Sinus Problems as a Cause of Headache Refractoriness and Migraine Chronification

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Sinus headache is not a diagnostic term supported by the academia, yet it appears to be understood by the general public and larger medical community. It can be considered both a primary and secondary headache disorder. As a primary headache disorder, most of the patients considered to have sinus headache indeed have migraine (migraine with sinus symptoms). Yet it is also possible that some attacks of sinus headache may represent a unique clinical phenotype of migraine or be a unique clinical entity. Potentially, primary sinus headache can chronify and be refractory through immune-mediated mechanisms or as a catalyst for migraine chronification through ineffective treatment or medication overuse and misuse. As a secondary headache disorder, sinus headache can be associated with a wide range of underlying etiologies such as infection, anatomical abnormalities, trauma, and immunological disease or sleep disorders. It is possible that these underlying pathophysiological processes generate long-standing activation of nociceptive mechanisms involved in headache and can lead to chronification and refractoriness of the headache symptomatology. This article explores some of the potential mechanisms and the available scientific studies that may explain how sinus headache can become chronic and present to the clinician as a refractory headache disorder.

Introduction

The patient with refractory headaches often presents as one of the most challenging and perplexing problems that faces a clinician managing headache patients. Questions often loom for the health care professional as to the etiology of the condition, the possibility of misdiagnosis, and even at times, the legitimacy of the patient's complaint. So too, for the patient, refractory headache is frequently associated with frustration and a medical odyssey featuring multiple medical consultations, inconclusive diagnostic procedures, and multiple trials of failed therapy that only serve to heighten a downward spiral of failure. This article focuses on one specific etiology for headache refractoriness and its possible role in the chronification of migraine: the sinuses. Ironically, "sinus problems" could potentially impact on headache refractoriness and migraine chronification as a result of misdiagnosis and both under- and overdiagnosis of sinus pathology.

A Clinical Paradox: Sinuses and Chronic Headache

Sinus disease as an etiology of chronic headache is widely accepted by patients, clinicians, and the general public [1]. Yet in many respects, the scientific underpinnings for this assumption are lacking. In large part, this reflects the fact that there is no diagnostic marker to confirm the existence of a primary headache disorder, leaving only the clinician's interpretation and understanding of a patient's symptomatology on which to base a diagnosis. Thus, when patients present with a headache that they believe to be related to allergies and sinus problems, the clinical interview is often oriented by them in a way that supports their assumption. So too the physician's orientation and training enter into the equation. A neurologist, for example, may be more likely to interpret nasal congestion associated with disabling headache as a consequence of autonomic activation as observed in the syndrome of migraine, whereas an allergist may consider the same symptom the result of immunological mechanisms involved in allergic rhinitis. Given the right clinical situation, either or both diagnoses could, on academic grounds, be correct. It may be that only after long periods of repeated treatment failure that a specific patient receives further diagnostic studies that alter the original misdirected diagnostic and therapeutic pathways.

Sinus headache is not an accepted diagnostic term by either the International Headache Society (IHS) or American Academy of Otolaryngology Association–

Table 1. International Headache Society criteria for headache attributed to rhinosinusitis*

1. Frontal headache accompanied by pain in one or more regions of the face, ears, or teeth and fulfilling criteria 3 and 4
2. Clinical, nasal endoscopic, CT, and/or MRI imaging and/or laboratory evidence of acute or acute-on-chronic rhinosinusitis
3. Headache and facial pain develop simultaneously with onset or acute exacerbation of rhinosinusitis
4. Headache and/or facial pain resolve within 7 days after remission or successful treatment of acute or acute-on-chronic rhinosinusitis

*Clinical evidence may include purulence in the nasal cavity, nasal obstruction, hyposmia/anosmia, and/or fever. Chronic sinusitis is not validated as a cause for headache or facial pain unless relapsing into an acute stage.
(*Data from* the Headache Classification Subcommittee of the International Headache Society [3].)

Head and Neck Surgery (AAO-HNS), although both societies acknowledge that the term is widely used by the public and larger medical community. To be clear, using the term in this article is not intended to support "sinus headache" as a validated clinical diagnosis but rather to suggest that a wide array of medical conditions are included in this diagnostic concept, making it imprecise and confusing. Clinicians should pursue a clear diagnostic understanding of patients presenting with "sinus headache." In this article the term *sinus headache* refers to headache associated with or perceived to be associated with sinus structures or pathology.

Nasal Anatomy

The nasal cavity is divided by the nasal septum. The lateral wall of the nasal cavity has three or four turbinates: inferior, middle, superior, and, occasionally, supreme turbinate. The frontal, maxillary, and anterior ethmoid sinuses drain through a structure called the anterior ostiomeatal complex (OMC), while the sphenoid and posterior ethmoid sinuses drain through the posterior OMC. Sensory innervations of the naval cavity and sinuses are provided by the trigeminal nerve through branches of both the first (ophthalmic) and second (maxillary) divisions of the nerve. The cribriform plate of the ethmoid bone supports the olfactory nerve as it passes into the frontal fossa—a point of clinical interest given the close association of migraine and olfactory triggers.

Early work by Wolff [2] demonstrated that the sinuses are relatively pain insensitive. However, Wolff demonstrated that the nasal mucosa and OMCs are pain sensitive structures and frequently implicated in nasal and sinus pain. Also, the sinuses can refer pain to many locations of the head and face, as well as being the site of referred pain from intracranial structure. Thus, the clinical understanding of sinus pain is complex.

Are the Sinuses a Cause of Headache?

Headache, particularly chronic headache, attributed to sinus pathology is a subject of considerable clinical debate. From the perspective of the headache specialist, most sinus headaches are misdiagnosed migraines. According to the IHS Classification of Headache and Facial Pain Disorders, headache can be a symptom of acute rhinosinusitis but is not a symptom of chronic sinusitis [3]. Further, for acute rhinosinusitis, the IHS criteria require headache and rhinosinusitis to develop simultaneously, respond to appropriate treatment within 7 days, and that the condition is confirmed by clinical, nasal endoscopy, CT, or MRI evidence (Table 1). Recently, however, results of a study by Mehle and Kremer [4•] challenged the validity and value of radiographic evidence for diagnosis of sinusitis in migraineurs. The authors found that a majority of patients with sinus headache met criteria for migraine; many also had radiographic evidence of sinus disease on CT scans. One explanation of this finding could be that sinus disease and migraine are comorbid diseases. Other studies have concluded that diagnostic procedures such as CT scans and MRI are notorious for overdiagnosing sinus pathology and suggest their value is limited in evaluating a patient with migraine [5].

The otolaryngology literature also cautions against overzealous attribution of sinus pathology as the cause of chronic headache [6]. In fact, headache is considered a minor criterion in the diagnosis of acute and chronic rhinosinusitis. Pain in chronic rhinosinusitis is typically described in more subtle terms such as *facial pressure* or *fullness*—a nuance that could be easily lost on clinicians having 10 minutes or less to evaluate, diagnose, and treat a headache patient. Given the precautionary tone of these academic guidelines, it is ironic that there exists considerable documentation, particularly in the otolaryngology literature, of successful patient outcomes for relief of chronic headache following surgical procedures on the nose and sinus structures [7–11]. Based on these reports, it appears that sinus pathology can be a cause for headache, although some of these studies have been criticized as having poor research design and lacking long-term outcome data.

Sinus Headache as a Misdiagnosis of a Primary Headache Disorder

Most clinical studies of patients with self- or physician-diagnosed episodic sinus headache appear to have migraine [12–14]. The largest of these studies, conducted by Schreiber et al. [13], reported on a multicenter study of 2991 subjects with self- or physician-diagnosed sinus headache. In this study, 80% of subjects met IHS criteria for migraine with or without aura, and another 8% met IHS criteria for migrainous headache (probable migraine). However, these individuals experience many symptoms attributable to the nose and sinuses, along with symptoms included in the IHS definition of migraine. Subjects

with evidence of infection or an abnormal CT scan were excluded from the study. Despite this limitation, it remains obvious that in most instances episodic sinus headache is a primary headache disorder and can be successfully treated as such [6,15].

Extrapolating data from studies on episodic sinus headache to patients with chronic sinus headache may be misleading. Most current studies of the epidemiology and diagnosis of sinus headache have focused on patients with episodic headaches. Yet most of the surgical literature has focused on patients with chronic and refractory headaches. These chronic populations were excluded from most studies on sinus headache, suggesting the serious possibility that there may be two distinct populations of patients. This is indirectly supported by large epidemiological studies in the United States of patient populations with self-reported, physician-diagnosed migraine, revealing that more than 40% of patients report that at least some of the headaches they experience are related to their sinuses [16]. It would appear that there is a serious disconnect between patients, primary care specialists, perhaps ear, nose, and throat (ENT) surgeons, and the academic community that sets diagnostic criteria for headaches and rhinosinusitis.

Sinus Headache as a True Secondary Headache Disorder

Sinus headache can also be a secondary headache disorder. The IHS classification in both 1988 and 2004 defines sinus headache as a secondary headache disorder. They also state that chronic sinusitis is not a valid cause for headache or facial pain unless it has relapsed into an acute stage [3]. The classification of rhinosinusitis proposed by the AAO-HNS also considers headache as a secondary headache arising from underlying rhinosinusitis [17]. Rhinosinusitis is diagnosed by manipulating various major and minor factors, with headache being classified as minor factor. The term *minor criteria* refers to the value of the symptom in diagnosis and not necessarily the intensity or quality of the headache. However, headache is frequently described in these criteria as pressure rather than pain. Subtypes of rhinosinusitis include acute, recurrent acute, subacute, chronic, and acute exacerbations of chronic. Each of these diagnostic schemes relies heavily on symptom interpretation and tends to minimize the symptom of headache, particularly in the chronic form of the disease.

In addition, several pathological entities that occur in the nose or sinus tract have been reported as causing headache such as contact points, concha bullosa, and septal deviations. These anatomical abnormalities are considered by many to be a cause of headache, although this is a matter of debate. This is in part because these abnormalities can be located in pain-sensitive structures of the nose and, as such, produce pain and nasal symptomatology. Further, sleep disturbances such as snoring and sleep apnea can be associated with disease in the upper airway and are documented causes of migraine chronification and treatment refractoriness [18–20]. A detailed discussion of sleep is outside the scope of this article.

Surgical Experience of Patients with Headache

Despite the promotion of standardized diagnostic criteria that do not support chronic headache as being secondary to rhinosinusitis or nasal pathology, reports in the literature suggest improvement of refractory disabling chronic headache with nasal or sinus surgery [21–23]. In 1990, Levine [21] reported that if headache was reported along with other diagnostic criteria for rhinosinusitis, there was a positive outcome from surgery for headache relief in 75% of cases. If, however, headache was the only symptom used as an indication for surgery, a positive outcome occurred in less than 20% of cases [20]. Tosun et al. [23] reported on a study of 30 patients undergoing endoscopic surgery for headaches presumed secondary to contact points and found that 45% had relief of headache. Behin et al. [22] reported excellent results on a surgical cohort with contact point headaches. The authors suggested that the temporary termination of the headache with topical anesthetic in conjunction with careful ENT evaluation could be used as a screening test to decide which patients may benefit from surgery.

These studies are often criticized as having ambiguous criteria for headache diagnosis and lacking long-term outcome data. Nonetheless, they suggest that in some patients with chronic headache who failed to respond to medical treatment, surgery may be effective in correcting underlying anatomical abnormalities or nasal pathology and relieving headache. Although patient selection varied in these studies, most patients went to surgery because of protracted headache patterns and poor response to prescribed therapy. However, many had not been screened for chronic migraine, medication overuse headache, or in some instances, treated with migraine-specific medications.

The Chronification of Headache

The concept of migraine as a progressive disease was first proposed by Mathew et al. [24], called *transformed migraine*. Simply put, the authors proposed that there is a population of individuals with episodic migraine that "transforms" into chronic migraine over time. Chronic migraine was not included as a diagnostic category in the original IHS headache classification, but it was included in the revised 2004 criteria. Transformed migraine is mentioned as an alternate although not preferred diagnostic term [11]. In 2006, Olesen et al. [25] proposed an appendix definition of chronic migraine because the original criteria were found to be impractical and a hindrance to research [26]. Others have suggested that it was not only headache that changed through the process of migraine chronification, but that other aspects of neurological function also were altered [27]. More recent epidemiological studies

Table 2. Risk factors associated with chronification of migraine

Nonmodifiable risk factors
Female gender
Lower socioeconomic status
Not married
Modifiable risk factors
Obesity
Comorbid pain
Head or neck injury
Stressful life events
Medication use

(*Data from* Scher et al. [18].)

have begun to identify numerous factors associated with migraine chronification, establishing the comorbidity of migraine with allergy and sinus disease [28].

The role of allergy and sinus pathology in migraine chronification is controversial. A theory proposed by Meggs [29], called *immunological switching*, has been suggested as a possible mechanism for how nasal disease could have an etiological role in migraine chronification [30•]. Simply put, immunological switching proposes that immune activation may stimulate the trigeminovascular system, which could facilitate the development of a headache that meets IHS diagnostic criteria for migraine. If the immune factors are chronic and unremitting (or frequent), they could serve as a risk factor for chronic headache. Clinically, at least in my practice, it is common for patients to report a worsening or chronification of migraines at the same time they are having frequent exacerbations of allergy symptoms. Recently, Lipton et al. [28] reported that migraine and allergy are significant bidirectional comorbidities, suggesting they share a common pathophysiological mechanism.

In addition, there may be structural mechanisms by which allergic factors and nasal/sinus pathology could chronically activate trigeminal signaling to produce headache. Nasal contact point could be one such example. Any disorder that would increase mucosal swelling in the area of a contact point could, in theory, exacerbate contact and increase physical pressure between the two opposing mucosal surfaces. These, in turn, could increase sensory traffic to the central nervous system and sensitize pain, promoting pathways resulting in headache. Over time, without addressing these provoking mechanisms, headache could become more intense or frequent. Whether this is more likely to occur in individuals with the genetic predisposition for migraine is unknown.

A number of factors have now been identified that associate with migraine chronification (Table 2). To transform or chronify episodic migraine, many of these associated factors require long-term temporal interaction between the migraine-susceptible nervous system and the predisposing environmental event. For example, obesity, medication, and stress are associated with transformation, but in most instances there is a longitudinal time-related exposure that appears necessary for transformation to occur. Potentially, the same concept may apply to migraine transformation in the environmental context of allergy. Possibly long-standing exposure to an allergic inflammatory/immune response may increase the likelihood of headache chronification through biochemical and possibly augmented by structural mechanisms. It is interesting to note that although the association of stress, medication, or obesity are accepted as etiological factors for migraine chronification, physical associations frequently observed in migraine patients are much less accepted as having an etiological association with chronification of migraine.

Chronification of Rhinosinusitis

As stated earlier, rhinosinusitis is classified as acute, acute recurrent, subacute, chronic, and acute exacerbations of chronic [17]. The differentiation of acute and chronic is based on both clinical symptomatology and duration of symptoms. Thus, it appears there is a spectrum of diagnoses that define rhinosinusitis as a potentially progressive disease. As in migraine, the acute form of the disease is considered a precursor to the chronic dimension of the disease, but a clear understanding or natural history of the chronification of rhinosinusitis has not been clearly described.

Pathophysiological Mechanisms to Consider

There are several mechanisms by which sinus or nasal pathology may lead to chronic headaches that are refractory to treatment. In a person with the genetic predisposition to migraine, sinus pathology may act as a trigger or risk factor for acute migraine. If that triggering mechanism persists over time (eg, > 6 months), it may serve as a mechanism for chronification of the underlying migraine pathophysiology. In other words, if the triggering event is chronic and persistent, it may potentially transform episodic into chronic migraine. This may occur because of the unremitting nature of the triggering event or may contribute to chronification as one of many transforming events occurring in close association with each other. For example, stress can be a risk event for both migraine and rhinosinusitis. As migraine chronifies, treatment may become less effective, forcing the individual to take more medication, which leads to a refractory headache pattern. Another potential mechanism for chronification may be the underlying pathologic process itself. As noted previously, there are important pain-sensitive structures in the nose and upper airway. If an individual without a genetic predisposition to migraine has a pathological condition in the sinus tract (eg, a nasopharyngeal tumor), this could drive the trigeminal pain pathways and generate the sensory drive to chronic headache that may for several reasons be refractory to treatment.

In both scenarios, a secondary headache is masquerading as a primary headache. Conversely, a person with frequent migraine misdiagnosed with sinus disease may be provided medication such as opioid analgesics that if used frequently and chronically could, independent of the underlying pathology, result in a medication overuse headache—again, headache patterns that can over time become refractory to treatment. Finally, one could consider scenarios of traumatic surgery for the observed pathology, which may or may not be the etiology of the presenting headache; yet the surgical trauma becomes a physical and/or psychological trauma, leading to a new post-traumatic headache that again is potentially refractory to treatment. Thus, there are a number of potential mechanisms and models by which sinus pathology or the belief in sinus pathology could lead to chronic refractory headache. However, little scientific study is available on which to support any of these hypotheses.

Potential Explanations for Headache Chronification and Sinus Disease

Seminal work by Burstein [31,32] has depicted the physiological process of migraine as a two-step process. The initial step involves activation of peripheral nociceptive mechanisms, which, if unabated, results in peripheral sensitization. In turn, the sensitized peripheral neurons bombard second-order neurons in the brainstem, resulting in sensitization of neurons in the nucleus caudalis of the trigeminal nerve. At this point, activation of central pain mechanisms is no longer required to continue central driving of the painful stimuli. Eventually, the pathophysiology is amplified to the point in which migraine becomes an allodynic pain state, which in and of itself is often refractory to standard treatment. More recent work by Durham [33] suggested that there is a peripheral spread of sensitization. Sustained activation of a single branch of the trigeminal nerve can, over time, activate and sensitize other branches of the trigeminal nerve. In other words, unremitting activation of the ophthalmic branch during migraine may lower the threshold for activation of the other divisions of the trigeminal nerve. To the point of this article, unremitting activation of the maxillary branch could likewise lower the sensory threshold of the ophthalmic branch of the trigeminal nerve, thus giving rise to a migraine-like headache secondary to nasal activation. Undoubtedly, further research is required to elucidate these mechanisms, but isolating neuronal function into specific tracts and functions no longer explains many clinical observations.

Calcitonin Gene–related Peptide in Migraine, Rhinosinusitis, and Temporomandibular Joint Disease

Calcitonin gene–related peptide (CGRP) has played a central role in migraine pathophysiology for several decades. In large part, CGRP was used to explain the mechanism of action of the triptans. Triptans and ergotamines are known to suppress the release of CGRP from trigeminal afferents when administered during an acute attack of migraine. CGRP, in turn, is known to be a potent vasodilator, and given that triptans were developed at a time when migraine was consider a "vascular" disease, the role of inhibiting vasodilatation was an attractive mechanism for explaining the efficacy of triptans.

Recently, a new class of compounds have demonstrated efficacy as an abortive agent for acute migraine. These compounds are antagonists of the CGRP receptor. Hence, they do not cause vasoconstriction, yet they have demonstrated efficacy in acute migraine [34,35]. This observation of clinical efficacy in acute migraine without vasoconstriction has generated interest in CGRP as a neuromodulator in the peripheral trigeminal system as well as the central nervous system. In the peripheral nervous system, CGRP lowers the sensory threshold of trigeminal afferents, whereas in the central nervous system it appears to be involved in central pain transmission.

Interestingly, CGRP levels are elevated in migraine [36], rhinosinusitis [37•], and temporomandibular joint disease [38]. This suggests that common pathophysiological mechanisms are shared by these three common pain disorders involving the trigeminal system.

Convergence Theory

The Convergence Hypothesis was proposed in 2000 to explain the clinical observation that multiple clinical phenotypes are observed in the pathophysiological event of migraine [39]. For example, an entire spectrum of disabling primary headaches in individuals with migraine responded to migraine-specific treatment (sumatriptan) [40]. Later, patients with nasal symptoms associated with their headache or self- or physician-diagnosed migraine when evaluated actually met criteria for IHS migraine and responded to migraine-specific treatment [41]. In addition, the Convergence Hypothesis provided a mechanism to interpret the symptom of muscle pain in the head and neck commonly observed during an episode of migraine.

Succinctly put, the Convergence Hypothesis suggests that input from all branches of the trigeminal nerve and input from upper cervical dermatomes are integrated in a group of brainstem nuclei called the nucleus caudalis of the trigeminal nerve, and all of these peripheral inputs can be observed in the event observed as migraine.

Conclusions

The concepts of migraine chronification and refractory headache are only now receiving legitimate attention by the medical community. Classification efforts have only recently been initiated to define chronic migraine and classify refractory headache. Both are surrounded by considerable debate

and have undergone several attempts to refine the definition of these conditions.

"Sinus headache" too is a clinical concept that has received little serious attention by the medical and research community. Early studies were quick to conclude that this clinical entity was nothing more than misdiagnosed migraine. However, despite the efforts to extinguish this concept from medical thought, it remains a common and real factor in the headache and otolaryngological fields. Undoubtedly, further research guided by an open mind is needed that will bring serious science and understanding to the relationship of sinus disease and headache.

Disclosure

Dr. Roger K. Cady is a consultant for Aradigm Corporation, GlaxoSmithKline, Jazz Pharmaceuticals, Merck & Co., Inc., and Ortho-McNeil Neurologics. He serves on the advisory board for Allergan, Atrix Laboratories, Inc., Capnia, Inc., Endo Pharmaceuticals, Inc., GlaxoSmithKline, MedPointe, Merck & Co., Inc., and Ortho-McNeil Neurologics. He has received research grants from Advanced Bionics, Alizyme, Allergan, Alexza, BioAlliance, Capnia, Inc., Forest Pharmaceuticals, GlaxoSmithKline, Jazz Pharmaceuticals, King Pharmaceuticals, MAP Pharmaceuticals, Merck & Co., Inc., Minster Pharmaceuticals, Neuralieve, Novartis, Ortho-McNeil Neurologics, Pfizer, Quality Metrics, Schwarz Biosciences, TorreyPines Therapeutics, Wyeth, and Zogenix.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Sheftell F, Dodick D, Cady R: **Sinus or migraine? Considerations in making a differential diagnosis.** *Neurology* 2002, **58(Suppl 6):**S10–S14.
2. Wolff HG: *Wolff's Headache and Other Head Pain,* edn 3. New York: Oxford University Press; 1972.
3. Headache Classification Subcommittee of the International Headache Society: **The International Classification of Headache Disorders, edn 2.** *Cephalalgia* 2004, **24(Suppl 1):**9–160.

4.• Mehle ME, Kremer PS: **Sinus CT scan findings in "sinus headache" migraineurs.** *Headache* 2008, **48:**68–71.

This article reviews imaging studies and the relationship of sinus pathology in migraine patients.

5. Shields G, Seikaly H, LeBoeuf M, et al.: **Correlation between facial pain or headache and computerized tomography in rhinosinusitis in Canadian and US subjects.** *Laryngoscope* 2003, **113:**943–945.
6. Cady RK, Dodick DW, Levin HL, et al.: **Sinus headache: a neurology, otolaryngology, allergy, and primary care consensus on diagnosis and treatment.** *Mayo Clin Proc* 2005, **80:**308–316.
7. Tosun F, Gerek M, Ozkaptan Y: **Nasal surgery for contact point headache.** *Headache* 2000, **40:**237–240.
8. Levin HL: **Functional endoscopic sinus surgery: evaluation, surgery, and follow up of 250 patients.** *Laryngoscope* 1990, **100:**79–84.
9. Clerico DM: **Sinus headaches reconsidered: referred cephalalgia of rhinological origin masquerading refractory primary headache.** *Headache* 1995, **35:**185–192.
10. Behin F, Behin B, Behin D, Baredes S: **Surgical management of contact point headaches.** *Headache* 2005, **45:**204–210.
11. Behin F, Behin B, Bigal ME, Lipton RB: **Surgical treatment of patients with refractory migraine headaches and intranasal contact points.** *Cephalalgia* 2005, **25:**439–443.
12. Cady RK: **Distinguishing "sinus headache" from migraine headache.** *Adv Stud Med* 2002, **2:**582–585.
13. Schreiber CP, Hutchinson S, Webster CJ, et al.: **Prevalence of migraine among patients with a history of self-reported or physician-diagnosed "sinus" headache.** *Arch Intern Med* 2004, **164:**1769–1772.
14. Eross EJ, Dodick DW, Eross MD: **The sinus, allergy and migraine study (SAMS) [abstract OR14].** *Headache* 2004, **44:**462.
15. Ishkanian G, Blumenthal H, Webster CJ, et al.: **Efficacy of sumatriptan tablets in migraineurs self-described or physician-diagnosed as having sinus headache: a randomized, double-blind, placebo-controlled study.** *Clin Ther* 2007, **29:**99–109.
16. Diamond ML: **The role of concomitant headache types and non-headache co-morbidities in the underdiagnosis of migraine.** *Neurology* 2002, **58(9 Suppl 6):**S3–S9.
17. Lanza DC, Kennedy DW: **Adult rhino-sinusitis defined.** *Otolaryngol Head Neck Surg* 1997, **117:**S1–S7.
18. Scher AI, Midgette LA, Lipton RB: **Risk factors for headache chronification.** *Headache* 2008, **48:**16–25.
19. Sahata RK, Dexter JD: **Sleep and headache: clinical review.** *Headache* 2005 **30:**80–84.
20. Alberti A, Mazzotta G, Gallinella E, Sarchielli P: **Headache characteristics in obstructive sleep apnea syndrome and insomnia.** *Acta Neurol Scand* 2005, **111:**309–316.
21. Levine HL: **Functional endoscopic sinus surgery: evaluation, surgery and follow-up of 250 patients.** *Laryngoscope* 1990, **100:**79–84.
22. Behin F, Behin B, Bigal ME, Lipton RB: **Surgical treatment of patients with refractory migraine headaches and intranasal contact points.** *Cephalalgia* 2005, **25:**439–443.
23. Tosun F, Gerek M, Ozkaptan Y: **Nasal surgery for contact point headaches.** *Headache* 2000, **40:**237–240.
24. Mathew NT, Reuveni U, Perez F: **Transformed or evolutive migraine.** *Headache* 1987, **27:**102–106.
25. Olesen J, Bousser MG, Diener HC, et al.; Headache Classification Committee: **New appendix criteria open for a broader concept of chronic migraine.** *Cephalalgia* 2006, **26:**742–746.
26. Bigal ME, Rapoport AM, Sheftell F, et al.: **The International Classification of Headache Disorders revised criteria for chronic migraine-field testing in a headache specialty clinic.** *Cephalalgia* 2007, **27:**230–234.
27. Cady RK, Farmer KU, Dexter JK, Schreiber CP: **Consensitization of pain and psychiatric comorbidity in chronic daily headache.** *Curr Pain Headache Rep* 2005, **9:**47–52.
28. Lipton RB, Buse DC, Serrano D, et al.: **Differences in rates of common comorbid medical and psychiatric conditions in chronic and episodic migraine individuals.** *Presented at the 22nd Annual Practicing Physician's Approach to the Difficult Patient*. Scottsdale, AZ; February 9–13, 2009.
29. Meggs WJ: **Neurogenic switching: a hypothesis for a mechanism for shifting site of inflammation in allergy and chemical sensitivity.** *Environ Health Perspect* 1995, **103:**54–56.

30.• Cady RK, Schreiber CP: **Sinus headache: a clinical conundrum.** *Otolaryngol Clin North Am* 2004, **37:**267–288.
This article is a good overview of sinus disease and headache.
31. Burstein R, Cutrer MF, Yarnitsky D: **The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine.** *Brain* 2000, **123:**1703–1709.
32. Burstein R, Collins B, Jakubowski M: **Defeating migraine pain with triptans: a race against the development of cutaneous allodynia.** *Ann Neurol* 2004, **55:**19–26.
33. Durham PL: **Inhibition of calcitonin gene-related peptide function: a promising strategy for treating migraine.** *Headache* 2008, **48:**1269–1275.
34. Olesen J, Diener HC, Husstedt IW, et al.: BIBN 4096 BS Clinical Proof of Concept Study Group: **Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine.** *N Engl J Med* 2004, **350:**1104–1110.
35. Ho TW, Ferrari MD, Dodick DW, et al.: **Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial.** *Lancet* 2008, **372:**2115–2123.
36. Goadsby PJ, Edvinsson L: **The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats.** *Ann Neurol* 1993, **33:**48–56.
37.• Bellamy JL, Cady RK, Durham PL: **Salivary levels of CGRP and VIP in rhinosinusitis and migraine patients.** *Headache* 2006, **46:**24–33.
This is an excellent study of CGRP in related pain disorders involving the trigeminal nerve.
38. Abbey MJ, Patil VV, Vause CV, Durham PL: **Repression of calcitonin gene-related peptide expression in trigeminal neurons by a theobroma cacao extract.** *J Ethnopharmacol* 2008, **115:**238–248.
39. Cady RK, Schreiber CP, Farmer KU, Sheftell F: **Primary headaches: a convergence hypothesis.** *Headache* 2002, **42:**204–216.
40. Lipton RB, Cady RK, Stewart WF, et al.: **Diagnostic lessons from the spectrum study.** *Neurology* 2002, **58(9 Suppl 6):** S27–S31.
41. Ishkanian G, Blumenthal H, Webster CJ, et al.: **Efficacy of sumatriptan tablets in migraineurs self-described or physician-diagnosed as having sinus headache: a randomized, double-blind, placebo-controlled study.** *Clin Ther* 2007, **29:**99–109.