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# Antidepressants and Older Age: Risks of Pharmacothera

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## ABSTRACT

High prevalence of depression among older adults is a significant global public health concern. The situation is further aggravated by population aging, which increases the number of individuals requiring care. Alongside with psychotherapy, pharmacotherapy is widely used in depression management. However, its use in older adults poses substantial challenges due to age-related physiological changes and an elevated risk of adverse drug reactions. Multimorbidity and associated polypharmacy further contribute to the likelihood of harmful drug-drug interactions. In addition, aging-related changes affect drug elimination.

Various classes of antidepressants with generally comparable efficacy are available on the pharmaceutical market. Tricyclic antidepressants, such as amitriptyline and imipramine, are not recommended in older adults due to a high incidence of adverse effects, including sedation, dry mouth, constipation, and orthostatic hypotension. Serotonin reuptake inhibitors, such as fluoxetine, sertraline, and citalopram, have a more favorable safety profile and are considered first-line agents in the treatment of depression in the elderly, although they are not without drawbacks. Selective serotonin and norepinephrine reuptake inhibitors, such as venlafaxine and duloxetine, act on two neurotransmitter systems, which may increase the likelihood of adverse effects. Atypical antidepressants (mirtazapine, trazodone, vortioxetine, and agomelatine) constitute a heterogeneous group of agents that differ in their mechanisms of action and safety profiles.

Thus, when treating older adults, the rational choice of an antidepressant should consider its side effect profile, potential drug interactions, comorbid conditions, and cost of therapy.

**Keywords:** antidepressants; mechanisms of action; adverse effects; withdrawal syndrome; elderly and senile age.

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# Антидепрессанты и пожилой возраст: риски фармакотерапии

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## АННОТАЦИЯ

Высокая распространённость депрессии среди пожилых людей является значимой проблемой здравоохранения во всём мире. Старение населения лишь усугубляет эту ситуацию, увеличивая число пациентов, нуждающихся в помощи. Наряду с психотерапевтическими методами лечения депрессии широкое применение находит медикаментозная терапия. Однако её использование у пожилых пациентов сопряжено со значительными трудностями, обусловленными возрастными изменениями организма и высоким риском развития нежелательных реакций на лекарственные препараты. Определённую негативную роль играют полиморбидность и связанная с ней полипрагмазия, что неизбежно увеличивает вероятность нежелательных лекарственных взаимодействий. Кроме того, изменения, характерные для процессов старения, влияют на элиминацию лекарственных средств.

На фармацевтическом рынке представлены различные классы антидепрессантов, эффективность которых сопоставима. Трициклические антидепрессанты, такие как амитриптилин и имипрамин, в силу большого количества побочных действий, включая седативный эффект, сухость во рту, запоры и ортостатическую гипотензию, не рекомендованы для применения у пожилых пациентов. Селективные ингибиторы обратного захвата серотонина, например флуоксетин, сертралин и циталопрам, обладают более благоприятным профилем безопасности и являются препаратами выбора в лечении депрессии у лиц пожилого и старческого возраста, хотя и не лишены недостатков. Ингибиторы обратного захвата норадреналина и серотонина, такие как венлафаксин и дулоксетин, оказывают действие на два нейромедиатора, что может увеличивать вероятность развития побочных эффектов. Атипичные антидепрессанты (миртазапин, тразодон, вортиоксетин и агомелатин) представляют собой гетерогенный класс препаратов, различающихся по механизму действия и профилю безопасности.

Таким образом, при лечении пожилых пациентов рациональный выбор антидепрессанта должен проводиться с учётом его побочных эффектов, взаимодействия с другими лекарственными средствами, а также наличия сопутствующих заболеваний и стоимости лечения.

**Ключевые слова:** антидепрессанты; механизмы действия; побочные эффекты; синдром отмены; пожилой и старческий возраст.

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## INTRODUCTION

The high prevalence of mental disorders among older adults represents a significant global public health issue, particularly in the context of progressive population aging, as shown by demographic studies across many countries. According to the World Health Organization, the global population is steadily aging, and by 2050, the number of individuals aged 60 years or older is projected to reach 1.5 billion [1].

Depression is the most common psychiatric disorder in this age group, characterized by prolonged periods of low mood and sadness, as well as a loss of interest and ability to experience pleasure. It typically manifests with decreased activity, sleep disturbances, excessive feelings of guilt and hopelessness, suicidal ideation, impaired concentration, and reduced appetite. In addition, individuals with depression often experience anxiety and irritability [2]. These symptoms significantly impair daily functioning and markedly reduce the quality of life. Currently, approximately 5% of the global adult population has depressive disorders, with higher prevalence among older adults (> 10%) and rates reaching up to 35% among hospitalized individuals and nursing home residents [3–5].[1] Despite this, depression in the elderly often goes unrecognized and untreated, even after diagnosis [6, 7]. Therefore, adequate management of this condition in older populations is a critically important issue.

In addition to motivational psychotherapy aimed at reinterpreting past events and promoting lifestyle modifications (greater social engagement and increased physical activity), pharmacotherapy with antidepressants is widely used. The relevance of these medications in older adults also stems from their broad range of indications, including anxiety disorders, obsessive-compulsive disorder, and chronic pain syndromes.

Several clinical studies have shown that the efficacy of different classes of antidepressants is generally comparable; however, their tolerability varies significantly [8, 9]. Older adults are more likely to experience adverse drug reactions and are especially vulnerable to the risks of polypharmacy, which is often unavoidable. These differences arise from both drug-specific side effects and aging-related changes that affect the pharmacodynamics and pharmacokinetics of medications, as well as multiple comorbidities.

Aging is associated with alterations in neurotransmitter systems and receptor sensitivity, making patients more susceptible to the pharmacologic effects that determine the pharmacodynamics of psychotropic agents [10]. Loss of neurons in the cerebral cortex, locus coeruleus, and hippocampus enhances the sedative effects of these agents. Reduced baroreceptor sensitivity enhances the hypotensive effects of certain antidepressants, although decreased cholinergic activity in the central nervous system contributes to confusion and cognitive impairment when using agents with antimuscarinic effect [11].

Elderly patients also exhibit alterations in the pharmacokinetic profile of antidepressants. These include slower absorption, increased volume of distribution (due to a relatively higher proportion of adipose tissue), elevated plasma levels of unbound drug, reduced hepatic metabolism, and diminished renal excretion.

Taking into account that age-related changes in the pharmacodynamics and pharmacokinetics of antidepressants may increase the risk of adverse drug reactions, prescribing these medications to older adults requires a tailored and cautious approach based on individual patient characteristics.

Most modern antidepressants increase synaptic levels of serotonin and norepinephrine in the brain, thereby improving mood and alleviating depressive symptoms [12]. However, they are classified not only by their mechanisms of action but also by chemical structure, which is essential for understanding their clinical use.

In general, five primary classes of antidepressants are recognized [13]:

- tricyclic antidepressants (TCAs);
- selective serotonin reuptake inhibitors (SSRIs);
- serotonin-norepinephrine reuptake inhibitors (SNRIs);
- selective reversible monoamine oxidase A inhibitors;
- atypical antidepressants.

A thorough understanding of the pharmacodynamics of antidepressants, their potential adverse effects, and drug interactions, as well as close clinical monitoring, is essential for the rational and safe use of these agents in older adults. To minimize the risk of adverse effects and enhance drug tolerability, treatment should start with the lowest effective doses, followed by gradual titration.

## TRICYCLIC ANTIDEPRESSANTS

In Russia, the most commonly used TCAs are amitriptyline and imipramine. TCAs inhibit the reuptake of serotonin and norepinephrine at the presynaptic membrane, resulting in increased concentrations of these neurotransmitters in the synaptic cleft and, consequently, enhanced neurotransmission. Moreover, they exhibit antagonistic activity at $M_1$ muscarinic receptors as well as at $H_1$, $H_2$, and $\alpha_1$-adrenergic receptors. Most TCAs also inhibit cardiac sodium and L-type calcium channels, which may contribute to their cardiotoxic (proarrhythmic) effects and potential lethality in case of overdose.

These agents are not considered first-line treatments for depression in elderly and senile patients due to their numerous dose-dependent, clinically significant adverse

[1] Depressive disorder (depression); [1 page]. In: World Health Organization [Internet]. 2021. Available at: https://www.who.int/ru/news-room/fact-sheets/detail/depression Accessed on August 15, 2024.

effects. Dry mouth, which causes discomfort and predisposes to dental complications (e.g., caries, poor denture retention); blurred vision; increased intraocular pressure; constipation; urinary retention; cognitive impairment; memory loss; confusion; and sinus tachycardia result from their anticholinergic activity. $\alpha_1$-Adrenergic blockade may lead to postural hypotension and dizziness. The antihistaminic effect, particularly pronounced with amitriptyline, contributes to sedation, somnolence, and weight gain.

Use of TCAs in older adults can exacerbate angle-closure glaucoma, trigger acute urinary retention in patients with benign prostatic hyperplasia, worsen constipation, and significantly increase the risk of falls and fatal fractures. It is important to recognize that this class of antidepressants carries a high risk of overdose due to their narrow therapeutic index.

TCAs potentiate the sedative effects of alcohol and other central nervous system depressants (e.g., benzodiazepines, first-generation antihistamines, antipsychotics), which may impair psychomotor and cognitive function, posing particular danger for the elderly. In addition, TCAs interact unfavorably with many medications, including antiarrhythmic and antihypertensive drugs, as well as oral anticoagulants. Concomitant use with class I and III antiarrhythmics or other agents that prolong the *QT* interval on ECG is especially hazardous, as it may precipitate life-threatening arrhythmias and sudden death [14].

## MONOAMINE OXIDASE INHIBITORS

These antidepressants inhibit the activity of monoamine oxidase, thereby preventing the degradation of norepinephrine, serotonin, and dopamine in the presynaptic axon terminal, leading to increased concentrations of these neurotransmitters in the synaptic cleft. Monoamine oxidase inhibitors (MAOIs) were among the first drugs used to treat major depressive disorder. Currently, due to the substantial number of adverse effects and drug–food interactions, this class of antidepressants is rarely used in elderly and senile patients.

One of the most well-known agents in this class is moclobemide,[2] a selective reversible inhibitor of monoamine oxidase A. Its adverse effects are primarily related to increased serotonin levels, making coadministration with serotonergic agents contraindicated. However, its cholinergic side effects are minimal. Moclobemide has an activating effect and, in addition to sleep disturbances, may cause pronounced agitation in elderly patients.

## SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Chemically, SSRIs represent a heterogeneous class of antidepressants that includes fluoxetine, citalopram, fluvoxamine, paroxetine, and sertraline. These agents are significantly better tolerated than TCAs and are currently considered first-line treatment for depression in older adults. In addition, most SSRIs have a convenient once-daily dosing regimen [15].

The adverse effects of SSRIs are generally milder and less diverse. Compared with TCAs, their cardiac and anticholinergic adverse effects, except for paroxetine, which induces moderate cholinergic receptor blockade, are minimal, significantly reducing the risk of fatal overdose [16].

The most common side effects of SSRIs, reflecting their central and peripheral inhibition of serotonin reuptake, include gastrointestinal symptoms (nausea, anorexia, vomiting, and diarrhea), central nervous system dysfunction (insomnia, agitation, dizziness, tremor, and headache), and sexual dysfunction (decreased libido, anorgasmia, delayed ejaculation, and erectile dysfunction). Gastrointestinal symptoms and headache typically occur early in treatment and usually resolve spontaneously, whereas sexual side effects may persist for a long time. SSRIs can also cause postural instability in older adults, increasing the risk of fall. One observational study reported a dose-dependent increase in the risk of fracture from minor trauma [17].

Serotonin promotes platelet aggregation, while SSRIs inhibit this process, which may increase the risk of bleeding. Specifically, their use has been shown to increase the risk of gastrointestinal bleeding (relative risk = 3) [18]. This risk is further elevated when SSRIs are used concomitantly with nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants.

Rare but potentially serious adverse effects include the syndrome of inappropriate antidiuretic hormone secretion and related hyponatremia. Most cases of reduced serum sodium concentration, which is often asymptomatic, have been reported in older adults during the first month of treatment, necessitating close monitoring of serum sodium during this period.

In cases of overdose or concurrent use with illicit psychostimulants (e.g., cocaine or ecstasy), a life-threatening condition known as serotonin syndrome may occur. This syndrome is characterized by tachycardia, nausea, abdominal cramps, agitation, facial flushing, excessive sweating, tremor, confusion, and myoclonic seizures. As the condition progresses, hyperthermia, altered mental status, muscular hypertonia, rhabdomyolysis, and renal failure may develop, potentially resulting in death.

SSRIs are known for their pharmacokinetic interactions, as they serve both as substrates and as inhibitors of cytochrome P450 (CYP) enzymes. Therefore, in older adults, especially those on multiple concurrent medications, sertraline and citalopram are preferred due to their lower interaction potential. However, the US Food and Drug

[2] The drug is not approved in the Russian Federation.

Administration has issued a warning that citalopram may prolong the *QT* interval on electrocardiogram, increasing the risk of fatal ventricular arrhythmias. Accordingly, sertraline is the preferred option in such cases [19].

## SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS

SNRIs, such as duloxetine and venlafaxine, are considered alternatives to SSRIs in the treatment of depression in older and elderly adults when SSRIs are ineffective or contraindicated. These agents increase synaptic concentrations of serotonin and norepinephrine without affecting other neurotransmitter systems. They are typically used for severe depression, anxiety disorders, and chronic pain syndromes. Although they have a relatively favorable safety profile, SNRIs, like SSRIs, are not without adverse effects. In a comparative study involving elderly nursing home residents, venlafaxine was found to be less well tolerated than sertraline [20].

The most common adverse effects of SNRIs include nausea, dizziness, hyperhidrosis, and arterial hypertension. Sexual dysfunction is also frequently reported and may include decreased libido, erectile dysfunction, delayed ejaculation, and anorgasmia.

Similar to SSRIs, SNRIs are associated with an increased risk of bleeding, which poses a significant concern for patients receiving antithrombotic therapy [21].

Hyponatremia is another adverse effect to consider when prescribing SNRIs. The highest risk has been noted in women older than 65 years, especially those taking concurrent medications that may also induce electrolyte disturbances [22]. Monitoring of serum sodium is generally necessary only in patients with a history of hyponatremia or those who exhibit confusion shortly after therapy initiation.

Caution is warranted when prescribing serotonin-norepinephrine reuptake inhibitors to older patients with osteoporosis, as these agents may enhance bone resorption [23].

## ATYPICAL ANTIDEPRESSANTS

This class includes several agents with distinct mechanisms of antidepressant action: tetracyclic antidepressants (e.g., mirtazapine), triazolopyridines (e.g., trazodone), multimodal serotonin modulators (e.g., vortioxetine), and melatonergic-serotonergic antagonists (e.g., agomelatine).

### Mirtazapine

The antidepressant effect of this drug is associated with its ability to enhance noradrenergic and serotonergic neurotransmission in the central nervous system. It blocks presynaptic $\alpha_2$-adrenergic receptors on both noradrenergic and serotonergic neurons, increasing the release of norepinephrine and serotonin. Serotonergic transmission is further enhanced via postsynaptic 5-$HT_1$ receptor stimulation, facilitated by blockade of 5-$HT_2$ and 5-$HT_3$ receptors [24]. Mirtazapine also exhibits high affinity for $H_1$-histamine receptors and low affinity for cholinergic, $\alpha_1$-adrenergic, and dopaminergic receptors. As it does not inhibit cytochrome P450 isoenzymes, mirtazapine presents a lower risk of pharmacokinetic interactions than SSRIs.

The most frequently reported adverse effects of mirtazapine include sedation and somnolence, as well as increased appetite and weight gain, attributed to its antihistaminic activity. Anticholinergic effects such as dry mouth and constipation are typical but occur much less frequently than with amitriptyline [25]. Biochemical abnormalities may include elevated hepatic aminotransferases, cholesterol, and triglycerides. Rarely, the drug may induce neutropenia or agranulocytosis. Sexual dysfunction, blood pressure fluctuations, and nausea are uncommon.

Mirtazapine is generally well tolerated in older adults and may be considered a second-line option when first-line antidepressants fail to achieve the desired response [26].

### Trazodone

Trazodone exerts dose-dependent modulatory effects on the serotonergic system of the central nervous system. At low doses, it acts as a serotonin antagonist by blocking 5-$HT_{2A}$ receptors, producing anxiolytic, sedative, and hypnotic effects. At higher doses, trazodone inhibits the presynaptic serotonin transporter and antagonizes both 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors, mechanisms believed to underlie its antidepressant activity. Trazodone lacks anticholinergic activity and exhibits weak antagonism at presynaptic $\alpha_2$-adrenergic receptors. At low doses, it also blocks postsynaptic $\alpha_1$-adrenergic and $H_1$ receptors, further enhancing its sedative and hypnotic properties [27, 28].

Due to its lack of muscarinic receptor blockade, trazodone does not increase heart rate and may be considered a first-line antidepressant in patients with comorbid glaucoma or benign prostatic hyperplasia. It does not potentiate adrenergic transmission or cause extrapyramidal side effects.

Common adverse effects of trazadone include transient somnolence, headache, dizziness, and dry mouth. In older adults, constipation and orthostatic hypotension related to $\alpha_1$-blockade may occur. This effect is transient and plasma concentration–dependent. Trazodone is metabolized primarily by the cytochrome P450 isoenzyme CYP3A4, necessitating caution when used with inducers or inhibitors of this enzyme. Potential pharmacodynamic interactions include additive sedative and proarrhythmic effects. Due to the theoretical risk of serotonin syndrome, trazodone should not be combined with tricyclic antidepressants, monoamine oxidase inhibitors, or fluoxetine.

A rare but serious adverse effect is priapism, likely due to blockade of $\alpha_1$- and $\alpha_2$-adrenergic receptors and increased arterial blood flow to the corpus cavernosum of the penis [29]. This is considered an urologic emergency, and any prolonged spontaneous erection warrants immediate medical attention.

### Vortioxetine

Clinical experience with vortioxetine, a multimodal antidepressant, is relatively limited. The US Food and Drug Administration approved it in 2013 for the treatment of major depressive disorder in adults.

Although its exact mechanism of action remains unclear, experimental data suggest that vortioxetine acts through both inhibition of serotonin reuptake and direct modulation of serotonergic receptor activity. Specifically, vortioxetine is a 5-$HT_{1A}$ receptor agonist, a partial agonist at 5-$HT_{1B}$ receptors, and an antagonist at 5-$HT_3$, 5-$HT_{1D}$, and 5-$HT_7$ receptors [30]. In addition to its antidepressant effects, vortioxetine is believed to possess anxiolytic properties and may enhance cognitive function, which is particularly relevant in the treatment of older adults [31].

Vortioxetine undergoes hepatic metabolism mainly via oxidation by CYP2D6 and, to a lesser extent, CYP3A4/5 and CYP2C9, followed by glucuronidation. When vortioxetine is coadministered with CYP inducers (e.g., rifampicin, carbamazepine, and phenytoin) for more than 14 days, an increase in the vortioxetine dose is recommended, but not to exceed three times the original dose [32]. Concomitant use with serotonergic agents, including SSRIs, tramadol, or sumatriptan, may cause serotonin syndrome.

A 2015 meta-analysis and systematic review of 11 randomized clinical trials involving 6145 patients found that nausea and vomiting were the most frequently reported adverse effects of vortioxetine [30]. Constipation is another common side effect, occurring less frequently than with duloxetine [33]. Both nausea and constipation are more common at higher doses of vortioxetine and in patients older than 65 years. Unlike other serotonergic antidepressants, sexual dysfunction is rare with vortioxetine and occurs at rates similar to placebo [34]. Overall, vortioxetine is well tolerated by older adults and is currently considered a second-line pharmacologic treatment for depression in this population when first-line agents prove ineffective [15]. In some countries, such as Canada, vortioxetine is recommended as an initial treatment option [35].

### Agomelatine

Agomelatine is structurally similar to melatonin and acts as a non-selective agonist at melatonin receptors ($MT_1$, $MT_2$), while selectively antagonizing 5-$HT_{2C}$ serotonin receptors. Clinical trial data, including large phase 3 studies, have demonstrated that agomelatine is at least as effective as SSRIs and serotonin-norepinephrine reuptake inhibitors [36, 37]. In addition to its antidepressant effects, agomelatine resynchronizes circadian rhythms, thereby improving nighttime sleep. The lack of affinity of agomelatine for adrenergic, dopaminergic, GABAergic, muscarinic, and histaminergic receptors enhances its tolerability in elderly patients. However, due to limited data, its use is not recommended in individuals over 75 years of age.

The most commonly reported side effects of agomelatine are headache and dizziness. It may also increase hepatic transaminase activity, and liver function tests should be performed prior to and during treatment. Agomelatine therapy should be discontinued if transaminase activity increases to more than three times the upper limit of normal. The drug is contraindicated in patients with cirrhosis or active liver disease.

## ANTIDEPRESSANT DISCONTINUATION SYNDROME

The reported prevalence of antidepressant discontinuation syndrome (also known as antidepressant withdrawal syndrome) varies widely in the scientific sources, with older adults being at greater risk [38]. A recent meta-analysis of 79 studies (44 randomized trials and 35 observational studies) involving 21,002 patients found that the incidence of at least one withdrawal symptom was significantly higher in those taking antidepressants than in those taking placebo (31% vs 17%). However, the incidence of severe symptoms was relatively low: 3% in the antidepressant group and less than 1% in the placebo group [39].

Unlike withdrawal syndromes associated with opioids, alcohol, and other psychoactive substances, antidepressant discontinuation syndrome lacks pathognomonic or temporally consistent features [40]. Common symptoms include flu-like syndrome, mood swings, anxiety, insomnia, nausea, imbalance, sensory disturbances, and agitation. These symptoms are generally mild, last 1–2 weeks, and resolve quickly after therapy reinstitution. The likelihood of antidepressant discontinuation syndrome increases with longer treatment duration and shorter elimination half-life of the drug [41]. For instance, unlike fluoxetine, which has a long half-life, medications such as paroxetine, sertraline, fluvoxamine, venlafaxine, and TCAs may induce discontinuation symptoms within 24–48 h of abrupt cessation or significant dose reduction, even after short-term use (3–4 weeks). In cases where it is difficult to distinguish whether nonspecific symptoms represent discontinuation syndrome or a relapse of depression, assessing symptom severity is essential.

A general recommendation is to taper the antidepressant dose gradually over several weeks when discontinuation is necessary [42].

## CONCLUSION

Prescribing antidepressants to older and senile patients can significantly improve their quality of life by alleviating depressive symptoms. However, it is associated with certain risks related to age-dependent physiological changes that influence the pharmacodynamics and pharmacokinetics of drugs. A wide array of antidepressants is available on the pharmaceutical market today, and their efficacy

is generally considered comparable. Thus, rational antidepressant selection should be based on the drug's adverse effect profile, comorbid conditions, potential drug interactions, and treatment cost.

## ADDITIONAL INFORMATION

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