Slovenian Medical Journal

Recommendations for treatment of unipolar depressive disorder

Priporočila za zdravljenje unipolarne depresivne motnje

Anja Plemenitaš Ilješ,[1] Maja Drobnič Radobuljac,[2,3] Blanka Kores Plesničar,[2,3] Peter Pregelj,[2,3] Borut Škodlar,[2,3] Tea Terzić,[2] Jurij Bon[2,3]

Abstract

Depression is a common mental disorder with a high burden of disease worldwide and requires effective treatment. On behalf of the General Advisory Council for Psychiatry, clinical recommendations were formed to help clinicians make decisions to improve the treatment of patients with unipolar depressive disorder; several international guidelines served as the basis for developing these recommendations. In terms of therapeutic approaches, pharmacological treatment is discussed with additional recommendations on the management of a partial response to treatment and treatment resistance. Psychotherapy, psychoeducation, and other psychosocial approaches represent non-pharmacological interventions for the treatment of depressive disorder. Biological methods for treating depression include non-invasive brain stimulation methods. The second part of the recommendations addresses special populations: children and adolescents, the elderly, and the treatment of depression in the perinatal period.

Izvleček

Depresija je pogosta duševna motnja z velikim bremenom bolezni po vsem svetu in zahteva učinkovito zdravljenje. Pod okriljem Razširjenega strokovnega kolegija za psihiatrijo so bila oblikovana klinična priporočila kot vodilo zdravnikom za izboljšanje zdravljenja bolnikov z unipolarno depresivno motnjo. Za pripravo teh priporočil je služilo več mednarodnih smernic. V smislu terapevtskih pristopov je obravnavano farmakološko zdravljenje z dodatnimi priporočili pri zdravljenju delnega odziva in pri terapevtsko odporni depresiji. Nefarmakološki pristopi za zdravljenje depresivne motnje so: psihoterapija, psihoedukacija in drugi psihosocialni pristopi. Biološke metode zdravljenja depresije vključujejo neinvazivne metode stimulacije možganov. Drugi del priporočil je namenjen posebnim populacijam: otrokom in mladostnikom, starejšim ter zdravljenju depresije v obporodnem obdobju.

[1] Department of Psychiatry, University Clinical Centre Maribor, Maribor, Slovenia
[2] University Psychiatric Clinic Ljubljana, Ljubljana, Slovenia
[3] Department of Psychiatry, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Correspondence / Korespondenca: Anja Plemenitaš Ilješ, e: anja.plemenitas@ukc-mb.si

Key words: major depressive disorder; clinical practice guidelines; pharmacotherapy; psychotherapy; biological methods

Ključne besede: velika depresivna motnja; klinične smernice; farmakoterapija; psihoterapija; biološke metode

Received / Prispelo: 7. 3. 2023 | **Accepted / Sprejeto:** 19. 4. 2023

Cite as / Citirajte kot: Plemenitaš Ilješ A, Drobnič Radobuljac M, Kores Plesničar B, Pregelj P, Škodlar B, Terzić T, et al. Recommendations for treatment of unipolar depressive disorder. Zdrav Vestn. 2023;92(7–8):D9–D24. **DOI:** https://doi.org/10.6016/ZdravVestn.3431

1 Introduction

Depression is a common, recurrent mental disorder associated with decreased functioning, poorer quality of life, medical comorbidity, and increased mortality (1). Regarding the global burden of disease, depression ranks highly, even when compared to somatic disorders (2). Effective treatment of depressive disorders is a public health priority and is associated with a significantly reduced disease burden (3).

The purpose of these recommendations is to assist clinician decision-making and thereby improve the treatment of patients with unipolar depressive disorder. The 13th edition of Maudsley Prescribing Guidelines in Psychiatry (4), the British Association for Psychopharmacology Guidelines (BAP) (5), the American Psychiatric Association Practice Guidelines (APA) (6), World Federation of Societies of Biological Psychiatry Guidelines (WFSBP) (7), Canadian Network for Mood and Anxiety Treatments Clinical Guidelines (CANMAT) (8), National Institute for Health and Care Excellence Guidelines (NICE) for the treatment of depressive disorders in children and adolescents (9) and adults (10) served as the basis for the development of these recommendations.

The Expert Council for Psychiatry at the Slovenian Medical Association approved these recommendations on 18 January 2023, and the Main Expert Council of the Slovenian Medical Association approved these recommendations on 27 March 2023.

Unipolar depressive disorder may consist of one or more depressive episodes. European International Classification of Diseases, 10th Revision - ICD-10 (11) states that a depressive episode is characterized by decreased mood, energy, and activity. Symptoms of a depressive episode include persistent low mood, sleep, and appetite disturbances, anhedonia, decreased interest and poor concentration, marked fatigue, decreased self-esteem, feelings of guilt or worthlessness, psychomotor retardation or agitation, and suicidal behaviour.

Various questionnaires or rating scales can serve as basic tools for monitoring the course of the illness and response to treatments. A partial response to treatment is defined as at least a 50% improvement in clinical symptoms. In Slovenia, the Zung Self-Rating Depression Scale (13), the Hamilton Rating Scale for Depression (HAM -D) (14), the Montgomery-Åsberg Depression Rating Scale (MADRS) (15), and the Hospital Anxiety and Depression Scale (HADS) (16) are commonly used when screening for a depressive episode. The Patient Health Questionnaire - 9 (PHQ-9) can be similarly used for screening in primary care (17). The Geriatric Depression Scale is suitable for use in the geriatric population with depressive disorder (18). Currently, the Slovenian validation of clinical questionnaires and scales is on the way that will serve as formal tools for objective assessment of clinical pictures of patients.

Based on the principle included foreign guidelines, we defined Criteria for the level of evidence in line of treatment and Strength of recommendation listed in Table 1 and Table 2. Table 3 contains a list of Slovenian recommendations for the treatment of unipolar depressive episode.

Table 1: Criteria for the level of evidence in line of treatment.

Level	Criteria
I	Meta-analysis with narrow confidence intervals and/or 2 or more RCTs with an adequate sample size, preferably placebo controlled
II	Meta-analysis with wide confidence intervals and/or 1 or more RCTs with an adequate sample size
III	Small-sample RCTs or nonrandomized, controlled prospective studies or case series or high-quality retrospective studies
IV	Expert opinion/consensus

Table 2: Criteria for the strength of recommendation in line of treatment.

Strength of recommendation	Criteria
A	directly based on category I evidence
B	directly based on category II evidence or extrapolated# recommendation from category I evidence
C	directly based on category III evidence or extrapolated# recommendation from category I or II evidence
D	directly based on category IV evidence or extrapolated# recommendation from category I, II or III evidence
S	standard of good practice

Table 3: List of Slovenian recommendations for treatment of unipolar depressive episode.

Description of the recommendation	Level of evidence	Strength of recommendation
In a mild depressive episode, use pharmacotherapy.		B
In a mild depressive episode, use psychological therapies.		S
In moderate or severe depressive episode, use pharmacotherapy as the initial treatment.	I	A
In a depressive episode that lasts more than two years, regardless of the severity of symptoms, use pharmacotherapy.		A
Selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine inhibitors (SNRIs) and mirtazapine represent the first-line therapy in depression treatment.		A
Bupropion, trazodone and vortioxetine represent the first-line therapy in depression treatment.		B
Agomelatine, tianeptine, tricyclic antidepressants (TCAs) represent the second-line therapy in depression treatment.		A
Reboxetine and moclobemide represent the second-line therapy in depression treatment.		B
In a severe depressive episode, TCAs may be used as the first choice of treatment.		A
In a depressive episode with psychotic symptoms, an atypical antipsychotic can be added to the antidepressant.	I	A
In the initial phase of depression treatment, it is useful to add benzodiazepines or a hypnotic.		A
For the first depressive episode, it is reasonable to continue medication at an effective dose for at least 6 to 9 months after remission has been achieved.		A
In recurrent depressive episodes, chronic depressive episodes with residual symptomatology, and in the presence of family stress, persistent psychosocial stressors, suicidality, or associated psychosis, it is reasonable to continue maintenance therapy for at least 2 years.		A
If lowering or discontinuing the antidepressant leads to a relapse, it is reasonable to reintroduce the antidepressant at the original dose and continue treatment for another 6 months.		B
In the second phase of treatment, switching to another antidepressant from the first or second group of choice, augmenting the response (using other types of medication in combination with an antidepressant), and combination therapy (a combination of two antidepressants from different therapeutic groups) can be used.	III	A
In the second phase of depression treatment, an antidepressant with psychotherapy can be used.		B
In the second phase of depression treatment, an antidepressant with non-invasive brain stimulation electroconvulsive therapy – ECT can be used.		B
In the second phase of treatment, transcranial magnetic stimulation – TMS can be used.		D
In the third phase of depression treatment, all strategies mentioned for treating treatment-resistant depression – TRD are used, as well as other methods, such as third-line antidepressants.		S
For severe major depression, psychological or behavioural treatment is not recommended as sole therapy.		B
Cognitive behavioural therapy (CBT) is a useful method in the treatment of depressive episodes.	I	A
Interpersonal psychotherapy is a useful method in the treatment of depressive episodes.	I	A
Psychodynamic psychotherapy is a useful method in the treatment of depressive episodes.	II	B

Description of the recommendation	Level of evidence	Strength of recommendation
Problem-oriented psychotherapy is a useful method in depression treatment.		S
If partner or family conflict is present, partner or family psychotherapy in depression treatment is recommended.	II	S
The addition of intense physical exercise to antidepressant therapy may help patients with a mild or moderate depressive episode.		B
Dietary supplements - omega-3 fatty acids can be used as potentially effective additions to the treatment of depression.	II	B
St. John's Worth can also be used as a dietary supplement in depression treatment, but patients should be advised of interactions with SSRIs.		D
High-frequency (10 Hz or more) repetitive transcranial magnetic stimulation – rTMS of the left dorsolateral prefrontal cortex (DLPFC) is the most commonly used biological method in the treatment of depressive episodes.		A
Low-frequency (1 Hz) rTMS of the right DLPFC can be used in the treatment of depressive episodes.		B
Intermittent TBS of left DLPFC is also possible in the treatment of depressive episodes.		S
rTMS is recommended as a possible first-line treatment for patients who cannot take antidepressant medication.		C
Transcranial direct current electrical stimulation (tDCS) techniques are also possible in the treatment of depressive episodes.		B
ECT is used to treat severe depressive episodes, especially when psychotic features are present and in life-threatening conditions such as agitation, stupor, severe physical exhaustion due to refusal to eat, and high risk of suicide.		A
In the treatment of depression in children and adolescents, cognitive-behavioral psychotherapy and interpersonal psychotherapy are recommended.	II	D
In the treatment of depression in children and adolescents, psychodynamic psychotherapy and brief psychosocial interventions are recommended.	I	D
Family-oriented therapies are more effective than individual therapies in treating depression in children, and group therapies are effective in adolescents in addition to individual therapies.	II	D
Combining psychotherapy and treatment with antidepressants in treating depression in children and adolescents is more effective than either treatment alone.		D
For moderate to severe depressive episode in children and adolescents, psychotherapy is recommended first, to which fluoxetine may be added.		D
In children older than 12 years, fluoxetine may be added immediately; in younger children, it may be added after at least four psychotherapy sessions have failed to produce adequate effects.		D
In the case of ineffective initial treatment, TRD, psychotic or recurrent depressive disorder in children and adolescents, fluoxetine, sertraline, citalopram or antipsychotic augmentation during intensive psychotherapy are recommended.		D
Sertraline or citalopram are recommended as second-line antidepressants; venlafaxine, paroxetine, or tricyclic antidepressants should not be prescribed because of significant side effects in the treatment of depression in children and adolescents.		D
In the treatment of depressive disorders in the elderly, the first choice pharmacotherapy is duloxetine, mirtazapine, nortriptyline.	I	
In the treatment of depressive disorders in the elderly, the first choice of pharmacotherapy is also bupropion, citalopram/escitalopram, desvenlafaxine, sertraline, venlafaxine, and vortioxetine.	II	

Description of the recommendation	Level of evidence	Strength of recommendation
In the treatment of depressive disorders in the elderly, the second choice of pharmacotherapy is replacement with nortriptyline and combination with aripiprazole, and lithium.	I	
In the treatment of depressive disorders in the elderly, the second choice pharmacotherapy is also moclobemide, phenelzine, quetiapine, trazodone, and methylphenidate.	II	
In the treatment of depressive disorders in the elderly, the third choice of pharmacotherapy is replacement with amitriptyline or imipramine.	II	
In the treatment of depressive disorders in the elderly, the third choice pharmacotherapy is also a combination of SSRI or SNRI with bupropion, SSRI.	III	
The prescription of psychotropic drugs to women of childbearing age should be guided by the latest evidence on the risks to pregnancy and the fetus. Treatment decisions should include the use of non-pharmacological methods such as psychoeducation, psychotherapy, and other modalities (meditation, relaxation techniques, mindfulness, hypnosis, and occupational therapy).		S
In mild to moderate perinatal depressive episodes, psychoeducation, psychotherapy, and sometimes medication is required.		S
In moderate to severe depressive perinatal episodes, medication is usually required in addition to psychoeducation, and psychotherapy.		S
Benzodiazepines and hypnotics are avoided in the postpartum period, with the exception of short-term treatment of severe anxiety and agitation.		S
Long-acting benzodiazepines should not be prescribed before delivery.		S
Atypical antipsychotics may be prescribed in low doses to enhance antidepressant effects.		S
If pharmacological treatment before and during pregnancy is required, continue with an effective current antidepressant if its benefits outweigh the risk and if the drug is not contraindicated during pregnancy.		S
If pharmacological treatment before and during pregnancy is required, SSRI is prescribed as the first choice (not paroxetine or fluoxetine in the first trimester) and an SNRI as the second choice.		S
If pharmacological treatment is required during birth, a therapeutic dose of the same antidepressant is maintained.		S
If pharmacological treatment is required after birth, the currently effective antidepressant is continued, and the dose may need to be adjusted. If an antidepressant is needed, an SSRI that allows breastfeeding is prescribed.		S

2 Therapeutic approaches in the treatment of depression

2.1 Pharmacological treament

Treatment of depressive disorder is divided into treatment of an acute depressive episode and maintenance treatment. In the acute phase, the goal is to achieve remission and restore functionality. Further on, treatment is needed to prevent relapse or recurrence of the disorder (5-8). In a mild depressive episode, therapeutic effects can be achieved using pharmacotherapy (Strength of recommendation B) or psychological therapies (Strength of recommendation S). In moderate or severe depressive episodes, pharmacotherapy is recommended as the initial treatment (Strength of recommendation A) (4-8,10). An antidepressant is also recommended as first-line therapy for a depressive episode that lasts more than two years, regardless of the severity of symptoms, as in dysthymia (Strength of recommendation A) (5).

Considering different clinical guidelines (6,8), sequential steps are recommended in the treatment of a patient with a depressive episode:

1. A structured approach to the diagnosis of a depressive episode using objective clinical scales and identification of dimensions that may affect treatment resistance.

2. Selection and initiation of first-line antidepressant treatment.
3. Objective determination of the response rate after the appropriate duration of treatment.
4. In partial response to treatment, the dose of antidepressant is optimized to the maximum tolerated dose.
5. In the absence of response to first-line treatment, treatment methods for treatment-resistant depression (TRD) are used, including switching the antidepressant, combination therapy (two antidepressants, an antidepressant and psychotherapy, or non-invasive brain stimulation), or augmentation (antidepressant and a drug from another therapeutic class).
6. Once the response has improved or remission has been achieved, consideration should be given to the length of maintenance treatment.

According to a report by the National Institute of Public Health, 7.3% of the Slovenian population received antidepressants in 2020. They report that the most commonly prescribed antidepressants have been selective serotonin reuptake inhibitors for many years. In line with prescribing recommendations, there has been a steady increase in the prescription of antidepressants and a decrease in the prescription of anxiolytics (20).

Antidepressants do not differ significantly in terms of efficacy (Level of evidence I) (21,22). Significant differences exist in side effects, tolerability, and other characteristics, necessitating flexibility in choosing the right antidepressant for the individual patient (4). Which antidepressant is appropriate is decided based on its potential therapeutic effects, taking into account potential side effects, the likelihood of withdrawal symptoms, and the estimated time to respond (4). Previous responses to drugs and the patient's wishes (5-8) are also important, as well as the level of risk in the event of an overdose (5,7) (Strength of recommendation S).

Table 4 shows the recommended distribution of antidepressants by groups of choice, which takes into account the latest guidelines, established clinical practice and formal prescribing rules, and the availability of individual medications in Slovenia. Selective serotonin reuptake inhibitors (SSRIs) represent the first-line therapy (4,5,10), together with selective serotonin and norepinephrine inhibitors (SNRIs) (Strength of recommendation A) and some other antidepressants such as mirtazapine (Strength of recommendation A) bupropion, trazodone, and vortioxetine (Strength of recommendation B) (7,8). Second-line antidepressants include agomelatine, tianeptine, tricyclic antidepressants (TCAs) (Strength of recommendation A), reboxetine, and moclobemide (Strength of recommendation B). In a severe depressive episode, TCAs may also be used as the first choice of treatment (Strength of recommendation A) (7). In a depressive episode with psychotic symptoms, an atypical antipsychotic can be added to the antidepressant at the beginning of treatment (5,7,8), which is more effective than monotherapy with an antidepressant (Strength of recommendation A, Level of evidence I) (23). Quetiapine and olanzapine are the most recommended because of their partial antidepressant effects (Level of evidence I) (4). In the initial phase of treatment, it is useful to add benzodiazepines or a hypnotic (e.g., zolpidem) (6) to relieve symptoms of anxiety (Strength of recommendation A) (6,7).

Table 4: Antidepressants by groups of choice.

MEDICATION	THERAPEUTIC DOSE	MECHANISM OF ACTION	SPECIAL FEATURES
FIRST CHOICE			
SSRI		Inhibition of serotonin reuptake	
fluoxetine	20–60 mg		registered for treatment in children over 12 years of age
paroxetine	20–50 mg		not recommended for children
sertraline	50–200 mg		in children and adolescents as second-line therapy
citalopram	20–40 mg		in children and adolescents as second-line therapy
escitalopram	10–20 mg		
fluvoxamine	100–300 mg		

MEDICATION	THERAPEUTIC DOSE	MECHANISM OF ACTION	SPECIAL FEATURES
SNRI		Inhibition of serotonin and norepinephrine reuptake	
venlafaxine	75–375 mg		not recommended for children and adolescents
duloxetine	60–120 mg		
NaSSA		Alpha$_2$ adrenergic receptor antagonism	
mirtazapine	30–45 mg		
SARI		Inhibition of serotonin reuptake and 5-HT$_{2A}$ receptor antagonism	
trazodone	75–600 mg		
NDRI		Inhibition of norepinephrine and dopamine reuptake	
bupropion	150–300 mg		
Others			
vortioxetine	10–20 mg	Inhibition of serotonin reuptake and modulation of serotonin receptors	
SECOND CHOICE			
NRI		Inhibition of norepinephrine reuptake	
reboxetine	8–12 mg		
TCA		Inhibition of serotonin and norepinephrine reuptake; interactions at other receptors	
amitriptyline	50–150 (300)* mg		
maprotiline	75–150 mg		
clomipramine	50-150 (250) mg		
imipramine	50-200 (300) mg		
MAO-I			
moclobemide	300–600 mg	Reversible monoamine oxidase inhibition	
Other			
tianeptine	37.5–75 mg	Serotonin uptake enhancement and glutamate transfer modulation	
agomelatine	25–50 mg	MT$_1$ & MT$_2$ receptor agonism, 5-HT$_{2C}$ receptor antagonism	
THIRD CHOICE			
esketamine	56–84 mg	NMDA glutamate receptor antagonism	indication for resistant depression, special rules for prescribing and use

Legend: * Values in parentheses denote maximum permitted in-hospital doses; MAO -I – monoamine oxidase inhibitors; NaSSA – noradrenergic and specific serotonergic antidepressants; NDRI – norepinephrine and dopamine reuptake inhibitors; NMDA – N-methyl-N-aspartate; NRI – norepinephrine and dopamine reuptake inhibitors; MT – melatoninergic receptors, 5HT^{2A} ; $_{2C}$ – serotonergic receptors; SARI – serotonergic receptor antagonists and various monoamine reuptake inhibitors; SSRIs – serotonin reuptake inhibitors; SNRI – serotonin and norepinephrine reuptake inhibitors; TCA – tricyclic antidepressants.

For the first depressive episode, it is reasonable to continue medication at an effective dose for at least 6 to 9 months after remission has been achieved (Strength of recommendation A) (4,5,7,8). In recurrent depressive episodes, chronic depressive episodes with residual symptomatology, and in the presence of family stress, persistent psychosocial stressors, suicidality, or associated psychosis, it is reasonable to continue maintenance therapy for at least two years (Strength of recommendation A) (6,8).

If no relapse occurs during maintenance therapy, the antidepressant is gradually discontinued. During this process, the patient is constantly monitored for the stability of remission. The antidepressant is discontinued gradually over several weeks to avoid withdrawal symptoms unless other clinical reasons are present (4-6,8). If lowering or discontinuing the antidepressant leads to a relapse, it is reasonable to reintroduce the antidepressant at the initial dose and continue treatment for another 6 months (Strength of recommendation B) (5).

2.2 Dealing with partial response to treatment and treatment resistance

In 15% to 33% of patients, repeated attempts to modify treatment are ineffective despite intensive drug therapy and other therapeutic approaches (24,25). For

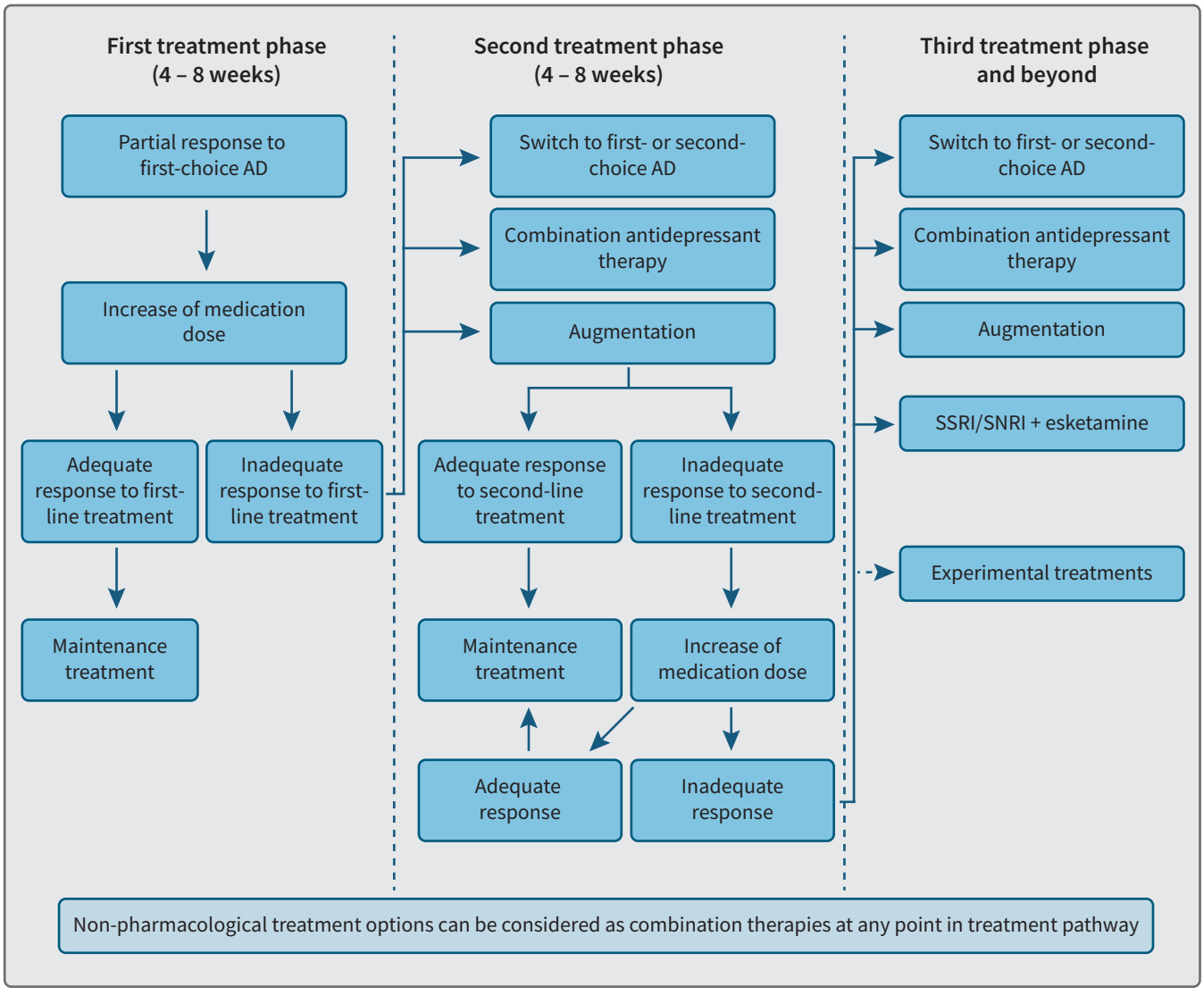

Figure 1: Clinical pathway for treatment of depression. Adapted from Kasper S, et al., 2020 (28).
Image shows generally recommended course of treatment. Inadequate response is defined as less than 50% reduction in symptoms on a clinical rating scale (e.g., MADRS) after 4 to 8 weeks of treatment.
Legend: AD – antidepressant; SSRI – serotonin reuptake inhibitor; SNRI – serotonin and norepinephrine reuptake inhibitor. Non-pharmacological treatments, such as psychotherapy and non-invasive brain stimulation, are considered combination therapies at each stage of treatment.

patients who do not respond to therapy, the term treatment-resistant depression (TRD) is used (26). A simpler definition of TRD, also used by the European Medicines Agency (EMA), states that resistance occurs when with the use of at least two antidepressants (from the same or different groups and at the appropriate dose and duration) fails to achieve an adequate response (27). Sometimes the term "refractory depression" is used, which denotes an inadequate response to three treatment attempts, one of which is electroconvulsive therapy. Because the duration of an inadequately treated depressive episode is increasingly recognized as relevant for developing resistance, recent guidelines recommend shorter periods of individual antidepressant treatment trials. The use of additional treatments (psychotherapy, newer groups of antidepressants, non-invasive brain stimulation) is recommended at an earlier stage of treatment when the development of treatment resistance is less likely (28).

When treating TRD, it is always important to recognize the possibility of pseudoresistance, which can be present in up to 60% of all patients with an initial diagnosis of TRD (29,30). Pseudoresistance may include inappropriate diagnosis, a wrong type of treatment, inappropriate dose or duration of treatment, poor treatment adherence, or significant psychiatric and/or physical comorbidities (31). The clinical pathway used in treatment-resistant depression is shown in Figure 1. In the event of a partial therapeutic response in the initial treatment phase, the antidepressant should be continued and the dose adjusted within the recommended range. When an antidepressant is introduced, it is reasonable to continue treatment for 4 to 8 weeks (with a minimum of 2-3 weeks at higher doses) before it can be judged ineffective (4,5,26,32).

In the second phase of treatment, which should also last at least 4 to 8 weeks (Strength of recommendation B), different strategies can be used, such as switching to another antidepressant from the first or second group of choice (Table 4), augmenting the response (using other types of medication in combination with an antidepressant, Table 5), and combination therapy (a combination of two antidepressants from different therapeutic groups (Strength of recommendation A), an antidepressant with psychotherapy (Strength of recommendation B) for CBT specifically (Strength of recommendation A), or an antidepressant with non-invasive brain stimulation – ECT (Strength of recommendation B) and TMS (Strength of recommendation D) (5-8,28).

In the third phase of treatment, all of the strategies already mentioned for TRD treatment are used, as along with other methods, such as third-line antidepressants (Table 4). Esketamine is approved for clinical use in moderately and severely resistant depressive disorder

Table 5: Augmenting the response using other types of medication. Adapted from Taylor DM, et al., 2018 and Cleare A, et al., 2015 (4,5).

Medication	Therapeutic dose	Special features
MOOD STABILIZERS		
lithium *(A) #(I)	target plasma level 0.4 - 0.8 mmol/l, possibility of dose escalation up to 1.0 mmol/l with partial response	
lamotrigine *(C)	100–400 mg	
ATYPICAL ANTIPSYCHOTICS		
olanzapine + fluoxetine	5–15 mg + 20–60 mg	most data for this combination is available for bipolar depression
olanzapine *(B) #(I)	5–15 mg	
quetiapine *(A) #(I)	150–300 mg	
risperidone *(B) #(I)	0.5–3 mg	
aripiprazole *(A) #(I)	2–20 mg	
OTHER		
thyroid hormones *(B) #(I)	20–50 µg	

Legend: * – Strength of recommendation; # – Level of evidence.

(EMA and US Food and Drug Administration - FDA, since 2019). In Europe, esketamine is used in combination with an SSRI or SNRI. Due to the complexity of its use and the possibility of complications, treatment is performed in a supervised, preferably inpatient, setting. The introduction of esketamine is possible after two failed treatment attempts with first- or second-line antidepressants (28).

Electroconvulsive therapy (ECT) is also effective for treatment-resistant perinatal depression. There is no evidence of harm to the mother or fetus with ECT, although general anesthesia during pregnancy may have side effects (33).

2.3 Psychotherapy, psychoeducation and other psychosocial approaches

There are no significant differences between the efficacy of psychological and pharmacological approaches in the initial treatment of depression in adult patients. Treatment outcome is better when both approaches are combined (Level of evidence III) (34). Psychotherapeutic/psychological therapies are uniformly recommended as the treatment of choice for a mild depressive episode or in combination with pharmacotherapy for patients with a moderate to severe depressive episode. Psychotherapy is also helpful in patients with partial response or poor adherence to pharmacotherapy. Psychological and behavioural treatments should be administered by appropriately trained practitioners with fidelity to techniques showing evidence-based efficacy (Strength of recommendation S). For severe major depression, psychological or behavioural treatment is not recommended as sole therapy (Strength of recommendation B) (4-8). Available evidence supports the efficacy of cognitive behavioural therapy (CBT) (Strength of recommendation A, Level of evidence I), interpersonal (Strength of recommendation A, Level of evidence I), psychodynamic (Strength of recommendation B, Level of evidence II), and problem-oriented psychotherapy (Strength of recommendation S), which can be delivered individually or in a group setting. CBT is recommended if psychological treatment is used as monotherapy for recurrent depression (Strength of recommendation B) (5,6,10,35). If partner or family conflict is present, partner or family psychotherapy is recommended (Strength of recommendation S, Level of evidence II) (6,10). The NICE guidelines also recommend using specific psychotherapeutic methods in the treatment of depression, such as CBT-based self-help techniques and structured group exercises (10). Behavioural activation is a similar and comparably effective brief psychotherapeutic approach (Level of evidence II) (36).

In Slovenia, mindfulness is positioned as a modern, scientifically and anthropologically based psychotherapy for treating depressive disorders (37). According to our experience in Slovenia, the combination of systemic family therapy and pharmacotherapy is a useful and effective method for treating depressive disorders when unfavourable life circumstances and problems in interpersonal relationships coincide (38). Group psychotherapy for the geriatric population with depressive symptoms offers partial compensation for losses, the possibility to recognise and strengthen preserved aspects of the personality, and a place for processing inevitable losses in old age (39).

During treatment, it is important to maintain the therapeutic relationship and monitor the risk of suicidal behaviour, response to therapy, the occurrence of side effects and changes in physical well-being (7,10). Psychoeducation and psychotherapeutic/psychosocial approaches can significantly improve patient participation in the treatment, decrease suicide rates, improve treatment efficacy, help patients and their families recognize signs of relapse, and understand the purpose and benefits of various forms of treatment (40).

Adding intense physical exercise to antidepressant therapy may help patients with mild or moderate depressive episodes (Strength of recommendation B) (5,7). Studies have shown an association between healthy eating and a lower risk of depression (41) or suicide (42). Dietary supplements such as omega-3 fatty acids (Level of evidence II), S-adenosylmethionine (SAM), and folates can be used as potentially effective additions to therapy (Strength of recommendation B). St. John's wort can also be used as a dietary supplement, but patients should be advised of interactions with SSRIs (Strength of recommendation D) (5,6).

Nutritional counselling services in Slovenia can contribute to the holistic treatment of our patients. A combination of nutrients that meet the body's natural physiological needs can be much more effective than taking isolated supplements (43).

2.4 Brain stimulation methods in the treatment of depression

Biological methods for the treatment of depression include non-invasive methods in which the brain is stimulated with electric current (transcranial electrical stimulation - tES, ECT) or electromagnetic pulses (transcranial magnetic stimulation - TMS) (44). The use

of invasive methods in treatment-resistant depression (TRD) is currently not justified because the exact anatomical targets in the brain have not yet been identified (45). In Slovenia, the Mental Health Act (ZDZdr) (46) explicitly prohibits the use of invasive methods for mental disorders treatment in general.

Among non-invasive brain stimulation methods, repetitive transcranial magnetic stimulation (rTMS) has recently gained popularity in TRD treatment due to its combination of practicality, safety, and efficacy (6-8,10). rTMS is a safe method without significant side effects and with high short-term efficacy, although the individual patient response is variable (47). Various treatment protocols can be used. High-frequency (10 Hz or more) rTMS of the left dorsolateral prefrontal cortex (DLPFC) is the most commonly used method (Strength of recommendation A), whereas low-frequency (1 Hz) rTMS of the right DLPFC is also possible (Strength of recommendation B). Newer versions of treatment protocols use variable treatment parameters or more complex patterns of stimulus sequences that can be administered in much shorter treatment sessions (47). The most widely researched is theta burst stimulation (TBS), which regulatory agencies recently approved for clinical use after being compared with HF-rTMS in a noninferiority trial. Intermittent TBS of left DLPFC probably has the highest treatment efficacy in depression; however, the relative lack of data still precludes a specific recommendation (Strength of recommendation S) (47). For safety reasons, rTMS is also recommended as a possible first-line treatment for patients who cannot take antidepressant medication for various reasons (Strength of recommendation C) (47,48). Transcranial direct current electrical stimulation (tDCS) techniques enhance activity in the left DLPFC with anodal stimulation or reduce activity in the right DLPFC with cathodal stimulation. Currently, only anodal stimulation has sufficient evidence of treatment efficacy to recommend it for non-treatment-resistant depression (Strength of recommendation B), whereas tDCS does not appear to be superior to a placebo for treatment-resistant depression (Strength of recommendation B) (49).

Electroconvulsive therapy (ECT) is the most effective short-term treatment for depression, with remission rates between 60-80% for non-treatment-resistant depression and 50% for treatment-resistant depression but with a very high relapse rate without maintenance therapy (50). ECT is used to treat severe depressive episodes (Strength of recommendation A), especially when psychotic features are present and in life-threatening conditions such as agitation, stupor, severe physical exhaustion due to refusal to eat, and high risk of suicide (50,51). Newer treatment protocols with unilateral application and shorter pulse duration are similarly effective to standard procedures, with a lower risk of severe side effects such as cognitive impairment (Strength of recommendation B) (10,50,52).

ECT treatment is not currently offered in Slovenia, as various obstacles limit its availability. Patients who need this type of therapy are usually referred to treatment centers in neighbouring countries such as Croatia. Other brain stimulation methods, such as rTMS and tDCS, are only used on a case-by-case basis (53) or in research. Wider adoption of brain stimulation methods in clinical practice for depression treatment in Slovenia is currently limited due to the lack of available services and reimbursement by public health insurance (54).

3 Treatment of depression in children and adolescents

While there is a lack of quality RCTs with a high number of participants for all the treatments of depression in children and adolescents, the strengths of recommendation in the following recommendations are D. Cognitive-behavioral psychotherapy (Level of evidence II), interpersonal (Level of evidence II), and psychodynamic psychotherapy are effective for the treatment of depression in adolescents, with brief psychosocial interventions showing similar effectiveness to individual CBT and psychodynamic psychotherapy (Level of evidence I) in some studies. Family-oriented therapies are more effective than individual therapies in treating depression in children (Level of evidence II), and group therapies (Level of evidence II) are effective in adolescents in addition to individual therapies.

Treatment with antidepressants and/or psychotherapy likely reduces suicidality, but in some children or adolescents, treatment with SSRIs, in particular. increases suicide risk (55). Despite the lack of robust evidence, psychopharmacological treatment of depression in children and adolescents is recommended because treatment outweighs the risks of untreated depression (56). The combination of psychotherapy and treatment with antidepressants is more effective than either treatment alone.

The NICE guidelines (9) recommend that children and adolescents with moderate to severe depressive episodes are treated by a specialist in child and adolescent psychiatry, whereas those with mild depressive episodes can be treated initially by a paediatrician. All should receive specific psychological interventions

with the possibility of concomitant use of psychotropic drugs. For a moderate to severe depressive episode, psychotherapy is recommended first, to which fluoxetine may be added. In children older than 12 years, fluoxetine may be added immediately; in younger children, it may be added after at least four psychotherapy sessions have failed to produce adequate effects. In the case of ineffective initial treatment, TRD, psychotic or recurrent depressive disorder, fluoxetine, sertraline, citalopram, or antipsychotic augmentation during intensive psychotherapy are recommended. While sertraline or citalopram are recommended as second-line antidepressants, venlafaxine, paroxetine, or tricyclic antidepressants should not be prescribed because of significant side effects. In addition, treatment of depressive disorder at this developmental period should definitely include psychosocial assessment with appropriate interventions, help with schooling, and assessment and treatment of a possible mental disorder in parents or guardians (9).

Treatment of depression in children and adolescents requires careful and fully informed shared decision making between the child, parent/guardian, and clinician. Information about the current availability and waiting times for psychological support services should be included in the decision-making process, as well as the expected effects and side effects of the various forms of treatment and the risks associated with not treating the disorder (9,56).

In Slovenia, the current accessibility to child and adolescent psychiatry services is extremely poor, with waiting times for the first non-urgent examination exceeding one year, and psychotherapeutic treatment is almost inaccessible in public health care (57). Currently, the only readily accessible psychiatric services for children and adolescents are emergency outpatient clinics, which have seen a remarkable increase in the number of admissions in recent years (58). As a result, we see a 43.3% increase in the use of antidepressants prescribed to under-19s, even though guidelines do not recommend this. In girls aged 15-19 years, antidepressants account for 69.5% of all drugs prescribed for the treatment of mental and behavioural disorders (59).

4 Treatment of depression in the elderly

Depressive disorders in the elderly often present with concomitant physical illness or impaired higher nervous system abilities and cognitive decline, making them difficult to recognize and treat (8). Compared with depressive episodes that begin at other ages, depressive disorders with onset later in life have a poorer prognosis. They are more likely to be chronic, with a higher risk of illness relapse and mortality (8,60). In terms of treatment choice, similar principles apply as described for the general population. The advantages and disadvantages of a particular treatment should be carefully weighed when selecting a drug, as there is an increased risk of treatment side effects at this age (61).

Choice of antidepressant based on The Canadian guidelines for the treatment of a depressive episode (8) recommend the selection of an antidepressant in the following order: the first choice duloxetine, mirtazapine, nortriptyline (Level of evidence I), bupropion, citalopram/escitalopram, desvenlafaxine, sertraline, venlafaxine, vortioxetine (Level of evidence II); the second choice: replacement with nortriptyline (Level of evidence I), moclobemide, phenelzine, quetiapine, trazodone (Level of evidence II), bupropion (Level of evidence III) combination with aripiprazole, lithium (Level of evidence I), methylphenidate (Level of evidence II); the third choice: replacement with amitriptyline, imipramine (Level of evidence II), combination with SSRI or SNRI with bupropion, SSRI (Level of evidence III).

A clinical pharmacist is a relatively new profession in Slovenia. Services include a review of pharmacotherapy to optimise the number of medications and drug-drug interactions to improve the quality of life of patients with depressive disorders in the geriatric population (62).

5 Treatment of perinatal depression

A Slovenian study from 2014 showed that 21.7% of pregnant women experienced depressive episodes during pregnancy (63). There are no RCTs for the treatment of perinatal depression. The prescription of psychotropic drugs to women of childbearing age should be guided by the latest evidence on the risks to pregnancy and the fetus. Treatment decisions should include the use of nonpharmacologic methods such as psychoeducation, psychotherapy, and other modalities (meditation, relaxation techniques, mindfulness, hypnosis, occupational therapy), as well as balancing the effects of a depressive episode on pregnancy and the fetus against possible adverse effects of medication (Table 6).

General recommendations are as follows (64):

1. Patients with a history of depressive disorder should be encouraged to plan pregnancy when they are in remission.
2. The Edinburgh Postnatal Depression Scale (EPDS)

Table 6: Recommendations for treating perinatal depressive disorder. Adapted from Williams J, 2014 (70).

CHOICE OF THERAPEUTIC TREATMENT IN PREGNANCY AND POSTPARTUM PERIOD		
	Clinically stable depression in remission (6 months), low probability of relapse: Psychoeducation, psychotherapy, sometimes medications are required	**Currently symptomatic or asymptomatic with a high probability of relapse:** • **Mild to moderate depressive episode:** psychoeducation, psychotherapy, sometimes medication is required. • **Moderate to severe depressive episode:** medication usually required, in addition to psychoeducation, psychotherapy.
PHARMACOLOGICAL TREATMENT		
Before and during pregnancy	• The AD can be discontinued before pregnancy if there is little chance of relapse. • If AD cannot be discontinued, continued use of AD is advisable only if the benefit of taking it outweighs the risk and the drug is not contraindicated during pregnancy.	• If the current AD is effective, continued treatment is advisable if the benefits of taking it outweigh the risk and if the drug is not contraindicated during pregnancy. • If the AD is needed, an SSRI is prescribed as the first choice (not paroxetine or fluoxetine in the first trimester) and an SNRI as the second choice.
During birth	A therapeutic dose of the same AD is maintained.	
After birth	• The currently effective AD is continued, and the dose may need to be adjusted. • If an AD is needed, an SSRI that allows breastfeeding is prescribed. • After remission of the first depressive episode, the AD should be taken for 6-12 months (or at least 2 years after the second depressive episode).	

Legend: AD – antidepressant; SSRI – serotonin reuptake inhibitor; SNRI – serotonin and norepinephrine reuptake inhibitor .

is the most commonly used instrument for screening postpartum depression (65).

3. The patient should be informed about the benefits of treatment, possible side effects, and the consequences of changing or discontinuing treatment during pregnancy.
4. Abrupt medication discontinuation because of pregnancy without consultation with a psychiatrist is not recommended and may lead to relapse (66).
5. If a woman is taking an effective antidepressant at the start of pregnancy, treatment should be continued with the same antidepressant if the benefit of taking it outweighs the risk and it is not contraindicated during pregnancy. Antidepressants with higher risk (e.g., paroxetine, fluoxetine) are replaced with a lower risk antidepressant.
6. Psychotropic medications cross the placenta. During pregnancy, we prescribe those medications that have not shown teratogenic or other significant effects on the fetus and pregnancy.
7. The drug with the least risk and at the lowest effective dose should be prescribed, but subtherapeutic doses are ineffective. Whenever possible, monotherapy should be used.
8. The drug dose may need to be adjusted during pregnancy due to altered absorption and protein binding. Higher doses are often required in the third trimester because plasma volume increases by one-third (67).
9. During lactation, sertraline and paroxetine are less likely to be excreted into milk (68). When taking medications during lactation, it is advisable to consider the percentage of the mother's dose that the infant absorbs in milk (relative infant dose - RID), which allows an estimate of the infant's exposure to the drug. The online database LactMed (Drugs and lactation database) can be helpful.

When introducing an antidepressant in pregnancy, previous response to antidepressants, the pregnancy term, the drug's reproductive safety, and the potential effects on the newborn must be considered. In pregnancy, SSRIs are the antidepressants of choice, with sertraline being the most commonly prescribed medication. The FDA has used the ABCDX risk categories for safety in pregnancy. Since 2015, a description of the risks and clinical dilemmas of taking the drug during pregnancy and lactation, as well as the effects of the drug on fertility, has been available as Lactation Labeling Rules (PLLR). The teratogenic influence is important during

organogenesis in the first trimester (69). Benzodiazepines and hypnotics are avoided in the postpartum period, except for short-term treatment of severe anxiety and agitation. Long-acting benzodiazepines should not be prescribed before delivery. Atypical antipsychotics may be prescribed in low doses to enhance antidepressant effects (70).

Conflict of interest

None declared.

Acknowledgements

The paper was supported by Slovenian Research Agency grants P5-0110 and J3-1763.

References

1. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health. 2013;34(1):119-38. DOI: 10.1146/annurev-publhealth-031912-114409 PMID: 23514317
2. World health organization. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017.
3. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, et al. Burden of depressive disorders by country, sex, age, and year: findings from the globalburden of disease study 2010. PLoS Med. 2013;10(11):e1001547. DOI: 10.1371/journal.pmed.1001547 PMID: 24223526
4. Taylor DM, Barnes TR, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. 13th ed. New York: Wiley-Blackwell; 2018.
5. Cleare A, Pariante CM, Young AH, Anderson IM, Christmas D, Cowen PJ, et al.; Members of the Consensus Meeting. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol. 2015;29(5):459-525. DOI: 10.1177/0269881115581093 PMID: 25969470
6. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). Am J Psychiatry. 2000;157(4):1-45. PMID: 10767867
7. Bauer M, Severus E, Kohler S, Whybrow PC, Angst J, Moller HJ, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biologicaltreatment of unipolar depressive disorders-update 2015. World J Biol Psychiatry. 2015;16:76-95. DOI: 10.3109/15622975.2014.1001786 PMID: 25677972
8. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al.; CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. PharmacologicalTreatments. Can J Psychiatry. 2016;61(9):540-60. DOI: 10.1177/0706743716659417 PMID: 27486148
9. National institut for health and care excellence. Depression in children and young people: identification and management. London: NICE; 2019.
10. National institut for health and care excellence. Depression in adults: recognition and management. Clinical guideline 90, last updated March 2020. London: NICE; 2009.
11. Nacionalni inštitut za varovanje zdravja. Mednarodna klasifikacija bolezni in sorodnih zdravstvenih problemov za statistične namene: MKB-10 : deseta revizija. 2. izd. Ljubljana: IVZ RS - Inštitut za varovanje zdravja Republike Slovenije; 2005.
12. American psychological association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washingon: APA; 2013.
13. Zung WW. A Self-Rating Depression Scale. Arch Gen Psychiatry. 1965;12(1):63-70. DOI: 10.1001/archpsyc.1965.01720310065008 PMID: 14221692
14. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23(1):56-62. DOI: 10.1136/jnnp.23.1.56 PMID: 14399272
15. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134(4):382-9. DOI: 10.1192/bjp.134.4.382 PMID: 444788
16. Snaith RP. The Hospital Anxiety And Depression Scale. Health Qual Life Outcomes. 2003;1(1):29. DOI: 10.1186/1477-7525-1-29 PMID: 12914662
17. Spitzer RL, Kroenke K, Williams JB; Primary Care Evaluation of Mental Disorders. Validation and utility of a self-report version of PRIME-MD: the PHQ primary carestudy. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA. 1999;282(18):1737-44. DOI: 10.1001/jama.282.18.1737 PMID: 10568646
18. Strbad M, Kogoj A. Prevalenca depresije pri starostnikih. In: Novak Šarotar B, Pregelj P, Bon J, eds. Zbornik 5. slovenskega psihiatričnega kongresa. Portorož: Združenje psihiatrov pri slovenskem zdravniškem društvu; 2012.
19. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. BMJ. 1999;318(7183):593-6. DOI: 10.1136/bmj.318.7183.593 PMID: 10037645
20. Nacionalni inštitut za javno zdravje. Poraba ambulantno predpisanih zdravil v Sloveniji v letu 2020. Ljubljana: NIJZ; 2020 [cited 2021 Sep 2]. Available from: https://nijz.si/publikacije/poraba-ambulantno-predpisanih-zdravil-v-sloveniji-v-letu-2020/.
21. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018;391(10128):1357-66. DOI: 10.1016/S0140-6736(17)32802-7 PMID: 29477251
22. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatmentsmeta-analysis. Lancet. 2009;373(9665):746-58. DOI: 10.1016/S0140-6736(09)60046-5 PMID: 19185342
23. Farahani A, Correll CU. Are antipsychotics or antidepressants needed for psychotic depression? A systematic review and meta-analysis of trials comparing antidepressant or antipsychotic monotherapywith combination treatment. J Clin Psychiatry. 2012;73(4):486-96. DOI: 10.4088/JCP.11r07324 PMID: 22579147
24. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatmentsteps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-17. DOI: 10.1176/ajp.2006.163.11.1905 PMID: 17074942
25. Hollon SD, DeRubeis RJ, Fawcett J, Amsterdam JD, Shelton RC, Zajecka J, et al. Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: a randomized clinical trial. JAMA Psychiatry. 2014;71(10):1157-64. DOI: 10.1001/jamapsychiatry.2014.1054 PMID: 25142196

26. Planinc D, Videtič Paska A, Pregelj P, Bon J. Na zdravljenje rezistentna depresija. Viceversa. 2018;64:4-12.
27. European medicines agency International scientific guideline: Guideline on clinical investigation of medicinal products in the treatment of depression. Amsterdam: EMA; 2013 [cited 2021 Apr 20]. Available from: https://www.tga.gov.au/resources/resource/international-scientific-guidelines/international-scientific-guideline-guideline-clinical-investigation-medicinal-products-treatment-depression.
28. Kasper S, Cubala WJ, Fagiolini A, Ramos-Quiroga JA, Souery D, Young AH. Practical recommendations for the management of treatment-resistant depression with esketamine nasal spray therapy. World J Biol Psychiatry. 2020;22(6):1-15. DOI: 10.1080/15622975.2020.1836399 PMID: 33138665
29. Trevino K, McClintock SM, McDonald Fischer N, Vora A, Husain MM. Defining treatment-resistant depression: a comprehensive review of the literature. Ann Clin Psychiatry. 2014;26(3):222-32. PMID: 25166485
30. Kornstein SG, Schneider RK. Clinical features of treatment-resistant depression. J Clin Psychiatry. 2001;62:18-25. PMID: 11480880
31. Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. Can J Psychiatry. 2007;52(1):46-54. DOI: 10.1177/070674370705200108 PMID: 17444078
32. Dold M, Kasper S. Evidence-based pharmacotherapy of treatment-resistant unipolar depression. Int J Psychiatry Clin Pract. 2017;21(1):13-23. DOI: 10.1080/13651501.2016.1248852 PMID: 27848269
33. Miller LJ. Use of electroconvulsive therapy during pregnancy. Hosp Community Psychiatry. 1994;45(5):444-50. DOI: 10.1176/ps.45.5.444 PMID: 8045538
34. Alang S, McAlpine D. Treatment Modalities and Perceived Effectiveness of Treatment Among Adults With Depression. Health Serv Insights. 2020;13:1178632920918288. DOI: 10.1177/1178632920918288 PMID: 32425544
35. Cuijpers P, Berking M, Andersson G, Quigley L, Kleiboer A, Dobson KS. A meta-analysis of cognitive-behavioural therapy for adult depression, alone and incomparison with other treatments. Can J Psychiatry. 2013;58(7):376-85. DOI: 10.1177/070674371305800702 PMID: 23870719
36. Uphoff E, Ekers D, Robertson L, Dawson S, Sanger E, South E, et al. Behavioural activation therapy for depression in adults. Cochrane Database Syst Rev. 2020;7(7). DOI: 10.1002/14651858.CD013305.pub2 PMID: 32628293
37. Šodlar B. Novak Šarotar B, Bon J, eds. Zbornik 6. slovenskega psihiatričnega kongresa. Portorož: Združenje psihiatrov pri slovenskem zdravniškem društvu; 2016.
38. Trampuž L, Rus Makovec M. Družinska sistemska terapija kot del obravnave depresivne motnje. In: Koprivšek J, Bon J, Čelofiga A, Novak Šarotar B, eds. 7. Psihiatrični kongres. Program in zbornik povzetkov. Portorož: Združenje psihiatrov pri slovenskem zdravniškem društvu; 2021.
39. Vodušek V. Skupinska psihoterapija za gerontopsihiatrično populacijo – izhodišča, terapevtski dejavniki ter principi sestave in vodenja skupine starostnikov. In: Novak Šarotar B, Preglej P, Bon J, eds. Zbornik 5. Slovenskega psihiatričnega kongresa. Portorož: Združenje psihiatrov pri slovenskem zdravniškem društvu; 2012.
40. Kores-Plesničar B, Dernovšek Z, Groleger U, Koprivšek J, Gregorič-Kumperščak H, Kravos M, et al. Smernice za zdravljenje bipolarne motnje razpoloženja. Zdrav Vestn. 2006;75:225-33.
41. Lai JS, Hiles S, Bisquera A, Hure AJ, McEvoy M, Attia J. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. Am J Clin Nutr. 2014;99(1):181-97. DOI: 10.3945/ajcn.113.069880 PMID: 24196402
42. Nanri A, Mizoue T, Poudel-Tandukar K, Noda M, Kato M, Kurotani K, et al.; Japan Public Health Center-based Prospective Study Group. Dietary patterns and suicide in Japanese adults. Br J Psychiatry. 2013;203(6):422-7. DOI: 10.1192/bjp.bp.112.114793 PMID: 24115342
43. Plemenitaš A. Prehrana, gastrointestinalni sistem in duševne bolezni. In: Novak Šarotar B, Bon J, eds. Zbornik 6. Slovenskega psihiatričnega kongresa. Portorož: Združenje psihiatrov pri slovenskem zdravniškem društvu; 2016.
44. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, rootsand peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol. 2015;126(6):1071-107. DOI: 10.1016/j.clinph.2015.02.001 PMID: 25797650
45. Morishita T, Fayad SM, Higuchi MA, Nestor KA, Foote KD. Deep brain stimulation for treatment-resistant depression: systematic review of clinicaloutcomes. Neurotherapeutics. 2014;11(3):475-84. DOI: 10.1007/s13311-014-0282-1 PMID: 24867326
46. Zakon o duševnem zdravju - ZDZdr. 2008(77); 2015(46).
47. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018). Clin Neurophysiol. 2020;131(2):474-528. DOI: 10.1016/j.clinph.2019.11.002 PMID: 31901449
48. Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS. The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder. Brain Stimul. 2016;9(3):336-46. DOI: 10.1016/j.brs.2016.03.010 PMID: 27090022
49. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128(1):56-92. DOI: 10.1016/j.clinph.2016.10.087 PMID: 27866120
50. Scott A. College guidelines on electroconvulsive therapy: an update for prescribers. Adv Psychiatr Treat. 2005;11(2):150-6. DOI: 10.1192/apt.11.2.150
51. Holtzheimer PE. Advances in the Management of Treatment-Resistant Depression. Focus Am Psychiatr Publ. 2010;8(4):488-500. DOI: 10.1176/foc.8.4.foc488 PMID: 25960694
52. Tor PC, Bautovich A, Wang MJ, Martin D, Harvey SB, Loo C. A Systematic Review and Meta-Analysis of Brief Versus Ultrabrief Right Unilateral Electroconvulsive Therapy for Depression. J Clin Psychiatry. 2015;76(9):e1092-8. DOI: 10.4088/JCP.14r09145 PMID: 26213985
53. Pugelj T, Užmah Kučina A, Novak Šarotar B. Zdravljenje rezistentne depresije s transkranialno stimulacijo z direktnim električnimtokom - predstavitev primera. In: Koprivšek J, Bon J, Čelofiga A, Novak Šarotar B, eds. 7. Psihiatrični kongres. Program in zbornik povzetkov. Ljubljana: Združenje psihiatrov pri slovenskem zdravniškem društvu; 2021.
54. Bon J, Plemenitaš Ilješ A. Challenges and opportunities with treatment of medication-resistant depression in Slovenia. Psychiatr Danub. 2022;34:s47-8.
55. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry. 2006;63(3):332-9. DOI: 10.1001/archpsyc.63.3.332 PMID: 16520440
56. Hussain H, Dubicka B, Wilkinson P. Recent developments in the treatment of major depressive disorder in children and adolescents. Evid Based Ment Health. 2018;21(3):101-6. DOI: 10.1136/eb-2018-102937 PMID: 30045844
57. Gregoric Kumperscak H. Child and adolescent psychiatry in Slovenia in comparison with other European countries. Eur Child Adolesc Psychiatry. 2019;28(1):147-51. DOI: 10.1007/s00787-018-1232-y PMID: 30311006
58. Kirič B, Leben Novak L, Lušicky P, Drobnič Radobuljac M. Suicidal Behavior in Emergency Child and Adolescent Psychiatric Service Users Beforeand During the 16 Months of the COVID-19 Pandemic. Front Psychiatry. 2022;13:893040. DOI: 10.3389/fpsyt.2022.893040 PMID: 35633784
59. Roškar S, Jeriček Klanšček H, Vinko M, Hočevar-Grom A, eds. Mental health of children and adolescents in Slovenia: a summary of a publication. Ljubljana: National Institute of Public Health; 2019.

60. Ismail Z, Fischer C, McCall WV. What characterizes late-life depression? Psychiatr Clin North Am. 2013;36(4):483-96. DOI: 10.1016/j.psc.2013.08.010 PMID: 24229652

61. Taylor WD. Clinical practice. Depression in the elderly. N Engl J Med. 2014;371(13):1228-36. DOI: 10.1056/NEJMcp1402180 PMID: 25251617

62. Štuhec M. Strategije za racionalno uporabo psihofarmakov pri starostnikih. In: Koprivšek J, Bon J, Čelofiga A, Novak Šarotar B, eds. 7. Psihiatrični kongres. Program in zbornik povzetkov. Ljubljana: Združenje psihiatrov pri slovenskem zdravniškem društvu; 2021.

63. Podvornik N, Globevnik Velikonja V, Praper P. Depression and Anxiety in Women During Pregnancy in Slovenia. Zdr Varst. 2014;54(1):45-50. DOI: 10.1515/siph-2015-0006 DOI: 10.1515/sjph-2015-0006 PMID: 27646621

64. Ter Horst PG, Jansman FG, van Lingen RA, Smit JP, de Jong-van den Berg LT, Brouwers JR. Pharmacological aspects of neonatal antidepressant withdrawal. Obstet Gynecol Surv. 2008;63(4):267-79. DOI: 10.1097/OGX.0b013e3181676be8 PMID: 18348740

65. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150(6):782-6. DOI: 10.1192/bjp.150.6.782 PMID: 3651732

66. Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA. 2006;295(5):499-507. DOI: 10.1001/jama.295.5.499 PMID: 16449615

67. Sit DK, Perel JM, Helsel JC, Wisner KL. Changes in antidepressant metabolism and dosing across pregnancy and early postpartum. J Clin Psychiatry. 2008;69(4):652-8. DOI: 10.4088/jcp.v69n0419 PMID: 18426260

68. Molyneaux E, Telesia LA, Henshaw C, Boath E, Bradley E, Howard LM. Antidepressants for preventing postnatal depression. Cochrane Database Syst Rev. 2018;4(4). DOI: 10.1002/14651858.CD004363.pub3 PMID: 29669175

69. Huybrechts KF, Bateman BT, Palmsten K, Desai RJ, Patorno E, Gopalakrishnan C, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertensionof the newborn. JAMA. 2015;313(21):2142-51. DOI: 10.1001/jama.2015.5605 PMID: 26034955

70. Williams J. Best Practice guidelines for mental health disorders in the perinatal period. Vancouver: BC Reproductive Mental Health Program; 2014.