

# Management of psychiatric comorbidities in migraine

## Manejo das comorbidades psiquiátricas na migrânea

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### ABSTRACT

Psychiatric comorbidities are one of the main issues in migraine management. Diagnosis and treatment strategies are deeply affected by mental health diagnosis and symptoms. Depression and anxiety has been the most studied topics, anxiety aspects such as excessive worry, inability to control worries, inability to relax are highlighted. It is also reviewed in this paper data on the relation of psychiatric symptoms and migraine; the rationale for using a symptom-based approach; how migraine overlaps with anxiety, ADHD, and bipolar symptoms. Screening tools addressing specific mental health topics are discussed, as a comprehensive approach for frequent acute medication intake considering psychiatric comorbidity. An algorithm is proposed for the general management of psychiatric comorbidity in migraine.

**Keywords:** Migraine; Psychiatric comorbidities; Anxiety; Depression; Bipolar; ADHD

### RESUMO

As comorbidades psiquiátricas são um dos principais problemas no manejo da migrânea. As estratégias de diagnóstico e tratamento são profundamente afetadas pelos diagnósticos e sintomas na esfera da saúde mental. Depressão e ansiedade têm sido os tópicos mais estudados, aspectos de ansiedade como preocupação excessiva, incapacidade de controlar preocupações e incapacidade de relaxar são elevados. Também é revisado neste artigo os dados sobre a relação entre sintomas psiquiátricos e migrânea; a justificativa para usar uma abordagem baseada em sintomas; como a enxaqueca se sobrepõe a ansiedade, TDAH e sintomas bipolares. Ferramentas de triagem abordando tópicos específicos de saúde mental são discutidas, como uma abordagem abrangente para ingestão frequente de medicação aguda considerando comorbidade psiquiátrica. Um algoritmo é

proposto para o tratamento geral da comorbidade psiquiátrica na migrânea.

**Palavras-chave:** Enxaqueca; Comorbidades psiquiátricas; Ansiedade; Depressão; Bipolar; TDAH

### INTRODUCTION

Migraine is a neurological condition affecting near 12% of the population worldwide,<sup>(1)</sup> considered to be the third most disabling disorder in adults less than 50 years-old age.<sup>(2)</sup>

Psychiatric comorbidities have been linked to migraine, interfering substantially with its diagnosis and treatment. Anxiety and mood disorders have been the most studied conditions, shown to be 2-10 times more common in migraine when compared to healthy controls in general population.<sup>(3)</sup>

In clinical settings, psychiatric comorbidities lead to poorer quality of life<sup>(4)</sup> more health care expenditures,<sup>(5)</sup> increase risk for progression from episodic to chronic migraine,<sup>(6)</sup> being a more difficult to treat patient.<sup>(7)</sup>

In this paper we review the relevant data on psychiatric comorbidity in migraine, propose algorithms for its management and how the field have to move in the next five years.

#### Psychiatric disorders in the population

Psychiatric disorders are common and debilitating conditions. Although overlap between mental health diseases

is the rule, the field divides in several areas, the following are the ones considered to be the most prevalent and relevant: mood disorders (major depression, bipolar depression), substance abuse disorders (nicotine, alcohol, cannabis, cocaine), anxiety disorders (generalized anxiety disorder, panic disorder, phobias), psychotic disorders (schizophrenia, psychosis).<sup>(8)</sup>

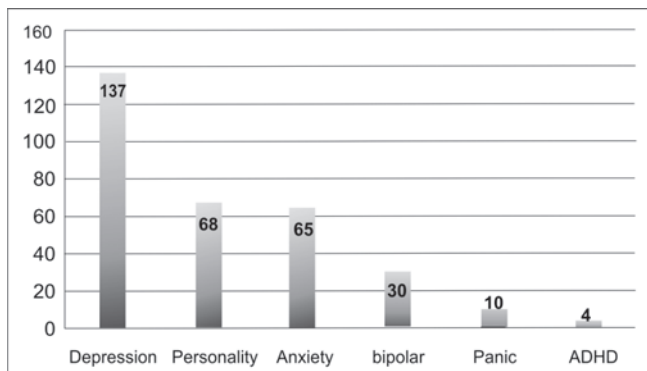
The prevalence of having any mental health disorder have been found to be 15.4% worldwide, ranging from 12.1% in low/lower-middle income countries to 15.4% for upper-middle and to 17.0% in high-income.<sup>(9)</sup>

The global burden of disease study calculated disability-adjusted life years (DALYs) by the sum of years of life lost due to premature mortality (YLL) and years lived with disability (YLD), showing major depression the 11th cause of DALYs. Considering YLDs, seven out of the 19 highest where mental health disorders (Major depression, #2, anxiety disorders, #7; drug use disorders, #12; alcohol use disorders, #15; bipolar disorder, #17; schizophrenia, #18; dysthymia, #19; while pain disorders ranked also very high, including migraine being #8.<sup>(2)</sup>

### Psychiatric comorbidities in migraine

Psychiatric comorbidities are common in migraine patients, affecting its management considerably. Studies in general population, clinical settings, tertiary headache specialty centers have all shown high rates of psychiatric diagnosis in migraine, particularly more in women, in patients with aura, and in chronic versus episodic migraine subjects.<sup>(10)</sup> Depression and anxiety disorders have been the most studied topics, as shown in the Graph 1.

Epidemiological studies suggest a bidirectional relationship between depression and migraine,<sup>(11)</sup> high prevalence of bipolar disorders and a significant impact



Graph 1. Number of studies published with migraine and psychiatric comorbidity keywords appearing in title (PubMed)

have been described, particularly in bipolar II women, migraine with aura or cyclothymic temperament.<sup>(12)</sup> In general, psychiatric symptoms are associated with severe migraine-related disability.<sup>(11)</sup>

### Diagnostic approach of psychiatric disorders in headache patients

The diagnosis of psychiatric disorders are challenging for all specialties dealing with headache patients, from family practice physicians to headache specialists. Training in psychiatry is limited among neurologists and other clinical specialties. Diagnosis in psychiatry, like in headache disorders, is based in clinical, subjective information given by patients, analyzed and defined by physicians throughout a non-biological, arbitrary criteria. As important as taking headache related clinical history for diagnosis according to the International Classification of Hedache Disorders<sup>(13)</sup> is a mental health history for defining not only psychiatric disorders associated with headaches but physical and mental symptoms that could interfere with patients quality of life.

The approach to the psychiatric diagnosis in headache patients has the difficult task of stablishing what is cause what is consequence, or even if a third factor could be causing both conditions, such as hormonal, metabolic, renal, hepatic, or cardiovascular disorders, trauma, substances (medications, alcohol, caffeine, other drugs). A detailed clinical history plays pivotal role in determining the time of occurrence and causality between one or another condition, however, a memory recall bias limits a perfect definition.

Like in headache disorders, the concepts of spectrum and/or continuum in psychiatric disorders are critical. The current understanding of bipolar disorders consider a wide variety of clinical presentations.<sup>(14)</sup> Overlap between psychiatric disorders, in diagnostic criteria and symptoms occurs. As the migraine/tension-type headache continuum is familiar for the headache care physician, continuums between depression and anxiety, anxiety and ADHD, bipolar spectrum and ADHD are part of daily clinical dilemmas for the psychiatrist,<sup>(15)</sup> and naturally should also happen in the management of psychiatric comorbidity in migraine patients. More complexity adds to the issue when migraine is considered, as a possible spectrum/continuum between migraine and anxiety, as migraine and mood disorders exist.

When looking at anxiety and mood related symptoms one may understand how much of migraine features are actually part of psychiatric symptoms or exacerbate them.

In generalized anxiety disorder (GAD) diagnosis, criteria C symptoms are very influenced by chronic headaches and headache attacks, including sleep complaints, irritability, muscle tension, concentration, and fatigue, all occurring prior, during or after the headache phase (Table 1).

Table 1 - Generalized Anxiety Disorder diagnostic criteria and how a migraine attack affects symptoms

| GAD  | Amount migraine affects symptoms |
|--|----------------------------------|
| A. Excessive anxiety and worry (>15 days/month for > 6 months)                               | -                                |
| B. Difficult to control  | -                                |
| C. 3 or more   | -                                |
| 1. Restlessness, feeling keyed up or on edge   | -                                |
| 2. Being easily fatigued   | X                                |
| 3. Difficulty concentrating or mind going blank  | XX                               |
| 4. Irritability  | XX                               |
| 5. Muscle tension  | XXX                              |
| 6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep) | XXX                              |

In depression, the two main symptoms, loss of pleasure and mood are directly affected by pain experience. Other symptoms such as decrease or excessive sleep, fatigue, poor concentration, psychomotor retardation, can also be part of the migraine attack. Weight loss or gain, guilt, and death thoughts are not part of migraine.

In addition, when further analyzing mood swings in bipolar depression, the clear depressive mood of being in a headache attack, and the swing to a pain-free state is

already a mood fluctuation, confounding diagnosis. Migraine itself maybe a factor for a specific modulation, possibly interfering in how comorbidities develop over time.

In the Venn diagram we exemplify how migraine interacts with ADHD, anxiety and the bipolar spectrum symptoms, where irritability lies in the middle, being part of four clinical syndromes.

The diagnostic based approach can be performed through a referral to a psychiatrist or psychologist, or performed by the headache care provider, using screening and diagnostic tools such as CIDI (Composite International Diagnostic Interview) or SCID (Standardized Clinical Evaluation),<sup>(16)</sup> based on DSM-V, or individually, using specific self-report measures by asking patients to complete paper-and-pencil, tablet or smartphone-based tools. Another way of assessing psychiatric comorbidities in migraine is by a symptom-based approach.

Rationale for the symptom-based approach in migraine psychiatric comorbidity

Symptom-based approach is a new paradigm in mental health research.<sup>(17)</sup> Diagnosis in headache as in mental health is based in clinical criteria, where classification systems try to find cluster of symptoms and define specific diagnosis, separating one disease to another. Defining disorders as separate entities is important for the advance of medicine, but this has brought an artificial concept, lacking the fact that most of disorders overlap. In addition, mental health

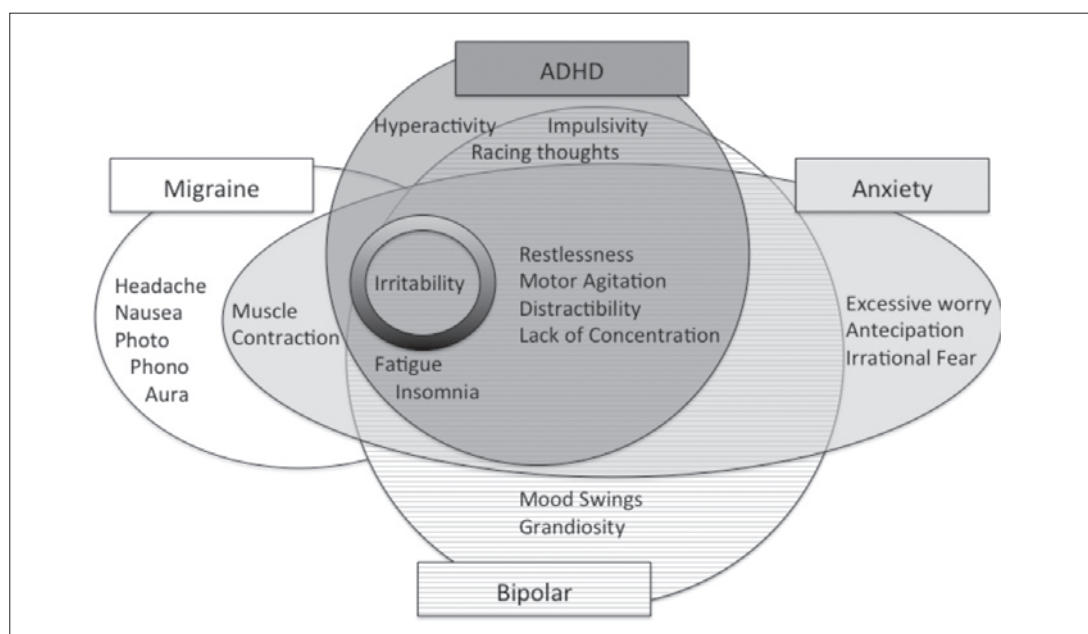


Figure 1. Venn diagram showing the overlap in symptoms between migraine and ADHD, anxiety and bipolar disorders.

symptoms may occur and affect substantially the migraine clinical picture and response to treatment, therefore mental health diagnosis should consider subsyndromic diagnosis, and even further, looking at main symptoms, such as excessive worry, irritability, lack of control anxiety or inability to relax.

We studied recently anxiety and mood symptoms in a symptom-based approach.<sup>(18)</sup> We found anxiety symptoms were more relevant in migraine than depression, where physical symptoms were more commonly related than psychological, such as felling down and deaths thoughts.

Moreover, the most significant aspects found in migraine sufferers versus controls where not being able to control worrying, if occurring on a daily basis showed OR of 49. Trouble relaxing, excessive worry, and being anxious, all on a daily basis range OR near 25, as shown in Figure 2, much higher than the 2 to 10 range found in all previous epidemiological studies.

When choosing the strategy of self-administered screening and get more information on specific aspects of psychiatric comorbidities in migraine one may consider the following tools as shown in Table 2.

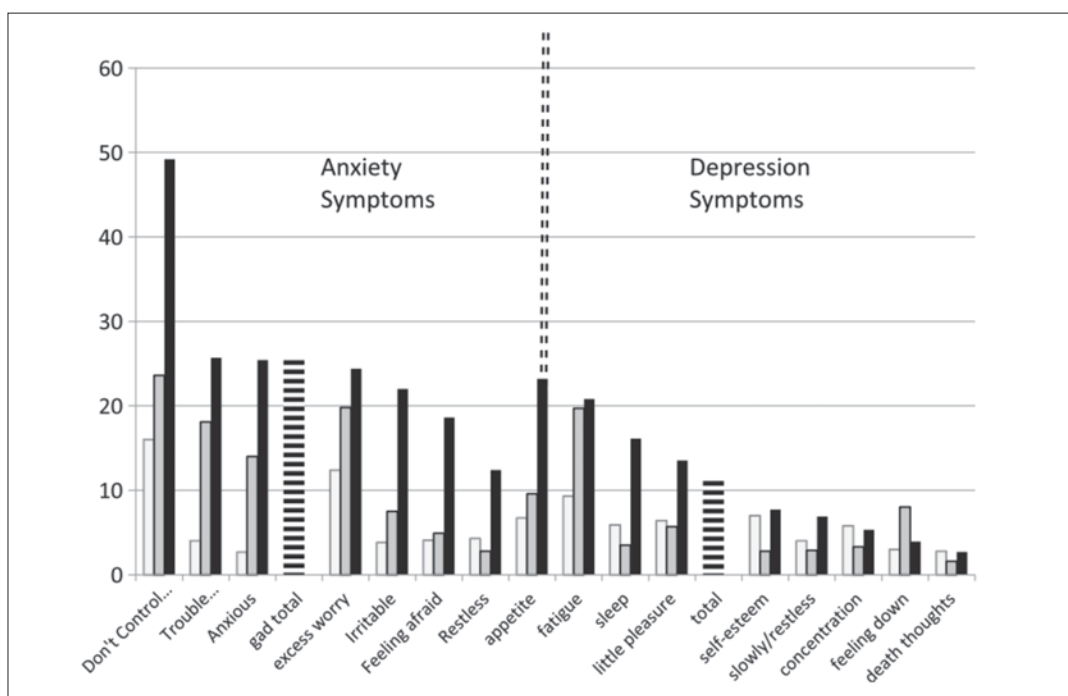


Figure 2. Odds ratios for migraine risk according to anxiety (left) and depression symptoms (right)

Table 2 - Self administered screening tools for bipolar, anxiety, ADHD and substance abuse

| Disorder        | Questionnaire / Screening Tool               |
|-----------------|--|
| Bipolar         | MDQ Mood Disorders Questionnaire*            |
|                 | BSDS Bipolar Spectrum Diagnostic Checklist** |
|                 | HCL-32 Hypomania checklist***                |
| Anxiety         | GAD-7 Generalized Anxiety Disorder           |
| Depression      | PHQ-9 Patient Health Questionnaire           |
| ADHD            | ARSR-18 Self-rating                          |
| Substance Abuse | NIDA   |

\*performs well on bipolar I, more severe

\*\*performs well bipolar II

\*\*\* bipolar I and II

### Other relevant mental health related aspects

Other mental health aspects are important, not only in general population and across several cultures but also in headache patients. Optimism, pessimism, catastrophization, religiosity/spirituality, traumatic life events need further studies on how they are related to symptoms, psychiatric diagnosis and their influence in migraine management.

### Treatment challenges

After choosing the ideal approach according to the setting of headache provider, and getting a correct diagnosis, treatment challenges arise.

One of the main issues in migraine management is medication overuse. Its approach has to be tailored and therapy chosen according to how medication overuse is classified. For management purposes is important to stratify acute medication/analgesic use in headache patients in five different categories.

First is when daily intake is excessive because headaches are frequent, analgesic use then is just the consequence of having frequent headaches, no cause relationship exist. Second is when acute medication is causing side effects, such as tachycardia, insomnia, sleepiness, concentration problems, gastritis, tremor. Third when psychiatric comorbidity lead migraineurs to be more prone to excessive use, because of lack of control in anxiety or ADHD(18), or fear of having a headache(19); fourth when analgesic intake is causing a headache through rebound; and fifth is when a substance abuse disorder is present. All topics may occur together but has different management approaches (Figure 3).

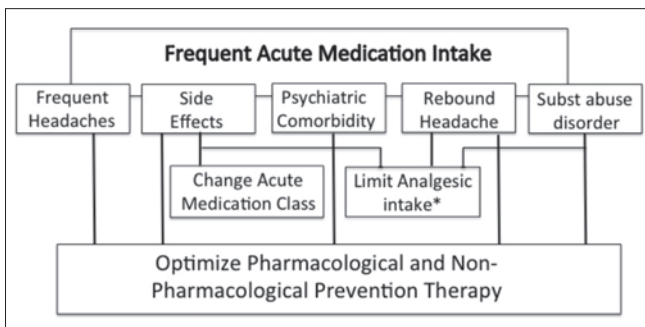


Figure 3. Frequent acute medication decision tree.  
\* Limit analgesic intake may exacerbate anxiety in daily headache patients.

### Psychiatric commorbidity algorithm management in migraine patients

In Figure 4 we find a symptom-based and diagnostic approach to psychiatric comorbidity in migraine. As observed in Figure 1, irritability is part of anxiety, ADHD and bipolar diagnosis. If it is present in the migraineur one may have to explore the correct diagnosis, also considering the possibility of all occurring altogether. Sometimes the definition would be done in a therapeutic trial. All patients should be given a nonpharmacological customized prescription, whereas according to what is present, the pharmacological regimen should be chosen. Associations of different drug classes may be needed. Sleep problems could shift toward a different approach, but this is not being further considered in this paper.

Many of the medication may cause weight gain, what can decrease patient satisfaction, reducing adherence, as well as lead to clinical complications, such as obesity, diabetes, hypertension and other. In this case, a specific strategy should be inserted, with dietary and physical exercise advise and medications such as topiramate, melatonin or stimulants.

### Expert commentary

I (MFPP) find in my clinical practice the symptom-based approach a lot more suitable for the management of psychiatric comorbidity in migraine than the full-blown, DSM diagnosis approach. When the disorder is severe, diagnosis

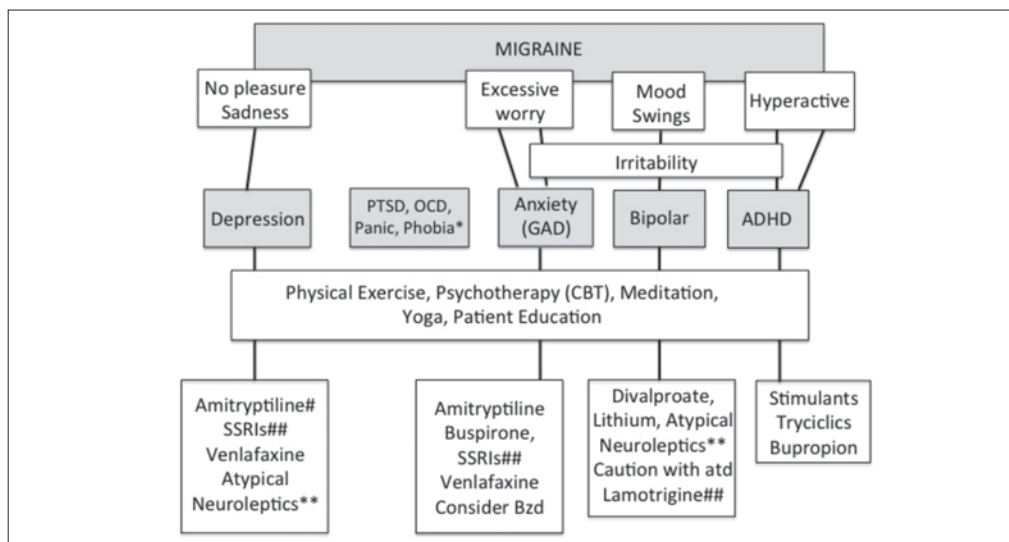
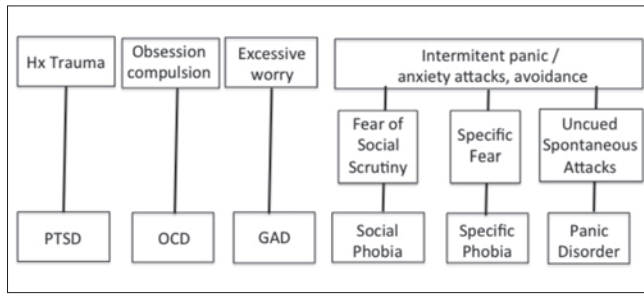


Figure 4. Psychiatric commorbidity algorithm management in migraine patients  
\* Complete decision tree for anxiety disorders in Figure 5.  
\*\* Olanzapine and quetiapine have antidepressant effect and anecdotal efficacy in migraine; \*\*\* Lamotrigine is a good choice for bipolar disorder but limited evidence in migraine prevention; # Amitriptylin needs doses 75 mg or higher for antidepressant efficacy; ## SSRIs such as fluoxetine and sertraline failed migraine prevention trials, citalopran, escitalopran, paroxetine are better options.





**Figure 5. Decision tree for the diagnosis of anxiety disorders.**

PTSD: Posttraumatic stress disorder  
 OCD: Obsessive-compulsive disorder  
 GAD: Generalized anxiety disorder

become easier, but many patients bring only the main symptom and will not fill out complete diagnostic criteria.

Referring to a psychologist or psychiatrist for a diagnosis is often difficult, due to availability, timing, and clinical severity, therefore, the symptom-based approach and the use of diagnostic self-administered tools speed up patients management.

The more severe cases are definitely more complex in psychiatric comorbidity, with more severity and more features involved, refractory patients are in general not diagnosed or not well managed in their mental health needs.

Although an evidence-based guideline is ideal, some caveats from our clinical experience we would like to share, as this topic allows. Olanzapine is very effective and fast, may be difficult to manage in long term, because of weight gain and metabolic consequences, but for initial therapy is equally effective for severe headaches, severe depression, refractory insomnia, and anxiety. When patients are stabilized one may shift to a more long term strategy.

If depression and sleep are the most important aspects, mirtazapine is one of the most effective antidepressives, being weight gain limits its use in long term. Escitalopram is in our experience the most effective of the SSRIs, not only for depression and anxiety, but also effective for migraine control, although fluoxetine and sertraline failed migraine prophylaxis trials, and limited evidence for others SSRIs, escitalopram has been one of the main options in my clinical practice in the past 15 years.

For patients with anxiety, sleep problems and migraine, and some depression (not severe) agomelatine appears to be a safe option. It is not clear to me yet whether melatonin could have the same effect.

If ADHD is suspected, don't be afraid of a stimulant trial, the experience is favorable not only for ADHD symptoms but also for migraine control.

It gets more complicated when you think the overlap with depression/bipolar spectrum, anxiety and ADHD

themselves, without considering other pain disorders, other headache disorders, and migraine headaches.

### Five-year view

In this topic, we bring a speculative viewpoint on how the field will evolve in 5 years time. One view is derived from what is desirable but other is what actually may happen if nonpharmaceutical stake holders don't move in the right direction.

Pharmaceutical companies invest annually 60 billion US\$ in drug discovery, whereas the NIH budget for medicine is 30 billion. Notwithstanding, 90 billions are spent in marketing by pharmaceutical companies. Only for comparison, 600 billion is spent annually in defense.<sup>(20)</sup> Therefore, one may not expect any extreme change in medical discoveries when 20 times more is spent in war than in health.

Nowadays innovation in health sciences is not patient centered. Many effective therapies could be discovered if investment in psychological, physical, dietary-based treatments were studied. In addition, pharmacological options deserving more studies, such as non patent protected medication (old medications, vitamins, minerals, herbs). But the reality is that only new drugs with financial return on investment have the chance to be studied.

The new era of CGRP monoclonal antibody compounds may bring some insights for the treatment of psychiatric comorbidity itself or even opening windows in psychiatric therapy. CGRP is released in the bed nucleus of the stria terminalis, and has been related to reward and anxiety mechanisms.<sup>(21)</sup>

### Key issues

1. Psychiatric comorbidity is an important topic in migraine management
2. Depression has been the most studied topic but anxiety symptoms have the strongest connection in migraine patients.
3. The symptom-based approach is useful approaching mental health aspects in migraine patients.
4. Generalized anxiety disorder symptoms such as fatigue, irritability, muscle tension, concentration, and sleep complaints are common issues in migraine patients.
5. Migraine overlaps with anxiety, ADHD, and bipolar symptoms, irritability connects all.
6. Screening tools addressing specific topics maybe useful in psychiatric comorbidity assessment.

7. Frequent acute medication intake may occur in five different situations: a) increase in intake is just because headaches are frequent (non-causality), b) acute medication is causing side effects, c) rebound, d) psychiatric is predisposing acute medication intake, and e) there is a substance abuse disorder.

8. Consider also other anxiety diagnosis in migraineus including PTSD, OCD, panic, and phobias.

9. An algorithm (proposed in this paper) may be followed in psychiatric comorbidity management in migraine.

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