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Effect of Brexpiprazole on Prolactin

An Analysis of Short- and Long-Term Studies in Schizophrenia

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Abstract:

Background: Hyperprolactinemia is an undesirable effect of most antipsychotics because of D_2-receptor blockade. We assessed the effect of the D_2-receptor partial agonist brexpiprazole on prolactin, based on pooled data from three 6-week, randomized, placebo-controlled studies and two open-label extension studies in patients with schizophrenia.

Methods: In the short-term studies, patients received 0.25, 1, 2, 4 mg brexpiprazole or placebo; or flexible-dose brexpiprazole (2–4 mg/d), placebo, or active reference. The extension studies were 52-week, flexible-dose (1–4 mg/d) studies. We studied changes from baseline and shifts in prolactin status in patients with normal or elevated prolactin levels at baseline, and prolactin-related treatment-emergent adverse events (TEAEs).

Results: Median changes from baseline to week 6 in brexpiprazole-treated patients in short-term studies were as follows: 3.63 ng/mL (females), 0.26 ng/mL (males); placebo: −2.15 ng/mL (females), −1.08 ng/mL (males).

Median changes from baseline to week 52 in long-term studies were 0.60 ng/mL (females) and 0.18 ng/mL (males). Prolactin levels in patients with baseline values greater than 1× upper limit of normal tended to decrease over time regardless of previous treatment.

The proportions of brexpiprazole-treated patients with greater than 3× upper limit of normal postbaseline prolactin values in short-term studies were as follows: 1.5% (females), 1.6% (males); placebo: 3.6% (females), 3.4% (males). Corresponding figures in long-term studies were 5.3% (females) and 2.0% (males).

In short-term studies, the incidence of prolactin-related TEAEs was 1.8% for brexpiprazole and 0.6% for placebo. In long-term studies, the incidence of prolactin-related TEAEs was 1.7%.

Conclusions: Small changes in prolactin levels, low proportions of patients with postbaseline elevated prolactin values, and low incidence of prolactin-related TEAEs were observed after treatment with brexpiprazole.

Key Words: antipsychotic, brexpiprazole, partial dopamine agonist, prolactin

(*J Clin Psychopharmacol* 2019;39: 13–19)

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Received May 14, 2018; accepted after revision September 25, 2018.

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Johan Hellsten, PhD (a full-time employee of H. Lundbeck A/S), wrote the first draft and edited subsequent versions under direction of the authors.

Funding for this trial was provided by Otsuka Pharmaceutical Development & Commercialization Inc, and H. Lundbeck A/S.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

ISSN: 0271-0749

DOI: 10.1097/JCP.0000000000000979

Hyperprolactinemia is an undesirable effect of most antipsychotics, considered to primarily be due to dopamine D_2-receptor blockade, which causes loss of the dopaminergic inhibitory effect on prolactin secretion.[1,2] Women are more sensitive than men to the hyperprolactinemic effect of the drugs because of estrogen involvement in modulation of prolactin secretion.[3]

The increase in prolactin levels can be associated with clinical symptoms, leading to patient distress and impaired quality of life (eg, sexual dysfunction), be stigmatizing (eg, gynecomastia in men, hirsutism and amenorrhea in women), put overall health at risk (eg, osteoporosis), and ultimately affect functionality, treatment adherence, and satisfaction.[4–8]

Although all antipsychotic drugs can induce elevations in prolactin levels, various antipsychotics differ in their potential for prolactin elevation.

The degree of hyperprolactinemia is dependent on the dopamine D_2 receptor occupancy[9] and the antagonist properties of the antipsychotics.[10]

Antipsychotics having a high potential for prolactin elevation (amisulpride, risperidone, and paliperidone) can have a large impact at relatively low doses, whereas prolactin levels, in most cases and across all doses, remain unchanged with quetiapine, or even decrease, during treatment with the partial dopamine agonist aripiprazole.[2]

Brexpiprazole is a serotonin–dopamine activity modulator that is a partial agonist at 5-HT_{1A} and dopamine D_2 receptors, and an antagonist at 5-HT_{2A} and noradrenaline $\alpha_{1B/2C}$ receptors, all with subnanomolar potency.[11]

Brexpiprazole is currently approved in the United States, Saudi Arabia, Honduras and Mexico for use as adjunctive therapy to antidepressants for the treatment of major depressive disorder and in the United States, Saudi Arabia, Australia, Canada, and Japan as monotherapy for treatment of schizophrenia, including maintenance treatment.

The aim of the current analysis was to evaluate the effect of brexpiprazole on prolactin in an analysis of pooled data from three short-term studies[12–14] and pooled data from two long-term extension studies (Zenith[15] and NCT01810783) in patients with schizophrenia.

MATERIALS AND METHODS

Study Designs

A detailed summary of studies included in this article is presented in Supplementary Tables 1 and 2 (Supplementary Digital Content 1, http://links.lww.com/JCP/A535). The studies were designed and conducted in accordance with the principles of the Declaration of Helsinki, and the study protocols were approved by the governing institutional review board or independent ethics committee for each investigational site or country, as appropriate. All patients provided written informed consent prior to the start of the studies. The short-term studies were randomized, double-blind, placebo-controlled, fixed-dose (Beacon,[12] Vector[13]) and flexible-dose (Lighthouse[14]), phase 3 studies, which included a 14-day screening phase and a 6-week double-blind treatment phase.

The studies were designed to assess the safety and efficacy of brexpiprazole in adults with acute schizophrenia. Briefly, patients were 18 to 65 years of age, with a current diagnosis of schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*) confirmed by Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies. Patients experiencing an acute exacerbation who would benefit from hospitalization were recruited.

Eligible patients in the fixed-dose studies were randomized to oral placebo or brexpiprazole 0.25, 2, or 4 mg once daily (2:1:2:2) in the Vector study and to oral placebo or brexpiprazole 1, 2, or 4 mg once daily (3:2:3:3) in the Beacon study. Eligible patients in the flexible-dose study were randomized to oral placebo, brexpiprazole 2–4 mg, or quetiapine XR 400–800 mg once daily (1:1:1). For all 3 studies, prior antipsychotic medications were washed out during the screening period, lasting up to 14 days.

The extension studies were open-label, flexible-dose (1–4 mg/day) studies. Zenith[15] enrolled de novo patients (patients not participating in either of the two fixed-dose lead-in studies, or any other clinical study with brexpiprazole), patients completing one of the two fixed-dose studies, or patients from a maintenance study (Equator[16]); Lighthouse extension (NCT01810783) enrolled patients completing the flexible dose study.

The extension studies consisted of an open-label treatment period (52 weeks [study duration for Zenith was amended to 26 weeks as the safety profile of brexpiprazole was considered to be well established]) and a safety follow-up period (30 days).

Assessments

In the short-term studies, baseline was defined as start of study medication (placebo or brexpiprazole). In the long-term studies, baseline was defined as last assessment prior to treatment start in the respective long-term study.

We studied changes from baseline, clinically relevant prolactin values, and shifts in prolactin status in patients with normal or elevated prolactin levels at baseline.

Prolactin was measured at baseline and weeks 3 and 6 in the short-term studies and at regular intervals throughout the long-term studies. Mean and median changes from baseline are reported at week 6 for the short-term studies and at weeks 26 and 52 for the long-term studies.

Dependent on which central laboratory was used and its respective standard, 2 definitions of upper limit of normal (ULN) prolactin levels were used in the studies included in this analysis. The ULN in Lighthouse and Lighthouse extension was as follows: females = 29.19 ng/mL, males = 17.69 ng/mL. The ULN in Vector, Beacon, and Zenith was as follows: females = 26.72 ng/mL, males = 13.13 ng/mL.

Clinically relevant prolactin values were defined in accordance with those used in regulatory submission documents, that is, any value larger than ULN (>1× ULN).

Incidences of shifts in prolactin status are presented as shifts from baseline to any time postbaseline. Percentages were obtained by dividing the number of patients with potential clinically relevant shift with the total number of patients who met the baseline criteria and had a postbaseline result.

The search for treatment-emergent adverse events (TEAEs) related to prolactin was made using the MedDRA 16.1 System Organ Class *Reproductive system and breast disorder* and the following preferred terms: *blood prolactin increased*, *hyperprolactinaemia*, *galactorrhoea*, *gynaecomastia*, *breast swelling*, *breast enlargement*, *breast mass*, *breast tenderness*, *amenorrhoea*, *oligomenorrhea*, *anovulatory cycle*, *hypomenorrhoea.*

Statistical Analysis

All analyses were performed on the safety population (all patients who received at least 1 dose of study medication), but

TABLE 1. Disposition, Demographics, and Clinical Characteristics

	Short Term		Long Term (by Prior Treatment)		
	Placebo (n = 529)	**Brexpiprazole 2–4 mg (n = 882)**	**Prior Placebo/De Novo (n = 490)**	**Prior Brexpiprazole (n = 671)**	**Prior Quetiapine (n = 79)**
Disposition					
Completed	335 (63.3)	617 (70.0)	227 (46.3)	342 (51.0)	40 (50.6)
Discontinued	194 (36.7)	265 (30.0)	263 (53.7)	329 (49.0)	39 (49.4)
Adverse event	65 (12.3)	70 (7.9)	61 (12.4)	115 (17.1)	15 (19.0)
Lack of efficacy	63 (11.9)	70 (7.9)	25 (5.1)	27 (4.0)	3 (3.8)
Protocol violation	1 (0.2)	4 (0.5)	7 (1.4)	3 (0.4)	2 (2.5)
Withdrawal of consent	48 (9.1)	103 (11.7)	80 (16.3)	112 (16.7)	4 (5.1)
Lost to follow-up	1 (0.2)	0	34 (6.9)	18 (2.7)	5 (6.3)
Other	11 (2.1)	13 (1.5)	8 (1.6)	6 (0.9)	9 (11.4)
Met withdrawal criteria	1 (0.2)	3 (0.3)	42 (8.6)	38 (5.7)	0
Withdrawn by investigator	4 (0.8)	2 (0.2)	4 (0.8)	9 (1.3)	0
Noncompliance	0	0	2 (0.4)	1 (0.1)	1 (1.3)
Demographics					
Age, mean (SD), y	39.9 (10.7)	39.1 (10.9)	42.0 (11.2)	38.4 (10.9)	40.8 (11.1)
BMI, mean (SD), kg/m^2	26.5 (5.4)	27.0 (6.1)	28.4 (7.0)	27.3 (6.2)	28.0 (6.1)
Male, n (%)	320 (60.5)	541 (61.3)	301 (61.4)	390 (58.1)	35 (44.3)
White, n (%)	354 (66.9)	574 (65.1)	279 (56.9)	480 (71.5)	65 (82.3)
Clinical characteristics					
PANSS total score at baseline, mean (SD)	96.2 (11.8)	95.9 (12.4)	68.9 (17.3)	69.1 (16.6)	70.5 (14.8)

BMI indicates body mass index; PANSS, Positive and Negative Syndrome Scale.

TABLE 2. Short-Term Studies—Mean Changes From Baseline by Sex and Baseline Prolactin Status

Sex	Females				Males			
Baseline Status	Normal		>1× ULN		Normal		>1× ULN	
Treatment	Placebo	Brexpiprazole 2–4 mg	Placebo	Brexpiprazole 2–4 mg	Placebo	Brexpiprazole 2–4 mg	Placebo	Brexpiprazole 2–4 mg
Baseline, mean (median) [n]	10.58 (8.87) [164]	10.29 (8.85) [271]	66.70 (46.63) [44]	67.43 (50.68) [63]	6.77 (6.33) [240]	6.54 (5.79) [399]	25.95 (21.86) [77]	26.62 (20.90) [137]
Change, week 6, mean (median) [n]	0.08 (−0.91) [98]	6.72 (5.22) [195]	−38.79 (−30.78) [26]	−33.41 (−25.12) [47]	0.66 (−0.24) [158]	2.35 (1.60) [267]	−11.29 (−11.93) [49]	−12.64 (−10.64) [95]

excluding the low-dose brexpiprazole treatment groups (0.25 and 1 mg) in the short-term studies. Patients in the short-term studies randomized to placebo were pooled for the analysis, as were patients randomized to fixed-dose brexpiprazole 2 or 4 mg or to flexible-dose brexpiprazole 2–4 mg. Patients treated with flexible-dose brexpiprazole 1–4 mg in the long-term studies (including patients from the short-term low-dose groups) were pooled for the analysis. Calculation of mean and median prolactin changes in the studies used observed case data.

RESULTS

Patients

Baseline demographic and clinical characteristics were similar between the treatment groups in the short-term studies and by prior treatment in the long-term studies (Table 1).

Short-Term Studies—Changes From Baseline

Both mean and median values were provided given the skewed distribution of the prolactin values. Mean (median) baseline prolactin values in the brexpiprazole-treated patients in the short-term studies were as follows: 21.07 (10.44) ng/mL for females, 11.67 (7.63) ng/mL for males; in the placebo-treated patients: 22.45 (11.11) ng/mL for females, 11.43 (7.99) ng/mL for males.

Mean (median) change values from baseline to week 6 in the brexpiprazole-treated patients in the short-term studies were as follows: −1.08 (3.63) ng/mL for females, −1.58 (0.26) ng/mL for males; in the placebo-treated patients: −8.07 (−2.15) ng/mL for females, −2.17 (−1.08) ng/mL for males.

As shown in Table 2, among females with prolactin values within normal range at baseline, a modest increase was observed in the brexpiprazole group. In females with >1× ULN prolactin values at baseline, there was a decrease from baseline, and the magnitude of the change was similar in the brexpiprazole and placebo groups.

In males, changes over time were small in patients with normal values at baseline. In males with >1× ULN prolactin values at baseline, a decrease was observed in both the brexpiprazole and placebo groups.

No apparent dose-dependent increase in prolactin levels at week 6 was noted in the 2 fixed-dose studies (Supplementary Table 3; Supplementary Digital Content 1, http://links.lww.com/JCP/A535).

Long-Term Studies—Changes From Baseline

Both mean and median values were provided given the skewed distribution of the prolactin values. Mean (median) baseline prolactin values in the long-term studies were as follows: 17.29 (12.79) ng/mL for females, 9.64 (7.71) ng/mL for males.

Mean (median) change values from baseline to week 52 in long-term studies were 0.48 (0.60) ng/mL for females and 0.85 (0.18) ng/mL for males.

As shown in Table 3, among females with normal values at baseline, a slight increase over time was observed. The magnitude of the change was smallest in the prior brexpiprazole group and less pronounced than in the short-term studies.

Prolactin in females with >1× ULN values at baseline tended to decrease over time regardless of the previous treatment given. A similar pattern was seen in males.

In male patients with normal values at baseline, changes were almost negligible.

Postbaseline Elevated Values and Shifts

The proportion of brexpiprazole-treated patients with postbaseline >3× ULN prolactin values at any visit in the short-term studies were

TABLE 3. Long-term Studies—Mean Changes From Baseline by Sex, Baseline Prolactin Status, and Prior Treatment

Sex	Females						Males					
Baseline Status	Normal			>1× ULN			Normal			>1× ULN		
Treatment	Prior Placebo/ De Novo	Prior Brexpiprazole	Prior Quetiapine	Prior Placebo/ De Novo	Prior Brexpiprazole	Prior Quetiapine	Prior Placebo/ De Novo	Prior Brexpiprazole	Prior Quetiapine	Prior Placebo/ De Novo	Prior Brexpiprazole	Prior Quetiapine
Baseline, mean (median) [n]	9.62 (8.51) [171]	14.50 (13.78) [224]	11.21 (10.95) [38]	52.64 (40.77) [17]	45.68 (36.56) [49]	52.23 (36.09) [5]	6.40 (6.19) [251]	7.57 (7.61) [312]	7.39 (5.75) [24]	22.44 (18.36) [45]	20.59 (16.92) [70]	30.54 (25.38) [8]
Change, week 26, mean (median) [n]	7.48 (5.07) [100]	3.78 (0.56) [150]	8.19 (5.94) [26]	−4.69 (−25.11) [11]	−15.49 (−11.62) [30]	−36.45 (−28.05) [4]	1.68 (1.14) [151]	0.85 (0.25) [173]	1.55 (0.97) [8]	−8.00 (−7.43) [22]	−4.22 (−3.16) [44]	−13.43 (−13.29) [4]
Change, week 52, mean (median) [n]	4.64 (1.63) [76]	1.95 (0.60) [100]	8.47 (7.00) [26]	−24.25 (−33.97) [7]	−21.59 (−19.71) [15]	−41.08 (−34.72) [4]	1.66 (1.16) [107]	0.47 (0.05) [101]	7.60 (1.80) [8]	−7.10 (−7.74) [16]	2.74 (−1.74) [34]	−12.60 (−7.71) [3]

as follows: 1.5% for females, 1.6% for males; in the placebo-treated patients: 3.6% for females, 3.4% for males.

The proportion of patients with postbaseline >3× ULN prolactin values at any visit in the long-term studies were 5.3% for females and 2.0% for males.

As shown in Table 4, a larger proportion of patients on brexpiprazole than placebo shifted from normal to >1× ULN in the short-term studies. This effect was more pronounced for females than for males during long-term treatment. A shift from normal at baseline to >3× ULN or more was observed in a small proportion of patients, regardless of the length of the study.

Thirty-eight percent of females and 52% of males in the brexpiprazole group with >1× ULN prolactin values at baseline had normalized prolactin values during the short-term studies; corresponding proportions in the long-term studies were 26% and 23%.

The vast majority of patients with normal prolactin values at baseline did not shift during the course of the studies.

Treatment-Emergent Adverse Events Related to Hyperprolactinemia

The incidence of TEAEs related to hyperprolactinemia was low (Table 5). Three of 529 patients (0.6%) in the placebo group and 16 of 882 patients (1.8%) in the brexpiprazole 2–4 mg group in the short-term studies experienced TEAEs related to hyperprolactinemia. The incidence of hyperprolactinemia-related TEAEs in the long-term studies was 1.7% (21/1240). The most common TEAEs related to hyperprolactinemia in the short- and long-term studies were blood prolactin increase and dysmenorrhea, respectively, both with an incidence of 0.6%.

DISCUSSION

In both short- and long-term studies, we observed small changes in prolactin values and low proportions (1.5%–3.6% in short-term studies, 2%–5.3% in long-term studies) of patients with postbaseline elevated prolactin values of >3× ULN after treatment with brexpiprazole. The magnitude of the changes in prolactin levels appears smaller during long-term use compared with short-term use, indicating that brexpiprazole is not associated with sustained prolactin increase after chronic treatment. Furthermore, in patients with prolactin values above normal at baseline, values tended to decrease over time, and a substantial proportion of patients with elevated values at baseline shifted to normal range. The incidence of adverse events related to hyperprolactinemia and sexual dysfunction was low.

Leucht et al[17] performed a meta-analysis of all placebo-controlled trials to date in patients with acute exacerbations of schizophrenia. All antipsychotic drugs, except aripiprazole, led to more prolactin increase compared with placebo, and brexpiprazole ranked fourth lowest after aripiprazole, cariprazine, and quetiapine, whereas paliperidone and risperidone ranked highest. In a clinical review by Solmi et al,[18] the authors categorized brexpiprazole, based on its D_2 partial agonism, along with cariprazine and aripiprazole, as compounds that can lower baseline prolactin levels. Although indirect comparisons between drugs should be performed with caution, owing to differences in study lengths, settings, and methodologies, a closer look at cariprazine and aripiprazole is warranted, given the similarities in their D_2 receptor binding, that is, partial agonism. Cariprazine, in licensed dose ranges, has been shown to decrease prolactin mean levels from baseline to study endpoint in short-term[19] and long-term studies[20] in the range of −13.4 to −17.1 ng/mL. Aripiprazole is often referred to as being a prolactin-sparing compound, a term meaning that it produces little or no clinically significant prolactin elevation.[21]

TABLE 4. Shifts in Prolactin Status

	Short Term				Long Term	
Sex	**Females**		**Males**		**Females**	**Males**
Shift From Baseline to Any time Postbaseline	**Placebo, % (n/N)**	**Brexpiprazole 2–4 mg, % (n/N)**	**Placebo, % (n/N)**	**Brexpiprazole 2–4 mg, % (n/N)**	**Brexpiprazole 1–4 mg, % (n/N)**	
Normal to >1× ULN*	12% (19/153)	20% (52/260)	17% (37/218)	19% (70/377)	28% (117/414)	20% (112/562)
Normal to >3× ULN*	1% (1/153)	0% (0/260)	1% (2/218)	1% (2/377)	3% (14/414)	1% (3/562)
Normal to >5× ULN*	0% (0/153)	0% (0/260)	0% (0/218)	0.3% (1/377)	0.2% (1/414)	0.2% (1/562)
>1× ULN to normal†	59% (24/41)	38% (23/60)	46% (32/70)	52% (66/128)	26% (17/66)	23% (26/111)
Normal to normal†	88% (134/153)	80% (208/260)	83% (181/218)	81% (307/377)	72% (297/414)	80% (450/562)

Normal: ≤1× ULN.

*Shifts are inclusive; all values >3× ULN and >5× ULN are included in the shift to >1× ULN, and all values >5× ULN are included in the shift to >3× ULN.

†Postbaseline shifts are based on the worst case any time postbaseline; normal is obtained only if no postbaseline values were classified as greater than ULN for a patient.

N indicates the total number of patients who met the baseline criteria and had a postbaseline result; n, number of patients with relevant shift (the denominator for percentage calculation is N).

TABLE 5. Treatment-Emergent Adverse Events Related to Hyperprolactinemia

	Short Term		Long Term
	Placebo (n = 529)	**Brexpiprazole 2–4 mg (n = 882)**	**Brexpiprazole 1–4 mg (n = 1240)**
Patients with hyperprolactinemia-related TEAEs	3 (0.6)	16 (1.8)	21 (1.7)
Endocrine disorders			
Hyperprolactinemia	1 (0.2)	3 (0.3)	3 (0.2)
Investigations			
Blood prolactin increased	0	1 (0.1)	7 (0.6)
Reproductive system and breast disorders			
Dysmenorrhea	1 (0.5)	2 (0.6)	1 (0.2)
Menstruation irregular	0	1 (0.3)	1 (0.2)
Erectile dysfunction	0	1 (0.2)	1 (0.1)
Breast tenderness	0	1 (0.3)	0
Menopausal symptoms	0	1 (0.3)	0
Vulvovaginal pain	0	1 (0.3)	0
Vulvovaginal pruritus	1 (0.5)	1 (0.3)	0
Ejaculation disorder	0	1 (0.2)	0
Genital pain	0	1 (0.2)	0
Scrotal pain	0	1 (0.2)	0
Spontaneous penile erection	0	1 (0.2)	0
Testicular pain	0	1 (0.2)	0
Menstrual disorder	0	0	2 (0.4)
Galactorrhea	0	0	1 (0.2)
Hypomenorrhea	0	0	1 (0.2)
Breast discomfort	0	0	1 (0.2)
Cystocele	0	0	1 (0.2)
Hysterocele	0	0	1 (0.2)
Menorrhagia	0	0	1 (0.2)
Ovarian cyst	0	0	1 (0.2)
Polycystic ovaries	0	0	1 (0.2)
Uterine polyp	0	0	1 (0.2)
Vaginal discharge	0	0	1 (0.2)
Gynecomastia	0	0	1 (0.1)

Data are n (%). Dictionary: MedDRA 16.1. Search based on the following preferred terms: *blood prolactin increased*, *hyperprolactinaemia*, *galactorrhea*, *gynaecomastia*, *breast swelling*, *breast enlargement*, *breast mass*, *breast tenderness*, *amenorrhoea*, *oligomenorrhea*, *anovulatory cycle*, *hypomenorrhoea*, and System Organ Class *Reproductive system and breast disorder.*

Decreases from baseline in mean prolactin levels in the range of −6.4 to −8.1 ng/mL were observed in short- and long-term studies with aripiprazole.[22–24] Further, aripiprazole has been shown to reverse antipsychotic-induced hyperprolactinemia.[25,26] Some treatment guidelines recommend the use of aripiprazole, either as monotherapy or as adjunctive, as a treatment for patients with antipsychotic-induced hyperprolactinemia (for review, see Grigg et al[8]). One meta-analysis[27] concluded that adjunctive aripiprazole is a safe and effective treatment for patients with antipsychotic-induced hyperprolactinemia, whereas a more recent meta-analysis[28] recommended longer trials of higher quality before fully endorsing adjunctive aripiprazole as a treatment for patients with antipsychotic-induced hyperprolactinemia.

Based on the data from patients with elevated prolactin levels at baseline in our analysis, in which values generally decreased over time, and considering that brexpiprazole is a D_2 partial agonist, although with lower intrinsic activity than aripiprazole,[29] brexpiprazole could have potential utility as a prolactin-stabilizing/lowering agent in schizophrenia, but research is needed before any such use can be recommended.

Antipsychotic-induced hyperprolactinemia occurs in up to 70% of patients with schizophrenia.[30] A recent longitudinal naturalistic study in first-episode psychosis showed that the prevalence of hyperprolactinemia at baseline for antipsychotic-naive patients was 11%,[31] whereas the prevalence in the general population is 0.4%.[32] Lally et al[31] conclude that measurement of prolactin levels should be routinely performed before the start of treatment with any antipsychotic and, in case of raised levels already at baseline, that a prolactin-sparing antipsychotic is used.

A meta-analysis[33] concluded that sexual dysfunction, as measured with dedicated scales, is a common adverse effect of antipsychotics, although sexual dysfunction is also frequently associated with schizophrenia in itself. Further, the authors found that significant differences existed in the rate of sexual dysfunction observed with different antipsychotics, partially in agreement with the categorization into prolactin-raising and prolactin-sparing compounds.

While the incidence of adverse events related to hyperprolactinemia is low in our analysis (no event had an incidence >0.6%), no dedicated assessments of sexual functioning were performed during the conduct of the studies, and this thus limits our ability to evaluate the effect of brexpiprazole on sexual functioning.

Further limitations of our analysis should also be taken into consideration and include the use of post hoc analysis approach, the evaluation of patients with schizophrenia fulfilling eligibility criteria that may limit generalizability, and the lack of head-to-head comparisons with other antipsychotics. A strength of the analysis is that it is based on large, high-quality data set.

In conclusion, antipsychotic-induced hyperprolactinemia can have severe clinical consequences and cause distress and altered quality of life for patients. Our analysis suggests that brexpiprazole has minimal impact on prolactin, which, in combination with its generally favorable safety and tolerability profile,[34–37] makes it a good alternative to current therapeutic options in the treatment of patients with acute schizophrenia, including first-episode schizophrenia.

AUTHOR DISCLOSURE INFORMATION

J.I., A.L., and H.E. are full-time employees of H. Lundbeck A/S, Valby, Denmark. V.G. and M.H. are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc, Princeton, NJ.

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