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Dopamine D2 receptor partial agonists in the treatment of schizophrenia – example of brexpiprazole

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Summary

Since the 1950s, there have been rapid developments in psychiatric pharmacotherapy, resulting not only in more effective treatment of patients, but also in improvements in minimizing adverse effects of therapy.

Modern third-generation antipsychotics, in addition to antagonism toward D2 receptors, also exhibit partial agonism toward dopamine receptors. Such a mechanism of action is intended to regulate dopaminergic transmission – inhibit (antagonism) it in pathways where it is excessive (excessive transmission in the mesolimbic pathway in psychotic patients, excessive transmission in the tuberoinfundibular pathway in patients with hyperprolactinemia) and stimulate (agonism) it in pathways where it is too low (mesocortical pathway). This has a beneficial effect on both the reduction of adverse symptoms and the negative, affective and cognitive symptoms of patients suffering from schizophrenia.

The purpose of this review article is to present the most important clinical aspects of the use of dopamine D2 receptor partial agonists in the treatment of schizophrenia, using brexpiprazole as an example, and to define the profile of patients to whom this drug could be dedicated – based on recent studies.

Key words: brexpiprazole, schizophrenia, D2 receptor partial agonists

Introduction

The history of antipsychotic drugs spans some 70 years. Its beginning is considered to be in 1952, when French psychiatrist Jean Delay first described the use of chlorpromazine in the treatment of patients with psychotic disorders [1, 2]. Since then, psychiatric pharmacotherapy has developed rapidly, resulting not only in more effective treatment of patients, but also in improvements in minimizing adverse effects of therapy. Classical antipsychotics (first-generation) show primarily non-selective antagonistic

effects against dopamine receptors, which is associated with their high efficacy in the treatment of positive symptoms of schizophrenia (in the results of blockade within the mesolimbic pathway), but also with the risk of adverse symptoms, e.g., extrapyramidal symptoms or hyperprolactinemia, resulting from inhibition of dopaminergic transmission also in the mesocortical, nigrostriatal and tuberoinfundibular pathways.

The purpose of this review article is to present the most important clinical aspects of the use of dopamine D2 receptor partial agonists in the treatment of schizophrenia using brexpiprazole as an example.

Mechanism of action

Modern third-generation antipsychotics, in addition to antagonism to D2 receptors, also exhibit partial agonism to dopamine receptors. Such a mechanism of action is intended to regulate dopaminergic transmission – inhibit (antagonism) it in pathways where it is excessive (excessive transmission in the mesolimbic pathway in psychotic patients, excessive transmission in the tuberoinfundibular pathway in patients with hyperprolactinemia) and stimulate (agonism) it in pathways where it is too low (mesocortical pathway). This has a beneficial effect on both the reduction of adverse symptoms and the negative, affective and cognitive symptoms of patients suffering from schizophrenia [2, 3] (Fig. 1).

Dopamine receptor partial agonists, or so-called third-generation antipsychotics, include aripiprazole, brexpiprazole and cariprazine. A similar mechanism of action is also exhibited by lumateperone, which is not available in Poland, and shows antagonism to postsynaptic D2 receptors (antipsychotic effect) and agonism to presynaptic D2 receptors (fewer side effects) [3]. Table 1 compares the pharmacodynamic effects of these drugs.

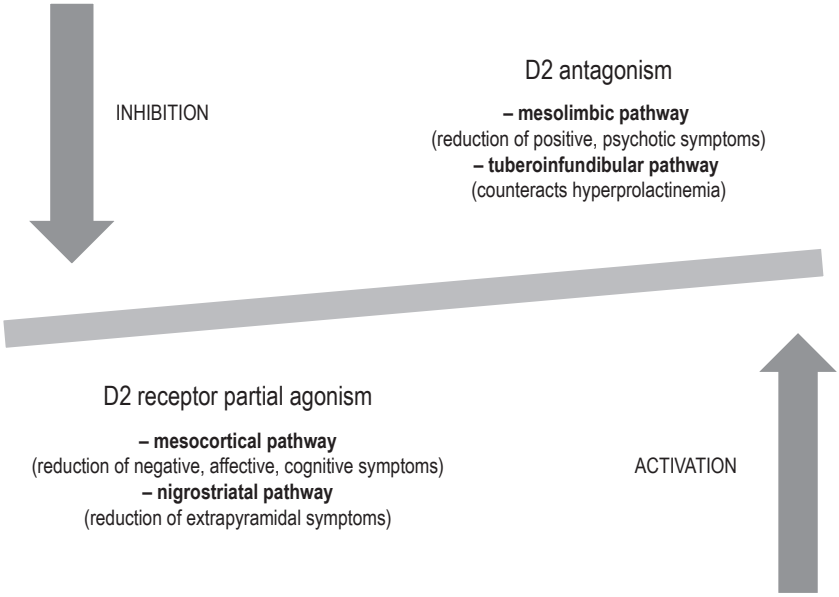

Figure 1. **Scheme of mechanism of action of third-generation antipsychotic drugs**

Table 1. **Comparison of pharmacodynamic effects of D2 receptor partial agonists [3-6]**

Receptor	Aripiprazole	Brexpiprazole	Cariprazine	Lumateperone
D1	-	-	-	agonism (Ki = 52 nmol/L)
D2	partial agonism (Ki = 0.34 nmol/L)	partial agonism (Ki = 0.30 nmol/L)	partial agonism (Ki = 0.49 nmol/L)	antagonism postsynaptically, partial agonism presynaptically (Ki = 32 nmol/L)
D3	partial agonism (Ki = 0.8 nmol/L	partial agonism (Ki = 1.1 nmol/L)	partial agonism (Ki = 0.085 nmol/L)	-
D4	-	antagonism	-	-
5-HT_{2A}	antagonism (Ki = 3.4 nmol/L)	antagonism (Ki = 0.47 nmol/L	antagonism (Ki = 18.8 nmol/L)	antagonism (Ki = 0.5 nmol/L)
5-HT_{2B}	antagonism	antagonism	agonism	-
5-HT_{2C}	partial agonism (Ki = 15 nmol/L)	antagonism (Ki = 34 nmol/L)	antagonism (Ki = 134 nmol/L)	antagonism (Ki = 173 nmol/L)

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5-HT_7	antagonism (Ki = 29 nmol/L)	antagonism (Ki = 3.7 nmol/L)	antagonism (Ki = 111 nmol/L)	-
Other:	H1 antagonism (Ki = 61 nmol/L), alpha1 antagonism (Ki = 57 nmol/L), alpha2 antagonism (Ki =37.9 nmol/L)	H1 antagonism (Ki = 19 nmol/L), alpha1 antagonism (Ki = 3.8 nmol/L), alpha2 antagonism (Ki = 0.59 nmol/L)	H1 antagonism (Ki = 23.2 nmol/L), alpha1 antagonism (Ki = 6.88 nmol/L)	SERT* inhibition, alpha1 antagonism (Ki = 73 nmol/L) *strongest effect of all antipsychotics on serotonin reuptake

Ki dissociation constant – the lower the value, the higher the affinity for the receptor.

The first registered antipsychotic drug to exhibit partial agonism toward D2 receptors was aripiprazole. Its intrinsic activity, however, is closer to antagonistic than agonistic action. Precisely because of its relatively high intrinsic activity, aripiprazole can cause agitation, anxiety or akathisia. Hence, efforts have been made to develop a drug that would retain the positive beneficial effects of aripiprazole, but present an even more favorable clinical profile [3, 7].

Brexpiprazole has a similar structure to aripiprazole. However, unlike it, brexpiprazole has lower intrinsic D2 activity (43% vs. 61% for aripiprazole). This means that despite having a higher affinity for this receptor than aripiprazole (Ki = 0.34 nmol/L), brexpiprazole (Ki = 0.30 nmol/L) achieves lower activity toward it. This translates into a lower risk of extrapyramidal symptoms. Brexpiprazole shows higher potency at 5HT2A receptors which also translates into a lower risk of akathisia, and 5HT1A (Ki = 0.12 nmol/L for brexpiprazole and 1.17 nmol/L for aripiprazole), which may result in better efficacy against affective and cognitive symptoms [6, 7].

However, no other D2 receptor partial agonist, except for aripiprazole, exhibits partial agonism toward serotonin 5-HT2C receptors, which is associated with beneficial effects normalizing metabolic disturbances and counteracting weight gain [3].

Pharmacokinetics

Another very important aspect for comparing partial D2 agonists among themselves is the pharmacokinetics of their action (Table 2). Of note is the fact that cariprazine has the longest half-life.

Table 2. **Comparison of pharmacokinetics of partial D2 agonists [3, 8]**

Feature	Aripiprazole	Brexpiprazole	Cariprazine	Lumateperone
Bioavailability	87% when administered p.o.	95%	52-63%	4.4%
T_{max}	3-5h when administered p.o. 5-7 days when administered as LAI	4 h	3-6 h	3-4 h

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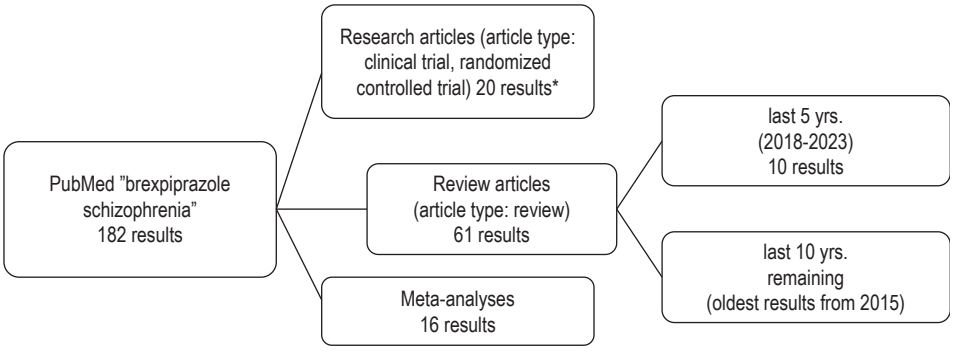
$T_{1/2}$	48-68 h after p.o. administration. *according to some data, metabolites 94 h 47 days after LAI administration (400 mg i.m.)	91 h	2-4 days, and active metabolites for up to 3 weeks	13-21 h
Binding to plasma proteins	99%	99%	91-97%	97.4%
Metabolism	CYP3A4, CYP2D6	CYP3A4, CYP2D6	CYP3A4	CYP3A4, UGT
Other			Long half-life of active metabolites	A meal rich in fat reduces the maximum concentration by about 33%

T_{max} – time of maximum concentration; $T_{1/2}$ – half-life

Efficacy and safety of brexpiprazole in the treatment of schizophrenia

As the aim of the present study was also to present the most important clinical aspects (i.e., efficacy and safety) of brexpiprazole in the treatment of schizophrenia, an analysis of the PubMed medical publications database was performed by typing "brexpiprazole schizophrenia" (Fig. 2). This yielded 182 results, of which as many as 61 items were review articles. Selecting only original papers (article type: clinical



*Exclusions: 3 results were excluded from analysis because they did not involve patients treated for schizophrenia, 1 because it was an analysis of two previous clinical trials, 2 phase I trials

Figure 2. **Decision diagram for source search**

trial, randomized controlled trial) yielded 20 items. All of them were papers from the last 10 years. Also highlighted were 16 meta-analyses.

Correll et al. [9, 10] described the results of three randomized, double-blind, placebo-controlled trials evaluating the efficacy of brexpiprazole in treating patients with an acute episode of schizophrenia. In the first (phase 2 study), patients received treatment according to one of six regimens: brexiprazole at a fixed dose of 0.25 mg or flexible doses of 1 ± 0.5 mg, 2.5 ± 0.5 mg or 5 ± 1 mg, placebo or aripiprazole at a dose of 15 ± 5 mg for 6 weeks. In the other two studies (phase 3), patients were randomly assigned to a group receiving brexpiprazole at a fixed dose of 0.25 mg, 1 mg, 2 mg or 4 mg, or placebo. The primary efficacy endpoint was the change in Positive and Negative Syndrome Scale (PANSS) total score from baseline at week 6; the key secondary endpoint was the change in Clinical Global Impressions Scale (CGI-S) score at week 6. There were no statistically significant differences between the brexpiprazole and aripiprazole groups in the phase 2 study with respect to primary and key secondary endpoints compared to placebo. The combined brexpiprazole 2 mg (n = 359) and aripiprazole 4 mg (n = 359) groups of patients outperformed placebo (n = 358) in terms of change in PANSS total score (mean least squares difference vs. placebo: – 5.46, p = 0.0004 and – 6.69, p < 0.0001, respectively) and CGI-S (– 0.25, p = 0.0035 and – 0.38, p < 0.0001, respectively). Changes from baseline in efficacy endpoints were minimal in the group of patients receiving brexpiprazole 0.25 mg, while the group receiving 1 mg showed suboptimal improvement. No significant moderators (i.e., gender, age, race or disease duration) were confirmed to affect response to brexpiprazole treatment [9]. Based on the above studies, it can be concluded that brexpiprazole 2 mg and 4 mg is effective in treating acute episodes of schizophrenia [9-11]. This conclusion was also confirmed by Kane et al. [11, 12] and Ishigooka et al. [13]. One limitation of the Kane et al. [11] (2015) study was the lack of an active comparator. In the case of the Correll et al. study, it was aripiprazole [9]. All of the studies described above were quite short (6 weeks) and focused on evaluating efficacy in acute episodes of schizophrenia.

Later that year (2018), Ishigooka and colleagues published the results of a 52-week study with flexible doses (1-4 mg) of brexpiprazole [14], which enrolled both patients already taking brexpiprazole (98 patients – a continuation of their earlier 6-week study [13]) and de novo patients who switched from other antipsychotics (184 patients). This was a study without a placebo control [14]. A total of 53.2% of patients (150 patients) completed the study (52 weeks). Treatment-emergent adverse events (TEAEs) occurred in 83.6% of patients. They were mostly of mild to moderate severity. There were no deaths or clinically significant mean changes in laboratory values, vital signs or electrocardiogram parameters. A worsening of schizophrenia symptoms was noted in 22.4% of patients. Mean scores on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression-Severity (CGI) remained stable through week 52.

The Forbes et al. [15] study was also a long study (52 weeks). However, it focused primarily on the safety of brexpiprazole. A total of 1,072 patients were included in

the study, 47.4% of whom completed the trial, while 14.6% of patients discontinued treatment due to treatment-related adverse events, most commonly due to worsening of psychotic symptoms. Treatment-related adverse events with an incidence of ≥5% were schizophrenia (11.6%), insomnia (8.6%), weight gain (7.8%), headache (6.4%) and agitation (5.4%). Most treatment-related adverse events were mild to moderate in severity. The mean weight gain from baseline to week 26 was 1.3 kg, and 2.1 kg by week 52. There were no clinically significant prolactin, lipid or glucose results or QT interval prolongation. On average, patients' symptoms and functioning showed steady improvement [15].

Fleischhacker and colleagues [16] conducted a study to evaluate the efficacy, safety and tolerability of brexpiprazole maintenance treatment in adults with schizophrenia. Patients with exacerbation of psychotic symptoms ($N = 524$) were switched to brexpiprazole (1-4 mg/d). Patients who met criteria for stabilization for 12 weeks (202 patients) were randomized to double-blind maintenance treatment with brexpiprazole (stabilization dose) ($N_1 = 97$) or placebo ($N_2 = 105$) for up to 52 weeks. The percentage of patients meeting criteria for impending relapse was 13.5% with brexpiprazole and 38.5% with placebo ($p < 0.0001$). During the maintenance phase, the incidence of adverse events was comparable to placebo [16].

Corell et al. [17] also described a successful change in treatment of patients in an acute episode of schizophrenia from other antipsychotics to brexpiprazole. In the majority, 72% of the 404 patients in the study, the conversion (treatment change) phase lasted about 1 month (22-33 days). Treatment discontinuation rates due to lack of efficacy or adverse events were low. As many as 72.3% of patients completed 8 weeks of treatment [17]. Similarly, a study by Ishigooka et al. [18] performed a post hoc analysis using data obtained over 8 weeks from 200 Japanese patients with schizophrenia who were switched to brexpiprazole monotherapy (4-week treatment change phase and 4-week post-change phase). When switching antipsychotics, brexpiprazole was first administered at a dose of 1 mg/day and then increased to 2 mg/day at the end of week 4. At the same time, the previous antipsychotic drug was gradually reduced from the beginning of week 3 and discontinued by the end of week 4. Then the dose of brexpiprazole could be increased to 4 mg/day. After 8 weeks (4 weeks after the change), 50% of patients were taking brexpiprazole at 4 mg, 25% 3 mg, 23.2% 2 mg and 1.8% 1 mg. The rate of treatment discontinuation after this time was 17% with most (9.5%) of the reasons being withdrawal of consent to participate in the study. The discontinuation rate was 4.9% for patients who were switched from aripiprazole as their primary antipsychotic and 25.4% for those who were switched from other antipsychotics. It was emphasized that due to the serious adverse events (exacerbation of schizophrenia symptoms, including stupor) that led to discontinuation of treatment, a cautious switch from this drug to brexiprazole is necessary in patients who had previously used olanzapine as their primary antipsychotic. Frequently reported adverse events were nasopharyngitis (13.5%), schizophrenia (9.0%), insomnia (6.5%), headache (5.5%) and akathisia (5.5%) [18].

Citrome et al. [19] compared the efficacy of treatment with aripiprazole (at a dose of 15 mg/d, $n = 33$) and brexpiprazole (at a dose of 3 mg/d, $n = 64$) for 6 weeks. Patients treated with brexpiprazole or aripiprazole showed a reduction in schizophrenia symptoms as assessed by the PANSS scale (-22.9 and – 19.4, respectively). Moderate reductions in impulsivity were observed with brexiprazole but not aripiprazole (mean change on the 11-point Barratt impulsivity scale: – 2.7 and 0.1, respectively). No change in cognitive function scores (Cogstate) was observed with either therapy. Brexpiprazole was well tolerated, and the incidence of akathisia was lower in patients treated with brexpiprazole (9.4%) than with aripiprazole (21.2%) [19]. A large meta-analysis comparing brexpiprazole and aripiprazole found no differences in short-term efficacy and safety in acute schizophrenia between the drugs [20].

An important observation was the positive effect of brexpiprazole on impulsivity in patients treated for schizophrenia. A post-hoc study confirmed that brexpiprazole improves PANSS-EC (Positive and Negative Syndrome Scale – Excited Component, assessing agitation) scores over 6 weeks, with mean least squares differences compared to placebo of – 0.69 (95% confidence limits, – 1.28, – 0.11) for 2 mg/d ($P = 0.020$) and – 1.11 (-1.70, – 0.53) for 4 mg/d ($P = 0.0002$). It can be concluded that brexpiprazole is an effective and well-tolerated drug for the treatment of agitation and hostility in patients with schizophrenia [21]. A multicenter, randomized, double-blind study using functional magnetic resonance imaging (fMRI) assessing the effects of brexpiprazole on brain areas controlling impulsive behavior also confirmed these clinical observations. Thirty-eight outpatients with stable schizophrenia and symptoms of impulsivity were randomized to six weeks of treatment with brexpiprazole at a dose of 2 or 4 mg/day. The pre-established outcome measure was blood oxygen-level dependent (BOLD) activation in the right ventrolateral prefrontal cortex (VLPFC) during inhibitory/control impulsivity tasks: the go/no-go task and the stop-signal task. At 6 weeks, patients receiving brexpiprazole had no statistically significant change in BOLD activation of the right VLPFC during the go/no-go task, but showed a significant decrease in BOLD activation of the right VLPFC during the stop task. The use of brexpiprazole was also associated with a significant improvement in stop-signal reaction time (SSRT) [22].

A 16-week flexible-dose study (1, 2, 3 or 4 mg/day; target dose 3 mg/day) in outpatients with early schizophrenia (18-35 years old, ≤5 years of disease duration) conducted by Malla and his team [23], confirmed that brexpiprazole can be an effective (PANSS score reduction) and safe treatment option in this group of patients. Post-hoc studies indicate that brexpiprazole is effective and safe in patients with both mild schizophrenia symptoms and severe schizophrenia [24, 25]. However, a large meta-analysis comparing as many as 32 neuroleptics, published in 2019 in the prestigious journal Lancet, found that the standardized mean difference from placebo for positive symptom reduction with brexpiprazole was quite low (– 0-17 range from – 0-31 to – 0-04) [26].

Table 3. **Summary of brexpiprazole clinical trials**

RESEARCH STUDY		CONCLUSION
Short-term studies	Correll et al. 2015 [9]	Brexpiprazole at doses of 2 and 4 mg/day showed statistically significant efficacy compared to placebo and good tolerability in patients with an acute episode of schizophrenia.
	Kane et al. 2015 [11]	Brexpiprazole 4 mg is effective and well tolerated in the treatment of acute episodes of schizophrenia in adults.
	Ishigooka et al. [13]	Brexpiprazole was effective and well tolerated in adult Japanese patients with an acute episode of schizophrenia.
	Citrome et al. 2016 [19]	Brexpiprazole was well tolerated. There was a moderate reduction in impulsivity with brexpiprazole, but not with aripiprazole. The incidence of akathisia was lower in patients treated with brexpiprazole than with aripiprazole.
Long-term studies	Ishigooka et al. 2018 [14]	Brexpiprazole was generally safe and well tolerated and maintained therapeutic effects in the long-term treatment of Japanese patients with schizophrenia.
	Forbes et al. 2018 [15]	Treatment with brexpiprazole 1-4 mg/d was generally well tolerated for up to 52 weeks in patients with schizophrenia.
	Fleischhacker et al. 2017 [16]	In patients with an acute episode of schizophrenia who responded to brexpiprazole and met criteria for stabilization, brexpiprazole was an effective option as maintenance therapy at 1 year, with an adverse event rate comparable to placebo and a good safety profile.
Switching studies	Correll et al. 2019 [17]	In most patients, the conversion phase (change of treatment from other antipsychotics-cross-titration “overlap”) lasted about 1 month (22-33 days). Low rates of treatment discontinuation due to lack of efficacy or adverse events.
	Ishigooka et al. 2020 [18]	Effective change of treatment from other antipsychotics to brexpiprazole. NOTE: use caution when changing from olanzapine to brexpiprazole.
Research on effect on impulsivity	Citrome et al. 2019 [21]	Brexpiprazole can be an effective and well-tolerated drug for treating agitation and hostility in patients with schizophrenia.
	van Erp et al. 2020 [22]	Beneficial effects of brexpiprazole on brain activation associated with inhibition.
	Malla et al. 2016 [23]	Brexpiprazole is effective and safe in a group of young patients with early schizophrenia (in outpatient treatment)

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Post-hoc analyses	Meade et al. 2020 [24]	Brexpiprazole is an effective and well-tolerated drug used to treat schizophrenia in patients with more severe and less severe symptoms.
	Correll et al. 2022 [25]	Treatment with brexpiprazole is associated with clinically significant improvements in the functioning of patients with schizophrenia, both in the short and long term.

Brexpiprazole in patients with comorbidities

A working group of the Polish Psychiatric Association, in a paper on the use of partial dopamine receptor agonists in patients with comorbidities, assessed that drugs in this group (including brexpiprazole) can be considered first-line drugs when antipsychotics are required in a patient with a diagnosis of diabetes or metabolic syndrome or its components [27]. However, the risk of weight gain during brexpiprazole treatment warrants some attention [27]. Admittedly, Huhn et al. [28] in their meta-analysis showed that there were no significant differences in terms of body weight between those receiving brexpiprazole and placebo. On the other hand, in a meta-analysis including 3 short-term randomized controlled clinical trials conducted among schizophrenic patients, taking brexpiprazole was associated with an approximately 3-fold higher risk of weight gain of ≥ 7% of baseline compared to placebo [29]. A study by Pillinger et al. [30] found that brexpiprazole was among the antipsychotics with greater weight gain risk compared with placebo. It ranked roughly in the middle of the pack [30]. Barton et al. [31] estimated that the NNH (Number Needed to Harm) rate of clinically significant weight gain during brexpiprazole treatment compared to placebo use was 20 [27, 31]. Studies indicate that the use of brexpiprazole is not associated with an increased risk of QT interval prolongation [28]. Its use was also not associated with a significant risk of hyperprolactinemia [28]. In fact, it has been reported that prolactin levels normalized during brexpiprazole administration. The percentages of patients who developed hyperprolactinemia three times above normal during brexpiprazole therapy were ≤ 1% in short-term studies and ≤ 3% in long-term studies [27, 32].

Note that in patients with moderate or severe renal or hepatic insufficiency, it is necessary to modify the dosage of brexpiprazole – in the treatment of patients with schizophrenia, the maximum daily dose of the drug is 3 mg [27].

Brexpiprazole appears to be a safe drug in somatically burdened patients. However, further studies and clinical observations on its safety in specific patient groups are needed.

Summary

Answering the question about the place of brexpiprazole in the clinical practice of treating patients with schizophrenia, it can be said that it is a drug aimed at: (1) patients

with a preponderance of negative symptoms of the underlying disease, (2) patients in whom akathisia has been observed with treatment with other antipsychotic drugs (including third-generation), and (3) schizophrenic patients struggling with increased impulsivity.

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