MINI-SENTINEL ASSESSMENT
METABOLIC EFFECTS OF SECOND GENERATION ANTIPSYCHOTICS IN YOUTH

SUBPROJECT 2A ADDENDUM

AVAILABILITY OF BODY MASS INDEX (BMI) MEASUREMENTS IN THE YEAR AFTER SECOND GENERATION ANTIPSYCHOTIC INITIATION AMONG YOUTH WITH BASELINE BMI MEASUREMENTS

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I.   INTRODUCTION

A.   BACKGROUND/PRIOR SUBPROJECTS 1 AND 2A PROJECT WORK

In the first activity in this series, we conducted a comparative analysis of type 2 diabetes risk among young patients newly initiated on second generation antipsychotic agents (SGAs) across Mini-Sentinel Data Partner sites (view the final report here). That work, known as Subproject 1, used the Mini-Sentinel Distributed Database (MSDD) to replicate an AHRQ and FDA funded study conducted with Medicaid Analytic Extract (MAX) data by the Rutgers and Vanderbilt CERTs. Small event numbers in Subproject 1 results did not allow inferences regarding the comparative risk for type 2 diabetes across individual SGAs in MSDD youth. Further, we found substantial differences in demographic and clinical characteristics between initiators of individual SGAs as well as changes in use patterns over time.

In the second activity, Subproject 2A, we explored the feasibility of using body mass index (BMI) and laboratory results data for baseline confounding adjustment (view the final report here). Defining the baseline time period as between 90 days before and three days after SGA initiation, we found only a small proportion (13%) of the youth in the Subproject 2A cohort had baseline glycosylated hemoglobin or random or fasting glucose results available. Thus, the baseline glucose data availability was inadequate for use in baseline covariate adjustment.

The Subproject 2A sub-cohort for assessing availability of BMI data was comprised of patients between the ages of 2 and 24 who newly initiated a SGA between January 1, 2006 and December 31, 2011 who met the Subproject 1 inclusion and exclusion criteria, who were from the eight participating Data Partners, who had vital signs (height and weight to calculate BMI) data in the MSDD. Using -90 through +3 day time period to define baseline, we found that 36% (n=2420 of 6807) of youth had baseline BMI (i.e., both height and weight) data available. While the availability of baseline BMI data was more limited than optimal, the proportion of youth with baseline BMI available indicated those data could potentially be useful for targeted baseline confounding adjustment. We also identified that 27% (n=1860 of 6807) of these youth had both at least one baseline and at least one post-SGA initiation BMI measurement.

Given these BMI availability findings, the FDA requested that we collect additional information about the availability of BMI measurements in this cohort during the year after SGA initiation. This additional activity, known as the Subproject 2A Addendum, is the subject of this report.

B.   OVERVIEW OF SUBPROJECT 2A ADDENDUM

This addendum work was proposed to assist in deciding whether to proceed with Subproject 3 (Examining Longitudinal Change in BMI and Laboratory Parameters[1] between Young Patients Newly Initiated on Individual Second Generation Antipsychotics [SGA]).

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[1] Due to low rates of glucose monitoring, it was decided not to proceed with the laboratory (glucose) parameters portion of Subproject 3.

Specifically, the FDA requested information on the following:

- Among individuals with a baseline BMI, how many (and %) have at least one follow up BMI measurement after initiating a SGA?
- Of those with a follow up BMI within the first 12 weeks after SGA initiation, how many (and %) have (any) subsequent BMI measurements within the year post-SGA initiation?
- Among those with at least one follow up BMI measurement, how many post-baseline BMI measures are recorded, and what is the distribution of these measurements by week and by month?

II.   SUBPROJECT 2A ADDENDUM

A. SPECIFIC AIMS

The specific aims of this additional work were to provide data to address the following questions:

1. Whether there are sufficient youth with baseline and at least two follow up BMI measurements to warrant Subproject 3 going forward.
2. Whether there is differential BMI measurement by drug (e.g., channeling away from olanzapine and towards aripiprazole for youth at high risk).

B. PROJECT COHORT

In the initial Subproject 2A work, because the baseline period was the only timeframe of interest, the Workgroup had defined baseline BMI as -31 (and up to -90) days before through +3 days after SGA initiation. For this Subproject 2A Addendum work, because we are assessing presence and distribution of BMI in the follow up year after SGA initiation, the <u>baseline BMI period was re-defined as between -31 (and up to -90) through 0 days (i.e., day of) of SGA initiation.</u> This enabled inclusion of post-SGA initiation days +1 through +3 in the follow up days considered. Therefore, the first data developed was a reassessment of baseline BMI availability using days -31 (and -90) through day 0. We considered height and weight measurements obtained on the same or different days the same as had been done in Subproject 2A.

C. DATA DEVELOPMENT APPROACH

1. Among those with baseline BMI according to the revised definition, we determined the n (%) of youth who have at least one follow up BMI during the following time periods:

   - Weekly categories: Each of weeks 1 through 12 and combinations of weeks 1 through 12. This weekly assessment recognizes the fact that weight gain is anticipated to begin relatively soon after SGA initiation.

   - Monthly categories: Determine BMI measure in months 4-6 and 7-12 assessing combinations of these monthly categories with the weekly categories described above (i.e., BMI present in week 1 and month 4, BMI present in week 2, month 4, and month 7, etc).

2. Descriptive tables for youth with BMI with height and weight measured the same day are prepared for:

- Revised numbers of youth with baseline BMI using the revised definition (same day height and weight measured days -31 through day 0 and days -90 through day 0).

- Weekly categories for follow up weeks 1 through 12 for youth with at least one BMI at baseline: Descriptive tables overall, by Data Partner, by drug, by age group, and by gender.

- Weekly plus monthly categories for youth with at least one BMI at baseline: Descriptive tables overall for youth with at least one follow up BMI in both a weekly and a monthly category (unique measurements). If at least 1/3 of youth with baseline BMI also have a BMI measurement in both a weekly and a monthly follow up category, then descriptive tables will also be provided by Data Partner, by drug, by age group, and by gender.

3. Descriptive tables similar to those listed above for youth with follow up BMI measured with height and weight taken on different days (no more than 90 days apart) will also be provided.

D. RESULTS AND DISCUSSION

Redefining the baseline period (moving days +1 through +3 to the follow up period) revised the numbers of youth with baseline BMI data available only slightly (Table 1). Previously, using the -90 through +3 day time period to define baseline, we found 36% (n=2420 of 6807) of youth had a baseline BMI. With the revised definition, using the timeframe of -90 through 0 days, we found 35% (n=2372 of 6807) had a baseline BMI.

Table 1. Subproject 2A Addendum: Cohort of Youth (n= 6807) with Baseline BMI Data Available

Baseline BMI Measurement Timeframe Allowed	Number of Youth with Baseline BMI Available (%)	
	Height and Weight (BMI) Measured on the Same Day	Height and Weight (BMI) Measured on the Same or Different Days
Day -31 through 0	1353 (20) [a]	1355 (20)
Day -90 through Day 0	2368 (35)	2372 (35) [b]
[a] Most restrictive definition [b] Least restrictive definition		

Of the 1353 youth with baseline height and weight measured on the same day and between day -31 and day 0 ("same day BMI, day -31 through 0"; most restrictive definition), as shown in Table 2, n=1081 (80%) had a BMI measurement available at least once during the 12 months after starting the SGA. Of the 2372 youth with a baseline height and weight measured on the same or on different days and between day -90 and day 0 ("different day BMI, day-90 through 0"; least restrictive definition), n=1951 (82%) had a BMI measurement available at least once during the 12 months after starting the SGA. The most and least restrictive BMI availability definitions are the definitions applied and the groups shown in Tables throughout the remainder of this report.

Summary descriptive statistics for follow up BMI availability among youth with at least one BMI measured during the follow up period are shown in Table 2. The mean number of BMI among the youth with same day BMI was 3.2 (median 2) and among the youth with different day BMI was 4.6 (median 3).

Table 2. Descriptive Statistics of Follow up BMI Measurement Availability among Youth with a Baseline BMI Measurement who started any Second Generation Antipsychotic at Any Data Partner

Descriptive Statistic	Baseline BMI Same Day and between Days -31 and 0 (n=1353)	Baseline BMI Same or Different Days and between Days -90 and 0 (n=2372)
N with any Follow-up BMI	1081 (80%)	1951 (82%)
Min	1.0	1.0
10th percentile	1.0	1.0
25th percentile	1.0	2.0
Mean	3.2	4.6
Median	2.0	3.0
75th percentile	4.0	6.0
90th percentile	6.0	9.0
95th percentile	8.0	12.0
99th percentile	12.0	20.0
Max	21.0	53.0

Combinations of follow up BMI data availability for time categories after starting SGA for weeks 1-12, months 4-6, and months 7-12 for all youth with baseline BMI are shown in Table 3.

Applying the most restrictive BMI definition (Table 3),

- 603 (45%) of those with a baseline BMI had a first follow up BMI measurement within 12 weeks after SGA initiation, including 262 (43% of 603) with at least one follow up BMI in the first 12 weeks, in months 4-6, and in months 7-12; 118 (20% of 603) did not have any further follow up BMI beyond the BMI measurement in weeks 1-12.
- Among youth with a baseline BMI and a first follow up BMI within the 12 weeks after starting an SGA, 485 had at least one additional BMI data point within 12 months after starting an SGA (i.e., total of a baseline BMI and at least two BMI measurements within the year after starting the SGA).
- Among youth with a baseline BMI and a first follow up BMI four or more months after starting an SGA (i.e., no BMI in the first 12 follow up weeks), 153 had at least two BMI data points within 12 months after starting an SGA (i.e., total of a baseline BMI and at least two BMI Measurements within the year after starting the SGA).
- Thus, applying the most restrictive BMI definition, a total of 638 (47%) youth with a baseline BMI had at least two BMI measurements within the year after starting an SGA.
- Also, as summed from Table 3, 963 (71%) youth with a baseline BMI had at least one BMI measurement within the year after starting an SGA.

Applying the least restrictive BMI definition (Table 3),

- 1326 (56%) of youth with a baseline BMI had a first follow up BMI measurement within 12 weeks after SGA initiation, including 612 (46% of 1326) with at least one follow up BMI in each of the first 12 weeks, months 4-6, and months 7-12; 278 (21% of 1326) did not have any further follow up BMI after the initial follow up BMI measurement in weeks 1-12.

- Thus, among youth with a baseline BMI and a first follow up BMI within the 12 weeks after starting an SGA, 1048 had at least one additional BMI data point within 12 months after starting an SGA (i.e., at least two BMI measurements after starting the SGA).
- Among youth with a baseline BMI and a first follow up BMI four or more months after starting an SGA, 214 had at least two BMI data points within 12 months after starting an SGA.
- Thus, applying the least restrictive BMI definition, a total of 1262 youth with a baseline BMI had at least two BMI measurements within the year after starting an SGA.
- Also, as summed from Table 3, 1673 (71%) youth with a baseline BMI had at least one BMI measurement within the year after starting an SGA.

Table 3. Follow up BMI Data Availability for All Youth with Baseline BMI, Stratified by Availability of a First Follow up BMI Measurement during Weeks 1 through 12

BMI Measurement Timeframe Combinations during Follow up Months 4-12 [a]			Height and Weight (BMI) Measurement Timeframe during Baseline and Follow up Weeks 1-12 [a]			
			Baseline BMI Same Day and between Days -31 and 0 (n=1353); Follow up BMI Same Day		Baseline BMI Same or Different Days and between Days -90 and 0 (n=2372); Follow up BMI Same or Different Days	
			>=1 BMI Measurements in Follow up Weeks 1-12 n=603 (45%)	No BMI Measurement in Follow up Weeks 1-12 n=750 (55%)	>=1 BMI Measurements in Follow up Weeks 1-12 n=1326 (56%)	No BMI Measurement in Follow up Weeks 1-12 n=1046 (44%)
Availability of Follow up BMI Measurement in Months 4-12	Any BMI in Follow up Months 4 - 6	Any BMI in Follow up Months 7-12				
>=1	none	>=1	151 (25)	245 (33)	267 (20)	314 (30)
>=1	>=1	none	72 (12)	80 (11)	169 (13)	97 (9)
>=1	>=1	>=1	262 (43)	153 (20)	612 (46)	214 (21)
None	none	none	118 (20)	272 (36)	278 (21)	421 (40)
[a] Days 1-84 are weeks 1-12; days 85-180 are months 4-6; days 181-365 are months 7-12						

Tables 4 and 5 provide detailed information about the number of BMI measurements and the distribution of BMI measurements for the subset of youth with at least one BMI measurement during follow up weeks 1-12. As shown in Table 4, applying the same day, most restrictive BMI definition, 68% (n=410 of 603) had one BMI measurement during weeks 1-12, 23% (n=139) had two measurements, 6% (n=34) had three measurements, and 3% (n=20) had BMI measured four or more times across these 12 weeks. Applying the different day, least restrictive definition, the corresponding percentages and numbers are: 49% (n=652 of 1326), 28% (n=371), 12% (n=164), and 11% (n=139), respectively (Table 4).

Table 4. Youth with First Follow up BMI Measurement during Weeks 1 through 12 Stratified by Number of Follow up BMI Measurements during Weeks 1 through 12

Count of BMI Measurements during Weeks 1-12	Baseline BMI Same Day and between Days -31 and 0; Follow up BMI Same Day; >=1 BMI in Weeks 1-12 n=603 (%)	Baseline BMI Same or Different Days and between -90 and 0 (n=2372); Follow up BMI Same or Different Days; >=1 BMI in Weeks 1-12 n=1326 (%)
	N with BMI Measurement (%)	
1	410 (68)	652 (49)
2	139 (23)	371 (28)
3	34 (6)	164 (12)
>=4	20 (3)	139 (11)

As shown in Table 5, using the most restrictive BMI definition, 70% (n=420 of 603) had a BMI measurement during only one of weeks 1 through 12, 23% (n=136) had BMI measurements during two of those weeks, 5% (n=31) had BMI measurements during three of those weeks. Very few youth had BMI measurements during more than three of the weeks between weeks 1-12. The corresponding numbers and percentages of youth with BMI measurements during one, two, three, or more weeks using the least restrictive BMI definition is also shown in Table 5.

Table 5. Distribution of Number of Weeks with BMI Measurements across Weeks 1 through 12 among Youth with at Least One Follow up BMI Measurement during Weeks 1 through 12 across all Second Generation Antipsychotic Agents and Data Partners

Follow up BMI Measurement(s) during Weeks 1 - 12	Number of Youth when Most Restrictive and Least Restrictive BMI Definitions are Applied	
	Baseline BMI Same Day and between Days -31 and 0; Follow up BMI Same Day n=603 (%)	Baseline BMI Same or Different Days and between Days -90 and 0; Follow up BMI Same or Different Days n=1326 (%)
Number of Weeks with BMI Measured [a]		
1 (see detail below)	420 (70)	690 (52)
2	136 (23)	373 (28)
3	31 (5)	148 (11)
4	7 (1)	59 (4)
5	8 (1)	31 (2)
6	0	14 (1)
7	0	2 (<1)
8	0	2 (<1)
9	1 (<1)	5 (<1)
10	0	1 (<1)
11	0	0
12	0	1 (<1)
Detail of Week of Measurement among those with BMI Measured Only One Week during Weeks 1-12 [a]		
1	27	63
2	45	76
3	43	60
4	41	79
5	50	79
6	33	63
7	32	42
8	33	61
9	36	49
10	26	39
11	22	36
12	32	43
[a] One or more BMI measurements the same week		

The availability of BMI data varied by Data Partner (Table 6), regardless of whether a more or less restrictive definition was applied and regardless of whether the availability of follow up BMI measurement was assessed for any measurement within the year or whether the availability of a follow up measurement during weeks 1-12 was assessed (all p<0.001).

Table 6. Follow up BMI Availability across all Second Generation Antipsychotic Agents by Data Partner

Measurement description	Number of Youth with Baseline BMI Same Day and between Days -31 and 0 at each Data Partner (%)									p-value [a]
	DP 4 n=232	DP 9 n=93	DP 10 n=1	DP 11 n=235	DP 12 n=185	DP 13 n=56	DP 14 n=196	DP 16 n=355	Total n=1353	
Baseline BMI Same Day and between Days -31 and 0; >=1 follow up measurement	194 (84)	87 (94)	1 (100)	186 (79)	159 (86)	43 (77)	146 (75)	265 (75)	1081 (80)	<0.001
Baseline BMI Same Day and between Days -31 and 0; >=1 BMI in Weeks 1-12	111 (48)	71 (76)	0 (0)	93 (40)	99 (54)	24 (43)	72 (37)	133 (38)	603 (45)	<0.001
Measurement description	Number of Youth with Baseline BMI Same or Different Days and between Days -90 and 0 at each Data Partner (%)									
	DP 4 n=390	DP 9 n=132	DP10 n=12	DP 11 n=443	DP 12 n=300	DP 13 n=101	DP 14 n=399	DP 16 n=595	Total n=2372	
Baseline BMI Same or Different Days and between Days -90 and 0; >=1 follow up measurement	336 (86)	125 (95)	10 (83)	366 (83)	266 (89)	76 (75)	310 (78)	462 (78)	1951 (82)	<0.001
Baseline BMI Same or Different Days and between Days -90 and 0; >=1 BMI in Weeks 1-12	232 (60)	110 (83)	4 (33)	211 (48)	184 (61)	60 (59)	192 (48)	333 (56)	1326 (56)	<0.001

[a] Chi-Square test across sites, excluding Site 10 where there was a data linking problem at the time data were collected for this project

As shown in Table 7, availability of follow up BMI differed by age group, with in general, the age groups of 2-4, 5-9, and 10-12 years having higher percentages with available BMI than older age groups (all p≤0.001).

Table 7. Follow up BMI Measurement Availability across all Second Generation Antipsychotic Agents by Age Group

Measurement description	Number of Youth with Baseline BMI Same Day and between Days -31 and 0 by Age Group in Years (%)							p-value [a]
	Age 2-4 n=23	Age 5-9 n=274	Age 10-12 n=174	Age 13-15 n=278	Age 16-18 n=269	Age 19-24 n=335	Total n=1353	
Baseline BMI Same Day and between Days -31 and 0; >=1 follow up measurement	19 (83)	243 (89)	147 (85)	228 (82)	195 (73)	249 (74)	1081 (80)	<0.001
Baseline BMI Same Day and between Days -31 and 0; >=1 BMI in Weeks 1-12	12 (52)	141 (52)	96 (55)	117 (42)	107 (40)	130 (39)	603 (45)	<0.001
Measurement description	Number of Youth with Baseline BMI Same or Different Days and between Days -90 and 0 by Age Group in Years (%)							
	Age 2-4 n=42	Age 5-9 n=419	Age 10-12 n=292	Age 13-15 n=502	Age 16-18 n=513	Age 19-24 n=604	Total n=2373	
Baseline BMI Same or Different Days and between Days -90 and 0; >=1 follow up measurement	37 (88)	377 (90)	256 (88)	418 (83)	397 (77)	466 (77)	1951 (82)	<0.001
Baseline BMI Same or Different Days and between Days -90 and 0; >=1 BMI in Weeks 1-12	28 (67)	259 (62)	183 (63)	260 (52)	272 (53)	324 (54)	1326 (56)	0.001
[a] Chi-Square test								

As shown in Table 8, the availability of follow up BMI data did not differ by specific SGA.

Table 8. Follow up BMI Measurement Availability across All Data Partners by Specific Second Generation Antipsychotic Agent

Measurement description	Number of Youth with Baseline BMI Same Day and between Days -31 and 0 by Second Generation Antipsychotic Agent (%)							p-value [a]
	Aripiprazole n=258	Olanzapine n=70	Paliperidone n=1	Quetiapine n=317	Risperidone n=692	Ziprasidone n=15	Total n=1353	
Baseline BMI Same Day and between Days -31 and 0; >=1 up measurement	193 (75)	54 (77)	0 (0)	254 (80)	567 (82)	13 (87)	1081 (80)	0.15
Baseline BMI Same Day and between Days -31 and 0; >=1 BMI in Weeks 1-12	103 (40)	32 (46)	0 (0)	135 (43)	325 (47)	8 (53)	603 (45)	0.30
Measurement description	Number of Youth with Baseline BMI Same or Different Days and between Days -90 and 0 by Second Generation Antipsychotic Agent (%)							
	Aripiprazole n=487	Olanzapine b=123	Paliperidone n=2	Quetiapine n=579	Risperidone n=1145	Ziprasidone n=36	Total n=372	
Baseline BMI Same or Different Days and between Days -90 and 0; >=1 follow up measurement	387 (80)	105 (85)	1 (50)	471 (81)	956 (84)	31 (86)	1951 (82)	0.26
Baseline BMI Same or Different Days and between Days -90 and 0; >=1 BMI in Weeks 1-12	256 (53)	71 (58)	1 (50)	318 (55)	656 (57)	24 (67)	1326 (56)	0.27
[a] Chi-Square test, excluding palperidone								

As shown in Table 9, when the most restrictive BMI definition was applied, BMI measurement availability did not differ by gender. However, when the least restrictive BMI definition was applied, more females had BMI data available for both any follow up BMI measurement and for a follow up BMI measurement during weeks 1 – 12 (both p <0.001).

Table 9. Follow up BMI Measurement Availability across All Data Partners by Gender

Measurement description	Number of Youth with Baseline BMI Same Day and between Days -31 and 0 by Gender (%)			p-value [a]
	Female n=596	Male n=757	Total n=1353	
Baseline BMI Same Day and between Days -31 and 0; >=1 up measurement	490 (82)	591 (78)	1081 (80)	0.06
Baseline BMI Same Day and between Days -31 and 0; >=1 BMI in Weeks 1-12	277 (47)	326 (43)	603 (45)	0.21
Measurement description	Number of Youth with Baseline BMI Same or Different Days and between Days -90 and 0 by Gender (%)			
	Female n=1091	Male n=1281	Total n=2373	
Baseline BMI Same or Different Days and between Days -90 and 0; >=1 follow up measurement	932 (85)	1019 (80)	1951 (82)	<0.001
Baseline BMI Same or Different Days and between Days -90 and 0; >=1 BMI in Weeks 1-12	662 (61)	664 (52)	1326 (56)	<0.001
[a] Chi-Square test				

III.   CONCLUSION

The number of youth with a baseline BMI measurement and at least two follow up BMI measurements available after starting an SGA differs by whether the height and weight data used to calculate the BMI must be measured on the same day or can be measured on different days, as well as by whether the baseline BMI timeframe allowed includes -31 or -90 days before starting the SGA.

Applying the most restrictive BMI definition (baseline BMI timeframe of day -31 through 0 and requiring height and weight to be measured the same day), among 1353 youth with a baseline BMI, 603 (45%) had a first follow up BMI within the 12 weeks after starting an SGA; 485 (of 603) had at least one additional BMI data point within 12 months after starting an SGA. Among youth with a baseline BMI and a first follow up BMI four or more months after starting an SGA, 153 had at least two BMI data points within 12 months after starting an SGA. Overall, applying the most restrictive BMI definition, a total of 638 (47% of 1353) youth with a baseline BMI had at least two BMI measurements within the year after starting an SGA. Further, 963 (71%) youth with a baseline BMI had at least one BMI measurement within the year after starting an SGA.

Applying the least restrictive BMI definition (baseline BMI timeframe of day -90 through 0 and allowing height and weight to be measured on the same or different days), among 2372 youth with a baseline BMI, 1326 (56%) had a first follow up BMI within the 12 weeks after starting an SGA; 1048 (of 1326) had at least one additional BMI data point within 12 months after starting an SGA. Among youth with a baseline BMI and a first follow up BMI four or more months after starting an SGA, 214 had at least two BMI data points within 12 months after starting an SGA. Overall, applying the least restrictive BMI definition, a total of 1262 (53% of 2372) youth with a baseline BMI had at least two BMI measurements within the year after starting an SGA. Further, 1673 (71%) youth with a baseline BMI had at least one BMI measurement within the year after starting an SGA.

BMI data availability varied across Data Partners and across age groups, but did not differ across specific SGAs. BMI data availability did not differ by gender when the most restrictive BMI definition was applied. However, when the least restrictive BMI definition was applied, more females had at least one follow up BMI measurement and more females had a BMI measurement during follow up weeks 1 – 12.