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Treatment-resistant depression – recommendations of the National Consultant in the field of psychiatry

Piotr Gałecki, Katarzyna Bliźniewska-Kowalska

[1] Department of Adult Psychiatry, Medical University of Lodz

Summary

Depression is one of the most common mental disorders, it affects about 5–17% of the population. Depressive disorders are a serious economic and social problem. Depression has a significant impact on the employment status, financial success and interpersonal relationships. It is the reason for the greatest number of days of absence from work among all diseases. Patients who do not respond to standard antidepressant treatment cost twice as much as patients who do respond to treatment (response to standard antidepressant treatment occurs only in 60–70% of patients suffering from depressive disorder). According to epidemiological data, even one-third of patients may have treatment-resistant depression, which is defined as depressive disorder in adults who have not responded to at least two different antidepressants (used at the right dose for the appropriate period) in the current episode of moderate to severe depression. The purpose of this publication is to present the problem of drug resistance in depression and to present strategies for dealing with treatment-resistant depression.

Key words: depression, treatment-resistant depression, antidepressant treatment

Prevalence of depression

Depression is one of the most common mental disorders. According to the estimates by the World Health Organization (WHO), in 2015 depression occurred in 322 million people worldwide, including the estimated number of depressive disorder cases in the European region at 40.3 million [1]. Data regarding the prevalence of depression in different studies may vary depending on the methodology of these studies and the population that they describe. In 2012, a screening study entitled *Epidemiology of mental disorders and access to mental health care EZOP – Poland* was carried out in Poland. This study showed that up to 3% of Poles in the productive age had at least one episode of depression, i.e., 766 thousand adult residents of Poland at least once during their life manifested the symptoms of any depressive episode [2]. It is currently estimated that around 1.5 million people in Poland suffer from depression [3]. In 2016,

about 20 million packages of antidepressants were sold in Poland [4, 5]. The risk of a depressive episode throughout life reaches from 14 to 18% [4, 6]. Depression affects approximately 5–17% of the population [3, 6, 7].

Depression can occur at any age. Symptoms of depression usually appear for the first time in the late adolescence up to the age of about 25 years [8]. The peak incidence falls on older adult (55–74 years) [1].

According to epidemiological studies, depressive disorders are more common in women than men (5.1 and 3.6%, respectively) [1]. However, it seems reasonable to state that due to some personality traits and social acceptance, women more often report to the doctor with their mood disorders, which is why they are also diagnosed more often.

Depressive disorders – a social problem

Depressive disorders are among the main causes of lost years of life due to health disability (Years Lost due to Disability – YLD) – 76.4 million years lost, which accounts for as much as 10.3% of the total burden of diseases worldwide [9, 10]. Depression has a significant impact on employment status, financial success and interpersonal relations because it is the reason for the largest number of days of absence from work among all diseases in Poland [11]. In Europe, up to 50% of long-term sick leave is caused by depression or anxiety disorders [12]. These disorders are also associated with more frequent comorbidities, which has a huge impact on the number of health services provided and the quality of life of patients [13]. Depressive disorders shorten the predicted survival time by up to 10 years [14].

In Poland, in 2017, the costs incurred by the Social Insurance Institution as a result of sick leave due to depressive disorders amounted to 567.6 million PLN in total. In the same year, 279 million PLN and 12.8 million PLN, respectively, were spent on disability and social pensions due to depression [15].

In the period from 2008 to 2018, the costs incurred by the National Health Fund in Poland for the treatment of depressive disorders were increasing systematically, totaling over 23 billion PLN (23,767,691,223.93 PLN). In 2018, the costs of hospital treatment, both in stationary and day wards, outpatient and environmental treatment of patients with depressive disorders amounted to over 2.5 billion PLN [16]. In 2013, the National Health Fund spent 167 million PLN on treating patients with depression in hospital and specialist care. It is estimated that depression is responsible annually for nearly 25,000 years of lost productivity in Poland. In Poland, indirect costs incurred by society due to depression range from about 1.0 billion PLN to about 2.6 billion PLN per year [5, 17].

Suicide issues

In the worst case, depression can even lead to death, as it is associated with a significant increase in the risk of suicide compared to the general population [18]. The OECD report from 2014 places Poland in seventh place among the countries with

the largest increase in the number of suicides [19, 20]. According to data from the National Police Headquarters, in the last decade (2008–2018) 54,268 people committed suicide in Poland [21]. It should be emphasized, however, that in Poland there is no central register to which all suicide attempts would be reported, which is why police data on suicide cases that were not fatal may be quite underestimated. It is estimated that there are about 10 times more suicide attempts than suicides [22].

In 2015, suicides accounted for nearly 1.5% of all deaths in the world, making them one of the 20 most common causes of death [1]. The risk of suicide occurs at all ages and, according to WHO 2015 data, it was the second most common cause of death among people aged 15–29 [1].

The main causes of suicidal behavior include psychiatric disorders, also untreated or poorly treated depression. The risk of suicide based on MINI criteria in European patients is greater in TRD (Treatment-resistant depression) (68.5% versus 49%) [23].

Suicides are also associated with lost productivity. According to the data of the Ministry of Health from 2010, suicide of a person aged 25 costs over 597 thousand PLN. It can be estimated that the total state losses due to this amount to about 2 billion PLN [24]

Depression as a huge economic challenge

Mental disorders lead to reduced work efficiency and an increase in health and social care costs [25]. In the European Union, the estimated costs of depression in 2010 were 92 billion EUR [26]. Patients who do not respond to standard antidepressant treatment cost twice as much as patients who respond to treatment. The total direct and indirect costs for a patient with drug-resistant depression are 20,120 $, compared with 10,592 $ spent on a patient responding to treatment [27].

Definition of treatment-resistant depression

Treatment-resistant depression (TRD) can be defined as depressive disorder in adults who have not responded to at least two different antidepressants (used at the right dose for proper period) in the current episode of moderate to severe depression [28, 29]. Only 60–70% of patients with depressive disorders respond to standard antidepressant treatment (first and second line of treatment), and therefore as much as one-third of patients can suffer from treatment-resistant depression (TRD) [30, 31].

In the STAR*D study, which included 3,671 patients with depressive disorder, it was found that 36.8% of patients achieved remission after the first treatment line, and a further 31% improved after the second treatment line. Remission was defined as a score < or = 5 on the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR (16)) scale [equivalent to a score < or = 7 on the 17-point Hamilton depression scale – HRSD (17)], i.e., no depressive symptoms. This means that over 30% of patients suffer from drug-resistant depression [31].

Patients with refractory depression are less likely to have functional remission and are more likely to have a relapse than those who respond to treatment [32]. Patients

requiring more treatment lines are more burdened with diseases, both in the context of the severity of depression and comorbidities [31], and the time to relapse is shorter in patients with refractory depression [31].

There are also the concepts of therapeutic response and improvement, without achieving full remission. The term improvement means a 20–30% reduction in scores on the scales measuring the severity of depression (e.g., the Hamilton Scale – HDRS) compared to the baseline measurement. The most frequently analyzed parameter in studies on the short-term effectiveness of antidepressant treatment is the therapeutic response defined as a reduction of depressive symptoms of at least 50% compared to the baseline [33].

Risk factors for drug resistance in depression

There is no single defined cause for drug resistance in depression. There are many factors that may affect the ineffectiveness of antidepressant treatment [5]. Table 1 presents the most important risk factors for drug resistance, including inadequacy of therapy – using an antidepressant for a too short period or a too low dose of an antidepressant, lack of cooperation with the patient, external factors such as problems in family relationships or socioeconomic problems [5]. It should not be forgotten that the key to the success of depressive episode therapy is the right diagnosis. Diagnosis of other concomitant psychiatric disorders, e.g., personality disorders or other somatic diseases, may be an important factor interfering with antidepressant therapy (Table 1).

Table 1. **Risk factors for drug resistance [5, 39]**

A – Inadequacy of treatment	Inadequate selection of antidepressant (symptom profile, type of depression, tolerance, interaction with other drugs) Lack of patient's acceptance of treatment Inadequate therapy time and dose The level of the drug in the blood (fast versus slow metabolism) No strategies to improve the efficiency No psychoeducation, no attempts to build therapeutic cooperation
B – Behavioral and external factors supporting the illness	Life events requiring adaptation Problems in family relationships, partnerships Losses Socioeconomic and professional problems (unemployment, poverty) Secondary benefits from the illness Symptoms as part of control over the environment
C – Compliance	40% of patients discontinue therapy within the first 30 days, a further 30% within the next 60 days When taking the drug 1 x daily in the morning, 80% of patients follow the recommendations, and with the administration scheme 1 x daily in the evening, 60% of patients follow the recommendations

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D – Diagnosis	Coexisting somatic diseases (e.g., hypothyroidism) Vitamin B12 and folate deficiency Organic mood disorders Depressive episodes in the course of bipolar disorder (BD) Comorbid personality disorders and/or anxiety disorders Addiction and abuse of psychoactive substances (SPA)

Algorithm of treatment-resistant depression

Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) are considered as first-line drugs in the treatment of depression [5]. In accordance with the general principles of treatment of a depressive episode, recommended by a national consultant in the field of psychiatry in Poland, the assessment of the effectiveness of antidepressant treatment is made 4–6 weeks after the start of therapy. In the absence of satisfactory improvement, first the dose of the used antidepressant is increased and then we should wait for another 2–4 weeks. If after this time no improvement is observed, it is advisable to switch to another antidepressant and reassess its effectiveness after 4–6 weeks. If there is no response to at least two different antidepressants, strategies recommended for drug-resistant depression should be used. Figure 1 shows the algorithm for managing a depressive episode (Figure 1).

Strategies for managing treatment-resistant depression (TRD)

There are five main therapeutic strategies for treatment-resistant depression (TRD). These include: (1) optimizing the dose and time of taking the antidepressant; (2) changing the antidepressant; (3) combining antidepressants; (4) potentialization; and (5) non-pharmacological therapies. The choice of strategy depends on the patient's somatic state (comorbidities), the severity of depressive symptoms, suicidal risk, and environmental factors.

Optimization of antidepressant treatment

Only 11% of patients requiring antidepressant treatment receive the drug in an adequate dose and for a sufficiently long time [34]. The use of too low doses is often common in elderly patients [35]. Optimization of antidepressant treatment involves verification of both the dose and duration of antidepressant use.

Switch to another antidepressant

It is possible to switch the treatment to a drug from a different or less common therapeutic group. In both cases, the effectiveness of the therapy is comparable [36],

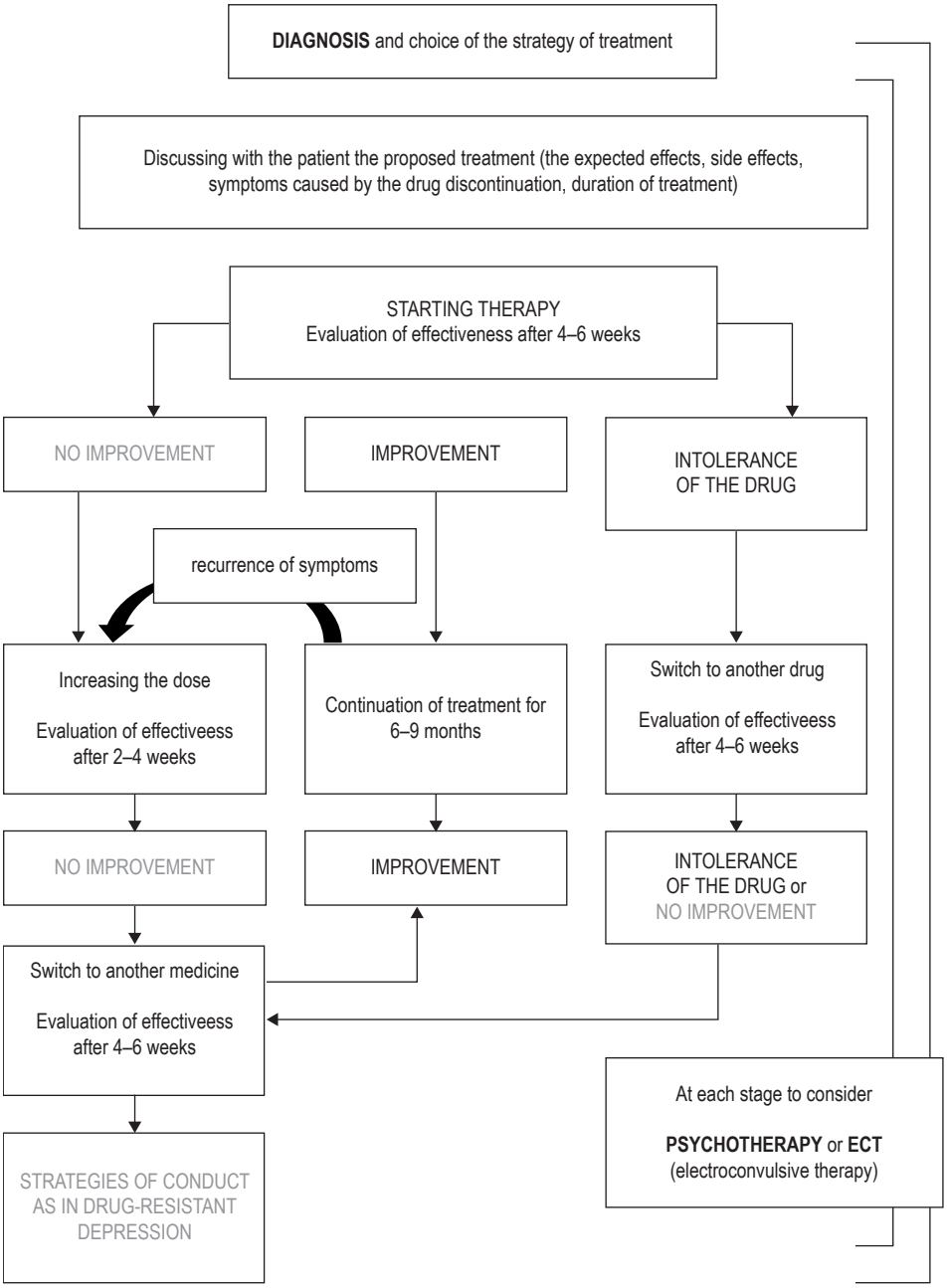

Figure 1. **Algorithm of conduct in a depressive episode [5, 33, 39]**

although many researchers recommend replacing antidepressant with a drug with a different mechanism of action [33, 37].

If the patient's mental state does not require a quick switch of medication, the first antidepressant should be gradually discontinued and the next antidepressant introduced after a break (wash-out = 5 x half-life of the drug). This approach is recommended primarily for the elderly, burdened with many somatic diseases, in the case of polypragmasia, to minimize drug interactions and the risk of drug accumulation. An adequate interval between discontinuation of one drug and the implementation of another is absolutely recommended when using monoamine oxidase inhibitors due to the high risk of serotonin syndrome.

However, when the patient's condition (the severity of depressive symptoms) requires more dynamic intervention, then another way to change the antidepressant drug is the so-called overlap method – after reducing the dose of the first antidepressant by half, the second antidepressant is added and gradually increases its dose, and then the first preparation is discontinued. However, this requires great caution and frequent assessment of the occurrence of adverse effects [33].

Combining antidepressant drugs

The strategy of combining two antidepressants is widely used in clinical practice. The goal of this strategy is primarily to broaden the pharmacological profile. That is why drugs with different mechanisms of action are most often combined. However, it should be remembered that due to unfavorable interactions and a high risk of serotonin syndrome, when 'overlap' replacement and combining for example, two SSRIs, SSRIs and SNRIs, SSRIs or SNRIs and clomipramine, mirtazapine with SSRIs, particular caution should be exercised as well as frequent monitoring of the occurrence of adverse effects [38]. The simultaneous use of moclobemide with other antidepressants of all therapeutic groups is strongly contraindicated [33, 38, 39]. A meta-analysis by Henssler et al. [40] shows that combining a serotonin reuptake inhibitor (SSRI) with an antagonist of presynaptic α2 autoreceptors appears to be much more effective than other combinations.

Potentialization of antidepressant treatment

The potentialization for antidepressant treatment means adding a second medicine that is not an antidepressant (Table 2).

Table 2. **Methods of potentialization of antidepressant treatment**

Name of the drug	Recommended dose	Mechanism of action – potentialization	Clinical trials
Lithium carbonate	The initial dose of 1 x 250 mg, then the dose may be increased (under the control of serum lithium and the occurrence of side effects).	Strengthens serotonergic neurotransmission; modulates the phosphatidyl-inositol pathway [46]	Limited number of randomized controlled clinical trials with SSRIs [41, 42] Positive action when combined with TCA [43] Efficacy compared to T3 in the STAR*D study, but more side effects [31]
Thyroid hormones	L-Thyroxine 25–50 µg/day for 3 weeks	Increases noradrenergic neurotransmission; corrects subclinical hypothyroidism that causes depression-like symptoms [46]	Limited number of randomized controlled clinical trials with SSRIs [41, 44] Positive action when combined with TCA [43, 45] Efficacy compared to lithium in the STAR*D study, but fewer adverse effects [31]
Lamotrigine	Starting dose of 25 mg 1 x daily, then the dose can be gradually increased by 25 mg once every 1–2 weeks to a dose of 2 x 100 mg	Blocks 5-hydroxytriptamine 3 receptors; potentiates the action of dopamine [46]	Used as a mood stabilizer with anti-depressant potential. Still unreliable randomized controlled clinical trials (too small groups, mixed populations) [47, 48]
Atypical antipsychotics	Olanzapine 2.5–5 mg/day Aripiprazole 2–20 mg/day [39] Quetiapine modified-release (XR) 150–300 mg/day	Affects serotonergic, noradrenergic and dopmianergic transmission in frontal lobes [46]	Used as mood stabilizers. Many studies confirm the effectiveness of the combination of antidepressants and atypical antipsychotics in drug-resistant depression – the following combinations are best documented: aripiprazole + SSRI/venlafaxine [49–51], olanzapine + fluoxetine [52–54], the addition of modified release quetiapine for antidepressant treatment [55, 56]
Psychostimulants	Methylphenidate 5–30 mg/day Modafinil 200 mg/day	Improves noradrenergic and dopmianergic transmission [46]	Reduction of fatigue, drowsiness and anergy has been reported [39, 57].

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Omega-3 fatty acids	EPA 6 g and DHA 2 g	Normalize communication between neurons, lower the level of TNF-alpha, some interleukins and prostaglandins, and increase BDNF levels [46]	Equivocal data [58]
Esketamine	-	Glutamatergic effect	Positive data from clinical studies [59–61]

In March 2019, the Food and Drug Administration (FDA) approved intranasal esketamine for the treatment of drug-resistant depression. The drug is being registered by EMA for use in Europe[1].

To date, results for three key randomized, phase 3 clinical studies have been published. Patients who did not achieve the expected therapeutic response after using one to five antidepressants in the ongoing depressive episode were qualified for the study. A new antidepressant was initiated in these patients and the efficacy was re-evaluated. With no further therapeutic response, patients were randomized and assigned to the group with newly initiated SSRI or SNRI antidepressant (escitalopram, sertraline or venlafaxine with prolonged release, duloxetine) with the addition of intranasal esketamine twice-weekly at a dose of 58 mg or 84 mg, or a group with newly initiated SSRI or SNRI antidepressant supplemented with a placebo administered twice a week intranasal.

Two of the studies [59, 60] assessed the efficacy and safety of intranasal esketamine over a 28-day period of drug administration by assessing the improvement of the patient's condition using the MADRS (Montgomery-Asberg Depression Rating Scale). In the study with a flexible dose of intranasal esketamine [59], it was shown that the change in the MADRS after 28 days of therapy was significantly higher in the group receiving intranasal esketamine and antidepressant compared to the group receiving placebo and antidepressant. A clinically significant difference in the MADRS between groups was already observed 24 hours after the first dose, indicating a rapid effect of intranasal esketamine. A study with a fixed dose of intranasal esketamine [60] did not achieve statistical significance for the difference between the MADRS score between the group receiving intranasal esketamine at a dose of 84 mg with antidepressant and the group receiving placebo with antidepressant. Analysis of the group receiving esketamine at a dose of 56 mg showed a difference of – 4.1 points on the MADRS ($p = 0.027$).

[1] Note from the Editors: on December 18, 2019, esketamine nasal spray (SPRAVATO) was registered by the European Medicines Agency (EMA) for use in combination with a selective serotonin reuptake inhibitor or serotonin and noradrenaline reuptake inhibitor (SSRI or SNRI) in the treatment of adults with treatment-resistant major depressive disorder who have not responded to at least two different antidepressant therapies in the current moderate to severe depressive episode

In a third randomized clinical trial [61], out of 297 patients who completed the 16-week induction and optimization phase during which oral antidepressant and esketamine were administered, 176 achieved stable remission (persistent decrease in the MADRS score below 12 points from baseline) and 121 – stable response (sustained improvement on the MADRS by at least 50% from baseline).

In the group of people who achieved a stable remission prior to randomization and continued treatment with intranasal esketamine, a lower relapse rate was obtained (26.7% vs. 45.3%; $p = 0.003$; NNT = 6), compared to the placebo group. Esketamine when used intranasal in combination with an antidepressant reduced the risk of relapse by 51% among patients who achieved stable remission and by 70% among those who achieved a stable response compared to antidepressant and placebo. The most common adverse events reported in patients treated with intranasal esketamine after randomization were transient dysgeusia, dizziness, dissociation, drowsiness, and dizziness [61].

Non-pharmacological strategies

Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) can be applied in conditions where there is a need for a quick response to treatment, e.g., a life-threatening episode of severe depression, when the patient refuses to eat and drink fluids despite cachexia or in patients with depression with suicidal thoughts and tendencies. We also use electroconvulsive therapy in clinical situations in which the risk of pharmacotherapy is greater than the risk associated with ECT, e.g., severe depression or psychosis in pregnancy, depression in a patient with agranulocytosis or leukopenia, in the case of polypragmasia, as well as in patients with drug-resistant depression.

Treatments are usually performed 2–3 times a week, in total depending on the rate of improvement, 6 to 12 treatments are performed. Before qualifying the patient for ECT, in order to ensure safety, it is recommended to perform neurological, internist, ophthalmological and anesthesiological consultation. Electroconvulsive therapy is a safe method and the only absolute contraindication to its use is an increase in intracranial pressure [5, 39]

Most methods of non-pharmacological treatment of depression (except ECT) are not generally available in Poland. They are also not included in the guaranteed benefits basket of the Ministry of Health. However, they are methods recognized and recommended by scientific societies. There are centers in Poland that perform these procedures.

Vagus nerve stimulation (VNS)

Vagus nerve stimulation (VNS) was approved in 2005 by the Food and Drug Administration (FDA) as a treatment method for adult patients who experience an episode of major depressive disorder and have not responded to at least 4 adequate

antidepressant attempts. Experts from the World Federation of Societies of Biological Psychiatry (WFSBP) recommend VNS to patients suffering from depression in whom more than 3 previously used antidepressants failed. It should be remembered that the therapeutic effect of using VNS may be visible 3–12 months after pacemaker implantation.

Electroconvulsive therapy (ECT) and VNS are seen as complementary neuromodulatory methods; ECT – when rapid improvement is required in seriously ill patients; VNS as a method ensuring well-tolerated long-term treatment [5, 39]

Deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS) are also used in the therapy of depression resistant to pharmacological treatment. Many randomized controlled studies and published literature have confirmed the safety and efficacy of rTMS antidepressant therapy. Further research is indicated to determine optimal treatment parameters and algorithms for implementing rTMS at various stages of antidepressant treatment and preventing relapse [62, 63]

The inclusion of psychotherapy should be considered in all stages of depression.

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Address: Katarzyna Bliźniewska-Kowalska
Department of Adult Psychiatry
Medical University of Lodz
91-229 Łódź, Aleksandrowska Street 159
e-mail: katarzyna.blizniewska-kowalska@umed.lodz.pl