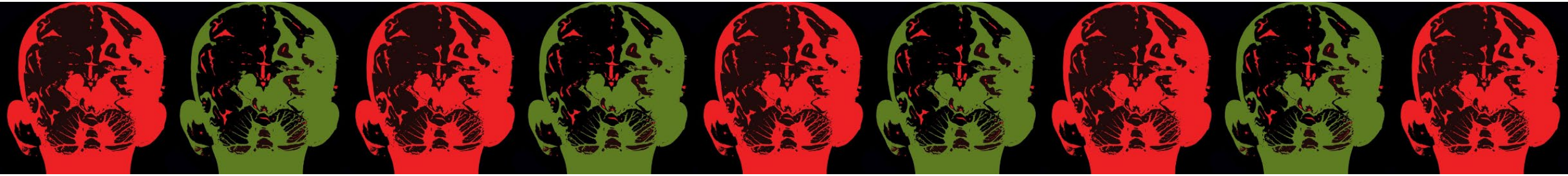


Who's on First? Psychiatric and Neurologic Management of Migraine

Charles Argoff, MD

Michael R. Clark, MD, MPH, MBA

BRAINWEEK™

Titles & Affiliations

Charles Argoff, MD

Professor of Neurology

Director, Comprehensive Pain Center

Albany Medical College

Michael R. Clark, MD, MPH, MBA

Professor of Psychiatry and Behavioral Sciences

George Washington School of Medicine and Health Sciences

Disclosures

Charles Argoff, MD

- Consulting Fee (e.g., Advisory Board): BDSI, Vertex, Teva, Amgen, Lilly, Neumentum, Collegium, Lundbeck, Gruenenthal, Redhill Pharma
- Contracted Research (Principal Investigators must provide information, even if received by the institution): Teva, Lilly, Amgen, Abbvie
- Speakers' Bureau: Abbvie, Amgen, Lilly, Teva, Lundbeck, Biohaven, Red Hill Pharma, Gruenenthal

Michael R. Clark, MD, MPH, MBA

- Nothing to disclose

Learning Objectives

- Describe prevalence of migraine in the US
- Explain the 3-question validated migraine screener
- Describe pathophysiology of migraine
- Using a case study, describe the psychiatric and neurologic treatment approaches

Introduction

Migraine: current concepts in pathophysiology and treatment

Did You Know?

- Migraine affects 20% of women in the US, and affects 3 times as many women as men
- Migraine is the second most common cause of disability by years living with disability (low back pain is number one)
- Compared with individuals without migraine, those with migraine have greater than 1.5-fold more office visits and greater than 2-fold more ED visits and inpatient admissions
- Migraine is associated with an estimated $36 billion in total costs in the US annually

Migraine Research Foundation. https://migraineresearchfoundation.org/about-migraineifacts. Accessed 10.31/20. Global Burden Disease. Lancet Neurol. 2018;17(11):954-976; BonafedeM et al. Headache2018;58(5):700-714; AHS Headache2019;59(1):1-18.

Migraine Is a Highly Prevalent Disease and Imposes a Heavy Burden[1]

39 million

people in the US are affected by migraine[2]

Impact on people with migraine:

1 in **3**

patients avoid planning activities because they fear having to cancel[3]

54%

of patients have attacks severe enough to require bed rest[4]

3 in **4**

patients report difficulty attending and functioning at work[5]

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2017;390:1211-1259. 2. Migraine Research Foundation. Migraine Facts. https://migraineresearchfoundation.org/about-migraine/migraine-facts/. Accessed January 27, 2020. 3. Lipton RB et al. *Cephalalgia*. 2003;23:429-440. 4. Lipton RB et al. *Neurology.* 2007;68:343-349. 5. Buse DC et al. *Mayo Clin Proc*. 2009;84(5):422-435.

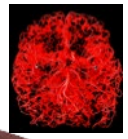
Would You Prefer a Simpler Way to Diagnose Migraine? ID Migraine

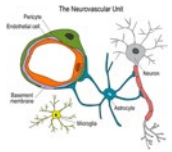
The 3-item ID Migraine screener is a validated tool to assist in rapidly making the migraine diagnosis:

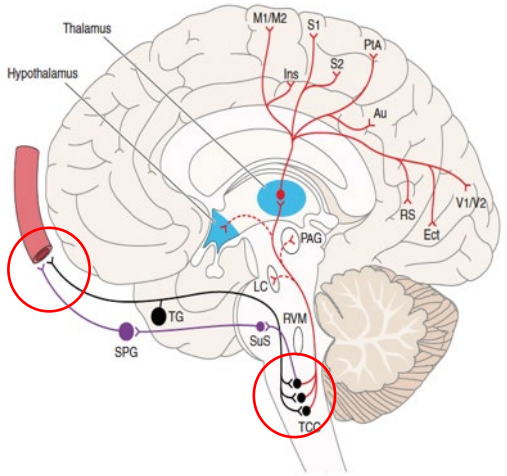
1. Has a headache limited your activities for a day or more in the last 3 months?
2. Are you nauseated or sick to your stomach when you have a headache?
3. Does light bother you when you have a headache?
   Answering yes to 2/3 indicated that a migraine diagnosis is likely (sensitivity of 0.81 95%CI 0.77-0.85)- 3/3 over 90% sensitive

Lipton RB et al. Neurology. 2003;61(3):375-382

The Anatomy of Migraine Headache





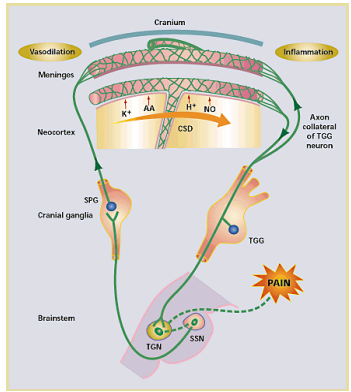


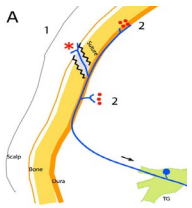
Ophthalmic Division of Trigeminal Nerve

Dura

Trigeminal Cervical Complex (TCC)

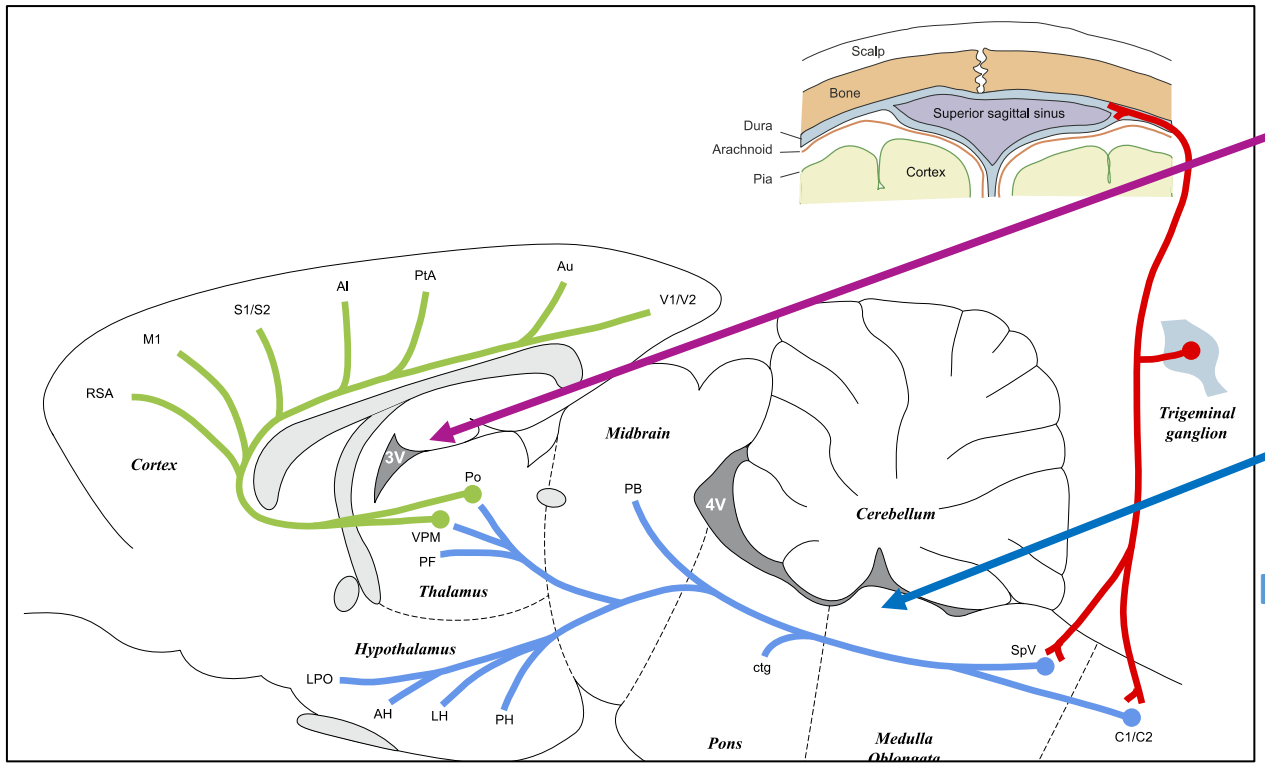
Trigeminal Ganglion





Pathways Mediating Migraine Symptoms

Symptoms associated with migraine are mediated by trigeminovascular neurons that project to multiple brainstem, thalamic, hypothalamic, and cortical areas[1-5]



Thalamocortical projections mediate photophobia, phonophobia, osmophobia, motor clumsiness, aphasia, and transient decline in cognitive functions

Spinal projections to brainstem, thalamic, and hypothalamic nuclei mediate irritability, anxiety, low energy, depression, yawning, frequent urination, teary eyes, loss of appetite, nausea, and sleep disturbances

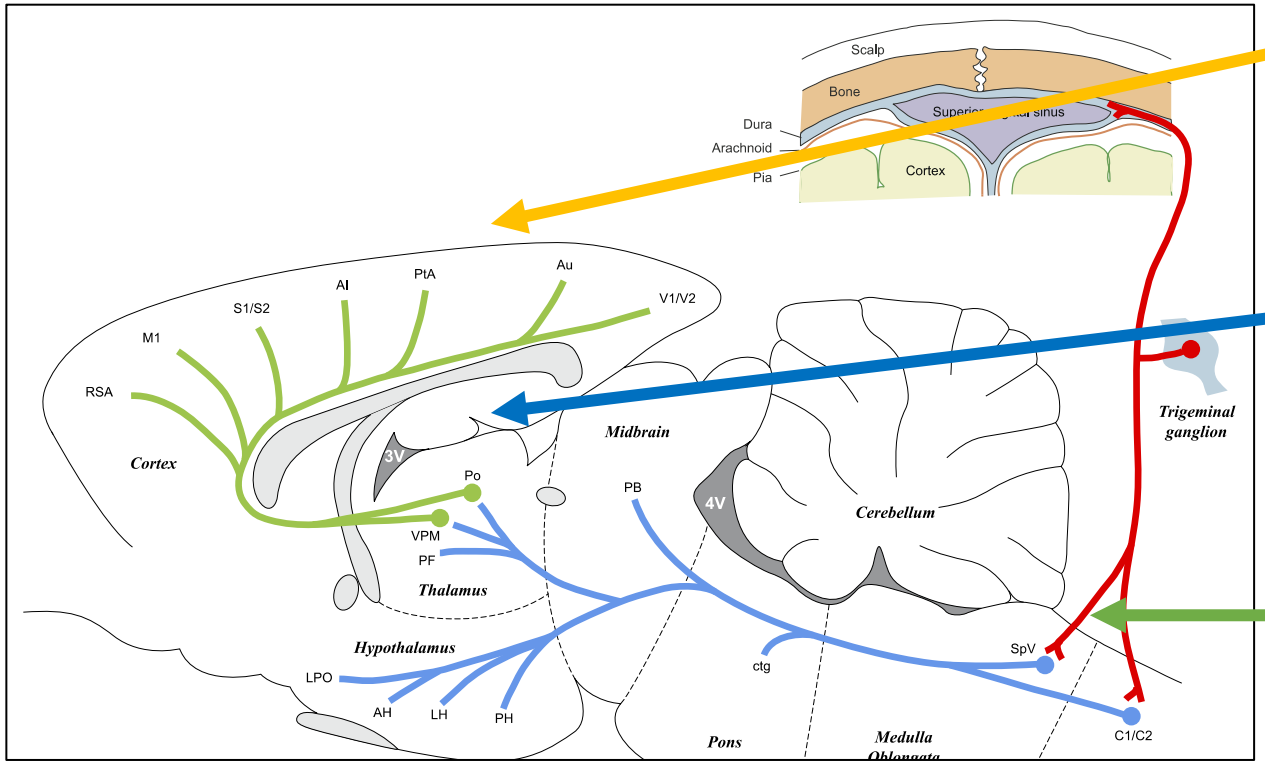
Exposure to light during migraine can bombard many cortical areas with many signals, which also causes a variety of migraine-associated symptoms[6,7]

Au, auditory cortex; Ect, ectorhinal cortex; Ins, insular cortex; LP, lateral posterior thalamic nucleus; M1/M2, primary and secondary motor cortices; PAG, periaqueductal gray; PB, parabrachial nucleus; Po, posterior; PtA, parietal association cortex; RS, retrosplenial cortex; S1/S2, primary and secondary somatosensory cortices; SSN, superior salivatory nucleus; TG, trigeminal ganglion; V1/V2, primary and secondary visual cortex; VPM, ventral posteromedial.

1. Burstein R, et al. *J Neurosci*. 2015;35(17):6619-6629.
2. Burstein R, et al. *J Neurophysiol*. 1998;79(2):964-982.
3. Malick A, et al. *J Neurophysiol*. 2000;84(4):2078-2112.
4. Noseda R, et al. *J Neurosci*. 2011;31(40):14204-14217.
5. Noseda R, Burstein R. *Pain*. 2013;154(suppl 1):S44-S53.
6. Burstein R, et al. *J Neuroophthalmol*. 2019;39(1): 94-102.
7. Noseda R, Copenhagen D, Burstein R. *Cephalalgia*. 2019;39(3): 1623-1634.

Pathways Mediating Migraine Chronification

Chronic migraine: a never-ending migraine attack[1-4]



Chronically hyperexcitable cortex mediates interictal hypersensitivity to light, sound, smell, and touch

Chronically sensitized thalamus mediates extra-cephalic allodynia and lowers the threshold for the next migraine attack

Chronically sensitized spinal trigeminal nucleus mediates the ongoing headache and cephalic allodynia

- Au, auditory cortex; Ect, ectorhinal cortex; Ins, insular cortex; LP, lateral posterior thalamic nucleus; M1/M2, pr and secondary motor cortices; PAG, periaqueductal gray; PB, parabrachial nucleus; Po, posterior; PtA, parieta association cortex; RS, retrosplenial cortex; S1/S2, primary and secondary somatosensory cortices; SSN, superior salivatory nucleus; TG, trigeminal ganglion; V1/V2, primary and secondary visual cortex; VPM, ventral posteromedial.

1. Burstein R, et al. *J Neurosci*. 2015;35(17):6619-6629.;
2. Borsook D, Dodick DW. *Neurol Clin Pract*. 2015;5(4):317-325.
3. Coppola G, et al. *J Headache Pain*. 2013;14(1):76.
4. Noseda R, et al. *Pain*. 2013;154(suppl 1):S44-S53.

Migraine Involves a Dysfunctional Trigeminal System

Peripheral components:[1-4]

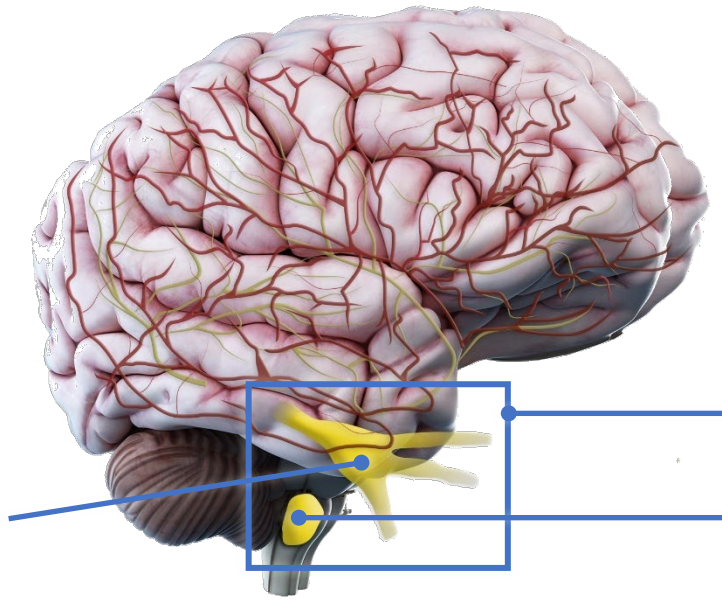
Trigeminal ganglion:

- Contains neurons with sensory fibers that:
  - Innervate cerebral vessels in the dura (middle meningeal artery)
  - Relay pain signaling to the central nervous system (CNS)

Central components:[1,3,5]

Trigeminocervical complex:

- Consists of neurons in the dorsal horn (C1–C2) and trigeminal nucleus caudalis (TNC)
- Relays pain signal from the periphery (C1–C2 and TG) to the thalamus and then the cortex



Feedback from a sensitized brain may further exacerbate pain signaling in the trigeminal system[1,3,6]

The trigeminal system has components on both sides of the blood–brain barrier[3,4]

1. Russo AF. *Annu Rev Pharmacol Toxicol*. 2015;55:533–552. 2. Eftekhari S, Edvinsson L. *Ther Adv Neurol Disord*. 2010;3:369–378.
3. Raddant AC, Russo AF. *Expert Rev Mol Med*. 2011;13:e36. 4. Edvinsson L. *Brit J Clin Pharmacol*. 2015;80:193–199.
5. Karsan N, Goadsby PJ. *Curr Neurol Neurosci Rep*. 2015;15:25. 6. Bigal ME, et al. *Headache*. 2013;53:1230–1244.
7. Gasparini CF, et al. *Curr Genomics*. 2013;14:300–315. 8. Burstein R, et al. *J Neurosci*. 2015;35:6619–6629.

Conclusions

- Migraine disease is common
- It is common for those experiencing migraine to also be experiencing a psychiatric comorbidity
- Although multiple recent advances in migraine pathophysiology have led to numerous new migraine mechanism based medical options, management of people experiencing migraine and psychiatric conditions concurrently often add a layer of complexity
- For those experiencing migraine as well as those treating migraine, there have never been more opportunities to collaborate to achieve personalized successful treatment outcomes

Cases

Management of migraine:
collaborative care between neurology and psychiatry

Case 1: Major Depression & Migraine

Presented By Michael Clark, MD - Psychiatrist

- 33 y/o woman w/refractory migraine and depressed mood
- Classic migraine since age 14, episodic w/increased frequency
- Treatment has progressed from abortive therapies to prevention
- Headaches less responsive and headache-free periods are less
- Depression was first diagnosed in college w/anhedonia and fatigue
- Treatment w/SSRIs caused sexual dysfunction +/- headache frequency
- TCAs caused sedation, bupropion worsened headaches
- Patient has been referred to neurology with the Dx chronic migraine

Discussion

Commentary by Charles Argoff, MD - Neurologist

- Would you diagnose chronic migraine?
- What are the risk factors for “chronification”?
- What are the priorities for successful management?
- Should treatment by psychiatry occur first, last, or in parallel?

Episodic and Chronic Migraine Have Distinct Characteristics

Episodic Migraine[1-3]	Chronic Migraine[1-3]
Intermittent disability	Persistent disability
Lower prevalence of common comorbidities like depression	Higher prevalence of common comorbidities like depression
May be associated with structural changes to the brain	Likely associated with structural changes to the brain

A chronic migraine diagnosis may highlight the importance of appropriate preventive treatment and management of comorbidities/medication overuse[4,5]

1. Aurora. *Cephalalgia.* 2009; **2.** Buse et al. *J Neurol Neurosurg Psychiatry.* 2010; **3.** Blumenfeld et al. *Cephalalgia.* 2011; **4.** Dodick. *N Engl J Med.* 2006; **5.** Silberstein. *Neurology.* 2000.

Risk Factors for Chronification and Suboptimal Management

- Acute medication use 10 or more days/month
- Use of barbiturates or opioids
- Poor acute migraine management

Lipton RB, et al. Neurology. 2015;84(7):688-695. 2. Katsarava Z, et al. Curr Pain Headache Rep. 2012;16(1):86–92

The Reality is that Migraine Prevention is Underutilized[1]

Guidelines recommend offering preventive therapy to patients who report **≥4 headache days per month** with some impairment, but why doesn't this happen?[1]

Among migraine patients who could benefit from preventive therapy

<15% currently use it[1]

80%

of patients who, in one study, initiated a trial of oral migraine preventive medicines were no longer taking preventive treatment

months later[2]

1. Lipton RB et al. *Neurology.* 2007;68:343-349. 2. Hepp Z et al. *Cephalalgia*. 2017;37(5):470-485.

Interactions Between Depression and Pain

- Patients with chronic pain and depression
  - Experience greater pain intensity
  - Feel they have less life control
  - Use more passive coping strategies
  - Report greater interference from pain
  - Exhibit more pain behaviors / disability
  - Have poorer surgical outcomes
  - Utilize more healthcare services
  - Retire from work earlier

Depression and Chronic Pain

- 60% of patients with depression report pain symptoms at the time of diagnosis
- After 8 years, depression was the best predictor of persistence of chronic pain symptoms in GP
- Patients with depression are at twice the risk of
  - Chronic daily headache
  - Atypical chest pain
  - Musculoskeletal pain
  - Low back pain

Major Depressive Disorder Critical Elements

- Sustained change in mood, self-attitude, and vital sense disconnected from varying circumstances
- Suicidality is not normal
- Anhedonia
- Deterioration in self-image
- Cognitive dysfunction
- Vegetative signs
  - Diurnal mood variation
  - Early morning awakening

Antidepressant Antinociception

- NE and 5-HT: ↑ diffuse noxious inhibitory control
- Alpha-adrenergic: ↓ NE stimulation of receptors
- NMDA: ↓ neuronal hyperexcitability
- Sodium / calcium channel: ↑ membrane stability

Antidepressants Summary

- TCAs are the old “gold” standard
  - Toxicity, serum level monitoring, metabolic/CV effects
- SSRIs have been overly relied on
  - Less efficacy in neuropathic pain, MDD still undertreated
  - Fewer side effects improve compliance
- SNRIs are the current focus
  - Independent efficacy in RCTs for CP & MDD
  - Norepinephrine a critical “co-factor” for neuropathic pain
- Remission of MDD is the overall goal
  - Achieves the greatest impact on chronification and refractory pain
  - May require augmenting antidepressants with adjuvant medications

Case 2: Addiction, Overuse, & Migraine

Presented By Michael Clark, MD - Psychiatrist

- 56 y/o man w/low back pain and headache s/p MVA w/TBI
- Pain everywhere, worst in low back, shoulders, and neck
- Pulsating headaches associated with sensitivity to light and noise, nausea, dizziness, vomiting, insomnia, poor concentration, fatigue
- Treated w/opioids, gabapentin, muscle relaxants, and OTC analgesics
- Any attempt at trying to be functional makes the pain much worse
- Activity is followed by extended periods of rest and more medications
- Treatment team includes PCP, PM&R, and Sports Medicine
- Referred to Neurology w/Dx post-concussive migraine; r/o addiction

Discussion

Commentary by Charles Argoff, MD - Neurologist

- Is post-concussive headache a subtype of migraine?
- Is medication overuse headache a subtype of chronic migraine?
- Are you more concerned about coordination of care or a SUD?
- Do you still use the term “aberrant drug-taking behavior” (ADTB)?
- Would you refer the patient to psychiatry?

Observations from the Clinic

- The patient is “stuck” repeating a deviant behavior
- The patient self-identifies as “needing” the medication
- The patient reports intolerable pain as the primary driver
- ADTB has become a way of life not a disruption of life
- The actual outcome is rejected as a temporary state
- The focus is on wishes not the consequences of choices

Paths to Disordered Behavior

- Innate drives by disease
  - Seek relief from pain
- Acquired drives by exposure
  - Take pain medications
- Provoked by social attitude resting on assumption, over-valued ideas, or role search
  - Assume the sick role
- Emotional arousal by expression
  - Relief from suffering

Is Aberrant Drug-Taking Behavior (ADTB) a Behavioral Disorder?

- Behaviors where either the control of choice is impaired or the exercise of choice is careless
  - Mechanisms and means
- Behaviors the practice of which obstruct human flourishing
  - Purposes and goals
- Essence of all behavioral disorders
  - Expressed through willful action

How to Approach ADTB

- Addressing the conflict of wills
- Confronting the reluctance to change
- Strengthening the relationship
- Striving to make better choices

Changing a Habit

- Identify the routine
- Experiment with rewards
- Isolate the cue

The Power of Habit: Why We Do what We Do in Life and Business, Duhigg, 2012

Cue Questions

- Where are you?
- What time is it?
- What's your emotional state?
- Who else is around?
- What action preceded the urge?

Cementing Change

- You can change to a better routine by planning for the cue and choosing a behavior that delivers the reward you are craving but you need a plan

- Design a plan
  - What can you do when the urge strikes?
  - Will it give you the same sense of satisfaction?
  - Analyze the result and modify the routine

The Final Ingredient

- Why do new habits fail at critical moments?
  - Doubt creeps in when alone and under stress
  - Surrender (to the new group) has not occurred
  - Suspending disbelief ≠ belief change is feasible

- A new habit does not repair why the old habit started in the first place

- A person must believe that the new habit will address the underlying cause of the old habit

Case 3: Borderline Personality Disorder

Presented by Michael Clark, MD - Psychiatrist

- 28 y/o woman w/uncontrollable headaches
- Common migraine treated successfully during adolescence
- Difficulties with gaining independence after college
- Experimented with recreational use of “everything”
- Multiple somatic symptoms are noted in the Review of Systems
- Angry with lack of progress and anxiety over symptoms
- Medications from multiple consultants purported to be world experts
- Spending excess time researching new therapies
- Requesting more consultations to find the “right fit”

Discussion

Commentary by Charles Argoff, MD - Neurologist

- Would you diagnose an active migraine syndrome?
- What are the pitfalls managing a difficult patient?
- How can a mental health referral help you?
- What mental health profession would you consult?

Borderline Personality Disorder

- Frantic efforts to avoid real or imagined abandonment.
- A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
- Identity disturbance: markedly and persistently unstable self-image or sense of self.
- Impulsivity in at least two areas that are potentially self-damaging (eg, spending, sex, substance abuse, reckless driving, binge eating).
- Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior.
- Affective instability due to a marked reactivity of mood (eg, intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
- Chronic feelings of emptiness.
- Inappropriate, intense anger or difficulty controlling anger (eg, frequent displays of temper, constant anger, recurrent physical fights).
- Transient, stress-related paranoid ideation or severe dissociative symptoms.

BPD and Chronic Pain

- 30% prevalence (Sansone and Sansone, 2012)
- Personality traits act as modifying factors that have the potential to complicate the treatment process rather than serve as the sole explanation for illnesses such as chronic pain (Vendrig, 2000)
- Axis I disorders in patients with chronic pain can affect the experience of chronic pain
- When controlling for depression, no association between increased pain severity and increased BPD symptomatology (Tragesser et al., 2010)

BPD and Chronic Pain

- Traits are useful in getting attention when ill, protecting oneself from misuse when vulnerable, and obtaining assistance during convalescence

- The emotions are not foreign but simply too much of a good thing

- Catastrophizing is maladaptive and characterized by overwhelming amplification of negative feelings and worries that undermine the capacity to function with discomfort (Sullivan et al., 2001)

Integrating Therapy

Goals for BPD and CP are similar:

- Improve functioning
- Improve ability to tolerate discomfort
- Improve coping skills for difficult situations
- Emphasize behaviors based on thoughts rather than feelings

Working with Traits

- Identify strengths and build on them
- Reframe vulnerabilities as assets not liabilities
- Describe ways to optimize survival
- Practice makes perfect but it takes repetition

Planning for Follow-up

- Plan on failure and be prepared not angry

- Respond to inappropriate behavior immediately
  - Ignore as much as possible
  - Set limits when necessary
  - Describe the appropriate alternative

- Reward desired behavior
  - Applaud ANY success
  - Make a fuss over progress
  - Discuss the patient's feelings

What Not To Do

- Don’t lower your expectations for the patient
- Don’t offer less than your expertise
- Don’t accept feelings as excuses
- Don’t quit unless the patient fires you

Conclusions

All of us can learn to succeed with “refractory” cases

Conclusions

- Migraine disease is common
- It is also common for those experiencing migraine to also be experiencing a psychiatric comorbidity
- Although multiple recent advances in migraine pathophysiology have led to numerous new migraine mechanism based medical options, management of people experiencing migraine and psychiatric conditions concurrently often add a layer of complexity
- For those experiencing migraine as well as those treating migraine, there have never been more opportunities to collaborate to achieve personalized successful treatment outcomes

Treat Comorbid Conditions

- A life in chaos produces more problems
  - Emotional distress has many causes
- Affective disorders are underdiagnosed
  - The benefits of overdiagnosing MDD > the risks
  - Treating MDD serves many purposes
- Substance use disorders ≠ ADTBs
  - Lack of efficacy
  - Inadequate treatment
  - Noncompliance