

# Why are migraineurs more depressed?

## A review of the factors contributing to the comorbidity of migraine and depression

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The comorbidity of migraine and depression is well-known. Patients with both conditions show stronger headache-related symptoms, a more severe clinical course and higher risk for migraine chronification. Therefore, it's important to identify factors underlying comorbid migraine and depression. The growing body of literature suggests complex, biopsychosocial mechanisms in the background, including shared genetic risk factors and abnormal brain mechanisms, and also different environmental (stress) and psychological variables (for example: rumination, neuroticism). In this short review we summarize the most important findings regarding the interacting factors in the pathomechanism of the co-existence of migraine and depression. Finally, we conclude some therapeutical considerations regarding treatment of patients with the migraine-depression phenotype.

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There is a well-known connectivity between migraine and several psychopathological illnesses, especially mood and anxiety disorders. In patients with major depressive disorder (MDD) the risk of comorbid migraine is two to three times higher than in non-MDD controls (Ligthart et al., 2014). The connection between migraine and anxiety is similarly strong, and the association of MDD and anxiety might be particularly strong in persons with comorbid migraine (Breslau et al., 1994). Others (Oedegaard and Fasmer, 2005; Oedegaard et al., 2010) also highlight the high degree of comorbidity between migraine and bipolar disorder, and the possibility that migraine in patients with unipolar depression might be a bipolar spectrum trait (because their symptom profile resembles more the symptom profile of pa-

tients with bipolar disorder compared to the pure MDD-group).

Some suggest a specific order of onset: anxiety disorders tend to precede migraine, whereas depression tends to follow it; but a bidirectional relationship between depression and migraine seems to be the most plausible model: each condition increases the incidence of the other (Buse et al., 2013). It has been demonstrated that many health conditions increase the risk of depression and in turn depression negatively affects the treatment outcome and the associated disability rate in these patients (Prince et al., 2007). There is also evidence suggesting that migraineurs with comorbid psychiatric disorders have worse headache-related symptoms (e.g., frequency, disability) and lower quality of life than migraineurs

without psychiatric comorbidities, and depression and anxiety seem to be risk factors for migraine chronification (Buse et al., 2013). Allodynic symptoms and higher susceptibility to migraine triggers were found to be related to anxiety and depression symptoms among migraineurs (Baldacci et al., 2015). Patients with comorbid migraine and depression also have a more serious clinical course (Cahill and Murphy, 2004) and are less likely to respond to selective serotonin reuptake inhibitors (SSRIs) (Leuchter et al., 2010).

A growing body of evidence suggests complex, biopsychosocial mechanisms in the background of the comorbidity between migraine and depression. In this short review we collect the most relevant possible factors underlying this relationship of the two disorders.

### SHARED GENETIC FACTORS IN THE COMORBIDITY BETWEEN MIGRAINE AND DEPRESSION

Both depression and migraine are around 40-50% heritable, and both conditions have a polygenic background (Ligthart et al., 2014). It has been hypothesized that common genetic variants can predispose to comorbidity of migraine, anxiety and depression. Twin studies suggest that about 20% of the variability in depression and migraine headaches was due to shared genes (Ligthart et al., 2010; Schur et al., 2009).

Altered serotonin neurotransmission is a key finding in both depression and migraine, and most previous hypotheses about the pathomechanism of comorbidity in these disorders were built on this observation (Cahill and Murphy, 2004). Genetic findings support the involvement of the serotonin system in shared biological processes: one of the main candidates is the serotonin transporter (5HTT) gene (*SLC6A4*) that has a functional polymorphism in the promoter region (*5HTTLPR*): the short form (s) of which is transcriptionally less active (Lesch et al., 1996). This short form (s) is associated with anxiety-related traits (Gonda et al., 2009; Lazary et al., 2011; Lazary et al., 2009; Lazary et al., 2008; Lesch et al., 1996; Munafo et al., 2009) and risk of depression (Caspi et al., 2010; Caspi et al., 2003; Gonda et al., 2005). Furthermore, it was demonstrated that the s allele also increases the risk of migraine (Gonda et al., 2007; Juhasz et al., 2003; Schurks et al., 2010). On the other hand, fundamental differences exist at the 5HT receptor level between these two conditions that questions the

serotonergic explanation of the increased comorbidity between migraine and depression, which will be explained in the next section.

A dopamine dysfunction was also suggested as an underlying cause of the comorbidity between migraine and depression (Buse et al., 2013), but the literature on alterations in dopamine genetics in migraine shows highly mixed results (Akerman and Goadsby, 2007).

The endocannabinoid system also seems to have a role in the comorbidity of migraine and depression. The cannabinoid receptor 1 (CB1) gene (*CNR1*) was found to be a risk factor for depression through a high neuroticism-low agreeableness phenotype (Juhasz et al., 2009a); and the *CNR1* gene also has a significant effect on migraine (Juhasz et al., 2009b; Juhasz et al., 2017).

A study investigating the shared genetics of migraine and anxious depression (Ligthart et al., 2010) showed that the heritability of migraine was higher when it wasn't accompanied by comorbid depression. The researchers concluded that some depression-related disturbances in the brain could also be a risk factor for migraine, and thus depressed individuals would still develop migraine regularly without a severe genetic predisposition to migraine. Indeed, the genetic background of migraine patients with comorbid depression resembled more to depression than migraine using a polygenic risk score analysis (Ligthart et al., 2014).

Another study (Oedegaard et al., 2010) suggested that some genes may predispose to both bipolar disorder and migraine: a susceptibility locus was identified on chromosome 20 pointing to a genetic overlap between migraine and bipolar disorder. The authors highlighted that the identified overlapping region harbors a potassium-dependent sodium/calcium exchanger gene, *SLC24A3*, which has an important role in neuronal calcium homeostasis and electrical conduction. Based on their findings the researchers suggested that ionic disturbances seem to be relevant in the migraine-bipolar disorder phenotype.

### BRAIN MECHANISMS OF COMORBIDITY BETWEEN MIGRAINE AND DEPRESSION

Modern neuroimaging studies showed abnormal function, structure, and connectivity of brain regions that could contribute to the comorbidity of migraine and psychiatric disorders (Minen et al., 2016).

As we mentioned, there are some basic differences between depression and migraine at the 5HT receptor

level. Positron emission tomography (PET) studies demonstrated that in depression, both in the acute phase and in remitted patients, there is an extensive reduction of 5HT<sub>1A</sub> receptors in the brain (Drevets et al., 2007; Sharp and Cowen, 2011). In parallel with this, neuroendocrine challenge paradigms in depressed patients repeatedly found blunted cortisol response to agents that acutely increase extracellular 5HT concentrations (Sharp and Cowen, 2011). In contrary to depression, migraine patients show increased 5HT<sub>1A</sub> receptor density (Lothe et al., 2008; May, 2009) and they are sensitive to brain serotonin increasing agents and usually respond with a delayed migraine attack and an augmented cortisol response compared to controls (Panconesi, 2008). In addition, the first-line antidepressant drugs in the treatment of major depression, the SSRIs, are not effective in preventing migraine attacks (Evers et al., 2009; Moja et al., 2005; Panconesi, 2008). In contrary, the most effective migraine prophylactic drugs, the beta-blockers, have pro-depressive side effects.

The above results, therefore, don't support the serotonergic explanation of depression-migraine comorbidity. FMRI studies, however, investigating the effect of *5HTTLPR* and emotional information processing repeatedly found increased amygdala activation in *s* allele carriers for emotionally salient stimuli (Hariri et al., 2002; Munafo et al., 2008). In addition, comparing *s* carriers with *ll* homozygotes in healthy volunteers the connectivity between the amygdala and the ventro-medial prefrontal cortex (vmPFC) increased, reflecting increased coupling between these areas (Heinz et al., 2005), whereas decreased coupling was found between the amygdala and the perigenual anterior cingulate cortex (pACC) (Pezawas et al., 2005). The *s* allele was also associated with alterations in frontal-limbic white matter microstructure indicating abnormalities in their connectivity (Pacheco et al., 2009). These observations suggest that the top-down frontal cortical control on stress-, emotion-, and pain-processing limbic brain areas is under genetic control, and altered connection between these regions can be detected even before any symptoms develop. Thus these genes through these brain alterations can contribute to the development of both altered mood state and chronic or recurrent pain symptoms.

In migraine, voxel-based morphometric studies (VBM) repeatedly found decreased grey matter volume in the pain network, including the ACC (May, 2009). These regions highly overlap with the stress response-processing networks. Decreased grey

matter volume in the frontal lobe was associated with significantly slower response time during a cognitive task (set-shifting) in migraine patients (Schmitz et al., 2008). Altered top-down control of the visual cortex has been identified in migraine patients when attempting to suppress unattended visual events (Mickleborough et al., 2011). In addition, a diffusion-weighted MRI study demonstrated microstructural alterations in the right frontal white matter and its connection to the orbitofrontal cortex, insula, thalamus, dorsal midbrain (Szabo et al., 2012). In summary, several lines of evidence suggest that impaired frontal cortical control is present in migraine. It has been argued that these grey matter and microstructural changes might be secondary to repeated pain, as similar alterations can be observed in other chronic pain conditions (May, 2009; Szabo et al., 2012). However, as we mentioned, the typical order of onset of symptoms is usually anxiety → migraine → depression. This suggests that impaired top-down frontal cortical control-elicited reduced stress resilience precedes the occurrence of repeated migraine pain and thus it can constitute an important mechanism in the development of comorbid depression and migraine.

A review collected the most important results of functional imaging studies of migraine (Schwedt and Chong, 2015). Evidence suggests that the migraine brain is hyperresponsive to different sensory stimuli, and there's a potential imbalance of pain facilitation and inhibition within the migraine brain that possibly contributes to higher sensitivity to noxious stimuli and development of cutaneous allodynia during migraine attacks. The authors mentioned that the majority of studies are cross-sectional, so direction of the found associations can't be determined. Only a single longitudinal study suggested that the imaging abnormalities identified in migraine could be a result of recurrent migraine attacks.

Some affective-motivational brain regions have been commonly identified with abnormal function or structure in migraineurs (including the anterior cingulate cortex, anterior insula, prefrontal cortex, hippocampus and amygdala), and imaging studies in people with psychiatric disorders (including depression) showed similar affected brain regions (Minen et al., 2016). A prospective longitudinal study followed a sample from midlife to late life and found that migraine with comorbid MDD is associated with reduced total brain volume, white matter volume, and gray matter volume (Gudmundsson et al., 2013).

## THE ROLE OF STRESS IN THE COMORBIDITY OF MIGRAINE AND DEPRESSION

As seen above, biological factors are important in the connection of migraine and depression, biological factors, however cannot fully explain the comorbidity of these two disorders. Thus we have to consider possible environmental and psychological factors contributing to this comorbidity. Many researchers indeed highlight the role of stress in this conversation.

A prospective longitudinal study (Swanson et al., 2013) examined the contribution of stress to the migraine-MDD comorbidity using several types of stressors (e.g., childhood trauma, marital and financial problems, work stress). The results supported the bidirectional connection between migraine and depression, but both directions of this relationship were largely explained by stressors, and the associations were no longer significant after adjusting for all the measured stressor types. Importantly, all the studied stressors attenuated the associations, and the strongest risk factor was chronic stress for both disorders.

A review on stress-migraine interaction (Sauro and Becker, 2009) defines the different possible roles of stress in this interaction. Stress can contribute to the onset of migraine, act as a trigger for migraine attacks and amplify their intensity and duration, and may also be a risk factor of migraine chronification. The authors also highlighted that migraine itself can be a stressor, creating a vicious cycle; and depression and anxiety can be considered as stressors too, because these states cause an imbalance of one's homeostasis, and share components with the physiological stress reaction. Stress is also connected with psychiatric disorders, and stressful events (especially early in life) increase the risk of MDD (Minen et al., 2016). A study (Hung et al., 2008) found that migraineurs with comorbid MDD are more sensitive to emotional and perceptual stimuli and stress of daily activities than patients with other headache types and comorbid MDD – suggesting a particularly important role of stress among migraineurs with comorbid depression.

Acute stress is necessary for survival and can be adaptive, but chronic stress leads to hyperalgesia and central sensitization (Sauro and Becker, 2009). In migraine as a result of the repeated stress allostatic load occurs creating a feedforward cascade with alterations in normal homeostatic mechanisms, failure to habituate to repeated stressors, and to normally shut down the stress response and inefficient response to stress (Borsook et al., 2012). Psychological factors (e.g., depression and anxiety) also play a role (among

multiple processes) in the formation of altered allostasis in migraine (Borsook et al., 2012).

A study of a nationally representative U.S. sample of young adults tested whether emotional, sexual and physical abuse are associated with migraine, with and without accounting for other types of abuse and for comorbidities of depression and anxiety (Tietjen et al., 2017). Each type of abuse was consistently more frequent in migraineurs, and they were associated with significantly higher odds of migraine. In the fully adjusted model data supported a relationship between migraine and (only) emotional abuse, which was independent of (although attenuated by) depression and anxiety. Over two-thirds of participants reported that their diagnosis of migraine preceded or was concomitant with the diagnoses of depression and anxiety – the authors interpreted this finding as the adjustment for depression and anxiety might be an overcorrection. Abuse in the past possibly modifies the hypothalamic-pituitary-adrenal (HPA) axis leading to higher stress reactivity, and through that strengthen the chance of migraine (Minen et al., 2016) and possibly also depression.

## PSYCHOLOGICAL FACTOR MEDIATING THE EFFECT OF STRESS IN DEPRESSION-MIGRAINE COMORBIDITY

Most of the studies addressing psychological factors that contribute to distress in migraine focused on pain-related variables and general coping strategies, but not assessed stress-related psychological factors that are reliably associated with psychiatric disorders (Kokonyei et al., 2016). A recent study (Kokonyei et al., 2016) identified such a factor: rumination (a stable tendency to focus on distress-related feelings in a passive and repetitive way), which is strongly associated with depression and anxiety, partially mediated the relationship between migraine and psychological distress (controlling for lifetime depression). The authors speculated that rumination could increase allostatic load in migraine.

Previously other personality traits have been implicated in the comorbidity between depression and migraine. Neuroticism (emotional lability), a major risk factor for depression sharing part of its genetic background (Kendler et al., 2006) has been found to be associated with migraine (Breslau and Andreski, 1995; Breslau et al., 1996), partly explained by the same genetic and nonshared environmental factors (Ligthart and Boomsma, 2012). These results suggest that neuroticism is a shared risk factor of migraine

and depression, and the level of neuroticism could be possibly remarkably high in patients with migraine and comorbid depression. Interestingly, rumination also mediates the connection between neuroticism and depression or anxiety (Kokonyei et al., 2016).

Figure 1 summarizes the discussed shared factors of comorbid migraine and depression.

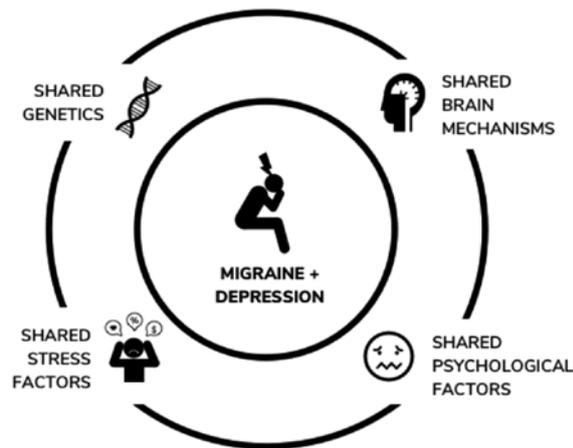


Figure 1. Shared factors of comorbid migraine and depression

### THERAPEUTIC CONSIDERATIONS REGARDING THE COMORBIDITY OF MIGRAINE AND DEPRESSION

The strong connection between migraine and depression calls for some therapeutic considerations in the treatment of patients with this comorbidity.

It's recommended to screen for psychiatric disorders in migraineurs (Minen et al., 2016), and given the bidirectional relationship between migraine and depression (and other psychiatric conditions), it could possibly also be recommended to screen for migraine in patients with psychiatric disorders, especially considering the fact that migraine is frequently underdiagnosed and about half of migraine patients never received a diagnosis and proper treatment (Lipton and Bigal, 2007). The underdiagnosis of migraine could be particularly representative among men, because they are less likely to seek out medical advice for their migraine compared to women (Vetvik and MacGregor, 2017).

We have seen that stress has a substantial role in the connection between depression and migraine, so use of stress-management techniques is important in these patients – some relevant techniques, including relaxation training, cognitive behavioral therapy

(CBT) addressing stress management, and biofeedback were consistently found to be effective in managing migraine (Sauro and Becker, 2009). Reducing rumination could be also a specific therapeutic target (Kokonyei et al., 2016). The combination of medication and behavioral treatment is more effective than either one alone in treating migraine (Minen et al., 2016), and probably also in the treatment of migraineurs with psychiatric comorbidities.

Autogenic training (AT) was shown to have a consistent and significant effect in reducing anxiety (Ernst et al., 2007; Kanji et al., 2006; Manzonei et al., 2008) and it's also effective as a preventive treatment in migraine by decreasing migraine headache frequency after long term practice (Zsombok et al., 2003; Zsombok et al., 2005), even though it cannot alleviate acute migraine pain (Juhasz et al., 2007). It can be assumed that the therapeutic potential of AT might also be relevant to prevent certain types of depression, especially in co-morbid migraine.

An important question is whether efficient treatment of depression leads to a reduction also in the migraine symptoms (Ligthart et al., 2014), and vice versa: can successful treatment of migraine reduce the comorbid psychiatric symptoms, too? The literature on the impact of comorbid psychiatric disorders on the effectiveness of headache treatment shows mixed results: some suggests that psychiatric comorbidities could lead to a failure of migraine treatment, while others report similar improvement rates after treatment comparing patients with and without psychiatric comorbidities (Minen et al., 2016). There is evidence that prophylactic use of onabotulinumtoxin A significantly reduced headache-related as well as depression and anxiety symptoms in patients with chronic migraine and comorbid depression (Boudreau et al., 2015). Another promising example is that a treatment program using CBT among patients with migraine and/or tension-type headache and comorbid MDD improved participants' headache symptoms, depression, anxiety and quality of life, and these improvements were maintained at least for 4 months (Martin et al., 2015).

### CONCLUSION

In this review we focused on the connection between migraine and depression, however, there is also evidence for the association between migraine and other psychiatric (and somatic) disorders. For example, post-traumatic stress disorder (PTSD) is also significantly more prevalent among migraineurs

than in the general population, and there are also data suggesting that PTSD mediates the association between abuse and migraine (Minen et al., 2016).

We also need to highlight that both migraine and depression shows high disease heterogeneity, and the biological aspect of the comorbidity between the two conditions could vary diagnosis by diagnosis. There's clearly a need to recognize the potential subgroups of this heterogenous patient population, and to stratify the possibly different biological pathways in the background of their conditions towards the way of precision medicine.

#### ABBREVIATIONS

<b>5HTT:</b>	serotonin transporter
<b>5HTTLPR:</b>	serotonin transporter-linked polymorphic region
<b>AT:</b>	autogenic training
<b>CB1:</b>	cannabinoid receptor 1
<b>CBT:</b>	cognitive behavioral therapy
<b>CNRI:</b>	cannabinoid receptor 1 (CB1) gene
<b>HPA axis:</b>	hypothalamic-pituitary-adrenal axis
<b>MDD:</b>	major depressive disorder
<b>MRI:</b>	magnetic resonance imaging
<b>pACC:</b>	perigenual anterior cingulate cortex
<b>PET:</b>	positron emission tomography
<b>SLC6A4:</b>	serotonin transporter gene
<b>SSRI:</b>	selective serotonin reuptake inhibitor
<b>VBM:</b>	voxel based morphometry
<b>vmPFC:</b>	ventro-medial prefrontal cortex

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## Miért gyakoribb a depresszió migrénesekben?

### A migrén és a depresszió komorbiditásához járuló faktorok áttekintése

A migrén és a depresszió jól ismertén kapcsolódik egymáshoz. A mindkét betegséget mutató betegek a fejfájáshoz köthető erősebb tüneteket és súlyosabb klinikai lefolyást mutatnak, valamint körükben nagyobb a migrén krónikussá válásának kockázata. Mindebből adódóan fontos a komorbid migrén és depresszió hátterében meghúzódó faktorok azonosítása. Az egyre növekvő szakirodalom komplex, biopszichoszociális mechanizmusokra utal a jelenség hátterében, beleértve közös genetikai rizikófaktorokat és kóros agyi mechanizmusokat, illetve különféle környezeti (stressz) és pszichológiai (például: rumináció, neuroticizmus) tényezőket egyaránt. Rövid összefoglalónkban összegezzük az együttesen jelentkező migrén és depresszió patomechanizmusában egymással interakcióban szerepet játszó faktorokkal kapcsolatos legfontosabb szakirodalmi eredményeket. Végül néhány terápiás megfontolást is közlünk a migrén-depresszió fenotípust mutató alanyok kezelése kapcsán.

**Kulcsszavak:** migrén, depresszió, komorbiditás, genetika, agyi mechanizmusok, stressz, rumináció, terápia, összefoglaló