ranges from mild to fatal. Recently, the U.S. Food and Drug Administration issued an alert that the risk of developing serotonin syndrome may be increased by the concomitant administration of triptan medications with certain other medications. However, a review of published data does not allow an accurate assessment of such risks related to triptans. We conclude that it is currently unclear whether administration of triptans with other serotonergic medications increases the risk of serotonin syndrome.

Triptans, Serotonin Agonists, and Serotonin Syndrome (Serotonin Toxicity): A Review

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The US Food and Drug Administration (FDA) have suggested that fatal serotonin syndrome (SS) is possible with selective serotonin reuptake inhibitors (SSRIs) and triptans: this warning affects millions of patients as these drugs are frequently given simultaneously. SS is a complex topic about which there is much misinformation. The misconception that 5-HT1A receptors can cause serious SS is still widely perpetuated, despite quality evidence that it is activation of the 5-HT2A receptor that is required for serious SS. This review considers SS involving serotonin agonists: ergotamine, lysergic acid diethylamide, bromocriptine, and buspirone, as well as triptans, and reviews the experimental foundation underpinning the latest understanding of SS. It is concluded that there is neither significant clinical evidence, nor theoretical reason, to entertain speculation about serious SS from triptans and SSRIs. The misunderstandings about SS exhibited by the FDA, and shared by the UK Medicines and Healthcare products Regulatory Agency (in relation to methylene blue), are an important issue with wide ramifications.

Serotonin Syndrome: SSRIs, SNRIs, Triptans, and Current Clinical Practice

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Serotonin syndrome (SS) or serotonin toxicity consists of the triad of altered mental status (confusion, agitation, seizures), dysautonomia (diarrhea, diaphoresis, hypertension, fever/shivering, mydriasis, tachycardia), and neuromuscular changes (myoclonus, tremor, ataxia, hyperreflexia, rigidity). There are 2 validated sets of criteria for diagnosing SS. The first are the Sternbach criteria, which require the recent addition of or increase in a known serotonergic agent *plus* the absence of other possible etiologies (infection, substance abuse, withdrawal, etc) *plus* no recent addition or increase of a neuroleptic agent *and* at least 3 of the following symptoms: mental status changes (confusion, hypomania), agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, or fever.[1] The Hunter criteria require one of the following in the presence of a serotonergic agent:

spontaneous clonus, inducible clonus *and*agitation or diaphoresis, ocular myoclonus *and* agitation or diaphoresis, ocular myoclonus or inducible clonus, tremor and hyperreflexia or hypertonia, or temperature >38°C *and* ocular myoclonus or inducible clonus.[2]

On July 19, 2006, the United States Food and Drug Administration (FDA) issued an alert, "Potentially Life-Threatening Serotonin Syndrome with Combined Use of SSRIs or SNRIs and Triptan Medications."[3] The FDA Alert was based on 29 cases the FDA diagnosed as SS in patients simultaneously taking serotonin-selective reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), and triptans. This alert was published against the background of warnings on co-administration already included in prescribing information for these therapeutic classes. The FDA described a potential for life-threatening SS with the combinations.

Dr. Randall Evans, using the Freedom of Information Act, obtained and reviewed the cases. Not one met the Hunter criteria, and only 10 of the 29 met the Sternbach criteria.[4] A second set of 11 patients was reported in the *New England Journal of Medicine* as proof of triptan monotherapy-induced SS.[5] Dr. Evans pointed out that the authors of this report did not describe whether either the Sternbach or Hunter criteria were met.[6] The authors also suggested the symptoms remitted with supportive care or intravenous diphenhydramine, the latter not a treatment for SS, which reverses with the antiserotonergic medication cyproheptadine. Their diagnoses thus were questionable.

In addition, there is reasonable doubt as to whether triptans alone can produce SS. As Dr. Ken Gillman wrote in a classic review, "The risk of serious morbidity and death in SS is from hyperthermia which is mediated in a dose related manner by the action of serotonin (5-HT) or 5-HT agonists, on 5-HT_{2A} receptors, and is ameliorated, or prevented, by 2A antagonists such as cyproheptadine."[7] Because triptans have no activity on 5-HT_{2A} receptors at any dose, they should not cause SS.

This is likely a situation in which absence of evidence is indeed evidence of absence. In the current issue of *Headache*, Sclar and colleagues used statistically weighted data from the US National Ambulatory Care Survey for 2007-2008, and estimated 5.2 million patients were prescribed a triptan, 68.6 million were prescribed an SSRI or SNRI, and 1.4 million were prescribed a triptan along with an SSRI or SNRI. Calculating the percent who received both, 25.1% of those who were prescribed triptans simultaneously were prescribed an SSRI or SNRI.[8] These numbers represent an increase from a previous study in 2003-2004, in which 3.8 million received a triptan and 50.4 million received an SSRI/SNRI, a 36% increase for both.[9,10] Although clinical outcomes are not available, the same question can be posed in response to the data from Sclar and colleagues as was asked regarding the co-prescription data from 2003-2004, "With so much co-prescription, where is the epidemic of SS?" Remarkably, the percentage *increase* of co-prescription of a triptan and an SSRI/SNRI in 2007-2008 compared with 2003-2004 was 90%, despite a 50% drop in co-prescription rates among primary care physicians (PCPs). This suggests that neurologists concluded that the alert was unjustified. The widespread use of electronic medical records with automatic warnings flashing when the medication types are co-prescribed could account for the decrease in co-prescribing by PCPs.

The American Headache Society (AHS) Position Paper on SS and co-prescription of these medications states, “With only Class IV evidence available in the literature and available through the FDA registration of adverse events, inadequate data are available to determine the risk of serotonin syndrome with the addition of a triptan to SSRIs/SNRIs or with triptan monotherapy. The currently available evidence does not support limiting the use of triptans with SSRIs or SNRIs, or the use of triptan monotherapy, due to concerns for serotonin syndrome (Level U).”[11]

Because of the high comorbidity of depression, anxiety, and migraine, the simultaneous need for drugs from these classes is common. The avoidance of co-prescription quite likely does more harm than good. Either a patient with mood disorder is deprived of therapeutic antidepressants or anxiolytics in order to terminate migraine effectively, or the patient on psychotropics is forbidden a migraine-specific treatment; both situations result in unnecessary disability.

SSRIs and SNRIs as monotherapy can cause SS.[12] The AHS Position Paper stated, “Clinicians should be vigilant to serotonin toxicity symptoms and signs to insure prompt treatment.” The combination of these psychotropics with triptans is unlikely to increase the risk of SS; indeed, triptans do not appear to exhibit a pharmacologic mechanism by which they could cause SS. The current study by Sclar and colleagues provides further reassurance for those who prescribe or take this combination.

Concomitant Use of Triptan, and SSRI or SNRI After the US Food and Drug Administration Alert on Serotonin Syndrome

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Objective.— The present study was designed to discern the prevalence of concomitant use of a 5-hydroxytryptamine receptor agonist (triptan), and a selective serotonin reuptake inhibitor (SSRI) or a selective serotonin/norepinephrine reuptake inhibitor (SNRI) after the US Food and Drug Administration issued an alert regarding serotonin syndrome in 2006 and to contrast findings with data published prior to the federal warning.

Background.— In July 2006, the US Food and Drug Administration warned patients and health-care professionals to be aware that use of a triptan in combination with an SSRI or SNRI may result in a potentially life-threatening problem known as serotonin syndrome. In 2010, the American Headache Society published a position paper noting that there existed conflicting and insufficient information to discern the risk of serotonin syndrome with the use of triptan, and SSRI or SNRI, and that said Class IV data were not to be used as the basis for limiting the prescribing of triptan with SSRI or SNRI (Level U). Clinicians were cautioned as to the seriousness of serotonin toxicity and that monitoring was warranted.

Methods.— We used weighted data from the US National Ambulatory Medical Care Survey for years 2007 and 2008 to derive national estimates of the number of office-based physician–patient encounters (visits), documenting the concomitant use of triptan, and SSRI or SNRI. Results are compared with previously published findings for the years 2003 and 2004.

Results.— During the time-frame 2007-2008, an annualized mean of 5,256,958 patients were prescribed a triptan (vs 3,874,367 in 2003-2004, a 35.7% increase), and 68,603,600 patients were prescribed an SSRI or SNRI (vs 50,402,149 in 2003-2004, a 36.1% increase). An annualized mean of 1,319,763 patients were simultaneously prescribed or continued use of triptan, along with SSRI or SNRI (vs 694,276 in 2003-2004, a 90.1% increase).

Conclusion.— Our study documents that 1.8% (1,319,763/73,860,558) of patients in 2007-2008 were prescribed triptan, and SSRI or SNRI (vs 1.3% in 2003-04, an increase of 38.5%). While this is a small fraction overall, the actual number of patients on a nationwide basis is substantial. What remains missing from the literature is documentation as to the number of cases of serotonin syndrome and resulting consequences (clinical and economic) because of the concomitant use of triptan, and SSRI or SNRI in the time-frame 2007-2008. Absent in these data, it remains difficult to assess the risk benefit associated with the use of triptan, and SSRI or SNRI.

"Mixing Triptans": Patient Satisfaction

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Background.— Although some patients may prefer using an oral triptan other than sumatriptan and injectable sumatriptan to treat an attack of persistent migraine, administration of 2 different triptans within a 24-hour period currently is contradicted.

Objective.— We sought to determine patient satisfaction with an acute migraine treatment regimen wherein patients were permitted to administer an oral triptan other than sumatriptan and injectable sumatriptan within 24 hours of one another

Methods.— We evaluated a consecutive series of migraine patients who either had tried and failed oral sumatriptan or were using another oral triptan and were satisfied with it. We advised subjects that they could administer their oral triptan and injectable sumatriptan within a single 24-hour period (but not within 2 hours of one another); we termed such treatment "mixing triptans." We asked all subjects to keep detailed written headache diaries for the 6-month treatment period, and at the 6-month end-of-study visit we asked subjects who had treated at least 3 migraine attacks by mixing triptans to rate their satisfaction with that treatment according to a 5-point Likert scale.

Results.— Of the 200 subjects enrolled, 132 (66%) used an oral triptan other than sumatriptan and injectable sumatriptan within a 24-hour period on at least 3 occasions. At their final follow-up visits, 117 (89%) of the 132 reported themselves "very satisfied" or "satisfied" with this specific treatment regimen. No serious adverse events were recorded.

Conclusion.— The option of sequentially using an oral triptan other than sumatriptan and injectable sumatriptan to treat a given attack of migraine appears to correlate with a high rate of patient satisfaction. While in our subject population this treatment regimen was well tolerated, our study results do not suffice to establish the safety of "mixing triptans."

SNOOP4

The Diagnostic Evaluation of Secondary Headache Disorders. Vincent T. Martin MD

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Dodick[1] has recently updated the SNOOP mnemonic to help physicians to remember the “red flags” for secondary headache disorders. The new mnemonic has been called “SNOOP4.” (Table 1) The primary difference between the current and the past SNOOP mnemonic is the addition of the 4 “P's,” which stand for progressive headache, precipitation by valsalva, postural aggravation, and papilledema. Progressive refers to the evolution of a headache disorder into a daily, continuous pattern. Precipitation by valsalva indicates a worsening with activities that cause patients to valsalva (eg, bearing down, lifting weights, etc). Postural aggravation is the accentuation of headache when going from a lying to a standing position or vice versa. It may also occur with neck movements, which could represent a sign of cervicogenic headache. Papilledema occurs with increased intracranial pressure that can result from the various causes of intracranial hypertension.

Mnemonic	Clinical Presentation	Common Secondary Headache Disorders
Systemic	New onset headache in patient with malignancy, immunosuppression or HIV • Unexplained fever, chills, weight loss •	Primary or metastatic tumors, meningitis, brain abscess, temporal arteritis
Neurologic	Abnormal neurological examination • Complaints of motor weakness, sensory loss, diplopia or ataxia •	Malignant, inflammatory, and vascular disorders of the brain
Onset sudden	Headache reaches peak intensity in • <1 minute	Vascular events such as subarachnoid hemorrhage (most common), CVA, carotid dissection, cerebral vasoconstriction syndromes, dural venous thrombosis
Onset after age 50	New onset headache after age 50 •	Neoplastic, inflammatory disorders, and temporal arteritis
Pattern change	Progressive headache (evolution to daily headache) •	Malignant, inflammatory, and vascular disorders of the brain
	Precipitated by valsalva •	Chiari malformation, primary and metastatic lesions of brain, hydrocephalus
	Postural aggravation •	Low pressure headache syndromes, cervicogenic headaches, intracranial hypertension, POTS
	Papilledema •	Malignant and inflammatory disorders of brain, idiopathic intracranial hypertension, dural venous thrombosis

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Adapted from Dodick D. *Semin Neurol*. 2010;30:74-81.

- CVA = cerebrovascular accident; HIV = human immunodeficiency virus; POTS = postural orthostatic tachycardia syndrome.

Table 1.—. SNOOP4 Mnemonic for Secondary Headache Disorders[†]

Certain red flags can increase the likelihood of specific types of secondary headache disorders. For example, the most likely diagnosis with a sudden onset headache would be a subarachnoid hemorrhage. However, other disorders such as dural venous thrombosis, pituitary apoplexy, and carotid dissection can occur also in patients with sudden onset headache, but are much less frequent.[2] Orthostatic headaches (eg, headaches reproducibly worse upon standing) are most commonly associated with intracranial hypotension, but can also occur less frequently with postural

orthostatic tachycardia syndrome.[3] Other red flags are less specific and can occur with a wide variety of headache disorders. See Table 1 for the secondary headache disorders associated with specific red flags.

The probability that a given red flag will identify a patient with a secondary headache disorder depends upon the red flag and the clinical setting (eg, primary care, emergency room settings, and specialty practices) in which the patients are seen. The incidence of secondary headache disorders will generally be higher in emergency room settings then in primary care or specialty practices secondary to the higher acuity of medical illnesses encountered in that setting. The red flags that have the most data to support their inclusion as red flags for secondary headache disorders include the following: (1) headache of sudden onset; (2) headache associated with neurologic signs and symptoms; and (3) headache onset after 50 years of age. The predictive value of these red flags for secondary headache disorders will be discussed below.

There have been several studies detailing the probability of secondary headache disorders in patients with sudden onset headache. Landtblom and colleagues[2] reported an incidence of secondary headache disorders of 21.4% in those patients presenting to the emergency room with sudden onset headaches (eg, onset <10 seconds). Subarachnoid hemorrhage (SAH), cerebral infarction, intracerebral hemorrhage, aseptic meningitis, cerebral edema, and dural venous thrombosis occurred in 11.3%, 3.6%, 2.2%, 2.9%, 0.7%, and 0.7%, respectively. Linn and colleagues[4] found an incidence of secondary headaches disorders of 46% (eg, subarachnoid hemorrhage in 30%, intracerebral hemorrhage in 8%, and others in 8%) in 110 primary care patients with sudden severe headaches peaking in 1 minute. Another study[5] of 434 emergency room patients with sudden onset headache demonstrated an incidence of 43% for secondary headache disorders with subarachnoid hemorrhage occurring in 16.3%. Perry and colleagues[6] enrolled 592 emergency room patients with headaches reaching maximal severity in <1 hour and discovered subarachnoid hemorrhage in 10.3% of patients. Therefore, the probability of secondary headache disorders ranges from 21% to 46% in patients presenting with sudden onset headache while SAH occurs in 10-30%.

Neurologic signs and symptoms are among the most predictive for secondary headache disorders. Ramirez and colleagues[7] found secondary headache disorders in 44% of emergency room patients with a complaint of headache and an abnormal neurologic examination as compared with 2% in those with a normal exam. The positive likelihood ratio for secondary headache disorders was 16.2 for an abnormal neurologic exam in this study. Locker and colleagues[8] reported that an up-going plantar reflex increased the likelihood of a secondary headache to 55% in 353 emergency room patients with a complaint of non-traumatic headache. Another study[9] conducted within an emergency room setting demonstrated a positive likelihood ratio of 3.56 for an abnormal neurological examination in the prediction of secondary headache disorders. Thus, an abnormal neurological examination confers a probability of secondary headache disorders of 44-55% within emergency room settings.

Older age has also been associated with the diagnosis of secondary headache disorders. Goldstein and colleagues[10] collected data from emergency room visits of patients presenting with a complaint of

headache as part of the National Ambulatory Medical Care Survey. They reported that patients ≥50 years of age were 3.3 times more likely to receive a serious secondary headache diagnosis (eg, stroke, meningitis, encephalitis, intracerebral and subarachnoid hemorrhage, temporal arteritis, hypertensive encephalopathy, and benign intracranial hypertension) than those <50 years of age. Overall, 6% of patients ≥50 years of age had secondary headache disorders compared with 1% of those <50 years of age. This study however did not report which of these headaches were "new onset." Kernig and colleagues[11] found that serious secondary headache disorders were 2-3 times more common in patients ≥50 years of age that presented to the primary care physician with a new complaint of headache. The incidence of secondary headaches (eg, malignant brain tumors, temporal arteritis, cerebrovascular events, and benign space-occupying lesions) was 4% in patients that were ≥50 years of age and 0.25% in those <50 years of age. Ramirez-Lassepas and colleagues[7] demonstrated intracranial pathology in 9.8% of emergency room patients presenting with headache that were ≥55 years of age as compared with 2% in those <55 years of age. Locker et al[9] reported a likelihood ratio of 2.34 for secondary headache disorders in emergency room patients greater than 50 years of age presenting with a complaint of headache. These data suggest that physicians should be particularly vigilant for secondary headache disorders in patients with headaches that are 50 years of age or older.

The above studies confirm that the red flags of "sudden onset headache" and "abnormal neurologic exam" are more predictive for secondary headache disorders than "older age." These results are most applicable to emergency room patients as most of the above studies were conducted within emergency room settings.

Topiramate vs Divalproex Sodium in the Preventive Treatment of Migraine: A Prospective "Real-World" Study.

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Background and objectives.— Certain neuromodulators, most notably topiramate (TPM) and divalproex sodium (DVP), are effective preventive agents for migraine. Published data from head-to-head studies comparing TPM and DVP are not available. The purpose of this study was to compare TPM and DVP for the prophyaxis of migraine in a "real-world" setting.

Methods.— At 2 centers and over a period of 12 months we prospectively evaluated and treated a consecutive series of migraine patients. At baseline all were experiencing less than 15 headache days/month, and we treated all patients requiring prophylactic therapy with either TPM or DVP. We evaluated adherence, headache frequency (HF) and tolerability after 3 months of treatment. TPM treatment was initiated at 25 mg daily and increased every 10 days (25 mg) to a target of 150 mg/day (2 divided doses/day). Treatment with DVP was initiated at 250 mg daily and sequentially titrated up to 500 mg twice daily. All patients were naïve to the use of TPM and DVP.

Results.— One hundred and twenty patients (104 women and 16 men of ages 18 to 68, mean 41.2 years) were included. Topiramate selectively was prescribed to 69 patients and DVP selectively to 51. Baseline HF for both groups was similar (8 ± 4 headache days/month). By intention to treat analysis at 3 months, 40 (58%) of patients initially treated with TPM and 26 (51%) of those initially treated with DVP experienced a reduction in HF of >50% (*P* = NS). Ten patients (14.5%) initially treated with TPM and 8 (15.7%) initially treated with DVP did not return for follow up or were begun on alternative prophylactic therapy. The most common side effects manifested by TPM patients were weight loss (50% of those who completed the treatment period), paresthesia (48%), and cognitive disturbances (20%), whereas DVP patients who completed the treatment period reported weight gain, hair loss, and gastrointestinal symptoms (approximately 24% for each). The mean doses achieved by those completing the study were 140 mg/day for TPM and 890 mg/day for DVP.

Conclusions.— Although any conclusions from this investigation necessarily are limited because of our study's open-label nonrandomized design, these results suggest that TPM and DVP are reasonably effective and generally well tolerated when used to treat a “real-world” population of episodic migraineurs who require prophylaxis.

Low-Dose Topiramate Plus Sodium Divalproate for Positive Responders Intolerant to Full-Dose Monotherapy

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Background.— Neuromodulators such as topiramate (TPM) and divalproex sodium (DVS) are effective in the preventive treatment of migraine. Nonetheless, patients often discontinue their use due to side effects.

Objectives.— The study aims to determine whether the combination of lower doses of TPM and DVS may be useful for patients responsive to higher doses of the individual drugs but experiencing intolerable side effects.

Methods.— This clinic-based study was conducted to evaluate a series of patients who experienced at least a 50% reduction in headache frequency after 6 weeks of treatment with either TPM 100 mg/day or DVS 750 mg/day, but suffered intolerable drug-related side effects. At that point, patients were switched to TPM (50 mg in the morning and 25 mg at night) plus DVS 500 mg/day (single dose) and reevaluated after 6 further weeks.

Results.— Thirty-eight patients were evaluated. Mean age was 37 years, and 84% were female. Of the 38, 17 (77.3%) initially were using TPM only, and 10 (62.5%) initially were using DVS only. After 6 weeks on combination therapy, 27 (62.9%) reported improved tolerability without any decrease in efficacy. Five patients who initially were using TPM only and six using DVS only failed to return for follow-up or were noncompliant with treatment due to persistent or worsening side effects.

Conclusions.— This small, open-label study suggests that the combination of TPM and DVS in doses lower than those typically used for migraine prophylaxis may be an effective option for patients who benefited from higher doses of these same medications used as monotherapy but were unable to tolerate such treatment due to side effects.

New Daily Persistent Headache: Clinical Perspective

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Abstract

New daily persistent headache is a recognized form of primary chronic daily headache. It is unique in its presentation and course. The goal of this article is to discuss the clinical characteristics, triggering factors, possible underlying pathogenesis and treatment options for this unique headache disorder. At present prognosis for new daily persistent headache is considered poor with very few effective treatment options. A new treatment paradigm for new daily persistent headache based on triggering events will be suggested. The current International Classification of Headache Disorders 2 criteria for new daily persistent headache will also be discussed including its apparent inadequacies and revised criteria will be recommended.

New daily persistent headache (NDPH) was first described by Vanast in 1986[1] as a benign form of chronic daily headache that improved without therapy. In the headache specialty clinic, however, NDPH is felt to be one of the most treatment refractory of all primary headache conditions. Overall, very little is known about this syndrome. It is unique in temporal profile as it is a headache condition that begins daily from onset, typically in a patient population with no prior headache history and can continue for years unabated without any sign of alleviation, despite aggressive treatment. In many instances patients can name the date their headache began even if it was many years prior. The objective of this manuscript is to discuss the clinical aspects of NDPH including its epidemiology, headache characteristics, triggering events, and provide treatment strategies. Evaluation for secondary mimics of primary NDPH will be also discussed. Finally, a critique of the International Classification of Headache Disorders, 2nd edition (ICHD-II) criteria for NDPH with proposed revised criteria will be presented based upon the current literature.

EPIDEMIOLOGY

Even though NDPH has probably been around for centuries, it has only recently been diagnosed as an entity separate from chronic tension-type headache, hemicrania continua, and chronic migraine. The prevalence of chronic daily headache (CDH) from population-based studies in the USA, Asia, and Europe is about 4%.[2] In older epidemiologic investigations, primary CDH subtypes were sometimes not mentioned in the analysis and NDPH was rarely stratified out from the data. Several studies have documented the prevalence of NDPH. Castillo et al[3] looked at 2252 subjects in Spain and found that

4.7% of the population had CDH of which 0.1% had NDPH. Bigal et al[4] noted that 10.8% of 638 patients with CDH in a headache specialty clinic had NDPH. Koenig et al[5] found that 13% of a pediatric CDH population, surveyed from selected pediatric headache specialty clinics, had NDPH. Meineri et al[6] from Italy diagnosed NDPH in 18 of 265 CDH patients (6.7%) from a headache specialty clinic. Wang et al[7] did not find a single adolescent with NDPH in a survey of 122 children from Taiwan with CDH, although this population was very age-restricted (12-14 years). In a recent population-based study from Norway,[8] which specifically was looking at the prevalence of NDPH, the authors found the overall 1-year prevalence to be 0.03% or 1 of 3500 individuals from the general population. The population studied was 30 to 44 years of age. As NDPH especially in women appears to be a disorder of adolescents and those in their early twenties, this study may have underestimated true prevalence rates in the general population.

CLINICAL FEATURES OF NDPH

It appears from clinical observation that there are 2 main subtypes of NDPH. A self-limited form which typically goes away within several months to several years without any therapy and rarely presents to a physician's office (at least a neurologist or headache specialist's office) and a refractory form which is basically resistant to aggressive outpatient and inpatient treatment and can continue for years to decades unabated. In Vanast's[1] original description of NDPH, he described the self-limited subtype and referred to NDPH as a benign daily headache.

There are now multiple small case series in the literature dedicated to describing the clinical characteristics of NDPH. Vanast[1] in the original description of this condition noted in 45 patients, whom he identified with NDPH over a 2-year period, a female predominance to the syndrome (26 women and 19 men). There was an earlier age of onset of NDPH in women compared to men and the age of onset of NDPH in women ranged from 16 to 35 years while in men from 26 to 45 years. Seventy-two percent of the patients stated the pain of NDPH was constant. Pain location was temporal in 9 of 45 patients, temporal plus other areas in 14 patients, occipital and extra sites in 20 patients, and holocranial in 5 patients. “Migrainous” associated symptoms were noted in a large percentage of patients: nausea 55%, vomiting 12%, photophobia 34%, and phonophobia 37%. Other associated symptoms included drowsiness and lethargy in 15%, vertigo in 13%, and near fainting spells in 1%. Li and Rozen[9] completed a retrospective chart review using a computerized database of patients from the Jefferson Headache Center (a university-based headache specialty unit). All patients who were seen at Jefferson between August 1997 and May 2000 and diagnosed with NDPH were included. Forty women and 16 men were identified (female to male gender ratio was 2.5:1). Age of onset ranged from 12 to 78 years. Peak age of onset was the second and third decade in women and the fifth decade in men. Eighty-two percent of patients were able to pinpoint the exact day their headache started. Headache onset occurred in relation to an infection or flu-like illness in 30%, extracranial surgery (eg, hysterectomy) in 12%, and a stressful life event in 12%. Over 40% of patients could not identify any precipitating event. A prior headache history was found in 38% of patients (episodic migraine 19%,

episodic tension-type headache 2%, unspecific headache 17%). No patient had a prior history of chronic daily headache or an increasing frequency of episodic headache just prior to the onset of NDPH. The duration of the daily headache ranged from 1.5 to 24 hours. In 79% of patients the pain was continuous throughout the day with no pain-free time noted. Baseline average pain intensity was moderate (4 to 6 out of 10 on a visual analog pain scale) in 61% of patients while 21% experienced severe pain (≥7 out of 10) all of the time. Headache location was bilateral in 64% of patients. Almost 60% of patients had some pain localized to the occipital-nuchal region, while 44% experienced retro-orbital pain and 18% had holocranial pain. Headache quality was described as a throbbing sensation in 55% and pressure-like in 54%, other descriptions included stabbing 45%, achy 43%, dull 37%, tightness 36%, burning 23%, and searing 4%. Headaches were aggravated by stress in 40%, physical exertion in 32%, and bright light in 29%. Headaches were relieved by lying down in 66%, being in a dark room 48%, with massage 23%, and with sleep 9%. In regard to associated symptoms, nausea occurred in 68% of patients, photophobia in 66%, phonophobia in 61%, lightheadedness in 55%, sore/stiff neck 50%, blurred vision in 43%, vomiting in 23%, osmophobia in 23%, and vertigo in 11%. Aura-type symptoms also were present in some patients including visual photopsias in 9%, and seeing zigzag lines in 5%. A family history of headache was documented in 29% of patients. Menieri et al[6] documented the clinical characteristics of 18 NDPH (11 women, 7 men) patients diagnosed in an Italian headache specialty clinic. Women had a younger age of onset of NDPH. A previous personal headache history was noted in 33%, while a family history of headache was noted in 33% of NDPH patients. All patients had bilateral pain, which was moderate intensity in most while some had mild daily pain. Severe pain was not noted in this population. Migrainous features were noted in 14 of 18 NDPH sufferers. In regard to triggering events, NDPH started with a flu-like illness in 11% while another 11% had their headaches begin after a surgical procedure. Takase et al[10] looked at the clinical characteristics of NDPH in 30 Japanese patients. In this study there was a male predominance (17 men and 13 women). Age of onset of NDPH ranged from 13 to 73 years. Headache onset was associated with a stressful life event in 20%, while the remainder could not identify a probable cause. The headache was of severe intensity in all patients. Headache was present throughout the entire day with little if any headache-free time. Headache quality was pressing or tightening in 73%, pulsating in 10%, and both pressing and pulsating in 5%. Associated symptoms were rare with mild nausea occurring in 10 patients while only 1 patient had photophobia. Kung et al[11] recently looked at a clinic-based pediatric population with NDPH. They looked at clinical records and headache diaries of 306 children and adolescents ages 6-18 years and identified 187 patients with chronic daily headache of which 58 children had NDPH. Almost half (48.1%) reported they could recall the month when their headaches started. NDPH was female predominant 1.8:1, but more boys had NDPH than other subforms of chronic daily headache. Patients with NDPH had headaches fulfilling criteria for migraine on an average of 18.5 days per month. On most days, they had migraine-associated symptoms. Robbins et al[12] looked at a NDPH in a headache specialty clinic-based population. Seventy-one patients met their criteria for NDPH (allowing migraine features). The patients were predominantly female, white, with moderate to severe pain, throbbing quality 45%, bilateral location 89% and

associated symptoms of nausea 48%, vomiting 13%, photophobia 45%, and phonophobia 41%. They noted 3 subforms: persistent 76%, remitting 16%, and relapsing–remitting 8.5%. Twenty-five percent of patients had a preexisting history of a primary headache disorder, either ETTH (18.3%) or migraine (7.0%). Almost 50% of patients had a family history of frequent headaches. Median age of onset was 28 years slightly younger in woman (26 years) than men (28 years). Triggering events were recalled by 46.5%: flu-like or upper respiratory 14%, stressful life event 10%, and menarche 4.2%. Two newly noted triggers were tapering of a selective serotonin reuptake inhibitor (SSRI) (of note the author has also noted this in several patients) and after vaccination for human papillomavirus (the author also has 2 cases of this in his patient population).

Table 1 presents an overview of the clinical characteristics of NDPH patients from the presented studies.

Gender: female predominance (gender ratio range 1.4-2.5:1) 1.

Age of onset: younger in women, many 2nd-3rd decade 2.

Location: bilateral in most 3.

Intensity: moderate to severe in most patients 4.

Pain duration: constant without pain free time 5.

Associated symptoms: migrainous features are common in almost all studies 6.

Recognized triggering event in 7. <50%

Table 1.—. Clinical Characteristics of New Daily Persistent Headache

ETIOLOGY OF NDPH

As a number of NDPH patients state that they had a cold or flu-like illness when their headache began, an infectious etiology for NDPH can be hypothesized. Some authors have linked Epstein-Barr virus (EBV) infection with NDPH. Diaz-Mitoma et al[13] identified oropharyngeal secretions of EBV in 20 of 32 patients with NDPH compared with 4 of 32 age- and gender-matched controls. A history of mononucleosis was identified in 12 of the patients with NDPH. Almost 85% of the NDPH patients were found to have an active EBV infection as opposed to 8 in the control group. The authors hypothesized that activation of a latent EBV infection may have been the trigger for the development of a chronic daily headache from onset. EBV titers were tested in 7 patients from the Li and Rozen[9] investigation of whom 5 had positive titers indicating past but not active infection. Meineri et al[6] did not find an EBV infection in any NDPH patient but did note that 6/18 patients had elevated IgM titers for herpes simplex virus (HSV) while 2/18 patients had elevated IgM cytomegalovirus (CMV) titers all indicating recent infection. Santoni and Santoni-Williams[14] demonstrated evidence of systemic infection in 108 patients with NDPH including Salmonella, adenovirus, toxoplasmosis, herpes zoster, EBV, and *Escherichia coli* urinary tract infections.

An infectious etiology is not the presumed cause of NDPH in every patient, as almost 40% to 60% of NDPH sufferers have no recognized trigger. A stressful life event has been shown to trigger NDPH in a subset of patients. Stewart et al[15] documented that stressful life events are a risk factor for chronic daily headache in the general population. In the year before or same year of onset of CDH, individuals who

developed headache compared to controls more likely had a change in personal relationships, had moved, had a problem with their children, or had an extremely stressful ongoing situation. The study did not define CDH subtypes, so the number of patients who developed NDPH after a stressful life event could not be ascertained.

The only study to date looking at the possible cause of NDPH in children was completed at the Mayo Clinic in 2003. Mack[16] identified 41 children with NDPH of which 15 patients had their onset of headache during a viral infection. A positive EBV titer was found in 60% of these patients. Of the remaining children, 8 had their headaches begin after mild head injury, 3 patients after a surgical procedure, and 1 patient during high-altitude camping. In 5 patients no inciting event was identified while in 4 patients an initial diagnosis of intracranial hypertension was made but the headache persisted after treatment and normalization of pressures.

From the author's experience with NDPH there appears to be another important triggering event outside of infection, stress, post-surgical, and that is toxic exposure. The author has seen patients who were exposed to toxic levels of refrigerants or fungicides, fumes from fires and those individuals who were at ground zero of the World Trade Center who developed a daily headache out of the blue. Some of these settings included times of high stress while others were not stress-related events (Table 2).

Post-infectious-cytokines 1.

Post-toxic exposure-cytokines 2.

Post stressful life event-cytokines and cervicogenic 3.

Post-surgical, unknown event-cervicogenic until proven otherwise 4.

Table 2.—. Precipitating Events for New Daily Persistent Headache and Possible Etiology

NEWER INSIGHT INTO TRIGGERING EVENTS

As NDPH is really in its infancy compared to the other primary headache syndromes, very little research has been completed looking at the pathogenesis of this syndrome. This section will look at 2 new studies which have helped to unravel some of the mysteries of this complicated headache condition.

Cervical Spine Joint Hypermobility as a Predisposing Factor for the Development of NDPH Rozen and colleagues[17] noticed a similar body habitus in NDPH patients at a headache speciality clinic of tall height, thin weight and a long neck reminiscent of the physical characteristics seen in individuals with hereditary connective tissue disorders. In addition, on examination NDPH patients also appeared to have lax joints suggesting underlying joint hypermobility. As joint hypermobility is recognized as a predisposing factor for the development of chronic pain in the rheumatology literature, Rozen et al[17] looked for the presence of joint hypermobility in NDPH patients, hypothesizing that joint hypermobility, especially of the cervical spine, may be a predisposing factor for the development of NDPH. Twelve individuals (10 women, 2 men) with primary NDPH were evaluated by 1 of 2 physical therapists. Each patient was tested for active cervical range of motion and for the presence of excessive intersegmental vertebral motion in the cervical spine. All patients were screened utilizing the Beighton score, which determines degree of systemic hypermobility. Eleven of the 12 NDPH patients were found

to have cervical spine joint hypermobility. Ten of the 12 NDPH patients had evidence of widespread joint hypermobility with the Beighton score. The authors concluded that joint hypermobility specifically of the cervical spine may be a predisposing factor for the development of NDPH. How joint hypermobility in the cervical spine can lead to persistent daily head pain can only be hypothesized. Evidence exists that there is a convergence of trigeminal and cervical afferents in the trigeminal nucleus caudalis.[18] Thus, cervical spine pathology can present as head pain typically in a trigeminal nerve V1 distribution.[19] Cervical spine joint hypermobility in some manner may influence cervical afferent input into the trigeminal nucleus caudalis with the subsequent development of head pain. It may also set up upper cervical facet or atlantoaxial joint inflammation leading to head and neck pain. Limitations to the study included: a small sample size, lack of a double-blinded examination by both physical therapists, and no age- and gender-matched control group population.

What was evident in this population is that the cervical spine may be a key player in the development of NDPH. The author in the last year has gone back and requestioned individuals who stated they had no triggering event for their NDPH. In almost all there was something they did that could have potentially irritated their cervical spine a day or 2 prior to headache initiation. For example, several stated that the headaches began on days when they were sleeping away from their home bedroom; some of the younger women were on sleepovers and were sleeping on the floor, some were in hotels and others were in cottages sleeping on cots. Others were playing sports and even 1 patient started a day after riding a mechanical bull. When looking back at the post-surgical cases in most if not all instances, these patients were intubated during their procedures thus had undergone neck hyperextension or had their neck extended for a prolonged period of time such as with dental procedures. Events that could cause cervical irritation seem to be the norm in NDPH patients who did not have their headaches precipitated by infection or toxic exposures.

Elevation of Cerebrospinal Fluid (CSF) Tumor Necrosis Factor Alpha Levels in NDPH Patients As a certain percentage of NDPH patients have their headaches start after an infection, the possibility of a persistent state of systemic or central nervous system (CNS) inflammation comes into question. Tumor necrosis factor alpha (TNF alpha) is a pro-inflammatory cytokine involved in brain immune and inflammatory activities, as well as in pain initiation. Rozen and Swidan[20] looked at TNF alpha levels in the CSF of primary NDPH patients from an inpatient headache unit. Twenty patients with NDPH were studied and TNF alpha levels were elevated in 19 of the 20 CSF samples. Serum TNF alpha levels, however, were normal in most of the study subjects. The authors, based on their results, suggested a role for pro-inflammatory cytokines (specifically TNF alpha) in the pathogenesis of NDPH. As serum TNF alpha levels were not elevated in most NDPH patients, NDPH does not appear to be a disorder derived from systemic inflammation, but rather inflammation solely involving the CNS. Glial cells are known manufacturers of cytokines in the CNS. Interestingly in laboratory animals, recognized triggers of glial cell activation and thus cytokine production include infection, stress, and surgical procedures.[21-23] These are the recognized triggering events of NDPH in humans. How elevated TNF alpha levels can produce head pain can only be postulated. There is recent evidence that TNF alpha will induce

calcitonin gene-related peptide production, which is a known factor in the pathogenesis of other primary headaches including migraine and cluster headache.[24] Interestingly, as most of the positive tested patients showed minimal to no improvement during aggressive inpatient treatment, this suggested that persistent elevation of CSF TNF alpha levels maybe one of the causes of treatment refractoriness in patients with NDPH. It also suggests that specific TNF alpha inhibitors may have an important future role in the treatment of NDPH and this needs to be investigated.

TRIGGERING EVENT OVERVIEW

After years of seeing a large number of patients with NDPH and looking at the precipitating events recorded, it appears that almost all patients can be grouped into 2 main categories (Table 3):

Low or elevated cerebrospinal fluid pressure 1.

Cerebral vein thrombosis 2.

Carotid or vertebral artery dissection 3.

Giant cell arteritis 4.

Meningitis 5.

Sphenoid sinusitis 6.

Cervical facet syndrome 7.

Intranasal contact (contact point headache)-pain caused by contact of intranasal structures (eg, nasal septum and nasal turbinate) 8.

Intracranial neoplasm or mass lesion 9.

Table 3.—. Secondary Mimics of New Daily Persistent Headache

- 1

Central nervous system inflammation with probable enhanced CSF cytokine production.
This would include the post-infection, post-toxic exposure, and stressful life event triggering groups.

- 2

Cervicogenic with underlying cervical hypermobility syndrome.
This would include post-surgical, the unknown trigger, and possibly stressful life event trigger (crying, laying in bed or curled up on the couch could lead to neck irritation)

Taking a careful history to tease out triggering events may help when deciding on further evaluation and treatment.

SECONDARY MIMICS OF NDPH

A diagnosis of primary NDPH is made only after secondary causes have been ruled out.[25] Two disorders in particular can mimic the presentation of NDPH: spontaneous CSF leak and cerebral venous sinus thrombosis. Spontaneous CSF leaks typically present as a daily headache with a positional component. However, the longer a patient suffers with a CSF leak-induced headache the less pronounced the positional component becomes. Thus if a patient is seen in a physician's office months to years after onset of a CSF leak, that patient may not even divulge a history of positional headaches as that trigger

may not have been evident to the patient for a very long time. In this setting the CSF leak headache may mimic a primary NDPH picture.

In the patient who presents with new daily headache and is subsequently found to have cerebral venous thrombosis, in many instances none of the typical features recognized of cerebral vein thrombosis are present including: no history of new onset seizures, focal neurologic deficits, change of consciousness, cranial nerve palsies, bilateral cortical signs, and no evidence of papilledema on fundoscopic examination. A recent patient of the author presented with a daily headache from onset of 4 months duration with mostly occipital-nuchal discomfort. Her neurologic examination was normal and she had no prior coagulopathy history. She obtained complete headache relief with greater occipital nerve blockade and the headache never returned after only a single nerve block. On subsequent magnetic resonance venography she was found to have an extremely large transverse sinus thrombosis. The presentation of NDPH is so unique, even if patients readily improve with therapy investigative studies still must be completed. Other recognized secondary causes of NDPH are noted in Table 3.

The evaluation of an NDPH patient should include neuroimaging, specifically brain magnetic resonance imaging with and without gadolinium and a magnetic resonance venography. Gadolinium must be given to look for the pachymeningeal enhancement associated with spontaneous CSF leaks while magnetic resonance venography will help make the diagnosis of cerebral vein thrombosis. If the headache started as a thunderclap headache, is one-sided or has significant autonomic features then magnetic resonance angiography of the intracranial and extracranial circulation is suggested to evaluate for aneurysms or arterial dissections. If those studies are negative then a lumbar puncture should be considered especially in a patient who is treatment-refractory. The lumbar puncture can rule out an indolent infection and can also determine CSF pressures. In some instances a patient may have a CSF leak without typical magnetic resonance imaging changes and with a loss of a positional headache; thus an opening CSF pressure on a lumbar puncture is the only way in which to diagnose a low CSF pressure syndrome. A syndrome of idiopathic intracranial hypertension may also mimic NDPH. Papilledema on fundoscopic examination would be a major reason to search for this diagnosis although some individuals may have elevated spinal pressure without papilledema and may not resemble the typical pseudotumor cerebri patient of a young obese woman with chronic daily headache, tinnitus, and visual obscurations.[26]

TREATMENT

New daily persistent headache can continue for years to decades after onset and be extremely disabling to the patient. Even with aggressive treatment many NDPH patients do not improve. Patients with NDPH can fail every possible class of abortive and preventive medications without any sign of pain relief. NDPH patients can even start to overuse medications as they have a daily chronic headache, but unlike with chronic migraine from analgesic overuse, getting NDPH patients out of analgesic overuse typically does nothing to change the natural course of the disorder.

At present no specific treatment strategy can be suggested for primary NDPH based on clinical evidence. Most headache specialists will treat NDPH with the same acute and preventive medications that they use to treat chronic migraine although based on nonresponse to most of these medications, NDPH and chronic migraine are 2 disparate syndromes.

Very few therapies for NDPH have been documented in the literature:

Anti-Epileptic Medication Rozen[27] presented 5 patients in which successful treatment of NDPH was obtained with gabapentin or topiramate but these agents do not work in the majority of cases.

Tetracycline Derivatives A promising treatment reported by Rozen[28] in abstract form is the use of daily oral doxycycline, which is a TNF alpha inhibitor. Four patients with treatment-resistant NDPH and elevated CSF TNF alpha levels (>8.2 pg/mL) were treated with doxycycline 100 mg 2× per day in an open-label fashion for 3 months. Headache frequency and pain intensity levels were assessed (pain scale levels were 0-5; 0: no pain, 1-2: mild pain, 3: moderate pain, 4-5: severe pain). All patients had failed at least 5 preventive agents and thus were deemed treatment-refractory. Three of 4 patients failed inpatient headache treatment while another failed outpatient infusion therapy. Age of onset of NDPH ranged from 13 to 39 years. Duration of NDPH prior to doxycycline therapy ranged from 8 months to 3 years. An infection precipitated NDPH in 3 of 4 patients. Four out of 4 patients had a positive response to doxycycline treatment. Two patients became pain-free. One patient had an 80% improvement in daily pain intensity (from daily level 4-5 to daily level 1, with no severe pain episodes), but did not achieve any pain-free time. One patient had a slight improvement in daily pain intensity from daily level 3-4 to a level 3, but had a >50% reduction in frequency of severe pain episodes from 3-5 ×/week to 1-2 ×/week with a much improved quality of life. Average time to see improvement on doxycycline was after 2 months of therapy; however, 1 patient responded within 2 weeks of starting treatment. The 2 patients with the highest CSF TNF alpha levels became pain-free with doxycycline. Doxycycline was well tolerated overall, but 1 patient developed a severe sunburn on the medication. The author has treated numerous patients with doxycycline or minocycline sometimes along with high-dose montelukast (10 mg 2× per day). Anecdotally, this treatment has helped a number of patients, but it certainly does not work in every patient with this syndrome.

Mexiletine Mamura et al[29] looked at mexiletine in 3 patients with NDPH who had been deemed treatment refractory. All 3 patients showed a reduced severity of pain on mexiletine but only 1 showed a reduced frequency of headaches. Significant side effects were noted on this medication.

IV Corticosteroids Recently, Prakash and Shah[30] reported on 9 patients with post-infectious NDPH. All patients were given high-dose intravenous methylprednisolone for 5 days. And 6 patients were given oral steroids for 2-3 weeks. All patients improved with 7 patients experiencing almost complete pain relief within 2 weeks while 2 patients needed between 6 and 8 weeks. The results of this study are of course very promising but there are 2 major drawbacks. First, none of the patients fit the ICHD-II criteria for NDPH because they were treated only several weeks after headaches began, thus we do not know if these patients would have improved on their own even without treatment. Secondly, most headache

specialists rarely ever see NDPH until after it has been ongoing for months to years. Theoretically high-dose steroids may work early in the course of NDPH but may not work as effectively in the more prolonged cases. From the multitude of patients this author has seen with NDPH if treatment is started within the first year of headache onset, the response rates are much higher than if the treatment is begun years after headache onset. It would be interesting to see if the response to high-dose IV corticosteroids is the same in patients with a more prolonged course of NDPH.

Nerve Blockade As a number of NDPH patients appear to have cervicogenic signs on examination (even without a history of head or neck trauma) possibly relating to their underlying cervical hypermobility sending them for anesthesiology/pain evaluation for nerve blocks is recommended when medication is not helping. Anecdotally, the author has had several NDPH patients achieve significant pain relief after cervical facet blocks, atlantoaxial blocks, or selective nerve blocks (greater occipital, auriculotemporal, supraorbital/trochlear, dorsal root ganglia) followed by radiofrequency ablation procedures. Robbins et al[12] reported on peripheral nerve block responses in patients with NDPH. Greater and lesser occipital, auriculotemporal, supraorbital, and supratrochlear nerve blocks were tried. Fifty-four percent of the persisting subform of NDPH or the prolonged subform had an acute response to nerve blockade but that correlated to only 1 day of pain relief. It appears no semipermanent radiofrequency procedures were tried. The author has 1 patient who presented with bilateral temporal pain and had a positive response to diagnostic auriculotemporal anesthetic blocks. After pulsed radiofrequency she would go 6-8 months pain-free and had positive response to subsequent radiofrequency procedures.

TREATMENT SUGGESTIONS

A suggested treatment paradigm for NDPH based on triggering event and the available literature is as follows:

Post-Infectious If caught early could try IV methylprednisolone up to 1 g per day for 2-3 days or if believed to be post viral with high serum viral titers IV acyclovir for 3 to 5 days plus minus corticosteroids can try tetracycline derivative can pulse with IV doxycycline for several days prior to PO usage.

Post Stressful Life Event Tetracycline derivative and evaluate for cervical hypermobility syndrome and cervical irritation on examination. If cervical hypermobility present physical therapy for neck strengthening exercises and possibly anesthesiologic blockade is suggested.

Post-Surgical Evaluate the neck aggressively for upper cervical facet inflammation and GON irritation; consider nerve blockade. Medications: consider combination of muscle relaxant and nonsteroidal anti-inflammatory drug (NSAID) or tetracycline derivative or antiepileptic drug (AED) (topiramate or gabapentin).

Unknown Trigger Tetracycline derivative or AED (topiramate or gabapentin) and if cervical issues consider nerve blockade and/or combination of muscle relaxant and NSAID.

In all subgroups if outpatient therapy fails consider inpatient treatment and or possible use of daily mexiletine.

PROGNOSIS

The self-limited form of NDPH has a fairly good prognosis as patients appear to improve without any intervention. In Vanast's[1] initial description of NDPH, 30% of the men affected were headache-free at 3 months, and 86% were headache-free at 2 years. In women, 30% were headache-free at 3 months, while 73% were pain-free at 2 years. In the patients who have the refractory form of NDPH their syndrome can go on unabated for years to decades even with aggressive treatment. Takase et al[9] evaluated the effect of treatment utilizing muscle relaxants, tricyclic and SSRI antidepressants, and valproic acid on NDPH. In 8 of 30 patients treatment was deemed very effective (daily headache intensity 3/10 or less), 1 patient had a moderately effective response (daily headache intensity 4-5/10), 6 patients mildly effective (daily headache intensity 6-7/10), while 15 patients showed no response to treatment. Only 2 patients developed headache-free time after therapy, the remainder continued with daily head pain although some had an improved quality of life. The authors concluded that NDPH is overall unresponsive to typical headache treatment. In the Robbins et al study[12] from New York, over half of the patients with the persisting subform had daily headaches for longer than 2 years. Of the patients who remitted, 63.6% did so within 24 months (this would come under the self-limited form of NDPH). In the relapsing-remitting subgroup, all patients remitted for the first time within 24 months, but relapses inevitably occurred. The authors stated that in the majority of cases NDPH can have a protracted course.

DIAGNOSTIC CRITERIA

New daily persistent headache has been included in the ICHD-II criteria (Table 4).[31] As there were only a few studies looking at the clinical characteristics of NDPH at the time the criteria were created these consensus criteria may not have reflected what is seen in everyday practice. The ICHD-II criteria reflect almost a daily form of tension-type headache, There are 3 main concerns with the current ICHD criteria for NDPH. The first is the duration of headache before a diagnosis of NDPH can be made. Three months is an arbitrary number and there is no available evidence to state that if a daily headache from onset extends beyond 3 months it is more likely to persist and less likely to be from an underlying secondary cause than if it went on for 2 months or 4 months. Sphenoid sinusitis, eg, can have a new daily persistent headache that can last for weeks to months if untreated and this is not primary NDPH. The author has seen carotid dissection headaches which in the literature are stated to last 2 to 3 weeks maximum, go on for a year plus in duration as it took this long for vessel recanalization on magnetic resonance angiography. When patients experience their first ever migraine these can last for weeks but then over time settle in to an episodic more typical pattern.

1. ICHD-II = The International Classification of Headache Disorders, 2ed edition.

Headache for A. >3 months fulfilling criteria B-D

Headache is daily and unremitting from onset or B. <3 days from onset

At least 2 of the following pain characteristics: C.

Bilateral location 1.

Pressing/tightening (non-pulsating) quality 2.

Mild or moderate intensity 3.

Not aggravated by routine physical activity such as walking or climbing stairs 4.

Both of the following D.

No more than one of photophobia, phonophobia, or mild nausea 1.

Neither moderate or severe nausea or vomiting 2.

Not attributed to another disorder E.

Table 4.—. ICHD-II Criteria for New Daily Persistent Headache

I do think that several weeks of daily headache is too short of a time for a diagnosis of NDPH to be made but further studies need to be done to see if 2 months, eg, is good enough to make a diagnosis of NDPH.

The main controversial issue with the current ICHD-II criteria for NDPH is the requirement for an almost absence of migrainous symptoms to make a diagnosis. Clearly, looking at the available descriptive studies of NDPH migrainous symptoms are not only common in these patients but they maybe almost as prevalent as that seen in migraine itself. Robbins et al[12] recently looked at patients with NDPH and utilized a revised ICHD criteria allowing migrainous symptoms. Of 71 patients who met the revised criteria, only 43% of those met the ICHD-II criteria thus demonstrating that the majority of NDPH patients do have migrainous symptoms along with their daily headache and if the current criteria stand it will exclude most true patients with NDPH. Table 5 demonstrates the percentage of migrainous symptoms in patients with NDPH from currently published studies. It would seem in the upcoming ICHD-III revised criteria migrainous symptoms should be included as a typical symptom of NDPH and not be an exclusion for a diagnosis of NDPH.

Study	Nausea (%)	Photophobia (%)	Phonophobia (%)	Severe Intensity
Vanast[1]	55	34	37	Did not comment
Li and Rozen[9]	68	66	61	Yes
Menieri et al[6]	50	27	17	No
Takase et al[10]	33	3	0	Yes
Kung et al[11]	42	67	61	Yes
Robbins et al[12]	48	45	41	Yes

Table 5.—. Migrainous Symptoms in Patients With New Daily Persistent Headache and Pain Intensity

Finally, the need to include severe intensity pain in the revised diagnostic criteria is necessary. Currently only mild to moderate pain intensity is allowed. Four of 5 studies that assessed pain intensity found that NDPH patients could complain of severe head pain with NDPH (Table 5).[1,6,9-12] The author has included his proposed revised ICHD criteria for NDPH (Table 6).

Acute onset of constant unremitting headache (daily from onset) A.

Daily head pain without significant pain-free time for B. >2 months

Average headache duration of C. >4 hours per day (if untreated) Frequently constant pain without medication

No history of migraine or tension-type headache that is increasing in frequency before the onset of new daily persistent headache D.

Prior history of any headache disorder is allowed E.

At least 2 of the following pain characteristics F.

Pulsating or pressing/tightening quality 1.

Mild, moderate or severe pain intensity 2.

Bilateral pain location 3.

Can be aggravated by walking stairs or similar routine physical activity 4.

At least 1 of the following can be present: G.

Nausea and/or vomiting 1.

Photophobia or phonophobia 2.

Does not fit the criteria for hemicrania continua H.

Secondary conditions have been successfully ruled out (eg, low CSF pressure syndrome, cerebral vein thrombosis) I.

Table 6.—. Proposed/Revised Criteria for New Daily Persistent Headache

CONCLUSION

New daily persistent headache is a recognized form of CDH. It is unique in its presentation and course. Many NDPH patients can state the exact date their headache began. NDPH is marked by a continuous daily head pain of varying intensity which can be associated with migrainous symptoms. Further research must be invested into studying NDPH as it is becoming more prevalent in the physician's office and in many instances is refractory to many of the known CDH preventive and abortive treatment strategies.