

## **Pharmacological treatment of a depressive episode and recurrent depressive disorder – guidelines of the Polish Psychiatric Association and the National Consultant for Adult Psychiatry**

Jerzy Samochowiec<sup>1</sup>, Dominika Dudek<sup>2</sup>, Jolanta Kucharska-Mazur<sup>1</sup>,  
Sławomir Murawiec<sup>3</sup>, Joanna Rymaszewska<sup>4</sup>, Wiesław Jerzy Cubała<sup>5</sup>,  
Janusz Heitzman<sup>6</sup>, Agata Szulc<sup>7</sup>, Małgorzata Bała<sup>8</sup>, Piotr Gałęcki<sup>9</sup>

<sup>1</sup>Chair and Department of Psychiatry, Pomeranian Medical University in Szczecin

<sup>2</sup>Chair of Psychiatry, Department of Adult Psychiatry,  
Jagiellonian University Medical College in Krakow

<sup>3</sup>Dialog Therapy Centre, Warsaw

<sup>4</sup>Department and Clinic of Psychiatry, Wrocław Medical University

<sup>5</sup>Department of Adult Psychiatry, Chair of Psychiatry, Medical University of Gdansk

<sup>6</sup>Department of Forensic Psychiatry, Institute of Psychiatry and Neurology in Warsaw

<sup>7</sup>Department of Psychiatry, Medical University of Warsaw

<sup>8</sup>Chair of Epidemiology and Preventive Medicine, Department of Hygiene and Dietetics,  
Jagiellonian University Medical College in Krakow

<sup>9</sup>Department of Adult Psychiatry, Medical University of Lodz

### **Summary**

Under the auspices of the Polish Psychiatric Association and the National Consultant in Psychiatry, on the basis of analysis of international guidelines, the expert group consisting of psychiatrists and an epidemiologist compiled recommendations for the treatment of a depressive episode and recurrent depressive disorder. The recommendations take into account the information that the patient should receive before starting the treatment, the selection criteria for the treatment method and the choice of the antidepressant, the method of assessing the efficacy of treatment, treatment monitoring, and the duration of treatment.

Formulating the recommendations, the experts analyzed the source data for their applicability in Poland. The current recommendations of scientific societies and an analysis of the literature on the treatment of depressive episodes and recurrent depressive disorder broken down by the treatment of acute episodes and maintenance treatment, as well as the recommendations on the method of creating guidelines have been taken into account. Furthermore,

the guidelines developed in collaboration with the Supreme Medical Council and the Polish Psychiatric Association, entitled: "Diagnostic work-up and treatment of depression in adults – guidelines for family physicians", and recommendations of the National Consultant in Adult Psychiatry have been taken into account. The recommendations were discussed among the experts and accepted by the General Board of the Polish Psychiatric Association. Subsequently, the recommendations were modified in line with the Board's comments and endorsed by the Association for use in the management of patients with depression in Poland.

**Key words:** guidelines, depression, treatment

## Introduction

Depression is an increasingly common and growing health problem. The guidelines are designed to define the treatment pathway for adult patients, with particular consideration of pharmacological treatment. The guidelines refer to the treatment of recurrent depression, with the exclusion of depression associated with bipolar disorder (BD). Due to the specificity of treatment of BD, this issue requires a separate study.

## Methodology

When agreeing upon the recommendations, the Working Group comprising the Board members and experts of the Polish Psychiatric Association, and also the National Consultant for Adult Psychiatry, took into account the organization of healthcare in Poland and the available methods of depression treatment. The recommendations were developed on the basis of the presentations prepared and presented by the experts at working meetings that took place on-line between October and December 2020. The expert panel comprised psychiatrists experienced in the treatment of depressive episodes and an epidemiologist. The Working Group formulated the following clinical questions along with their corresponding recommendations:

1. **What basic information should the patient receive before treatment initiation?**
2. **What criteria should be used to select the treatment method?**
3. **What are the rules of selection of antidepressants?**
4. **How and after what time should treatment efficacy and tolerability be assessed?**
5. **How should patient treatment be monitored?**
6. **How long should pharmacological treatment be continued?**

Formulating the recommendations for pharmacological treatment of patients with depression in the adult population, the experts analyzed the source data for their applicability in Poland. Presentations were prepared with the current recommendations of scientific societies and analyses of the literature on the treatment of depressive episodes and recurrent depressive disorder broken down by the treatment of acute episodes and maintenance treatment, and with the recommendations about the method of creating guidelines [1-6]. Furthermore, the guidelines developed in collaboration

with the Supreme Medical Council and the Polish Psychiatric Association, entitled: “Diagnostic work-up and treatment of depression in adults – guidelines for family physicians,” created according to the GRADE system of classification of recommendations [7], and recommendations of the National Consultant for Adult Psychiatry [8] have been taken into account.

**Classification of recommendations in the guidelines of the Royal Australian and New Zealand College of Psychiatrists [5]**

| The levels of evidence in the intervention studies [5]                         |  |
|--|--|
| Level  | Study design   |
| I  | Systematic review of level II research   |
| II   | Randomized trial (RCT)   |
| III  | Pseudo-randomized study (e.g. staggered allocation or other approach)<br>Comparative study with concurrent controls:<br>– Experimental study without randomization<br>– Cohort study<br>– Case-control study<br>– Time series analysis with a control group<br>Comparative study without concurrent controls:<br>– Historical control group study<br>– Two or more single-arm studies<br>– Time series analysis without a simultaneous control group |
| IV   | Case series description with analysis of effects only after the intervention or before-after   |
| Adapted from: NHMRC levels of evidence for intervention studies (NHMRC, 2009). |  |

**Classification of recommendations in the guidelines of the Registered Nurses’ Association of Ontario [3]**

| Classification of recommendations in guidelines of RNAO [3] |   |
|---|---|
| Level   | Data source   |
| Ia  | Data from a meta-analysis or systematic review of randomized controlled trials or the synthesis of multiple trials, mainly of the quantitative type |
| Ib  | Data from at least 1 randomized controlled trial  |
| IIa   | Data from at least 1 well-designed, non-randomized trial  |
| IIb   | Data from at least 1 other type of study, such as well-designed pseudo-experimental studies without randomization                                   |
| III   | The synthesis of multiple studies, of the qualitative type  |

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|   |   |
|---|---|
| IV  | Data obtained from well-designed non-experimental observational studies, such as analytical, descriptive, qualitative studies |
| V   | Data from expert opinions or committee reports, clinical experience of respected authorities                                  |
| Adapted from: the Scottish Intercollegiate Guidelines Network (Scottish Intercollegiate Guidelines Network [SIGN], 2011) and Pati (2011). |   |

**Classification of recommendations in the guidelines of Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder [2]**

| Canadian Network for Mood and Anxiety Treatments (CANMAT) Criteria for data confidence levels [2]  |  |
|--|--|
| Level <sup>a</sup>   | Criteria   |
| 1  | Meta-analysis with narrow confidence intervals and/or 2 or more randomized controlled trials (RCTs) with appropriate sample size and preferably placebo-controlled |
| 2  | Meta-analysis with broad confidence intervals and/or 1 or more RCTs with appropriate sample size   |
| 3  | Small-sample RCT or prospective, non-randomized controlled trial or case series or high-quality retrospective studies  |
| 4  | Expert opinion / consensus   |
| <sup>a</sup> Note: Level 1 and Level 2 are specifically relevant to treatment studies in which comparisons are available across randomized groups. Recommendations involving risk factors or epidemiological factors are mainly based on observational studies, and therefore the highest level of evidence is usually Level 3. Recommendations on general issues (e.g. policy of care) reflect a greater degree of judgment about the strength of evidence from different sources and therefore are assigned to mainly Level 4. |  |

**Classification of recommendations by the US Preventive Services Task Force [6]**

| US Preventive Services Task Force definitions of recommendation strength [6] |   |   |
|--|---|---|
| Strength   | Definition  | Importance for clinical practice  |
| A  | The USPSTF recommends this approach. There is a high degree of certainty that the net benefit is significant.   | This method of operation should be proposed or provided.  |
| B  | The USPSTF recommends this approach. There is a high degree of certainty that the net benefit is moderate, or there is a moderate degree of certainty that the net benefit is moderate to significant.                | This method of operation should be proposed or provided.  |
| C  | The USPSTF recommends proposing or providing this approach for selected patients based on clinician judgment and patient preferences. There is at least a moderate degree of certainty that the net benefit is small. | This method of management should be proposed or provided for selected patients depending on the individual situation. |

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|                |   |   |
|----------------|---|---|
| D              | The USPSTF recommends not to use this approach. There is moderate to high degree of certainty that there is no net benefit to this method or that the benefits are considered to be outweighed by the harmful effects.  | This method should be discouraged.  |
| I<br>Statement | The USPSTF concludes that the currently available scientific data are insufficient to assess the balance of benefits and adverse effects of this approach. Scientific data is lacking, of poor quality or contradictory, and the balance of benefits or adverse effects cannot be determined. | Refer to the section on Clinical Considerations in the USPSTF Recommendation Statement. When this method of management is proposed, the patient should understand the uncertainty about the balance of beneficial and negative effects associated with its use. |

### Recommendations

The proposed wording of the recommendations was discussed in detail at the subsequent meeting of the Working Group and all its members accepted it. The disputable issues were resolved during a consensus discussion.

A “strong recommendation” means that the Working Group judges that the desired effects outweigh the undesirable effects. With less certainty about the superiority of the desired effects over the undesirable effects, the recommendation is described as weak. Comments to the recommendations were prepared by the Working Group; they include references to the scientific data on which the recommendations are based and are supplemented by the information specific for the Polish conditions. The entire work was subjected to critical evaluation by the remaining members of the Board of the Polish Psychiatric Association (Adam Wichniak, Tomasz Szafranski, Przemysław Bienkowski, Łukasz Cichoński, Małgorzata Janas-Kozik, Maciej Matuszczyk). The agreed upon preliminary version of the Polish guidelines was presented for external consultations and peer-reviews. The recommendations were discussed once again among the experts and accepted, and then presented as a manuscript to the General Board of the Polish Psychiatric Association. Subsequently, the recommendations were modified in line with the Board’s comments and endorsed by the Association for use in the management of patients with depression in Poland. All of the experts in the Working Group accepted the final version of the document.

#### **Re 1. What basic information should the patient receive before treatment initiation?**

**We recommend that treatment planning should include patient education about the disease and treatment options, taking into account the benefits and risks. The individual treatment plan should operate on the basis of co-decision making and determining the roles of the person providing treatment, the patient and the support network. Strength of recommendation: strong recommendation [4].**

**It is suggested to educate patients with depression (and especially their families/caregivers) about depression, principles of mental hygiene, therapeutic interventions and continued care. Strength of recommendation: level of evidence V [3].**

The educational elements necessary at the initiation of pharmacological treatment include communicating the following to the patient (apart from the information found in the drug leaflet):

- Antidepressants are not addictive – their intake, even for a long time, is not associated with the risk of addiction.
- The onset of action of antidepressants occurs after 2-4 weeks of their systematic intake, which means that the first elements of an improvement of mental state or behavior that may be noticed by the patient appear after the indicated time of treatment, and subsequently the improvement is more and more visible.
- Antidepressants should be taken every day as recommended by the physician. These medicines are not intended for use on an as-needed basis.
- Antidepressants should not be discontinued immediately after obtaining an improvement of the mental state and functioning of the patient.
- The physician should inform the patient about the most frequent adverse drug reactions (that are foreseeable and occur with a significant frequency in the specified patient groups). It is worth informing the patient that the adverse reactions of antidepressants occur most commonly only at the beginning of the treatment, and most of them are non-serious and transient. In situations of their greater intensity or occurrence of unusual adverse drug reactions, direct contact with the treating physician is indicated.
- Information should be obtained from every patient about all currently received medications and dietary supplements and other substances used (e.g. products taken for sports activities or herbal remedies – in particular St. John's Wort).
- It is advisable to inform the patient about the need to adhere to the rules of daily activity adapted to the treatment principles (e.g. regular time of going to sleep in a situation of using sleep-promoting antidepressants), to avoid ingesting food, drinking alcohol and smoking before going to sleep, and about the benefits arising from physical activity.

**Re 2. What criteria should be used to select the treatment method?**

**What should be the principles of treatment of a depressive episode?**

**As the treatment of first choice of an uncomplicated mild to moderate depressive episode, we recommend evidence-based pharmacological treatment and/or psychotherapy – the scientific evidence does not indicate superiority of either of the treatment methods (pharmacological treatment or psychotherapy) in the case of mild depression. Strength of recommendation: strong recommendation [4].**

The choice of the treatment method depends on the availability, patient preference, drug safety profile, history of response to the previous treatment, family history of the patient, coexisting somatic diseases, concomitant medication, costs of therapy, and competences of the treating physician [9-24].

**In the case of using psychotherapy, we leave the detailed conditions of determining if the requirement of professionalism in this area is met for the decision of the appropriate administrative or professional bodies. Strength of recommendation – consensus of the Working Group.**

**Patients diagnosed with depression for the first time should undergo medical evaluation to diagnose/rule out the basic coexisting diseases such as arterial hypertension, obesity, diabetes and sleep apnea, as well as thyroid, renal and hepatic dysfunction. Strength of recommendation: level of evidence II [5].**

**In the course of the treatment, disease-related behaviors, as well as lifestyle-associated risk factors should be identified and monitored, and interventions to modify them and to prevent somatic comorbidities should be implemented. Strength of recommendation: level of evidence II [5].**

**Investigation of the effects of the treatment on the overall state of health should be personalized, conducted on a routine basis and include monitoring of body weight, lipid levels, blood glucose, blood pressure, thyroid, renal and hepatic function, white blood count, and in women also regularity of menstruation. Strength of recommendation: consensus of experts [5].**

**Caution should be exercised when prescribing and administering medicines to elderly persons; the use of medicines and their effects should be thoroughly monitored and documented. Particular attention should be paid to multi-drug treatment and medicines that increase the risk of adverse drug reactions and diseases at an elderly age. Strength of recommendation: Ia [3].**

Principles of treatment of a depressive episode after P. Gałecki [8]. Strength of recommendation – consensus of an expert group.

1. Thorough diagnostic work-up – assessment of severity of the depressive episode (mild, moderate, severe, with/without psychotic symptoms), assessment of phase/stage of the disease, assessment of accompanying symptoms. Additionally, an evaluation should be made to rule out depression associated with bipolar disorder, which requires a separate treatment approach.
2. Depending on disease severity, the dose should be increased to the lowest effective level, but the use of maximum doses should not be avoided.
3. The antidepressant effect appears after 2–4 weeks of using a sufficiently high dose.
4. If no improvement is observed after 6–8 weeks of use of the maximum dose, change of the medicine is necessary. The medicine is usually switched to another one (a different drug class, or a different drug from the same class but with different properties).
5. Treatment of the first episode should be continued for at least 6 months after an improvement is obtained.
6. If the patient is being treated for a subsequent depressive episode, treatment should last for up to 2 years; if there were more episodes, long-term antidepressant treatment should be considered.
7. Adverse reactions usually appear at the beginning of pharmacological treatment. They usually resolve within a few days of medicine use.

8. Substance intolerance may be permanent. In such a case, the medicine should be switched to another one.
9. It should be borne in mind that patients with depression do not always adhere to the physician's recommendations and sometimes discontinue therapy without consulting their physician.

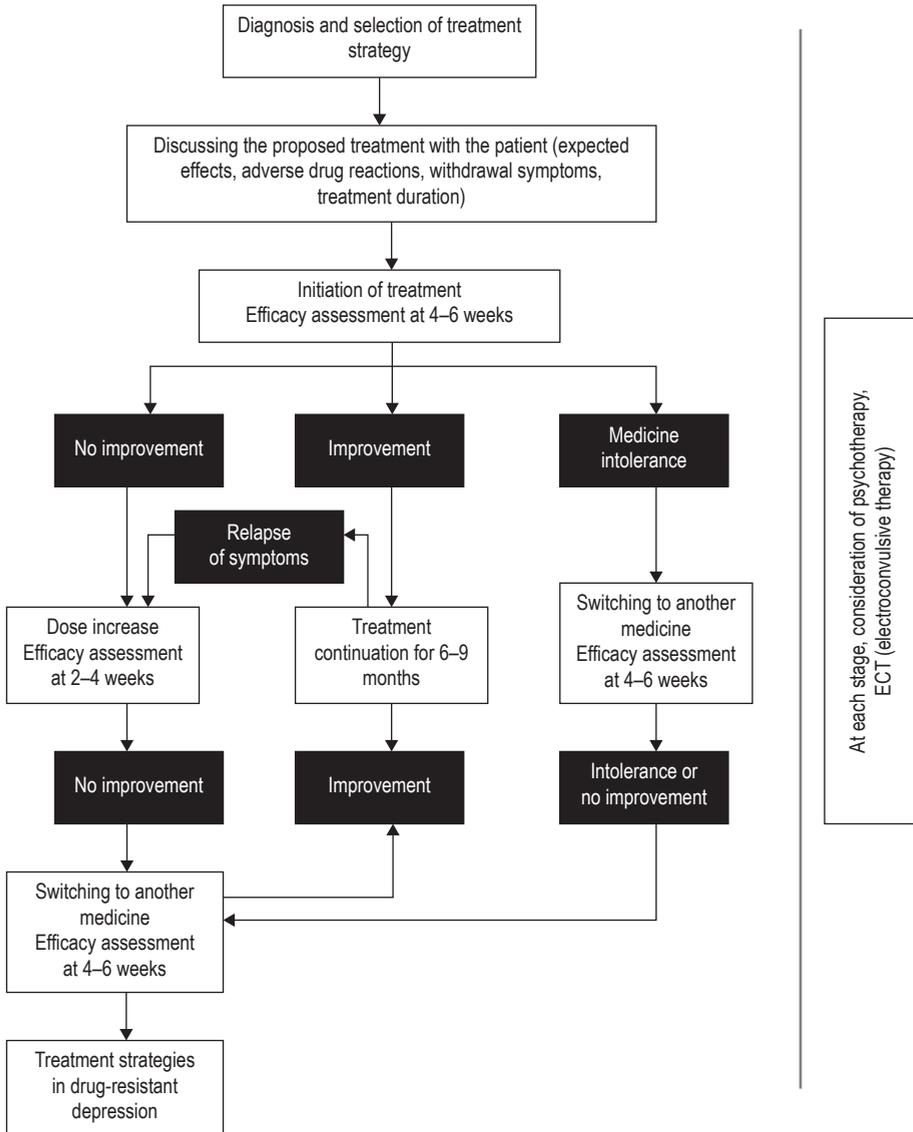


Figure 1. Principles of treatment of a depressive episode [8]

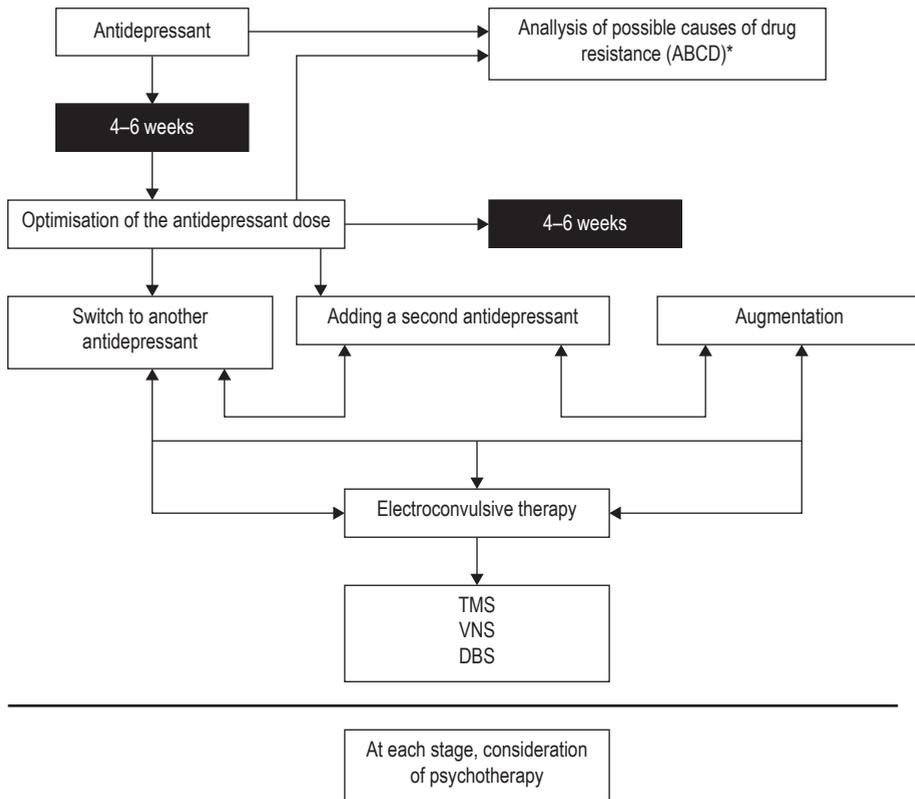


Figure 2. Algorithm of treatment of drug-resistant depression [8]

\* In the case of depression resistant to 2 treatment regimens, intranasal esketamine or ketamine/esketamine may be added to the treatment in combination with an SSRI/SNRI drug. The next treatment stage can be initiated with omission of electroconvulsive therapy, including when ECT is contraindicated.

DBS – Deep Brain Stimulation

TMS – Transcranial Magnetic Stimulation

VNS – Vagus Nerve Stimulation

**Re 3. What are the rules of selection of antidepressants? An adequate trial of treatment with antidepressants is understood as the treatment for at least 3 weeks at the recommended doses with the use of the appropriate medicine. Strength of recommendation: level of evidence II [5].**

**When implementing antidepressant treatment, the clinical response and the presence of adverse drug reactions should be systematically monitored. Strength of recommendation – consensus of an expert group [5].**

Basic principles of psychopharmacological treatment. Strength of recommendation – consensus of an expert group [2]:

- performing a thorough psychiatric examination, including an assessment of suicidal risk, bipolarity, comorbidities, medicines used, particularity of symptoms and groups of symptoms;
- analyzing pharmacological and non-pharmacological treatment options;
- taking into account patient preferences for the treatment method;
- analyzing the previous treatment, including the doses used, the duration, the treatment response, and occurrence of adverse reactions to antidepressants and other agents;
- performing laboratory tests, including lipid profile, hepatic enzyme levels and electrocardiogram, as clinically necessary;
- reassessment of the patient's condition at 2 weeks after treatment initiation for tolerability of the treatment, safety and initial improvement; consecutive follow-up examinations every 2–4 weeks;
- using psychometric tools for the assessment of symptom severity and for monitoring changes of symptoms over time, which facilitates clinical decision-making. It is recommended to monitor the mental state over time, both by using validated objective tools, which can be used by a competent clinician, as well as by self-assessment tools for use by the patient. The selection should be adjusted to the organizational capabilities of treatment.

### Characteristics of antidepressants

#### Drugs of first choice

As a first-line treatment, drugs with various mechanisms of action may be used. Selective serotonin reuptake inhibitors (**SSRIs**) are frequently used in the treatment of depression (level of evidence: 1 [2]).

Table 1. Selective serotonin reuptake inhibitors

| Drug        | Dose        | Therapeutic indications   |
|-------------|-------------|---|
| Fluoxetine  | 20-60 mg/d  | Major depressive episodes<br>Obsessive-compulsive disorders<br>Bulimia nervosa: fluoxetine is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity |
| Fluvoxamine | 50-300 mg/d | Major depressive episodes<br>Obsessive-compulsive disorders   |
| Citalopram  | 10-40 mg/d  | Depressive episodes<br>Prevention of recurrent depressive disorder<br>Panic disorder with or without agoraphobia  |

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|              |             |   |
|--------------|-------------|---|
| Escitalopram | 5-20 mg/d   | Major depressive episodes<br>Panic disorder with or without agoraphobia<br>Social phobia<br>Generalized anxiety disorder<br>Obsessive-compulsive disorders  |
| Sertraline   | 50-200 mg/d | Major depressive episodes, also with accompanying anxiety symptoms<br>Obsessive-compulsive disorders<br>Panic disorder with or without agoraphobia<br>Post-traumatic stress disorder<br>Social phobia |
| Paroxetine   | 10-60 mg/d  | Severe depressive episode<br>Obsessive-compulsive disorders<br>Panic disorder with or without agoraphobia<br>Social phobia<br>Generalized anxiety disorder<br>Post-traumatic stress disorder          |

#### Drugs of first choice – continued

The next class of first-line drugs that are most commonly used in the treatment of depression are selective serotonin and norepinephrine reuptake inhibitors (SNRIs) (level of evidence: 1 [2, 4]).

Table 2. Selective serotonin and norepinephrine reuptake inhibitors

| Drug        | Dose                                  | Therapeutic indications   |
|-------------|---------------------------------------|---|
| Venlafaxine | 75-225 mg/d (maximum dose 375 mg/d)   | All types of depression, including depressive disorders with anxiety<br>Prevention of depression relapses or recurrences<br>Generalized anxiety disorder<br>Social phobia<br>Panic disorder with or without agoraphobia |
| Duloxetine  | 30-90 mg/d<br>(maximum dose 120 mg/d) | Major depressive episodes<br>Generalized anxiety disorder<br>Treatment of pain in diabetic peripheral neuropathy in adults  |

## Drugs of first choice – continued

For the individual drugs – level of evidence: 1 [2], consensus of an expert group. Other antidepressants with various mechanisms of action. Including:

- **SARI** (serotonin antagonist and reuptake inhibitor) – trazodone.
- **NDRI** (norepinephrine-dopamine reuptake inhibitor) – bupropion.
- Noradrenergic and specific serotonergic antidepressants – mirtazapine and mianserin.
- **RIMA** (reversible inhibitor of monoamine oxidase A) – moclobemide.
- Agents acting on multiple receptors (vortioxetine, agomelatine).

Table 3. Antidepressants with various mechanisms of action

| Drug   | Dose   | Therapeutic indications   |
|--|--|---|
| Trazodone<br>(serotonin reuptake inhibitor and 5-HT <sub>2</sub> receptor antagonist)  | 75-300 mg/d (max. dose 600 mg/d)                   | Depressive disorders of various etiologies, including depression with accompanying anxiety  |
| Bupropion<br>(selective inhibitor of the neuronal reuptake of catecholamines (norepinephrine and dopamine) with minimal effect on the reuptake of indoloamines (serotonin); does not inhibit MAO activity)   | 150-300 mg/d                                       | Major depressive episodes (modified-release tablets)<br>Treatment of nicotine dependence (sustained-release tablets)<br>Part of compound preparation (bupropion + naltrexone, used in the treatment of obesity) |
| Mianserin<br>(tetracyclic antidepressant, an alpha <sub>2</sub> -adrenergic receptor antagonist, it increases the turnover of brain norepinephrine, does not inhibit peripheral reuptake of norepinephrine, has an antagonistic effect on some serotonergic receptors and H <sub>1</sub> receptor, practically devoid of anticholinergic properties)   | 30-90 mg/d<br>(the maximum daily dose is 200 mg/d) | Depressive syndromes  |
| Mirtazapine<br>(noradrenergic and specific serotonergic antidepressant (NaSSA). It stimulates noradrenergic and serotonergic neurotransmission via 5-HT <sub>1A</sub> receptors by blocking central alpha <sub>2</sub> -adrenergic autoreceptors and heteroreceptors and blocking 5-HT <sub>2</sub> and 5-HT <sub>3</sub> receptors postsynaptically. The medicine has no effect on norepinephrine and serotonin reuptake) | 15-45 mg/d   | Major depressive episodes   |

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|   |              |                                       |
|---|--------------|---------------------------------------|
| <p>Agomelatine<br/>(agonist of MT<sub>1</sub> and MT<sub>2</sub> melatonergic receptors and antagonist of 5-HT<sub>2C</sub> receptors with antidepressant activity. Has no effect on monoamine reuptake, has no affinity for α – and β-adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors. Agomelatine increases the release of norepinephrine and dopamine, especially in the frontal cortex)</p> | 25-50 mg/d   | Major depressive episodes             |
| <p>Moclobemide<br/>(reversible monoamine oxidase inhibitor, especially of type A (MAO-A). It inhibits the breakdown of dopamine, serotonin and norepinephrine, which increases their levels in the synaptic gap)</p>  | 300-600 mg/d | Depressive disorders<br>Social phobia |
| <p>Vortioxetine<br/>(modulator of serotonergic transmission, antagonist of 5-HT<sub>3</sub>, 5-HT<sub>7</sub> and 5-HT<sub>1D</sub> receptors, partial antagonist of 5-HT<sub>1B</sub> receptor, agonist of 5-HT<sub>1A</sub> receptor. The above properties lead to modulation of serotonergic and probably also noradrenergic, dopaminergic, histamine, acetylcholine, GABA and glutamate transmission)</p>                     | 5-20 mg/d    | Major depressive episodes             |

### Drugs of second choice

Level of evidence: 1 [2], consensus of an expert group.

**TCAs** (tricyclic antidepressants) – class of psychotropic agents with a similar chemical structure (molecule consisting of three rings), used in the treatment of depression. These medicines are highly effective in the treatment of depressive symptoms, but due to their numerous side effects are treated as second-line drugs.

**NRI** (norepinephrine reuptake inhibitor) – selective norepinephrine reuptake inhibitor – reboxetine.

Table 4. Tricyclic antidepressants and selective norepinephrine reuptake inhibitor

| Drug   | Dose                       | Therapeutic indications   |
|--|----------------------------|---|
| Clomipramine   | 150-300 mg/d               | <p>Depressive states of varying etiology and symptomatology (endogenous, reactive, neurotic, organic, masked and involuntal forms of depression)</p> <p>Depression in the course of schizophrenia (in combination with a neuroleptic) and personality disorders</p> <p>Age-related depressive syndromes, in the course of chronic pain conditions and chronic psychosomatic disorders</p> <p>Obsessive-compulsive syndromes</p> <p>Phobias and panic attacks</p> <p>Additionally: treatment of nocturnal enuresis in children over 5 years of age, provided that organic causes are ruled out</p> |
| Amitriptyline  | 150-300 mg/d               | <p>Major depressive disorders</p> <p>Neuropathic pain</p> <p>Prevention of chronic tension headache and migraine.</p> <p>Additionally: nocturnal enuresis in children over 6 years of age, when organic causes (such as spina bifida) have been excluded and no response has been achieved to all other treatment methods, including antispasmodics and vasopressin or its analogues.</p>   |
| Reboxetine<br>(a potent selective norepinephrine reuptake inhibitor with antidepressant activity. It has a weak effect on serotonin reuptake and no effect on dopamine reuptake) | 4-8 mg/d<br>(max. 12 mg/d) | Depressive syndromes  |

### Basic principles of treatment of depression

In moderate-to-severe depressive disorders, the treatment of choice is pharmacological therapy with antidepressants. In the treatment of mild depression, antidepressants may be used, but psychotherapeutic and psychosocial interventions may be sufficient [10, 14]. In such cases, the initial choice of treatment is commonly dictated by patient preferences and access to a psychotherapist [25]. Cognitive behavioral psychotherapy is the preferred psychotherapeutic method in the treatment of depression. Access to psychotherapy in the public healthcare setting is substantially limited in Poland, especially outside metropolitan areas, which should be taken into account when the treatment method is selected.

It is worth noting that the efficacy of antidepressants increases along with increasing severity of depression [26].

As demonstrated by a very large number of controlled clinical trials and their meta-analyses, antidepressants generate comparable response rates to treatment regardless of their mechanism of action, ranging between 50% and 75% and significantly greater in comparison with placebo, usually without significant superiority over an active drug comparator [19-22, 27, 28]. In 2009 a meta-analysis was published that compared the efficacy and safety of 12 antidepressants, indicating that the most effective antidepressants are sertraline, escitalopram, venlafaxine and mirtazapine, the first two of which have the best tolerability profile. Reboxetine proved to be the least effective of the analyzed medicines [29]. Also in the meta-analysis of 2010, the efficacy of reboxetine proved to be similar to that of placebo [30]. In the recently published meta-analysis of 21 antidepressants performed by Cipriani et al. [31], 28,553 citations were identified, including 522 studies with 116,477 subjects. All antidepressants were more effective than placebo. In head-to-head comparisons, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine and vortioxetine were more effective than other antidepressants. Agomelatine, citalopram, escitalopram, fluoxetine, sertraline and vortioxetine were better tolerated than other antidepressants [31]. An additional effect of vortioxetine treatment, unique among the antidepressants, is the positive effect on cognitive functions that are impaired in depression, i.e. memory, attention and executive function impairment [32, 33].

In the case of severe depressive episodes that require hospitalization, some data indicate higher efficacy of tricyclic antidepressants (TCAs; amitriptyline, clomipramine) and venlafaxine in comparison with SSRIs and comparable efficacy of TCAs, venlafaxine, mirtazapine and trazodone. Higher doses of trazodone (at least 300 mg/d), especially of the XR (extended release) formulation, have an antidepressant effect comparable with that of other classical drugs used in the treatment of depression. Trazodone is also used in first-line therapy [34-38].

The individual antidepressants differ significantly by their adverse effects. This may determine treatment tolerability and patient collaboration, and the usefulness of the specific medication in patients with somatic comorbidities. For example, in patients with ischemic heart disease, the drugs of choice are those that have no effect on blood pressure or cardiac conduction. The criteria for selecting an antidepressant are its effectiveness, treatment risk, tolerability and possibility of cooperation with the patient [39].

SSRIs are generally considered to be the safest. However, potentially dangerous complications should be borne in mind such as the risk of bleeding related to their effect on blood platelet function (especially in combination with anticoagulants), the risk of syndrome of inappropriate antidiuretic hormone secretion (SIADH; hyponatremia), the risk of QTc prolongation (especially during the use of high doses of citalopram and escitalopram) and the risk of serotonin syndrome (especially as a result of interactions with other substances with serotonergic activity) [28].

An important limitation of agomelatine use is hepatic failure. This medicine may cause an up to 10-fold increase in transaminase levels; isolated cases of jaundice, hepatitis and hepatic failure have been described. Therefore, it is recommended to monitor hepatic enzyme levels, especially during treatment initiation and dose increase [28]. When properly used, agomelatine is well tolerated, regulates the sleep–wake cycle and reduces depressive anhedonia (inability to feel pleasure).

### **Patient clinical profile and selection of the antidepressant agent**

It is recommended to select such a medicine that it does not contribute to progression of symptoms and has a spectrum of clinical activity against the highest possible number of symptoms or groups of symptoms [40]. A thorough clinical assessment of the symptom profile of an individual patient is necessary. The basis of such an assessment is the psychiatric examination. Commonly used scales and symptom questionnaires may be helpful.

**In depression with coexisting anxiety disorders, it is recommended to use medicines that are also effective against generalized anxiety disorder. Level of evidence: 4 [2].**

The antidepressants with the activity profile encompassing anxiety disorders include SSRIs, venlafaxine, duloxetine, and trazodone.

**Depression with insomnia is an indication for use of antidepressants with sleep-improving effects. These include trazodone, mirtazapine, mianserin and agomelatine. Level of evidence: 1 or 2 [2].**

It is important to note that higher doses of trazodone are required to obtain its antidepressant effect in comparison with its hypnotic effect. Therefore, trazodone XR can be used in monotherapy, as needed, and, importantly, once daily. In contrast to the CR (controlled release) formulation, trazodone XR used in the morning has a hypnotic effect manifested in the evening [36, 37].

**Depression with suicidal tendencies.** Suicide risk should always be assessed when treating a patient with depression. No medicines with a rapid anti-suicide effect are available. Addition of benzodiazepines to antidepressants may increase the short-term control of suicidal behavior. The anti-suicide effect of lithium in long-term treatment has been demonstrated, but there are no data on such an effect in the acute treatment phase [28]. In persons with a high risk of suicide, the use of ECT should be considered as the first-line treatment. When selecting the antidepressant, it is necessary to take into account potential toxicity of the product when overdosed (TCAs > venlafaxine, mirtazapine > citalopram > other SSRIs) and limitation of the quantity of the medicine prescribed at a single time. It is recommended to add psychotherapy and – in patients under outpatient treatment – to increase the frequency of visits [28].  
**Strength of recommendation – consensus of the Working Group.**

**Depression with cognitive dysfunction.** Despite data on an improvement in both depression and some cognitive aspects under the treatment with SSRIs, duloxetine or

bupropion (level of evidence: 2 [2]), cognitive deficits may persist also in the remission period [41].

Vortioxetine has a positive effect on cognitive functions that are impaired in depression, i.e. memory, attention and executive function impairment [32, 33]. **Level of evidence: 1 [2].**

**In atypical depression**, SSRIs, moclobemide and bupropion are recommended as the drugs of first choice. Bupropion is also a drug recommended in seasonal depression (that often has atypical features). In this depression subtype, the first-line treatment is phototherapy [25]. **Strength of recommendation: consensus of the Working Group.**

**In depression with appetite increase and weight gain**, medicines that do not cause weight gain and/or support weight loss are recommended, such as bupropion, fluoxetine (use with caution in patients with diabetes because of the risk of hypoglycemia), moclobemide, trazodone and vortioxetine. **Strength of recommendation: consensus of the Working Group.**

**Depression in somatic comorbidities and in elderly patients.** Elderly patients are particularly susceptible to adverse effects of pharmacological therapy. Drugs with cholinergic effects, mainly tricyclic antidepressants, have a markedly worse tolerability profile in the population of patients over the age of 65. When selecting the medicine for this group of patients, the increased risk of postural hypotension and precipitation of cardiac conduction disorders should be taken into account. The justified drugs of first choice are selective serotonin reuptake inhibitors. Nevertheless, this requires particular caution of the treating physician because of the risk of gastrointestinal bleeding when concomitant treatment with non-steroidal anti-inflammatory drugs is used. Long-term use of SSRIs in elderly patients increases the risk of hypotension-unrelated falls and bone fractures, observed mainly during the first 6 weeks of treatment. These medicines may also aggravate hyponatremia, especially when other factors contributing to its development are present. In patients with the risk of hyponatremia, a good alternative is trazodone. In the case of venlafaxine and duloxetine, it is important to pay particular attention to the possible blood pressure increase in the initial treatment period. The safest agents in patients with somatic comorbidities include agomelatine (except for hepatic failure), trazodone and vortioxetine. **Strength of recommendation: consensus of the Working Group.**

**Depression accompanied by pain.** Depression is often accompanied by pain symptoms: neuropathic pain, fibromyalgia, migraines, tension headaches. The antidepressant selection should take into account the potential beneficial analgesic activity. Antidepressants with such a profile include amitriptyline, duloxetine, mirtazapine (mainly in tension headaches) and venlafaxine [42, 43]. **Strength of recommendation: consensus of the Working Group.**

**In psychotic depression**, the treatment of choice is the combination of an antidepressant and a typical or atypical antipsychotic. Usually lower doses of the antipsychotic are required than in the case of schizophrenic psychosis. Monotherapy, with both antidepressants and antipsychotics, is less effective than combination therapy.

A promising direction is the use of atypical antipsychotics that have antidepressant effects (e.g. quetiapine). First-line treatment can also be ECT.

Therefore, when selecting the antidepressant, the following premises should be taken into account: efficacy, tolerability, presence of other mental disorders, profile of adverse drug reactions (including weight gain, sexual dysfunction), safety of use of the given drug with potential coexisting somatic diseases, the patient's age, the medications used (possible interactions), the clinical features of depression (e.g. severity, atypical features, depression with anxiety, depression with insomnia), patient's compliance, efficacy of the drug in first-degree relatives, physician's experience with the given medication, patient's preferences, convenience of use, availability and price of the medication.

**Re 4. How and after what time should treatment efficacy and tolerability be assessed? What contributes to treatment failure?** The therapeutic response is defined as a reduction of symptoms by at least 50% from the baseline [4]. The therapeutic response observed at 4–6 weeks of treatment is a predictor of remission [2, 44]. Currently, it is proposed to introduce the early threshold response as partial reduction of symptoms at 2 weeks of treatment from the baseline, which differentiates it from the treatment response defined as a reduction by  $\geq 50\%$  from the baseline. The cutoff for the assessment of early threshold response is the 20% reduction of depression severity from the baseline [45].

**Nevertheless, it is difficult to justify the usefulness of the early threshold response in everyday clinical practice, and thus the treatment should be guided by the classical assessment at 4–6 weeks of administration of an antidepressant agent at the therapeutic dose. Strong recommendation [4].**

In treatment efficacy monitoring, observation of the change in mental state from the point when the therapeutic dose was achieved is important [2, 44, 46].

The identified factors that contribute to the chronic course of depression include: young age at onset, the severity of the first episode, multiple past episodes, circadian rhythm disturbances, coexistence of other psychiatric disorders, family history of psychiatric disorders, presence of maladaptive negative beliefs, neuroticism, lack of social support, and lifetime stress burden and comorbidities, especially addictions. Level of evidence: 3 [2]. Resistance to monotherapy treatment of depression may be a result of undiagnosed bipolarity. The efficacy of antidepressant treatment is influenced by: appropriate drug selection that is suitable for the symptom profile, tolerability, and patient's acceptance of the treatment, as well as a drug that will have a proper blood concentration level, will be given at the right dose and will be administered for a sufficient duration.

Physician-patient collaboration is a key issue, similarly to placing a correct diagnosis. Treatment efficacy can also be influenced by environmental factors (difficult life events, career and family problems). Also, potential secondary benefits of the illness must be borne in mind.

**Re 5. How should patient treatment be monitored?**

**After initiation of adequate depression treatment, we recommend monitoring of the patient's condition at least monthly until remission is achieved. This monitoring should include as a minimum the assessment of symptom severity, treatment compliance and adverse drug reactions. Strong recommendation [4].**

Patient compliance with the pharmacological treatment of depression should be assessed at every visit. Patients treated for depression are at a high risk of non-compliance. The monitoring of pharmacological treatment compliance may apply to: filling the prescription for the antidepressants recommended by the physician, treatment initiation, systematic use of treatment (daily intake of medicines with full compliance versus omitting doses or interruptions of the treatment with only partial compliance), dose modification by the patient, premature treatment discontinuation or other circumstances related to deviations from the interventions recommended by the physician. The monitoring should also address the issues of alcohol use by the patient and concomitant intake of other medicines (in particular psychotropic agents), dietary supplements or herbal remedies during the antidepressant treatment, because of the risk of dangerous interactions.

The assessment of treatment efficacy should encompass both the mental state of the patient with regard to depressive symptoms as well as the level of functioning. Complete remission is indicated by concomitant improvement of the patient's mental state (resolution of symptoms) and return to the pre-disease level of functioning (which may, but does not have to, mean return to the same activities that were performed by the patient before the depressive episode).

The patient should be monitored for adverse drug reactions at each follow-up visit. The use of antidepressants is usually associated with transient adverse drug reactions (especially during the first 2 weeks of treatment), which should be discussed with the patient. Persistent (long-term) adverse drug reactions that negatively affect patient functioning or are atypical may make it necessary to switch the treatment to another antidepressant agent. In each situation, a subjective assessment of adverse drug reactions by the patient and the assessment of their effects on patient functioning (e.g. subjective importance of sexual dysfunction in the context of patient relations) is important. If adverse effects that are not typical for antidepressants occur, it should be assessed together with the patient if these adverse effects are actually related to the antidepressant agent used.

If the initial improvement obtained during the treatment is markedly reduced with time or the patient reports a relapse of symptoms, it is indicated to evaluate patient compliance, the presence of psychosocial stressors (traumatic events, changes of the patient's situation in the personal, occupational, financial or another context), and the addition of somatic factors that may influence the treatment. Finding any of the above circumstances requires implementation of the appropriate intervention (e.g. discussing the causes of non-compliance and treatment resumption, referring the patient to psychotherapy or crisis intervention).

**Re 6. How long should pharmacological treatment be continued?**

**In patients with depression who have achieved remission, we recommend to continue treatment with the antidepressant agent for at least 6 months at the stable previously effective dose to reduce the risk of relapse. Dose reduction in prophylactic therapy is not justified and is associated with an increased risk of relapse. Strong recommendation [4].**

**In patients with a high risk of recurrent depressive episodes who receive pharmacological therapy, we recommend continuation of maintenance therapy for at least 12 months and consideration of lifelong therapy. Strong recommendation [4].**

According to the CANMAT guidelines (level of evidence: 3 and 4 [2]), the risk factors in favor of extension of maintenance treatment (for two years or longer) with antidepressants are:

- frequent recurrent depressive episodes,
- severe episodes (with psychotic symptoms, marked functional impairment, or suicidal ideation or intention),
- chronic course of episodes,
- presence of other mental or somatic disorders,
- presence of residual depressive symptoms,
- refractory episodes [47-50].

The first episode of depression requires 6–12 months of pharmacological treatment. In patients receiving pharmacological treatment, who have a high risk of recurrent depressive episodes, maintenance treatment should be continued for at least 12 months, and study results justify a period of at least 24 months of prophylactic treatment continuation, which should be indefinite in many cases. It can be assumed that prophylactic therapy of a second depressive episode should be conducted for 2–3 years after symptomatic remission is obtained [2, 3, 51-55]. For patients with a complicated course of treatment, including those with chronic depression, the lack of full remission, coexisting psychiatric disorders and rapid relapse of depression, it is justified to administer preventive treatment with antidepressants indefinitely, which also applies to the treatment of the third depressive episode [2, 3, 51-55].

For long-term treatment, drugs that can be dosed once daily are worth considering when selecting the antidepressants, because such administration contributes to improved treatment compliance.

Table 5. Treatment duration depending on the depressive episode

| Depressive episode   | Duration of treatment        |
|--|------------------------------|
| First  | 6-12 months after remission  |
| Second   | 24-36 months after remission |
| Third episode or chronic course/incomplete remission/rapid relapse of depression/psychiatric comorbidities | indefinite treatment         |

## Summary

Treatment of depression is a challenging process that requires knowledge and experience. Antidepressants have been used for years and have a well-established role in therapy, but sometimes their efficacy is put into question. At the same time, there are numerous literature data that confirm the efficacy of pharmacological treatment of depression, which provides the basis for formulating detailed patient management guidelines. The above recommendations are based on scientific evidence, and thus they have a robust basis for their implementation in practice.

Certainly, psychotherapy constitutes an important element of depression treatment, and its role changes along with the severity of a depressive episode. We suggest a stronger statement: psychotherapy constitutes an integral element of depression treatment, and its role changes along with the severity of a depressive episode, phase of treatment, comorbidities and the long-term strategy of relapse prevention.

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*Jerzy Samochowiec, Dominika Dudek, and Jolanta Kucharska Mazur equally contributed to the development of the present guidelines and are all equal first co-authors*

Address: Jerzy Samochowiec  
Chair and Department of Psychiatry  
Pomeranian Medical University in Szczecin  
71-460 Szczecin, Broniewskiego Street 26  
e-mail: samoj@pum.edu.pl