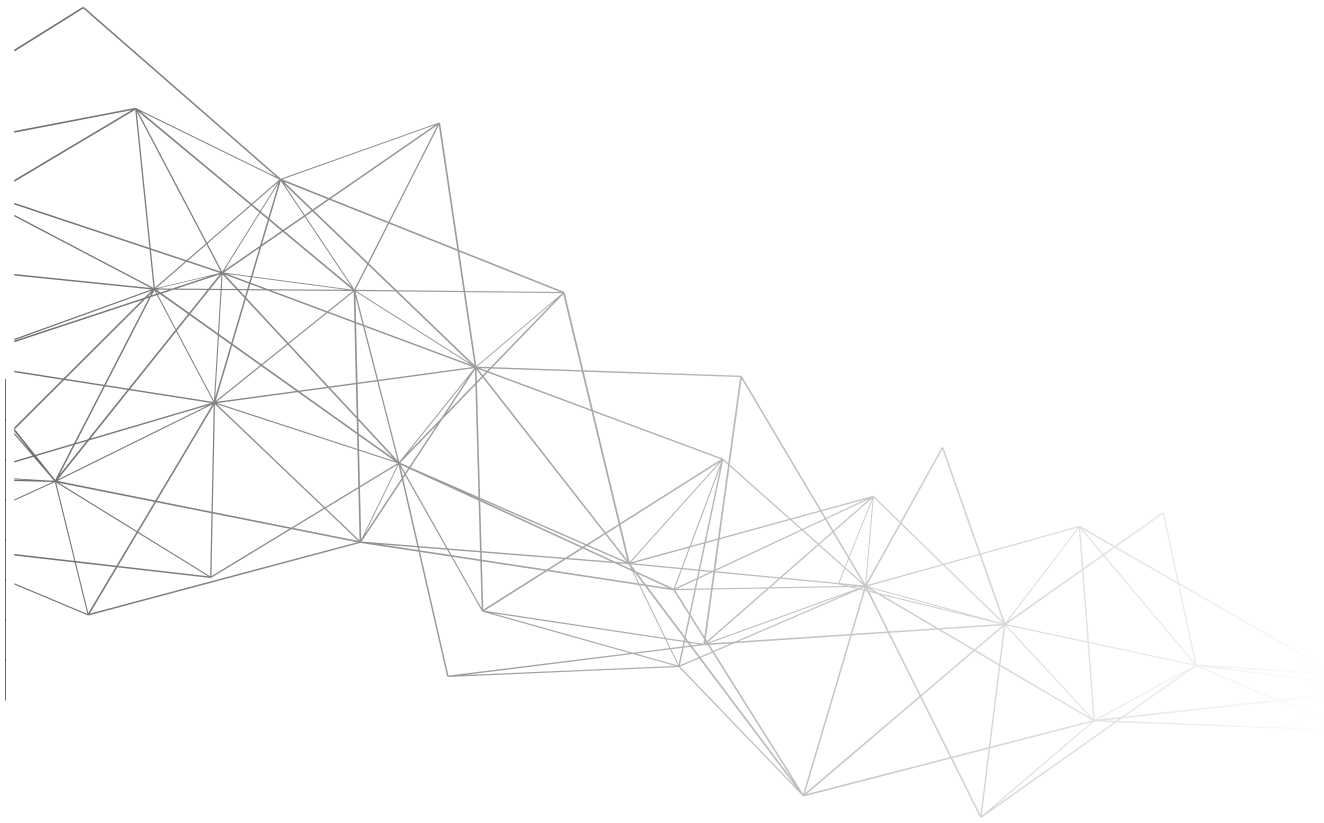
9 CHAPTER | Summary and general discussion



9.1 Summary

In **chapter 1** I provide a general introduction in the topic of this thesis. It describes epidemiology, criteria, pathophysiology, genetics and treatment of migraine and depression, and also migraine chronification and the role of medication overuse. Furthermore, an introduction in comorbidity of both diseases is given, focusing on what we know already, and specific remaining questions to be answered in this thesis.

In **chapter 2**, I describe that 45% of migraineurs fulfilled the criteria for lifetime depression. A high migraine attack frequency and the presence of cutaneous allodynia were migraine specific factors associated with an increased prevalence of depression. Furthermore, being a poor sleeper, female gender, high BMI, being single, smoking, and a low alcohol consumption were general determinants of depression in our population. This study identified allodynia, in addition to high migraine attack frequency, as a new migraine specific factor associated with depression.

In **chapter 3** I essay that cutaneous allodynia was highly prevalent in our migraineurs: 70% reported allodynia during migraine attacks. Allodynia was associated with the presence of depression, and also with female gender, low age at onset, and high migraine attack frequency. Analysis of the longitudinal data showed that allodynia was an independent predictor for increase in migraine frequency.

In **chapter 4**, I show that hemiplegic migraine patients had increased odds for lifetime depression compared with controls. Use of acute anti-migraine medication was associated with lifetime depression.

In **chapter 5**, I describe that migraine patients differed significantly from healthy controls on all 3 dimensions of affective disorders: lack of positive affect, somatic arousal, and negative affect. For the lack of positive affect and negative affect dimensions, migraine patients were predominantly similar to a 'past psychopathology' group. For the somatic arousal dimension, migraine patients scores were more comparable with a 'current psychopathology' group.

Chapter 6 provides evidence that successful withdrawal from medication overuse was significantly higher in the group supported by a headache nurse than in the group without support. Support by a headache nurse was not associated with response (≥ 50% reduction in headache days after successful withdrawal). The underlying headache primary headache diagnosis, determined after withdrawal, was significantly correlated with response (with increased response in the group with underlying migraine, when compared with the group with tension type headache).

I describe a study in **chapter 7** which aimed to search for evidence that genetic factors are involved in the chronification process of migraine. No loci survived replication, which left us without significant findings.

In **chapter 8** I show that 44% of cluster headache patients fulfilled the criteria for lifetime depression. Chronic vs. episodic patients had a higher prevalence of lifetime depression and more sleeping problems. Current depression was associated with having active attacks, but no effect remained after correction for sleep disturbances.

9.2 General Discussion and future perspectives

9.2.1 Clinical determinants of depression in migraine patients

A broad range of studies, with mostly cross-sectional and sparsely longitudinal designs, have been published on the topic of migraine and depression. (1-14) **Chapter 2** showed that our population of migraine patients was comparable to other studies with respect to the prevalence of lifetime depression (varying from 20% to 60%). The quality of migraine characterization and depression characterization, however, has in most of the previous studies been moderate, if not poor. A major strength of our study, and a clear difference with most earlier published studies, is the extensive characterization of patients. We could show clear associations with a large number of determinants. This detailed information on clinical and socio-demographic variables allowed for specific subsequent studies, with broad opportunities for statistical adjustment to prevent bias. The question could be raised whether the found association might be the artefact of our definitions. A part of the comorbidity between migraine and affective disorders could be due to overlapping symptomatology, as some of the characteristic features of migraine attacks, such as nausea, loss of energy, anhedonia, and sleep disturbances, could lead to misclassification of depressive disorder in migraine patients. However, the association of migraine and depression is still present when questionnaires focusing on the non-somatic aspects of depression are applied, such as the Hospital Anxiety and Depression Scale. (15) Furthermore, the robust trend in published literature on the issue of migraine and depression is that, irrespective the extensiveness of the depression characterization, all studies show an association. In our opinion, this strongly suggests that we have confirmed a real association between 2 genuine disorders.

9.2.2 High migraine attack frequency is associated with depression

We identified migraine frequency to be associated with depression (**chapter 2**), which confirmed findings from two other studies with poor characterization of

depression. (16) (17) The direction of this causation in our study remained unclear due to its cross-sectional character. We addressed this problem in **chapter 3**. There we showed that lifetime depression at baseline was associated with an increase in migraine days over a median follow-up period of 2 years. These findings confirm that depression is a risk factor for migraine chronification.

9.2.3 Genetic factors involved in migraine and depression

As it remains unclear which specific genetic factors are involved in the increased liability to migraine and depression (11, 18), we performed a GWAs study to identify shared genetic factors for migraine and depression (not presented in this thesis). A total of 1450 migraine patients of our LUMINA cohort had migraine and depression, of which GWAs data was obtained for 598 patients. A GWAs study was performed for these patients and combined with GWAs data of three additional cohorts in a meta-analysis for migraine and depression. This resulted in 4 peaks (loci) that reached the threshold of suggestive significance. The study included a total amount of 1700 cases and 5600 controls. Four study samples were made available for replication, and 20 SNPs located in these four top loci were genotyped in these cohorts using the Sequenom technique. Unfortunately, we could not replicate our initial findings. The negative outcome in our first GWAs on migraine and depression is less surprising in view of findings in GWAs studies of depression, where only the latest GWAs in June 2016 provided first evidence of genetic factors in depressive symptoms in large amounts of cases. (19) Regardless, our approach to test migraine and depression combined (as an endophenotype) may yield more positive results, although the challenge seems considerable. To increase power, we increased our sample size by adding new cohorts to our discovery sample. Additional GWAs for migraine and depression are currently being performed. Hitherto we have not been able to present or definitely refute evidence from genetic studies that migraine and depression share an aetiological basis.

9.2.4 Cutaneous allodynia is associated with migraine chronification

The study described in **chapter 2** was the first to identify cutaneous allodynia as a determinant of lifetime depression in migraineurs. The prevalence of allodynia in our study is in line with all previous studies on allodynia in migraine (ranging from 50% to 80%). (20) Migraine, depression and allodynia are intertwined, and allodynia plays an important role in the migraine triad of chronification, depression, and medication overuse. As cutaneous allodynia is considered a clear marker for a central sensitization process of the brain, (21) this finding could shed new light on the pathophysiological mechanisms behind the relationship between migraine chronification and depression.

Chapter 3 shows that recurrent migraine with cutaneous allodynia probably leads to a decreased threshold for subsequent migraine attacks. A possible explanation may be that repetitive activation of trigeminovascular neurons and of modulatory pain pathways may lead to impairment of function or neuronal cell damage in brain areas involved in migraine generation. This might lead to decreased thresholds for activation, leading to chronification of migraine. (20, 22) Another concept is that of nociception-induced plasticity, suggesting that kindling and related models of neuroplasticity can be used to describe ways in which exposure to a noxious stimulus may, under certain conditions, lead to a permanently sensitized state, and to chronification of pain. (23)

The finding that repeated migraine attacks increase the susceptibility for subsequent attacks, which may also lead to structural and functional changes within pain pathways, could in the future also be validated in wild type mice and our transgenic knock-in migraine mouse models that harbour human pathogenic mutations for familial hemiplegic migraine. (24-26) These mice exhibit increased neuronal calcium influx and glutamatergic neurotransmission, resulting in lowering of the induction-threshold for cortical spreading depression and an increase of the frequency of cortical spreading depression. By repeating induced cortical spreading depression, it could be determined whether there is a critical window for chronification. Daily administration of analgesics or triptans could possibly induce a state comparable to medication overuse headache. Study designs with an experimentally evoked anhedonic depressive-like status could investigate the relationship between anhedonia and sensitivity for cortical spreading depression. Measurements of cutaneous allodynia have been performed before in mice, and could be associated with the sensitivity for cortical spreading depression. Altogether, mouse models could provide supporting evidence and new insights about the relationship between migraine chronification, cutaneous allodynia, and depression.

9.2.5 Dimensions of affective disorders in migraine patients

Not only migraine, but also several other somatic disorders (like diabetes, obesity, and cardiovascular disease) show increased associations with the somatic-affective dimension rather than cognitive-affective symptoms of affective disorders, as described in **chapter 5.** (27-30) Therefore, it has often been hypothesized that the association between a somatic disease and depression is primarily through the somatic-affective dimension of depression, the so-called somatic depression. (31, 32)

One might argue that we did not find a comorbidity between migraine and depression, but between migraine and 'feeling unwell', as a consequence of the somatic disease. We would however like to object to this argumentation. First, the

source papers for the relationship between migraine and depression have been for years the longitudinal studies of Breslau et al. (1, 2) These papers describe not only an increased risk of first onset depression in migraine patients, but also *vice versa* an increased risk of first onset migraine in patients with a depression. This argues against depressed feelings following (frequent) migraine attacks. Furthermore, **chapter 5** clearly shows that the symptom profile of affective disorders in migraine patients differs from healthy controls for all three dimensions of the MASQ-D30 questionnaire, not only for the somatic arousal dimension. Therefore, our study shows that affective disorders in migraine patients cannot be fully explained by somatic depression or overlapping symptomatology.

Our study shows an even stronger comorbidity between migraine and symptoms of anxiety, than between migraine and symptoms of depression per se. This is particularly interesting, since most studies hitherto focused on the comorbidity between migraine and depression, whilst the comorbidity of migraine and anxiety is a largely unexplored area. Our study shows that anxiety arousal might be the corresponding component, but the underlying mechanism should be further investigated.

9.2.6 Depression in hemiplegic migraine

Our finding from **chapter 4** that the lifetime prevalence of depression in patients with hemiplegic migraine compares to the prevalence found in migraineurs with and without aura (**chapter 2**), fits well with the hypothesis that hemiplegic migraine is part of the migraine spectrum. (33) Probably the same pathophysiological mechanisms play a role in the comorbidity of depression with migraine with and with aura at the one hand, and hemiplegic migraine at the other.

The genes involved in hemiplegic migraine may, directly or indirectly, make patients more susceptible to depression (**chapter 4**). Hitherto three genes have been identified for hemiplegic migraine. FHM1 is caused by missense mutations in *CACNA1A* on chromosome 19p13. (34) FHM2 is caused by missense mutations in *ATP1A2* on chromosome 1q23. (35) FHM3 is caused by missense mutations in *SCN1A* on chromosome 2q24. (36) The functional effects of FHM1, FHM2 and FHM3 gene mutations all predict increased levels of glutamate in the synaptic cleft. Clinical data also suggest the involvement of the glutamatergic system in the pathophysiology of depression. (37) Proton magnetic resonance spectroscopy (^{1}H-MRS) data suggest alterations to glutamatergic concentrations in several brain areas, whereas post-mortem studies indicate alterations in NMDA receptor subunit expression in patients with major depressive disorder. The finding that depression is highly prevalent in patients with hemiplegic migraine contributes to the evidence that the glutamatergic system might be involved in the pathophysiology

of depression. It would be interesting to study the role of ion channels encoded by *CACNA1A*, *ATP1A2* and *SCN1A* in large cohorts with comorbid depression and common forms of migraine.

9.2.7 Genetic factors involved in chronic migraine

An important drawback of focusing on subgroups of patients, as we did in **chapter 7** with chronic and high-frequent migraine, is that the number of available patients decreases. Thus, to increase homogeneity, we had to sacrifice statistical power. Although we collaborated in the International Headache Genetics Consortium, the patient numbers were relatively small, largely because of the rarity of chronic migraine and poor clinical characterization of migraineurs in other cohorts. Considering the negative results of the study, our approach may have had insufficient statistical power, or we may have selected SNPs irrelevant to migraine chronification. If the problem of statistical power will remain problematic, we would like to put forward that perhaps other genetic approaches will be more fruitful in detecting genes and pathways involved in chronic migraine, such as gene expression studies, epigenetic studies or the analysis of rare variants.

9.2.8 Depression in cluster headache

The marked relationship of depression and sleep disturbances in cluster headache (**chapter 8**) adds to the hypothesis that hypothalamic dysfunction plays a role, as depression, sleep disorders and cluster headache have all been associated with both functional and structural changes in this part of the brain. (38-42) Interestingly, depression scores were increased in patients with chronic cluster headache, when compared with patients with episodic cluster headache. This reminds of the relationship between depression and migraine chronification, as described in **chapters 2** and **3**. However, due to the cross-sectional nature of our study, we could not distinguish between cause and consequence. Likewise, we could not determine whether depression and cluster headache show bidirectional comorbidity. It could still be possible that the pain in cluster headache is thus severe, that depression is an almost unavoidable consequence – an argument supported by the fact that a stronger association was found for chronic cluster headache. The necessary long-term, prospective follow-up design for a study to prove bidirectional comorbidity (1, 2), will be challenging because of the low prevalence of cluster headache. Longitudinal studies within a cluster headache population could shed more light on the process of cluster headache chronification, and its relation with depression, cutaneous allodynia and sleep disturbances. Further research should also focus on the pathophysiological background of the interactions between cluster headache, sleep disturbances, chronification of disease, and depression. Comparable to migraine, cutaneous

allodynia might provide clues to pathophysiological processes involved in this comorbidity. Genetic analyses could either way contribute, with consideration of the limitations that rare diseases involve, in particular a lack of statistical power to detect genetic variants with a small effect.

9.2.9 The treatment of medication overuse headache

Psychological phenomena play an important role in patients with chronic headache or high headache related disability. They are more prone to use unsuitable coping mechanisms, score low on pain acceptance and high on catastrophizing scales, and experience a low internal pain control. (43-45) Interestingly, in patients with migraine, pain control and self-management can be improved by cognitive behavioural therapy. (46) It seems likely that all these elements play a role in successful withdrawal with support of a headache nurse (**chapter 6**). Further research, specifically focusing on cognitive-behavioural interventions before and during withdrawal, might further improve the success rate of withdrawal therapy.

Over the last few years a shift has occurred in the approach of patients with medication overuse. Traditionally, it was advised to withdraw patients from their overused medication before starting any prophylactic agent. Randomised trials in chronic migraine with topiramate and onabotulinum toxin A, however, contributed significantly to the debate whether, and when detoxification is necessary in the treatment of medication overuse headache. (47-51) In our opinion, it would be interesting to study whether Onabotulinum toxin A could be effective for patients who do not respond to withdrawal therapy, or whether Onabotulinum toxin A could mitigate the process of medication withdrawal.

9.2.10 A critical discussion of the methodology

An important part of the analyses in this thesis was carried out with material from two large databases we have compiled over the course of years: the LUMINA migraine population (52) and the LUCA cluster headache population. (53) The LUMINA database started in 2008 as a web-based method to include migraine patients in several research projects, but first and foremost in our genetic data collection project. The LUCA database, including cluster headache patients, started a few years later, using the same methodology and technical infrastructure as LUMINA. During the years, an increasing number of satellite projects was added to the LUMINA and LUCA databases, meaning that participants received additional requests for questionnaires, biochemical research, Magnetic Resonance Imaging and –Spectroscopy studies, migraine attack provocation studies, and even a clinical trial on the effect of Onabotulinum Toxin A in the treatment of chronic migraine. Collection of a healthy control population started years after the first migraine patients were included. Also, data collection via our outpatient clinic was introduced into the LUMINA project.

As described, the primary focus of the LUMINA database had always been the collection of DNA samples from migraine patients, in order to be able to participate with considerable numbers of samples in the International Headache Genetics Consortium. This meant that the database was not optimally equipped for epidemiological research questions. We unfortunately had to go back to our patients with additional questionnaires a few times, thereby decreasing the adherence of our population, and decreasing the numbers of eligible patients.

Another consideration regarding the LUMINA and LUCA databases is the question whether the use of these kinds of database for a range of different clinical questions is allowed by the rules of statistics. Conservative voices might argue that only 1 pre-defined question could be answered using such a database, with a number of included patients calculated beforehand using a power calculation. Probably they will state that for every new question, a correction for multiple comparison should be introduced in the analyses, to reduce the risk of a false positive result to 5% (the type-I error). The exact count of the number of tests however, remains a difficult issue. Should we count all statistical tests regarding a specific issue, or all tests in one chapter of this thesis, or all tests ever performed within the LUMINA database during its lifetime? According to the well-known epidemiologist Rothman, 'the policy of not making adjustments for multiple comparisons is preferable because it will lead to fewer errors of interpretation when the data under evaluation are not random numbers but actual observations on nature', whereas a basic premise of empirical research is that nature follows a regular law, and an expected order, that may be studied through observations. (54) We have concluded that, if the hypothesis is strictly defined in advance, with one primary outcome measure and at most a few secondary outcome measures, and a statistical plan has been designed which is followed exactly during the analyses, without extensive post-hoc sub-group analyses, no correction for multiple testing is needed if it were only for the fact that several papers arise from one and the same database. LUMINA and LUCA are both progressively growing databases, with new patients entering almost on a daily basis. As a consequence, future research questions will be answered in a (partially) different population. It is needless to say that the extent of both databases allows for more than one research question. Lastly, research questions in LUMINA and LUCA are most of the time not fully independent, which makes strict correction for multiple testing (i.e. following the Bonferroni correction) a too conservative choice.

Although we previously described the LUMINA population as a clinical based cohort, we now feel that it is better to describe it as a 'well-defined, web-based migraine population'. In fact, it is a mix of clinical based and population based participants, because of the collection via our website. In the LUMINA population 70% used triptans. Compared to other countries this may seem high but in the Netherlands and some Scandinavian countries the use of triptans in population

based studies is amongst the highest. Furthermore, 87% was previously diagnosed with migraine by a physician, 26% is currently seen by a neurologist, 43% by a general practitioner. The remaining 31% is not seen by a neurologist or a general practitioner. This proves that the LUMINA population contains the full range of migraine patients.

For the LUCA population, a clinically confirmed diagnosis of cluster headache by a physician was available for 94%. For the remaining 6%, no clinically confirmed diagnosis was available, for instance because they never consulted a doctor. Still, for cluster headache it is almost impossible to collect a population based cohort, because of the low prevalence.

Lastly, we would not use our algorithm for lifetime depression in our daily psychiatric practice, whereas we think that the eye of the experienced and evidence-based working clinician is the only guarantee for reliable depression diagnoses. In clinical practice it is most important to combine symptoms, as presented by the patients, with the archetypical presentation of depression as we want to observe in our psychiatric examination, and which thereafter might fit into our classification system as a ´DSM-5 defined depression'. Clearly, the use of self-report questionnaires could never replace this kind of diagnostic finesse. Nevertheless, we would like to defend our depression definition as an accurate measurement for purposes of scientific research, knowing that extensive psychiatric examination is impracticable if the primary purpose of the project is to collect thousands of patients for genetic research.

9.2.11 Clinical implications of our findings

Chapter 2 and **chapter 3** show clear involvement of cutaneous allodynia in the triad of migraine chronification, depression, and medication overuse. Clinically, central sensitization causes refractoriness to acute treatment. (21) Thus, allodynia has consequences for disease progression and treatment, and it should lead to an increased awareness of comorbidity of migraine and depression, and of risk of chronification of migraine. As described in **chapter 3**, the clinical findings from this study correspond with the pathophysiological mechanism of CA. The underlying mechanism of migraine and allodynia is activation of the trigeminovascular neurons. (55) The activation of the trigeminovascular pathway contributes: i) to the headache phase of the migraine attack by sensitization of peripheral trigeminovascular neurons innervating the meninges; ii) to the cephalic allodynia by sensitization of second-order neurons in the spinal trigeminal nucleus (in the medullary dorsal horn) that receive input form the meninges, scalp and facial skin; and iii) to the development of extracephalic allodynia by third-order neurons in the posterior thalamic nuclei which receive input form meninges, facial and body skin. (55) Importantly, once established, sensitization of second order

trigeminovascular neurons becomes activity independent, and maintains itself in the absence of sensory input later on. (55) The activity-independent form is the consequence of neurotransmitter and neuromodulator induced activation of multiple intracellular signalling pathways. Activity-independent sensitization develops slowly over several hours and lasts for a prolonged period of time. (56) This has important clinical implications, as late treatment with triptans during an attack is unsuccessful when this independent activity has occurred. (21) Finding out which critical thresholds are exceeded before central sensitization occurs will potentially lead to new medications preventing sensitization.

The high prevalence of depression in our HM cohort, described in **chapter 4**, also may have clinical implications. HM patients should be screened for depression, and migraine prophylactics such as flunarizine or topiramate which may provoke depressive symptoms should perhaps be prescribed with caution in HM patients with active depression. (57)

Previous studies suggest that patients with (chronic) headache or high headache related disability, are more prone to use unsuitable coping mechanisms (43), score low on pain acceptance (44) and high on catastrophizing scales, and experience a low internal pain control. (45) In patients with migraine, pain control and self-management can be improved by behavioural therapy. (46) We hypothesize that contact with a headache nurse (**chapter 6**) influences the above-mentioned factors and thus will help patients to endure the withdrawal period. With the support of a headache nurse, comprising only one face-to-face contact and a median of three contacts by telephone, 75% of patients with medication overuse headache succeed to undergo a highly cost-effective outpatient withdrawal therapy, which is easily implemented in general neurology practice.

Our data from **chapter 8** suggest that current cluster headache attacks are associated with increased symptoms of depression, and worse sleep quality. Therefore, we may conclude that unsuccessful treatment of cluster headache is associated with poor outcomes: depression and sleeping problems. This underlines the importance of adequate treatment for cluster headache. Another striking and clinically potentially relevant finding of our study was that, in all likelihood, depression is considerably underdiagnosed and undertreated in cluster headache patients. Early detection of comorbid depression in cluster headache may be important to prevent suicide in this unbearably painful primary headache disorder.

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