

21st Century Trends in Migraine Management

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Migraine Program Objectives

- Awareness of the Need for Aggressive Migraine **Prevention**
- Understand Migraine vs. Headache
 - Migraine is a common, disabling disease process
- Classification of Migraine
 - Episodic vs. Chronic
- Migraine Treatment
 - Preventative – Primary objective
 - Abortive – Secondary Consideration
- 21st Century Class of Migraine Prevention Drugs
 - CGRP Blockers

Migraine – a Disease Process

- Migraine is a chronic disease process similar to many other chronic medical conditions
- Migraine has a low mortality but high morbidity
- 38+ million Americans suffer with migraines
 - Only 60% are treated
 - 15 million U.S. Citizens are suffering needlessly
- Migraines are widely undertreated
- Most common medical cause of temporary, total disability in the U.S.
- Worldwide 1 billion migraine sufferers –
 - #2 on World Health Organization of cause of disability

Migraine Prevalence

- Female Predominate Disease
- Annually 1 out of 5 US females will have migraine
 - 6% of US males have migraine
- Chronic migraine: 3+ million migraineurs in U.S. alone
- CM puts a greater social, financial and emotional burden on patients than does EM
- CM with higher rates of disability
 - Annual medical costs 4 times higher
- CM with higher comorbidities: HTN, CAD, Lipids, COPD
Psychiatric Ds., Suicide

Diagnosing Migraine

- International Classification of Headache Disorders (ICHD)
 - Recurrent Headaches – at least 5 lifetime attacks
 - Duration: 4 – 72 hours
 - At least **two** of the following:
 1. Unilateral
 2. Pulsating
 3. Moderate or severe intensity
 4. Aggravated by routine physical activity.
 - Additionally **one** of:
 - Photophobia and phonophobia
 - Nausea and/or vomiting

Episodic Migraine (EM)

- Less than 15 headache/migraine days a month
- Have typical migraine features
 - Photophobia
 - Phonophobia
 - Nausea and/or vomiting
 - Pulsatile
 - Made worse with movement
- Triggered by weather, alcohol, stress, menses, others...
- Meets ICHD-3 criteria for migraine headaches

Chronic Migraine (CM)

- Fulfill the ICHD-3 criteria for migraine headaches
 - Headache symptoms for over 3 months
 - **15 or more headache days a month**
 - 8 out of 15 days must have classic migraine features
 - Migraine attacks aborted with triptan treatment – but have lack of adequate headache control
- Need to exclude Analgesic Overuse Headaches
 - **Common in most CM sufferers**
- Exclude Occipital Neuralgia & generic headaches
- Chronic Daily Headache is NOT Chronic Migraine

Progression to Chronic Migraine

- EM progresses to CM at 3% annually
- Risk Factors:
 - Head Injuries
 - Obesity
 - Sleep Apnea
 - Depression
 - Stressful Life Events: divorce, job or job changes
 - Major Life Changes
 - Controlled substance analgesic overuse

Migraine – Major Life Burden

- WHO – World Health Organization ranks migraine as one of the most debilitating medical illnesses
- Only 10% of patients on preventative medications
 - 3.8 million of 38 million migraine sufferers
- Migraine is associated with:
 - Personal disease burden – poor Quality of Life
 - Societal burden of chronic, recurrent pain
 - Chronic disability
 - High financial costs
- Chronic Migraine remains under-diagnosed and under-treated
 - Only 5% of CM patients receive correct diagnosis/treatment

Comprehensive Treatment

- Identify what types of headaches patient has:
 - **Multiple headache disorder is common**
 - Migraines – most common neurological disorder
 - “Sinus” – really migraines
 - Tension-type
 - Occipital Neuralgia
 - Analgesic Overuse
 - Cervicalgia
- Eliminate Causes
 - Stop analgesics, treat occipital neuralgia/cervicalgia
 - Educate patient about “sinus” headaches = “Unicorns”
- **Headache Diary** – important clinical tool for all CM

Comprehensive Treatment (cont.d)

- Patient Education on Realistic Expectations
 - They have a chronic medical condition
 - 3-4 months of aggressive preventative treatment needed to get headaches controlled
 - “Quick Fix” Interventions
 - Wean off analgesics and **ALL** narcotics
 - Occipital nerve blocks
 - Start preventative therapy immediately
 - Explain that Headache Diary is important for both the patient and you to monitor their progress
 - Patient may be 50-70% better but tell you nothing has changed. Diary helps patient to recognize improvement

Comorbid Conditions

- Depression is common in migraine population
 - Start aggressive depression therapy immediately
- Blood pressure control
 - Low normal range
- Screen for Sleep Apnea
- Obesity Counseling – dietary consultation
- Get your patient to do some type of exercise
 - **Sitting is the new smoking.**
- Cardiac, diabetes, lipid screening

Depression & Anxiety

- Prevalence of Neuropsychiatric Disorders is 3X Higher in Migraine Population
 - Depression – up to 50%
 - Anxiety – 30-40%
 - Other Phobias
 - Suicide
- Common comorbidity in all headache patients
- Patient may not be aware of condition
- High index of suspicion in All Chronic Migraine
 - Treat with effective SSRI or SNRI

Obesity

- Obesity is a national epidemic in the U.S.
- Higher in the CM population
- Multiple Medical Complications
 - Hypertension
 - Cardiac disease
 - Hyperlipidemia
 - Sleep apnea – not a benign condition
 - Chronic Insomnia
 - Metabolic Syndrome
- Get Dietary Consultation and Counseling

Sleep Apnea

- Frequently not recognized
 - Insomnia
 - Daytime Fatigue
 - Not always easy to diagnose
- Get a sleep study – Untreated Sleep Apnea is **NOT** benign
- Untreated Sleep Apnea Morbidity
 - Obesity – Metabolic Syndrome
 - Diabetes
 - Hypertension
 - Hyperlipidemia
 - Cardiac disease – MI, arrhythmias
 - Sudden Death

Insomnia & Apnea

- Chronic insomnia is common in CM
- Sleep deprivation leads to poor health & medical disease
- Excessive daytime sleepiness
 - Increase risk for MVA
 - Risk of losing job
 - Drop out of school
- Migraine patients typically have poor sleep hygiene
 - Counsel on good sleep habits
 - Computer, TV, news, video games, eating late

Botox for Chronic Migraine

- Botox has been demonstrated to be effective in the long term treatment of **Chronic Migraine only**
 - The only headache type approved for Botox by FDA
- No clinical evidence that Botox is effective for:
 - Episodic Migraine or High Frequency EM
 - Chronic Tension-type Headaches
 - Chronic Daily Headaches (Persistent Daily Headache)
- Need to see a $\geq 50\%$ reduction in migraine days to say Botox was effective for a given patient with CM
 - Maximum benefit after 3 treatments – 9 months
 - Headache diary – Check at every visit
- Placebo rate in migraine studies is about 40%

Botox for Chronic Daily Headache

- No scientific evidence of therapeutic efficacy
- Insurance & Medicare have multiple restrictions on approval of use of Botox for CM
 - Meet ICHD criteria for *chronic migraine* headaches
 - Need adequate documentation of trial/failure of multiple **preventative agents**
 - Anticonvulsants, SSRIs, SNRIs, beta-blockers, verapamil, muscle relaxants
 - Some response to triptan therapy is needed
 - Document migraines ≥ 15 days with headache diary
 - Failed physical therapy and “other modalities”

Insurance Companies Lie

- Many patients want Botox for their headaches
- Media hype – “Botox is *the treatment* for headaches”
- “My friend had it and it worked great.”
- Insurance companies tell patients they will cover Botox
 - What they don’t tell patients is under what conditions
 - Complete failure to inform public under what criteria Botox will be paid for – “Just have your doctor call.”
 - “I’m entitled to Botox because my insurance told me they will cover it.”
 - Authorization – time-consuming, painful prior authorization
 - Cost: A single treatment with Botox for CM: \$1250
 - Most do not meet necessary criteria for Migraine Botox therapy

Botox for Chronic Migraine

- Botox may work for your CM patient
 - Typically adjunctive therapy
- Careful patient selection is important
- Meets ICHD classification for CM
- Eliminate other causes of headache
- Meets Medicare/Insurance requirements
- Response Rate: 3 out of 4 CM patients respond to Botox
- Need experienced physician giving Botox
 - Follow the published Botox Migraine Protocol

Migraine - Prevention is Key

- Prevention of headache is key in all migraine & headache treatment
- Preferred therapy – antidepressants
 - Prozac, Lexapro, Celexa
 - Effexor XR, Savella
 - Amitriptyline, nortriptyline, imipramine
- Other Migraine preventatives
 - Topiramate
 - Valproic Acid
- Baclofen
- Beta-blockers

20th Century Preventative Therapies

- Start immediately at first visit
- Pick initial drug depending on comorbidities
- Use therapeutic dosages
 - SSRIs – 40-80 mg
 - SNRIs – 75-400 mg
 - Tricyclics – up to 75 mg nightly
 - Baclofen 20-80 mg daily
 - Topiramate – 200-600 mg daily
 - Affects OCP therapy over 200 mg daily dose
- Botox – only about 3% of all migraine patients

21st Century

Migraine Prevention Therapy

- Total shift in Migraine Treatment Paradigm
- CGRP Monoclonal Antibodies – for Migraine Prevention
 - 1st new anti-migraine drug developed in over 25 years
- Designed from the ground up to **block initiation of the migraine cascade**
- CGRP (calcitonin gene related peptide)
 - Inflammatory neuropeptide – released from the trigeminal nerve terminals
 - Modulates pain and vasodilation
 - Involved in the early migraine cascade to full blown headache
- New MABs block effect of CGRP in migraine genesis

CGRP Blockers for Migraine

- New class of drug therapy for **Migraine Prevention**
 - Indicated for both Episodic and Chronic Migraine
- CGRP Monoclonal Antibodies
 - Attach at the CGRP Receptor site blocking CGRP-R
- Or:
 - Attach to the CGRP ligand, prevention receptor binding
- Mechanism of Action
 - Inhibit pain transmission
 - Decrease artery dilation
 - Block neurogenic inflammation
- High safety profile
 - No drug-drug interaction
 - Do not have any immunomodulatory effect
 - Not renally or hepatically metabolized

CGRP Blockers For Migraine

- Use in patients with 4 or more migraine days a month
 - High frequency Episodic Migraines
 - Chronic Migraine
 - Prolonged episodic migraines
- Self-injected, once a month therapy
 - Ajovy™ (TEVA) has a once every 3 month dosing
- **Have all Migraine patients keep a Headache Diary**
 - Will need this for prior authorizations

CGRP-R Blocker

- **Aimovig™** - (erenumab-aooe) – Amgen
 - The only CGRP Receptor Blocker
 - 100% human IgG₂ MAB
 - FDA approved May 17, 2018
 - Specifically blocks only the CGRP receptor
 - 70 mg & 140 mg sub-q monthly dosing
 - No CGRP receptor agonist activity
 - Approved for both EM & CM
 - 4 or more migraine days a month
 - Side effects: injection site reaction, constipation, hypersensitivity reactions

CGRP Ligand Blocker

- **Ajovy™** - (fremanezumab-vfrm) – TEVA
 - CGRP ligand blocker – fully humanized IgG₂ MAB
 - Targets CGRP (calcitonin gene-related peptide)
 - FDA Approval - Sept. 14, 2018
 - Approved for EM and CM
 - ≥ 4 migraine days/mo
 - Dosing:
 - Monthly: 225 mg sub-q monthly
 - Quarterly: 675 mg sub-q every 90 days
 - Side effects: injection site reaction, hypersensitivity reactions

CGRP Ligand Blocker

- **Emgality™** - (Galcanezumab-gnlm) – Eli Lilly
 - CGRP ligand blocker - fully humanized IgG₄ MAB
 - Targets CGRP(calcitonin gene-related peptide)
 - FDA Approval – September 27, 2018
 - Approvals for EM and CM
 - Has been studied in Botox Failure migraine patients
 - Dosing:
 - 240 mg loading dose then 120 mg sub-q monthly
 - Side effects: injection site reaction, hypersensitivity reactions

CGRP Ligand Blocker

- **Eptinezumab** – Alder
 - CGRP blocker - fully humanized IgG₁ MAB
 - Targets CGRP(calcitonin gene-related peptide)
 - FDA Approval pending – PDUFA: Feb, 2020
 - Approvals for EM and CM pending
 - Unique Dosing:
 - 100 mg or 300 mg IV infusion quarterly
 - Side effects (>2% over placebo)
 - nasopharyngitis (6.3%), URI (4.0%), nausea (3.4%), UTI (3.1%), arthralgia (2.3%), dizziness (2.6%), anxiety (2.0%), fatigue (2.0%)

Use of CGRP MABs & Botox®

- CGRP MABs
 - 60% of all migraineurs could be candidates
- Botox®
 - To meet FDA indications – 3% of migraine patients qualify
 - Indicated for Chronic Migraine only
 - No scientific evidence effective for ANY other headache type
 - Must have failed at least 3 other migraine preventatives
- CGRP MABs are highly effective in Migraine Prevention
 - Commonly reducing migraine days by over 50%
 - With CGRP therapy, migraineurs no longer meet criteria for Chronic Migraine, therefore Botox® is not indicated

Abortive Migraine Therapy

- Secondary concern for most migraine patients
- Therapeutic goal is 4 headache days or less a month
- Need to avoid Analgesic Overuse Headaches
- Triptans are the mainstay in acute migraine treatment
 - Tablets
 - Sumatriptan Injections
 - Onzetra Nasal System (sumatriptan)
- NSAID therapy
 - Gel cap preparations
 - Cambia – uniquely different diclofenic acid therapy
- Anti-emetic therapy
 - Tablets – Zofran, Reglan, Phenergan
 - Suppositories
 - Phenergan, Compazine

Quality of Life for Migraineurs

- Keep your patients out of the Emergency Room
 - Equip them all with **Migraine Rescue Kit**
 - **Injectables**
 - Sumatriptan
 - Toradol
 - DHE-45
 - **Anti-emetics**
 - Tablets
 - Suppositories
 - **AVOID NARCOTICS ALL TOGETHER**
 - Fiorinal/Fioricet, Hydrocodone, Tramadol

Future Migraine Therapies

- Migraine Abortive Therapy
 - **Ditans**
 - Selectively bind to the 5-HT_{1F} receptor - agonist
 - Lasmiditan - 1st ditan that will be released – 2019 Q4?
 - **Gepants** – Migraine Abortive Therapy
 - 2nd generation (CGRP) receptor antagonists
 - Use for treatment of acute migraine
 - No vasoconstrictive effect – may be safe in cardiac patients
 - Rimegepant, Ubrogepant and Atogepant
 - All in Phase 2 or 3 studies
 - May be seen sometime mid 2020

Summary – Migraine

- Migraine contributes significantly to the burden-of-disease related disability in the U.S. & worldwide
- CM is associated with multiple system disease
 - Higher morbidity
 - Higher incidence of neuropsychiatric illness
- Screen patients carefully for comorbid conditions
 - Sleep Apnea
 - Depression/Anxiety
- Treat aggressively with Preventative Therapy
 - 21st Century Preventative Agents – CGRP Blockers
 - Do not use narcotics
- Dramatic improvement in Quality of Life of your patients

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