**Outpatient withdrawal treatment vs inpatient withdrawal treatment**

| Study details | Patients | Interventions | Outcome measures | Effect size | Comments |
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| **Author & Year:**<br>Creach et al, 2011[173]<br><br>**Study design:**<br>Randomised trial, open label<br><br>**Setting:**<br>Headache clinics, France<br><br>**Duration of follow-up:**<br>2 years (March 2003-December 2005) | **Patient group:** Patients with suspected medication overuse headache (MOH) referred to pain clinic by their primary care physician.<br><br>**Inclusion criteria:** Patient with suspected MOH defined as headache ≥15 days/month for at least 3 months combined with an intake of acute symptomatic treatments for headache ≥15 days/ month over the same period; age≥18 years, patients accepting allocation to treatment by randomisation, patients who agreed to halt their professional activity for 8 days in order to complete an abrupt drug withdrawal<br><br>**Exclusion criteria:**<br>Patients who had suffered from any significant illness or major depression in the past month, pregnancy, unable to describe precisely describe their headaches or their medication consumption, patients whose medication overuse included WHO step III opioids, no improvement after a previous well conducted withdrawal<br><br>**All patients**<br>N: 82 (randomised)<br>**Group 1- Outpatient withdrawal group**<br>N:41 **(randomised)**, 36 (analysed at 2 months follow up), 34 (analysed at 2 years follow up)<br>Dropouts:5 excluded (1-spontaneous decrease of MOH, 1- desire for inpatient treatment, 3-incomplete withdrawal) | **<u>Group 1 Outpatient withdrawal therapy</u>**<br>Outpatient withdrawal treatment<br>Patients told to consult general practitioner if needed<br><br>**<u>Group 2 Inpatient withdrawal therapy</u>**<br>Inpatient withdrawal treatment<br>Monitored by neurologist<br><br>**In both groups:**<br>• Both groups were seen by a neurologist on the first visit.<br>• Patients completed a questionnaire and a daily headache diary for one month between visits 1 and 2<br>• A preventive treatment, chosen by the neurologist in the second visit, was introduced on the first day of withdrawal based on previous preventive treatments already used by the patient<br>• Both groups received oral amitriptyline in progressively decreasing doses over one month and metoclopramide to minimise withdrawal syndrome<br>• At the end of withdrawal, patients received a prescription for acute symptomatic treatment (usually triptans or NSAIDs) with instructions not to take them for more than 8 days per month. | Responder rate at 2 years follow up (n/N, %)<br>Responder rate defined as patients who 2 months after the onset of withdrawal treatment, experienced no headache or had reverted to an episodic pattern of headache (<15 headache days /month) and whose intake of symptomatic medication was <10 days/month | Outpatient group: 16/34, 47%<br><br>Inpatient group: 14/32 , 44% | **Funding:**<br>Grants from Fondation de France and Fondation CNP<br><br>**Limitations:**<br>• Details of randomisation and allocation concealment not reported.<br>• Open label trial<br>**Additional outcomes:**<br>• Reduction in percentage of headache days(numbers not extractable)<br>• Number of patients with episodic headaches<br>• Severity of withdrawal symptoms<br>• Psychological distress induced by withdrawal<br>• Craving for acute symptomatic medication<br>• Percentage of |

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| | Age in years (mean ±SD):45±11<br>Duration of headache in years (mean ±SD):23.9±13.9<br>Number of headache days per month (mean ±SD): 27.3±4.6<br>Number of days per month with ATH use (mean ±SD):<br>**26.4±5.7**<br><br>**Group 2- In patient withdrawal group**<br>N:41**(randomised)**, 35 (analysed at 2 months follow up), 32 (analysed at 2 years follow up)<br>Dropouts: 6 excluded(3- spontaneous decrease of MOH, 1- concomitant surgery, 1- desire for outpatient withdrawal, 1- incomplete withdrawal)<br>Age in years (mean ±SD):50±11<br>Duration of headache in years (mean ±SD): 25.1±13.4<br>Number of headache days per month (mean ±SD): 25.8±5.6<br>Number of days per month with ATH use (mean ±SD):<br>25.8±5.6 | | | | subjective improvement |

*Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD: Standard deviation, N: Number, MOH: Medication overuse headache, WHO: world Health Organisation, ATH: Acute treatment of headaches, NSAIDs: Non steroidal anti-inflammatory drug*

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| **Author & Year:** Rossi et al, 2006 & 2008[670,671]<br><br>**Study design:** RCT<br><br>**Setting:** Headache Inpatient clinic, Grottaferrata, Italy<br><br>**Duration of follow-up:** 12 months | **Patient group:** People aged 16-65 years suffering from probable medication overuse headache (MOH) plus migraine.<br><br>**Inclusion criteria:** Age 16-65 years; diagnosed with MOH plus migraine according to ICHD-II criteria; attending a subspecialty headache centre(INI Headache clinic); had low medical needs and unlikely to experience problems as withdrawal treatment out-patients.<br><br>**Exclusion criteria:** Current diagnosis or history of coexistent, significant and complicating medical illness (which could complicate withdrawal undertaken as an out-patient); current diagnosis (fulfilment of diagnostic criteria in the past month) of mood disorder, anxiety disorder or addiction disorder (for substances other than the overused medication); overuse of agents containing opioids, barbiturates and benzodiazepines; treatment with migraine prophylactic drugs within the past three months; previous detoxification treatments; inability to furnish reliable information about medical history and psychiatric symptoms and contraindications to the use of corticosteroids and indomethacin.<br><br>**All patients**<br>**N:** 120 (randomised), 2(diagnosed with chronic migraine and not included in analysis) 89 (successfully completed withdrawal therapy and recruited for follow up), 83 (data available for analysis at end of 1 year)<br>**Age (mean ± SD):** 43.97±12.9 years | **Group 1 Intensive advice**<br>Received advice to withdraw medication. Advice included explaining role of medication overuse in making headache chronic, symptoms of withdrawal, long term effects and importance of patient playing an active role in management of their headache.<br><br>**Group 2 Outpatient detoxification programme**<br>Advised to abruptly withdraw the overused medication.<br>Prednisone for the first two 8 days (60 mg/day, 2 days; 40 mg/day, 2 days, 20mg/day, 4 days).<br>Preventive treatment chosen on basis of patient's history and preferences.<br><br>**Group 3 Inpatient detoxification programme**<br>Advice to withdraw symptomatic medication<br>Admitted to hospital and received following treatment:<br>Abrupt discontinuation of overused medication; Close observation and support for 8 | **Change in acute medication use** *percentage reduction in number of doses of symptomatic mediation/month (mean ± SD)* | **Group 1**: 76.6±22<br>**Group 2**: 71.7±32<br>**Group 3:** 81±13 | **Funding:** NR<br><br>**Limitations:**<br>Open label study.<br>Method of allocation concealment unclear.<br><br>**Additional outcomes:**<br>Adherence to treatment<br><br>**Notes:**<br>All outcomes after two months reported in Rossi et al, 2008.<br>Preventive medication used:<br>Valproic acid, β-blockers, amitriptyline and topiramate. |
| | | | **Relapse back to medication overuse headache within 1 year** | **Group 1:** 13.8% (4/29)<br>**Group 2:** 23.1% (6/26)<br>**Group 3:** 25% (7/28) | |
| | | | **Responder rate** patients who 2 months after the onset of withdrawal treatment, experienced no headache or had reverted to an episodic pattern of headache (<15 headache days /month) and whose intake of symptomatic medication was <10 days/month | **Group 1:** 77.5% (31/40)<br>**Group 2:** 71.7% (28/39)<br>**Group 3:** 76.9% (30/39) | |
| | | | **Change in patient reported headache days** *percentage reduction* | **Group 1:** 67.6 ± 25<br>**Group 2:** 61.2 ± 34 | |

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| | **Drop outs:** 13 (by second follow up visit)<br><br>**<u>Group 1 Intensive advice</u>**<br>**N:** 40 (randomised); 29 (data available at 1 year)<br>**Age (mean ± SD):** 43.5±14.2 years<br>**Drop outs:** 3 (7.5%)-at 12 weeks<br>**Duration of MOH (mean ± SD):**4±5<br>**Number of doses of medication/month (mean ± SD**): 37±23<br><br>**<u>Group 2 Outpatient detoxification</u>**<br>**N:** 39 (randomised), 26 (data available at 1 year)<br>**Age (mean ± SD):** 44.1±12.8 years<br>**Drop outs:** 5 (12.8%)-at 12 weeks<br>**Duration of MOH (mean ± SD): 4**.4±3.6<br>**Number of doses of medication/month (mean ± SD):** 40±27<br><br>**<u>Group 3 Inpatient detoxification</u>**<br>**N:** 39 (randomised); 28 (data available at 1 year)<br>**Age (mean ± SD):** 46.1±11.9 years<br>**Drop outs:** 5 (12.8%)-at 12 weeks Duration of MOH (mean ± SD): 4.6±4.2<br>**Number of doses of medication/month (mean ± SD):** 40.2±20 | days; Prednisone (60 mg/day, 2 days; 40 mg/day, 2 days, 20mg/day, 4 days); Preventive treatment chosen on basis of patient's history and preferences; Parenteral fluid replacement and administration of antiemetics (metoclopramide 10 mg i.v twice daily). | *in number of headache days/ month (mean ± SD)* | **Group 3:** 73 ± 19 | |

*Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, MOH= Medication overuse headache*

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| **Author & Year:** Suhr et al, 1999[769]<br><br>**Study design:** RCT<br><br>**Setting:** Headache clinic , Germany<br><br>**Duration of follow-up:** 5.9±4.0 years | **Patient group:** Patients with drug induced headache<br><br>**Inclusion criteria:** Diagnosis of drug induced headache according to IHS criteria and admitted between 1983 and 1995; had discontinuation of chronic headache after withdrawal therapy; if admitted before 1989, enrolled only if a diagnosis of drug induced headache could be made from the history.<br><br>**Exclusion criteria:** NR<br><br>**All patients:**<br>**N:** 257 (identified with drug induced headache and randomised); 101(enrolled for follow up study)<br>**Age (mean):** 46.0±12.0 years<br>**Drop outs:** 39(lost to follow-up); 117 (did not answer questionnaire/interview sufficiently)<br><br>**Group 1 Outpatient withdrawal therapy (ambulatory)**<br>**N:** 110 (randomised); 41 (data available at follow up)- 40.6%<br>**Age (mean):** NR<br>**Drop outs:** 69<br><br>**Group 2 Inpatient withdrawal therapy (Stationary)**<br>**N:** 147 (randomised); 60 (data available at follow up)- 59.4%<br>**Age (mean):** NR<br>**Drop outs:** 87 | **Group 1 Outpatient withdrawal therapy (ambulatory)**<br>Analgesic medication stopped abruptly<br>Patients observed regularly during 4 week treatment as outpatients<br><br>**Group 2 Inpatient withdrawal therapy (Stationary)**<br>Analgesic medication stopped abruptly<br>Patients observed regularly during 2 week treatment in hospital.<br><br>**In both groups:**<br>No analgesic intake was allowed during the withdrawal therapy.<br>10% received antidepressants and 20% received migraine prophylactic agents.<br>After successful withdrawal therapy, treatment of primary headache was started in accordance with the principles recommended by the German Migraine and Headache Society.<br>Follow up done in 1995 by standard interview (postal questionnaire, personal examination or telephone interview) to evaluate history of headache and its treatment after withdrawal therapy. | **Relapse back to medication overuse headache** | **Group 1:** 14.6% (6/41)<br>**Group 2:** 25% (15/60)<br>P value<0.2 | **Funding:** NR<br><br>**Limitations:**<br>Unclear randomisation.<br>No blinding of participants, care administrators or investigators.<br>Significant loss to follow up and no reasons outlined.<br>Unclear what the interventions were- no details reported other than abrupt withdrawal of medication.<br><br>**Additional outcomes:**<br>Maximal pain intensity, rate of drug intake after withdrawal therapy in patients with relapse and patients without relapse (not separated by group). |
| | | | **Change in patient reported headache days/ month** | **Group 1:** 9.6±10.1<br>**Group 2:** 12.6±11.3<br>P value<0.2 | |
| | | | **Change in patient reported headache intensity** *visual analogue scale from 1 to 10 (mean*±SD*)* | **Group 1:** 6.4±2.6<br>**Group 2:** 6.5±2.2<br>P value<1.0 | |

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