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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 special populations

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**Summary**

D2/D3 dopamine receptor partial agonists (aripiprazole, brexpiprazole, cariprazine) are increasingly often used in the treatment of mental disorders due to a more favourable tolerability profile as compared to other antipsychotics. The article presents the position statement on the use of these drugs in the treatment of special populations: people with comorbid somatic diseases, people over 65 years of age, including those with dementia, children and adolescents, pregnant and breastfeeding women.

The position statement was developed by the panel of experts appointed by the Executive Board of the Polish Psychiatric Association consisting of people experienced in the treatment of patients with mental disorders. The evaluation included the analysis of literature databases

and information obtained from summaries of product characteristics, as well as reports and registers on the safety of the three evaluated drugs.

D2/D3 dopamine receptor partial agonists can be used in the treatment of people who must be provided with the highest safety standards of the therapy. It results from their low risk of producing side effects, such as weight gain, metabolic disorders, akathisia, extrapyramidal symptoms, increased prolactin levels, prolongation of QT interval in ECG, sedation and anticholinergic effects. Since dopamine receptor partial agonists are available for a relatively short time, there is less information on their use in pregnant women than for other antipsychotics.

**Key words:** antipsychotic drugs, special populations, D2/D3 dopamine receptor partial agonists

## Introduction

Since their introduction, second generation antipsychotics (SGAs) have become increasingly often used in the treatment of mental disorders, not only in registered indications, but also off-label [1]. In order to ensure the safety of the therapy, it is necessary to constantly monitor their side effects, particularly those associated with weight increase, metabolic disorders and cardiovascular diseases [2]. In terms of their clinical profile of action and tolerability, D2/D3 dopamine receptor partial agonists, that is aripiprazole (ARI), brexpiprazole (BREX) and cariprazine (CARI), constitute a distinctive group of antipsychotics. They differ significantly from other SGAs and represent a different approach to the concept of "atypicality" [3].

The objective of the article is to present the position statement of the expert group of the Polish Psychiatric Association on the use of ARI, BREX and CARI in the treatment of special populations who must be provided with high safety standards of the therapy. It concerns mainly people with comorbid somatic diseases, people over 65 years of age, including those with dementia, children and adolescents, and pregnant and breastfeeding women.

## Method

The position statement was developed by the panel of experts appointed by the Executive Board of the Polish Psychiatric Association. The panel consisted of people experienced in the treatment of patients with mental disorders. On the basis of literature review, information obtained from summaries of product characteristics, as well as reports and registers on the safety of the three evaluated drugs, experts have developed a position statement in the form of reports and presentations. The materials were discussed at an online working meeting and then presented to the Executive Board of the Polish Psychiatric Association. After considering remarks, the position statement was accepted as the opinion of the Association on the use of this group of drugs in the treatment of special populations.

## Safety of aripiprazole, brexpiprazole and cariprazine in selected somatic diseases and conditions

People with mental disorders suffer from comorbid somatic diseases significantly more often than people from the general population. This contributes to the decreased level of their functioning and the quality of life, worse prognosis and decreased effectiveness of treatment of both mental and somatic disorders, as well as increased mortality. Somatic disease may also reduce the choice of pharmacotherapy due to contraindications to some antipsychotics [4]. For this reason, it is necessary to take into consideration the potential risk associated with the use of the drug in somatic comorbidities at the beginning of the treatment or before a switch of antipsychotics. A summary of the safety profile of ARI, BREX and CARI in selected somatic diseases is presented in Table 1.

Table 1. **The risk of complications or worsening of somatic diseases during treatment with aripiprazole (ARI), brexpiprazole (BREX) and cariprazine (CARI)**

| | Disease/somatic condition that requires attention | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug | Diabetes mellitus | Dyslipidaemias | Obesity | QT prolongation | Leukopaenia/ neutropaenia | Epilepsy | Parkinson's disease | Glaucoma | Liver damage | Hyperprolactinaemia | Liver or kidney impairment |
| ARI | L | L | L | L | L/M | L | M | L | L | L# | L* |
| BREX | (L) | L | L/M | L | (L) | (L) | ? | (L) | (L) | L# | L** |
| CARI | (L) | L | L | L | (L) | (L) | ? | (L) | (L) | L | L*** |

The risk of complications or worsening of somatic diseases: L – low; (L) – probably low, requires further verification; M – moderate; ? – unknown, difficult to estimate; * – no dosage adjustment is required, caution required in severe impairment; ** – in moderate and severe impairment the dose should be reduced to 1.25 mg in the treatment of depression and to 3 mg in the treatment of schizophrenia; *** – no dosage adjustment is required in mild and moderate impairment, contraindicated in severe impairment; # – possibility to normalise prolactin levels in patients with hyperprolactinaemia induced by other antipsychotics

### Diabetes mellitus and metabolic disorders

In the literature review on patients with diabetes treated with SGAs, a total of 83 cases (mainly of patients treated for schizophrenia or other psychotic disorders) of ketoacidosis were described; only 6 cases were aripiprazole-induced; most of them were associated with olanzapine (32) and clozapine (19) [5]. So far, there has been one report of hyperosmolar hyperglycaemic state with subsequent coma in an alcohol-

dependent patient with schizophrenia, without a history of diabetes mellitus, treated with aripiprazole, benzatropine, valproic acid, clonazepam and diphenhydramine [6]. Most of the available randomised controlled trials (RCTs) (mainly including patients diagnosed with schizophrenia) and their meta-analyses or post-hoc analyses indicate that the risk of adverse metabolic changes – such as increased fasting glucose (FG), total cholesterol (CHL), low-density lipoproteins (LDL), high-density lipoproteins (HDL) or triglycerides (TG) – associated with ARI treatment is comparable to that with placebo, lower than for olanzapine (OLA), quetiapine (QUE) or clozapine (CLO) and that the treatment with ARI is associated with a lower risk of diabetes and cardiovascular diseases than for QUE, OLA or risperidone (RIS) [7–9]. ARI is not associated with clinically significant weight gain compared to placebo, and the aripiprazole-induced weight gain is significantly lower than for OLA, RIS, QUE, CLO, sertindole and iloperidone [9–11]. There are also studies showing that in subjects diagnosed with schizophrenia the addition of ARI as adjunctive therapy to OLA, RIS, CLO or QUE helps to reduce body weight [12] and that in patients treated for schizophrenia or schizoaffective disorder the switch from OLA, RIS or QUE to ARI provides an opportunity to improve the components of metabolic syndrome (including reduction of body weight) and reduce the 10-year risk of a fatal cardiovascular disease event [13, 14].

There have been no reports of worsening of the course of diabetes in patients treated with BREX. Results of the short-term RCTs and long-term observations show that the percentage of patients with schizophrenia or major depressive disorder (MDD) who experience adverse effects of the drug on glucose levels were comparable in the group of BREX and placebo and that in most patients with MDD treated with BREX, a decrease in glucose levels was observed more often than an increase [15]. There have been no reports of significant changes in CHL, LDL, HDL and triglyceride levels in patients treated with BREX compared to placebo (in the long-term study there was a slight increase of 15 mg/dL of TG observed) [15]. Data on the effects of BREX on body weight are inconclusive – a meta-analysis by Huhn et al. [10] did not show any significant differences in body weight between patients receiving BREX and placebo. In this respect, there were also no differences found between ARI, CARI and BREX. On the other hand, the meta-analysis of three short-term RCTs conducted in patients with schizophrenia showed that brexpiprazole-treated patients had three times higher risk of increase in body weight ≥ 7% from baseline compared to placebo [16]. Similarly, the meta-analysis of Pillinger et al. [9] showed that BREX was one of the antipsychotics associated with greater weight gain than placebo. On the basis of statistical analyses, authors of the meta-analysis ranked antipsychotics by their weight gain risk and BREX was found to be in the middle of the list. Barton et al. [11] showed in their meta-analysis that NNH (number needed to harm) for clinically significant weight increase in BREX-treated patients was 20 compared to placebo.

So far, there have been no reports on the safety of CARI in patients with diabetes. Most of the short-term studies including patients with schizophrenia and mania showed that treatment with CARI is not associated with a higher risk of increase in glucose levels than placebo or ARI [9, 17]. Less numerous data show a statistically significant but clinically insignificant increase in blood glucose levels compared to placebo [18]. Phase 2 and 3 studies preceding the European Medicines Agency approval of CARI for the treatment of schizophrenia showed that diabetes mellitus was diagnosed *de novo* in < 1% of patients. Available data suggest that the treatment with CARI is associated with a similar risk of increase in total cholesterol, LDL, HDL and triglyceride levels as placebo [9] and a similar, low risk of weight gain [9, 10]. NNH for cariprazine-induced, clinically significant weight gain was 50 compared to placebo [11].

In summary, ARI, CARI and BREX may be considered the first-line treatment for patients with diabetes, metabolic syndrome or its components who require the use of antipsychotics. The issue of the risk of BREX-induced weight increase requires more consideration.

## Cardiac conduction disorders

Results of meta-analyses including data pooled from thousands of patients treated with ARI showed that ARI is not associated with an increased risk of the prolongation of the QT interval. Since the introduction of ARI to the market, there have been only 15 reports of QT interval prolongation and 21 reports of Torsades de Pointes in patients using aripiprazole in combination with other psychotropic drugs [10, 19]. The meta-analysis by Huhn et al. [10] based on 402 RCTs showed that the treatment with BREX was not associated with greater QT prolongation than with placebo. Since the introduction of BREX to the market, there have been no reports of QT interval prolongation or Torsades de Pointes in patients treated with BREX (also in combination with other drugs) [10, 19]. The available data also indicate that CARI is not associated with an increased risk of QT prolongation compared to placebo [10]. In conclusion, ARI, BREX and CARI are characterised by an exceptionally low risk of cardiac conduction disorders and arrhythmias and for this reason they should be considered the first-line treatment for patients with QT prolongation or risk of QT prolongation who require the use of antipsychotics.

## Hyperprolactinaemia

On the basis of available RCTs it may be concluded that ARI is associated with a significantly lower risk of hyperprolactinaemia than placebo [10]. It has also been reported that a switch from typical antipsychotics (haloperidol, thioridazine), OLA or RIS to ARI was associated with a decrease in prolactin levels [20]. Moreover, it was found that the addition of ARI to OLA, RIS, amisulpride or sulpiride resulted in a de-

crease in prolactin serum levels [21]. In a small group of patients (< 5% of those treated with ARI) with a rare combination of polymorphisms in genes encoding CYP2D6 and CYP3A enzymes, D3 receptors and P-glycoprotein, treatment with ARI resulted in an increase in prolactin levels [22]. The meta-analysis of Huhn et al. [10] showed that treatment with BREX was not associated with a significant increase in prolactin levels compared to placebo. The analysis of three short-term RCTs including patients with hyperprolactinaemia showed that treatment with BREX resulted in a normalisation of prolactin levels. Studies conducted so far have shown that the proportions of brexpiprazole-treated patients with more than 3x upper limit of normal prolactin values were ≤ 1% in short-term studies and ≤ 3% in long-term studies [23]. The meta-analysis of available studies also showed that treatment with CARI did not result in an increase in prolactin levels compared to placebo [10]. The above data indicate that ARI, CARI and BREX may be considered the first-line treatment for patients with hyperprolactinaemia (regardless of its cause) who require the use of antipsychotics or patients with a history of antipsychotic-induced hyperprolactinaemia.

### Liver and kidney diseases

Available data suggest that no adjustment in the dose of ARI is required in patients with hepatic and kidney impairment [24]. There have been no reports of aripiprazole-induced hepatic or kidney dysfunctions. A case-control study involving patients with the diagnosis of chronic kidney disease (CKD) and healthy controls showed that the treatment with all antipsychotics (QUE, CLO, OLA, RIS), except for ARI, was associated with an increased risk of CKD [25]. In the RCTs involving patients with schizophrenia, only one person receiving BREX had a rise in serum levels of aspartate aminotransferase [26] and one patient was diagnosed with non-alcoholic fatty liver disease. In the long-term study, a significant increase in serum liver enzymes was observed in two patients [27]. There have been no reports of BREX-induced kidney disorders. It should be noted that the dose of BREX should be modified in patients with moderate and severe liver and kidney impairment; the maximum daily dose of the drug in the treatment of patients with schizophrenia is 3 mg, and in MDD — 1.25 mg. No dosage adjustment of CARI is required in mild and moderate hepatic and kidney impairment. Cariprazine is not recommended in patients with severe hepatic and renal impairment due to the lack of data.

### Blood disorders

There are several case reports of patients who developed neutropaenia and/or leukopaenia or thrombocytopaenia after introduction of ARI or the addition of ARI as adjunctive therapy. In all cases discontinuation of ARI resulted in the normalisation of blood count (one person was also given granulocyte growth factor) [28, 29].

Currently, there are no studies assessing the impact of BREX or CARI on the bone marrow function, but there are also no case reports of any abnormalities in blood count resulting from their use.

### Epilepsy

In the study assessing the risk of antipsychotic-induced seizures and including patients with schizophrenia, bipolar disorder (BD) and MDD from Taiwan, aripiprazole, as opposed to other antipsychotics, was the only drug with a lower risk of seizures and epilepsy than RIS [30]. To date, there have been no studies published on the safety of ARI, BREX or CARI in the treatment of patients with epilepsy. There have been isolated reports of seizures in patients treated with BREX, and the studies on the efficacy of CARI reported the incidence of seizures to be less than 1 in 1,000 patients. Available data show that ARI may be considered one of the least seizure-inducing antipsychotics; CARI and BREX also appear safe in this respect, but this requires further verification and caution is advised when using these drugs in patients with epilepsy.

### Parkinson's disease

The American Geriatrics Society (AGS) does not recommend the use of ARI in patients with Parkinson's disease (PD) due to the significant risk of worsening motor functions [31], as shown in case reports and in two open-label studies including small groups of patients [32]. It may be related to the high affinity of ARI for D2 receptors and the predominance of antagonistic effects over agonist effects on these receptors [3]. There are no studies or case reports on the safety of CARI in patients with PD. There is one case report of an 82-year-old female patient with Parkinson's disease psychosis treated with BREX with good effect and tolerability [33]. For the above reasons, the use of ARI, CARI or BREX in patients with Parkinson's disease should be considered only when other antipsychotics of more favourable or better-documented safety profile are ineffective or if they are contraindicated and special caution is required.

### Glaucoma

There has been one report of a patient diagnosed with glaucoma who had aripiprazole-induced elevation of intraocular pressure and which subsided after treatment discontinuation [34]. To date, there have been no studies on the safety of ARI, BREX or CARI in the treatment of patients with glaucoma, but due to the very low affinity of these drugs for cholinergic muscarinic receptors, their use in patients with glaucoma seems to be associated with a low risk.

## Aripiprazole, cariprazine and brexpiprazole in geriatric psychiatry and in dementia

The treatment of patients aged 65 years or older requires taking into consideration comorbidities, concurrent medications and possible interactions. The efficiency of organs responsible for drug metabolism declines with age and, consequently, the risk of side effects increases. The absorption, distribution, elimination and biotransformation of drugs in the liver are impaired. Moreover, dehydration, often observed in this group of patients, heart failure and decreased renal function modify the pharmacokinetics of drugs. It is estimated that the risk of psychotropic drugs' side effects that require admission to hospital is 3.5 times higher in this group of patients. With regard to antipsychotics, it is associated mainly with anticholinergic effects, parkinsonism, tardive dyskinesia, orthostatic hypotension, cardiac conduction disorders, sedation and cognitive dysfunctions [35].

The treatment of neuropsychiatric symptoms, that is Behavioural and Psychological Symptoms of Dementia (BPSD), found in 90% of patients diagnosed with dementia, is a serious problem [36]. BPSD include apathy, depression, anxiety, psychosis, agitation, aggression, sleep disturbances, and sexually inappropriate behaviours [37], which are the cause of serious difficulties in interpersonal relationships, social functioning and everyday activities [38]. The drugs approved for the short-term treatment of aggression in Alzheimer's disease (AD) include haloperidol, risperidone and tiapride. Other antipsychotics, such as olanzapine and quetiapine, are also often used off-label [39], despite the warning that they are associated with increased risk of cerebrovascular events and death in older patients with dementia. If the treatment is ineffective, carbamazepine, citalopram or gabapentin may be used, although they have limited efficacy compared to SGAs [40].

Recent research has become increasingly interested in the use of dopamine receptor partial agonists in the treatment of mental disorders in the elderly. The essential feature of this class of drugs is that in the presence of agonists with a higher intrinsic activity, they inhibit D3/D2 dopamine receptors, but on their own they act as agonists [41]. Importantly, D3 receptors are localised mainly in the ventral striatum. For this reason, their activation does not produce extrapyramidal side effects, which are associated mainly with the dorsal striatum [42]. This explains the improvement of psychotic symptoms and a low risk of side effects.

ARI is associated with a low risk of extrapyramidal side effects, slight weight gain and a lack of significant increase in prolactin levels [43]. There is evidence supporting the use of the drug in the elderly. Aripiprazole is effective in both positive and negative symptoms of schizophrenia. It has also been proven that the adjunct of aripiprazole to antidepressants is significantly more effective in improving depressive symptoms in the elderly than antidepressants used in monotherapy [44]. In the studies of older patients, aged 50–67 years, who had an inadequate response to standard antidepressant

medication, adjunctive aripiprazole was effective in improving depressive symptoms. The drug was well tolerated and akathisia was less common in older than in younger patients [45].

Results of randomised trials suggest that ARI has a statistically significant beneficial impact on agitation in patients with AD and psychotic symptoms [46]. A meta-analysis of studies on various antipsychotics showed that ARI is significantly more effective in the treatment of psychomotor agitation than placebo [47]. Similar results were obtained in another meta-analysis including 5,373 patients with dementia. Compared to placebo, aripiprazole was associated with an improvement in the Neuropsychiatric Interview (NPI) and Brief Psychiatric Rating Scale (BPRS). Studies suggest that ARI may be the most effective and safe of all SGAs used in the treatment of the elderly [48].

By acting on D3 receptors, CARI can exert pro-cognitive effects, reduce negative symptoms [49, 50] and improve depressive symptoms [51]. Agonism at 5-HT1A receptors may improve negative and depressive symptoms, whereas antagonism at 5-HT2A receptors decreases the risk of motor side effects. Moreover, antagonism at 5-HT2C and 5-HT7 may be responsible for antidepressant and pro-cognitive effects [52]. Side effects, such as sedation, weight gain and decreases in blood pressure are associated with partial antagonism at H1 histamine receptors, M1 muscarinic receptors and α1 receptors, but due to low affinity of the drug to these receptors, the side effects are mild [53]. There is only a limited number of studies on the use of CARI in psychogeriatrics. A 48-week clinical study showed significant efficacy of the drug at a dose range of 1.5–9 mg/day with a relatively small risk of side effects. It has been shown that the most common side effects of CARI in patients aged 65 years or more were nasopharyngitis, insomnia, hypertension and weight increase. In the CARI group, glucose levels increased from the mean baseline value of 104.9 mg/dL by 20.8 mg/dL by the end of the study and prolactin levels decreased from 19.325 to 5.429 ng/mL. Moreover, it was found that people receiving the drug experienced an increase in diastolic blood pressure and a decrease in body weight. Importantly, treatment with CARI was associated with a lower risk of parkinsonism (17.6%) compared to risperidone (40%). However, it should be noted that the study was conducted on a small group of patients (17 patients aged 65 to 74 years) and for this reason the safety and applicability profile of CARI need to be addressed in future studies [35].

BREX has not been sufficiently studied in the elderly but there have been first reports of its favourable effects in patients with dementia. In phase 3 clinical trials from 2019 including almost 700 patients with AD, two dosing regimens were compared. In study 1, two fixed doses of BREX (2 mg/day and 1 mg/day) were evaluated and in study 2 a flexible dose of the drug (0.5 to 2 mg/day) was investigated. In study 1, patients receiving BREX 2 mg/day showed statistically significant greater improvement of mental state from baseline to Week 12 than placebo. In study 2, post-hoc analyses showed that only patients titrated to the maximum BREX dose of 2 mg/day at Week

4 showed greater improvement and exhibited only mild side effects (headaches, dizziness and somnolence). These studies provide evidence that BREX 2 mg/day has the potential to be an efficacious, safe, and well-tolerated treatment for agitated patients with AD. A slow BREX titration schedule (4 weeks) may be clinically more effective in the treatment of agitation and show a better safety profile than the available second generation antipsychotics [54].

## Aripiprazole, cariprazine and brexpiprazole in child and adolescent psychiatry

### Aripiprazole

ARI is approved for the treatment of schizophrenia in adolescents aged 15 years and older, bipolar disorder in adolescents aged 13 years and older, irritability associated with autistic disorder and tics associated with Tourette's syndrome. Since the first reports on the use of ARI appeared, it has been widely used in child and adolescent psychiatry. In 2017, it was prescribed over 6 million times in the United States alone. According to research by Kalverdijk et al. [55], the use of ARI in children and adolescents increased significantly between 2005 and 2012 in all studied countries, but in Germany, the Netherlands and the United Kingdom it joined the top five most frequently prescribed antipsychotics in this group of patients. Available literature confirms the efficacy of ARI in all mentioned indications with a satisfactory risk-benefit ratio and side effect profile [56].

A meta-analysis on the efficacy of 8 different antipsychotics in the treatment of youth with schizophrenia was conducted by Pagsberg et al. [57] in 2017. The analysis included twelve studies involving 2,158 patients aged 8–19 years. The study showed that the efficacy of ARI was significantly greater compared to placebo and comparable to other antipsychotics, with respect to both positive and negative symptoms. Compared to placebo, aripiprazole was associated with the risk of weight increase, akathisia, extrapyramidal symptoms and sedation, but the risk of weight increase and hyperprolactinaemia was lower than for other antipsychotics and the risk of other side effects was comparable to other APDs. The efficacy of ARI appears comparable to other APDs with a more favourable safety profile. The 2013 guidelines of the National Institute for Health and Clinical Excellence (NICE) [58] recommend oral antipsychotic medication in first-episode psychosis in children and adolescents. However, the guidelines do not specify which of the antipsychotics should be used. In the chapter on subsequent episodes of psychosis, NICE recommends ARI in patients who did not achieve a satisfactory effect on risperidone. Similarly, guidelines of the American Academy of Child and Adolescent Psychiatry (AACAP) from 2013 [59] do not specify the drug, but suggest that the use of aripiprazole and risperidone is based on solid evidence in the available literature. A similar position is expressed in the review by Kumar et al. [60] from 2013 conducted for the Cochrane Library, but

the authors of the study claim that the efficacy of ARI is similar at low (~10 mg) and high (~30 mg) doses.

With regard to bipolar disorder in children and adolescents, in 2016, Meduri et al. [61] conducted a meta-analysis of the efficacy and safety of ARI in this group of patients which included 16 RCTs and 6 non-RCTs involving 2,505 patients with a manic episode and 2,932 patients in remission. In the group of symptomatic patients, the efficacy of ARI was proved to be significantly higher than placebo and comparable to other mood stabilisers. It proved to be particularly effective in the maintenance phase, in which it was significantly more effective than placebo, especially in the paediatric population. With regard to the side effect profile, ARI was associated with a lower risk of hyperprolactinaemia and a comparable risk of other side effects compared to other medications. The 2014 NICE guidelines on the diagnosis and treatment of bipolar disorder and the 2013 guidelines on the use of ARI in severe and moderate manic episodes in children and adolescents recommend considering ARI as the first-line treatment of hypomanic and manic episodes. In the case of depressive episodes, current NICE guidelines recommend the combination of olanzapine and fluoxetine or quetiapine monotherapy [58]. According to the 2007 AACAP guidelines, aripiprazole, the same as valproate (note the restrictions of the European Pharmacovigilance Risk Assessment Committee of the European Medicines Agency on the use of valproate in girls and women of childbearing potential), olanzapine, risperidone, quetiapine and ziprasidone, is recommended for the treatment of acute manic episodes. Lamotrigine and olanzapine are recommended as maintenance therapy and the combination of olanzapine and fluoxetine is recommended in the treatment of depressive episodes [62]. The review by Brown et al. [63] conducted for the Cochrane Library in 2013 also showed that ARI is effective in the treatment of bipolar manic episodes, but due to the lack of literature data it is impossible to compare the efficacy of ARI to other drugs. For this reason, the place of ARI in the treatment of manic episodes in children and adolescents remains unclear.

The meta-analysis by Yang et al. [64] from 2019 summarises the results of studies on the safety and efficacy of different antipsychotics in the treatment of tic disorders. The review included 60 placebo-controlled clinical trials which showed significant efficacy of haloperidol, risperidone, ARI, quetiapine, olanzapine and ziprasidone in the treatment of tic disorders. In the summary, the authors concluded that ARI and risperidone have the most favourable efficacy and tolerability profile. Recommendation 8 of the 2013 AACAP Practice Parameters [65] states that medication for tic disorders should be considered for moderate to severe tics causing severe impairment in the patient's functioning or quality of life but it does not specify the preferred treatment strategy. ARI is listed as a safe therapeutic option along with risperidone, haloperidol, clonidine, guanfacine and pimozide but guanfacine is recommended for patients with comorbid ADHD, whereas ARI and risperidone are recommended in externalising

disorders. Polish guidelines also recommend ARI as the first-line antipsychotic in the treatment of patients with tic disorders with no comorbidities [66].

According to the current state of knowledge, none of the pharmacological methods of treatment is effective in improving core autism symptoms. AACAP recommends pharmacotherapy in patients with comorbidities and severe behavioural problems, such as physical aggression or self-injurious behaviour. Risperidone (from the age of 5) and aripiprazole (from the age of 6) are approved for the treatment of irritability associated with autism spectrum disorders. These drugs are also recommended by AACAP for this indication. Literature reports, such as the review for Cochrane Library from 2016 [67] and the review by Bartram et al. [68] from 2019, show that the efficacy of ARI is significantly greater than placebo and comparable to risperidone, while their side effect profile is similar. For this reason, it is impossible to say which of the drugs should be used in this group of patients.

The concept of using augmentation therapy, for example with ARI, in eating disorders is an interesting issue debated in the literature. However, it should be highlighted that current guidelines of national and international scientific associations state that there is no evidence for the efficacy of pharmacotherapy in the treatment of core symptoms of anorexia nervosa [69, 70]. Some authors suggest that the use of SGAs in patients with eating disorders may be beneficial due to their quasi-delusional beliefs about food [71]. With regard to this aspect, the literature mentions mainly olanzapine, then chlorpromazine and ARI [72]. In 2011, Trunko et al. [73] published a series of case reports of 8 patients with eating disorders, anorexia nervosa ($n$ = 5) and bulimia ($n$ = 3), who underwent treatment with ARI at a dose of 5–10 mg/day. All patients had reduced food-related anxiety, fewer obsessional thoughts about food, improved body image and satisfactory weight increase [73]. In another study by Frank et al. [74] from 2017, the authors reviewed the treatment of 106 adolescents with anorexia nervosa, including 22 patients treated with ARI at a dose of 1–5 mg/day who achieved a significantly greater increase in body mass index (BMI) than patients from a control group. In their latest work from 2020, Tahilhoglu et al. [75] published a series of case reports of 11 girls with anorexia nervosa treated with ARI at a mean dose of 6.86 mg/day (minimum 2.5 mg/day; maximum 15 mg/day) who achieved a significant improvement in psychopathological symptoms and satisfactory weight increase. It should be emphasised, however, that ARI is not approved for the treatment of eating disorders and its use in this group of patients is experimental. None of the generally recognised guidelines recommends the use of aripiprazole in this group of patients.

### Cariprazine

CARI is currently not approved for the treatment of children and adolescents. In March 2020, Szatmari et al. [35] published an overview of the phase 1 clinical trial on the use of CARI in children and adolescents with schizophrenia over the age

of 13 ($n$ = 49). This drug was generally well tolerated and was not associated with any serious adverse events throughout the 4 weeks of the study. The adverse events included akathisia, somnolence and fatigue. No significant differences were observed in clinical parameters or ECG. In another study by Poweleit et al. [76] from 2020, the authors examined the safety and tolerability profile of CARI in 16 patients with mood disorders aged 6–20 years who received the drug at a dose of 1.5–6 mg/day. Only 3 patients (19%) received CARI monotherapy compared with 13 patients (81%) who were treated with concomitant antipsychotic medication and/or lithium. The most common side effect was weight gain ($n$ = 3; 19%), but the comparison of baseline and endpoint BMI shows that neither BMI nor BMI percentile changed significantly. The clinical response rate was 44% ($n$ = 7), with responders being prescribed higher doses ($p$ = 0.005; 6 mg/day vs 3 mg/day). There is an ongoing clinical study that started in January 2019, the purpose of which is to evaluate the efficacy and safety of CARI in the treatment of schizophrenia in children and adolescents [77]. The study is going to enrol 330 children aged 13–17 years and the estimated completion date is December 2022.

### Brexpiprazole

BREX is currently not approved for the treatment of children and adolescents and there are no studies evaluating its use in this population of patients. There is only one PubMed report of a 16-year-old boy admitted to the emergency unit after taking 30 mg BREX, probably for suicidal purposes [78]. Initially, somnolence and ataxia were observed. However, 24 hours after the overdose, the patient developed tremors, myoclonus and psychomotor agitation, which were treated with lorazepam. After approximately 72 hours, the symptoms resolved and the patient was discharged home.

## Aripiprazole, cariprazine and brexpiprazole in the treatment of mental disorders in pregnant and breastfeeding women

Summaries of product characteristics (SmPCs) of ARI, CARI and BREX state that these medicinal products should not be used in pregnant women (Table 2). However, clinical experience shows that sudden discontinuation of the pharmacotherapy is associated with an increased risk of relapse and the negative impact of the disease on the pregnancy course and foetal development may outweigh the risk associated with the therapy. Systematic literature reviews and safety registers on the use of APDs in pregnancy show that the benefits of using ARI in pregnant women with schizophrenia or BD often outweigh the potential risks associated with the treatment [79]. Polish recommendations regarding pharmacological treatment of patients with MDD and BD also highlight the fact that proper pharmacotherapy of pregnant women with severe mental disorders has significant benefits for the mother and her child [80, 81]. For this reason,

the decision to maintain or initiate pharmacotherapy in a pregnant woman must be carefully considered on an individual level taking into account the course of the disease, response to the treatment, stage of pregnancy, the risk of relapse, the risk associated with the type of medication and dosage and, most importantly, the patient's preference after discussing potential risks and benefits associated with the use of pharmacotherapy.

Table 2. **Recommendations on the use of aripiprazole, cariprazine and brexpiprazole in the treatment of mental disorders in pregnant and breastfeeding women based on the summaries of product characteristics (SmPCs)**

| | Aripiprazole | Brexpiprazole | Cariprazine |
|---|---|---|---|
| Pregnancy category | C | C | Not classified |
| Recommendations on the use in pregnant women | Should not be used in pregnancy unless the expected benefit clearly justifies the potential risk | There are no data on the use of BREX in pregnant women. It is not recommended during pregnancy and in women of childbearing potential not using contraception | There are no data on the use of CARI in pregnant women. It is not recommended during pregnancy and in women of childbearing potential not using contraception |
| Recommendations on the use in breastfeeding women | It is excreted in human milk. Women taking aripiprazole should not breastfeed, particularly preterm and new-born babies | No data on excretion into human milk are available. BREX is excreted in milk of rats. If a decision is made to continue the BREX therapy, breast-feeding should be discontinued | No data on excretion into human milk are available. CARI is excreted in milk of rats. If a decision is made to continue the CARI therapy, breast-feeding should be discontinued |

ARI is excreted in human milk. The weight-adjusted exposure of a 5 kg infant is as much as 8.3% of the maternal dosage of ARI [82]. SGAs considered to be the safest in breastfeeding women are olanzapine (infant exposure of 1–4%) and risperidone (infant exposure of 3–4%).

## Summary

Treatment of patients from special populations requires more careful attention because they may have clinically significant problems with absorption, distribution, elimination and biotransformation of drugs. Moreover, taking other medication significantly increases the risk of dangerous drug-drug interactions.

D2/D3 dopamine receptor partial agonists are increasingly often used in the treatment of mental disorders in patients with somatic comorbidities, in older patients, including those with dementia, and in children and adolescents. This is associated with the low risk of side effects typical for most antipsychotics, that is: weight gain, metabolic disorders, akathisia, extrapyramidal symptoms, hyperprolactinaemia, QT interval prolongation in ECG, sedation and anticholinergic effects [10].

ARI was associated with an increased risk of side effects in patients with Parkinson's disease who required the use of antipsychotic medication. However, ARI appears to be the safest therapeutic option in patients who are at an increased risk of seizures. Due to the scarcity of data, it is difficult to reliably assess the safety of CARI and BREX in patients with Parkinson's disease or epilepsy. All three drugs should be used with caution in patients with a history of leukopaenia or agranulocytosis. Patients with renal/hepatic impairment should receive a reduced dose of the drug, depending on the level of organ failure.

ARI is an SGA effective in the treatment of older patients and it has a favourable safety profile. There have also been first reports on the efficacy and good tolerability of CARI and BREX in this group of patients. All three drugs may have beneficial effects on depressive and cognitive symptoms, as well as behavioural disorders associated with dementia.

With regard to child and adolescent psychiatry, it should be noted that only ARI is approved for the treatment of schizophrenia in adolescents aged 15 years and older, bipolar disorder in adolescents aged 13 years and older, irritability associated with autistic disorder and tics associated with Tourette's syndrome. Moreover, the analyses conducted so far have shown that ARI is safe in this group of patients. CARI and BREX are not approved for the treatment of children and adolescents in Poland. To date, there have been only two studies published on the use of CARI (one in the treatment of schizophrenia and the second one in the treatment of mood disorders) which showed that the drug is generally well tolerated and it is not associated with serious adverse events. BREX has not been studied in the population of children and adolescents.

Since dopamine receptor partial agonists have been available for a relatively short time, there are less data on their use in pregnant women than for other antipsychotics. Available data show, however, that ARI is one of the antipsychotics not associated with a high risk of negative impact on the pregnancy, delivery, postpartum period and infant's health.

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