Practical points in management of difficult to treat primary headache

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Practical points in management of difficult to treat primary headache

- Definition/meaning from Longman/Cambridge Dictionary
  - Difficult to treat
    - Hard to treat
    - Refractory to treat
  - Very difficult to treat
    - Intractable to treat
    - Refractory to treat (Neurol Sci. 2013;34 (Suppl 1):S109-12)

Difficult/refractory/intractable to treat primary headache

- Refractory/intractable: formal term for medicine – definition – debatable
  - Lack of response
  - Failure to respond

Neurol Sci 2013;34(Suppl 1):s109-12

Difficult/refractory/intractable to treat primary headache

- Refractoriness:
  - To acute treatments
    - Failure to respond to standard treatments or intolerant to the specific drugs
  - To preventive treatments
    - Failure to respond to standard treatments or intolerant to the specific drugs

Neurol Sci 2013;34(Suppl 1):s109-12

Difficult/refractory/intractable to treat primary headache

- Refractoriness to acute treatments: definition
  - Graded classification: class I-III intractability
    - Class I: mildest – failure to achieve a significant response to *two different classes of NSAIDs* or *combination analgesics*
    - Class II: moderate condition – *inadequate response to NSAIDs along with triptans, antiemetics or ergot derivatives*
    - Class III: worst/most severe situation – *failure to all analgesics, oral or parenteral opioids and corticosteroids*

Headache 2010;50:1499-506

Difficult/refractory/intractable to treat primary headache

- Refractoriness to preventive treatments: definition
  - Graded classification: class I-IV
    - Class I: failing *a single trial* of a proven preventive therapy *or combination therapies*
    - Class II: failing *two of these drugs*
    - Class III (severe condition): failure of an adequate trial of *3 preventive agents*
    - Class IV (every severe from): *failed aggressive infusions or detoxification protocol*

Headache 2010;50:1499-506

Difficult/refractory/intractable to treat primary headache

- Treatment failure: not specifically defined
  - Acute treatment
    - Headache response/pain free at 2 hour
    - Sustained headache response/pain-free response at 24 hour
  - Preventive treatment
    - Reduction in frequency/severity of headache attacks
      - < 50% reduction
    - Number of working days lost
    - Headache-related disability

Neurol Sci 2008;29 (Suppl 1):s55-8

Practical points in management of difficult to treat primary headache

- Treatment failure: etiology
  - Wrong diagnosis: re-evaluation
    - Primary vs secondary headache
    - Migraine vs tension-type headache or other primary headache

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- Differential diagnosis: primary vs secondary headache
  - Sinus headache
  - Intracranial hypertension/hypotension
  - Cerebral venous sinus thrombosis
  - Space occupying lesion
  - Ventricular tumor
  - Chiari malformation
  - AVM
  - MELAS
  - Medication overuse headache

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- Treatment failure: etiology
  - Wrong diagnosis: re-evaluation
    - Migraine vs tension-type headache or other primary headache

Practical points in management of difficult to treat primary headache

- Treatment failure: etiology
  - Wrong diagnosis: re-evaluation
    - Migraine vs tension-type headache vs cluster headache

The Journal of Headache and Pain 2019; 20:57

Practical points in management of difficult to treat primary headache

- Differential diagnosis: migraine vs other primary headache
  - Tension-type headache
  - Cluster headache
  - Paroxysmal hemicrania
  - Hemicrania continua

Practical points in management of difficult to treat primary headache

- Treatment failure: etiology
  - Wrong diagnosis
  - If correct diagnosis
    - Acute treatment
      - Inappropriate drug

Practical points in management of difficult to treat primary headache

- Medication selection
  - Step care within attacks
    - Initiating treatment with a low-cost nonspecific analgesic medication and, if unsuccessful,
    - They can advance themselves after several hours to more migraine-specific treatment options along a stepwise pattern within each individual attack
    - One of the drawbacks
      - Leading to suboptimal efficacy of treatment as many migraine-specific treatments, best taken early in the attack rather than several hours after an initial failed treatment

CONTINUUM (MINNEAP MINN)2018;24(4, HEADACHE):1032–1051

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- Medication selection
  - Stratified care
    - The patient determining which attacks will respond to various treatments and is given the autonomy to make the appropriate treatment decision based on his or her personal experiences and preferences
    - Best considers individual variance in headache severity and associated features such as nausea or vomiting
    - This allows the patient ability to make his or her own treatment decisions based on their unique needs
    - Stratified care is equated with higher patient satisfaction and also with decreased health care costs

CONTINUUM (MINNEAP MINN)2018;24(4, HEADACHE):1032–1051

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- Headache intensity and disability
  - Mild to moderate in intensity: acetaminophen, NSAIDs; if unsuccessful, triptans being tried
  - Severe disabling: triptans if no contraindications

Neurotherapeutics (2018) 15:274–290

Practical points in management of difficult to treat primary headache

- Treatment failure: etiology
  - Wrong diagnosis
  - If correct diagnosis
    - Acute treatment
      - Inappropriate drug
      - Inadequate dose

CONTINUUM (MINNEAP MINN)2018;24(4, HEADACHE):1032–1051

Practical points in management of difficult to treat primary headache

- Treatment failure: etiology
  - Wrong diagnosis
  - If correct diagnosis
    - Acute treatment
      - Inappropriate drug
      - Inadequate dose
      - Inappropriate time

Practical points in management of difficult to treat primary headache

- Treatment failure: etiology
  - Wrong diagnosis
  - If correct diagnosis
    - Acute treatment
      - Timing of administration
        - » As treatment is typically more effective when taken early in the headache phase

CONTINUUM (MINNEAP MINN)2018;24(4, HEADACHE):1032–1051

Practical points in management of difficult to treat primary headache

- Treatment failure: etiology
  - Wrong diagnosis
  - If correct diagnosis
    - Acute treatment
      - If true treatment failure: considering prevention

Practical points in management of difficult to treat primary headache

- Treatment failure: etiology
  - Wrong diagnosis
  - If correct diagnosis
    - Acute treatment
      - If true treatment failure: considering prevention
        - » Indication for migraine prevention
          - One criteria: contraindication to , failure, or overuse of acute treatments

Headache 2019;59:1-18

Practical points in management of difficult to treat primary headache

- Treatment failure: etiology
  - Wrong diagnosis
  - If correct diagnosis
    - Preventive treatment
      - Ignored preventive treatment

Headache 2019;59:1-18

Practical points in management of difficult to treat primary headache

- Treatment failure: etiology
  - Wrong diagnosis
  - If correct diagnosis
    - Preventive treatment
      - Ignored preventive treatment
      - Inadequate dose

Am Fam Physician. 2019;99:17-24.

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Am Fam Physician. 2019;99:17-24.

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  - Wrong diagnosis
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    - Preventive treatment
      - Inadequate dose
      - Inappropriate drug
      - Inadequate duration

Am Fam Physician. 2019;99:17-24.

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  - Wrong diagnosis
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    - Preventive treatment
      - Inadequate dose
      - Inappropriate drug
      - Inadequate duration
      - Treatment non-adherence
      - No withdrawal of overused medications?
      - Unrecognized exacerbating factors
      - Unrecognized co-morbidity: OSA, psychiatric conditions

Neurol Sci 2008;29 (Suppl 1):s55-8

Practical points in management of difficult to treat primary headache

- Medication overuse: criteria

Medication overuse headache [internet]. July 9, 2016 [cited 2019 Sep 25]. Available from: https://americanmigrainefoundation.org/resource-library/medication-overuse-headache-2/

Practical points in management of difficult to treat primary headache

- Chronic migraine with medication overuse
  - Most Authors have stressed the importance of treatment plans
    - Promoting the withdrawal of overused medications
    - Helping patients to overcome their withdrawal symptoms
  - These treatment plans: different across studies
    - Use of NSAIDs, dihydroergotamine infusion, oral/intravenous steroids, anti-emetics
    - Treatment in OPD or IPD
  - Preventive approaches: varying – no or presence
    - Topiramate: two multi-center; one single-centre

Neurol Sci. 2008;29:S55-8; Headache 47:1277–1281

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Diagnosis of medication-overuse headache (MOH) according to ICHD-3, must meet criteria A-C for the diagnosis of MOH:

- Headache on 15 or more days per month AND a pre-existing headache disorder
- Overuse of acute and/or symptomatic headache drugs for over 3 months (Regular intake of drugs on greater than or equal to 10 days/month for ergotamines, triptans, opioids, and combination analgesics and on greater than or equal to 15 days per month for acetaminophen, ASA and NSAIDs)
- No better explanation by another ICHD-3 diagnosis

Medication overuse headache by drug class and duration of headache:

- Ergotamine-->10 days/month for over 3 months
- Triptan-->10 days/month for over 3 months
- ASA-->15 days/month for over 3 months
- NSAIDs-->15 days/month for >3 months
- Acetaminophen/paracetamol-->15 days/month for over 3 months
- Opioids-->10 days/month for over 3 months
- Combination analgesics-->10 days/month for over 3 months
- Multiple drug classes-->10 days/month for over 3 months

J Headache Pain. 2010;11:373-7; Cephalalgia 2018;38:1–211

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- Medication overuse headache
  - Clinical evidence shows that the majority of patients with this disorder improve after discontinuation of the overused medication, as does their responsiveness to preventative treatment
  - Simple advice on the causes and consequences of 8.2 *Medication-overuse headache* is an essential part of its management and can be provided with success in primary care.
  - An explanatory brochure is often all that is necessary to prevent or discontinue medication overuse.
  - Prevention is especially important in patients prone to frequent headache

Cephalalgia 2018;38:1–211

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- Medication overuse headache
  - Withdrawal and preventive treatment
    - Chronic headache and medication overuse headache
      - Often reverting to episodic headache when preventive medication being initiated and the intake of acute medications limited

Lancet Neurol 2019;18 Sep:891-902

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- Medication overuse headache
  - A small study in Denmark
    - Randomized to a 2-month period of either no acute medication (programme A, n=35) or acute medication restricted to 2 days per week (programme B, n=37)
    - Withdrawal followed by appropriate preventive drug treatment if indicated
    - Reduction in monthly headache days after 6 months: 46% in programme A compared with 22% in programme B

Cephalalgia 2018;38:225-36

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- Medication overuse headache
  - The COMOESTAS multicentre and open-label study involved 492 of 694 patients
    - Prophylactic drugs were started in parallel with medication withdrawal
      - Frequency reduction of 44% in headache days occurred within the first month
      - and maintained and further increased to 60% after 6 months
      - 68% reverted to episodic headache
      - Coexisting depression, anxiety, and quality of life: markedly improved

Cephalalgia 2017; **37:** 1115–25.

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- Medication overuse headache
  - A 1-year open-label, multicentre study in 56 patients
  - Patients randomly assigned to
    1. Receiving prophylactic treatment without withdrawal
    2. Standard out-patient withdrawal programme without prophylactic treatment
    3. No specific treatment
  - The prevention group greatest decrease in headache frequency compared with the withdrawal group
  - At month 12, in the prevention group having more than 50% reduction in monthly headache frequency compared with the withdrawal group

Cephalalgia 2009; **29:** 221–32.

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- Medication overuse headache
  - Two similarly designed randomized, placebo controlled, multicentre studies in the USA and in the EU investigated the safety and efficacy of topiramate
  - A post hoc analysis in the subset of patients with medication overuse
  - In the US trial: no difference in reducing migraine and its frequency
  - however, the EU trial show a significant reduction

Cephalalgia 2009; **29:** 1021–27.

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- Medication overuse headache
  - Some cases, might be only minimal or no improvement when preventive medication initiated and the intake of acute medications limited
    - The treatment outcomes of 175 patients with medication overuse headache treated in the Danish Headache Centre in 2002 and 2003
      - During the first 2 months after withdrawal, no preventive medication offered
        - » 45% of patients: reduction in headache frequency by more than 50%,
        - » 48%: not improve in terms of headache frequency
        - » 7%: increase in headache frequency
        - » 80 of 88 patients with no improvement 2 months after drug withdrawal subsequently responded to pharmacological or non-pharmacological prevention

Cephalalgia 2006; **26:** 1192–98

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- Medication overuse headache
  - The use of onabotulinumtoxinA (botox) was investigated in patients with chronic migraine in two placebo-controlled trials
  - The subgroup of patients with medication overuse in the two trials assessed in secondary analyses
  - Botox superior to placebo for most efficacy endpoints

Headache 2010; **50:** 921–36. Cephalalgia 2010; **30:** 804–14

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- Medication overuse headache
  - A randomized study in the Netherlands investigated the add-on efficacy of botox to ambulant withdrawal therapy in the treatment of medication overuse headache
  - They randomly assigned 179 adults to botox injections (155 units) or placebo
  - the number of headache days reduced by 26・9% in the botox group (n=90) and by 20・5% (n=89) in the placebo group
  - This study was small compared with the PREEMPT studiesand had a shorter observation time, and the small amount of botox injected into the forehead might exert biological activity

Brain 2019; 142: 1203–14

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- Medication overuse headache
  - A systematic review of treatment strategies for medication overuse headache:
    - Evidence to support early withdrawal of overused medications alone was scarce
    - The addition of prophylactic medication to early discontinuation leading to a better outcome than early discontinuation alone
    - For patients with chronic migraine and medication overuse headache, the RCTs supporting the use of botox and topiramate without early discontinuation of overused medication

Cephalalgia 2016;36:371–86.

Practical points in management of difficult to treat primary headache

- Medication overuse headache
  - Further support of the potential efficacy of prophylactic treatment without acute medication withdrawal
    - Fremanezumab reduced the frequency and severity of headaches in patients with chronic migraine and medication overuse headache (N Engl J Med 2017;377:2113–22)
    - Fremanezumab significantly reduced the frequency of headache of at least moderate severity without withdrawal in patients with medication overuse at baseline by 4.7 days in the quarterly injections and 5.2 days in monthly injections, compared with a 2.5 days reduction in the placebo group (Headache 2018; 58(S2): 76–7.)

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- Medication overuse headache
  - Erenumab 667 patients with chronic migraine - 41% with medication overuse
    - Monthly migraine days reduced by 6.6 days versus 4.2 days for placebo after 12 weeks
    - Erenumab leading to improve in quality of life

Lancet Neurol 2017;16:425–34

Practical points in management of difficult to treat primary headache

- Medication overuse headache
  - Conclusion: prophylactic therapy without withdrawal leading to a reduction in headache or migraine frequency and acute medication consumption in the absence of deliberate withdrawal (discontinuation)
  - Reasonable approach in patients overusing analgesics or triptans

Lancet Neurol 2019; 18 Sep: 891–902

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The Consensus protocol for the treatment of MOH as follows:

Use a headache diary

- STEP 1: Withdraw overused medication (day 1)
  - Classification system for MOH created by Saper and Lake
    - MOH type I
      - Patients with neither behavioral conditions nor overused opioids or barbiturates: simple and manageable in outpatient setting with clear rescue medication program
      - Rapid withdrawal leading to rapid resolution
    - MOH type II
      - Patients with complex, suffering from behavioral conductions and chronic use of opioids and barbiturates – more likely to have withdrawal symptoms, emotional and sleep problems
      - Inpatient therapy
      - Tapering withdrawal due to significant and life-threatening withdrawal symptoms
      - Typical withdrawal symptoms: worsening headache, restlessness, anxiety, insomnia, nervousness, nausea, vomiting, tachycardia, or hypotension lasting 2-10 days up to 4 weeks

J Headache Pain. 2010;11:373-7; Eur. J. Neurol. 2009;16:705-12

Practical points in management of difficult to treat primary headache

The Consensus protocol for the treatment of MOH as follows:

Use a headache diary

- STEP 1: Withdraw overused medication (day 1)
- STEP 2A: Detoxification and rescue therapy (day 1 to 7) – minimized withdrawal symptoms and maximized comfort
  - Antiemetics/neuroleptics such as: Metoclopramide 10 mg IM or PO three times daily or equivalent (chlorpromazine, prochlorperazine, domperidone, levomepromazine, diphenhydramine, promethazine)
  - Analgesics for a maximum of 3 days within the first week such as (Do not use rescue medication that is the same class of drug as previously overused):
  - Acetaminophen 1000 mg PO, PR or IV,
  - Naproxen 500mg PO
  - Indomethacin
  - Ketorolac
  - Adjunctive treatment with tizanidine
  - Infusion with DHE, lidocaine, magnesium, sodium valproate
  - Transition with long-acting opioids, phenobarbital, and clonidine for overused narcotics, barbiturates, and tranquilizers
  - Steroid therapy: no or minimal effects

J Headache Pain. 2010;11:373-7; Fischer MA, Jan A. Medication-overuse Headache (MOH). 2019 Mar 1. StatPearls [Internet].

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The Consensus protocol for the treatment of MOH as follows:

Use a headache diary

- STEP 1: Withdraw overused medication (day 1)
- STEP 2A: Detoxification and rescue therapy (day 1 to 7)
  - Antiemetics such as: Metoclopramide 10 mg IM or PO three times daily or equivalent (chlorpromazine, prochlorperazine, domperidone, levomepromazine)
  - Analgesics for a maximum of 3 days within the first week such as (Do not use rescue medication that is the same class of drug as previously overused): Acetaminophen 1000 mg PO, PR or IV, Naproxen 500mg PO
- STEP 2B: Preventative treatment (day 1 to 7), optional but chosen based on side effects, co-morbid conditions, previous therapeutic experiences from the following:
  - Beta-blockers--propanolol 80-240 mg/day, atenolol 75-200 mg/day, metoprolol 100-200 mg/day
  - Valproic acid 500-1500 mg/day
  - Topiramate 50-200 mg/day
  - Flunarizine 5-10 mg/day
  - Amitriptyline 20-100 mg/day
  - Candesartan 8-16 mg/day
- STEP 3: Headache symptomatic medications (from day 8 and on) Take headache medications at a maximum of 2 days per week. It should not with the same class of drug previously overused and based upon the patient's medical history, headache characteristics and past therapeutic experiences

J Headache Pain. 2010;11:373-7; Fischer MA, Jan A. Medication-overuse Headache (MOH). 2019 Mar 1. StatPearls [Internet].

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- Treatment failure: causes
  - Wrong diagnosis
  - If correct diagnosis
    - Preventive treatment
      - Inadequate dose
      - Inappropriate drug
      - Inadequate duration
      - Treatment non-adherence
      - No withdrawal of overused medications?
      - Unrecognized exacerbating factors
      - Unrecognized co-morbidity: OSA, psychiatric conditions

Neurol Sci 2008;29 (Suppl 1):s55-8

Practical points in management of difficult to treat primary headache

- Common exacerbating factors
  - Stress
  - Menstrual cycle changes
  - Weather changes
  - Sleep disturbances
  - Sensory stimuli: visual, noise, olfactory, and other stimuli
  - Alcohol
  - Other foods

Curr Pain Headache Rep. 2018;22:81

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Neurol Sci 2008;29 (Suppl 1):s55-8

Practical points in management of difficult to treat primary headache

- Treatment failure: causes
  - Wrong diagnosis
  - If correct diagnosis
    - If true preventive treatment failure
      - Use of new approval medicines for migraine prevention

J Headache Pain2019;20:58; Headache 2019;59:1-18