The Journal of Clinical Psychiatry

Supplementary Material

- Article Title:The Effectiveness of Metformin in Managing Second Generation Antipsychotics Induced
Weight Gain in Children and Adolescents
- Author(s): Hua Chen, MD, PhD; Ning Lyu, MS; Chadi Calarge, MD; Austin De La Cruz, PharmD, BCPP; and Wenyaw Chan, PhD
- DOI Number: https://doi.org/10.4088/JCP.23m14894

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. Figure 1 The duration between SGA initiation and metformin initiation 2. Figure 2 Visualization of piecewise linear mixed regression models 3. Table 1 Sociodemographic and clinical characteristics of adjuvant metformin users and matched nonusers Sociodemographic and clinical characteristics for adjuvant metformin users with various 4. Table 2 pre-metformin weight statuses 5. Table 3 **Glossary Table**

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



Supplementary Figure 1: The duration between SGA initiation and metformin initiation



Supplementary Figure 2: Visualization of piecewise linear mixed regression models.

	Metformin users $(n = 570)$	Non-users $(n = 2280)$	Chi-square
	Mean (SD)	Mean (SD)	P value
Baseline BMI z-score	2.06 (0.56)	1.12 (1.21)	<0.0001*
	N (%)	N (%)	
Age			
5-11	150 (26.32)	936 (41.05)	< 0.0001*
12-17	409 (71.75)	1,308 (57.37)	
18-19	11 (1.93)	36 (1.58)	
Sex	· · · · · · · · · · · · · · · · · · ·		< 0.0001*
Male	296 (51.93)	1,462 (64.12)	
Female	273 (47.89)	818 (35.88)	
Unknown	1 (0.18)	0	
Race	· · ·		0.1636
Non-Hispanic White	371 (65.09)	1,604 (70.35)	
Non-Hispanic Black	69 (12.11)	232 (10.18)	
Hispanic	1 (0.18)	7 (0.31)	
Asian	5 (0.88)	17 (0.75)	
Others	20 (3.51)	87 (3.82)	
Unknown	104 (18.25)	333 (14.61)	
Region			<0.0001*
South	271 (47.54)	1,038 (45.55)	
Midwest	115 (20.18)	652 (28.61)	
Northeast	117 (20.53)	342 (15.01)	
West	67 (11.75)	247 (10.84)	
SGA prescriber specialty			< 0.0001*
PCP	222 (38.95)	992 (43.51)	
Mental health specialists	120 (21.05)	309 (13.55)	
Others	155 (27.19)	631 (27.68)	
Unknown	73 (12.81)	348 (15.26)	
Non-psychiatric Comorbidities			
Hyperglycemia /Diabetes ^a	168 (29.47)	178 (7.81)	<0.0001*
Polycystic ovarian syndrome	402 (70.53)	5 (0.42)	<0.0001*
Psychiatric comorbidities			
ADHD	302 (52.98)	1,306 (57.28)	0.0642
Mood disorder	322 (56.49)	1,138 (49.91)	0.0049*
Anxiety disorder	233 (40.88)	788 (34.56)	0.0049*
Conduct disorder	167 (29.30)	750 (32.89)	0.1002
Substance use disorder	38 (6.67)	112 (4.91)	0.0934
Schizophrenia-related ^b	38 (6.67)	68 (2.99)	<0.0001*
Tics disorder	21 (3.68)	95 (4.17)	0.6021
Autism disorder	190 (33.33)	630 (27.66)	0.0074*
Comedications			
Antidepressants	275 (48.25)	860 (37.72)	<0.0001*
ADHD medications	232 (40.70)	988 (43.33)	0.2561
Anxiolytics	80 (14.04)	292 (12.81)	0.4363
Topiramate	30 (5.26)	51 (2.24)	0.0001*
Weight loss medications ^c	12 (2.11)	23 (1.01)	0.0335*

Supplementary Table 1. Sociodemographic and clinical characteristics of adjuvant metformin users and matched nonusers.

Dietician Counselling	4 (0.70)	12 (0.53)	0.6161
SGA Switch	195 (34.21)	339 (14.87)	< 0.0001*
Lower risk to higher risk	92 (16.14)	192 (8.42)	< 0.0001*
Higher risk to lower risk	55 (9.65)	62 (2.72)	< 0.0001*
Same risk	48 (8.42)	85 (3.72)	< 0.0001*
Family history of mental disorders	150 (26.32)	436 (19.14)	0.0002*
Type of index SGA			
Aripiprazole	215 (37.72)	796 (34.91)	0.2103
Risperidone	128 (22.46)	932 (40.88)	< 0.0001*
Quetiapine	64 (11.23)	322 (14.12)	0.0709
Olanzapine	64 (11.23)	87 (3.82)	< 0.0001*
Lurasidone	38 (6.67)	54 (2.37)	< 0.0001*
Ziprasidone	38 (6.67)	56 (2.46)	< 0.0001*
Paliperidone	10 (1.75)	18 (0.79)	0.0367*
Clozapine	3 (0.53)	3 (0.13)	0.0659
NI-4			

Note:

a: Hyperglycemia /Diabetes includes type 1 or type 2 diabetes and abnormal blood glucose. b: Schizophrenia-related diagnosis includes schizophrenia, schizoaffective disorder, and psychosis.

c: Weight loss medication includes Bupropion-naltrexone), Liraglutide, Orlistat, and Phentermine-topiramate.

*: Indication of statistical significance at 0.05 level.

	Severely	Mild to	Non-obese (n	Chi-square
	obese $(n - 312)$	moderately	= 176)	
	(n - 312)	103)		
	Mean (SD)	Mean (SD)	Mean (SD)	P-value
BMI z-score	2.32 (0.05)	1.83 (0.13)	0.80 (0.71)	<0.0001*
	N (%)	N (%)	N (%)	
Age				
5-11	66 (21.15)	29 (28.16)	60 (34.09)	0.0211
12-17	240 (76.92)	73 (70.87)	111 (63.07)	
18-19	6 (1.92)	1 (0.97)	5 (2.84)	
Sex				0.6200
Male	158 (50.64)	59 (57.28)	87 (49.43)	
Female	153 (49.04)	44 (42.72)	89 (50.57)	
Unknown	1(0.32)	0	0	
Race				0.2872
Non-Hispanic White	187 (68.18)	76 (73.79)	120 (68.18)	
Non-Hispanic Black	46 (14.74)	9 (8.74)	18 (10.23)	
Hispanic	0	0	1 (0.57)	
Asian	2 (0.64)	1 (0.97)	2 (1.14)	
Others	12 (3.85)	2 (1.94)	7 (3.98)	
Unknown	65 (20.83)	15 (14.56)	28 (15.91)	
Region				0.0449
South	145 (46.47)	53 (51.46)	79 (44.89)	
Midwest	76 (24.36)	12 (11.65)	35 (19.89)	
Northeast	58 (18.59)	28 (27.18)	34 (19.32)	
West	33 (10.58)	10 (9.71)	28 (15.91)	
Time to metformin initiation				0.0196*
Early initiation (<=90 days)	132 (42.31)	33 (32.04)	54 (30.68)	
Late initiation (>90 days)	180 (57.69)	70 (67.96)	122 (69.32)	
SGA prescriber specialty				< 0.0001*
PCP	116 (37.18)	32 (31.07)	79 (44.89)	
Mental health specialists	38 (12.18)	31 (30.10)	55 (31.25)	
Others	126 (40.38)	17 (16.50)	18 (10.23)	
Unknown	32(10.26)	23 (22.33)	24 (13.64)	
Non-psychiatric comorbidities				
Hyperglycemia /Diabetes ^a	119 (38.14)	26 (25.24)	33 (18.75)	< 0.0001*
Polycystic ovarian syndrome	21 (6.73)	6 (5.83)	3 (1.70)	0.0487*
Psychiatric comorbidities	× ,			
Mood disorder	163 (52.24)	63 (61.17)	109 (61.93)	0.0699
ADHD	151 (48.40)	57 (55.34)	106 (60.23)	0.0375*
Anxiety disorder	113 (36.22)	47 (45.63)	85 (48.30)	0.0217*
Conduct disorder	75 (24.04)	35 (33.98)	65 (36.93)	0.0064*
Substance use disorder	16 (5.13)	5 (4.85)	19 (10.80)	0.0397*
Schizophrenia-related ^b	13 (4.17)	9 (8.74)	20 (11.36)	0.0094*
Tics disorder	11 (3.53)	4 (3.88)	6 (3.41)	0.9782
Autism disorder	105 (33.65)	37 (35.92)	55 (31.25)	0.7157
Comedications			· · ·	

Supplementary Table 2. Sociodemographic and clinical characteristics for adjuvant metformin users with various pre-metformin weight statuses.

Antidepressants	166 (53.21)	47 (45.63)	72 (40.91)	0.0280*
ADHD medications	133 (42.63)	41 (39.81)	71 (40.34)	0.8260
Anxiolytics	50 (16.03)	12 (11.65)	20 (11.36)	0.2776
Topiramate	20 (6.41)	4 (3.88)	7 (3.98)	0.4054
Weight loss medications ^c	9 (2.88)	1 (0.97)	2 (1.14)	0.2963
SGA Switch	90 (28.85)	38 (36.89)	78 (44.32)	0.0024*
Lower risk to higher risk	44 (14.10)	20 (19.42)	32 (18.18)	0.3167
Higher risk to lower risk	22 (7.05)	12 (11.65)	25 (14.20)	0.0335*
Same risk	24 (7.69)	5 (4.85)	21 (11.93)	0.0951
Family history of mental disorders	61 (19.55)	41 (39.81)	54 (30.68)	< 0.0001*
Type of index SGA				
Aripiprazole	135 (43.27)	36 (34.95)	55 (31.25)	0.0241*
Risperidone	57 (18.27)	34 (33.01)	42 (23.86)	0.0070*
Olanzapine	25 (8.01)	8 (7.77)	33 (18.75)	0.0007*
Quetiapine	31 (9.94)	14 (13.59)	20 (11.36)	0.5793
Ziprasidone	28 (8.97)	2 (1.94)	9 (5.11)	0.0286*
Lurasidone	22 (7.05)	5 (4.85)	11(6.25)	0.7281
Paliperidone	5 (1.60)	2 (1.94)	4 (2.27)	0.8689
Clozapine	1 (0.32)	1 (0.97)	1 (0.57)	0.7165

Note:

a. Schizophrenia-related diagnosis includes schizophrenia, schizoaffective disorder, and psychosis.

b. Schizophrenia-related diagnosis includes schizophrenia, schizoaffective disorder, and psychosis.

c. Weight loss medication includes Bupropion-naltrexone), Liraglutide, Orlistat, and Phentermine-topiramate.

*: Indication of statistical significance at 0.05 level.

Supplementary Table 3. Glossary Table

Terminology	Definition
Immortal time bias	A statistical bias occurs in observational studies when the exposure period is incorrectly defined, leading to overestimating the treatment effect. ¹ For our study, the duration between SGA initiation and metformin initiation was incorrectly considered as the follow-up period in the exposed group, leading to an overestimation of the outcome rate for metformin users.
Spaghetti plot	A graphical representation used in longitudinal or time-series data analysis. It displays individual trajectories or trends over time, resembling a tangled "spaghetti" of lines. ²
LOESS curve	Locally Weighted Estimation Scatterplot Smoothing (LOESS) is a nonparametric regression technique used to estimate the underlying trend in data. The LOESS curve represents a smoothed line that adapts to local variations and the relationship between two variables. ³ The relationship between time and BMI z-score was displayed in our study.
Piecewise linear mixed-effect regression model	A statistical model approach using longitudinal or repeated measures data to estimate different linear relationships between variables in different segments or intervals. Particularly useful when the relationship between variables is expected to change at specific breakpoints or thresholds. ⁴ Metformin initiation was the critical breakpoint for our study, and there were different linear trends for pre- and post- metformin initiation.
Propensity score matching	A statistical technique used in observational studies to reduce bias and mimic a randomized controlled trial. It matches individuals with similar probability (propensity scores), which estimate the likelihood of receiving a particular treatment, thereby reducing confounding. ⁵

References:

1. Suissa, S. (2008). Immortal time bias in pharmacoepidemiology. American journal of epidemiology, 167(4), 492-499.

2. Gibbons, R. D., & Hedeker, D. (2006). Longitudinal data analysis. John Wiley & Sons.

3. Cleveland, W. 5.(1979). Robust locally weighted regression and smoothing scatterplots. J. Amer. Stat. Ass, 74, 829-836.

4. Naumova, E. N., Must, A., & Laird, N. M. (2001). Tutorial in biostatistics: evaluating the impact of 'critical periods' in longitudinal studies of growth using piecewise mixed effects models. International journal of epidemiology, 30(6), 1332-1341.

5. Caliendo, M., & Kopeinig, S. (2008). Some practical guidance for the implementation of propensity score matching. Journal of economic surveys, 22(1), 31-72.