Changes in Metabolic Parameters and Body Weight in Patients With Prediabetes Treated With Adjunctive Brexpiprazole for Major Depressive Disorder:

Pooled Analysis of Short- and Long-Term Clinical Studies

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Abstract

Objective: Certain atypical antipsychotics, while efficacious as adjunctive treatments in major depressive disorder (MDD), are associated with metabolic adverse effects and weight gain. This analysis determined the effect of adjunctive brexpiprazole on metabolic parameters and body weight in adults with MDD and prediabetes (ie, at risk of developing diabetes) based on pooled data from 3 short-term studies and 1 long-term study.

Methods: The short-term studies were 6-week, randomized, double-blind, placebo-controlled studies of adjunctive oral brexpiprazole 1–3 mg/d in outpatients with MDD (*DSM-IV-TR* criteria) and inadequate response to antidepressant treatment, conducted between June 2011 and May 2016. The long-term study was a 26- to 52-week, open-label extension study conducted between October 2011 and May 2017. *Prediabetes* was defined based on fasting serum glucose and glycated hemoglobin (HbA1c) levels. Shifts in diabetes status and shifts/changes in fasting metabolic parameters and body weight were determined.

Results: Most patients receiving adjunctive brexpiprazole maintained their baseline diabetes status in the short term (568/751; 75.6%) and long term (1,919/2,746; 69.9%). The incidence of categorical shifts in fasting metabolic parameters generally did not differ between treatment groups or between prediabetes and non-diabetes subgroups. Mean changes from baseline in metabolic parameters were small in the short term (all < 5 mg/dL) and long term (all < 6 mg/dL, except < 20 mg/dL for triglycerides). Moderate weight gain was observed in the short term (1.5 kg) and long term (3.4–4.1 kg).

Conclusions: Adjunctive brexpiprazole had a limited impact on the metabolic profile of patients with MDD, regardless of diabetes status (prediabetes/non-diabetes).

Trial Registration: Data used in this post hoc analysis came from studies with ClinicalTrials.gov identifiers NCT01360645, NCT01360632, NCT02196506, and NCT01360866.

J Clin Psychiatry 2023;84(5):23m14786

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Patients with major depressive disorder (MDD) have an increased risk of developing metabolic syndrome (a combination of metabolic factors that increases the risk of developing type 2 diabetes mellitus and cardiovascular disease) and type 2 diabetes mellitus.[1–5] One suggested contributor to this increased risk is that patients with depression may have unhealthy lifestyles and poor diet.[3,6,7] It has also been hypothesized that depression and diabetes share common pathophysiologic alterations in the stress response system.[3,4] In addition, the use of antidepressant treatments (ADTs) may be an independent risk factor for type 2 diabetes, potentially due to drug-related weight gain or via a direct effect on glucose metabolism by altering insulin resistance or secretion.[8,9]

Up to half of patients with MDD do not adequately respond to ADTs,[10,11] and randomized trials show that the adjunctive administration of certain atypical antipsychotics can improve depressive symptoms in some of these patients.[12] However, many antipsychotics are associated with metabolic adverse effects and weight gain that further increase the risk of developing diabetes.[12–16] Consequently, in the population of patients with MDD for whom adjunctive antipsychotic treatment is deemed appropriate, it is vital that prescribing physicians select an

Clinical Points

- Patients with prediabetes and major depressive disorder treated with adjunctive brexpiprazole may experience small changes in metabolic parameters and moderate weight gain over the short and long term, which are unlikely to be clinically meaningful.
- Adjunctive brexpiprazole can improve depressive symptoms in patients with prediabetes and major depressive disorder.

agent that has minimal effect on metabolic parameters and weight—particularly among patients who may be clinically vulnerable to diabetes, such as those with prediabetes.

Brexpiprazole has a therapeutic action attributed to high-affinity partial agonism at serotonin 5-HT_{1A} (K_i = 0.12 nM) and dopamine D_2 (K_i = 0.30 nM) receptors and high-affinity antagonism at serotonin 5-HT_{2A} (K_i = 0.47 nM) and norepinephrine α_{1B}/α_{2C} (K_i = 0.17/0.59 nM) receptors.[17,18] Relative to its 5-HT_{1A}/D_2 receptor affinity, brexpiprazole has moderate-to-low affinity antagonism at histamine H_1 receptors (K_i = 19 nM), limiting the risk for weight gain and diabetes.[14,17] In clinical studies in patients with MDD and inadequate response to ADTs, the addition of brexpiprazole to ADT was efficacious and well-tolerated and was associated with only small changes in metabolic parameters (all < 2 mg/dL in the short term, and < 4 mg/dL in the long term, except triglycerides, 15.8 mg/dL) and moderate weight gain (approximately 1.5 kg in the short term and 3.8 kg in the long term).[19,20] Although brexpiprazole has demonstrated a favorable metabolic profile in MDD, its metabolic profile in patients with MDD and prediabetes has not specifically been investigated.

The aim of this post hoc analysis was to determine the effect of brexpiprazole as an adjunctive treatment to ADT on metabolic parameters and body weight in adults with MDD and prediabetes compared with those who do not have prediabetes/diabetes (termed *non-diabetes*), based on pooled data from 3 short-term studies and 1 long-term extension study. It was hypothesized that adjunctive brexpiprazole would have limited impact on the metabolic profile of such patients.

METHODS

Study Design and Patients

The clinical studies included in this analysis were conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guideline and local regulatory requirements. The study protocols were approved by independent ethics committees or institutional review boards at each site/country. All patients provided written informed consent to participate after procedures and possible side effects were explained to them.

The 3 short-term studies included in the present analysis were conducted in North America and Europe between June 2011 and May 2016 (ClinicalTrials.gov identifiers: NCT01360645, NCT01360632, and NCT02196506). The methods have been published in detail for each study[21–23] and are described in brief in this section.

These were randomized, double-blind, placebo-controlled studies with similar designs. The studies enrolled adult outpatients with a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) diagnosis of single or recurrent nonpsychotic MDD, a current depressive episode of ≥ 8 weeks in duration, and inadequate response to 1–3 prior ADTs during the current episode, for which inadequate response was defined as < 50% improved according to the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.[24] Exclusion criteria included treatment with an adjunctive antipsychotic medication during the current episode, suicidal ideation or behavior, substance abuse or dependence, hallucinations or delusions during the current episode, another specified *DSM-IV-TR* disorder, or a clinically significant medical condition. Patients with insulin-dependent diabetes mellitus (IDDM; ie, any patients using insulin) were excluded, as were patients with non-IDDM who had glycated hemoglobin (HbA1c) ≥ 7.0% or screening glucose > 125 mg/dL (fasting) or ≥ 200 mg/dL (non-fasting). Minor or well-controlled medical conditions were permitted if not expected to interfere with safety or efficacy assessments. The following medications were prohibited during the studies: psychotropic agents (including but not limited to antipsychotics other than the study drug, antidepressants other than those prescribed as part of the study, mood stabilizers, and anticonvulsants), investigational agents, cytochrome P450 2D6 (CYP2D6) inhibitors, CYP3A4 inhibitors and inducers, and barbiturates.

Eligible patients received 1 of 6 investigator-determined, open-label ADTs (escitalopram, fluoxetine, paroxetine controlled-release, sertraline, duloxetine, or venlafaxine extended-release) + single-blind placebo for 8 weeks, during which their response was prospectively assessed. Patients who responded to ADT + placebo based on rating scale score thresholds (clinician-rated depression and global improvement) continued on the same ADT at the same dose for another 6 weeks, whereas patients with inadequate response to ADT + placebo entered a randomized treatment phase. In the randomized phase, patients continued the same ADT at the same dose and were randomized to double-blind treatment with adjunctive brexpiprazole (fixed doses in the range of 1–3 mg/d) or placebo for 6 weeks.

The long-term safety study was conducted in North America and Europe between October 2011 and May 2017 (ClinicalTrials.gov identifier: NCT01360866). The methods have been published in detail.[25] In brief,

this was an open-label extension study that enrolled patients who had completed the last scheduled visit of 1 of 3 short-term studies,[21,22,26] regardless of whether or not they had been randomized in the short-term study. Eligible patients continued the same ADT they received in the parent study (dose adjustments were permitted) and were administered adjunctive brexpiprazole 0.5–3 mg/d (flexible dose). Prohibited medications were the same as for the short-term studies. The study duration was originally 52 weeks, but was amended to 26 weeks midway through because the safety profile of brexpiprazole was considered to be well established.

Assessments

The focus of this analysis was fasting metabolic parameters, especially those relating to prediabetes: serum HbA1c and glucose (diagnostic for diabetes/prediabetes), as well as triglycerides and high-density lipoprotein (HDL) cholesterol (which are characteristically altered in metabolic syndrome and diabetes[27,28]). For completeness, fasting serum total and low-density lipoprotein (LDL) cholesterol were analyzed, as well as fasting insulin to assess insulin resistance. In the short-term studies, a fasting blood draw was collected for clinical laboratory tests including metabolic parameters at randomization and at week 6 of the randomized phase, as well as at weeks 2 and 4 in two of the three studies. Body weight was measured at randomization and at weekly visits. In the long-term study, metabolic parameters and body weight were measured at multiple visits from week 1 to week 26 (post-amendment) or week 52 (pre-amendment).

The present analysis also investigated whether adjunctive brexpiprazole remains an efficacious treatment option for patients with MDD and inadequate response to ADTs, regardless of prediabetes status. Efficacy was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS), a 10-item, clinician-rated measure of depressive symptom severity in MDD, with total scores ranging from 0 (least severe) to 60 (most severe).[29] The MADRS was completed at randomization and at weekly intervals during the randomized phase.

Data Analysis

In this post hoc analysis, patients were split into subgroups according to diabetes status at baseline based on definitions adapted from the American Diabetes Association (plasma definitions were applied to serum data).[30] *Non-diabetes* was defined as fasting serum glucose < 100 mg/dL and HbA1c < 5.7%. *Prediabetes* was defined as fasting serum glucose ≥ 100 mg/dL and < 125 mg/dL or HbA1c ≥ 5.7% and < 6.5%. *Diabetes* was defined as fasting serum glucose ≥ 125 mg/dL or HbA1c ≥ 6.5%. However, since patients with fasting serum glucose > 125 mg/dL or HbA1c ≥ 7.0% were excluded from the studies, only those with HbA1c ≥ 6.5% and < 7.0% met the criteria for diabetes (approximately 4% of patients); these patients were included in analyses of shift in diabetes status, but were not analyzed for changes in metabolic parameters due to the low number of patients and because this was beyond the scope of the study. Patients without a baseline fasting serum glucose or HbA1c measurement were also excluded from the present analyses.

Shifts in diabetes status and HbA1c status were determined in the short- and long-term samples from baseline to last visit using the American Diabetes Association definitions.[30] Categorical shifts in fasting metabolic parameters (glucose, triglycerides, cholesterol) were determined for the following time periods: from baseline to any post-baseline visit during the first 6 weeks (short-term studies), from baseline to any post-baseline visit up to week 26 (ie, the first 6 months of treatment), and from week 26 to any post-week 26 visit (ie, the last 6 months of treatment). Glucose category definitions were those of the American Diabetes Association[30]; triglyceride and cholesterol category definitions were adapted from guidelines of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III.[31] Mean changes in metabolic parameters from baseline were also determined. To assess insulin resistance, mean homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as: (insulin [μU/mL] × glucose [mmol/L])/22.5.[32] For body weight, mean changes from baseline and the proportions with clinically relevant change from baseline to any post-baseline visit were calculated. All analyses used observed-cases data.

In the short-term analysis, data were pooled for all patients randomized to ADT + brexpiprazole (any dose) and similarly for all patients randomized to ADT + placebo. The baseline value was defined as the last value prior to randomization. The long-term analysis included a greater number of patients than the short-term analysis since the extension study enrolled patients regardless of whether or not they were randomized in the short-term studies. In the long-term analysis, the baseline value was defined as the last value obtained prior to the start of adjunctive brexpiprazole treatment, whether at the start of the extension study (for those patients who had rolled over from adjunctive placebo) or at the start of the parent study (for those patients who had rolled over from adjunctive brexpiprazole). Thus, long-term data covered up to 58 weeks of brexpiprazole exposure (ie, 0 or 6 weeks from the parent study, plus up to 52 weeks from the extension study). Metabolic and weight analyses were performed on the safety sample, defined per final protocol in the short-term studies as all patients who received at least 1 dose of randomized treatment (brexpiprazole or placebo) and in the long-term analysis as all patients who received at least 1 dose of brexpiprazole.

In the short-term efficacy analysis, mean change in MADRS total score was calculated using a mixed model for repeated measures (MMRM) with terms of treatment, site nested within trial, visit, treatment by visit, and baseline by visit interaction for ADT + brexpiprazole

Table 1.

Baseline Characteristics and Metabolic Parameters, Stratified by Diabetes Status[a]

Variable	Short-Term Studies				Long-Term Analysis, ADT + Brexpiprazole 0.5–3 mg	
	Non-Diabetes		Prediabetes			
	ADT + Placebo (n = 354)	ADT + Brexpiprazole 1–3 mg (n = 477)	ADT + Placebo (n = 194)	ADT + Brexpiprazole 1–3 mg (n = 262)	Non-Diabetes (n = 1,712)	Prediabetes (n = 932)
Demographic Characteristics						
Age, y	41.6 (12.0)	40.8 (11.5)	49.2 (10.0)	49.3 (10.6)	42.0 (11.5)	48.4 (10.6)
Female, n (%)	254 (71.8)	351 (73.6)	124 (63.9)	169 (64.5)	1,185 (69.2)	615 (66.0)
Weight, kg	79.9 (20.4)	80.0 (19.3)	90.3 (21.8)	89.6 (21.6)	79.6 (19.9) *(n=1,711)*	87.6 (20.6)
BMI, kg/m^2	28.1 (6.9)	28.4 (6.2)	31.8 (7.0)	31.5 (7.3)	28.0 (6.5) *(n=1,711)*	31.0 (7.0)
White, n (%)	320 (90.4)	418 (87.6)	150 (77.3)	210 (80.2)	1,555 (90.8)	780 (83.7)
Black or African American, n (%)	26 (7.3)	42 (8.8)	39 (20.1)	45 (17.2)	119 (7.0)	129 (13.8)
Clinical Characteristics						
Duration of current depressive episode, mo	15.2 (35.5)	15.3 (23.7)	19.7 (38.1)	17.9 (41.9)	...	...
Recurrent episode, n (%)	295 (83.3)	409 (85.7)	173 (89.2)	224 (85.5)	...	...
Number of lifetime episodes	3.4 (3.3)	3.2 (2.5)	3.7 (3.1)	3.8 (3.9)	...	...
MADRS total score	26.6 (5.6)	26.7 (5.7)	26.7 (5.9)	27.2 (5.5)	...	...
Fasting Metabolic Parameters						
HbA1c, %	5.2 (0.3) *(n=335)*	5.2 (0.2) *(n=457)*	5.7 (0.4) *(n=186)*	5.7 (0.4) *(n=256)*	5.2 (0.3) *(n=1,610)*	5.7 (0.3) *(n=905)*
Glucose, mg/dL	87.4 (7.8) *(n=315)*	87.4 (7.8) *(n=412)*	99.8 (9.6) *(n=173)*	100.6 (10.7) *(n=237)*	89.2 (18.9) *(n=1,689)*	100.7 (14.9) *(n=926)*
Triglycerides, mg/dL	122.8 (87.9) *(n=319)*	120.9 (71.4) *(n=413)*	143.7 (82.3) *(n=173)*	142.0 (75.9) *(n=237)*	126.9 (89.6) *(n=1,690)*	148.5 (88.8) *(n=926)*
HDL cholesterol, mg/dL	62.1 (18.1) *(n=319)*	61.9 (18.7) *(n=413)*	57.0 (16.5) *(n=172)*	57.1 (15.5) *(n=236)*	62.6 (25.4) *(n=1,690)*	58.0 (19.9) *(n=926)*

[a]Data are mean (SD) unless otherwise stated. Non-diabetes: fasting serum glucose < 100 mg/dL and HbA1c < 5.7% at baseline; prediabetes: fasting serum glucose ≥ 100 mg/dL and < 125 mg/dL or HbA1c ≥ 5.7% and < 6.5% at baseline.

Abbreviations: ADT = antidepressant treatment, BMI = body mass index, HbA1c = glycated hemoglobin, HDL = high-density lipoprotein, MADRS = Montgomery-Åsberg Depression Rating Scale.

2–3 mg/d (the recommended-to-maximum dose for MDD in some countries[33]) and ADT + placebo. Efficacy analyses were performed on the efficacy sample per final protocol, defined as all patients in the safety sample with a baseline and post-baseline MADRS evaluation.

All analyses were performed using SAS Enterprise 8.1 software (SAS Institute Inc; Cary, NC).

RESULTS

Patients

In the short-term analysis, 743 of 797 patients (93.2%) randomized to brexpiprazole 1–3 mg and 557 of 586 patients (95.1%) randomized to placebo completed 6 weeks of treatment. In the long-term study (which was amended to a 26-week duration midway through), 2,132 of 2,938 patients (72.6%) in the safety sample received ADT + brexpiprazole for at least 6 months and 781 of 2,938 (26.6%) for at least 12 months.

During the short-term studies, lipid-modifying agents (eg, statins) were used by 124 of 1,383 randomized patients (9.0%), and drugs for diabetes (eg, metformin) were used by 41 of 1,383 randomized patients (3.0%). During the long-term study, lipid-modifying agents were used by 263 of 2,938 patients (9.0%), and drugs for diabetes were used by 97 of 2,938 patients (3.3%).

At baseline in the short-term analysis, across treatment groups, 831 patients (62.0%) did not have diabetes, 456 (34.0%) had prediabetes, and 54 (4.0%) had diabetes. At baseline in the long-term analysis, 1,712 patients (62.3%) did not have diabetes, 932 (33.9%) had prediabetes, and 102 (3.7%) had diabetes.

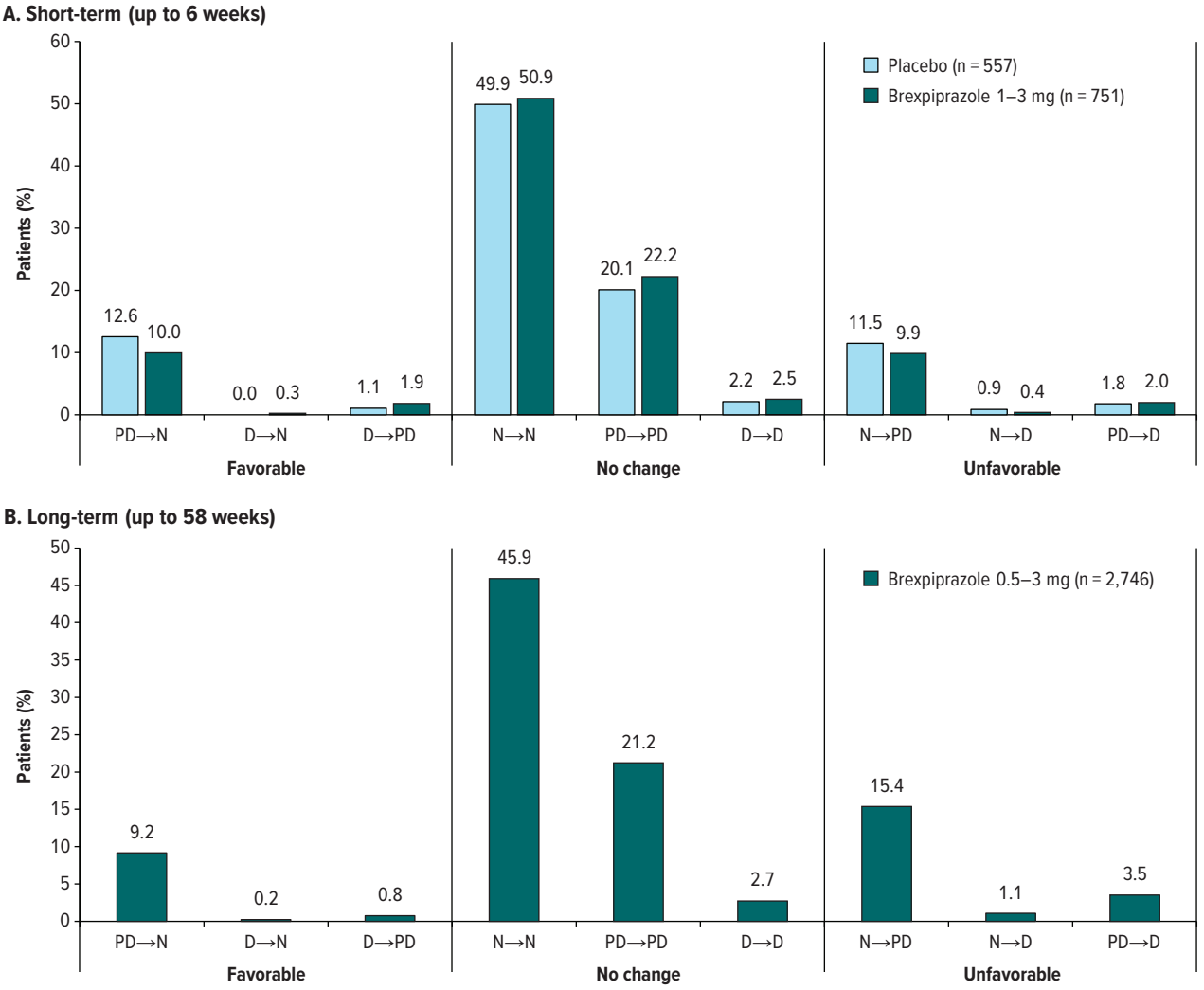
At baseline, on average, the prediabetes subgroups were older, had higher body weight and body mass index (BMI), and had a greater proportion of Black/African American patients than the non-diabetes subgroups (Table 1). Baseline clinical (ie, depression) characteristics were similar between the non-diabetes and prediabetes subgroups (Table 1).

Baseline mean fasting glucose (by definition) and triglycerides were higher in the prediabetes subgroups than in the non-diabetes subgroups, and mean fasting HDL was lower in the prediabetes subgroups than the non-diabetes subgroups (Table 1).

There were no notable differences in baseline characteristics between the ADT + brexpiprazole and ADT + placebo groups (Table 1).

Figure 1.

Diabetes Status: Incidence of Categorical Shifts From Baseline to Last Visit for ADT + Brexpiprazole or ADT + Placebo Therapy[a]



[a]Percentages are relative to the number of patients in each treatment group with a baseline and post-baseline measurement. Non-diabetes (N): fasting serum glucose < 100 mg/dL and HbA1c < 5.7% at baseline; prediabetes (PD): fasting serum glucose ≥ 100 mg/dL and < 125 mg/dL or HbA1c ≥ 5.7% and < 6.5% at baseline; diabetes (D): fasting serum glucose ≥ 125 mg/dL or HbA1c ≥ 6.5% at baseline.
Abbreviations: ADT = antidepressant treatment, HbA1c = glycated hemoglobin.

Diabetes Status Changes

Diabetes categorical shifts. At last visit in the short-term studies (up to 6 weeks), the majority of patients maintained their baseline diabetes status (74.2%; 970/1,308), with no notable differences between the ADT + brexpiprazole group (75.6%; 568/751) and the ADT + placebo group (72.2%; 402/557) (Figure 1A).

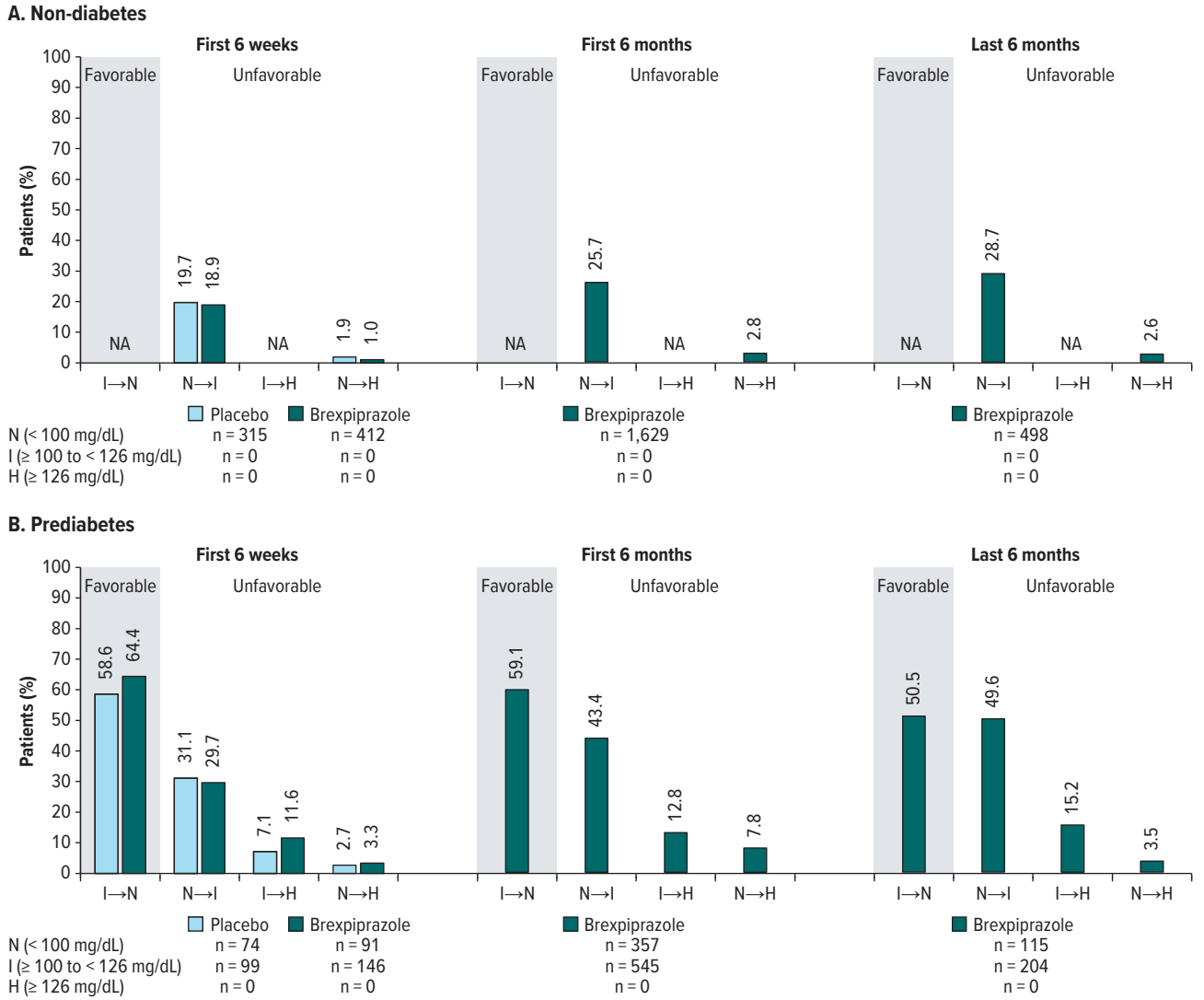
Similarly, at last visit in the long-term analysis (up to 58 weeks), the majority of patients receiving ADT + brexpiprazole maintained their baseline diabetes status (69.9%; 1,919/2,746) (Figure 1B). The most common shifts in the long-term analysis were non-diabetes to prediabetes (15.4%; 422/2,746) and prediabetes to non-diabetes (9.2%; 252/2,746).

HbA1c categorical shifts. At last visit in the short-term studies (up to 6 weeks), 90.6% of patients (585/646) in the non-diabetes subgroup remained in their baseline HbA1c category (ie, non-diabetic HbA1c), with no notable differences between treatment groups. Similarly, 76.7% of patients (283/369) in the prediabetes subgroup remained in their baseline HbA1c category (ie, prediabetic or non-diabetic HbA1c), and 16.0% (59/369) shifted from prediabetic HbA1c to non-diabetic HbA1c, with no notable differences between treatment groups. Other possible shifts each occurred in < 10% of patients.

At last visit in the long-term analysis (up to 58 weeks), in the non-diabetes subgroup, 66.7% of patients (394/591) remained in their baseline HbA1c category

Figure 2.

Fasting Serum Glucose: Incidence of Categorical Shifts From Baseline to any Post-Baseline Visit During ADT + Brexpiprazole or ADT + Placebo Therapy, Stratified by Diabetes Status[a]



[a]Percentages are relative to the number of patients in each baseline glucose category with a baseline and post-baseline measurement, given below each figure. Non-diabetes: fasting serum glucose < 100 mg/dL and HbA1c < 5.7% at baseline; prediabetes: fasting serum glucose ≥ 100 mg/dL and < 125 mg/dL or HbA1c ≥ 5.7% and < 6.5% at baseline.

Abbreviations: ADT = antidepressant treatment, H = high, HbA1c = glycated hemoglobin, I = impaired, N = normal, NA = not applicable to this subgroup.

(ie, non-diabetic HbA1c), 33.2% (196/591) shifted from non-diabetic HbA1c to prediabetic HbA1c, and 0.2% (1/591) shifted from non-diabetic HbA1c to diabetic HbA1c. In the prediabetes subgroup, 67.3% of patients (602/895) remained in their baseline HbA1c category, 20.4% (183/895) shifted from prediabetic HbA1c to non-diabetic HbA1c, 6.4% (57/895) shifted from non-diabetic HbA1c to prediabetic HbA1c, 5.8% (52/895) shifted from prediabetic HbA1c to diabetic HbA1c, and 0.1% (1/895) shifted from non-diabetic HbA1c to diabetic HbA1c.

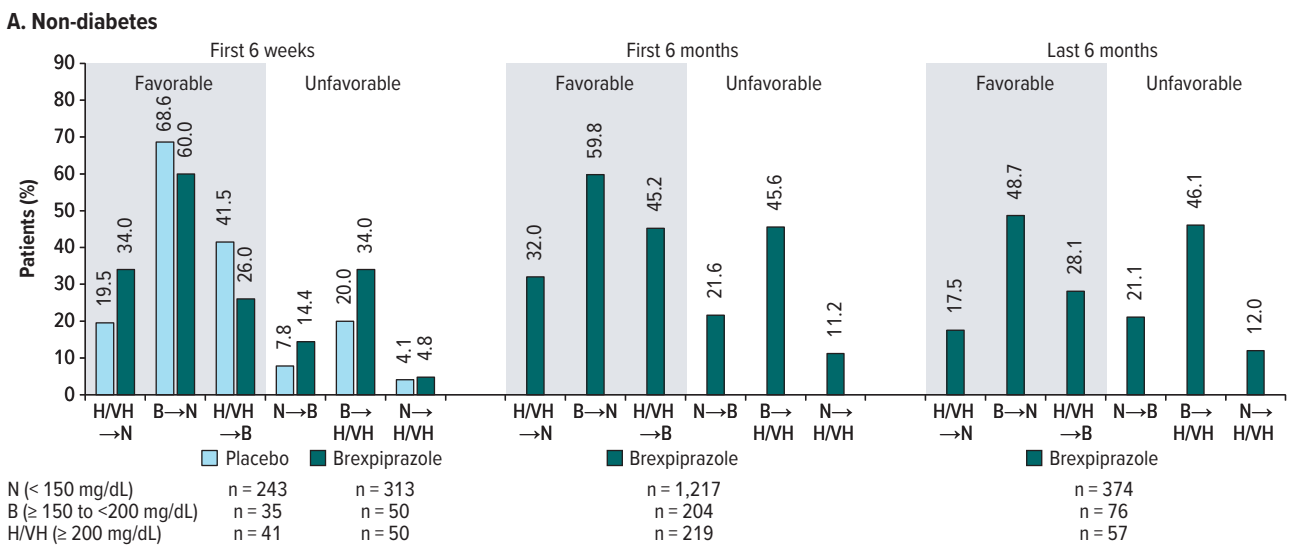
Fasting glucose categorical shifts. There were no notable differences between treatment groups in the incidence of favorable and unfavorable shifts in fasting glucose (Figure 2). By definition, only unfavorable shifts were possible for patients who did not have diabetes. Among patients with prediabetes, the proportion who shifted from impaired to normal glucose was similar to or greater than the proportion who shifted from normal to impaired glucose.

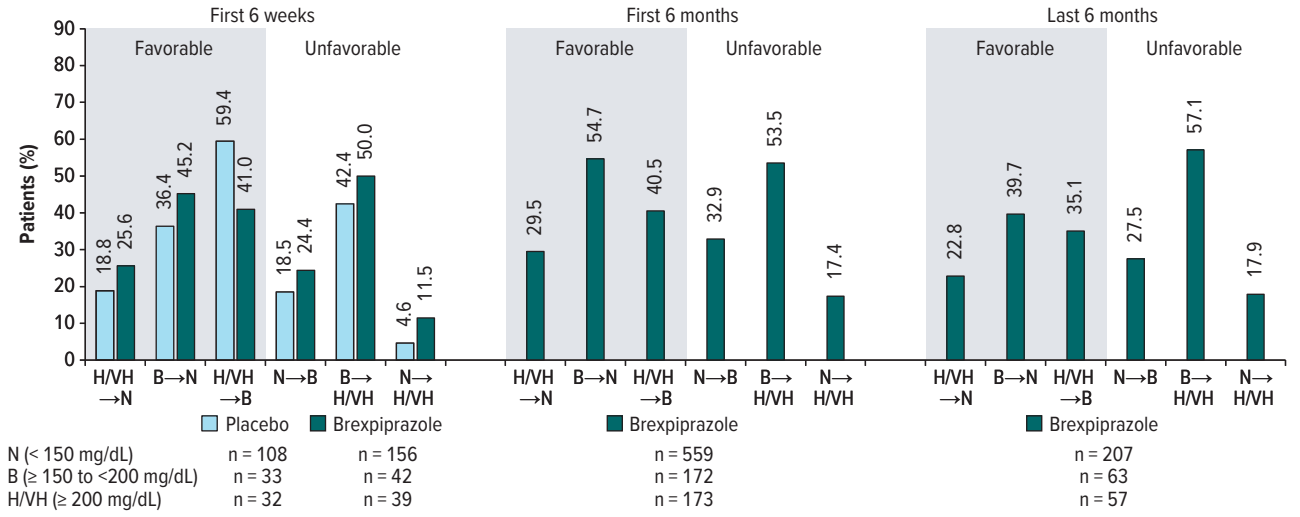
Fasting glucose mean changes. Mean changes in glucose from baseline to week 6 and week 52 (up to 58 weeks of adjunctive brexpiprazole treatment) were small in the non-diabetes and prediabetes subgroups (all < 4 mg/dL) (Supplementary Table 1).

Figure 3.

Fasting Serum Triglycerides and HDL Cholesterol: Incidence of Categorical Shifts From Baseline to any Post-Baseline Visit During ADT + Brexpiprazole or ADT + Placebo Therapy, Stratified by Diabetes Status[a]

Triglycerides





(continued)

Serum Lipid Changes

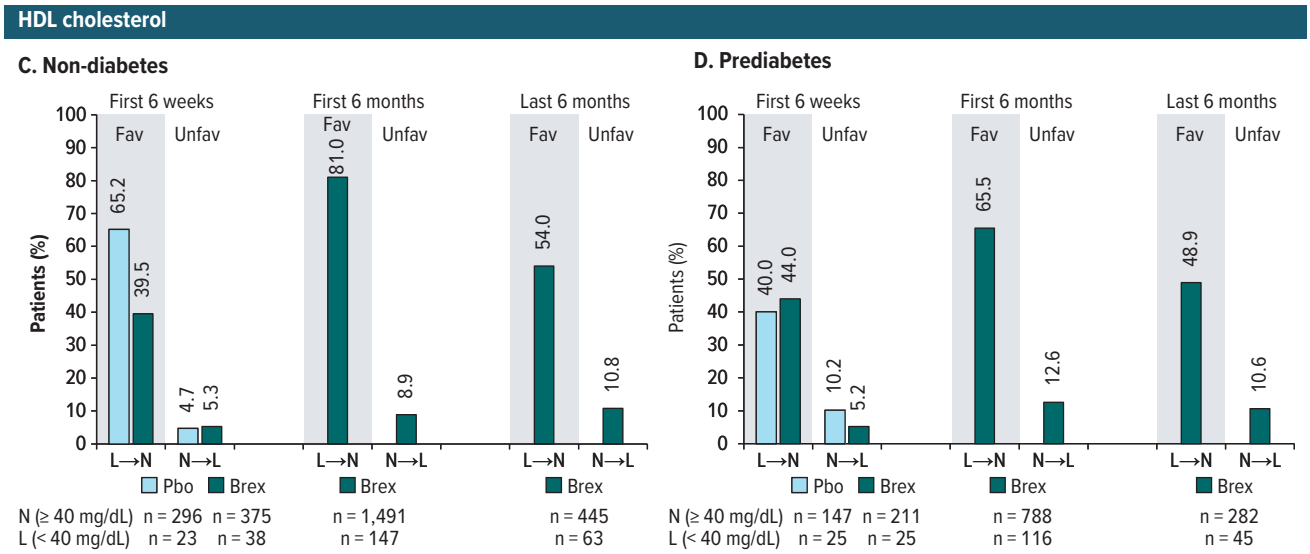
Fasting triglyceride and cholesterol categorical shifts. There were no notable differences between the treatment groups, or between the non-diabetes and prediabetes subgroups, in the incidence of favorable and unfavorable shifts in triglycerides (Figures 3A and 3B), HDL cholesterol (Figures 3C and 3D), total cholesterol (Supplementary Figure 1), or LDL cholesterol (Supplementary Figure 2), except where influenced by low patient numbers in a subgroup.

For most serum lipid parameters, the overall proportion of patients with favorable shifts was similar to or greater than the proportion with unfavorable shifts. An exception was serum LDL cholesterol, in which 57.4% (non-diabetes subgroup) and 65.8% (prediabetes subgroup) of patients with normal LDL cholesterol at baseline shifted to borderline LDL cholesterol over the last 6 months.

Fasting triglyceride and cholesterol mean changes. Mean changes from baseline in serum lipid parameters after 6 weeks of ADT + brexpiprazole or ADT + placebo therapy were small in the non-diabetes and prediabetes subgroups (all < 5 mg/dL) (Supplementary Table 1).

Mean changes in serum lipid parameters from baseline to week 52 (up to 58 weeks of adjunctive brexpiprazole

Figure 3 (continued).



[a]Percentages are relative to the number of patients in each baseline triglyceride or HDL cholesterol category with a baseline and post-baseline measurement, given below each figure. Non-diabetes: fasting serum glucose < 100 mg/dL and HbA1c < 5.7% at baseline; prediabetes: fasting serum glucose ≥ 100 mg/dL and < 125 mg/dL or HbA1c ≥ 5.7% and < 6.5% at baseline.

Abbreviations: ADT = antidepressant treatment, B = borderline, Brex = brexpiprazole, Fav = favorable, H = high, HbA1c = glycated hemoglobin, HDL = high-density lipoprotein, L = low, N = normal, Pbo = placebo, Unfav = unfavorable, VH = very high.

treatment) were generally small (all < 6 mg/dL) and similar between the subgroups, except for triglycerides: non-diabetes subgroup, 18.3 mg/dL; prediabetes subgroup, 12.9 mg/dL (Supplementary Table 1).

HOMA-IR Changes

In the short-term analysis, mean (SD) HOMA-IR at baseline was 1.1 (0.1) in the non-diabetes subgroups (ADT + brexpiprazole, n = 425; ADT + placebo, n = 310) and 1.4 (0.2) in the prediabetes subgroups (ADT + brexpiprazole, n = 243; ADT + placebo, n = 177). Mean (SD) HOMA-IR scores did not change from baseline to last visit.

In the long-term analysis, in the non-diabetes subgroup, mean (SD) HOMA-IR was 1.1 (0.1) at baseline (n = 1,516), 1.1 (0.1) at week 26 (n = 952), and 1.1 (0.1) at week 52 (n = 338). In the prediabetes subgroup, mean (SD) HOMA-IR was 1.4 (0.2) at baseline (n = 868), 1.4 (0.2) at week 26 (n = 654), and 1.4 (0.2) at week 52 (n = 312).

Weight Changes

Considering body weight, mean (SD) increases from baseline to last visit of the short-term studies in the non-diabetes subgroups were 1.5 (2.2) kg (ADT + brexpiprazole, n = 476) and 0.3 (1.7) kg (ADT + placebo, n = 353); corresponding values in the prediabetes subgroups were 1.5 (2.2) kg (n = 260) and 0.5 (1.8) kg (n = 194), respectively. The proportion of patients with ≥ 7% weight increase from baseline to any post-baseline visit was low (< 5% of patients in each subgroup), and very few patients (< 1%) had ≥ 10% weight increase or ≥ 7% weight decrease from baseline to any post-baseline visit.

With long-term treatment, the mean (SD) body weight increase from baseline to week 26 (up to 32 weeks of adjunctive brexpiprazole treatment) was 3.1 (4.3) kg in the non-diabetes subgroup (n = 1,185) and 2.9 (4.3) kg in the prediabetes subgroup (n = 687). At week 52 (up to 58 weeks of adjunctive brexpiprazole treatment), mean weight increase was 4.1 (5.9) kg in the non-diabetes subgroup (n = 432) and 3.4 (5.3) kg in the prediabetes subgroup (n = 296). The proportion of patients with clinically relevant weight change from baseline was comparable between subgroups (Figure 4).

Efficacy

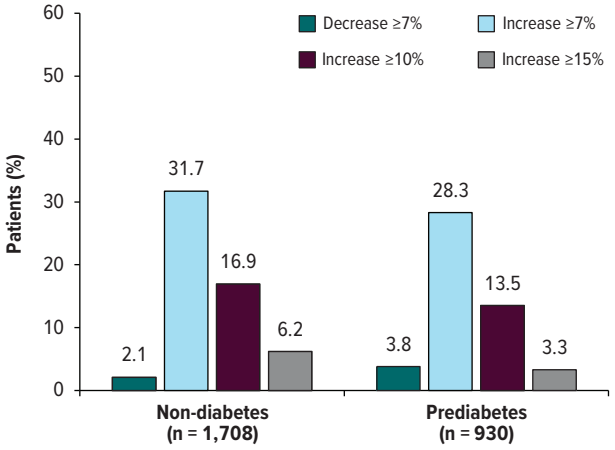
Over 6 weeks, in the non-diabetes subgroup, MADRS total score improved by a least-squares (LS) mean (SE) of −9.4 (0.5) points in the ADT + brexpiprazole 2–3 mg group and −6.6 (0.5) points in the ADT + placebo group, with an LS mean difference of −2.89 points (95% CI, −4.10 to −1.67; $P < .0001$). In the prediabetes subgroup, improvements were −8.6 (0.7) points in the ADT + brexpiprazole 2–3 mg group and −6.6 (0.6) points in the ADT + placebo group, with an LS mean difference of −2.01 (95% CI, −3.78 to −0.24; $P = .026$).

DISCUSSION

In this analysis of over 2,000 patients with MDD from several clinical trials, adjunctive brexpiprazole

Figure 4.

Body Weight: Incidence of Clinically Relevant Change From Baseline to any Post-Baseline Visit During Long-Term Therapy (up to 58 Weeks) With ADT + Brexpiprazole 0.5–3 mg, Stratified by Diabetes Status[a]



[a]Percentages are relative to the number of patients with a baseline and post-baseline weight measurement in each subgroup. Non-diabetes: fasting serum glucose < 100 mg/dL and HbA1c < 5.7% at baseline; prediabetes: fasting serum glucose ≥ 100 mg/dL and < 125 mg/dL or HbA1c ≥ 5.7% and < 6.5% at baseline.

Abbreviations: ADT = antidepressant treatment, HbA1c = glycated hemoglobin.

had a small effect on metabolic parameters and a moderate effect on weight, regardless of diabetes status (prediabetes or non-diabetes).

Patients with prediabetes were identified using baseline serum glucose and HbA1c levels, as defined by the American Diabetes Association.[30] At baseline, a large proportion of the sample had prediabetes (34%), putting them at high risk of developing diabetes.[30] Over 6 weeks, the majority of patients maintained their baseline diabetes status, regardless of whether they received ADT + brexpiprazole or ADT + placebo. Similarly, over the long term (≤ 58 weeks of ADT + brexpiprazole therapy), most patients (69.9%) maintained their baseline diabetes status, and the proportions with favorable and unfavorable shifts were similar, indicating that treatment did not adversely affect their risk. HbA1c, which indicates average glucose over the previous 8–12 weeks,[34] followed a similar pattern of categorical shifts to overall diabetes status, which is unsurprising given that diabetic status is defined based on HbA1c in addition to blood glucose concentration.

Considering fasting glucose levels among patients with prediabetes, the incidence of a favorable shift from impaired to normal glucose was greater than the corresponding unfavorable shift, differences from adjunctive placebo were small, and mean changes in fasting glucose were minimal, suggesting that there was no adverse effect of treatment with adjunctive brexpiprazole. Minimal effect of treatment on glucose was also observed in the non-diabetes group. Increased triglycerides and decreased HDL cholesterol, characteristic of metabolic syndrome and diabetes,[27,28] were observed at baseline among patients with prediabetes. In most cases, during ADT + brexpiprazole therapy, the overall proportion of patients with favorable shifts was similar to or greater than the proportion with unfavorable shifts, regardless of diabetes status. Mean changes in triglycerides were < 20 mg/dL, and mean changes in HDL cholesterol were small in all subgroups.

HOMA-IR over the long term indicated no mean change in insulin resistance in the non-diabetes subgroup (1.1) or the prediabetes subgroup (1.4). In longitudinal studies, a HOMA-IR cutoff of approximately 2 has been suggested to identify type 2 diabetes.[35,36]

Other adjunctive atypical antipsychotics used in MDD show varying risks for abnormal metabolic parameters in clinical trials, with quetiapine and olanzapine-fluoxetine combination having the highest risk.[12,37] In general, antipsychotics are thought to increase the risk of diabetes via weight gain and/or a direct effect on insulin resistance or secretion.[16] Across diagnoses, real-world data suggest that duration of antipsychotic treatment could be a relevant factor for the occurrence of diabetes.[38] In a study of adolescents and young adults with no history of diabetes who were exposed to second-generation antipsychotics (amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, or ziprasidone), the highest risk of developing diabetes was among patients who received a total of ≥ 365 daily doses.[39] Thus, a strength of the present study is that it assessed up to 58 weeks of data.

With regard to weight, adjunctive brexpiprazole was associated with moderate weight gain that was comparable between the non-diabetes and prediabetes subgroups. Following a mean increase in weight of approximately 1.5 kg in the short-term studies, comparable to that reported in clinical trials of adjunctive aripiprazole, quetiapine, and risperidone,[12,40] mean weight increased by another 1.5 kg (approximately) to week 26 and then showed changes ≤ 1 kg over the final 6 months of the study. Previously, adjunctive brexpiprazole and adjunctive aripiprazole have shown a similar effect on weight in long-term clinical trials in MDD.[40] Across diagnoses, a study of long-term, real-world, outpatient data suggested that the weight gain associated with brexpiprazole may be lower than with olanzapine, comparable to cariprazine and iloperidone, and higher than with asenapine and lurasidone.[41] A second study of long-term, real-world, outpatient data that did not include brexpiprazole found that olanzapine was associated with a larger weight increase than quetiapine and risperidone, which had comparable weight increases.[42]

Adjunctive brexpiprazole was efficacious on clinician-rated depressive symptoms over 6 weeks among patients with prediabetes and patients without diabetes, and

the magnitude of effect was similar to that previously reported for adjunctive brexpiprazole.[19] Thus, adjunctive brexpiprazole remains a viable treatment option for patients with MDD, inadequate response to ADTs, and prediabetes, thereby helping to meet the clinical need for an efficacious antipsychotic with a favorable metabolic profile. Long-term continuation of successful MDD treatment is often recommended to prevent relapse and to treat residual symptoms.[43] The optimal duration of efficacious adjunctive atypical antipsychotic therapy in MDD has not been established, and clinicians should monitor each patient's weight and metabolic status as well as their depression status over time.[44]

Limitations of this post hoc analysis include that, due to the lack of an adjunctive placebo arm in the long-term analysis, it was not possible to separate the effects of ADT and brexpiprazole on metabolic parameters and weight. Of note, ADT use is itself associated with an increased risk of diabetes.[8,9] A small proportion of patients were taking concomitant drugs for metabolic conditions, which may have impacted the metabolic outcomes. With regard to the generalizability of the results to real-world populations, clinical trial data are limited by their study inclusion and exclusion criteria. In particular, most patients with diabetes were excluded from the present trials, meaning that there was insufficient power to assess metabolic parameters in patients with diabetes. However, the inclusion of patients with other minor or well-controlled medical conditions increased the generalizability of the results. Finally, the included patients had a high mean BMI (28–32 kg/m^2), which affects generalizability to populations associated with lower BMIs.

In conclusion, among patients with baseline prediabetes, adjunctive brexpiprazole was associated with small changes in metabolic parameters and moderate weight gain during short- and long-term treatment, which are unlikely to be clinically meaningful. Results were comparable between subgroups with and without prediabetes, suggesting that adjunctive brexpiprazole had a limited impact on the metabolic profile of patients with MDD, regardless of diabetes status (prediabetes or non-diabetes).

Article Information

Published Online: August 28, 2023. https://doi.org/10.4088/JCP.23m14786

Submitted: January 6, 2023; accepted June 26, 2023.

To Cite: Newcomer JW, Meehan SR, Chen D, et al. Changes in metabolic parameters and body weight in patients with prediabetes treated with adjunctive brexpiprazole for major depressive disorder: pooled analysis of short- and long-term clinical studies. *J Clin Psychiatry.* 2023;84(5):23m14786.

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Relevant Financial Relationships: Dr Newcomer has received grant support from the National Institutes of Health and the Substance Abuse and Mental Health Services Administration and has served as a consultant for Alkermes, Inc.; Merck; Otsuka; and Sunovion and on a Data Safety Monitoring Board for Amgen. **Dr Meehan** is a full-time employee of H. Lundbeck A/S. **Drs Chen** and **Brubaker** are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc. **Dr Weiss** was a full-time employee of Otsuka Pharmaceutical Development & Commercialization Inc. at the time that this work was conducted.

Funding/Support: This work was supported by Otsuka Pharmaceutical Development & Commercialization Inc. (Princeton, NJ, USA) and H. Lundbeck A/S (Valby, Denmark).

Role of the Funders/Sponsors: Authors affiliated with the sponsors were involved in the design of the study, the analysis and interpretation of data, and the writing and reviewing of this article.

Acknowledgments: Writing support was provided by Chris Watling, PhD, assisted by his colleagues at Cambridge—a Prime Global Agency (Knutsford, UK), and funded by Otsuka Pharmaceutical Development & Commercialization Inc. and H. Lundbeck A/S.

Previous Presentation: Poster presented at the American Society of Clinical Psychopharmacology (ASCP) annual meeting, virtual conference; June 1–4, 2021.

Supplementary Material: Available at Psychiatrist.com.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Changes in Metabolic Parameters and Body Weight in Patients With Prediabetes Treated With Adjunctive Brexpiprazole for Major Depressive Disorder: Pooled Analysis of Short- and Long-Term Clinical Studies

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DOI Number: https://doi.org/10.4088/JCP.23m14786

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Table 1** Fasting metabolic parameters at baseline and changes at Week 6 and Week 52 of ADT + brexpiprazole or ADT + placebo therapy, stratified by diabetes status
2. **Figure 1** Fasting serum total cholesterol: incidence of categorical shifts from baseline to any post-baseline visit during ADT + brexpiprazole or ADT placebo therapy, stratified by diabetes status
3. **Figure 2** Fasting serum LDL cholesterol: incidence of categorical shifts from baseline to any post-baseline visit during ADT + brexpiprazole or ADT + placebo therapy, stratified by diabetes status

DISCLAIMER

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Material

Supplement to: Changes in metabolic parameters and body weight in patients with prediabetes treated with adjunctive brexpiprazole in major depressive disorder: pooled analysis of short- and long-term clinical studies

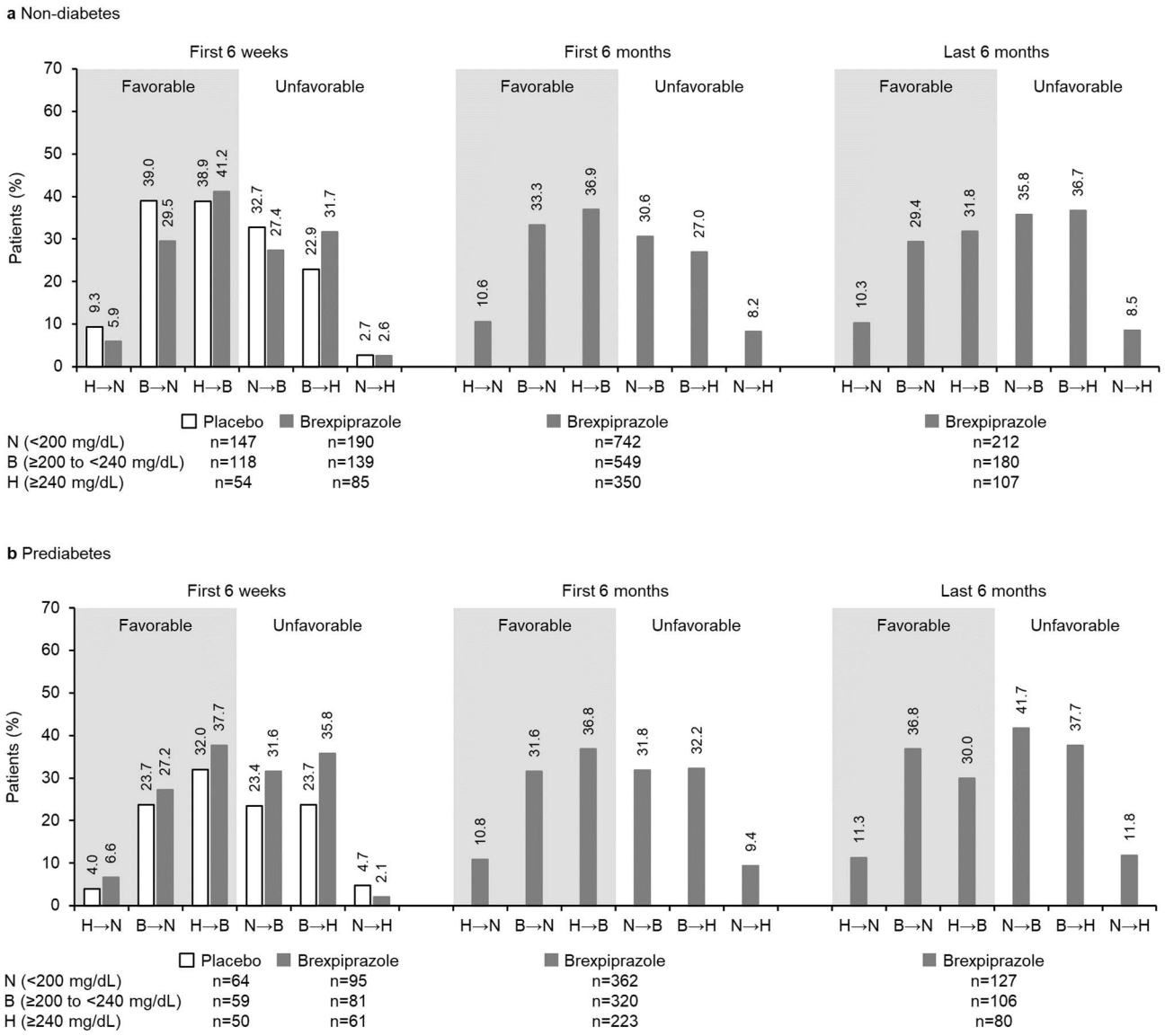
Supplementary Table 1. Fasting metabolic parameters at baseline and changes at Week 6 and Week 52 of ADT + brexpiprazole or ADT + placebo therapy, stratified by diabetes status

	Short-term studies				Long-term analysis	
	Non-diabetes		Prediabetes		Non-diabetes	Prediabetes
	ADT + placebo	ADT + brexpiprazole 1–3 mg	ADT + placebo	ADT + brexpiprazole 1–3 mg	ADT + brexpiprazole 0.5–3 mg	ADT + brexpiprazole 0.5–3 mg
Glucose (mg/dL)						
Baseline	87.4 (7.8) (n=315)	87.4 (7.8) (n=412)	99.8 (9.6) (n=173)	100.6 (10.7) (n=237)	89.2 (18.9) (n=1,689)	100.7 (14.9) (n=926)
Change at Week 6[a]/Week 52[b]	2.5 (10.6) (n=306)	2.1 (10.5) (n=391)	-1.4 (11.5) (n=168)	-2.7 (12.1) (n=224)	3.9 (20.4) (n=408)	1.9 (22.8) (n=267)
Triglycerides (mg/dL)						
Baseline	122.8 (87.9) (n=319)	120.9 (71.4) (n=413)	143.7 (82.3) (n=173)	142.0 (75.9) (n=237)	126.9 (89.6) (n=1,690)	148.5 (88.8) (n=926)
Change at Week 6[a]/Week 52[b]	-3.6 (70.3) (n=311)	0.1 (57.9) (n=393)	4.5 (70.5) (n=169)	2.3 (59.9) (n=224)	18.3 (72.9) (n=410)	12.9 (72.4) (n=273)
HDL cholesterol (mg/dL)						
Baseline	62.1 (18.1) (n=319)	61.9 (18.7) (n=413)	57.0 (16.5) (n=172)	57.1 (15.5) (n=236)	62.6 (25.4) (n=1,690)	58.0 (19.9) (n=926)
Change at Week 6[a]/Week 52[b]	0.7 (9.0) (n=311)	2.2 (9.0) (n=393)	0.4 (8.1) (n=168)	0.9 (7.3) (n=223)	-4.7 (15.7) (n=410)	-4.4 (16.6) (n=272)
Total cholesterol (mg/dL)						
Baseline	205.2 (39.8) (n=319)	207.1 (43.1) (n=414)	215.5 (45.3) (n=173)	214.3 (42.6) (n=237)	206.8 (46.0) (n=1,690)	212.7 (44.8) (n=926)
Change at Week 6[a]/Week 52[b]	0.3 (23.9) (n=311)	3.1 (25.1) (n=394)	2.2 (29.0) (n=169)	-0.3 (28.9) (n=224)	4.7 (36.8) (n=402)	5.3 (38.0) (n=260)
LDL cholesterol (mg/dL)						
Baseline	119.1 (35.6) (n=311)	121.8 (38.3) (n=407)	130.8 (40.3) (n=168)	129.0 (38.3) (n=231)	120.1 (40.8) (n=1,687)	125.7 (40.0) (n=923)
Change at Week 6[a]/Week 52[b]	-0.4 (20.1) (n=302)	1.1 (21.9) (n=386)	0.1 (26.8) (n=163)	-2.2 (26.0) (n=218)	3.0 (29.6) (n=402)	5.3 (31.7) (n=267)

[a]Short-term studies; [b]long-term analysis (up to 58 weeks of adjunctive brexpiprazole treatment). Data are mean (SD). Non-diabetes: fasting serum glucose <100 mg/dL and HbA1c <5.7% at baseline; prediabetes: fasting serum glucose ≥100 mg/dL and <125 mg/dL or HbA1c ≥5.7% and <6.5% at baseline.

Abbreviations: ADT=antidepressant treatment; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; LDL=low-density lipoprotein; SD=standard deviation.

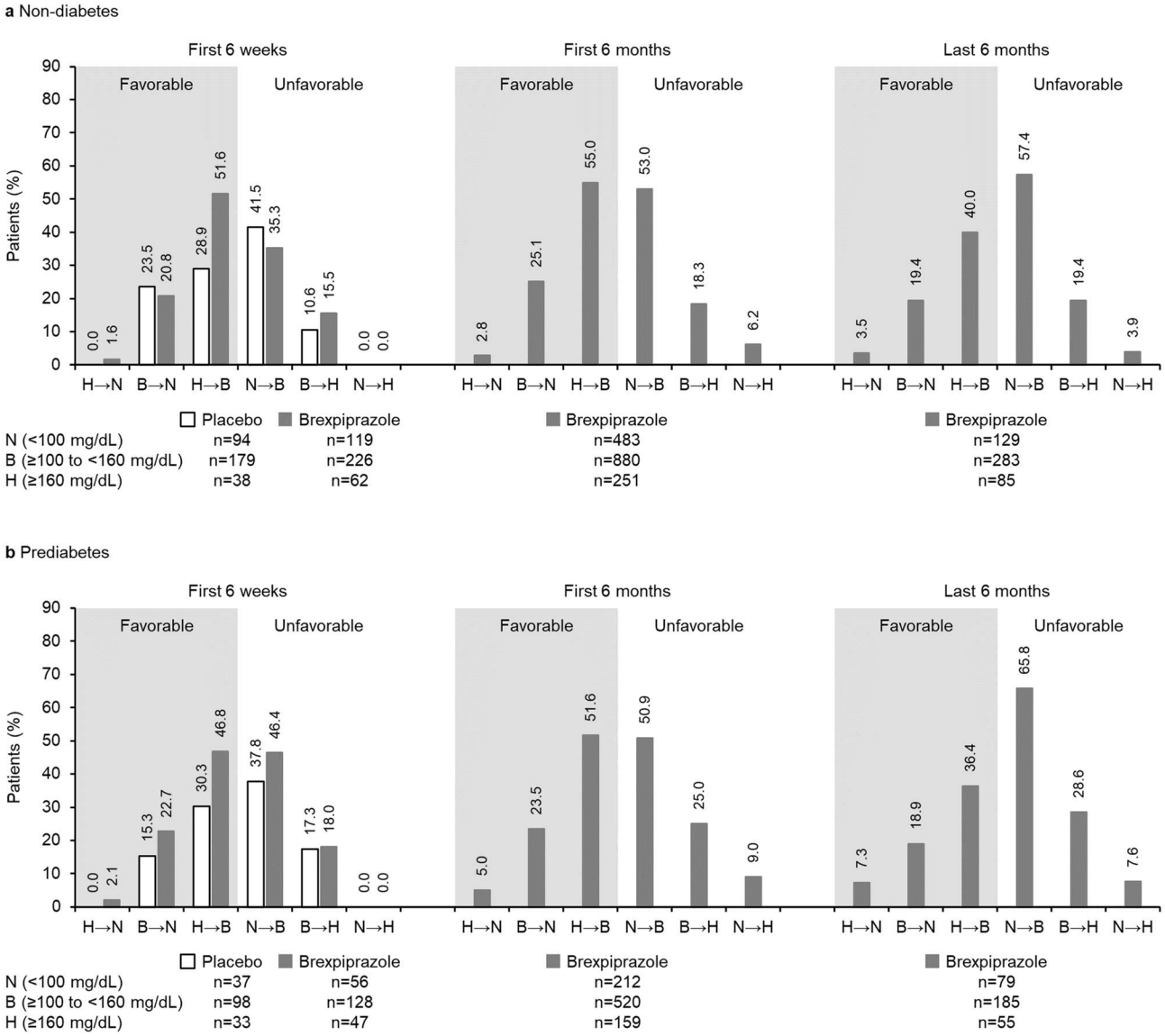
Supplementary Figure 1. Fasting serum total cholesterol: incidence of categorical shifts from baseline to any post-baseline visit during ADT + brexpiprazole or ADT + placebo therapy, stratified by diabetes status[a]



[a]Percentages are relative to the number of patients in each baseline total cholesterol category with a baseline and post-baseline measurement, given below each figure. Non-diabetes: fasting serum glucose <100 mg/dL and HbA1c <5.7% at baseline; prediabetes: fasting serum glucose ≥100 mg/dL and <125 mg/dL or HbA1c ≥5.7% and <6.5% at baseline.

Abbreviations: ADT=antidepressant treatment; B=borderline; H=high; HbA1c=glycated hemoglobin; N=normal.

Supplementary Figure 2. Fasting serum LDL cholesterol: incidence of categorical shifts from baseline to any post-baseline visit during ADT + brexpiprazole or ADT + placebo therapy, stratified by diabetes status[a]



[a]Percentages are relative to the number of patients in each baseline LDL cholesterol category with a baseline and post-baseline measurement, given below each figure. Non-diabetes: fasting serum glucose <100 mg/dL and HbA1c <5.7% at baseline; prediabetes: fasting serum glucose ≥100 mg/dL and <125 mg/dL or HbA1c ≥5.7% and <6.5% at baseline.

Abbreviations: ADT=antidepressant treatment; B=borderline; H=high; HbA1c=glycated hemoglobin; LDL=low-density lipoprotein; N=normal.