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Experts and national consultants' recommendations regarding management of patients treated for migraine with comorbid depression. Diagnosis. Therapeutic strategies. Part 2

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Summary

Depressive disorders are currently diagnosed based on the ICD-10 and DSM-5 diagnostic criteria and include axial depressive symptoms and additional symptoms that must coexist for at least two weeks. Migraine is diagnosed based on the International Classification of Headache Disorders. It is generally divided into migraine with and without aura, and with regard to the frequency of attacks into episodic and chronic migraine. The therapeutic strategy in the treatment of depression is pharmacotherapy combined with psychotherapy, whereas in the treatment of migraine the strategy depends on the frequency of headache attacks (episodic migraine vs. chronic migraine) and comorbidities. A novelty is the introduction of monoclonal antibodies directed against CGRP or the receptor of CGRP. There are numerous reports which

indicate specific usefulness of monoclonal antibodies that modify the action of CGRP in the treatment of migraine in people suffering from depression.

Key words: migraine, depression

Introduction

Major depressive disorders (MDDs) are the most common condition observed in patients with migraine [1-3], and the risk of MDD in migraine headache sufferers exceeds the population risk [4].

The standard approach to the management of migraine, before starting pharmacological or non-pharmacological treatment, is the correct diagnosis of the disease [5], followed by a detailed discussion with the patient about the nature of the disease and the planned management. It is important to identify the factors that trigger attacks or exacerbate migraine discomfort and to recommend that the patient should try to avoid them. The patient needs to understand the nature of the disease and accept the fact that migraine treatment is aimed at improving his or her functioning, but not at curing it, since it is a lifelong ailment. The choice of appropriate treatment depends on the existence and comorbidity of other diseases, as well as the age and gender of the patient. Thus, emergency and prophylactic treatment is the last element of a proper diagnostic and therapeutic process [6]. The standards of diagnostic and therapeutic management as well as *ad ho*c and prophylactic treatment of episodic migraine, together with the standards of prophylactic treatment of chronic migraine, have been developed by international – American and European – and local societies, including the Polish Headache Society and the Polish Neurological Society [5, 6-17].

Migraine diagnosis criteria

Migraine has well-defined diagnostic criteria, which clearly distinguish it from tension-type headache, trigeminal autonomic cephalgias or even rarer spontaneous headaches. According to the International Classification of Headache Disorders (ICHD-3), migraine is divided into migraine without aura and migraine with aura [5].

The criteria for the diagnosis of migraine without aura include:

A. At least five attacks fulfilling criteria B-D.
B. Headache attacks lasting 4 to 72 hours (when untreated or treated ineffectively).
C. The headache exhibits at least two of the following four characteristics:
    1) is located on one side;
    2) has a pulsating character;
    3) is of moderate or severe intensity;
    4) intensifies during normal physical activity (e.g. walking or climbing stairs) or forces to avoid such activity.
D. At least one of the associated symptoms is present during the headache:
    1) nausea and/or vomiting;
    2) photophobia and phonophobia.

E. Is not better described by another ICHD-3 diagnosis.

The term aura is used to indicate recurrent attacks of completely reversible unilateral visual disorders, unilateral sensory disorders, or other unilateral central neurological disorders. Such attacks usually develop gradually, last a few minutes, and in the majority of cases precede headache and other migraine symptoms.

The criteria for the diagnosis of migraine with aura include:

A. At least two attacks fulfilling criteria B and C.
B. At least one of the following fully reversible aura symptoms:
   1) visual disorders;
   2) sensory disorders;
   3) speech and/or language (linguistic) disorders;
   4) motor disorders;
   5) brainstem dysfunctions;
   6) retinal dysfunctions.
C. At least three of the following six characteristics:
   1) at least one aura symptom develops gradually over ≥ 5 minutes;
   2) two or more aura symptoms occur one after the other;
   3) each single aura symptom lasts from 5 to 60 minutes;
   4) at least one aura symptom is unilateral;
   5) at least one aura symptom is 'positive';
   6) headache appears during aura or within 60 minutes after its cessation.
D. Is not better described by another ICHD-3 diagnosis.

According to ICHD-3, migraine with aura is divided into:

1) Migraine with typical aura;
2) Migraine with brainstem aura;
3) Hemiplegic migraine;
4) Retinal migraine.

The division into episodic migraine and chronic migraine is more important from a clinical perspective. The latter is derived from episodic migraine, which is a consequence of chronification, i.e. an increase in the number of episodic migraine headaches.

The ICHD-3 classification defines chronic migraine as headache occurring on 15 or more days per month for more than three months, which, on at least eight days per month, has the features of migraine headache.

The diagnostic criteria for chronic migraine include:

A. Headache (resembling tension-type headache and/or migraine headache) occurring on 15 or more days per month for more than three months and meeting criteria B and C.
B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for migraine without aura and/or criteria B and C for migraine with aura.
C. Exhibits one of the following characteristics on at least eight days per month for more than three months:

1) meets criteria C and D for migraine without aura;
2) meets criteria B and C for migraine with aura;
3) in the patient's opinion it has the character of migraine from the beginning and subsides after taking triptan or ergot alkaloid.

D. Is not better described by another ICHD-3 diagnosis.

The presence of aura in patients with migraine determines the type of emergency medication prescribed. Triptans and ergotamine derivatives should not be used in patients suffering from non-visual migraine with aura.

Different preventive therapies are recommended in episodic migraine and chronic migraine. Not all drugs effective in the treatment of episodic migraine have proven efficacy in chronic migraine. Conversely, not all drugs registered for the treatment of chronic migraine show efficacy in episodic migraine.

Depression – diagnostic criteria

In psychiatry, the term depression includes three diagnostic categories: depressive episode and recurrent depressive disorder (RDD), and depression in the course of bipolar disorder. In the context of this paper, focus will be placed on the first two diagnostic categories: depressive episode and RDD. The diagnostic criteria for a depressive episode found in the ICD-10 [18] include the axial symptoms (depressed mood, anhedonia, and energy loss) and additional symptoms (including aspects of cognitive functioning, disturbances in circadian rhythms and others) [18]. Somatic syndrome in the course of depression has at least four of the following symptoms: loss of interest or lack of pleasure in performing activities that usually delight; lack of emotional reactivity to events that usually bring pleasure; early morning awakening (two or more hours prematurely), increasing depression in the morning hours; objective manifestations of a pronounced slowing down or psychomotor agitation (noticed by others); pronounced loss of appetite; weight loss (by 5% or more per month). Based on the severity of symptoms, we can distinguish mild, moderate and severe episodes with or without psychotic symptoms [18].

Recurrent depressive disorders according to ICD-10 include a history of at least one depressive episode of any severity, lasting at least two weeks, and separated from the current episode by at least two months free from any significant symptoms of mood disorders [18].

The gold standard for self-report of depressive symptoms [19] includes two scales: *Beck Depression Inventory* (BDI) and *Patient Health Questionnaire-9*.

Beck Depression Inventory (BDI)

The test is used to perform a self-assessment of the severity of depressive symptoms. It consists of 21 questions to which the patient provides answers by choosing the severity of the symptoms observed. For each question, there are 4 response options, for which points are awarded on a scale from 0 to 3.

Results evaluation: 0-10 pts – no depression; 11-19 pts – mild severity of symptoms; 20-27 pts – moderate severity of symptoms; >28 pts – severe depression [19].

Patient Health Questionnaire-9

The *Patient Health Questionnaire-9* is part of the larger *Patient Health Questionnaire* tool. It is composed of 9 questions that correspond to the symptoms of depression included in the DSM-IV diagnostic criteria.

Results evaluation: 0-4 pts – no depression; 5-9 pts – mild depression; 10-14 pts – moderate; 15-19 pts – moderately severe; 20-27 pts – severe [20].

Migraine treatment standards

Migraine attack treatment

The goals of emergency treatment [21] are to quickly stop the pain and bring about resolution of other symptoms of a migraine attack, to permanently stop the attack, to return to pre-attack functioning, to reduce the need for repeat medication, and to minimise the need for acute specialist care. The first standard of treatment for interrupting a migraine attack is appropriate drug selection [7]. Treatment to interrupt a migraine attack should be tailored to the severity of the migraine discomfort, assessed on a four-point scale (0 – no pain, 1 – mild pain, 2 – moderate pain, 3 – severe pain) or a visual scale called the *Visual Analogue Scale* (VAS) [6]. It is a clinimetric method where '0' means no pain and '10' means unbearable pain. Depending on the severity of the attack, appropriate treatment is selected. Mild to moderate pain attacks are managed with simple analgesics or non-steroidal anti-inflammatory drugs (NSAIDs). The drug is selected individually; it is important to take it as soon as possible and in a dose that is high enough [6, 21]. In severe attacks, we use preparations containing ergotamine (slowly withdrawn from migraine therapy) or drugs from the triptan group, which remain the gold standard of treatment for migraine attacks.

Class A recommendations include drugs that are recommended to be taken in a single dose [5, 6-17]:

- Paracetamol – 1000 mg.
- Acetylsalicylic acid (ASA) – 1000 mg.
- Acetylsalicylic acid lysinate – 900 mg.
- Naproxen – 500-1000 mg.
- Diclofenac (potassium salt) – 50-100 mg.
- Ibuprofen – 600-800 mg.
- ASA + Paracetamol + Caffeine – 250+200+50 mg.
- Triptans – contraindicated in patients with cardiovascular disease, uncontrollable hypertension [22]; should not be used during aura:
  - Sumatriptan – 50-100 mg (additionally: 25 mg rectally, 10-20 mg intranasally, 6 mg subcutaneously) – must not be combined with serotonin reuptake inhibitors [23];

- Zolmitriptan – 2.5-5 mg (additionally: soluble/orally disintegrating tablets, intranasal spray – not available in Poland) – must not be combined with serotonin reuptake inhibitors;
- Rizatriptan – 10 mg – must not be combined with serotonin reuptake inhibitors; a lower dose with concomitant use of propranolol;
- Eletriptan – 40-80 mg;
- Almotriptan – 6.25-12.5 mg;
- Naratriptan – 2.5 mg – not available in Poland;
- Frovatriptan (not available in Poland) is a drug particularly effective in the prevention of menstrual migraine attacks – used in a dose of 5 mg daily, two days before the expected monthly bleeding for five consecutive days.

Class B migraine attack interruption treatment recommendations (oral doses) include:

- Metoclopramide – 10-20 mg (additionally: 20 mg rectally, 10 mg parenterally).
- Domperidone – 20-30 mg.
- Ergotamine – 1-2 mg.
- Dihydroergotamine – 1-2 mg.
- Prochlorperazine – 10 mg.
- Metamizole – 1000 mg.
- Tolfenamic acid – 200-400 mg.

Combinations of drugs are sometimes beneficial [24-26] – we can combine drugs from the group of simple analgesics or NSAIDs with others that increase absorption and provide analgesic effect (metoclopramide, codeine, caffeine). A new combination used is an NSAID (e.g. naproxen – 500 mg) with a triptan (e.g. sumatriptan – 85 mg) – this reduces the risk of attack recurrence after single attack therapy with triptans [27].

Prophylactic treatment in episodic migraine

The aim of prophylactic treatment is to reduce the frequency, severity and duration of attacks, to alleviate the resulting disability, to improve the response to short-term treatment, to improve the patient's functioning and quality of life, and to reduce the costs of migraine treatment. Prophylactic treatment should be initiated when attacks significantly impair daily functioning and are frequent, i.e. 4 or more migraine days per month [21]. Moreover, prophylactic treatment should be recommended if there are contraindications to the use of emergency drugs, serious side effects of the used medicines, their misuse (or significant risk of misuse) and a significant risk of transformation of episodic migraine into chronic migraine. Additionally, the patient's choice and preferences should be taken into consideration.

In some specific forms of migraine (hemiplegic migraine, migraine with brainstem aura, migraine with prolonged aura, migrainous infarction), the administration of prophylactic treatment is standard. Prophylactic treatment should be started with

a low dose of the drug and gradually increased to the effective dose. Treatment should continue at an effective dose for a minimum of 8 weeks to finally establish its effect. In the absence of adverse effects such prophylactic treatment should be maintained for 6 to 12 months (min. 3 months). The effectiveness of treatment is defined as halving of the number of days with headache (for this purpose, the patient is advised to keep a diary), as a significant reduction in the duration of a single attack as perceived by the patient, as a significant reduction in the severity of a single attack as perceived by the patient, as an improvement in the efficacy of short-term treatment, as a reduction in the patient's disability, and as an improvement in the patient's daily functioning and quality of life.

The standard (class A recommendations) for preventive treatment of episodic migraine [7, 11, 12, 28] are:

- Beta-adrenergic receptor antagonists (beta-blockers) [28-30] – daily doses:
  - Propranolol – 40-240 mg;
  - Metoprolol – 50-200 mg;
  - Timolol – 10-15 mg – not used in Poland due to the absence of oral form.
- Antiepileptics [31-36] – daily doses:
  - Valproic acid – 500-1500 mg – the latest recommendations of the European Medicines Agency (EMA) are unequivocally negative for use in girls and women of childbearing age [37-39];
  - Topiramate – 25-200 mg.
- Calcium channel blockers [7, 8] – only according to European recommendations:
  - Flunarizine – 5-10 mg/day.
- Shortened prophylaxis in menstrual migraine [40, 41]:
  - Frovatriptan – 2 x 2.5 mg/day, taken two days before the planned date of monthly bleeding, for five consecutive days.
- Other:
  - Butterbur (*Petasites hybridus)* root/leaf – 50-75 mg/day – acc. to AAN, which in recent days has changed the positioning of *Petasites* without a recommendation.

Other drugs recommended for the prophylactic treatment of migraine include the following class B preparations [42-46]:

- Antidepressants – daily doses:
  - Amitriptyline – 50-150 mg;
  - Venlafaxine – 150 mg.
- Beta-adrenergic receptor antagonists (beta-blockers) [29, 30, 44] – daily doses:
  - Atenolol – 100 mg;
  - Nadolol – 40-80 mg;
  - Bisoprolol – 5-10 mg.
- Menstrual migraine prophylaxis – triptans – daily doses [40, 41]:

– Naratriptan – 2 x 1 mg;
– Zolmitriptan – 2-3 x 2.5 mg.

Other preparations whose efficacy has not been sufficiently confirmed include vitamin B6, magnesium, galenic preparations such as *Tanacetum parthenium* [45], sartans, and estrogens; little possible prophylactic efficacy in migraine occurs with the use of: SSRIs/SSNRIs, acetazolamide, bisoprolol, pindolol, verapamil, gabapentin, NSAIDs or dietary supplements and many galenic preparations [45]. Potential non-pharmacological methods (neurostimulation techniques [46, 47]) are being considered. Neuromodulation and behavioural therapies may be used in cases of patient preference for non-pharmacological treatment, inadequate response to available pharmacological treatment, significant contraindications to pharmacological treatment, overuse of emergency treatment, and diagnosis of drug-induced headache, planning for pregnancy, pregnancy, and breastfeeding [21]. New drugs, recently available in Poland, i.e. monoclonal antibodies against calcitonin gene-related peptide (CGRP) receptor – erenumab, or against CGRP – fremanezumab (both available in Poland), galcanezumab, eptinezumab are becoming a new and effective standard of treatment in migraine [48].

Chronic migraine treatment

In chronic migraine, *ad hoc* treatment is not recommended as there is a high risk of developing drug-induced headache [5]. Prophylactic treatment of chronic migraine is somewhat different than in episodic migraine, as three agents are recommended in class A: two oral antiepileptics [35] (with the same reservations as in episodic migraine), i.e. valproic acid at a daily dose of 500-1500 mg and topiramate at a daily dose of 25-200 mg, and botulinum toxin injections at a dose of 150-195 U every 12 weeks (A/B) [47]. Class B recommendations include only amitriptyline [42] used in a daily dose of 50-150 mg. A new group of drugs are monoclonal antibodies directed against CGRP receptor (erenumab available in Poland – 70 or 140 mg subcutaneously once a month) and against CGRP [48] (fremanezumab available in Poland – 225 mg subcutaneously once a month or 675 mg once every 3 months) (next to galcanezumab – available in Europe, but not in Poland, and eptinezumab which has not been registered yet) [48].

Depression treatment standards

Current antidepressants are safe and effective in treating the underlying disease. They result in an improvement and remission in 70% of cases during three months of therapy. The basis for starting depression treatment is a properly established diagnosis, an assessment of the severity of the current episode and medical history concerning the number of previous episodes, their duration, applied treatment and its efficacy [49]. Important elements also include the information on somatic and psychiatric comorbidity, medications used, suicide risk assessment, and – in justified cases – laboratory tests assessing, e.g. liver function, thyroid function, blood count and ECG [50, 51].

The decision to start treatment and the choice of antidepressants depends on the severity of the depressive symptoms. Non-pharmacological approaches – psychotherapy, psychosocial interventions – can be considered for a mild episode, as pharmacotherapy may be less effective [50]. For moderate to severe episodes, treatment with an antidepressant in combination with psychotherapy should be implemented [50].

The first line of treatment are drugs from the SSRI group – selective serotonin reuptake inhibitors [49]. By inhibiting serotonin reuptake in the synaptic gap, these drugs increase the amount of serotonin [49]. These agents are indicated as the safest ones in the literature [50]; however, possible adverse effects, including the risk of bleeding, hyponatraemia, QTc prolongation and serotonin syndrome, should be considered [50].

The second frequently used group of drugs are serotonin norepinephrine reuptake inhibitors (SNRIs). These are reuptake inhibitors of two neurotransmitters – serotonin and norepinephrine – from the synaptic cleft [49]. The third group of drugs are tricyclic antidepressants (TCAs) [49]. A characteristic feature of these drugs is their multi-receptor effect (e.g. anticholinergic, anti-adrenergic), which is a risk factor of numerous complications [51]; therefore, they are used less frequently nowadays [49]. A summary of these drug groups is presented in Tables 1-3.

Table 1. **Characteristics of selective serotonin reuptake inhibitors (SSRIs)**

Drug	Dose	Characteristics
Fluoxetine	10-60 mg/day	It can have a 'stimulating' effect, indicated in states of slowness or inhibition.
Fluvoxamine	100-300 mg/day	Interacts with other drugs.
Citalopram	10-40 mg/day	Highly selective, low risk of interaction.
Escitalopram	5-20 mg/day	Highly selective, low risk of interaction, low risk of side effects.
Sertraline Paroxetine Vortioxetine	50-200 mg/day 10-60 mg/day 5-20 mg/day	Low risk of side effects. Recommended for co-occurring somatic disorders. Recommended for coexisting anxiety and fear. Recommended in the case of cognitive disorders.

Table 2. **Characteristics of serotonin norepinephrine reuptake inhibitors (SNRIs)**

Drug	Dose	Characteristics
Venlafaxine	75-225 mg/day (maximum dose 375 mg/day)	One of the most effective antidepressants. Watch out for interactions and side effects.
Duloxetine	30-90 mg/day (maximum dose 120 mg/day)	In depression with accompanying anxiety and pain symptoms.

Table 3. **Other groups of drugs used in depressive episode pharmacotherapy**

Drug	Dose	Characteristics
Bupropion	150-300 mg/day	Impacts mainly dopaminergic transmission. Considered a 'stimulant' drug. Risk of epileptic seizures. Anxiety.

table continued on the next page

Mianserin	30-90 mg/day	Impacts mainly noradrenergic transmission. Recommended in depression with sleep disturbance (recommended to be administered at night). Side effects: weight gain, leukopenia.
Mirtazapine	15-45 mg/day	Impacts noradrenergic and selective serotonergic transmission. Effective antidepressant, recommended e.g. in depression with sleep disturbance (recommended to be administered at night). Side effects: weight gain, daytime sleepiness.
Reboxetine	4-8 mg (max. 12 mg/day)	Selective inhibitor of norepinephrine transporter. Recommended in depression with associated inhibition. Side effects: anxiety, sleep disturbances, etc.
Trazodone	75-300 mg/day	Acts mainly through the serotonergic system. In lower doses (up to 150-300 mg/day) recommended as a concomitant medication in depression with sleep disturbance (e.g. together with an SSRI in the morning; watch out for serotonergic syndrome). At higher doses in monotherapy for depression. Side effects: anxiety, headache.
Tianeptine	37.5 mg/day	Impacts serotonergic transmission. Drug well tolerated, recommended in depression with accompanying somatic disorders.
Agomelatine	25-50 mg/day	Affects melatonergic receptors and regulates circadian rhythms. Recommended for depression with sleep disturbance and/or anhedonia. Administered at night. Side effects: anxiety, headache.
Moclobemide	300-600 mg/day	Reversible inhibitor of monoamine oxidase B. Recommended for depression with inhibition, for depression in Parkinson's disease; should not be given at night. Side effects: anxiety, headache. Do not combine with SSRIs and SNRIs.

Individual drugs from these groups are selected primarily based on the patient's detailed clinical picture, previous psychiatric treatment and response, comorbidity, and according to the experience and preferences of the treating physician. The treatment algorithm for depression is shown in Figure 1 [49].

A separate issue is the pharmacotherapy of treatment-resistant depression. According to the recommendations of the National Consultant in the field of psychiatry, five main methods of treatment of drug-resistant depression are indicated [52]. Possible treatment pathways include optimising the dose and duration of treatment, changing the drug, combining different drugs, enhancing treatment by adding a drug from a different class, and considering non-pharmacological therapy, e.g. vagus nerve stimulation and electroconvulsive therapy [52, 53]. When deciding on the selected treatment method, the patient's somatic and mental state should be taken into account [52].

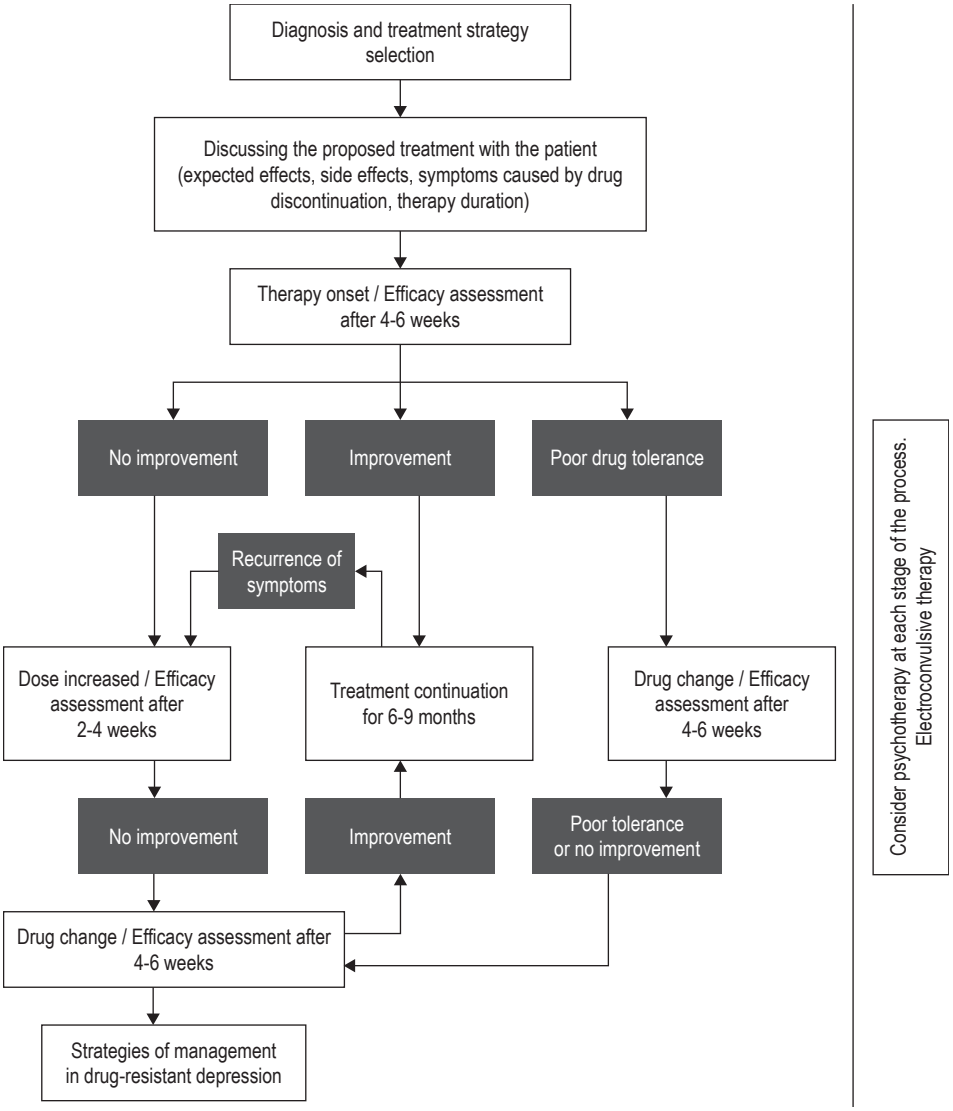

Figure 1. **Depressive episode treatment [49]**

The treatment of a severe depressive episode with psychotic symptoms requires a separate description. For these patients, an antipsychotic medication should be implemented in addition to an antidepressant [51].

The primary goal of treatment for depression is to achieve symptomatic and functional remission. Lack of remission increases the risk of possible mental deterioration and even recurrence of depression [49].

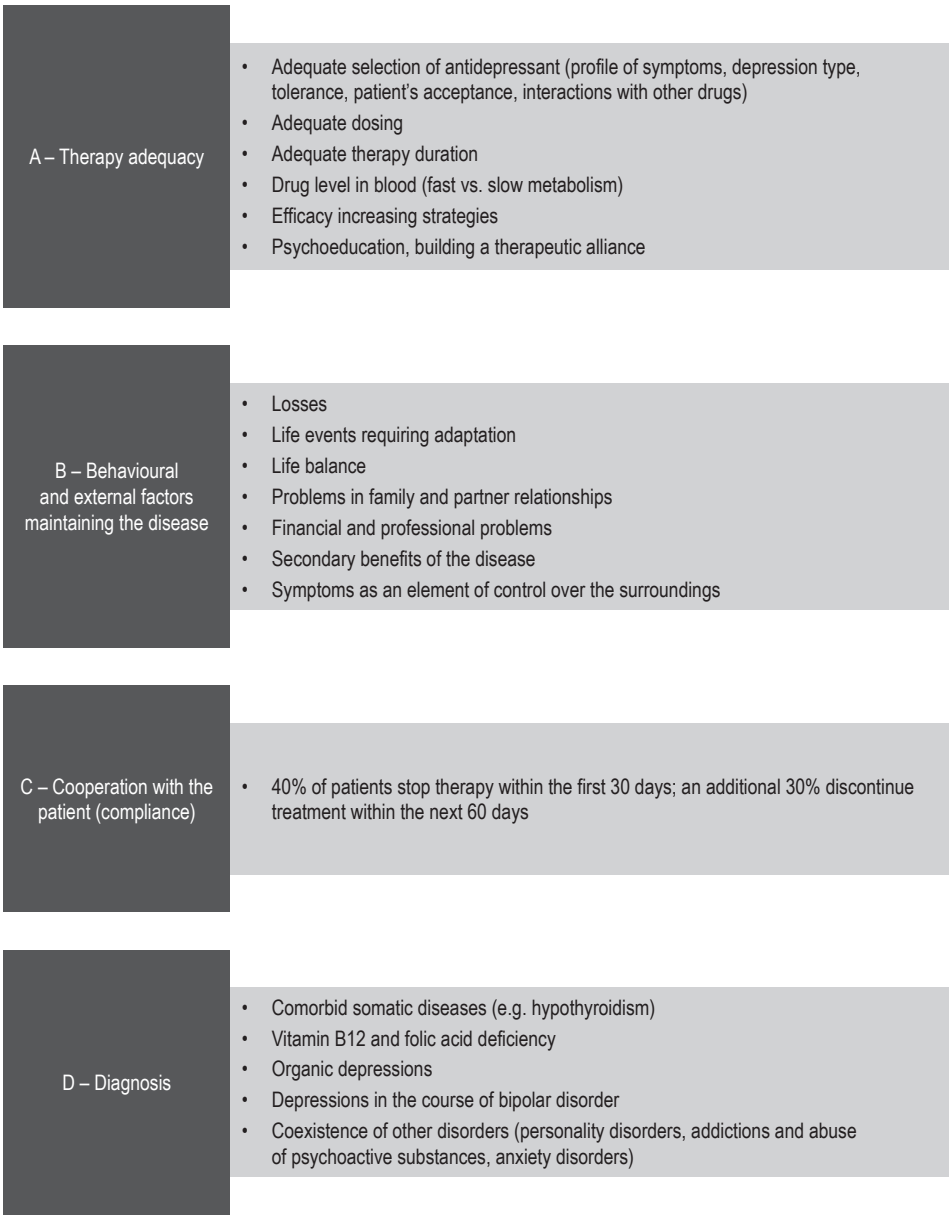

Figure 2. **Diagnostic and clinical guidelines in the treatment of depression**

Summary. Diagnostic and therapeutic management of migraine and depression

The treatment of patients with migraine and comorbid depression or with other comorbid psychiatric disorders is a major therapeutic problem. Almost all medications, whether used *ad hoc* for a migraine attack or used as prophylaxis, can have a significant impact on the clinical course and response to treatment of comorbid psychiatric conditions.

In depressed patients treated with antidepressants from the group of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), the use of triptans (serotonin receptor agonists) for short-term treatment of a migraine attack may cause symptoms of serotonin syndrome (a complex of very serious neurological, psychiatric and autonomic symptoms, in some cases even life-threatening). Hence the recommendation that people who suffer from migraine and coexisting depression should not be administered triptans as an *ad hoc* medication to abolish migraine attacks. Therefore, these patients are only treated with simple analgesics (paracetamol), acetylsalicylic acid (ASA), non-steroidal anti-inflammatory drugs (NSAIDs), and complex analgesics (ASA, paracetamol, NSAIDs, caffeine, codeine). These drugs, however, are much weaker in the elimination of migraine pain and associated symptoms than triptans and are not characterised by their specificity of action. They also carry a risk of numerous side effects. Some of these drugs contain codeine, which, especially if taken frequently, poses a high risk of developing drug dependence and symptomatic 'medication overuse headaches'. This fact significantly reduces the efficacy of migraine treatment, and also adversely affects the frequency of attacks and increases the risk of transformation of episodic migraine into chronic migraine. Pharmacological prevention of migraine is based primarily on the use of drugs indicated in other areas of medicine.

Beta-blockers (beta-adrenergic receptor antagonists), such as propranolol or metoprolol, effective in episodic migraine prophylaxis, apart from numerous cardiovascular adverse effects in some patients in the form of significant drop in blood pressure and significant slowing of heart rate, may exacerbate depressive symptoms and decrease libido. These drugs have not shown efficacy in chronic migraine and are contraindicated in migraine with coexisting depression.

Calcium channel blockers (calcium antagonists), especially flunarizine which is effective in episodic migraine, can cause significant daytime sleepiness, increased appetite, and significant weight gain. This drug has not shown efficacy in chronic migraine with coexisting depression.

Among the antiepileptic drugs used in migraine, topiramate and valproic acid/valproate sodium are drugs with proven effects in reducing the frequency of migraine attacks. The first of these drugs, in addition to frequent weight loss, which is not always desirable, has other badly tolerated side effects in the form of impaired memory, concentration, attention or unpleasant paraesthesia of the extremities. It can also exacerbate symptoms of depression and increase the risk of suicide. The second of these 'antiepileptic' antimigraine drugs has a side effect profile that is difficult to accept, ranging from significant weight gain, hair loss and increased nail brittleness, liver damage and increased liver function tests, to very significant teratogenic effects.

A medication to consider in migraine with comorbid depression is amitriptyline (a tricyclic antidepressant). It should be noted, however, that the doses of drugs effective in migraine, and at the same time recommended for the treatment of migraine, are much lower than those recommended for the treatment of depression [54]. Unfortunately, amitriptyline therapy is also burdened with the risk of numerous side effects and poor tolerance.

Although venlafaxine is still mentioned as a representative of SNRIs in therapeutic recommendations for migraine prevention (not in the first but in the second line of therapy), the scientific evidence for the efficacy of this drug in migraine is very weak. In addition, be aware of the risk of serotonin syndrome when treating attacks with *ad hoc* triptans in these patients.

From a practical point of view, a difficult clinical situation, which is a necessity to implement prophylactic treatment against migraine in a patient with coexisting depression without a risk of depression exacerbation or development of serious side effects, is reduced to two therapeutic options: botulinum toxin (onabotulinumtoxin A) and a group of monoclonal antibodies against CGRP protein or against the receptor for this neurotransmitter. Both clinical trials in migraine with botulinum toxin (PREEMPT, COMPEL, REPOSE) [55-58] as well as registration and off-label studies with erenumab, fremanezumab and galcanezumab have shown not only a very beneficial effect of these drugs on reducing the frequency of headaches, including migraine attacks, both episodic and chronic (for botulinum toxin only in chronic migraine), but also tolerance of these drugs comparable to placebo.

The dosing regimen of at least once a month and high tolerability have translated into very good adherence and compliance. For some of these formulations, particular benefits have been shown in the treatment of migraine with comorbid depression and anxiety.

Treating depression in people suffering from migraine headaches requires careful selection of drugs. Antidepressants have been shown to potentially prevent migraine. It seems advisable to use amitriptyline or nortriptyline. SNRIs, including venlafaxine and duloxetine, also have evidence of efficacy and may be considered in patients with comorbid depression and migraine. SSRIs, including fluoxetine, are not effective in most patients and may even exacerbate the symptoms of migraine. Drugs from the TCA group can be considered when the patient, in addition to migraine, suffers from insomnia. At the same time, some antidepressants may cause headaches – as a side effect of treatment (e.g. mirtazapine). Combining anti-migraine medications with antidepressants also requires consideration of potential interactions.

The frequent coexistence of chronic migraine and depression indicates the need for close cooperation between neurologists and psychiatrists. Chronic migraine increases the risk of depression and, conversely, depression increases the risk of migraines and episodic migraine chronification.

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