Archival Report

Toward a Precision Treatment Approach for Metabolic Depression: Integrating Epidemiology, Neuroscience, and Psychiatry

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ABSTRACT

BACKGROUND: Individuals with comorbid major depressive disorder and type 2 diabetes represent an important subgroup of patients for whom conventional treatment may be insufficient. A precision treatment approach that addresses insulin resistance with an outcome of a positive response to antidepressants may prove beneficial.

METHODS: This study utilized an emulated target trial on a large dataset from the Optum Clinformatics Data Mart Database. We evaluated the effect of adjuvant pioglitazone, an insulin-sensitizing drug, on antidepressant response among 4696 people with type 2 diabetes, comparing it with DPP4 (dipeptidyl peptidase-4) inhibitors (non–insulin-sensitizing). An additional analysis involving 6518 participants was conducted to assess the efficacy of pioglitazone versus sulfonylureas.

RESULTS: The instrumental variable analysis indicated that the initiation of an antidepressant with pioglitazone was superior to DPP4 inhibitors in terms of antidepressant response, with fewer treatment shifts and/or additions of new antidepressant or antipsychotic over a 1-year period. This result was consistent when pioglitazone was compared with sulfonylureas in a supplemental analysis.

CONCLUSIONS: Our findings suggest that pioglitazone may be more effective than DPP4 inhibitors or sulfonylureas in enhancing antidepressant response among people with comorbid major depressive disorder and type 2 diabetes. This provides a strong case for the use of pioglitazone in patients with these conditions, emphasizing the potential of precision medicine strategies. The results should be interpreted with caution due to inherent limitations associated with observational data.

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The Translational Challenge

Major depressive disorder (MDD) is a complex disorder that affects a large proportion of the population and accounted for $210.5 billion in economic burden in 2010 (1). Despite this, 50% to 60% of individuals with MDD do not respond adequately to treatment with 1 antidepressant (2). Furthermore, 30% to 40% of people who experience a depressive episode may suffer from treatment-resistant depression, which is defined as the failure of 2 consecutive antidepressant trials (3).

MDD is noted for its significant heterogeneity in disease etiology, symptomatology, course, and population characteristics, which pose significant challenges for creating viable treatments. Confronting this heterogeneity is essential for the early identification of at-risk populations, devising new classes of drugs, and informing a more precise approach to treating and preventing MDD.

Genetic and neuroscience approaches have transformed our thinking about major depression. They have shed light on the biological bases of this disorder but have also underscored the great challenges that we must confront to better understand and treat the illness. Thus, a major study on the genetics of MDD concluded that, "All humans carry lesser or greater numbers of genetic risk factors for major depression," implying "a continuous measure of risk that underlies the clinical phenotype" (4). Similarly, neurobiological studies have uncovered key mechanisms and neural circuitry that are of relevance to affective disorders but have also illustrated the challenges of translating basic studies into clinical applications (5,6). It has become clear that MDD does not simply reflect the unfolding of an intrinsic biological process but rather a sustained dysregulated response to environmental stress, which could be biological, psychological, or social (7). Thus, the very nature of this disorder is shaped by environmental context, and it appears critical to consider the interplay between biological, psychological, and social variables in devising better treatments for MDD.

The scope of this task appears daunting, and it is essential to think strategically about how we can streamline the process of discovery and translation—how do we identify the major variables that impact this disease, understand them sufficiently well to be able to target new drugs and other treatment modalities, and fine-tune the selection and clinical testing of treatments that are likely to be most effective in specific populations?

To address this challenge, we propose a vertically integrated translational process that fosters collaboration between neuroscience, psychiatry, and emerging conceptual frameworks from epidemiology. It may seem surprising that epidemiology would be a useful intermediary in an integrated approach between basic research and drug discovery. However, in this context, epidemiology can play at least 2 roles in the translational process: 1) it can identify some of the sources of heterogeneity in depression by defining the types of risk that are associated with its incidence and course, and 2) it can facilitate the translational process and streamline the selection of effective treatments using powerful analytical and computational tools that enable the prediction of targeted treatment outcomes.

Basic neuroscience research and translational studies can shed light on the molecular, cellular, and circuit-level interplay between the risk factors and the regulation of affect. This, in turn, can lead to specific hypotheses about points of intervention that are unique to that subtype of depression. However, testing these hypotheses through classical clinical studies carries a high risk of failure, especially if the target population is not well-defined. Epidemiology can provide conceptual tools, such as causal inference approaches, to lay the groundwork for clinical drug discovery that is less costly and time consuming.

Below, we explore the use of these emerging techniques in epidemiology in identifying new treatment approaches using the relationship between MDD and one modifiable risk factor for this illness: insulin resistance (IR). We use the example of target trial emulation, a strategy that allows us to make a preliminary assessment of the causal effect of a treatment aimed at ameliorating the effect of IR on depression outcomes using observational data alone as a prelude to performing a more classic randomized controlled trial (RCT) (8).

The Metabolic Subtype of MDD: IR and MDD

MDD is a multisystemic disorder that has been linked to several mechanisms of metabolic and neuroendocrine function (9). While major depression is primarily a brain illness, it is important to underscore that the brain is a plastic and vulnerable organ that not only regulates neuroendocrine and metabolic function but also responds to signals from the body, such as steroid and metabolic hormones, that change its structure and function over time (10). Thus, in the genesis of disorders such as MDD, scientists are beginning to recognize the reciprocal communication between the brain and the rest of the body in triggering and shaping the course of the illness. In cases of sustained physiological and/or psychological stress, this ongoing communication between the 2 entities can lead to high allostatic load, which is defined as a cumulative "wear and tear" of chronic stress that leads to a new, but suboptimal, equilibrium. According to the allostatic load model, the same mediators, such as glucocorticoids and excitatory amino acids, that promote adaptation in the brain to acute stressors can also cause damage when altered over prolonged periods (11). The effects of allostatic strain on the central nervous system and peripheral nervous system act as a fundamental etiological nexus for the development of multimorbidity. The classic example of this bidirectional relationship is the dysregulation of the hypothalamic-pituitary-adrenal axis,

wherein sustained stress prevents healthy neural mechanisms of feedback regulation of glucocorticoid levels, and elevated glucocorticoids, in turn, lead to neural damage, which further disrupts hypothalamic-pituitary-adrenal function (7).

A more recent example of brain-body interplay is the relationship between IR, stress biology, and the genesis of depression (12). IR is a pathological inflammatory condition in which the body's tissues have reduced responsiveness to insulin (13), including hippocampal volume, the same region implicated in allostatic load (12,14). It has been associated with several somatic disorders and is found in approximately 30% of adults in the United States (13–17). Here, we argue that it is a key risk factor for major depression in a subpopulation of individuals and that addressing IR may be essential to treating this specific metabolic subtype of depression.

An Integrated Approach for Testing the Role of IR in Depression

There are many potential reasons for the well-established epidemiological association between MDD and IR. However, the neuroscientific research summarized above led us to focus on IR as a major culprit, especially in view of its role in allostatic load and neuroplasticity. This led us to the following hypotheses: 1) that IR represents a distinct path to developing depression in certain individuals, and 2) that in individuals who are both depressed and insulin-resistant, ameliorating IR may be essential to successful treatment of depression, removing an obstacle that might otherwise result in treatment resistance.

Indeed, when we used an integrated approach, we found that the neuroscientific findings dovetailed with epidemiological research indicating a relationship between IR and MDD. A cross-sectional study from NESDA (Netherlands Study of Depression and Anxiety) found that adults with IR had greater odds of nonremitted MDD than those with no history of depressive or anxiety disorders, odds ratio: 1.51 (95% CI, 1.08–2.12) (18). IR was also associated with the severity of depressive symptoms and depression chronicity (18). In a subsequent NESDA study, a moderate increase in IR was associated with incident MDD over a 9-year follow-up period (19). Our team and others have also shown improvement in depressive symptoms in patients with IR through treatment with an insulin-sensitizing agent, pioglitazone (20,21).

Therefore, there is a convergence of evidence from basic neuroscience, human clinical observation, and epidemiological studies that points to insulin sensitization as a potential treatment target. This sets the stage for devising tailored approaches for the treatment of depression in patients with IR. However, logistical and financial challenges often thwart the translation of basic research findings into large-scale clinical trials. To circumvent these challenges, we have turned to the emulated target trial (ETT) as an intermediate step in evaluating the efficacy of treatments on depression outcomes in patients with IR.

METHODS AND MATERIALS

Target Trial Emulation

Target trial emulation is a causal inference method that entails asking a causal question using observational data by

employing the design and analytical components of an RCT. An ETT has been defined as "the application of design principles from randomized trials to the analysis of observational data, thereby explicitly tying the analysis to the trial it is emulating. The purpose is to improve the quality of observational epidemiology through the application of trial design principles, even when, or perhaps, especially when, a comparator trial is not yet available or feasible" (8).

More specifically, Hernan and Robins proposed identifying a study population from observational data by establishing the components of an RCT: eligibility criteria, intervention, assignment procedures, follow-up period, outcome, and analysis plan (described in detail for the example study in Table 1) (8). Below, we provide an example of an ETT in practice.

Findings From an ETT: Evaluating a Treatment for Metabolic Depression

Given the mechanisms that appear to link IR and MDD, one might ask whether reversing IR could induce the remission of a depressive episode. Indeed, evidence suggests that pioglitazone, an insulin-sensitizing medication, can be useful in ameliorating nonremitted MDD in patients with depression. Several small RCTs, the findings of which were summarized by a meta-analysis, indicated pioglitazone's efficacy in reversing nonremitted MDD and depression severity among individuals without type 2 diabetes mellitus (DM2) (21–28). However, while the population with DM2 is at increased risk for a major depressive episode, the antidepressant effect of pioglitazone among adults with DM2 has not been evaluated (29).

We hypothesized that the combination of antidepressant medication and an adjuvant insulin sensitizer, pioglitazone, would elicit a superior antidepressant treatment response compared with DPP4 (dipeptidyl peptidase-4) inhibitors over a 1-year follow-up period.

ETT Study Design and Methods

To investigate this hypothesis, we conducted an ETT of the effect of adjuvant pioglitazone on antidepressant response among people with DM2. Pioglitazone was compared with another class of non–insulin-sensitizing DM2 medications, DPP4 inhibitors.

The ETT was designed using health insurance claims from the Optum Clinformatics Data Mart version 3.0 (Optum Insight). The Clinformatics Data Mart Database is a deidentified database derived from a large adjudicated claims data warehouse.

Briefly, these data contain medical claims, laboratory results, prescription claims demographics, socioeconomic measures, and healthcare provider characteristics.

Eligibility Criteria

Study participants were required to meet the following inclusion criteria: 1) ≥18 years old; 2) a diagnosis of unipolar, nonpsychotic MDD; and 3) a diagnosis of DM2.

Study participants were excluded from participation if they met any of the following criteria: 1) pregnancy at the study's start date; 2) history of diabetic ketoacidosis; 3) history of severe renal impairment; 4) history of moderate-severe hepatic impairment; 5) history of acute or chronic heart failure; or 6) history of pancreatitis.

Exclusion criterion 1 was included because the safety and efficacy of pioglitazone use during pregnancy have not been sufficiently studied (30–32). Exclusion criteria 2 through 6 were contraindications for the use of one or more study treatments (33–35).

Treatment Strategies

We contrasted the initiation of an antidepressant and pioglitazone to an equivalent regimen with DPP4 inhibitors. Treatment was defined as 1) a newly filled prescription for an

Table 1. Summary of ETT Design

Study Design Element	Description
Emulated Trial	• Compared the initiation of antidepressant therapy plus pioglitazone with initiation of antidepressant therapy plus a DPP4 inhibitor on the 1-year risk of antidepressant response among individuals with MDD and DM2.
Eligibility Criteria	• Inclusion criteria: 1) ≥18 years old; 2) diagnosis of unipolar, nonpsychotic depression; 3) diagnosis of DM2. • Exclusion criteria: 1) pregnancy at the study start date; 2) history of diabetic ketoacidosis; 3) history of severe renal impairment; 4) history of moderate-severe hepatic impairment; 5) history of acute or chronic heart failure; 6) history of pancreatitis.
Treatment Strategies	• Treatment was defined as the initiation of both an antidepressant and an adjuvant DM2 drug within a 30-day grace period (30 days before or after one another), i.e., initiation of an antidepressant and pioglitazone vs. an antidepressant and a DPP4 inhibitor.
Assignment Procedures	• Treatments were nonrandomly provided by prescribing physicians. • Randomization to treatment assignment was emulated using strategies to account for measured and unmeasured confounding factors at the study start date.
Follow-up Procedures	• Participants who met eligibility criteria were enrolled in the study the first time that they initiated an antidepressant treatment and a DM2 treatment within a 30-day grace period. • The study start date was defined as the day when a participant had filled a prescription for the second of the 2 study treatments, i.e., either an antidepressant or an eligible adjuvant DM2 treatment, whichever came later.
Outcomes	• Antidepressant response was defined as the number of new antidepressants or antipsychotics prescribed within a year of the study start date. Treatment was defined as new if 1) it had never been prescribed, or 2) it had not been prescribed for at least 1 year plus the number of day's supply of the most recent prescription.
Causal Contrasts	• Intention-to-treat effect.
Analysis Plan	• Treatment effects were estimated using 1) unadjusted logistic regression, 2) adjusted logistic regression, and 3) near far matching followed by instrumental variable analysis (used for hypothesis testing).

DM2, type 2 diabetes mellitus; DPP4, dipeptidyl peptidase-4; ETT, emulated target trial; MDD, major depressive disorder.

antidepressant, and 2) a newly filled prescription for an anti-diabetic treatment. Patients were included in the study if the prescriptions were filled within 30 days of one another.

Initiation of a drug was defined using 2 criteria: 1) the first filled prescription for treatment after a patient had carried Optum insurance for >180 days, or 2) the re-initiation of a treatment >180 days after the supply from the previous prescription had ended.

In this study, we utilized filled prescription records as a proxy for medication use despite the inherent limitations of this approach. These records do not guarantee actual medication adherence. However, validity studies indicate that this approach was a reasonable and accurate proxy for medication use even though it may not perfectly capture medication adherence (36).

Assignment Procedures

In this study, participants were nonrandomly assigned to treatment by their prescribing physicians. In an RCT, participants are randomly assigned to treatment, and among its advantages is that it minimizes concerns about confounding due to measured and unmeasured factors. In this ETT, randomization of treatment assignment was emulated using strategies to account for measured and unmeasured confounding factors at the study start date.

Measured confounding was addressed using nearfar matching and statistical adjustment (37). Unmeasured confounding was addressed using nearfar matching and instrumental variable analysis. These strategies are described in detail in the statistical analysis section.

Follow-up Procedures

Participants who met eligibility criteria were enrolled in the study the first time that they initiated an antidepressant treatment and a DM2 treatment within a 30-day grace period. The study start date was defined as the day when a participant had filled a prescription for the second of the 2 study treatments, i.e., either an antidepressant or an eligible adjuvant DM2 treatment, whichever came later.

Causal Contrasts

We emulated an intention-to-treat analysis/comparison by estimating the effect of assignment to adjuvant pioglitazone versus assignment to DPP4 inhibitors. Because randomization was not possible, the instrumental variable analysis facilitated emulating the intention-to-treat analysis, i.e., produced a predicted probability of treatment assignment.

Outcomes

Antidepressant response was defined as the number of new antidepressants or antipsychotics that were prescribed within a year of the study start date. Treatment was defined as new if 1) it had never been prescribed, or 2) it had not been prescribed for at least 1 year plus the number of days' supply of the most recent prescription.

Covariates

Demographic, metabolic, cardiovascular, psychiatric, and physician-related covariates were identified for this study based on previous findings on the relationship between DM2 and MDD. These covariates were used for matching and subsequent regression and instrumental variable analyses.

Demographic covariates included age (years), sex (female, male), race/ethnicity (Asian, Black, Hispanic, White), education (years), and household income. Metabolic and cardiovascular covariates included a history of obesity (yes/no), history of hypertension (yes/no), history of hyperlipidemia (yes/no), and history of stroke (yes/no) at the start of follow-up. Similarly, data on psychiatric history were collected and dichotomized as present or absent at the start of follow-up for recurrent depression, severe depression, generalized anxiety disorder, mixed anxiety disorder, and unspecified anxiety disorder.

Covariates related to prescription medication use were derived from records of filled prescriptions. These included a history of statin use (yes/no), history of insulin use (yes/no), metformin use at the study start date (yes/no), number of antipsychotic medications used in the past year (count), number of concurrent DM2 medications at the study start date (count), and type of antidepressant at the study start date.

Physician characteristics were measured for each provider who prescribed DM2 treatment to the study participants. These data were derived from Optum's provider, member, and socioeconomic status databases. The mean characteristics of the physician's patient population were calculated using data from patients who filled an initial prescription for one of the study treatments in each study period. They included average patient age (years), sex (% female), annual income category (% <$40,000), race (% White), and education (years). In addition, we collected physician type (family/general practitioner, internist, endocrinologist, other provider).

Instrumental Variable

Calendar time for DM2 treatment selection was used to help account for possible unmeasured confounding in the relationship between treatment group and antidepressant response. Calendar time was evaluated as an instrument variable using the drug initiation year (trial year) from 2008 to 2014. The operationalization of this instrument is similar to those used in previous studies because, during this period, prescriptions for pioglitazone declined in the United States and were surpassed by prescriptions for DPP4 inhibitors (37).

The instrument was selected based on 3 assumptions (38):

1. The relevance assumption: this assumption states that the instrumental variable (calendar time) has a causal effect on treatment assignment. In this study, calendar time was evaluated using the drug initiation year from 2008 to 2014. During this period, the prescription patterns for diabetes medications changed, with pioglitazone prescriptions declining and being surpassed by prescriptions for DPP4 inhibitors. This change in prescription trends over time suggests that calendar time did influence treatment assignment, thus justifying the relevance assumption.

2. The exclusion restriction: this assumption requires that the instrumental variable (calendar time) affects the depression outcome only through treatment assignment. In other words, any effect of calendar time on antidepressant response should be solely due to its influence on treatment

selection. This is a crucial assumption for ensuring that the estimated causal effect is not biased by other factors that are related to calendar time. While it is difficult to definitively prove this assumption, the use of calendar time as an instrument is common in studies where it is reasonable to assume that it does not directly influence the outcome of interest.

3. The exchangeability assumption: this assumption states that the instrumental variable (calendar time) does not share a common cause with the study outcome. This means that any unmeasured factors that might influence both the instrument and the outcome should be unrelated. In this context, it is reasonable to assume that calendar time, as a measure of changing prescription trends, is independent of other factors that might contribute to antidepressant response. By selecting an instrumental variable that is not confounded by other factors, we aimed to produce unbiased causal effect estimates.

Statistical Analysis

Population characteristics were compared using measures of demographic, metabolic, psychiatric, and healthcare utilization variables. Standardized mean differences (SMDs) were estimated using the mean difference between exposure groups divided by the pooled variance.

Three approaches were used to evaluate the treatment effect of the ETT. First, data were nearfar matched to create 2 exchangeable treatment groups based on measured confounders as well as the instrumental variable. Then 3 analyses were conducted: 1) unadjusted logistic regression analysis, 2) adjusted logistic regression analysis, and 3) instrumental variable analysis. In the first and second stages of analysis, we conducted a logistic regression analysis of the association between treatment group (independent variable) and antidepressant response (dependent variable).

Our third analysis combined nearfar matching and instrumental variable analysis. Calendar year for DM2 treatment was used as an instrument to help account for unmeasured confounding in the relationship between treatment group and antidepressant response.

Study participants were paired using the nearfar package in R; individuals were pair matched based on 1) similarity of measured covariates, and 2) separation (dissimilarity) in the instrumental variable. Matches were divided into encouraged and discouraged groups, where the encouraged group had a higher estimated probability of assignment to pioglitazone treatment based on the instrumental variable. The discouraged group was less likely on average to be assigned to treatment with pioglitazone relative to the comparison treatment. To select pairs, the nearfar package created a rank-based Mahalanobis distance matrix of covariates. The residual imbalance for covariates was evaluated by comparing SMDs before and after matching.

After nearfar matching, two-stage residual inclusion, a form of instrumental variable analysis for nonlinear data, was used to evaluate the effect of treatment group on antidepressant treatment. Our models were adjusted for all covariates except those that were perfectly matched between groups. We estimated the local average treatment effect for the proportion of individuals who developed an antidepressant response between treatment groups. We used bootstrapping to estimate standard errors for our odds ratios as well as the local average treatment effect.

If the 95% CI for the treatment effect fell below the null value, we concluded that pioglitazone was superior. If the 95% CI included the null value, our interpretation was that pioglitazone was not superior.

Supplemental Analysis

In a supplemental analysis, we aimed to evaluate the consistency of our findings from the primary analysis by using an alternative active comparator. The primary analysis focused on estimating the effect of treatment with DPP4 inhibitors on treatment-resistant depression using pioglitazone as the reference treatment. In this supplemental analysis, we compared sulfonylureas with pioglitazone instead to assess whether the results remained consistent when using a different active comparator.

RESULTS

Demographic characteristics of participants are summarized by treatment group in Table 2 (N = 4696). Clinical characteristics of participants are summarized in Table 3. SMDs summarize the mean difference between exposure groups divided by the pooled variance. Pioglitazone users were younger, more likely to be male, had slightly lower income, were more likely to use statin medications, and were less likely to have generalized anxiety disorder than patients who were prescribed DPP4 inhibitors.

After matching, there were 2942 participants in ETT1 (pioglitazone users n = 1308; DPP4 inhibitor users n = 1634); these users were divided into 2 equal encouraged and discouraged groups, as described above, using the matching algorithm (n = 1471 in each group). The SMD for all covariates was <0.15, except for age (SMD = 0.17). The clinical characteristics of the encouraged and discouraged groups after nearfar matching are presented in Table 4. After matching, the groups were considerably more balanced. To account for residual confounding, including the age difference between groups, covariates were adjusted for in all regression models. Unadjusted linear regression, adjusted linear regression, and instrumental variable analysis in the nearfar-matched data are detailed in Table 5.

Findings from logistic regression and instrumental variable analyses in the matched sample are summarized in Table 5. The instrumental variable analysis showed that pioglitazone users added a new antidepressant or antipsychotic treatment 1.3 times on average as compared to 1.7 times among DPP4 users over a 1-year follow-up period. Therefore, the initiation of an antidepressant and pioglitazone was superior to an antidepressant and a DPP4 inhibitor for antidepressant response in our study population.

Supplemental Analysis

The ETT described in the primary analysis was replicated using sulfonylureas to pioglitazone to evaluate the consistency of our findings when using an alternative active comparator. All analyses and procedures were identical. There were 6518

Table 2. Demographic Characteristics of the DPP4 Inhibitor and Pioglitazone Treatment Groups

Demographic Characteristic	DPP4 Inhibitors, $n = 2793$	Pioglitazone, $n = 1903$	SMD[a]
Education, Years	13.3 (1.3)	13.3 (1.3)	0.00
Race/Ethnicity			0.06
Asian	64 (2.3%)	36 (1.9%)	
Black	385 (13.8%)	226 (11.9%)	
Hispanic	574 (20.6%)	390 (20.5%)	
White	1770 (63.4%)	1251 (65.7%)	
Household Income			0.01
<$40,000	462 (16.5%)	343 (18.0%)	
$40,000–$49,999	892 (28.2%)	537 (28.2%)	
$50,000–$59,999	218 (7.8%)	141 (7.4%)	
$60,000–$74,999	220 (7.9%)	158 (8.3%)	
$75,000–$99,999	256 (9.2%)	172 (9.0%)	
>$100,000	318 (11.4%)	254 (13.3%)	
Unknown	427 (15.3%)	298 (15.7%)	
United States Region			0.26
New England	75 (2.7%)	40 (2.1%)	
Mid-Atlantic	130 (4.7%)	64 (3.4%)	
East North Central	300 (10.7%)	229 (12.0%)	
West North Central	170 (6.1%)	124 (6.5%)	
South Atlantic	754 (27.0%)	504 (26.5%)	
East South Central	132 (4.7%)	74 (3.9%)	
West South Central	531 (19.0%)	351 (18.4%)	
Mountain	205 (7.3%)	152 (8.0%)	
Pacific	238 (8.5%)	190 (10.0%)	
Provider Type			0.05
Family/general practitioner	1051 (37.6%)	815 (42.8%)	
Internist	787 (28.2%)	487 (25.6%)	
Endocrinologist	193 (6.9%)	137 (7.2%)	
Other provider	762 (27.3%)	762 (27.3%)	

Values are presented as mean (SD) or n (%).

DPP4, dipeptidyl peptidase-4; SMD, standardized mean difference.

[a]SMD is the mean divided by the standard deviation of a difference between two random values, each from one of two groups.

Table 3. Clinical Characteristics of Nearfar-Matched DPP4 Inhibitor and Pioglitazone Groups

Clinical Characteristic	DPP4 Inhibitors, $n = 2793$	Pioglitazone, $n = 1903$	SMD[a]
Age, Years	61.3 (13.1)	59.6 (12.2)	0.13
Female	1874 (67.1%)	1147 (60.2%)	0.31
Medical History			
History of obesity	1167 (41.8%)	749 (39.4%)	0.05
History of hypertension	2387 (85.5%)	1578 (82.9%)	0.07
History of hyperlipidemia	2322 (83.1%)	1575 (82.8%)	0.01
History of myocardial infarction	72 (2.6%)	36 (1.9%)	0.05
History of stroke	214 (7.7%)	88 (4.6%)	0.13
History of severe MDD	417 (14.9%)	281 (14.8%)	0.00
History of recurrent MDD	1363 (48.8%)	919 (48.3%)	0.01
Unspecified anxiety disorder	1360 (48.7%)	862 (45.3%)	0.07
Medication Use			
Diabetes medications at start date	2.76 (1.60)	2.70 (1.56)	0.05
Metformin use at start date	598 (21.4%)	367 (19.3%)	0.05
History of insulin use	677 (24.2%)	407 (21.4%)	0.07
History of statin use	1197 (42.9%)	844 (44.4%)	0.03
Antidepressants used in past year	0.80 (0.74)	0.76 (0.72)	0.05

Values are presented as mean (SD) or n (%).

DPP4, dipeptidyl peptidase-4; MDD, major depressive disorder; SMD, standardized mean difference.

[a]SMD is the mean divided by the standard deviation of a difference between two random values, each from one of two groups.

regression analysis, and instrumental variable analysis in the nearfar-matched data are detailed in Table 5.

DISCUSSION

Individuals with IR and MDD represent an important subgroup with two highly prevalent comorbidities for whom treatment as usual may not always be effective and an evidence-based precision approach may prove highly beneficial. Our working hypothesis is that clinical improvement of depression in this group requires addressing their IR.

To ascertain whether this is a reasonable approach prior to conducting a clinical trial, we conducted an emulated trial using observational data on individuals with both MDD and DM2 (representing a more advanced stage of altered insulin responsiveness). We evaluated the relationship between treatment with pioglitazone and antidepressant therapy on 1-year risk of antidepressant response among individuals with MDD and DM2 compared with another class of adjuvant DM2 medications: DPP4 inhibitors. While the DM2 drugs do not substantially differ in their effect on glycemic control, pioglitazone was superior to DPP4 inhibitors in its impact on the course of response to antidepressant treatment over a 1-year period. These findings support the hypothesis that adjuvant pioglitazone leads to a stronger antidepressant treatment response than DPP4 inhibitors among individuals with MDD and DM2 as measured by fewer treatment shifts and/or

participants in this ETT (pioglitazone users $n = 1639$; sulfonylurea users $n = 4879$). Pioglitazone users were more likely to take statins, use insulin, and take a larger average number of antidepressant medications in the past year than those who used sulfonylureas. After nearfar matching, there were $n = 3258$ study participants in each group. The SMD for all matched covariates was <0.15.

Pioglitazone users added new antidepressant or antipsychotic treatment 0.8 times as compared to 1.4 times among sulfonylurea users over a 1-year follow-up period. Therefore, we found that the initiation of an antidepressant and pioglitazone was superior to an antidepressant and sulfonylurea for antidepressant response among people with MDD and DM2.

Notably, the 2 ETTs used a unique subset of pioglitazone patients who were matched to their counterparts (DPP4 inhibitor or sulfonylurea users), thereby accounting for differences in estimated treatment effects between the 2 ETTs. Unadjusted linear regression analysis, adjusted linear

Table 4. Clinical Characteristics of Nearfar-Matched Encouraged and Discouraged Groups

Clinical Characteristic	Discouraged Matches, $n = 1574$	Encouraged[a] Matches, $n = 1574$	SMD[b]
Age, Years	58.7[c]	60.8[c]	0.17
Female	963 (65.5%)	821 (66.1%)	0.01
Medical History			
History of obesity	479 (32.6%)	445 (35.8%)	0.07
History of hypertension	1252 (85.1%)	1275 (86.7%)	0.04
History of hyperlipidemia	1254 (85.2%)	1072 (86.4%)	0.03
History of stroke	45 (3.1%)	35 (2.8%)	0.02
History of severe MDD	210 (14.3%)	177 (12.0%)	0.07
History of recurrent MDD	697 (47.4%)	683 (46.4%)	0.02
Unspecified anxiety disorder	704 (47.9%)	689 (46.8%)	0.02
Medication Use			
Diabetes medications at start date	2.55[c]	2.59[c]	0.03
Metformin use at start date	280 (19.0%)	222 (17.9%)	0.03
History of insulin use	242 (16.5%)	198 (16.0%)	0.01
History of statin use	725 (49.3%)	557 (46.5%)	0.06
Antidepressants used in past year	0.74[c]	0.74[c]	0.00
Instrumental Variable			
Trial year	7.6[c]	14.3[c]	3.84

Values are presented as mean (SD) or n (%).

DPP4, dipeptidyl peptidase-4; MDD, major depressive disorder; SMD, standardized mean difference.

[a]Matches were divided into encouraged and discouraged groups, where the encouraged group had a higher estimated probability of assignment to pioglitazone treatment based on the instrumental variable.

[b]SMD is the mean divided by the standard deviation of a difference between two random values, each from one of two groups.

[c]SD is not available.

additions of a new antidepressant or antipsychotic. Similarly, a supplemental analysis found that the initiation of an antidepressant and pioglitazone was superior to an antidepressant

Table 5. Linear Regression and Instrumental Variable Analyses of Effect of Adjuvant Pioglitazone Compared With DPP4 Inhibitors and Sulfonylureas on Antidepressant Response[a] Within 1 Year

Model	Parameter Estimate	95% CI
ETT 1: Pioglitazone Compared With DPP4 Inhibitors		
Unadjusted Linear Regression	0.02	−0.05 to 0.07
Adjusted Linear Regression	0.03	−0.04 to 0.07
Instrumental Variable Analysis	−0.37	−0.56 to −0.02
ETT 2: Pioglitazone Compared With Sulfonylureas		
Unadjusted Linear Regression	0.06	0.02 to 0.11
Adjusted Linear Regression	0.06	0.01 to 0.11
Instrumental Variable Analysis[a]	−0.62	−1.01 to −0.23

Findings from the instrumental variable analysis were used to evaluate the superiority of pioglitazone compared with DPP4 inhibitors or sulfonylureas.

DPP4, dipeptidyl peptidase-4; ETT, emulated target trial.

[a]Antidepressant response was defined as the number of new antidepressants or antipsychotics initiated within a year of the study's start.

and a sulfonylurea for antidepressant response among people with MDD and DM2.

Animal studies have found that treatment with DPP4 inhibitors improved depression-like behavior in rodents (38). The findings from human observational studies are mixed. A few observational studies have suggested that the use of antidiabetic agents, including DPP4 inhibitors and sulfonylureas, is associated with lower depression prevalence and symptoms compared with no treatment (39–42). While a Taiwanese study reported that patients with DM2 who were taking sulfonylureas had a lower incidence of depression than patients who were not taking diabetes medication, a second study compared the effect of sulfonylureas and other antidiabetic agents on the risk of incident depression and found no difference between them (42). However, neither has been evaluated in the context of nonremitted depression. Moreover, early studies of sitagliptin, a DPP4 inhibitor, found a 4-fold increase in suicidal ideation among individuals with DM2, and it has been postulated that DPP4 inhibition may increase the risk for symptoms of MDD (43,44).

In contrast to these mixed results, the insulin-sensitizing pioglitazone emerged more consistently as an effective adjuvant therapy for nonremitted MDD among adults without DM2. A meta-analysis of RCTs found a pooled odds ratio of 3.3 (95% CI, 1.4–7.8) for a reduction in depression symptoms when compared to a placebo (28). There are a number of plausible mechanisms by which treatment with pioglitazone may impact the brain and have an antidepressant effect in a population of individuals with DM2, including insulin sensitization, anti-inflammatory pathways, mitochondrial alterations, and activation of the endocannabinoid system (12,22,45–47).

The fact that our emulated trial on a large group of records found that pioglitazone was superior to other DM2 drugs represents a proof of concept that this approach can be powerful in predicting clinical outcome. Our findings, coupled with previous evidence on the role of pioglitazone in MDD patients with IR, suggest that pioglitazone may prove useful in ameliorating nonremitted MDD among people with IR or comorbid DM2 (21,23–27). One limitation of our study is that the use of prescription medication records as a proxy measure for medication adherence assumes that patients take their prescribed medications as directed, which may not always be the case. If these findings are replicated, particularly the distinction between pioglitazone and DPP4 inhibitors, they would have clinical relevance for physicians considering the selection of treatment for patients with comorbid DM2 and MDD.

This ETT example underscores both the challenge and possibilities of matching appropriate treatments to the heterogeneous subpopulations of individuals with affective disorders. ETT is one of the numerous techniques originating from epidemiology, econometrics, and causal inference that can be applied to psychiatric research. Before performing costly and time-consuming clinical studies, these types of computational strategies can provide preliminary insight into the efficacy of a specific intervention in psychiatric subpopulations. Indeed, causal inference approaches may serve as a crucial translational step in evaluating treatments for affective disorders.

Thanks to breakthroughs in causal inference and epidemiological approaches as well as computational power, we are now uniquely able to handle this multidisciplinary translational

challenge. We can build research teams with linkages to neurobiology, epidemiology, clinical and computational psychiatry, and other biological domains. An integrated, team-driven framework would combine mechanistic neurobiological findings with those from quantitative methods, resulting in a translational process that is both iterative and bidirectional. Causal inference and related quantitative approaches would yield insight into the biological pathways that manifest as heterogeneity among individuals with psychiatric disorders. This, in turn, should drive neurobiological research forward, providing additional translational targets to evaluate using the aforementioned computational techniques.

Taken together, insights from these disciplines can provide a conceptual framework for better understanding the heterogeneity of psychiatric disorders, evaluating targeted treatments before conducting clinical trials, and establishing a platform for precision medicine procedures.

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REFERENCES

1. Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC (2015): The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry 76:155–162.
2. Al-Harbi KS (2012): Treatment-resistant depression: Therapeutic trends, challenges, and future directions. Patient Prefer Adherence 6:369–388.
3. Souery D, Oswald P, Massat I, Bailer U, Bollen J, Demyttenaere K, et al. (2007): Clinical factors associated with treatment resistance in major depressive disorder: Results from a European multicenter study. J Clin Psychiatry 68:1062–1070.
4. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. (2018): Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet 50:668–681.
5. Akil H, Gordon J, Hen R, Javitch J, Mayberg H, McEwen B, et al. (2018): Treatment resistant depression: A multi-scale, systems biology approach. Neurosci Biobehav Rev 84:272–288.
6. Garner JP (2014): The significance of meaning: Why do over 90% of behavioral neuroscience results fail to translate to humans, and what can we do to fix it? ILAR J 55:438–456.
7. McEwen BS, Akil H (2020): Revisiting the stress concept: Implications for affective disorders. J Neurosci 40:12–21.
8. Hernán MA, Robins JM (2016): Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol 183:758–764.
9. Rasgon NL, McEwen BS (2016): Insulin resistance-a missing link no more. Mol Psychiatry 21:1648–1652.
10. McEwen BS (1998): Protective and damaging effects of stress mediators. N Engl J Med 338:171–179.
11. McEwen BS, Rasgon NL (2018): The brain and body on stress: Allostatic load and mechanisms for depression and dementia. In: Strain JJ, Blumenfield M, editors. Depression as a Systemic Illness. Oxford: Oxford University Press, 14–36.
12. Watson K, Nasca C, Aasly L, McEwen B, Rasgon N (2018): Insulin resistance, an unmasked culprit in depressive disorders: Promises for interventions. Neuropharmacology 136:327–334.
13. DeFronzo RA, Ferrannini E (1991): Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 14:173–194.
14. Rasgon NL, Kenna HA, Wroolie TE, Kelley R, Silverman D, Brooks J, et al. (2011): Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease. Neurobiol Aging 32:1942–1948.
15. Ioannou GN, Bryson CL, Boyko EJ (2007): Prevalence and trends of insulin resistance, impaired fasting glucose, and diabetes. J Diabetes Complications 21:363–370.
16. Kan C, Silva N, Golden SH, Rajala U, Timonen M, Stahl D, Ismail K (2013): A systematic review and meta-analysis of the association between depression and insulin resistance. Diabetes Care 36:480–489.
17. Ginsberg HN (2000): Insulin resistance and cardiovascular disease. J Clin Invest 106:453–458.
18. Watson KT, Simard JF, Henderson VW, Nutkiewicz L, Lamers F, Rasgon N, Penninx B (2021): Association of insulin resistance with depression severity and remission status: Defining a metabolic endophenotype of depression. JAMA Psychiatry 78:439–441.
19. Watson KT, Simard JF, Henderson VW, Nutkiewicz L, Lamers F, Nasca C, et al. (2021): Incident major depressive disorder predicted by three measures of insulin resistance: A Dutch cohort study. Am J Psychiatry 178:914–920.
20. Colle R, de Larminat D, Rotenberg S, Hozer F, Hardy P, Verstuyft C, et al. (2017): PPAR-γ agonists for the treatment of major depression: A review. Pharmacopsychiatry 50:49–55.
21. Lin KW, Wroolie TE, Robakis T, Rasgon NL (2015): Adjuvant pioglitazone for unremitted depression: Clinical correlates of treatment response. Psychiatry Res 230:846–852.
22. Kemp DE, Ismail-Beigi F, Ganocy SJ, Conroy C, Gao K, Obral S, et al. (2012): Use of insulin sensitizers for the treatment of major depressive disorder: A pilot study of pioglitazone for major depression accompanied by abdominal obesity. J Affect Disord 136:1164–1173.
23. Kashani L, Omidvar T, Farazmand B, Modabbernia A, Ramzanzadeh F, Tehraninejad ES, et al. (2013): Does pioglitazone improve depression through insulin-sensitization? Results of a randomized double-blind metformin-controlled trial in patients with polycystic ovarian syndrome and comorbid depression. Psychoneuroendocrinology 38:767–776.
24. Zeinoddini A, Sorayani M, Hassanzadeh E, Arbabi M, Farokhnia M, Salimi S, et al. (2015): Pioglitazone adjunctive therapy for depressive episode of bipolar disorder: A randomized, double-blind, placebo-controlled trial. Depress Anxiety 32:167–173.
25. Kemp DE, Schinagle M, Gao K, Conroy C, Ganocy SJ, Ismail-Beigi F, Calabrese JR (2014): PPAR-gamma agonism as a modulator of mood: Proof-of-concept for pioglitazone in bipolar depression. CNS Drugs 28:571–581.
26. Salehi-Sadaghiani M, Javadi-Paydar M, Gharedaghi MH, Zandieh A, Heydarpour P, Yousefzadeh-Fard Y, Dehpour AR (2012): NMDA receptor involvement in antidepressant-like effect of pioglitazone in the forced swimming test in mice. Psychopharmacol (Berl) 223:345–355.
27. Sepanjnia K, Modabbernia A, Ashrafi M, Modabbernia MJ, Akhondzadeh S (2012): Pioglitazone adjunctive therapy for

moderate-to-severe major depressive disorder: Randomized double-blind placebo-controlled trial. Neuropsychopharmacology 37:2093–2100.

28. Colle R, de Larminat D, Rotenberg S, Hozer F, Hardy P, Verstuyft C, et al. (2017): Pioglitazone could induce remission in major depression: A meta-analysis. Neuropsychiatr Dis Treat 13:9–16.

29. Mommersteeg PM, Herr R, Pouwer F, Holt RI, Loerbroks A (2013): The association between diabetes and an episode of depressive symptoms in the 2002 World Health Survey: An analysis of 231,797 individuals from 47 countries. Diabet Med 30:e208–e214.

30. Moretti ME, Rezvani M, Koren G (2008): Safety of glyburide for gestational diabetes: A meta-analysis of pregnancy outcomes. Ann Pharmacother 42:483–490.

31. U.S. Food and Drug Administration: ACTOSTM (Pioglitazone Hydrochloride) Tablets Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/21073lbl.pdf. Accessed September 6, 2023.

32. Castillo WC, Funk MJ (2015): Association of adverse pregnancy outcomes with glyburide vs insulin in women with gestational diabetes. JAMA Pediatr 169:452–458.

33. Sweileh WM (2007): Contraindications to metformin therapy among patients with type 2 diabetes mellitus. Pharm World Sci 29:587–592.

34. Drugs@Fda (2011): Actos-Highlights of Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/21073lbl.pdf. Accessed September 6, 2023.

35. Emslie-Smith AM, Boyle DI, Evans JM, Sullivan F, Morris AD, DARTS/MEMO Collaboration (2001): Contraindications to metformin therapy in patients with type 2 diabetes – A population-based study of adherence to prescribing guidelines. Diabet Med 18:483–488.

36. Tangkiatkumjai M, Walker DM, Praditpornsilpa K, Boardman H (2017): Association between medication adherence and clinical outcomes in patients with chronic kidney disease: A prospective cohort study. Clin Exp Nephrol 21:504–512.

37. Montvida O, Shaw J, Atherton JJ, Stringer F, Paul SK (2018): Long-term trends in antidiabetes drug usage in the U.S.: Real-world evidence in patients newly diagnosed with type 2 diabetes. Diabetes Care 41:69–78.

38. Rigdon J, Baiocchi M, Basu S (2018): Near–far Matching in R: The nearfar Package. J Stat Soft 86: https://doi.org/10.18637/jss.v086.c05.

39. Soliman E, Essmat N, Mahmoud MF, Mahmoud AAA (2020): Impact of some oral hypoglycemic agents on type 2 diabetes-associated depression and reserpine-induced depression in rats: The role of brain oxidative stress and inflammation. Naunyn Schmiedebergs Arch Pharmacol 393:1391–1404.

40. Bai X, Liu Z, Li Z, Yan D (2018): The association between insulin therapy and depression in patients with type 2 diabetes mellitus: A meta-analysis. BMJ Open 8:e020062.

41. Noh JH, Park JK, Lee HJ, Kwon SK, Lee SH, Park JH, et al. (2005): Depressive symptoms of type 2 diabetics treated with insulin compared to diabetics taking oral anti-diabetic drugs: A Korean study. Diabetes Res Clin Pract 69:243–248.

42. Gamble J-M, Chibrikov E, Midodzi WK, Twells LK, Majumdar SR (2018): Examining the Risk of Depression or Self-Harm Associated With Incretin-Based Therapies Used to Manage Hyperglycaemia in Patients With Type 2 Diabetes: A Cohort Study Using the UK Clinical Practice Research Datalink. BMJ Open 8:e023830.

43. Akimoto H, Tezuka K, Nishida Y, Nakayama T, Takahashi Y, Asai S (2019): Association between use of oral hypoglycemic agents in Japanese patients with type 2 diabetes mellitus and risk of depression: A retrospective cohort study. Pharmacol Res Perspect 7:e00536.

44. Committee for Medicinal Products for Human Use (2014): Revlimid European Public Assessment Report (EPAR) Scientific Discussion. Available at: https://www.ema.europa.eu/en/documents/variation-report/revlimid-h-c-717-x-0046-g-epar-assessment-report-extension_en.pdf. Accessed September 6, 2023.

45. (2008): Sitagliptin: New drug. Type 2 diabetes: Limited efficacy, too many unknown risks. Prescrire Int 17:12–15.

46. Popa-Wagner A, Mitran S, Sivanesan S, Chang E, Buga AM (2013): ROS and brain diseases: The good, the bad, and the ugly. Oxid Med Cell Longev 2013:963520.

47. Jiang B, Huang C, Zhu Q, Tong LJ, Zhang W (2015): Wy14643 produces anti-depressant-like effects in mice via the BDNF signaling pathway. Psychopharmacology 232:1629–1642.