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The position statement of the Working Group of the Polish Psychiatric Association on the use of D2/D3 dopamine receptor partial agonists in the treatment of mental disorders

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Summary

Aripiprazole, cariprazine and brexpiprazole are antipsychotic drugs (APD) whose action is associated with partial agonism at the dopamine D2/D3 receptors. They are increasingly more widely used in clinical practice, also off-label. The aim of this article is to present the current state of knowledge on the use of these drugs in the treatment of mental disorders.

The position statement was developed by the panel of experts appointed by the Executive Board of the Polish Psychiatric Association, consisting of individuals with many years of experience in treating patients with mental disorders. The evaluation included the analysis of literature databases (Medline, Embase, Cochrane) and information obtained from meta-analyses and summaries of product characteristics.

A key property of D2/D3 partial agonists is that they display diverse effects on dopamine pathways: (a) blockade of mesolimbic signalling that is overactive in the acute phase of schizophrenia and mania, (b) stimulation of mesocortical pathways with an improvement (or at least with no deterioration) of cognitive functions and negative symptoms, (c) no blockade of the tuberoinfundibular pathway and, consequently, low risk of increased prolactin secretion, (d) no blockade of nigrostriatal pathway and, consequently, low risk of extrapyramidal symptoms. Selective profile of action and intrinsic activity at dopamine D2 (aripiprazole > brexpiprazole) and D3 (cariprazine) receptors in combination with the lack of antihistamine and anticholinergic properties make aripiprazole, brexpiprazole and cariprazine different form other APD in terms of their safety and tolerability. This is the reason for the increasing use of these drugs in the treatment of schizophrenia and mood disorders, and in the case of aripiprazole also in obsessive-compulsive, autism-spectrum and tic disorders.

Key words: antipsychotic drugs, mental disorders, D2/D3 dopamine receptor partial agonists

Introduction

The development of antipsychotic drugs (APD), followed by the introduction of clozapine and second generation antipsychotics (SGA) revolutionised the treatment of schizophrenia and many other mental disorders. SGA and clozapine inverted the pyramid of pharmacological effects typical for haloperidol and other first generation antipsychotics (FGA) characterised by strong, dominant even for small doses, antidopaminergic (dopaminolytic) activity [1, 2]. Relatively weaker antidopaminergic activity of clozapine and olanzapine and many other pharmacological effects superior to the blockade of D2/D3 dopamine receptors make SGA drugs of smaller risk of extrapyramidal symptoms and better subjective tolerability [1, 3].

Apart from evident clinical benefits, even small doses of SGA produce a range of other effects, such as antiserotonergic, anticholinergic and antihistaminic that are the cause of many practical problems typical for SGA of broad receptor profile (increased appetite, weight gain, metabolic disorders, excessive sedation, deterioration of cognitive functions) [1, 4]. There is still a theoretical and practical need to search for mechanisms of action that would modify the basic dopaminolytic effect of antipsychotics towards better subjective tolerability and lower risk of extrapyramidal symptoms and that would not be associated with metabolic syndrome or excessive sedation [3]. One of these mechanisms is partial agonism at D2/D3 dopamine receptors and antipsychotics that exhibit this effect include aripiprazole, brexpiprazole and cariprazine. This is a group of drugs that, apart from their effectiveness, show a favourable side effect profile. They are therefore increasingly used in the treatment of mental disorders, also off-label.

The aim of this article is to present the current state of knowledge on the use of D2/D3 dopamine receptor partial agonists in the treatment of mental disorders.

Pharmacological properties of dopamine D2/D3 receptor partial agonists

Aripiprazole is an example of a D2 receptor partial agonist with low intrinsic activity (dopamine-like), i.e. predominant antagonistic properties. Extensive clinical use of aripiprazole, also in the treatment of diseases other than schizophrenia, encouraged researchers to search for other partial agonists. Although it is still not clear whether drugs such as cariprazine and brexpiprazole are superior to aripiprazole with regard to efficacy and safety (Table 1), a subgroup of partial D2/D3 agonists may be distinguished within the broader category of SGA [1, 2].

Table 1. **Selected features of the pharmacological profile of dopamine D2/D3 receptor partial agonists compared to other second generation antipsychotics**

Characteristics	Aripiprazole	Brexpiprazole	Cariprazine	Practical implications of the comparison between partial agonists and other SGA
Partial agonism at dopamine D2/D3 receptors	++++	+++ lower intrinsic activity, probably lower risk of akathisia	+++*	lower risk of drug-induced parkinsonism, sedation and hyperprolactinaemia; possible akathisia and nausea, already at lower doses; risk of agitation when the treatment is changed from strong antipsychotics, dopamine D2 receptor antagonists, such as haloperidol and risperidone
Action at serotonin 5-HT_{1A}, 5-HT_2 and 5-HT_7 receptors	++	++	++	possible additional antidepressant and anxiolytic effects; favourable effect on negative symptoms of schizophrenia
Antihistamine effect, blockade of histamine H_1 receptors	+ weak, exhibited at higher doses	++ stronger than for aripiprazole and cariprazine, probably higher risk of sedation	+ weak, exhibited at higher doses	possible sedative effect, particularly at higher doses

table continued on the next page

Anticholinergic effect, blockade of muscarinic receptors for acetylcholine	virtually none	virtually none	virtually none	lower risk of sedation, cognitive impairment and atropine-like effects (reduction in visual acuity, constipation, urinary retention) than for other SGA
Dosage p.o.	2**–30 mg/day fast-acting and long-acting injections (LAI) are available	1–4 mg/day	1.5–6.0 mg/day	low starting dose and slow dose titration is usually recommended (see line below)
$T_{1/2}$	75–146 h, long compared to other SGA	approx. 90 h, long compared to other SGA	24–72 h, long compared to other SGA; active metabolites of longer $T_{1/2}$ (2–3 weeks)	long time for blood levels to stabilise, particularly for cariprazine (weeks); long time to eliminate the drug from the body
Hepatic metabolism	yes, isoenzymes 3A4 and 2D6 of cytochrome P-450	yes, isoenzymes 3A4 and 2D6	yes, isoenzyme 3A4 with a minor contribution of isoenzyme 2D6	risk of interactions with CYP2D6 and/ or CYP3A4 inhibitors (e.g. fluoxetine, paroxetine, quinidine, ketoconazole and other antimicrobial agents)

Developed on the basis of [1, 2, 4].

* preferential binding to D_3 receptor, ** starting dose recommended for adolescents

From a theoretical and practical point of view, partial agonism typical for aripiprazole and newer D2/D3 partial agonists translates mainly into: (a) self-limiting antagonistic effect on the activity of dopamine pathways, i.e. the blockade of D2/D3 receptors but not as strong as for first and second generation antipsychotics, and (b) eliminating the need to add other receptor effects to the drug profile, including anticholinergic or antiserotonergic — for many SGA their role is mainly to reduce the risk of extrapyramidal symptoms [1, 4].

Another advantage of partial agonists is that they may exhibit functionally differentiated action on the activity of different dopamine pathways. They may, in the same patient: (a) inhibit the activity of mesolimbic pathways, hyperactive in the acute phase of schizophrenia or mania, (b) stimulate dopamine receptors of low activity, e.g. in mesocortical pathways with improvement (or at least no deterioration) of cognitive functions and negative symptoms, or in the tuberoinfundibular pathway with inhibition (or at least no stimulation) of prolactin secretion [3, 5].

From a broader perspective (Table 1), basic features of partial D2/D3 agonists' pharmacological profile, apart from partial agonism itself, include: (a) relatively selective effects of lower doses of drugs on the dopamine system with no significant antihistamine and anticholinergic effects, (b) less selective effects of higher doses with significant antihistamine and α-adrenolytic effects resulting in further sedation, but also increased risk of orthostatic hypotension [3, 5].

Notably, long biological half-life (T1/2) is another feature that distinguishes partial agonists from the majority of SGA. Long T1/2 means that after initiating the treatment, the drug concentration increases slowly and the dose of aripiprazole, brexpiprazole and cariprazine should be titrated slowly in most patients [1, 2].

Schizophrenia and other primary psychotic disorders

The efficacy of aripiprazole in the treatment of acute and chronic symptoms of schizophrenia has been confirmed in over a dozen of short – and long-term studies. It also has a beneficial effect on negative symptoms and this effect is more evident than for most first and second generation antipsychotics [6]. Moreover, several meta-analyses summarising the data on the drug's efficacy have been published over the last few years. One of the most recent meta-analyses is the work presenting the summary of 402 studies on 32 different antipsychotics and including 53,463 participants [7]. Not only symptomatic improvement was assessed, but also the quality of life, social functioning, side effects, depressive symptoms, etc. Aripiprazole was ranked around the middle when it comes to symptom reduction and high with regard to the patients' quality of life. Specific antipsychotics, with the exception of clozapine, do not differ much from each other in terms of effectiveness, whereas differences in treatment tolerance are clearly marked. In this regard, aripiprazole belongs to the safest therapeutic options.

One of the latest summaries of aripiprazole's efficacy was published in 2018 and it was based on the analysis of 14 studies [8]. Aripiprazole showed efficacy comparable to other antipsychotics, both first and second generation (except for olanzapine and amisulpride), and a significantly better safety profile. It caused less extrapyramidal side effects, including akathisia, compared to first generation antipsychotics and risperidone. In 2020, a meta-analysis of 14 efficacy studies on aripiprazole and brexpiprazole in schizophrenia was published – it included 13 randomised and double-blind studies and one open study. Both drugs were proved to be effective and well-tolerated with no significant differences between them [9].

There is also evidence from short – and long-term studies on the beneficial cognitive effects of aripiprazole in schizophrenia. In one of these studies, aripiprazole (30 mg/day) compared to olanzapine (15 mg/day) showed a significantly better effect on verbal learning. This effect was stable and persisted after one year of treatment [10].

It is also important that aripiprazole can be used in the form of intramuscular injections for rapid control of agitation and disturbed behaviours in patients with

schizophrenia. Aripiprazole is also the first, and in Poland the only, partial D2 receptor agonist available in the form of long-acting injections (LAI). In Europe, aripiprazole LAI is registered for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole [6].

The most common side effects of aripiprazole include akathisia, nausea, insomnia and agitation [11]. Aripiprazole is associated with a low risk of sedation. Due to the favourable profile of side effects, aripiprazole can be used in young people with a first episode of psychosis because it practically does not cause Parkinsonism and dystonia. It may, however, cause akathisia [12].

Citrome et al. [13] distinguished four areas of particular importance in the long-term antipsychotic treatment: (1) cardiovascular and metabolic complications, (2) increased prolactin levels and their consequences (galactorrhoea, sexual and menstrual dysfunctions, osteoporosis), (3) excessive sedation, and (4) extrapyramidal symptoms and akathisia. Aripiprazole has been proved to be associated with the lowest incidence of side effects and the most favourable safety profile in the first three areas of all studied second generation antipsychotics. Aripiprazole did not cause clinically significant weight gain, metabolic disorders, development of diabetes mellitus, orthostatic hypotension and prolongation of QT interval in ECG. It did not cause sedation and decreased prolactin levels [13].

Dyskinesias rarely occur during treatment with aripiprazole because it is a partial agonist unlikely to cause up-regulation of dopamine receptors [5]. It is beneficial to add aripiprazole to other antipsychotics, because the combination with amisulpride, haloperidol and risperidone produces a decrease in prolactin levels [5]. It is also recommended to combine clozapine with aripiprazole in patients with drug-resistant schizophrenia. Such a combination improves positive and negative symptoms as well as clozapine side effects, such as weight gain and metabolic disorders [14].

Neuroleptic malignant syndrome (NMS) is a dangerous complication of antipsychotic treatment. Aripiprazole is associated with a lower incidence of NMS than other antipsychotics. Clinical manifestations of aripiprazole-induced NMS are "atypical" and rarely involve high fever and diaphoresis. Reported cases of aripiprazole-induced NMS involved younger patients who were promptly admitted to the intensive care unit, which might be the reason for low mortality [15].

Weight gain associated with antipsychotics, particularly the second generation, is often observed and it leads to many complications — circulatory disorders, diabetes and obesity with all its consequences [16]. One of the recent studies on this subject has shown that the mean aripiprazole-induced weight increase was 0.6 kg in short-term studies and 3.0 kg in long-term studies (one year). The studies confirmed aripiprazole's favourable side effect profile with regard to the metabolic risk when compared with other drugs, e.g. clozapine showed a mean weight increase of 4.27 kg over a 6-week observation period and 7.34 kg over a 38-week observation period [17]. The metabolic

safety of aripiprazole was confirmed in the most recent meta-analysis [18], which compared 18 different antipsychotic drugs. Aripiprazole is one of the top three safest drugs with regard to the metabolic profile (along with haloperidol and ziprasidone). The up-to-date analysis of tolerability of three dopamine D2/D3 receptor partial agonists used in the treatment of schizophrenia is also available (Table 2). It concludes that these are safe drugs with a low risk of sedation, extrapyramidal symptoms and hyperprolactinaemia. The risks for diabetes and tardive dyskinesia are unknown, but are likely to be low. Drugs of this group are associated with a risk of akathisia. Weight-gain risk is low with aripiprazole and cariprazine, but moderate with brexpiprazole [19].

Table 2. **NNT and NNH for aripiprazole, cariprazine and brexpiprazole compared to placebo in the treatment of schizophrenia**

Aripiprazole, dose 10–30 mg/day		
NNT	Response (≥ 30% reduction from baseline PANSS total score)	8
NNH	Akathisia	25
	Sedation	20
	≥ 7% increase in body weight from baseline	21
Brexpiprazole, dose 2–4 mg/day		
NNT	Response (≥ 30% reduction from baseline PANSS total score)	7
NNH	Akathisia	112 (ns)
	Sedation	50
	≥ 7% increase in body weight from baseline	17
Cariprazine, dose 1.5–6 mg/day		
NNT	Response (≥ 30% reduction from baseline PANSS total score)	10
NNH	Akathisia	15
	Somnolence and sedation	100 (ns)
	≥ 7% increase in body weight from baseline	34

Developed on the basis of [20].

NNT (Number Needed to Treat) – number of people who need to be treated in order for one person to receive a benefit; NNH (Number Needed to Harm) – number of people who need to be treated to cause one adverse event; PANSS – the Positive and Negative Syndrome Scale; ns = clinically not-significant

Brexpiprazole is a drug registered in Europe for the acute and maintenance treatment of schizophrenia. The American Food and Drug Administration (FDA) approved the drug as adjunctive therapy for major depressive disorder (MDD). Because brexpiprazole exhibits lower intrinsic activity at D2 receptors than aripiprazole [21], it is associated with a lower incidence of side effects, such as akathisia, insomnia, anxiety and nausea [22]. It is recommended to titrate the dose of brexpiprazole starting from 1 mg/day. In patients with schizophrenia the brexpiprazole dose can be titrated to

2 mg once daily on day 5 through day 7 and then to 4 mg on day 8. In MDD the dose should be titrated at weekly intervals up to the target dose of 2 mg/day. Two independent studies [23, 24] confirmed the efficacy of brexpiprazole in the treatment of acute schizophrenia. However, due to the inconsistent effects obtained at lower doses (2 mg/day), in clinical practice it may be necessary to use brexpiprazole at the higher end of the recommended dose range (4 mg/day). Moreover, higher doses of brexpiprazole were associated with significant improvement in the subscale of PANSS for the assessment of negative symptoms, disorganised thoughts and uncontrolled hostility/excitement (PANSS-EC). What is more, maintenance treatment with brexpiprazole was associated with a significantly longer remission than placebo over the 52-week observation period [25]. The same study showed significant benefits of using brexpiprazole with regard to psychosocial, occupational and cognitive functioning (particularly in terms of attention and visual learning). In contrast to aripiprazole [26], studies in animal models showed that brexpiprazole is associated with significant improvement in cognitive impairment in schizophrenia [26–28]. This may indicate the superiority of brexpiprazole over aripiprazole in the treatment of cognitive deficits [29]. However, short-term studies did not show any effect of brexpiprazole on cognitive functions. No head-to-head studies comparing brexpiprazole with aripiprazole were conducted. A favourable safety and tolerability profile of brexpiprazole was observed. The only common side effect was weight gain. In short-term studies the mean weight increase was 1 kg compared to patients in the placebo group. In the long-term perspective, the weight gain decreased both in patients receiving brexpiprazole and those receiving placebo. There was not any significant correlation between brexpiprazole and akathisia compared to placebo. However, higher doses induced it more often than low doses. Most of the side effects were mild or moderate and they were not the reason for the discontinuation of the treatment. The severity of other side effects, such as headache, insomnia, sedation, agitation, diarrhoea, nausea and dyspepsia were comparable to those induced by placebo. Brexpiprazole was found to have a minimal effect on glucose and lipid levels, as well as on prolactin levels. There was not any clinically significant effect of brexpiprazole on the QTc interval [30].

Cariprazine is registered for the treatment of schizophrenia and only FDA approved its use also in acute manic and mixed episodes of bipolar I disorder. Cariprazine is a D2/D3 dopamine receptor partial agonist but it displays 10-fold higher affinity for D3 than D2 receptors, which means that even very low doses of the drug lead to full saturation of the D3 receptor [31]. Inhibition of D3 receptors may have procognitive and antidepressive effects. It may also have a potential effect on the reduction of negative symptoms of schizophrenia [32]. Unlike other second generation antipsychotics, this unique aspect of cariprazine pharmacology (reduction of negative symptoms) is associated with preferential binding to dopamine D3 receptors, which is observed in studies using PET [33].

Pharmacological activity of cariprazine metabolites, desmethyl-cariprazine and didesmethyl-cariprazine, is similar to the parent drug, though didesmethyl-cariprazine has a much longer half-life (1–3 weeks vs 2–4 days). Thus, the systemic exposure to didesmethyl-cariprazine is several times higher than the biologic availability of cariprazine. Long half-life of didesmethyl-cariprazine may translate into the development of a once-a-week oral formulation which would significantly improve compliance and adherence to the treatment. Furthermore, compared to a formulation with a shorter half-life, there is a lower risk of sub-optimal receptor binding if a dose is missed. On the other hand, longer half-life may also lead to longer duration of side effects after treatment discontinuation [34].

The efficacy of cariprazine in the treatment of acute episodes of schizophrenia was studied in four trials [35–38]. The major advantage of cariprazine is its favourable profile in terms of negative symptoms. Following a post-hoc analysis suggesting this therapeutic effect of the drug [39], a 6-month, double-blind, risperidone-controlled trial was designed to assess the impact of cariprazine on negative symptoms.

The study confirmed that the efficacy of cariprazine in the treatment of predominant and persistent negative symptoms of schizophrenia is higher than that of risperidone [40]. The distinction between the two drugs emerged only after 14 weeks of treatment, that is much later than in patients with acute positive symptoms, which suggests other mechanisms of action. Improvement in PANSS total score and positive subscale score was similar for cariprazine and risperidone.

The superiority of cariprazine over placebo and aripiprazole in improving the PANSS-factor score for negative symptoms (PANSS-FSNS) emerged in post-hoc analyses of data pooled from two randomised, double-blind, placebo-controlled studies in patients with acute schizophrenia with moderate/severe negative symptoms and no predominance of positive symptoms. Importantly, the beneficial effect of cariprazine on negative symptoms was at least partially independent from improvements in positive and extrapyramidal symptoms [41]. A meta-analysis conducted by Corponi et al. [42] confirmed this specific domain of cariprazine efficacy and it also suggested that young patients with a relatively short history of disease may benefit the most from the drug. However, a limitation of this meta-analysis is that it included only short-term studies.

Hostility is another symptom domain targeted by cariprazine, as found by post-hoc analyses [43]. Notably, this beneficial effect was partially independent from PANSS positive symptom items and independent from sedation. On the other hand, the impact of cariprazine on acute positive symptoms appears similar to risperidone [42], but its efficacy in the treatment of predominant and persistent negative symptoms is higher [40].

Cariprazine is also a viable option for long-term treatment as showed by a 26 – to 72-week study investigating the time to first relapse in schizophrenia [44].

Study results suggest good safety and tolerability of cariprazine. Post-hoc analyses [45] showed that common adverse events with cariprazine were extrapyramidal

symptoms and akathisia, for which a dose-response relationship was observed. In a group of patients receiving cariprazine, a small weight increase (~1–2 kg) was reported compared to the placebo group. On the other hand, cariprazine does not induce changes in metabolic parameters or prolactin levels and it does not prolong the QT interval. Another noteworthy safety consideration is the low tendency to produce sedation and somnolence. Tolerability data over longer periods of time were similar to those observed in the 6-week trials [35–37, 40, 44, 46].

Mood disorders

There is evidence that dopamine (DA) may play an important role in the pathophysiology of affective disorders [47]. The dopamine hypothesis assumes that in the manic phase there is a hyperactivity of dopamine D2 receptor neurotransmission in mesolimbic structures resulting in the activation of regulatory mechanisms, i.e. reduction in the pre – and postsynaptic D2 receptor density. On the other hand, in depression, there is a decrease in dopamine neurotransmission observed and regulatory mechanisms lead to an increase in D2 receptor density [48]. Since "classic" antidepressant treatment is often ineffective in patients with affective disorders and there is a high incidence of drug-resistant depression, new therapeutic options, other than monoamine reuptake inhibitors, are much needed.

Aripiprazole is indicated for the treatment of moderate to severe manic episodes in bipolar I disorder in adults (15–30 mg/day) and in adolescents aged 13 years and older (10–30 mg/day) for a treatment duration of up to 12 weeks and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (therapy continued at the same dose). FDA approves other indications, including adjunctive therapy of major depressive disorder.

High doses of aripiprazole (> 15 mg/day) were proved to be effective in acute manic episodes. The mean odds ratio (OR) for the improvement in the acute manic episode for low doses of aripiprazole (< 15 mg/day) was 1.58 (95% CI: 0.8–3.13). For high doses of aripiprazole, OR for the clinical improvement in the manic episode was 3.00 (95% CI: 1.01–8.88) [49]. Another meta-analysis from 2017 proved the efficacy of high doses of aripiprazole in the treatment of manic episodes and in maintaining remission [50].

Polish standards of pharmacological treatment of manic episodes distinguish between moderate and severe manic episodes with agitation and/or psychotic symptoms [51]. In moderate manic episodes, second generation antipsychotics (aripiprazole/olanzapine/quetiapine) in combination with a classic mood stabiliser (MS) (lithium/valproate) are recommended as the second-line treatment. In severe manic episodes (with agitation and/or psychotic symptoms) combination therapy is used as the first-line treatment. If a patient refuses to take medication orally, injections (aripiprazole,

olanzapine, haloperidol, zuclopenthixol) should be administered. It is recommended to switch to oral medication (MS + SGA) as soon as possible.

Guidelines of the Canadian Network for Mood and Anxiety Treatments (CANMAT) recommend aripiprazole as the first-line treatment (both in monotherapy and in combination with valproate or lithium) of manic episodes and maintenance treatment [52]. Guidelines of the International College of Neuro-Psychopharmacology (CINP) from 2017 recommend aripiprazole monotherapy as the first-line treatment of manic episodes and maintenance treatment. Aripiprazole is particularly beneficial for patients with manic episodes with psychotic features and rapid cycling [53].

A meta-analysis from 2018 showed that in bipolar depression aripiprazole was not superior to placebo (OR 0.98, 95% CI: 0.7–1.37), whereas in patients with MDD, both low and high doses of aripiprazole were effective in combination therapy with an antidepressant. For low doses the odds ratio for remission was 1.68 (95% CI: 1.13–2.5), and for clinical response 1.8 (95% CI: 1.06–3.04). For high doses the odds ratio for remission was 1.96 (95% CI: 1.56–2.47) and for clinical response 1.93 (95% CI: 1.56–2.39). Safety and tolerability of the treatment were also assessed in the meta-analysis. There were no significant differences in tolerability and side effects between the doses of aripiprazole [49]. Low doses of aripiprazole are used and approved by FDA as adjunctive treatment of drug-resistant major depressive disorder [54]. Although aripiprazole is not registered for this indication in Poland, the national consultant in psychiatry recommends doses from 2 mg to 20 mg/day [55]. Aripiprazole is not only the most effective of antipsychotics in combination treatment with SSRI and SNRI, but it is also safe and well tolerated in combination with electroconvulsive therapy (ECT) [56].

Brexpiprazole was approved by FDA in 2015. Apart from schizophrenia treatment, it is registered as an adjunctive therapy to antidepressants in the treatment of MDD. Affective disorders were not included by the European Medicines Agency (EMA) as the registered indication for the use of brexpiprazole although it has been proved to be effective in the treatment of drug-resistant depression [57]. The meta-analysis of randomised clinical trials (RCTs) evaluating the efficacy of adjunctive brexpiprazole 1–3 mg/day in patients with MDD and inadequate response to antidepressants showed that brexpiprazole was superior to placebo in terms of improvement of mood disorders and the percentage of patients with therapeutic response and remission (OR respectively: 1.57 and 1.96) [58]. The meta-analysis of Romeo et al. [49] from 2018 also showed the advantage of brexpiprazole as an adjunct to antidepressants over placebo in terms of symptomatic remission (OR 1.52) and clinical response (OR 1.73). Another systematic review and meta-analysis, published in 2019 [59], revealed that brexpiprazole adjunctive treatment is effective for major depressive disorder when antidepressant treatment fails. At 6 weeks, doses ≤ 2 mg/day presented a better risk/benefit balance than doses > 2 mg/day.

There is only one open-label study performed on a small group of patients ($n = 21$) evaluating the efficacy of brexpiprazole in the treatment of bipolar depression. The drug was administered for 8 weeks at a dose of 2–4 mg/day. Significant reduction in depressive symptoms was observed. After 4 and 8 weeks, treatment response criteria were fulfilled by, respectively, 68.4% and 73.6% of the study group. Improvement in the quality of life was also observed [60].

EMA approved cariprazine for the treatment of adult patients with schizophrenia, whereas FDA also registered the drug for the treatment of manic, mixed and depressive episodes associated with bipolar disorder. There are studies suggesting the usefulness of cariprazine as adjunctive therapy for MDD [61].

The efficacy of cariprazine in the treatment of acute manic and mixed episodes was evaluated in three 3-week RCTs. Cariprazine was used at a dose of 3–12 mg/day and it proved to be significantly more effective than placebo in terms of symptom reduction and the percentage of patients with clinical improvement [38, 62, 63]. The meta-analysis of Romeo et al. [49] showed that the odds ratio for remission with cariprazine monotherapy was 2.08 (95% CI: 1.57–2.75), and for clinical response 2.25 (95% CI: 1.71–2.95), which indicates that cariprazine is highly effective in the treatment of manic episodes.

Cariprazine was also used in the treatment of depressive episodes in bipolar I disorder. Cariprazine at 1.5 mg/day demonstrated consistent efficacy, whereas cariprazine at 0.75 mg/day and 3 mg/day was not superior to placebo [64, 65]. In another study, 8-week therapy with cariprazine, at both 1.5 mg/day and 3 mg/day, resulted in a positive clinical effect [66]. In a recently published study, cariprazine at 1.5-3 mg/day consistently improved depressive symptoms in all patient subgroups with bipolar depression without regard to differences in baseline demographic and clinical characteristics [67]. Further studies should verify if cariprazine is effective in the long-term treatment of patients with bipolar disorder.

Cariprazine was also used as adjunctive therapy in patients with major depressive disorder who did not respond to monotherapy with an antidepressant. RCTs which evaluated the efficacy of such a treatment strategy showed heterogeneous, including negative, results [68], which means that the efficacy of adjunctive cariprazine cannot be clearly stated and further studies are needed [61].

Anxiety and anxiety-related disorders, post-traumatic and stress-related disorders

Anxiety disorders are a heterogeneous group of disorders, in the treatment of which psychotherapy plays an important role. However, if the symptoms are severe, in the case of other coexisting mental disorders, particularly depression, or unavailability of psychotherapy, pharmacotherapy is often used. First-line treatment includes antidepressants from the group of selective serotonin reuptake inhibitors (SSRI) and serotonin

norepinephrine reuptake inhibitors (SNRI). Other drugs are used if antidepressants are not well tolerated or in order to augment their effects [69]. Due to the severity of symptoms and the risk of not achieving full remission it might be necessary to search other pharmacotherapy options, particularly in post-traumatic stress disorder (PTSD) and generalised anxiety disorder (GAD).

SSRIs are considered the first-line treatment for patients with PTSD as they affect the whole spectrum of symptoms and improve the quality of life and behavioural functions [69]. Despite relatively high effectiveness of SSRIs, 20–40% of patients with PTSD do not respond to the treatment and require adjunctive therapy. There is an increasing body of evidence that second generation antipsychotics are effective adjunctive agents in the treatment of PTSD. Study results show that treatment outcomes (assessed with PTSD symptom severity scales) are better for patients receiving olanzapine, risperidone and quetiapine. It is associated with the fact that 36-46% of patients with PTSD experience psychotic symptoms. Aripiprazole used in the treatment of PTSD at a mean dose of 9.6 ± 4.3 mg/day proved to be well tolerated and effective in the treatment of sleep disorders, such as nightmares, and in reducing anxiety throughout the day. In patients with PTSD receiving aripiprazole, improvement was observed not only in terms of general symptoms of the disease, but also depression, anxiety, social adjustment and the quality of life [70].

Drugs of proven efficacy in the treatment of GAD are antidepressants (SSRIs, SNRIs, tricyclic antidepressants — TCAs), pregabalin and quetiapine. Benzodiazepines may be used temporarily. The efficacy of aripiprazole in the treatment of GAD was proved in two open-label, non-randomised trials performed on a small group of patients ($n = 9$ and $n = 13$) who did not achieve remission with SSRIs and SNRIs. Aripiprazole used at low starting doses of 2.5–10 mg/day reduced anxiety and improved the general mental state of patients assessed with the Hamilton Anxiety Rating Scale (HAM-A) and the Clinical Global Impression scale (CGI). Augmentation of antidepressants with aripiprazole was well tolerated. Treatment had to be discontinued due to adverse reactions in 11% and 13% of patients [71, 72].

Psychotherapy should be the method of choice in the treatment of other anxiety disorders, specific phobias and social anxiety. In the case of incomplete remission, it is recommended to intensify psychotherapy. In an open-label, non-randomised trial involving 10 patients with panic disorder and GAD, aripiprazole at a starting dose of 2.5 mg/day was proved to be a useful augmentation strategy for SSRIs and SNRIs [72].

Obsessive-compulsive disorder and other related disorders

Antipsychotics are not approved for the treatment of obsessive-compulsive disorder (OCD). However, in clinical practice, risperidone, paliperidone and aripiprazole, and then haloperidol as a drug of further choice, are used as augmentation when the treatment with at least two drugs registered in the treatment of OCD (i.e. SSRI and

clomipramine) has proved to be ineffective. However, before starting the augmentation therapy with an antipsychotic, antidepressants should be used for a sufficiently long time, that is for at least 12 weeks, including at least 6 weeks on the maximum well-tolerated dose [69].

Aripiprazole is often used as an adjunct for the treatment of OCD due to the favourable side effect profile compared to other antipsychotics. The risk of clinically significant akathisia, which is observed in up to 10% of patients receiving aripiprazole, is lower than for other antipsychotics which are potent dopamine D2 receptor antagonists [73]. The efficacy and tolerability of aripiprazole as an adjunct in the treatment of OCD has been proved in numerous case reports, open-label studies and in two randomised trials [74, 75]. In the studies patients received aripiprazole in a dosage of 10 mg/day or 15 mg/day for 12 or 16 weeks. The most common side effect that resulted in treatment discontinuation was excessive sedation. Open-label studies and case reports most often concern augmentation with aripiprazole of OCD treatment with antidepressants. There are only a few case reports on aripiprazole monotherapy in OCD, including reports on patients with schizophrenia and OCD symptoms induced by clozapine and olanzapine treatment. Single case reports suggested that OCD symptoms may be induced by aripiprazole used in the treatment of schizophrenia or bipolar disorder [73]. There is a case report of a patient with schizophrenia, in whom rapid remission of OCD symptoms was observed after adding cariprazine to long-acting paliperidone injections [76]. Reports on the use of brexpiprazole in the treatment of OCD have not been published so far.

Substance use disorders and addictive behaviours

Pre-clinical efficacy was the basis for the assumption that dopamine D2 and D3 receptor partial agonists and antagonists may prevent the recurrence of addiction in people. Although the drugs were not registered for this indication, they were the hope for a wider spectrum of pharmacological agents available in the treatment of addictions. Martinotti et al. [77] proved that aripiprazole decreased craving in alcohol-dependent patients with schizophrenia. Vergne and Anton [78] associated aripiprazole treatment with reduced craving and reduced money spent by alcohol-dependent patients with bipolar and schizoaffective disorders. Beresford et al. [79] observed reduction in cocaine craving in patients with schizophrenia treated with aripiprazole. Voronin et al. [80] showed significant reduction of alcohol consumption in patients treated with aripiprazole compared to placebo. In the same work the authors noted decreased impulsiveness, measured by the Barratt Impulsiveness Scale (BIS), in patients treated with aripiprazole compared to placebo. In the summary of studies on aripiprazole, Kranzler et al. [81] suggested that the effects of the drug were moderate and dose-dependent. However, it significantly increased sedative effects of alcohol and, consequently, reduced its euphoric effects [82].

Anton et al. [83] showed that one-week therapy with aripiprazole (15 mg/day) reduced the intake of alcohol compared to placebo. Alcohol-dependent, non-treatment seeking patients were stratified according to their BIS score. Individuals within each BIS strata (high: ≥ 68, low: ≤ 67) were further stratified based on sex and smoking status. Baseline drinking was greater in the aripiprazole group than the placebo group and it was included in the analyses as a covariate. It was concluded that among patients with low self-control and high impulsivity, those treated with aripiprazole showed lower alcohol consumption and longer latencies between drinks.

Personality disorders and impulse control disorders

Antipsychotics can be used in the treatment of personality disorders off-label, which means that they should be considered only when other recommended therapeutic options, mainly psychotherapy, are ineffective or unavailable. Moreover, data on the use of antipsychotics in the treatment of personality disorders come from small studies with significant methodological limitations. Therefore, guidelines and recommendations cannot be based on these study results. It should be remembered that doctors are bound to explain to patients the implications of the off-label use of a drug to ensure that the patient can give informed consent.

Pharmacotherapy data are available mainly for borderline personality disorder (BPD). They are, however, inconsistent and there are only single randomised, placebo-controlled studies, meta-analyses and systematic reviews on this subject [84]. These publications confirm the efficacy of selected drugs in the treatment of major BPD symptoms. It concerns mainly antiepileptic drugs and second generation antipsychotics, including aripiprazole. Patients with BPD have higher levels of dopamine metabolites in the cerebrospinal fluid. They may also experience brief psychotic symptoms and attention deficits, which suggests there is a link between the dopaminergic system and BPD. SGA may improve major symptoms of BPD, such as emotional dysregulation with frequent negative affective states, impulse control disorders, psychotic symptoms or interpersonal relationship dysfunctions [85]. Aripiprazole proved to be effective and well tolerated in two RCTs conducted in a group of patients with BPD, whereas in another study, aripiprazole and olanzapine proved to be comparably effective [84, 86].

In one of the studies, aripiprazole was effective in the treatment of schizotypal personality disorder (SPD). Two-month treatment with aripiprazole 10 mg/day resulted in at least 70% reduction of symptoms. The study concluded that aripiprazole, being a dopamine-serotonin system stabiliser with a favourable side effect profile can be used to treat the odd and eccentric behaviour, stereotyped thinking, social anxiety symptoms, and obsessive symptoms [87]. There are also literature reports on the efficacy of aripiprazole in self-harm, that may be associated with personality disorders [88].

Studies on the use of brexpiprazole and cariprazine in the treatment of personality disorders have not been published yet. There was only one study which concluded

that brexpiprazole was associated with a greater improvement in impulsive personality traits assessed by the Barratt Impulsiveness Scale-11 (BIS-11) than aripiprazole. It is an important finding because impulsiveness is associated with poorer treatment outcomes in patients with schizophrenia, and behavioural aspects of impulsiveness include agitation, aggression, hostility, substance abuse and risky behaviours [89, 90]. These recommendations, however, should be treated with caution as brexpiprazole is only an auxiliary drug in the treatment of personality disorders and it is used off-label in this group of patients.

Neurodevelopmental and tic disorders

According to current medical knowledge, there is no effective pharmacological treatment of core autism symptoms. However, guidelines of the American Academy of Children and Adolescent Psychiatry (AACAP) recommend pharmacological treatment in patients with autism spectrum disorder (ASD) in order to reduce serious behavioural problems and comorbid conditions that may impair their functioning in a peer environment and limit their access to education and therapeutic interventions. In this group of patients, pharmacotherapy is used mainly for comorbid mental disorders (according to the guidelines of scientific societies for specific diagnoses and age groups), aggressive or auto-aggressive behaviours and sleep problems [91]. Aripiprazole is currently approved by FDA for the treatment of irritability associated with ASD in children aged 6 years or older. Although it is not approved for use in this indication in Poland, it is prescribed off-label. Aripiprazole, along with risperidone, is recommended in the guidelines of AACAP for patients with ASD who exhibit severe tantrums and physical aggression. The combination of pharmacotherapy and psychotherapy has been proved to be significantly more effective with regard to behavioural disorders and patient's functioning. In the review by Bartram et al. [92] from 2019 including 5 RCTs, aripiprazole was proved to be significantly more effective than placebo and comparably effective to risperidone in the reduction of irritability in this group of patients [92]. The most common side effects observed during treatment were fatigue, tremor, changes in appetite and vomiting.

Antipsychotics have been used in the treatment of tic disorders since the 1950s. APDs remain the most effective therapeutic option which significantly reduces severity of tics in up to 70% of patients. However, they are also associated with numerous limitations, namely side effects, including irreversible ones (tardive dyskinesia). This is particularly important in children and adolescents, in whom tic disorders, including Gilles de la Tourette syndrome (GTS), are self-limiting and have an overall positive prognosis. The treatment of adults in whom the disorder, usually beginning in childhood, did not spontaneously remit is different. For this reason, there are different treatment recommendations for different age groups: in children, the method of choice is psychotherapy, and pharmacotherapy is used only when psychotherapy is unavailable,

ineffective or when the symptoms are very severe and impair the patient's functioning. There are also differences with regard to the choice of pharmacotherapy. Some guidelines recommend starting the therapy with alpha-mimetics. Aripiprazole was proved to be effective in children and adolescents with GTS in two RCTs [93, 94]. Open-label studies also showed significant efficacy of aripiprazole in the reduction of tic frequency. It should also be noted that the average dose of aripiprazole used in the open-label studies was 2.8–11.7 mg/day, that is significantly lower than the dose used in schizophrenia. Data on the safety of aripiprazole in the treatment of tic disorders were pooled in the systematic review [95]. The safety analysis included 50 studies which involved 2,604 patients. The most common side effects reported in the controlled studies included somnolence (17.2%), increased appetite (13.5%), excessive sedation (13.2%) and gastrointestinal problems (9.7%). In conclusion, aripiprazole seems to be an effective and well-tolerated drug in the treatment of tic disorders in patients who meet overall criteria for the initiation of pharmacotherapy. FDA approved the use of aripiprazole in this indication in 2016.

Cariprazine and brexpiprazole are not currently approved for the treatment of ASD, but they can be used in patients with ASD and comorbid mental disorders (schizophrenia in adults). There are also no studies on the use of these drugs in patients with ASD.

Summary

D2/D3 dopamine receptor partial agonists (aripiprazole, brexpiprazole and cariprazine) are antipsychotics that are atypical in a different manner than other SGA because of their selective profile of action and intrinsic activity at dopamine D2 (aripiprazole > brexpiprazole) and D3 (cariprazine) receptors. This results in clinically significant differences between this group of drugs and other SGA, mainly with regard to safety and tolerability of the treatment. Compared to the majority of first and second generation antipsychotics, D2/D3 dopamine receptor partial agonists are associated with a lower risk of weight gain, metabolic disorders, extrapyramidal symptoms, excessive sedation, hyperprolactinaemia and prolongation of QT interval in ECG. This favourable tolerability profile does not mean that they are less effective in the treatment of schizophrenia or bipolar disorder than other antipsychotics. On the contrary, D2/D3 dopamine receptor partial agonists exhibit efficacy comparable to other antipsychotics in terms of positive symptoms of schizophrenia (except for clozapine) and they seem more effective in terms of negative symptoms of the disease (particularly cariprazine). They are also an important therapeutic option in the treatment of bipolar disorder and depression, although they are not approved for this indication in Europe (Table 3).

Due to the favourable tolerability profile of D2/D3 dopamine receptor partial agonists, the drugs are also used off-label for mental disorders other than schizophrenia and bipolar disorder, in which adjunctive treatment is needed (Table 3) and in special

populations, in which the safety of the treatment is important, e.g. in patients with somatic diseases, the elderly, children and adolescents [96].

Table 3. **Strength of evidence for studies on the use of D2/D3 dopamine receptor partial agonists in the treatment of mental disorders**

Indication	Recommending organisations	Class of recommendations and EBM level of evidence	Starting dose; recommended dosage [mg/day]
Aripiprazole — approved indications in Europe			
Treatment of schizophrenia in adults	EMA, FDA	I, A	10–15; 10–30
Treatment of schizophrenia in adolescents aged 15 years or older	EMA, FDA	1, A	2; 10–30
Treatment of moderate and severe manic episodes in bipolar I disorder and the prevention of a new manic episode in adults	EMA, FDA	I, A	15; 15–30
Treatment up to 12 weeks of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 years and older	EMA, FDA	I, A	2; 10
Aripiprazole — off-label indications in Europe			
Adjunct to antidepressants for the treatment of major depressive disorder (MDD)	FDA	I, A	2–5; 5–15
Treatment of irritability associated with autistic disorders	FDA	I, A	2, 5–15
Tic disorders, including Gilles de la Tourette syndrome	FDA	I, B	2; 5–20
Adjunct to antidepressants for the treatment of obsessive-compulsive disorder	recommendations of scientific societies	IIa, A	2–5; 5–30
Alcohol and stimulants dependence	none	IIb, C	2–5; 5–30
Post-traumatic stress disorder, generalised anxiety disorder	none	IIb, C	2–5; 5–30
Borderline personality disorder, schizotypal personality disorder	none	IIb, C	2–5; 5–30
Aripiprazole in fast-acting injections			
Rapid control of agitation and disturbed behaviours in patients with schizophrenia or with manic episodes in bipolar I disorder, when oral therapy is not appropriate	EMA, FDA	I, A	9.75; 9.75–30
Aripiprazole in long-acting injections (LAI)			
Maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole	EMA	I, A	400; 300–400

table continued on the next page

Treatment of schizophrenia in adults	FDA	I, A	400; 300–400
Maintenance treatment for bipolar I disorder, also in monotherapy	FDA	I, A	400; 300–400
Brexpiprazole — approved indications in Europe			
Treatment of schizophrenia in adults	EMA, FDA	I, A	1; 2–4
Brexpiprazole — off-label indications in Europe			
Adjunct to antidepressants in the treatment of major depressive disorder (MDD)	FDA	1, A	0.5–1; 2–3
Cariprazine — approved indications in Europe			
Treatment of schizophrenia in adults	EMA, FDA	1, A	1.5; 1.5–6
Cariprazine — off-label indications in Europe			
Treatment of acute manic and mixed episodes in bipolar I disorder in adults	FDA	1, A	1.5; 3–6
Treatment of depressive episodes in bipolar I disorder in adults, also in monotherapy	FDA	1, A	1.5; 1.5–3

EBM — evidence-based medicine. Class of recommendations: I — evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective, II — conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure, IIa — weight of evidence/opinion is in favour of usefulness/efficacy, IIb — usefulness/efficacy is less well established by evidence/opinion, III — evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. EBM level of evidence: A — data derived from multiple randomised clinical trials or meta-analyses of such studies, B — data derived from single randomised clinical trial or large non-randomised studies, C — consensus opinion of experts and/or small studies, retrospective studies, registries. EMA — European Medicines Agency; FDA — Food and Drug Administration

Treatment with D2/D3 dopamine receptor partial agonists should be started with low doses due to their agonist action towards D2 dopamine receptors which may cause nausea, restlessness and insomnia. Starting at a low dose is particularly important for aripiprazole and during a switch from potent inhibitors of D2 dopamine receptors, e.g. haloperidol, risperidone, paliperidone or amisulpride. Then, the dose should be titrated, taking into consideration the long biological half-life (T1/2) of agents from this group. As a result, serum levels of the drug increase slowly and when side effects occur, they may last longer than for other antipsychotics. Apart from nausea, restlessness and insomnia, the side effect that may be troublesome is akathisia. When partial agonists are used in the treatment of depression and anxiety disorders, akathisia should be considered as one of the possible causes of restlessness and irritability.

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