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Research Article

Association of Disease Duration and Duration of Olanzapine Use with Blood Sugar, Blood Pressure, BMI, and Lipid Profile among Schizophrenic Patients in Iraq

Zinah Abdulhameed Alobaidi[1]*, Samer Imad Mohammed[2]

[1] *Department of Pharmacy, Iraqi Ministry of Health, Baghdad, Iraq;* [2] *Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq*

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Abstract

Background: The association of olanzapine with hyperglycemia, an elevated lipid profile, and high blood pressure was early recognized after its approval and has become of increased concern. ***Objective***: To determine the association of olanzapine use with blood sugar levels, lipid profiles, and blood pressure in hospitalized Iraqi patients with schizophrenia. ***Methods***: A cross-sectional study involving 50 hospitalized patients with schizophrenia who met the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V diagnostic criteria and had taken olanzapine for at least two years was carried out between November 2022 and February 2023 at two facilities in Baghdad, Iraq (Ibn Rushd Psychiatric Teaching Hospital and Al Rashad Hospital for Mental Health). Blood pressure, fasting blood sugar, and serum lipid profile (triglycerides [TG], high-density lipoprotein [HDL], low-density lipoprotein [LDL], and very-low-density lipoprotein [VLDL]) were measured at baseline and after olanzapine use. ***Results***: Olanzapine significantly increases fasting blood glucose ($P< 0.001$). After using olanzapine, both systolic and diastolic blood pressures significantly increased. It significantly increased the levels of cholesterol, triglycerides, and VLDL ($P<0.001$). Moreover, HDL levels were drastically lowered. The current investigation found no significant link between the patient's waist circumference and current weight and the length of their illness or olanzapine use. In addition, there was no association between the duration of olanzapine use and blood sugar, blood pressure, or lipid profiles. ***Conclusion***: Different doses and durations of olanzapine use in Iraqi schizophrenic patients are associated with a negative impact on glycemic control, blood pressure, and lipid profiles.

Keywords: Olanzapine, Blood sugar, Blood pressure, Lipid profile, Schizophrenic patients

ارتباط مدة المرض ومدة استخدام أولانزابين مع نسبة السكر في الدم وضغط الدم ومؤشر كتلة الجسم والدهون بين مرضى الفصام في العراق

الخلاصة

الخلفية: تم التعرف على ارتباط أولانزابين بارتفاع السكر في الدم وارتفاع نسبة الدهون وارتفاع ضغط الدم في وقت مبكر بعد اقراره للأستخدام السريري وأصبح مصدر قلق متزايد. **الهدف**: تحديد ارتباط استخدام أولانزابين بمستويات السكر في الدم، وملامح الدهون، وضغط الدم في المرضى العراقيين المصابين بالفصام الراقدين في المستشفى. **الطريقة**: أجريت دراسة مقطعية شملت 50 مريضا مصابا بالفصام في المستشفى واستوفوا معايير الدليل التشخيصي والإحصائي للاضطرابات العقلية V- (DSM) واستعملوا أولانزابين لمدة عامين على الأقل بين نوفمبر 2022 وفبراير 2023 في مركزين طبيين في بغداد، العراق (مستشفى ابن رشد التعليمي للأمراض النفسية ومستشفى الرشاد للصحة النفسية). تم قياس ضغط الدم وسكر الدم الصائم ومستوى الدهون الثلاثية (TG) والبروتين الدهني عالي الكثافة (HDL) والبروتين الدهني منخفض الكثافة (LDL) والبروتين الدهني منخفض الكثافة (VLDL) عند خط الأساس وبعد استخدام أولانزابين. **النتائج**: أولانزابين يزيد بشكل كبير من نسبة الجلوكوز في الدم الصائم، وارتفع ضغط الدم الانقباضي والانبساطي بشكل ملحوظ. وتسبب في ارتفاع كبير في مستويات الكوليسترول والدهون الثلاثية و VLDL علاوة على ذلك ، تم تخفيض مستويات HDL بشكل كبير. لم يجد التحقيق الحالي أي صلة كبيرة بين محيط خصر المريض ووزنه الحالي وطول فترة مرضه أو استخدام أولانزابين. بالإضافة إلى ذلك، لم يكن هناك ارتباط بين مدة استخدام أولانزابين وسكر الدم أو ضغط الدم أو ملامح الدهون. **الأستنتاج**: ترتبط الجرعات والفترات المختلفة لاستخدام أولانزابين في مرضى الفصام العراقيين بتأثير سلبي على التحكم في نسبة السكر في الدم وضغط الدم وملامح الدهون.

* Corresponding author: Zinah A. Alobaidi. Department of Pharmacy, Iraqi Ministry of Health, Baghdad, Iraq; Email: zina.abd2100m@copharm.uobaghdad.edu.iq

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INTRODUCTION

Schizophrenia is a mental disorder that is characterized by a complex and severe set of symptoms, and is known to have a high prevalence rate [1]. In comparison to conventional medications, innovative non-traditional antipsychotics have been found to offer notable benefits in the treatment of schizophrenia, primarily due to their lower incidence of extrapyramidal side effects [2]. Nevertheless, the administration of atypical antipsychotic medications may exacerbate cardiovascular risk factors such as hyperglycemia, hyperlipidemia, and weight gain. Furthermore, the utilization of antipsychotic medication in individuals diagnosed with schizophrenia has been linked to the development of hypertension, as indicated by previous research [3]. Several studies have established a correlation between the use of atypical antipsychotics and an increased likelihood of hyperglycemia, altered glucose levels, and lipid disturbance, which can ultimately result in the development of metabolic syndrome in individuals with schizophrenia [4]. Furthermore, it has been reported that olanzapine exhibits an elevation in serum triglyceride levels [5]. As per the findings of a study, prolonged utilization of antipsychotic medication may be linked to a considerably heightened susceptibility to obesity, a moderate impact on the onset of diabetes, and negligible or no impact on hypertension. [6] The negative impacts observed were largely attributed to the impact of olanzapine on various bodily organs and tissues, including the hypothalamus, liver, pancreatic cells, adipose tissue, and skeletal muscle, as reported in reference [7]. In Iraq, previous research has examined the impact of olanzapine on certain parameters in isolation, as evidenced by studies [8,9]. However, no prior investigation has been conducted in Iraq to comprehensively establish the effect of olanzapine on all parameters anticipated to be impacted by the drug. The objective of this investigation was to assess the impact of olanzapine on glycemic control, serum lipid profiles, and blood pressure among inpatients diagnosed with schizophrenia.

METHODS

Study design

A cross-sectional study with an observational design was carried out at two psychiatric institutions, namely Ibn Rushd Psychiatric Teaching Hospital and Al-Rashad Hospital for Mental Health, located in Baghdad, Iraq.

Ethical approval

The study received ethical clearance from the Ethical and Scientific Committee of the College of Pharmacy, University of Baghdad (REAFUBLP 16112021 on 29/1/2022). Furthermore, the study received approval from the Ministry of Health, Ibn Rushd Psychiatric Training Hospital, and Al-Rashad Hospital for Mental Health, all located in Baghdad, Iraq (Ref. No. AS 6751 on 6-11-2022 and Ref. No. AS 6752 on 6-11-2022, respectively).

Inclusion criteria

The study included adult patients aged 18 to 65 who had been diagnosed with either schizophrenia or schizoaffective disorder, and met the diagnostic criteria for schizophrenia as outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V. The inclusion criteria for this study stipulate that patients must have undergone uninterrupted antipsychotic therapy, with a prescribed dose of olanzapine ranging from 5 to 20 mg per day, for a minimum duration of two years.

Exclusion criteria

1) Individuals afflicted with substance-induced psychotic disorder, psychotic disorder caused by a general condition, or intellectual disability, 2) Individuals who have underlying medical conditions that are recognized to impact the brain or require treatment with psychotropic medication, 3) Patients concurrently using medications that have potential interactions with olanzapine, such as pregabalin, as well as vitamins B12, C, and D3, warrant careful consideration, 4) Women who are either pregnant or currently breastfeeding, 5) Patients presenting with pre-existing hypertension, diabetes mellitus, hyperlipidemia, or obesity at the onset of antipsychotic drug therapy; and 6) Patients receiving mood stabilizers such as carbamazepine, sodium valproate, and lithium.

Study groups

A total of 89 individuals diagnosed with schizophrenia were subjected to eligibility screening, resulting in the exclusion of 39 patients due to various reasons. There were 8 individuals who were administered carbamazepine, 7 who were administered sodium valproate, 4 of whom had pre-existing hypertension, 1 who was administered thyroxin, 7 who lacked baseline FBS glucose values prior to the initiation of olanzapine treatment, and 12 who lacked baseline lipid profile values prior to the initiation of olanzapine treatment. Fifty individuals diagnosed with schizophrenia and prescribed olanzapine were recruited and divided into two groups based on the metabolic syndrome classification criteria outlined in reference [26]. The study consisted of two groups: Group A, which included 30 patients diagnosed with both schizophrenia and metabolic syndrome, and Group B, which included 20 patients diagnosed with schizophrenia but without metabolic syndrome.

Data collection

Sociodemographic and clinical data were recorded for all participants, in addition to detailed information on lifestyle, smoking, and occupational status, in a predesigned data collection sheet. The patient's height was measured using an EMTOP steel measuring tape 5M (EMTP25101). The waist circumference was measured midway between the lower rib margin (12th rib) and the

iliac crest. Blood pressure was measured using a digital sphygmomanometer (Omron Digital Automatic Blood Pressure Monitor Model HEM-907, Omron Healthcare Co., Ltd., Kyoto, Japan).

Laboratory tests

The tests of blood glucose and lipid profile were done on a fasting blood specimen for at least 8 hours overnight with complete dietary restriction with the exception of water and medication. About 10 ml of blood was drawn from each patient, and the serum was centrifuged and kept at -20℃. The fasting blood sugar (FBS), cholesterol, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were assayed on an automated biochemical analyzer by the photometric method.

Statistical analysis

The SPSS for Windows 26.0 program was utilized for data analysis (SPSS, Inc., Chicago, IL, USA). Continuous data were presented as mean±SD while categorical data were presented as number and frequency. A Shapiro-Wilk test was used to test the results' normality, and the results' distribution was normal for all variables ($P > 0.05$). Group differences were ascertained by an unpaired t-test between the two groups. While the student-paired t-test was used to compare differences between the baseline and current values of the studied parameters, correlation analysis was performed using Pearson's correlation test. A P value less than 0.05 was considered for significant differences.

RESULTS

Demographic data for all participants is demonstrated in Tables 1A and 1B. The study recruited a convenient sample of hospitalized patients ($n = 50$) of both sexes, 22 women (44%) and 28 men (56%). The mean age of the patients was 47.60 years (SD = 9.293), with a range of 24–69 years. Overall, schizophrenia was more prevalent than delusional disorder ($n = 42$) and hallucinations ($n = 8$).

Table 1A: Demographic data, the study groups' clinical characteristics, and qualitative parameters

		Metabolic *n*=30 *n* (%)	Non-Metabolic *n*=20 *n* (%)	Total *n*=50 *n* (%)	*P*-value
Gender	Male	18 (36)	10 (20)	28 (56)	[a] 0.485
	Female	12 (24)	10 (20)	22 (44)	
Occupation	Unemployed	23 (46)	15 (30)	38 (76)	[b] 0.575
	Employed	7 (14)	5 (10)	12 (24)	
Marital Status	Divorced	6 (12)	7 (14)	13 (26)	[b] 0.171
	Single	19 (38)	9 (18)	28 (56)	
	Married	5 (10)	2 (4)	7 (14)	
	Widow	0 (0.0)	2 (4)	2 (4)	
Residence	Baghdad	13 (26)	11 (22)	24 (48)	[b] 0.443
	Karbala	2 (4)	2 (4)	4 (8)	
	Diyala	5 (10)	0 (0.0)	5 (10)	
	Qadsiya	1 (2)	0 (0.0)	1 (2)	
	Kirkuk	1 (2)	1 (2)	2 (4)	
	Mosul	1 (2)	1 (2)	2 (4)	
	Basra	1 (2)	2 (4)	3 (6)	
	Najaf	1 (2)	3 (6)	4 (8)	
	Wasit	1 (2)	0 (0.0)	1 (2)	
	Dhiqar	1 (2)	0 (0.0)	1 (2)	
	Babylon	2 (4)	0 (0.0)	2 (4)	
	Maysan	1 (2)	0 (0.0)	1 (2)	
Family History	Yes	19 (38)	12 (24)	31 (62)	[a] 0.812
	No	11 (22)	8 (16)	19 (38)	
Education	Illiteracy	13 (26)	3 (6)	16 (32)	[b] 0.088
	Primary	11 (22)	8 (16)	19 (38)	
	Secondary School	3 (6)	7 (14)	10 (20)	
	Bachelor	1 (2)	1 (2)	2 (4)	
	Diploma	2 (4)	1 (2)	3 (6)	
Smoking status	No	9 (18)	3 (6)	12 (24)	[b] 0.317
	Yes	21 (42)	17 (34)	38 (76)	
Medical History	Nil	28 (56)	17 (34)	45 (90)	[b] 0.517
	IHD	2 (4)	1 (2)	3 (6)	
	Stroke	0 (0.0)	1 (2)	1 (2)	
	Asthma	0 (0.0)	1 (2)	1 (2)	
Dose of olanzapine	5 mg/day	2 (4)	1 (2)	3 (6)	[b] 0.792
	10 mg/day	11 (22)	5 (10)	16 (32)	
	20 mg/day	17 (34)	14 (28)	31 (62)	

Results are presented as frequency and percentage. [a] Chi-square test. [b] Fisher-exact test.

Table 1B: Demographic data and the study groups' clinical characteristics and quantitative parameters

Parameter	Metabolic *n*=30	Non-Metabolic *n*=20	Total *n*=50	*P*-value
Age	47.40±9.25	47.90±9.59	47.60±9.29	0.854
Height (cm)	167.43±8.51	166.75±8.12	167.16±8.28	0.761
Waist Circumference (cm)	119.53±10.32	102.10±21.13	112.56±17.62	0.060
Weight (kg)	97.57±15.40	91.95±25.32	95.32±19.92	0.057
BMI (kg/m^2)	34.47±4.05	32.98±8.07	33.87±5.96	0.001
Duration of disease (yr)	9.03±6.55	7.45±3.93	8.40±5.66	0.410
Duration of treatment (yr)	8.60±5.46	6.85±3.27	7.90±4.75	0.234
No. of cigarettes	35.33±32.67	42.0±27.45	38.0±30.57	0.301
BP (systolic)	147±19	121±16	137±22	0.668
BP (Diastolic)	92±16	79±10	87±15	0.053
Pulse Rate	88±21	90±20	89±20	0.798

Results are reported as mean±SD. Independent samples *t*-test was used to detect significant differences at $P<0.05$.

Table 2 showed that other medications were administered with olanzapine (combination therapy) to control symptoms of schizophrenia, and only three patients used olanzapine alone. However, the only significant difference between the two groups was in the use of fluphenazine ampules and procyclidine tablets. According to the current study results, olanzapine treatment causes weight gain; the mean BMI is 33.87±5.96.

Table 2: Other medications used with olanzapine during treatment

Type of adjuvant therapy	Metabolic *n*=30	Non-metabolic *n*=20	*P*-value
Fluphenazine ampule	27	12	0.017*
Fluoxetine capsule 20mg	3	1	0.64
Quetiapine tablet 200mg	1	2	0.55
Procyclidine tablet 200mg	26	11	0.02*
Escitalopram	0	1	0.4
Haloperidol ampule	0	1	0.4
Diazepam tablet 5mg	2	4	0.20
Amitriptyline tablet 25mg	4	1	0.63
Nothing else	1	2	0.55

* significant differences between the two groups according to Fisher's exact test ($P<0.05$).

Table 3 details the mean systolic and diastolic blood pressure levels (prior to and after olanzapine administration). The mean systolic blood pressure increased considerably when olanzapine was administered, increasing from 129.44±16.80 mg/dL to 136.64±21.66 mg/dL. Additionally, after treatment with olanzapine, the mean diastolic blood pressure rose significantly from 82.06±9.16 to 87.06±15.28 mg/dL, respectively. Table 4 shows the changes in FBS and lipid profile values associated with the use of olanzapine. FBS levels were elevated significantly at the time of reporting post-treatment values ($P<0.001$).

Table 3: Effect of olanzapine on blood pressure

Parameter	Baseline	Current	*P*-value
Systolic BP (mmHg)	129.4±16.8	136.6±21.7	0.04
Diastolic BP (mmHg)	82.1±9.2	87.1±15.28	0.01
Pulse rate (pulse/min)	-	88.7±20.3	

Values are presented as mean±SD. Paired *t*-test was used to detect significant differences at $P<0.05$.

Table 4 also showed a significant elevation in all the lipid profile components at the time of reporting the results compared with baseline values ($P<0.001$). Regarding the association between the disease duration and the changes in waist circumference, bodyweight, and BMI at the time of reporting, the results showed no significant correlation between these parameters and the duration of the disease based on the Pearson's correlation coefficient values, as seen in Table 5.

Table 4: Effect of olanzapine on lipids profile and fasting blood glucose levels

Parameter	Baseline	Current	*P*-value
Triglycerides	145.2±88.1	193.8±41.9	<0.001
Cholesterol	156.4±32.8	189.7±16.1	<0.001
HDL	33.3±12.9	24.5±6.9	<0.001
VLDL	29.1±17.6	38.8±8.4	<0.001
LDL	94.0±32.9	126.5±15.3	<0.001
FBS	108.0±45.8	121.9±35.7	< 0.001

Results are reported as mean±SD. Paired *t*-test was used to detect significant differences at $P<0.05$.

Table 5: Association of disease duration with the changes in waist circumference, bodyweight, and BMI at the end of the study

Parameter	*r*-value	*P*-value
Waist circumference (cm)	0.097	0.502
Bodyweight (kg)	-0.050	0.730
BMI (kg/m^2)	-0.105	0.467

r: correlation coefficient (Pearson's correlation test)

In Table 6, the duration of the disease was not significantly correlated with any of the studied biochemical markers (FBS and lipid profile) based on Pearson's correlation analysis. Regarding the association between the duration of olanzapine treatment in schizophrenic patients and the waist circumference, current bodyweight, and BMI of the patients, the results of the current study showed that there was no significant correlation between these parameters and the duration of the olanzapine use based on Pearson's correlation analysis, as seen in Table 7. In Table 8, the *r* values of Pearson's correlation indicated that the duration of the olanzapine treatment was not significantly correlated with changes in any of the evaluated biochemical markers (FBS and lipid profile) or blood pressure.

Table 6: Association of disease duration with the changes in blood pressure, lipid profile, and fasting blood glucose levels at the end of the study

Parameter	*r*-value	*P*-value
Systolic BP	0.008	0.955
Diastolic BP	0.124	0.392
Triglyceride	-0.005	0.970
Cholesterol	-0.006	0.967
HDL	-0.125	0.387
VLDL	-0.005	0.970
LDL	0.049	0.737
FBS	0.053	0.714

r: correlation coefficient (Pearson's correlation test)

Table 7: Association of the duration of olanzapine use with the changes in waist circumference, bodyweight, and BMI at the end of the study

Parameter	*r*-value	*P*-value
Waist circumference (cm)	0.166	0.250
Bodyweight (kg)	0.034	0.816
BMI (kg/m^2)	-0.027	0.854

r: correlation coefficient (Pearson's correlation test)

Table 8: Association of disease duration with the changes in blood pressure, lipid profile, and fasting blood glucose levels at the end of the study

Parameter	*r*-value	*P*-value
Systolic BP	0.027	0.853
Diastolic BP	0.147	o.307
Triglyceride	-0.057	0.694
Cholesterol	-0.033	0.822
HDL	-0.148	0.306
VLDL	-0.057	0.694
LDL	o.057	0.693
FBS	0.041	0.776

r: correlation coefficient (Pearson's correlation test)

DISCUSSION

Recent studies indicate that individuals diagnosed with schizophrenia (SZ) are more susceptible to metabolic disorders compared to the general population, which is primarily attributed to the administration of atypical antipsychotics [12]. The findings of this investigation indicate a statistically significant increase in both systolic and diastolic blood pressures subsequent to the administration of olanzapine. This effect has been corroborated by several prior investigations [13-15]. The findings of this study unequivocally indicate an increase in blood glucose levels among the majority of individuals with schizophrenia who receive treatment with olanzapine. The aforementioned findings are congruent with numerous other investigations cited in references 16 through 18. The impact of olanzapine on blood glucose levels can be ascribed to a disturbance in glucose metabolism and insulin resistance, as suggested by previous research [3]. Furthermore, several studies have expounded upon the correlation between hyperglycemia and the administration of olanzapine. Research has indicated that the pharmacological properties of olanzapine, a second-generation antipsychotic, involve its antagonistic effects on serotonin (5HT2A) and dopamine (D2) receptors. Consequently, any medication that inhibits 5-HT1A receptors will lead to a decline in blood insulin levels, which in turn will cause an elevation in glucose levels due to a reduction in glucose uptake in skeletal muscle [28,29]. Previous research has demonstrated that antipsychotic medications may impede the accumulation of glucose at the protein level of the glucose transporter (GLUT) in both peripheral and brain tissue, resulting in hyperglycemia [2]. The findings of the present investigation indicate that the administration of olanzapine is associated with an increase in body weight, which is consistent with numerous prior studies [5]. The correlation between obesity and olanzapine can be attributed to the drug's potent antagonistic effects on 5-HT2c and histamine H1 receptors [19]. A noteworthy discovery from the present investigation is that the levels of plasma triglycerides in individuals with schizophrenia experience a significant surge subsequent to years of olanzapine treatment in comparison to previous treatment, owing to the impact of antipsychotic medications on lipid metabolism. The obtained outcome falls within the range of [7,20], which is in line with the findings reported in previous research [21,22]. Following the administration of olanzapine, our findings revealed an elevation in the overall cholesterol concentration and a reduction in the high-density lipoprotein levels. This finding is consistent with previous research studies [16,17] which have reported a reduction in high-density lipoprotein (HDL) levels, along with an increase in triglyceride (TG) and total cholesterol levels, among patients who were administered olanzapine for a duration of 12 weeks. Our study revealed that there is no correlation between the duration of schizophrenic disease and the incidence of changes in blood pressure, blood sugar, lipid profile, weight gain, and waist circumference. This finding is in contrast to the results reported in study [23]. The findings of our investigation indicate that there is no significant association between weight gain and the length of olanzapine treatment, a result that is consistent with previous research studies [24,25]. The present investigation involved the administration of various adjuvant therapies in conjunction with olanzapine. Nevertheless, the sole noteworthy disparity amid the two cohorts resided in the administration of the fluphenazine ampule and procyclidine tablet. The findings of this study can be rationalized by the fact that the utilization of fluphenazine is also linked with a rise in weight gain by 37%, as evidenced by a study conducted by Maslov *et al*. [27]. This factor may be deemed as a potential hazard for metabolic syndrome, particularly when employed in conjunction with olanzapine. While Parkinsonism has been associated with the use of procyclidine [28], there has been no prior research linking the use of procyclidine to metabolic syndrome. The present investigation was subject to various constraints, including the absence of a specified timeframe for olanzapine administration, which could be ascribed to the restricted number of patients that meet the eligibility requirements. Nonetheless, there was no significant difference in the duration of olanzapine usage between the metabolic and non-metabolic groups, and no association was observed with any of the examined variables, indicating that its impact was nullified in the analyzed population. An additional constraint pertained to the inability to assess the exclusive impact of olanzapine in isolation, as most individuals with schizophrenia require adjunctive

therapy. The findings of the present study indicate that the sole notable disparity observed between the two cohorts pertained to the administration of fluphenazine ampules and procyclidine tablets.

Conclusion

The administration of Olanzapine to individuals diagnosed with schizophrenia has been linked to adverse effects on blood glucose levels, blood pressure, and lipid profiles. There was no significant correlation observed between the duration of disease and olanzapine usage and the likelihood of developing metabolic disorders during the course of olanzapine treatment. Furthermore, no significant correlation was observed among any of the parameters investigated. Co-administration of fluphenazine and procyclidine with olanzapine has been observed to elevate the risk of metabolic disorders.

Conflict of interests

The author declares no conflict of interests.

Source of fund

No specific fund received.

Data sharing statement

Data can be provided based on a reasonable request to the corresponding author.

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