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# Efficacy and tolerability of brexpiprazole – a new antipsychotic drug from the group of dopamine $D_2$ receptor partial agonists

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**Summary**

Brexpiprazole is a new antipsychotic drug from the group of dopamine $D_2/D_3$ receptor partial agonists. It represents a development of the second-generation antipsychotics and is an important addition to the pharmacological treatment options for schizophrenia

The purpose of this article is to present, illustrated by the case of brexpiprazole, how advances in the pharmacological properties of new antipsychotics translate into improved results in the treatment of schizophrenia, not only in terms of symptom reduction, but also in terms of functional improvement.

The ratio of activation to blocking of the $D_2/D_3$ receptor is lower for brexpiprazole than for aripiprazole and cariprazine, which may translate into a lower risk of akathisia. Brexpiprazole has also stronger antihistaminic activity, which is likely to be associated with a stronger sedative effect, a lower risk of akathisia, excessive agitation and insomnia.

Brexpiprazole meets the traditional requirements for an antipsychotic drug's efficacy, i.e., compared to placebo, it brings a greater reduction in schizophrenia symptoms in short-term studies and prevents schizophrenia relapses in long-term follow-up. The highest antipsychotic efficacy was found with the highest registered dose (4 mg/day). In addition to reducing positive symptoms, brexpiprazole treatment also leads to a reduction in negative and depressive symptoms, as well as anxiety. It has also a positive effect on patients' social and personal functioning and quality of life. This action of the drug is in line with the expectations of patients and their families regarding effective treatment. It should not only reduce symptoms, but also enable a return to health, i.e., a state that, in addition to optimal health and a sense of psychological well-being, also makes it possible to maintain proper social relations.

**Key words:** schizophrenia, pharmacotherapy, brexpiprazole

## Introduction

The advances in the pharmacological approach to schizophrenia make it now possible not only to effectively reduce the symptoms of this disease, but also to conduct treatment in a way that leads to an improvement in functioning and quality of life, and even a return to full health, a condition that, in addition to optimal health and a sense of psychological well-being, also makes it possible to maintain satisfactory social relationships [1].

The basic principle of treating schizophrenia is to implement pharmacotherapy to reduce symptoms and achieve remission. Another goal is to prevent relapse through the continuation of antipsychotic drugs as so-called maintenance treatment. During this period, both the efficacy and tolerability of the medication matter [2]. Poor tolerance of treatment – most often in the form of extrapyramidal symptoms, weight gain, metabolic disturbances, sedation or hormonal imbalance resulting in sexual dysfunction and menstrual cycle disorders in women – is a common reason for treatment discontinuation or change. It should also be borne in mind that in the long term, a patient's motivation to take the drug regularly is more strongly influenced by a sense of recovery, e.g., easier social functioning, than by symptom reduction [3]. For these reasons, current meta-analyses of clinical trials of antipsychotic drugs compare drugs not only in terms of their efficacy, but also in terms of tolerability [4]. Furthermore, the effectiveness of drugs is evaluated in various aspects. For example, in short-term studies multi-receptor antipsychotics, e.g., clozapine, olanzapine, or drugs with strong dopaminolytic properties, e.g., risperidone, amisulpride and haloperidol are characterized by a higher efficacy in reducing positive symptoms in PANSS scale assessment than drugs from the group of dopamine $D_2$ receptor partial agonists (aripiprazole, brexpiprazole, cariprazine). However, they do not prove superior in terms of improving patients' social functioning, and in the case of drugs with strong dopaminolytic properties, such an effect may be even less favorable [4]. Other areas where drugs without a strong dopaminolytic effect and without a sedative effect may be more beneficial is the treatment of patients with negative symptoms and cognitive impairment. This is noteworthy, since the negative symptoms and cognitive impairment are more strongly associated with poor patient functioning than the positive symptoms of schizophrenia in long-term observations [5]. It should also be considered that the most common cause of treatment failure in schizophrenia is patients' discontinuation of medication. It is associated with an approximately 5-fold increase in the risk of relapse [6]. These data indicate the importance of providing the patient with optimal, tailored pharmacotherapy.

The purpose of this article is to present, on the example of brexpiprazole, a new antipsychotic drug from the group of dopamine $D_2$ receptor partial agonists, how advances in the pharmacological properties of new antipsychotics translate into improved results in the treatment of schizophrenia, not only in terms of symptom reduction, but also in terms of functional improvement.

## Receptor profile of brexpiprazole

Brexpiprazole represents an interesting development and addition to second-generation antipsychotics, with particular emphasis on previously introduced dopamine $D_2/D_3$ receptor partial agonists (aripiprazole, cariprazine). From this point of view, the receptor and clinical profile of the drug should be considered primarily against the background of aripiprazole and cariprazine [7, 8].

Brexpiprazole is a partial agonist of dopamine $D_2/D_3$ receptors, meaning that when it binds to the receptors for dopamine, it does not block them completely, but leaves a certain level of arousal. Importantly, the ratio of arousal to blocking of the $D_2/D_3$ receptor is lower for brexpiprazole than for aripiprazole and cariprazine. This profile may translate into the lower risk of akathisia observed in meta-analyses of clinical trials than that of aripiprazole and cariprazine [8, 9].

Brexpiprazole has a high affinity for dopamine receptors. This is a feature of all partial agonists of dopamine $D_2/D_3$ receptors and translates in practice into displacement from the connection with the receptor and a rapid reduction in the effect of full antagonists (e.g., haloperidol, risperidone, olanzapine) [10]. The neuroleptic effect of risperidone may decrease when aripiprazole or brexpiprazole is added. Special attention should be paid to the inclusion of brexpiprazole (and other partial agonists) in patients previously receiving high doses of neuroleptics, in whom $D_2/D_3$ receptor "up-regulation" may have occurred [11, 12]. Sensitization of dopamine receptors through "up-regulation" (increase in number) most likely promotes agitation and akathisia after administration of partial agonists [12, 13]. The above considerations lead to the conclusion that in patients switched from high doses of neuroleptics to a partial agonist, or in patients in whom brexpiprazole (aripiprazole, cariprazine) is started as a second antipsychotic drug – the lowest available dose of the partial agonist should be used initially [11].

Regardless of the above-described differences in activity toward $D_2/D_3$ dopamine receptors, brexpiprazole is a formulation that differs from aripiprazole and cariprazine in its affinity for other receptor systems. Brexpiprazole has a higher affinity for histamine $H_1$ receptors. The stronger antihistamine effects of brexpiprazole are likely to be associated with a stronger sedative effect and a lower risk of excessive agitation, akathisia and insomnia than in the case of the other two partial agonists [4, 14, 15]. The stronger blocking effect of brexpiprazole on $\alpha_1$ receptors for norepinephrine ($\alpha_1$-adrenolytic action) may have similar practical implications [8, 9].

The lack of effect of $D_2/D_3$ receptor partial agonists on muscarinic receptors for acetylcholine, combined with weak antihistamine effects, means in practice that there is little risk of weight gain and little risk of other components of the metabolic syndrome compared to less selective second-generation drugs [16].

In summary, compared to cariprazine and aripiprazole, brexpiprazole may be a $D_2/D_3$ receptor partial agonist with stronger sedative properties and with a less pronounced risk of akathisia, as meta-analyses of clinical trials seem to confirm. The $D_2/D_3$ partial agonists are arranged "dimensionally" in those meta-analyses – from the most activating cariprazine to the most sedating brexpiprazole [4].

The main differences in the receptor profiles of $D_2/D_3$ partial agonists are shown in Table 1.

Table 1. **Comparison of pharmacological profile (receptor and pharmacokinetics) of brexpiprazole, aripiprazole and cariprazine (on the basis of: [4, 10, 15, 32])**

| Effect on receptors* | Partial $D_2/D_3$ agonists | | | Practical implications |
|---|---|---|---|---|
| | brexpiprazole | aripiprazole | cariprazine | |
| Partial agonism at $D_2/D_3$ dopamine receptors | +++<br>lower intrinsic activity than that of aripiprazole and cariprazine, lower risk of agitation, akathisia | ++++ | ++++** | advantages:<br>lower risk of drug-induced parkinsonism, sedation, hyperprolactinemia<br>disadvantages:<br>occurrence of nausea, akathisia, insomnia is possible already at lower doses;<br>risk of agitation, especially when changing treatment (adding to) from strong $D_2$ receptor antagonists, e.g., haloperidol and risperidone |
| Effects on serotonin receptors 5-$HT_{1A}$, 5-$HT_2$, 5-$HT_7$ | +++ | ++ | ++ | antidepressant and anti-anxiety effects, beneficial effect on negative symptoms |
| Antihistaminic action ($H_1$ receptor blocking) | ++<br>weak, but stronger than that of aripiprazole and cariprazine | +<br>weak | +<br>weak | possible sedative effect for higher doses, low risk of weight gain and metabolic complications;<br>for brexpiprazole, especially at higher doses, a stronger sedative effect within the partial agonist group |
| adrenolytic action | | | | |
| α1-adrenergic receptor blocking | ++<br>stronger than that of aripiprazole and cariprazine | + | + | orthostatic hypotonia, headache, potentiation of the effect of antihypertensive drugs, sedative effect |
| α2-adrenergic receptor blocking | ++<br>stronger than that of aripiprazole and cariprazine | + | + | antidepressant effect, reduction of sexual dysfunction |

*table continued on the next page*

| | | | | |
|---|---|---|---|---|
| Cholinolytic action (anti-muscarinic, "atropine-like") | practically none | practically none | practically none | low risk of weight gain and metabolic complications, lower risk of sedation, cognitive impairment and peripheral "atropine" effects (deterioration of visual acuity, constipation, urinary retention) |
| Dosage for oral administration | 1-4 mg per day | 2***-30 mg per day | 1.5-6.0 mg per day | low initial dose and slow increase in dose are commonly recommended |
| Biological half-life ($T_{1/2}$) | approx. 90 h | 75-146 h | parent molecule: 24-72 h, active metabolites: up to 2-3 weeks | long $T_{1/2}$ compared to other second-generation antipsychotics, once-daily dosing, long time (weeks) needed to stabilize the drug's blood concentration after the drug is introduced or the dose is changed, long time (weeks) needed for the drug to be flushed out of the body |
| Hepatic metabolism | yes, isoenzymes 3A4 and 2D6 of cytochrome P450 | yes, izoenzymes 3A4 and 2D6 of cytochrome P450 | yes, mainly isoenzyme 3A4, lesser contribution of isoenzyme 2D6 of cytochrome P450 | risk of metabolic interactions with enzyme inducers (e.g., carbamazepine) as well as 2D6 and/or 3A4 isoenzyme inhibitors (e.g., fluoxetine, paroxetine, duloxetine, bupropion, quinidine, ketoconazole, clarithromycin, verapamil, diltiazem) |

*receptor profiles of drugs are presented on the basis of available basic and clinical studies, it is not possible to simply translate the receptor profile into the final clinical effect, **cariprazine binds preferentially to dopamine $D_3$ receptors, *** low initial dose recommended in adolescents

## Pharmacokinetics of brexpiprazole

$D_2/D_3$ partial agonists are well absorbed after oral administration and penetrate the blood-brain barrier relatively easily. Compared to other second-generation antipsychotics, the biological half-lives ($T_{1/2}$) of $D_2/D_3$ partial agonists are exceptionally long [9, 10, 17]. In the case of brexpiprazole, the $T_{1/2}$ reaches 90 h, which translates into a long time needed to stabilize the drug's blood concentration around maximum values for a given dose (4 x $T_{1/2}$) [17]. From a practical point of view, therefore, it is worthwhile – especially in the out-of-hospital setting – to follow the principle of including a low initial dose and gradually increasing the dose, e.g., every 2 weeks or even less frequently for patients who may have previously experienced sensitization

("up-regulation") of dopamine receptors as a result of chronic use of potent neuroleptics [11, 12].

Brexpiprazole, like cariprazine and aripiprazole, is extensively metabolized in the liver via "common" metabolic pathways, i.e., cytochrome P450 isoenzymes 3A4 and 2D6. Interactions of brexpiprazole with other drugs are similar to those described for aripiprazole and at least partially similar to those of cariprazine. The dose of brexpiprazole should be halved in patients taking concomitant 2D6 or 3A4 isoenzyme inhibitors and in patients with a known slow rate of hepatic metabolism involving the 2D6 isoenzyme (e.g., those who metabolize risperidone poorly) [9, 18]. The dose of brexpiprazole should be reduced to 1/4 of the recommended dose in people using 2D6 and 3A4 inhibitors concurrently, or in people with reduced 2D6 activity using 3A4 inhibitors [18, 19].

Brexpiprazole is eliminated by the liver and kidneys. In moderate to severe renal or hepatic insufficiency, a drug dose higher than 3 mg/day should not be used [19].

The basic pharmacological properties of brexpiprazole, cariprazine and aripiprazole are compared in Table 1.

## Clinical efficacy of brexpiprazole

The clinical efficacy of brexpiprazole in the treatment of schizophrenia has been confirmed in four 6-week randomized double-blind clinical trials (RCTs). In two of these studies, the control group took placebo [20, 21]. Two more studies evaluated an active control group treated with aripiprazole [22] or quetiapine [23] in addition to the control group taking placebo. The efficacy of brexpiprazole in preventing schizophrenia relapse has been confirmed in one 52-week RCT with a placebo control group [24] (Table 2).

Table 2. **Randomized double-blind clinical trials with a control group (RCT) confirming the efficacy of brexpiprazole in the treatment and relapse prevention in schizophrenia**

| Study | Patients | Duration | Evaluation methods | Results |
|---|---|---|---|---|
| NCT00905307, STEP 203 [22] | 459 patients aged 18-65 years randomized to groups: placebo, BREX 0.25 mg, BREX 1 mg, BREX 2.5 mg, BREX 5 mg, ARI 15 mg | 6 weeks | PANSS, CGI-S, CGI-I, PSP | No significant differences between groups in PANSS, CGI-S, CGI-I scales, significant improvement in PSP in BREX 5 mg group |
| NCT01396421, VECTOR [21] | 636 patients aged 18-65 years, randomization to groups: placebo, BREX 0.25 mg, BREX 2 mg, BREX 4 mg | 6 weeks | PANSS, CGI-S, CGI-I, PSP | Significantly greater improvement in PANSS, CGI-S, CGI-I scales in BREX 2 mg and BREX 4 mg group than in placebo group, in BREX 2 mg group additionally significantly greater improvement in PSP scale than in placebo group |

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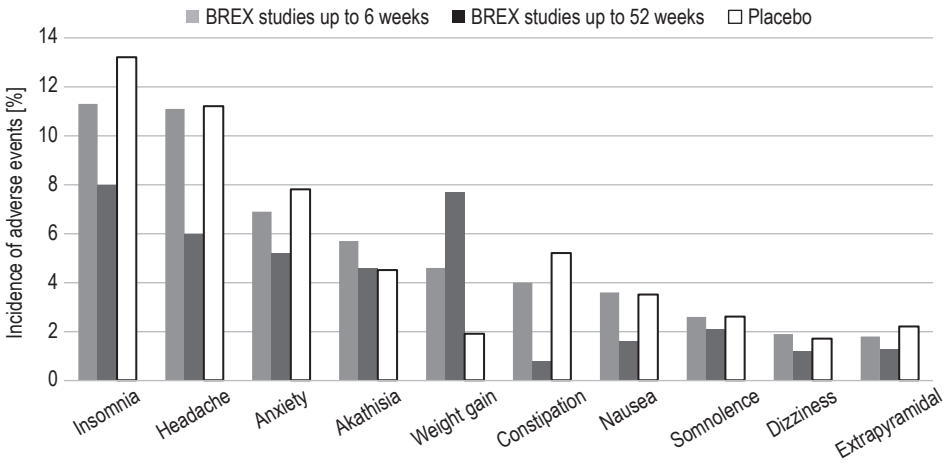
| | | | | |
|---|---|---|---|---|
| NCT01393613, BEACON[20] | 674 patients aged 18-65 years, randomization to groups: placebo, BREX 1 mg, BREX 2 lub BREX 4 mg | 6 weeks | PANSS, CGI-S, CGI-I, PSP | Significantly greater improvement in PANSS, CGI-S, CGI-I and PSP scales in BREX 4 mg group than in placebo group |
| NCT01810380 LIGHTHOUSE [23, 30] | 468 patients aged 18-65 years randomized to groups: BREX at a dose of 2-4 mg (average dose 3.5 mg), QUE XR at a dose of 400-800 mg (average dose 674 mg) or placebo | 6 weeks | PANSS, CGI-S, CGI-I, PSP, S-QoL | Significantly greater improvement in the CGI-S, CGI-I, PSP and S-QoL scales in the BREX 2-4 mg group than in the placebo group, the difference in the PANSS scale did not reach statistical significance (p=0.0560) in the original analysis [23], it was shown in the post-hoc analysis (p=0.0260) [30] |
| NCT01668797 EQUATOR [24] | 202 patients aged 18-65 years randomized to groups: BREX 1-4 mg (average dose 3.6 mg) or placebo | 52 weeks after 12-36 week stabilization of mental state during BREX treatment at a dose 1-4 mg | PANSS, CGI-S, C-SSRS | Significant difference between BREX 1-4 mg group and placebo group in percentage of patients with exacerbation of psychotic symptoms/ impending relapse (13.5% vs. 38.5%) |

BREX – brexpiprazole, ARI – aripiprazole, QUE – quetiapine, PANSS – Positive and Negative Syndrome Scale, CGI-S and CGI-I – Clinical Global Impression scales: severity and improvement, PSP – Personal and Social Performance Scale, S-Qol – Schizophrenia Quality of Life

The aforementioned studies that formed the basis for the registration of brexpiprazole for the indication "treatment of schizophrenia" are also extensively summarized in three review articles [22, 23, 25] and in the Summary of Product Characteristics (SmPC) of brexpiprazole [19]. Brexpiprazole meets the traditional requirements for antipsychotic drug efficacy, i.e., compared to placebo, it leads to a greater reduction in schizophrenia symptoms as assessed by the PANSS scale in short-term studies and prevents schizophrenia relapses more effectively than placebo in long-term follow-up. The highest antipsychotic efficacy was found with the highest registered dose of brexpiprazole, i.e., 4 mg/d. The average dose of brexpiprazole used in clinical trials was 3.4-3.6 mg/d. The lowest dose of the drug for which a significantly greater reduction in PANSS score was observed than with placebo was 2 mg/d. In addition to reducing positive symptoms, brexpiprazole treatment also leads to a reduction in negative symptoms, depressive symptoms and anxiety. Also relevant in the context of schizophrenia treatment goals are the observations that brexpiprazole treatment has a positive effect on patients' social and personal functioning as assessed by the Personal and Social Performance Scale (PSP) and quality of life [22, 23].

### Tolerability of treatment with brexpiprazole

In short-term studies of brexpiprazole at doses up to 4 mg, there were no adverse events with a frequency at least twice that of placebo (Figure 1).




In short-term studies, the data refer to brexpiprazole doses in the 2-4 mg range and in long-term studies the dose was 1-6 mg. Data for placebo are from short-term trials.

Figure 1. **Incidence of adverse events during treatment with brexpiprazole in short- and long-term studies compared to placebo (on the basis of [25])**

Insomnia and headache were the most commonly reported side effects during brexpiprazole treatment (11.3% and 11.1%, respectively, compared to 13.2% and 11.2% in the placebo group). Of the side effects common to neuroleptics, patients most frequently reported experiencing akathisia (5.8% versus 4.5% in patients taking placebo). Once the brexpiprazole dose of 4 mg was exceeded, the incidence of akathisia increased up to 15%. This was the main reason for abandoning the evaluation of doses of the drug above 4 mg in phase 3 clinical trials [25]. Excessive sedation was reported by 2.3% of patients (for brexpiprazole doses in the 2-4 mg range versus 0.6% when taking placebo). Excessive drowsiness was reported by 2.6% of patients treated with brexpiprazole at a dose of 2-4 mg and 2.6% of patients receiving placebo. The average change in body weight during brexpiprazole treatment in short-term studies was 1.1 kg (it was 0.2 kg for patients receiving placebo). In long-term studies, the average weight gain during brexpiprazole treatment was 1.1 kg, and 2.2 kg for patients taking brexpiprazole for a full 52 weeks. The percentage of patients with a weight gain of ≥7% was 18.2%. Changes in metabolic parameters were negligible. Newly diagnosed metabolic disorders were found in 1.2% of patients taking brexpiprazole and 0.8% of patients receiving placebo. In long-term studies, metabolic disorders were found in

3.1% of patients. No increase in serum prolactin concentration was observed during treatment with brexpiprazole.

## Discussion

Brexpiprazole is a new antipsychotic drug from the group of dopamine $D_2/D_3$ receptor partial agonists. Drugs in this group are characterized by their high safety (no cholinolytic effects, no prolongation of the ECG QTc interval, low risk of hypotonia and tardive dyskinesia) and good tolerability (low risk of weight gain, extrapyramidal symptoms, hyperprolactinemia and sexual dysfunction as well as excessive drowsiness and sedation).

Although in short-term studies, drugs in this group are inferior to numerous other antipsychotics in terms of reducing symptom severity on the PANSS scale [4], and in long-term studies – in terms of the effectiveness with which they prevent relapse [26], there is no doubt that dopamine $D_2/D_3$ receptor agonists, including brexpiprazole, are a valuable addition to the pharmacological treatment options for schizophrenia. The main obstacle to providing such treatment, with the exception of drug-resistant patients, is not that antipsychotic drugs are insufficiently effective, but that patients discontinue medication. Data from large epidemiological studies based on insurance records and prescription data indicate that in more than 30% of schizophrenia patients, discontinuation or change of antipsychotic treatment occurs within the first 30 days of taking a new second-generation antipsychotic. During 180 days of follow-up, this occurs in more than 70% of patients [27]. Besides lack of insight, the main reasons for this behavior are poor tolerance of treatment and insufficient effects of antipsychotic drugs on daily functioning from the patient's perspective. As a drug without cholinolytic effects and with a low risk of sedative effects, brexpiprazole is a favorable form of treatment for patients complaining of difficulties in daily functioning due to cognitive deficits. Also important in the context of restoring patients to normal social functioning are observations showing that brexpiprazole treatment leads to significant improvements in patients' social functioning as assessed by the PSP and GAF (Global Assessment of Functioning) scales in both short- and long-term studies [28]. This favorable profile of brexpiprazole seems to explain why the risk of discontinuing brexpiprazole treatment is lower than with other antipsychotics [29]. This, in turn, translates into brexpiprazole's effectiveness in preventing schizophrenia relapses. Data from the 52-week study indicated a 25 percentage-point difference between the group taking brexpiprazole and placebo for the risk of relapse after early stabilization (13.5% vs. 38.5%) [24]. This means that the NNT (number needed to treat) for brexpiprazole in preventing relapse of schizophrenia is 4; it is therefore a very effective treatment.

When evaluating the efficacy of brexpiprazole, attention should be paid to the doses of the drug used. In clinical trials with variable dosage regimens, they were in the upper range of registered doses and amounted to 3.5-3.6 mg/d [23, 24, 30]. In fixed-dose clinical trials, efficacy was found for the highest registered dose of 4 mg/d, while variable results were obtained for the 2 mg/d dose [20, 21]. These data demonstrate that in the case of brexpiprazole, physicians should follow the principle

of using the maximum well-tolerated dose rather than the principle of using the lowest effective dose, as is necessary with numerous neuroleptics, whose tolerability and safety profile is much less favorable than that of brexpiprazole. A lower dose of brexpiprazole should only be considered if side effects (e.g., akathisia) are present or if the patient is taking concomitant strong CYP450 2D6 or 3A4 isoenzyme inhibitors. It is also important to keep in mind that in order to improve patients' prognosis and functioning, pharmacological treatment should be used in conjunction with non-pharmacological treatment [31].

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