Psychiatr. Pol. ONLINE FIRST Nr 386: 1–15
Published ahead of print 17 November 2025
www.psychiatriapolska.pl
ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
DOI: https://doi.org/10.12740/PP/OnlineFirst/208213

Expert group recommendations on the use of antipsychotic drugs in patients with somatic diseases. Part I: metabolic syndrome, cardiovascular diseases

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Summary

Antipsychotic drugs/antipsychotics as a group, despite their similar clinical effect, differ both in their chemical structure, pharmacodynamic and pharmacokinetic properties, as well as in the possible side effects of their use. When selecting the appropriate treatment for a patient, the clinician should be guided not only by the expected therapeutic effect, but also weigh the possible side effects, especially in patients burdened with additional somatic conditions.

Almost all, with the exception of pimavanserin, which is not available in Poland, of the currently registered antipsychotics are D2 receptor antagonists. Second-generation drugs additionally exert significant effects on serotonergic transmission, primarily by blocking 5-HT2A receptors. On the other hand, modern third-generation antipsychotics, in addition to antagonism to D2 receptors, also exhibit partial agonism towards dopamine receptors, which allows modulation of dopaminergic transmission.

The aim of this paper is to provide guidance on the selection of antipsychotics for the treatment of psychiatric patients with co-morbid somatic conditions (part I of the recommendations concerns metabolic syndrome, hyperprolactinemia and cardiovascular conditions) based on the risk of possible side effects associated with the use of antipsychotics.

Key words: antipsychotics, safety, somatic diseases

1. Introduction

Antipsychotic drugs, despite their similar clinical effects, differ in chemical structure, pharmacodynamic and pharmacokinetic properties, as well as in the possible side effects of their use. When choosing the right treatment for a patient, we should be guided not only by the expected therapeutic effect, but also by weighing the possible side effects, especially in patients burdened with additional somatic conditions. It should be remembered that the group of patients using antipsychotic drugs is very large and is not limited to patients with psychotic disorders. Drugs in this group also show efficacy in a number of other disease entities, including bipolar affective disorder, treatment potentiation of drug-resistant unipolar depression, obsessive-compulsive disorder (OCD), the treatment of tics, as well as the treatment of behavioral disorders associated with dementia, intellectual disability and pervasive developmental disorders [1].

Almost all currently registered antipsychotics, with the exception of pimavanserin, which is not available in Poland, are D2 receptor antagonists. Second-generation drugs additionally exert significant effects on serotonergic transmission, primarily by blocking 5-HT2A receptors (except for amisulpride). In contrast, modern third-generation antipsychotics, in addition to antagonism of D2 receptors, also exhibit partial agonism toward dopamine receptors. This mechanism of action of third-generation neuroleptics is intended to regulate dopaminergic transmission – to inhibit it (antagonism) in pathways where it is excessive (e.g., excessive transmission in the mesolimbic pathway in psychotic patients) and to stimulate it (agonism) in pathways where it is too low (mescortical pathway). The exact pharmacodynamics of individual antipsychotic drugs are shown in Table 1 [1-4].

The purpose of this paper is to provide guidance on the selection of antipsychotic drugs for the treatment of psychiatric patients with somatic comorbidities, based on the risk of possible side effects associated with their use.

Table 1. **Pharmacodynamics of antipsychotic medications [1]**

GROUP	MEDICATION NAME	RECEPTORS		
		dopamine	**serotonin**	**other**
Other	Pimavanserin	-	5-HT2A: +++ antagonism 5-HT2C: ++ antagonism	-
First generation	Chlorpromazine	D1: + antagonism D2: +++ antagonism D3: ++ antagonism D4: antagonism	5-HT2A: ++ antagonism 5-HT2C: ++ antagonism 5HT6: ++ antagonism 5HT7: ++ antagonism	Alpha-1: +++ antagonism H1: +++ antagonism M1: ++ antagonism M3: ++ antagonism

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First generation	Levomepromazine	D2: ++ antagonism D4: ? antagonist	5-HT2A: +++ antagonism	Alpha-1: +++ antagonism H1: +++ antagonist M1: ++ antagonism Alpha-2: + antagonism M3: ? antagonist
	Perazine	D2: ++ antagonism	-	Alpha-1: ++ antagonism M1: ++ antagonism H1: ++ antagonism
	Haloperidol	D2: +++ antagonism D4: +++ antagonism D3: ++ antagonism	5-HT2A: + antagonism	Alpha-1: ++ antagonism
	Chlorprothixene	D1: ++ antagonism D2: ++ antagonism	5-HT2A: ++ antagonism 5-HT21A + antagonism	M1: +++ antagonism H1: +++ antagonism Alpha-2: ++ antagonism Alpha-1: ++ antagonism
	Zuclopenthixol	D1: +++ antagonism D2: +++ antagonism	5-HT2A: ++ antagonism	H1: ++ antagonism Alpha-1: ++ antagonism
	Flupentixol	D2: +++ antagonism D1: +++ antagonism D3: +++ antagonism	5-HT2A: ++ antagonism	alpha-1: ++ antagonism H1: 0/+ antagonism M1: 0/+ antagonism
	Sulpiride	D2: +++ antagonism D3: ++ antagonism	-	-
	Tiapride	D2: ++ antagonism D3: ++ antagonism	-	-
Second generation	Clozapine	D4: ++ antagonism D2: + antagonism	5-HT2A: +++ antagonism 5-HT2C: +++ antagonism 5HT6: ++ antagonism 5HT7: ++ antagonism 5-HT21A: + agonism	Alpha-1: +++ antagonism H1: +++ antagonism M1: +++ antagonism Alpha-2: ++ antagonism M4: + agonism (norclozapine)
	Olanzapine	D2: ++ antagonism D4: ++ antagonism D3: ++ antagonism	5-HT2A: +++ antagonism 5HT6: +++ antagonism 5-HT2C: +++ antagonism	H1: +++ antagonism M1: ++ antagonism Alpha-1: ++ antagonism Alpha-2: + antagonism

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Second generation	Quetiapine	D2: + antagonism	5-HT2A: +++ antagonism 5-HT21A: ++ agonism 5-HT2C: + antagonism 5HT7: + antagonism	H1: +++ antagonism Alpha-1: ++ antagonism M1: + antagonism (mainly norquetiapine) NET: inhibition (norquetiapine) Alpha-2: + antagonism (mainly norquetiapine)
	Risperidone	D2: +++ antagonism D3: ++ antagonism D4: ++ antagonism	5-HT2A: +++ antagonism 5HT7: +++ antagonism 5-HT21B: ++ antagonism 5-HT2C: ++ antagonism	Alpha-1: ++ antagonism Alpha-2: ++ antagonism H1: ++ antagonism
	Paliperidone	D2: +++ antagonism D3: +++ antagonism D4: ++ antagonism	5-HT2A: +++ antagonism 5HT7: +++ antagonism 5-HT21B: ++ antagonism 5-HT2C: ++ antagonism	Alpha-1: ++ antagonism Alpha-2: ++ antagonism H1: ++ antagonism
	Ziprasidone	D2: +++ antagonism D3: +++ antagonism D4: ++ antagonism	5-HT2A: +++ antagonism 5-HT2C: +++ antagonism 5-HT21A: +++ agonism 5-HT21B: +++ agonism 5HT7: +++ antagonism 5HT6: ++ antagonism	Alpha-1: ++ antagonism Alpha-2: + antagonism SERT and NET: inihibition
	Lurasidone	D2: +++ antagonism D3: ++ antagonism	5-HT2A: +++ antagonism 5HT7: +++ antagonism 5HT1: +++ partial agonism 5-HT2C: + antagonism	Alpha-2: ++ antagonism Alpha-1: + antagonism
	Sertindole	D2: +++ antagonism D3: +++ antagonism D4: +++ antagonism	5-HT2A: +++ antagonism 5-HT2C: +++ antagonism 5HT7: ++ antagonism 5-HT21B: ++ antagonism	Alpha-1: +++ antagonism
	Amisulpride	D2: +++ antagonism D3: +++ antagonism Limbic selectivity in dopaminergic transmission	5HT7: ++ antagonism 5-HT2B: ++ antagonism	-

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Third generation	Aripiprazole	D2: +++ partial agonism D3: +++ partial agonism	5-HT21A: +++ partial agonism 5-HT2A: +++ antagonism 5HT7: ++ antagonism 5-HT2B: ++ antagonism 5-HT2C: ++ partial agonism	Alpha-1: ++ antagonism H1: + antagonism Alpha-2: + antagonism
	Brexpiprazole	D2: +++ partial agonism D3: +++ partial agonism D4: +++ antagonism	5-HT21A: +++ partial agonism 5-HT2A: +++ antagonism 5-HT2B: +++ antagonism 5HT7: +++ antagonism 5-HT2C: ++ antagonism	Alpha-2: +++ antagonism Alpha-1: +++ antagonism H1: ++ antagonism
	Cariprazine	D2: +++ partial agonism D3: +++ partial agonism	5-HT2B: +++ agonism 5-HT21A: +++ partial agonism 5-HT2A: ++ antagonism 5HT7: + antagonism 5-HT2C: + antagonism	H1: ++ antagonism Alpha-1: ++ antagonism
Legend: the number of "+" indicates the strength of the affinity				

2. Recommendations for the use of antipsychotics in specific somatic conditions

The following are recommendations for the safe use of antipsychotic drugs in specific somatic conditions, i.e., metabolic syndrome, hyperprolactinemia or cardiovascular conditions (ischemic heart disease, cardiac arrhythmias or hypertension), as well as information on the risk of triggering these disorders with specific categories of antipsychotics.

2.1 Metabolic syndrome

The mechanism of action of antipsychotic drugs translates into potential side effects of their use. An important side effect of taking antipsychotics is adverse metabolic effects, which can be even more dangerous in patients already burdened with obesity, diabetes or dyslipidemia [5]. Research suggests that H1, 5-HT2A, 5-HT2C, 5-HT6, D2, α1 and M3 receptors are key mediators of metabolic side effects [5-8]. Acting both centrally in CNS regions such as the hypothalamus, reward system and brainstem, and peripherally, they can interfere with food intake and metabolic

regulation. The combination of 5-HT2C/D2/H1 antagonism represents the most dangerous profile in terms of antipsychotic drug-induced weight gain and diabetes. Antagonism of 5-HT2A, 5-HT6, M3 and α1 may represent additional adverse effects. Antipsychotics with lower metabolic risk appear to lack 5-HT2C antagonism or have additional protective mechanisms, such as partial D2/3 and/or 5-HT1 agonism and/or α2A antagonism [5-8].

D2 receptor antagonists, through inhibition of the reward system, can cause a lack of inhibition of food seeking and increased appetite. Additional actions of antipsychotics on the serotonergic system may result in weight gain, as 5-HT2C antagonism has an inhibitory effect on the satiety center, while 5-HT1B agonism and 5HT6 antagonism inhibit the hunger center [1]. Similarly, H1 receptors are present in the hunger and satiety centers, and antagonism at these receptors is associated with an increase in appetite [1]. Another mechanism leading to weight gain is antagonism to Alpha-1 receptors leading to sedation, increased appetite and insulin resistance [1, 5-8]. The presence of D2 receptors on the pancreatic islets may contribute to the effects of antipsychotics on insulin secretion. The inhibitory effects of 5-HT2A antagonists and 5-HT21A agonists on pancreatic insulin secretion have been demonstrated. Muscarinic receptors (M1 and M3) are also found on pancreatic islets and affect the regulation of both basal and glucose-dependent insulin secretion. Antagonism to these receptors may be associated with the risk of hyperglycemia and insulin resistance.

The occurrence of various factors (i.e., obesity, hypertension, dyslipidemia, glucose metabolism disorders) that increase the risk of developing atherosclerotic cardiovascular disease and type 2 diabetes is called metabolic syndrome.

An analysis of the PubMed medical publications database was conducted using the phrase "(antipsychotics) AND (metabolic syndrome)" and narrowing the search to meta-analyses and systematic reviews only, yielding 57 publications from the last 10 years (2014-2024) and 33 publications from the last 5 years (2019-2024). Particular attention was paid to meta-analyses from the last 5 years (16 studies).

Barton et al. [9] suggested that also relatively new compounds, such as cariprazine and brexpiprazole, caused significantly greater weight gain compared to placebo. Only aripiprazole, lurasidone and, interestingly, quetiapine XR (but only in its extended-release form) did not lead to clinically relevant weight gain of ≥7% [9]. A meta-analysis by Vancampfort and colleagues [10] classified antipsychotics based on their likelihood of causing metabolic syndrome in the following order: clozapine > olanzapine ≥ quetiapine = risperidone = first-generation antipsychotics = amisulpride ≥ aripiprazole > placebo. Pillinger and colleagues [11] also highlighted significant differences between antipsychotics in terms of metabolic side effects, with olanzapine and clozapine showing the worst profiles and aripiprazole, brexpiprazole, cariprazine, lurasidone and ziprasidone the safest profiles. Increased baseline body weight, male gender and non-white ethnicity are predictors of metabolic vulnerability [11]. Table 2 provides a heat map of the safety of each neuroleptic in terms of metabolic complications.

Table 2. **Heat map of the metabolic safety of individual neuroleptics [5, 12]**

Medication	Obesity/weight gain	Diabetes/glucose metabolism disorders	Dyslipidemia
Chlorpromazine	3-4	1-2	1-2
Haloperidol	1	1	1
Olanzapine	4	2	2
Clozapine	3 – 4	2	2
Quetiapine	3	1-2	2
Ziprasidone	1	1	1
Sertindole	3-4	1-2	1-2
Risperidone	3	1-2	1-2
Paliperidone	3	1-2	1-2
Amisulpride	2	1	2
Lurasidone	1	1	1
Aripiprazole	2	1	1
Brexpiprazole	1	1	1
Cariprazine	1	1	1

Legend: scale from 1 to 4, where: 1 means a drug that is relatively safe in terms of metabolism, and 4 means a drug with the least favorable metabolic profile.

The safest drugs are marked in green, and the drugs with the least favorable safety profile are marked in red.

Many authors suggest that third-generation neuroleptics, which are partial D2 receptor agonists, as well as lurasidone can be considered first-line medications when antipsychotics are needed in a patient with a diagnosis of diabetes or metabolic syndrome or its components [13].

2.2 Hyperprolactinemia

Hyperprolactinemia (HPRL) is defined as a sustained increase in prolactin (PRL) levels above the upper limit of the normal range, unrelated to lactation or pregnancy (20 ng/ml for men and 25 ng/ml for women). PRL levels should be measured on an empty stomach, approximately 2 hours after waking [1]. PRL secretion is regulated mainly by the inhibitory action of dopaminergic neurons of the tuberoinfundibular pathway on lactotroph cells, which express D2 receptors. Antagonism of the D2 receptor by most antipsychotic drugs results in disinhibition of lactotroph cells and increased PRL secretion [1, 2, 5]. Drugs associated with a high risk of hyperprolac-

tinemia include risperidone, paliperidone, sulpiride and amisulpride [1]. A meta-analysis by Krøigaard and colleagues [14] showed that, among children and adolescents, a statistically significant increase in prolactin occurred with risperidone, paliperidone and olanzapine. Aripiprazole significantly reduced prolactin levels, while the use of quetiapine and lurasidone was not associated with a significant difference in prolactin levels (compared to placebo).

The safest antipsychotics for use in patients with hyperprolactinemia or a history of symptomatic neuroleptic-induced hyperprolactinemia appear to be third-generation antipsychotics, particularly aripiprazole. Clozapine and other atypical neuroleptics such as lurasidone and quetiapine should be considered as secondary options [13, 15, 16].

2.3 Cardiac problems

2.3.1 Ischemic heart disease

Worldwide, cardiovascular disease (CVD) is estimated to be the leading cause of death and loss of disability-adjusted life years. Many well-known risk factors contribute to the development of CVD, and a large proportion of these are modifiable. A large case-control study conducted in 52 countries across all continents examined the effects of various risk factors on the development of acute myocardial infarction. Lipid disorders, cigarette smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, insufficient consumption of fruits and vegetables, alcohol abuse, and physical inactivity account for more than 90% of the risk of acute myocardial infarction [17]. Cardiovascular disease is responsible for more than half of premature deaths in people with bipolar disorder or schizophrenia, with a 35-150% increase in mortality risk [18]. The use of first-generation antipsychotics has been shown to increase the risk of cardiovascular complications, such as significant QTc interval prolongation, cardiac arrhythmias and sudden cardiac death. The use of second-generation antipsychotics also has a deleterious effect on long-term cardiovascular risk. In fact, both groups negatively affect glucose and lipid metabolism, as well as body weight, with clozapine and olanzapine exhibiting the worst profiles [18]. Studies have suggested that weight gain and metabolic syndrome induced by antipsychotic use may be risk factors for myocardial infarction [19].

In the meta-analysis by Rotella et al. [18], the primary objective was to determine the association of long-term antipsychotic use with rates of cardiovascular death, myocardial infarction and stroke. A total of 3,013 studies were identified, 92 of which met the selection criteria. Myocardial infarction, stroke and cardiovascular death were reported in 11, 6 and 24 studies, respectively. No significant differences were found for myocardial infarction or stroke. A significantly higher risk of cardiovascular mortality was observed for sertindole compared with risperidone [18].

A systematic review by Yu et al. [19] examined the effect of antipsychotic use on the risk of myocardial infarction and stroke. From 7,008 articles, 29 relevant observational studies were included: 19 on stroke and 10 on myocardial infarction.

The results of the cohort studies, which included the general population, showed a more than twofold increased risk of stroke in antipsychotic users, although with considerable heterogeneity. Patients diagnosed with a dementing process had a significantly lower risk of stroke with antipsychotic use compared with the general population. The incidence of stroke appeared to depend on the class of antipsychotics, with individual studies indicating that first-generation antipsychotics carry higher risk. No clear association was found between antipsychotic use and the risk of myocardial infarction. An increased risk of myocardial infarction was observed among patients on antipsychotics with diagnosed schizophrenia or in patients during the first 30 days of antipsychotic treatment [19, 20].

2.3.2 Arrhythmias

Cardiac arrhythmias are a widely reported adverse effect of psychopharmacotherapy and include right or left bundle branch block, atrioventricular block, and ventricular tachycardia. These arrhythmias may appear on electrocardiographic (ECG) recordings as prolongation of the PQ interval, widening of the QRS complexes, prolongation of the QT segment, changes in the ST segment, or flattening or inversion of the T wave [21]. The use of many antipsychotics is associated with the risk of prolongation of the QTc interval in the ECG, which is likely due to their affinity for hERG potassium channels. Prolongation of the QTc interval is a risk factor for polymorphic ventricular tachycardia (torsade de pointes, TdP), which may result in sudden cardiac death [1]. In addition to pharmacotherapy, the incidence of TdP and thus the increased risk of cardiac death are influenced by female gender; electrolyte disturbances (hypomagnesemia, hypokalemia, hypocalcemia); intracranial bleeding; stroke; hypothyroidism; liver and kidney dysfunction; and cardiac diseases, including ischemic heart disease, cardiomyopathies, myocarditis, heart failure, hypertension, bradycardia, atrial arrhythmias, sinoatrial block and atrioventricular block [21]. In a meta-analysis by Huhn et al. [22], QTc interval prolongation was observed with 7 out of 14 neuroleptics compared to placebo. The drugs with the lowest arrhythmogenic risk, in ascending order, were lurasidone < brexpiprazole < cariprazine < aripiprazole (lower than placebo). The highest arrhythmogenic risk was demonstrated by sertindole > amisulpride > ziprasidone [22]. Currently, there are insufficient studies to establish a direct link between neuroleptic dose and the risk of QTc prolongation and TdP [23, 24]. Table 3 presents the potential risk of arrhythmogenic effects of individual neuroleptics [1, 22].

Table 3. **Heat map of the arrhythmogenic risk of individual neuroleptics [1, 22]**

Medication	Risk of arrhythmia
Amisulpride	3
Aripiprazole	1

table continued on the next page

Asenapine	1
Brexpiprazole	1
Chlorpromazine	3
Chlorprothixene	1
Flupentixol	1
Haloperidol	2*
Cariprazine	1
Clozapine	2/3
Quetiapine	1/2
Levomepromazine	3
Loxapine	1
Lurasidone	1
Olanzapine	1
Paliperidone	1
Perazine	2
Risperidone	1/2
Sertindole	4
Sulpiride	3
Zuclopenthixol	1
Ziprasidone	3
Legend: scale from 1 to 4, where: 1 means a drug that is relatively safe in terms of metabolism, and 4 means a drug with the least favorable metabolic profile. The safest drugs are marked in green, and the drugs with the least favorable safety profile are marked in red. * – haloperidol use is associated with a high risk of polymorphic ventricular tachycardia, disproportionate to the induced QTc prolongation.	

Before initiating antipsychotic treatment in patients with cardiac conditions, including those with a primary diagnosis of cardiac arrhythmias, the potential benefits and risks of therapy should always be assessed individually [25]. Due to their low arrhythmogenic risk, the safest choices for at-risk patients appear to be third-generation neuroleptics – lurasidone and partial D2 receptor agonists such as aripiprazole, brexpiprazole, cariprazine [22].

2.3.3 Hypertension

The most common adverse effect associated with the use of antipsychotics on the circulatory system is the occurrence of orthostatic hypotension. Its risk is related to the antagonistic effect on the Alpha-1 receptor. Antipsychotic therapy may also increase blood pressure, particularly with drugs that antagonize presynaptic Alpha-2 receptors, thereby disinhibiting the secretion of noradrenaline. In addition, hypertension may be a component of antipsychotic-induced metabolic syndrome [1].

The meta-analysis by Rotella et al. [18] examined the long-term effects of antipsychotic therapy on cardiovascular and metabolic complications. Deviations from baseline systolic blood pressure were observed for olanzapine, and deviations from baseline diastolic blood pressure were observed for both olanzapine and quetiapine, compared with risperidone. No data were available on changes in blood pressure with first-generation neuroleptics compared to placebo. Similarly, no significant differences were found between second-generation neuroleptics and placebo, or between first- and second-generation antipsychotics [18].

A systematic review by Hirsch et al. [26] identified only one study that examined the effect of second-generation antipsychotics on blood pressure. This study found that olanzapine, quetiapine, and ziprasidone were strongly associated with an increase in blood pressure, while no effect was found in the case of aripiprazole and risperidone. The findings demonstrated a significant correlation with the occurrence of metabolic syndrome, a component of which is arterial hypertension secondary to antipsychotic therapy. Clozapine and olanzapine were associated with the highest risk of metabolic complications [10].

When prescribing antipsychotics to patients with hypertension, it is important to consider the risk of orthostatic hypotension, particularly in elderly patients, those with circulatory insufficiency, or patients receiving (especially in polytherapy) diuretics, β-blockers, and antihypertensive drugs [1, 27]. After initiating or increasing the dose of a drug known to affect blood pressure, regular monitoring of blood pressure is recommended [28]. In patients with hypertension, it is advisable to avoid antipsychotics with a high potential to induce metabolic syndrome and hypertension, such as clozapine, olanzapine, and quetiapine. Table 4 presents neuroleptics and their effects on blood pressure values.

Table 4. **Effects of neuroleptics on blood pressure values [29]**

Medication	Effect
Amisulpride	-?
Aripiprazole	↑/↓*
Asenapine	↓↓*
Brexpiprazole	↓*

table continued on the next page

Chlorpromazine	↓↓↓*
Chlorprothixene	↓↓*
Flupentixol	↓*
Haloperidol	↓*
Cariprazine	-/↓*
Clozapine	↑/↓↓↓*
Quetiapine	↑/↓↓*
Levomepromazine	↓↓↓*
Loxapine	↓*
Lurasidone	-/↓*
Olanzapine	↑/↓*
Paliperidone	↑/↓*
Perazine	↓↓*
Risperidone	↑/↓*
Sertindole	↓↓*
Sulpiride	-?
Zuclopenthixol	↓↓*
Ziprasidone	↑/↓*

Legend:
* – risk of orthostatic hypotension
[-] – no significant effect on blood pressure
↑ – possibility of causing an increase in blood pressure
↓ – possibility of causing a decrease in blood pressure
The number of arrows indicates the strength of the effect.

3. Summary of Part I

In striving for an individualized approach to patient care, attention should be paid not only to the psychopathological symptoms presented by the patient, but also to possible somatic comorbidity. This article is intended to guide psychiatrists in selecting appropriate pharmacotherapy for patients with common comorbidities, such as diabetes, hypertension, heart disease or hyperprolactinemia. It may also serve as a resource for

physicians in other specialties, including family physicians and cardiologists, who provide care for patients using antipsychotics for psychiatric indications.

Financing: statutory funds of the Department of Adult Psychiatry, Medical University of Lodz: 503/1-062-02/503-11-00

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