1. Potential Metabolic Syndrome Cases Reported during Post-Marketing

1.1. Methodology for identifying cases[GAB1]

Olanzapine was first marketed on September 27, 1996 in the United States and it has now been marketed in over 100 countries. Table 1X summarizes the estimated number of patients exposed since PSUR-5 in November of 1999. There has been extensive worldwide use of olanzapine with an estimated 14,927,000 patients exposed for an estimated 8,314,000 person years.

Table 1X. Global exposure table by PSUR reporting period.

OLANZAPINE WORLDWIDE PATIENT EXPOSURE NUMBERS FOR PSURs

PSUR #	DATE RANGE	CUMULATIVE PATIENT EXPOSURE
PSUR-1	9/27/96 thru 3/31/97	302,000
PSUR-2	4/1/97 thru 9/30/97	704,000
PSUR-3	10/1/97 thru 3/31/98	1,194,000
PSUR-4	4/1/98 thru 9/30/98	1,773,000
PSUR-5	10/1/98 thru 9/30/99	3,536,000
PSUR-6	10/1/99 thru 9/30/00	5,277,000
PSUR-7	10/1/00 thru 3/31/01	6,426,000
PSUR-8	4/1/01 to 9/30/01	7,645,000
PSUR-9	10/1/01 to 3/31/02	9,070,000
PSUR-10	4/1/02 to 9/30/02	10,432,584
PSUR-11	10/1/02 to 3/31/03	11,880,000
PSUR-12	4/1/03 to 9/30/03	13,319,000
PSUR-13	10/1/03 to 3/31/04	14,972,000

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Metabolic syndrome (MS) and the components that comprise MS have significant prevalence and incidence in the general population but are even more common in the schizophrenic population. Hence, one would expect many background MS cases in users of olanzapine by chance alone. Given that the expected number of MS cases is large irrespective of any drug effect, one would expect many cases to have been reported to the Lilly Global Product Safety Database (GPSD). As of 31 March 2004, the data lock date for this review, there have been no cases reported to the GPSD that were coded with the MedDRA Preferred Term METABOLIC SYNDROME, which was added to the MedDRA dictionary in version 7.1. However, as shown in Table XX, the number of cases coded with preferred terms that could indicate MS risk factors is quite large.

Table 2X. (Frequency table for all potential MS terms)

Because of the voluntary nature of reporting events that occur with pharmaceutical products in the post-marketing setting, interpretation of reports is always limited by under-reporting and incomplete reporting of medical information. Hence post-marketing surveillance works best for clinically specific events that are rare in the treated population where one can apply a case definition, conduct additional follow-up to collect more medical information, and identify positive dechallenges and rechallenges for events not expected to recur. Given (1) that the expected number of cases with MS is large even without a drug effect, (2) that MS is a clinically nonspecific syndrome that requires significant medical information for diagnosis, and (3) that MS is a chronic ongoing event that develops over a significant length of time with uncertain onset time, determining the strength of any signal in post-marketing is primarily limited to focusing on positive dechallenge and positive rechallenge.

The GPSD was searched for probable cases of MS that developed during olanzapine treatment that had information on dechallenge or rechallenge. To identify potential cases for further review, multiple searches for selected preferred terms and text strings were performed.

The three search strategies to identify potential cases of MS are summarized below.

(1) Search Strategy 1: Identification of potential cases using ATP-III risk factors

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Using the ATP-III definition of risk factors to defined MS, Lilly identified preferred terms suggestive of each of the five risk factors. Each case in the GPSD was coded for each of the five risk factors (yes vs. no for each factor) and cases that had 3 or more risk factors were identified for review. The preferred terms subsumed under each risk factor is listed below.

Elevation of blood pressure preferred terms (n = 10):
Blood pressure abnormal
Blood pressure diastolic increased
Blood pressure fluctuation
Blood pressure increased
Blood pressure systolic increased
Diastolic hypertension
Hypertension
Labile blood pressure
Labile hypertension
Hypertensive crisis

Elevation of blood sugar preferred terms (n = 33):
Blood glucose abnormal
Blood glucose fluctuation
Blood glucose increased
Diabetes mellitus
Diabetic cardiomyopathy
Diabetic eye disease
Diabetic retinopathy
Diabetes mellitus inadequate control
Diabetes mellitus insulin-dependent
Diabetes mellitus non-insulin-dependent
Diabetes with hyperosmolarity
Diabetic autonomic neuropathy
Diabetic coma
Diabetic complication
Diabetic foot
Diabetic hyperglycaemic coma
Diabetic hyperosmolar coma
Diabetic hyperosmolar non-ketoacidosis
Diabetic ketoacidotic hyperglycaemic coma

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Diabetic ketoacidosis
Gestational diabetes
Glucose tolerance decreased
Glucose tolerance impaired
Glucose tolerance impaired in pregnancy
Glucose tolerance test abnormal
Glycosylated haemoglobin increased
Hyperglycaemia
Increased insulin requirement
Insulin-requiring type-II diabetes mellitus
Insulin resistance
Insulin resistant diabetes
Ketoacidosis
Ketosis

Decrement of High Density Lipoprotein (HDL) cholesterol preferred terms (n = 2):
High density lipoprotein decreased
High density lipoprotein abnormal

Elevation of serum triglycerides preferred terms (n = 21):
Blood triglycerides increased
Blood triglycerides abnormal
Hyperlipidaemia
Hypertriglyceridaemia
Dyslipidaemia
Lipid metabolism disorder
Lipids increased
Lipids abnormal
Blood cholesterol abnormal
Blood cholesterol increased
High density lipoprotein decreased
Hypercholesterolaemia
Low density lipoprotein increased
Mixed hyperlipidaemia

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Type I hyperlipidaemia
Type II hyperlipidaemia
Type IIA hyperlipidaemia
Type IIB hyperlipidaemia
Type III hyperlipidaemia
Type IV hyperlipidaemia
Type V hyperlipidaemia

Elevation of BMI or weight gain preferred terms (n = 6):
Weight increased
Weight abnormal
Overweight
Obesity
Fat tissue increased
Body mass index increased

2) Search Strategy 2: Cases coded with metabolic disorder and insulin resistance

Cases already identified using strategy 1 were flagged and excluded. The remaining cases were searched for the following preferred terms: metabolic disorder and insulin resistance. As already noted, there were no cases coded with metabolic syndrome through March 31, 2004.

3) Search Strategy 3: Case reports that included a text string suggesting MS

Cases identified by search strategy 1 or 2 were flagged and excluded. The narrative text describing each event was searched for "metabolic syndrome", "syndrome X" or "insulin resistance".

1.2. Review of potential Metabolic Syndrome Cases

Overall, 88 potential cases of MS were found using the three search strategies with 75 [GAB2]cases identified using preferred terms that could indicate ATP-III risk factors. Appendix (Table 3X) provides a line listing of these 88 cases. Of the 88 patients, XX had events

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

that meet the regulatory definition of serious[GAB3]. Table 2X provides a frequency listing of the AEs reported in these 88 cases. Of the 88 patients, 7 had DKA.

Of the 88 cases, XX had positive dechallenge for at least one component of the MS. There were XX rechallenges.

The following two patient vignettes are good examples of cases that had a positive dechallenge.[GAB4] Both were identified using preferred terms that could indicate MS risk factors. Both cases had reduction in glucose and lipid values after olanzapine was discontinued. In addition, the second patient was able to discontinue insulin [GAB5]after olanzapine was discontinued. Insulin had been initiated in this patient after presenting in DKA. The first patient apparently did not have a decrease in weight concomitant with the normalization in glucose and lipids, and while the second patient had a decrease in weight, the patient had been placed on an ADA diet.

> Patient JP_030200417 is a 27 year-old Asian male who developed mild schizophrenia around August 2002 and initiated 2.5 mg of olanzapine on 14 September 2002. The patient had no history of diabetes mellitus but his family history was unknown. At baseline[GAB6], he was taking multiple concomitant medications including paroxetine, flunitrazepam, levomepromazine, and brotizolam. Lipid studies were not performed prior to the olanzapine therapy and on 09 November 2002, the patient's fasting blood sugar was 86 mg/dl. On 18 January 2003, the dosage of olanzapine was increased to 5mg daily. After increasing the olanzapine dosage, the patient reported an increase in appetite and weight. On 15 February 2003, approximately five months after starting olanzapine, the patient's body weight had increased to approximately 80 kg from 55kg at baseline and his fasting blood sugar was 152mg/dl, total cholesterol was 192mg/dl, and triglyceride was 702. Olanzapine was discontinued in February 2003 and no treatment was recommended for the elevated lipids and blood sugar. According to the patient, his appetite decreased shortly after stopping olanzapine. On 08 March 2003[GAB7], his fasting blood sugar was 97, hemoglobin A1C was 4.6 and his triglycerides were 48 but his weight continued to be elevated. Perospirone hydrochloride hydrate 8mg was started. No further follow-up is available because the patient discontinued with the reporting psychiatrist because of a job transfer.
>
> Patient USA020819832 is a 42 year-old black man with a history of polysubstance abuse and assaultive/ thought disorders. His family history was unknown and he was taking chlorpromazine, venlafaxine, clonazepam and ziprazidone at baseline[GAB8]. The patient began taking 20mg of olanzapine in August 1999 for treatment of schizophrenia. Before starting olanzapine, his weight was 218 pounds and his FBS was 74. According to the patient, he began gaining weight after starting olanzapine and gained approximately 50 pounds by July 2000. On 19 April 2000, his FBS was 105 and his triglycerides were 206. On 23 August 2000, one year after starting olanzapine, the patient was diagnosed with diabetic ketoacidosis and was started on a regimen of human insulin isophane suspension (humulin n) 25 units every morning at 7am and metformin 500 mg daily. His glucose level was 425. His weight as of 21-sep-2000 was 257 pounds. He continued olanzapine (at times up to 25 mg daily) and insulin through 2001 until June 2002 along with significant dietary changes. In June 2002, olanzapine was tapered and then discontinued. Venlafaxine was discontinued in March 2002. The patient was started on chlorpromazine then ziprasidone 20 mg twice daily which was increased to 60 mg twice daily. On 14 August 2002, the patient experienced a hypoglycemic episode (glucose 46) with hypotension

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

(97/80), increased pulse (115) and urinary incontinence. Insulin was discontinued on this date. As of 04-dec-2002, the patient was taking ziprasidone 160 mg daily, valproate 2000 mg daily, thorazine 700 daily, and clonazepam 2 mg daily. Blood glucose range had been 90-105 [GAB9]since the discontinuation of insulin in June 2002. The patient's weight was 226 pounds in November 2002 (a decrease from 267 pounds at the time of diagnosis of diabetes).

There were other cases of MS that were clearly treatment emergent but without follow-up information to determine if olanzapine was discontinued. The following patient vignette is a good example and it was identified using the preferred term, *metabolic disorder*.

Patient JP_031202249 is a 19 year-old man with a history of paranoid type schizophrenia. He had a family history of diabetes mellitus (his mother and maternal grandfather). His lab data and physician exam findings were normal before starting olanzapine: body mass index, 22.4; body fat percentage, 17.7%; fasting blood sugar, 94mg/dl; hemoglobin A1C (hba1c), 4.8%; total cholesterol, 138mg/dl; low-density lipoprotein-cholesterol, 87mg/dl; high-density lipoprotein-cholesterol, 41mg/dl; triglyceride, 60mg/dl. He continued to take haloperidol and levomepromazine as he initiated 5 mg olanzapine. About five months after starting olanzapine, haloperidol and levomepromazine were discontinued, and olanzapine was increased to 20mg daily. At about this same time, the patient's bmi and body fat percentage started to increase markedly[GAB10]. In addition, the patient's LDL and leptin started to increase. His olanzapine blood level was 83.54ng/ml. Approximately eight months after starting olanzapine, the patient experienced a slight decrease in HDL to under 40mg/dl. Approximately 11 months after starting olanzapine, his LDL was 140mg/dl and it was 144 about 3 months latter. Findings at 17 months after starting olanzapine included the following: (1) body weight had increased by 16.3kg with BMI increasing to 28 and body fat percentage increasing to 27.3%, (2) total cholesterol had increased 195mg/dl with an LDL of 144mg/dl and HDL slightly less than 40mg/dl; (3) triglyceride had increased to 91mg/dl. However, FBS, GTT and HgAIC were all normal with an increase in the insulin resistance of homeostatic model [GAB11]assessment (homa). At the same time, other lab data was as follows: fasting blood sugar 101mg/dl, hba1c 4.5%, 75g glucose tolerance test (two hours) close to 140ng/mg which was the upper limit of normal range, leptin reached the upper limit of normal range for men. The increased homa indicated that potentially impaired glucose tolerance, such as emergence of ir, was progressing. Additional follow-up after the testing at 17 months was not available.

The next three sections review the findings from each search strategy. Appendix, Table 4X contains all AE reports (append MedWatch forms) for all 88 cases.

1.2.1. Cases identified using ATP-III risk factor analysis

Across the GPSD, there were 75 cases that had three or more risk factors based upon the coded preferred terms subsumed to identify these risk factors. Table x summarizes the prevalence of the risk factors across the database for the 75 cases. Most potential MS cases

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

were identified based upon preferred terms suggesting blood sugar elevation, lipid elevation and weight gain. Table XX shows the counts of cases across preferred terms subsumed under each risk factor for the overall database and the 75 potential cases.

Table Y. Number of Cases (%) with clinical criteria associated with MS across the olanzapine post-marketing database.		
	All 6182 Cases	75 potential MS cases
BP Elevation	322 (5.2)	13 (17.3)
Blood Sugar Elevation	2058 (33.3)	73 (97.3)
Triglyceride Elevation	469 (7.6)	71 (94.7)
Weight Gain	4070 (65.8)	69 (92.0)
HDL Decrease	8 (0.1)	4 (5.3)

Table 2Y. Distribution of Cases across preferred terms Subsumed under each MS risk factor. (%)		
	All 6182 Cases	75 potential MS cases
BP Elevation	322 (5.2)	13 (17.3)
Blood pressure abnormal		
Blood pressure diastolic increased		
Blood pressure fluctuation		
Blood pressure increased		
Blood pressure systolic increased		

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Diastolic hypertension		
Hypertension		
Labile blood pressure		
Labile hypertension		
Hypertensive crisis		
Blood Sugar Elevation	2058 (33.3)	73 (97.3)
Blood glucose abnormal		
Blood glucose fluctuation		
Blood glucose increased		
Diabetes mellitus		
Diabetic cardiomyopathy		
Diabetic eye disease		
Diabetic retinopathy		
Diabetes mellitus inadequate control		
Diabetes mellitus insulin-dependent		
Diabetes mellitus non-insulin-dependent		
Diabetes with hyperosmolarity		
Diabetic autonomic neuropathy		
Diabetic coma		
Diabetic complication		
Diabetic foot		
Diabetic hyperglycaemic coma		
Diabetic hyperosmolar coma		
Diabetic hyperosmolar non-ketoacidosis		
Diabetic ketoacidotic hyperglycaemic coma		
Diabetic ketoacidosis		
Gestational diabetes		
Glucose tolerance decreased		
Glucose tolerance impaired		
Glucose tolerance impaired in pregnancy		

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Glucose tolerance test abnormal		
Glycosylated haemoglobin increased		
Hyperglycaemia		
Increased insulin requirement		
Insulin-requiring type-II diabetes mellitus		
Insulin resistance		
Insulin resistant diabetes		
Ketoacidosis		
Ketosis		
Triglyceride Elevation	469 (7.6)	71 (94.7)
Blood triglycerides increased		
Blood triglycerides abnormal		
Hyperlipidaemia		
Hypertriglyceridaemia		
Dyslipidaemia		
Lipid metabolism disorder		
Lipids increased		
Lipids abnormal		
Blood cholesterol abnormal		
Blood cholesterol increased		
High density lipoprotein decreased		
Hypercholesterolaemia		
Low density lipoprotein increased		
Mixed hyperlipidaemia		
Type I hyperlipidaemia		
Type II hyperlipidaemia		
Type IIA hyperlipidaemia		
Type IIB hyperlipidaemia		
Type III hyperlipidaemia		
Type IV hyperlipidaemia		

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Type V hyperlipidaemia		
Weight Gain	4070 (65.8)	69 (92.0)
Weight increased		
Weight abnormal		
Overweight		
Obesity		
Fat tissue increased		
Body mass index increased		
HDL Decrease	8 (0.1)	4 (5.3)
High density lipoprotein decreased		
High density lipoprotein abnormal		

Across the 75 cases, 13 were reported in the medical literature. Of these 13, 5 cases had information suggesting improvement in MS risk factors following discontinuation of olanzapine. The remaining 8 literature cases all developed metabolic syndrome during the course of olanzapine therapy but did not have information on dechallenge.

Comment: this is a list of the cases – JF has not reviewed [GAB12]the actual published reports. Bill said it might take some time to get them all.

GBS010608969

ASHIM S, WARRINGTON S, ANDERSON I. MANAGEMENT OF DIABETES MELLITUS OCCURRING DURING TREATMENT WITH OLANZAPINE: REPORT OF SIX CASES AND CLINICAL IMPLICATIONS. JOURNAL OF PSYCHOPHARMACOLOGY. 2004; 18(1): 128-132.

US_00236410

DOMON S, WEBBER J. HYPERGLYCEMIA AND HYPERTRIGLYCERIDEMIA SECONDARY TO OLANZAPINE. JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY. 2001; 11(3): 285-288.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

US_001254588
US_001254605
US_001254607

MELKERSSON K, HULTING A, BRISMAR K. ELEVATED LEVELS OF INSULIN, LEPTIN, AND BLOOD LIPIDS IN OLANZAPINE-TREATED PATIENTS WITH SCHIZOPHRENIA OR RELATED PSYCHOSES. JOURNAL OF CLINICAL PSYCHIATRY. 2000; 61: 742-749.

US_020281559
US_020281563
US_020281594

MEYER J. NOVEL ANTIPSYCHOTICS AND SEVERE HYPERLIPIDEMIA. JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY. AUGUST 2001; 21(4): 369-374.

US_020584526

HAGIWARA N, ET AL. A CASE EXPERIENCED REMARKABLE HYPERGLYCAEMIA. JAPANESE JOURNAL OF DIABETES FRONTIER. 2004; 15(1): 93-98.

US_030695383
US_030695387
US_030695410

BLOCH Y, VARDI O, MENDLOVIC S, ET AL. HYPERGLYCEMIA FROM OLANZAPINE TREATMENT IN ADOLESCENTS. JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY. 2003; 13(1): 97-102.

US_990725007
OBER S, HYPERGLYCEMIA AND OLANZAPINE. AMERICAN JOURNAL OF OBER S, HYPERGLYCEMIA AND OLANZAPINE. AMERICAN JOURNAL OF PSYCHIATRY. 1999; 56:970.56:970.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Of the remaining 67 cases, there were 11 that provided good baseline data and information on dechallenge. These 11 cases are summarized in Table 3Y.

Table 3Y[GAB13] – include case IDs, Response to Dechallenge, etc.

DE_31112399
EWC001108585
FR030302171
FR030602502
JP_030200417
JP_030901751
JP_031102246
USA020819832
USA030741569
US_001052572
US_020584604

1.2.2. Cases identified using preferred terms for Metabolic Syndrome

There were an additional 13 cases found that were coded with “metabolic disorder” or “insulin resistance”. Of these 13, 12 did not include enough clinical information to suggest MS.

Comment – There are 13 cases identified from this search strategy not 12- I do not know why he says 12. Bill feels 3 are indicative of MS. I feel the 1 case though mild is well documented.

Case Summary Report:

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Report Requested for the Following Case Numbers:

CL97075797A
FR_030602547
GBS030513113
JP_031202249
JP_040102528
USA020413774
USA021124117
USA030125466
USA030331349
USA030434645
USA030537978
USA030947450
US_020483750

1.2.3. Cases identified using text string search

After excluding the 87 potential cases identified using methods 1 and 2, there were an additional 18 cases with text strings in the narrative of "metabolic syndrome", "syndrome X" or "insulin resistance". Of the 18 cases 14 mentioned "insulin resistance" either in the past medical history or as a developing or worsening event. Three cases included the term "metabolic syndrome", in 2 cases it was used in the past medical history and in one case as a statement that the case was at increased risk for developing metabolic syndrome. Two cases included the term "syndrome X". One patient (USA20515135), a male in his forties with alcoholism, hypertension and hyperlipidemia developed elevated blood sugar during the course of olanzapine therapy that resolved on discontinuation. The reporter attributed the development of hyperglycemia to the patient's underlying syndrome X. The other case mentioning syndrome X is a male who developed hyperlipidemia and syndrome X while taking olanzapine. The reporter did not provide any further details after requests for further information. None of the 18 cases met the case definition of developing MS during the course of olanzapine therapy.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Comment- this is the listing from the string search- only the initial 75 were excluded so some cases from step 2 were included here. In going through the reports I found 5 cases from step 2 and 1 case from step 1. I am unsure how the step 1 case could get in. Anyway after excluding those case I get 18 not 16 identified in step 3.

Case summary report:

Report requested for the following case numbers:

Ca_010503671
Ca_030305793
Cl97075797a
De_000602613
Ewc000606856
Ewc010627215
Gbs030513113
Jp_031202249
Jp_040102528
Usa020110313
Usa020515135
Usa020616842
Usa021124117
Usa030433719
Usa030434555
Usa030947448
Usa030947450
Us_010770104
Us_011278580
Us_020483750
Us_020584395
Us_020584425
Us_990319397
Us_991232628

Bold = from step 2 or 1

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

1.3. Summary of Potential Metabolic Syndrome Cases

Overall, 88 potential cases of metabolic syndrome were found using the three search strategies with 75 [GAB14]cases identified using preferred terms that could indicate ATP-III risk factors. Medical review of these 88 (75?) reports identified 57 (65% of 88) that also met qualification for the elevated triglycerides review. Sixty-one of the 88 (69%) case reports included weight increased in temporal association with olanzapine therapy. Among the 88 reports identified as potential metabolic syndrome, there were 2 with fatal outcomes, 1 case report of pancreatitis, and 7 reports of diabetic ketoacidosis, and eleven dechallenge reports identified in temporal association with olanzapine therapy.

As of March 31, 2004, there were an estimated 14,927,000 patients exposed to commercially marketed olanzapine for an estimated 8,314,000 person-years. As of 31 March 2004, the reporting rate for potential cases of metabolic syndrome was 5.9 case reports per million patients exposed regardless of the presence of confounding factors.

The observed reporting rates among patients treated with olanzapine must be interpreted within the context of the known limitations of spontaneous report data, including the approximation of drug exposures on the basis of prescription data and potential differences in reporting practices and reporting environment (Goldman 1998). Given the high background rates of metabolic syndrome and individual components of metabolic syndrome in the general population, it is not unexpected that cases of metabolic syndrome will occur in temporal association with olanzapine treated patients. Moreover, it is not possible to reach conclusions about attribution of individual cases. Given that olanzapine is associated with weight gain, which by itself is associated with elevations in triglycerides and increases in blood sugar, the possible association of olanzapine treatment with metabolic syndrome, through unlikely, cannot be determined with these data. Given these limitations, these data cannot be used to establish causality or to determine the incidence of potential metabolic syndrome in patients treated with commercially marketed olanzapine.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

2. Cases with Large Increases in Triglycerides Reported during Post-marketing

2.1. Methodology

Since large increases in triglycerides can be associated with serious medical events like pancreatitis, the GPSD was searched to find all cases that reported a triglyceride value of 500 or more. The GPSD was searched for the following 16 MedDRA preferred terms: *blood triglycerides increased, blood triglycerides abnormal, hypertriglyceridaemia, dyslipidaemia, hyperlipidaemia, lipid metabolism disorder, lipids abnormal, lipids increased, mixed dyslipidaemia, type I hyperlipidaemia, type II hyperlipidaemia, type IIA hyperlipidaemia, type IIB hyperlipidaemia, type III hyperlipidaemia, type IV hyperlipidaemia* and *type V hyperlipidaemia.* In addition, a text string search was conducted for "triglyceride". Cases were then screened to find those with triglyceride elevations greater than 500 mg per dl.

2.2. Review of Cases

Table 4Y provides a summary of the 173 cases that had triglyceride values of 500 mg/dl or greater. There were significantly more males than females with males tending to be slightly younger. Of the 173 cases, 94 had triglyceride values 1000 mg/dl or greater. There were a XX cases with serious events and four deaths. Of the 173 cases, 14 may [GAB15]have developed pancreatitis with 1 death. Table XX summarizes all adverse events in the 173 cases. Appendix A[GAB16] lists the cases in the Global Product Safety database that had triglyceride elevations above 500 mg/dl by MedDRA preferred term and line listings (Tables 5X and 6X, respectively. See Table summary 5.5X for a summary of these cases).

Table 4Y. 173 Cases Reported to the GPSD with Triglyceride Values 500 mg/dl or more

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Number of Males	131
Number of Females	37
Mean Age Males	36.3
Mean Age Females	43.7
Triglyceride Value	
≥ 500mg to 999mg/dl	79
≥ 1,000mg to 5,000mg/dl	81
>5,000mg to 10,000mg/dl	12
> 10,000 mg/dl	1
Number of Deaths	4
Number of Serious Events	?????
Number of Cases of Pancreatitis	14

All four deaths were medically complicated patients who had marked elevations in glucose and lipids. The first two patients summarized below may have developed MS while on olanzapine with the second death occurred in association with pancreatitis.

Patient **USA020515251** was a 20-year-old African American male with a body mass index of 29.8 that died from respiratory failure (case #14 in Appendix A). The patient had a history of elevated cholesterol, renal insufficiency, pulmonary disease, mild amylase elevations and mild lipase elevations before initiating olanzapine but reported no history of diabetes mellitus or pancreatitis. The patient had a family history of diabetes mellitus. The patient was not considered to be an alcoholic. Olanzapine had been administered for approximately 4 ½ years in the treatment of schizophrenia. Concomitant medications included clonazepam, haloperidol decanoate, risperidone and trazodone. The baseline laboratory values prior to the start of olanzapine were serum cholesterol 242mg/dl, serum triglycerides 56mg/dl and fasting blood sugar 101mg/dl. No other baseline laboratories were provided. Upon admission to the hospital, the patient laboratory values were non-fasting blood sugar 736mg/dl, serum cholesterol 539mg/dl, HDL cholesterol 26mg/dl, serum triglycerides 3189mg/dl, urinary ketones 3+, plasma osmolality 287.5, blood urea nitrogen 23mg/dl and arterial blood pH of 7.148. The patient was diagnosed with diabetic ketoacidosis. Respiratory failure ensued leading to death.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Patient **USA031050393** was a 24-year-old male weighing 116 kilograms (no BMI) that died due to nonketotic hyperosmolar coma and pancreatitis. A blood sugar measured 2-years prior to death was 101mg/dl. The patient had taken olanzapine intermittently for about 6-years. Olanzapine had been discontinued and restarted 3-times over the course of therapy but he had received olanzapine consistently for about 2 ½ years prior to the hospital admission. Concomitant medications included trazodone, paroxetine and quetiapine. The patient had a 3-day history of nausea, emesis and abdominal pain along with excessive soda intake prior to hospital admission. Laboratory values were blood sugar 1214mg/dl, serum triglycerides 2195mg/dl, lipase 414 and white blood cell count 18,400. An enlarged pancreas was discovered. The patient according to the reporter did not have any known medical conditions at the time of hospital admission other than mental disease.

Patient **FR_020100595** was a 35-year-old male with a body mass index of 23.1 and a history of Klinfelter's syndrome, brucellosis along with chronic complaints of leg pain and fatigue that died while on olanzapine. The patient had taken olanzapine for approximately 15-months when the patient underwent a "biological" check-up and the following laboratory values were discovered: blood sugar: 478mg/dl, serum triglycerides: 895mg/dl, hemoglobin A1c: 13.3%, acetone and protein in urine. The patient was diagnosed with diabetes mellitus. Olanzapine was discontinued the same day as the laboratory abnormalities were discovered. Ten days later the patient was found dead by his mother. The reporting physician determined the cause of death was ketoacidosis. It was observed by the reporter that the patient had no history of suicidal ideation or history of alcohol ingestion. The reporter could not provide evidence of ketoacidosis at the time of death. No autopsy was performed. The patient had not been taking any concomitant medications.

Patient **US_011178209** was a 29-year-old Asian male with a BMI of 31.1, baseline blood sugar: 137mg/dl, baseline triglycerides: 547mg./dl and baseline cholesterol: 278mg/dl prior to starting olanzapine. In addition, the patient had a history of liver enzyme elevations (ALT, AST, GGT), drug-induced Parkinsonism, schizophrenia and autistic tendencies. Concomitant medications included timiperone, biperiden, cloxazolam and fenofibrate. The patient had no history of diabetes but had displayed hyperglycemia as evidenced by the baseline blood sugar of 137mg/dl. In addition, 30-days after the start of olanzapine the blood sugar was 230mg/dl. Olanzapine had been administered for approximately 40-days when a blood sugar of 723mg/dl, cholesterol of 362mg/dl, serum triglyceride of 960mg/dl, glycosuria, ketonuria and a hemoglobin A1c of 15.4% were discovered and the patient went into cardio-respiratory arrest. The patient was resuscitated and admitted to the hospital. A diagnosis of diabetic coma was made and the blood sugar had peaked at 854mg/dl upon admission. Treatment was initiated and the patient died some 72-hours later. The patient had suffered hypoxia due to the cardio-respiratory arrest and did not display normal brain activity after admission. The diabetic coma was considered to be a hyperosmolar hyperglycemic nonketotic coma.

Of the 14 cases of pancreatitis, [GAB17]1 was probably not diagnosed by the reporting physician. Five of the 14 patients had a previous history of pancreatitis prior to the start of olanzapine. Two of the patients had significant ingestion of alcohol and four of the patients had diabetic ketoacidosis at approximately the same time as pancreatitis. There were two cases that did not provide adequate medical history to assess for the presence or absence of contributing factors.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

We may need a vignette, but none of these sound particularly interesting to me.

There were also cases with triglyceride values of 500 mg/dl or greater with positive dechallenge. There were no [GAB18]rechallenges. The first patient summarized below had normal triglyceride values just prior to initiating olanzapine.

Patient us_021291011 was a 23-year-old Asian man who developed schizophrenia-like symptoms. On 29 November 2001, he began 5 mg of olanzapine. Concomitant medications included sulpiride, trazodone hydrochloride, and phenobarbital. In April 2002, the patient's triglyceride level was normal (72mg/dl). As of 11 November 2002, the patient's weight increased from 75kg to 80kg, and sulpiride was discontinued. On 09 December 2002, the patient experienced fatigueability and a blood test was performed which found a triglyceride level of 1053mg/dl. Olanzapine was discontinued on 10 December 2002. On 17 December 2002, the triglyceride level was 62 mg/dl.

Patient de_991001623 was a 55-year-old Caucasian woman with a history of increased triglycerides (297 mg/dl on 27 May 1999). She began taking olanzapine for acute psychosis on 18 August 1999. Concomitant medications included mirtazapine (remergil). Two days after the start of olanzapine therapy, the patient's triglyceride value was 864 mg/dl. Triglyceride level peaked on 23 September 1999 at 1440 mg/dl. Olanzapine was discontinued on 29 September 1999. A follow-up triglyceride value on 15 October 1999 was 640 mg/dl. The patient had no associated weight gain of elevation in blood glucose during the course of olanzapine therapy.

Patient us_020584604 was a 36-year old Asian woman with a history of hyperlipidemia (triglyceride 356 mg/dl on 26 July 2001) and mild fatty liver since 1999. She started olanzapine 5mg/day orally for schizophrenia on 09 August 2001. Concomitant medications included lorazepam, fluvoxamine, paroxetine hydrochloride hydrate, and trazodone hydrochloride. On 11 October 2001, dosage of olanzapine was increased to 10 mg/day. On 25 October 2001, approximately 10 weeks after beginning olanzapine, triglyceride level was 903 mg/dl. She developed obesity and received instructions about her diet and exercises. On 02 May 2002, approximately nine months after starting olanzapine, her blood sugar level was to 254mg/dl (hemoglobin a1c=10.4), which had been 120mg/dl on 26 July 2001. Her triglyceride was 2324mg/dl and total cholesterol was 481mg/dl. Following these laboratory findings, olanzapine was discontinued. On 17 May 2002, her blood sugar was 132 mg/dl and triglyceride was 280 mg/dl. Olanzapine was not restarted.

2.3. Summary of Case Reports with Elevated Triglycerides and Cholesterol

The evaluation of Lilly's adverse event surveillance database identified 447 case reports that met the search criteria for triglycerides ≥ 150 mg/dL in temporal association with olanzapine therapy. Medical review of these 447 reports identified thirteen reports of diabetic ketoacidosis. Out of the 447 case reports, 274 (61%) had triglyceride values < 500 mg/dL and 139 (39%) reports with triglycerides ≥ 500 mg/dL in temporal association with olanzapine therapy. In addition, 139 of the 447 (31%) were also reported as cases of weight

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

increased. Out of the 173 case reports with triglycerides ≥ 500 mg/dL, there were 49 (28%) reported with weight increased, 94 with triglycerides values reported ≥ 1000 mg/dL, and 4 cases reported with fatal outcomes in temporal association with olanzapine therapy. All four deaths were medically complicated patients who had marked elevations in glucose and lipids. In addition, 14 out of the 173 cases with triglycerides ≥ 500 mg/dL were reported as pancreatitis in temporal association with olanzapine therapy, and 8 cases were reported as pancreatitis in patients with triglyceride values < 500 mg/dL.

Further evaluation of Lilly's adverse event surveillance database identified 93 case reports with elevated cholesterol independent of elevated triglycerides (Table 7X and 8X). Medical review of these 93 reports identified 36 (39%) with total cholesterol > 240 mg/dL in temporal association with olanzapine therapy. Twenty-seven of the 93 (29%) case reports included weight increased. Among the 93 reports of elevated cholesterol, there were no cases of diabetic ketoacidosis. Thirty-eight out of the 93 cases were dechallenge reports, consisting of 8 cases of positive dechallenge and 13 cases of negative dechallenge in temporal association with olanzapine therapy.

As of March 31, 2004, there were an estimated 14,927,000 patients exposed to commercially marketed olanzapine for an estimated 8,314,000 person-years. As of 31 March 2004, the reporting rate for cases with triglycerides ≥ 150 mg/dL was 29.9 case reports per million patients exposed regardless of the presence of confounding factors. In addition, the reporting rate for cases with cholesterol ≥ 240 mg/dL was 2.41 case reports per million patients exposed regardless of the presence of confounding factors.

The observed reporting rates among patients treated with olanzapine must be interpreted within the context of the known limitations of spontaneous report data, including the approximation of drug exposures on the basis of prescription data and potential differences in reporting practices and reporting environment (Goldman 1998). Given these limitations, these data cannot be used to establish causality or to determine the incidence of abnormal blood levels of triglycerides or cholesterol profiles in patients treated with commercially marketed olanzapine.

Goldman SA. 1998. Limitations and strengths of spontaneous reports data. Clin Ther 20(Suppl C):C40-44.

Reference & Insert in the appendix TABLE 10X: MedWatch Forms for Elevated Triglycerides and Cholesterol Reports.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

3. Metabolic Syndrome Appendix (listing of tables referenced in Section 1)

Table 2X. . (Frequency table for all potential MS terms)

Cases (n=88) of Potential Metabolic Syndrome:
Preferred Terms (non-searched) by Decreasing Frequency

Adverse Events by Preferred Term	# Events
Diabetic ketoacidosis	**7**
Aggression	3
Fatigue	3
Headache	3
Ketonuria	3
Sedation	3
Anaemia	2
Anxiety	2
Aspartate aminotransferase increased	**2**
Blood alkaline phosphatase increased	2
Blood creatinine increased	2

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Diabetic coma	**2**
ECG QT prolonged	**2**
Hallucination, auditory	2
Hallucination, visual	2
Hepatic function abnormal	2
Hepatic steatosis	**2**
Hormone level abnormal	2
Ketoacidosis	**2**
Psychotic disorder	2
Abdominal pain	1
Acidosis	1
Affect lability	1
Agitation	1
Alanine aminotransferase increased	**1**
Alopecia	1
Anger	1
Angina pectoris	1
Apathy	1
Arterial occlusive disease	1
Asthenia	1
Back pain	1
Balanitis candida	**1**
Blood iron decreased	1
Blood lactic dehydrogenase increased	1
Blood potassium increased	1
Blood prolactin increased	1
Blood thyroid stimulating hormone increased	1
Blood urea nitrogen increased	1
Cerebrovascular accident	**1**
Chest pain	1
Coma	1

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Confusional state	1
Convulsion	1
Coronary artery disease	1
Cystitis	1
Delusion of grandeur	1
Depression	1
Diabetic hyperosmolar coma	**1**
Diarrhoea	1
Dizziness	1
Fluid retention	**1**
Folliculitis	1
Heart rate increased	1
Hepatic enzyme increased	1
Hyperosmolar state	1
Hypoglycaemia	1
Hypokalemia	1
Hypotension	1
Incoherent	1
Incontinence	1
Insomnia	1
Mental impairment	1
Mental status changes	1
Mononucleosis syndrome	1
Mood swings	1
Muscle cramp	1
Neutrophil count increased	1
Pancreatitis	**1**
Panic attack	1
Persecutory delusion	1
Pitting oedema	**1**
Protein total decreased	1

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Proteinuria	1
Reflux oesophagitis	**1**
Respiratory failure	**1**
Somnolence	1
Tachycardia	**1**
Thinking abnormal	1
Thrombocytopenia	1
Thyroid disorder	1
Urinary incontinence	1
Urinary tract infection	1
Ventricular extrasysoles	**1**
White blood cell count increased	1

Table 3X contains all AE reports for all 88 cases

POTENTIAL METABOLIC SYNDROME CASE REPORTS from CLINTRACE DATABASE

Cases identified by MedDRA Preferred Term search for risk factor terms

Case No	Case ID	Age, Sex	MedDRA Preferred Terms	Olanzapine dosing/ duration (mg/ days)	Blood Pressure (mmHg)	Weight Gain/ BMI	Peak serum triglyceride (mg/dL)	Cholesterol HDL/Total (mg/dL)	Blood Glucose (mg/dL)	Comments
1	DE_030110501	63, F	Hyperlipidemia Weight increased Coronary Artery disease Hypertension Hypokalemia ECG QTc interval prolonged Ventricular extrasysoles	15/900	Unknown	10 kg (unknown duration)/ unknown	Unknown	Unknown	Unknown	Patient developed hypertension soon after starting olanzapine. Olanzapine was continued and events are ongoing.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

2	DE_031112399	52, F	Weight increased Hyperlipidemia Hyperglycemia Hypercholesterolemia	Unknown	Unknown	34 kg over 3 years/ Unknown	Unknown	Unknown/ >1000	600	Olanzapine discontinued. Patient recovered
3	EWC001108585	22, F	Hypercholesterolaemia Hypertriglyceridaemia Hyperglycaemia Weight increased	25/480	Unknown	Unknown/ BMI = 34.7	660	Unknown	Unknown	Unknown if patient fasted
4	EWC011028613	60, F	Blood cholesterol increased Blood triglycerides increased Blood glucose increased High density lipoprotein decreased ECG QT prolonged	5/10	Unknown	Unknown/ BMI = 19.4	317	30/297	147 (fasting) 259 (post prandial)	**Literature case.** Wolff-Parkinson-White on baseline ECG
5	EWC020330154	39, M	Weight increased Hyperglycemia Hypercholesterolaemia	25/365	Unknown	9 kg gain over 18 months 10 kg **loss** over 4 months on 1800kcal diet/ Unknown	Unknown	Unknown/262	127 (fasting)	Obesity (106KG) prior to olanzapine Smoker (30/day) Insulin level was measured and found to be normal. After weight loss, glycemia was again normal and olanzapine was continued.
6	EWC030534921	36, M	Hypertension Weight increased Blood glucose increased	20/120	Unknown	34 kg over 1 year/ BMI = 33.2	Unknown	Unknown	113 (fasting)	Patient not yet recovered
7	EWC040137812	39, F	Blood glucose increased Weight increased Blood cholesterol increased	30/450	Unknown	25 kg over 15 months/ Unknown	Unknown	Unknown/305	191	Olanzapine was discontinued twice briefly during 15 months while other antipsychotics were tried. Patient preferred olanzapine treatment.
8	FR_020100595	35, M	Diabetes mellitus Weight increased Hypertriglyceridemia Ketoacidosis Ketonuria Proteinuria	15/540	Unknown	Unknown/ BMI = 23.1	829	Unknown/ Unknown	467	Medical history included Klinfelter's syndrome, brucellosis, phlebitis and a family history of phlebitis. Olanzapine was discontinued on 22-Dec-2001 (18 months after starting treatment) after diabetes was diagnosed. On the morning of 01-Jan-2003, **the patient was found dead.** No autopsy was performed.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

9	FR_030101871	36, F	Hyperglycaemia Hypertriglyceridaemia Hypercholesterolaemia Weight increased	15/330	Unknown	Unknown/ Unknown	7.44 Units not provided (if units are mmol/L = 662 mg/dl)	Unknown/ Unknown	122	Medical diet and atorvastatin started – glycemia, triglyceridemia and cholesterolemia normalized approximately 3 months after events occurred. Family history of diabetes mellitus History of anorexia
10	FR_030302171	70, M	Diabetes mellitus non-insulin dependent Weight increased Hypercholesterolaemia Hypertriglyceridaemia	5/730	Unknown	5 kg over 2 years/ Unknown	160	Unknown/222	143	Approximately 2 years of olanzapine treatment, non-insulin dependent diabetes was diagnosed. Olanzapine was discontinued, patient recovered. Family history of diabetes
11	FR_030602502	33, M	Diabetes mellitus non-insulin dependent Hypercholesterolaemia Hypertriglyceridaemia Weight increased	7.5/1125	Unknown	15 kg over 3 years/ BMI = 44.2	314	Unknown/304	134.8	Patient also experienced asthenia, polyuria, polydipsia. Olanzapine was discontinued Family history included hypercholesterolemia and unspecified diabetes mellitus.
12	FR_030802822	27, F	Diabetes mellitus insulin-dependent Hypertriglyceridaemia Weight increased	7.5/120	Unknown	Unknown/ BMI = 23.7	238	Unknown/ Unknown	272 (pre-prandial) 537 (post-prandial)	After 4 months of olanzapine therapy, patient experienced asthenia, polyuria, polydipsia and increased glucose. Insulin treatment was started. Olanzapine was discontinued, weight continued to increase and glycemia did not return to normal
13	FR_030902949	33, M	Diabetes mellitus insulin-dependent Weight increased Hypertriglyceridaemia Diabetic ketoacidosis	7.5/810	130/90	40 kg over 27 months/ BMI = 29.3	394	Unknown/ Unknown	952 (6/03) 101 (9/03) 93 (3/04)	Patient experienced polydipsia, was hospitalized and treated with insulin. Olanzapine was continued and with treatment, glycemia returned to normal. History of weight gain and neurological intolerance with risperidone Tobacco addiction withdrawn
14	FR_031003027	53, M	Diabetes mellitus non-insulin dependent Hypercholesterolaemia Weight increased Hypertriglyceridaemia	10/1095	120/80	10 kg over 2 years/ BMI = 28.4	Unknown	Unknown/394	152 (fasting)	Treatment for diabetes and hypercholesterolaemia initiated. Olanzapine was continued. Patient not yet recovered. Family history: non-insulin dependent diabetes
15	GBS010608969	31, F	Diabetes mellitus insulin-dependent Ketoacidosis Weight increased Hyperlipidaemia	20/420	Unknown	BMI = 26 6 kg over 14 months/ Unknown	Unknown	Unknown/ Unknown	Unknown	**Literature case.** After 14 months of olanzapine treatment, the patient developed insulin dependent diabetes mellitus and was hospitalized with acute ketoacidosis, polydipsia, and blurred vision. Follow-up in the literature noted that olanzapine

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

										was changed to quetiapine. Family history of non-insulin dependent diabetes mellitus
16	JP_030200417	27, M	Weight increased Hyperglycaemia Hyperlipidaemia Increased appetite Polydipsia	2.5/60 5/90	Unknown	25 kg over 5 months/ Unknown	702	Unknown/192	152	Olanzapine was discontinued and the hyperglycemia and hyperlipidaemia resolved.
17	JP_030300519	25, M	Weight increased Hyperglycaemia Hyperlipidaemia	10/450	Unknown	Unknown/ Unknown	Unknown	Unknown/ Unknown	160's	Olanzapine was switched to risperidone and the events resolved.
18	JP_030901751	25, M	Hyperglycaemia Blood triglycerides increased Weight increased Hepatic function abnormal Abdominal pain Diarrhoea Headache	10/150	Unknown	Unknown/ Unknown	1041	Unknown/ Unknown	220 (non-fasting)	Olanzapine was discontinued and the patient recovered from the events.
19	JP_031102246	56, F	Diabetes mellitus Blood pressure increased Hyperlipidaemia	10/540	160/110	Unknown/ BMI = 31.1	364	Unknown/305	277 (fasting)	Pravastatin and glimepiride treatment started. Olanzapine was discontinued and fasting glucose was 110mg/dl.
20	JP_031202249	19, M	Weight increased Fat tissue increased Blood cholesterol increased Low density lipoprotein increased High density lipoprotein increased Blood triglycerides increased Insulin resistance	20/510	Unknown	16.3 kg over 17 months/ BMI=28 (after weight gain)	91	41/195	94	After 8 months of olanzapine treatment, the HDL decreased slightly. After 11 months, the LDL cholesterol increased to 144mg/dl. Unknown if olanzapine was continued Family history of diabetes mellitus
21	US97093754A	21, M	Weight increased Diabetes Mellitus Hyperlipidaemia Hyperglycaemia Polyuria Reflux oesophagitis Polydipsia Nausea Vomiting	10/150	Unknown	16.8 kg over 5 months/ BMI = 46.7	>1575	Unknown/646	475	History of alcoholism.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			Tachycardia							
22	US98011711A	14, M	Blood glucose increased Blood triglycerides increased High density lipoprotein decreased Blood alkaline phosphatase increased Blood lactic dehydrogenase increased Aspartate aminotransferase increased Blood creatinine increased Hepatic steatosis Aggression	5/ Unknown	Unknown	Unknown/ BMI = 26.7	587	33/ Unknown	Unknown	Patient's LDH was 288, alkaline phosphatase was 763, and SGOT was 47. Creatinine was 1.1. Test indicated fatty infiltrates of the liver. After escalation of angry and aggressive behavior, olanzapine was restarted and liver function tests had normalized.
23	USA020110313	30, M	Blood glucose increased Blood triglycerides increased Weight increased Sedation Insomnia Headache	10/730	Unknown	13.6 kg over 18 months/ Unknown	600	***Unknown***	Unknown	After weight gain and sedation on olanzapine, patient switched to risperidone. Olanzapine was restarted with nizatidine to prevent weight gain. Glucose was normal to slightly elevated (value not provided). Metformin was started. Triglyceride level decreased to the mid 200s. After weight loss, weight gain again occurred (11.3 kg). Outcome of sedation, headache and elevated glucose levels were not provided. History of obesity
24	USA020110568	53, M	Diabetes mellitus Blood triglycerides increased Weight increased	7.5/210	Unknown	1.8kg over 5 months/ Unknown	1220	Unknown/116	557	Diabetes was diagnosed and olanzapine was discontinued. Patient received metformin and glyburide for diabetes and quetiapine for his psychiatric condition.
25	USA020211675	29, M	Blood triglycerides increased Blood glucose increased High density lipoprotein decreased High density lipoprotein decrease Glycosylated	5/90	Unknown	Unknown/ BMI = 25.8	7067	5/614	301 (fasting)	Events occurred 3 months after starting olanzapine. Patient was treated with metformin and atorvastatin. One month after discontinuing olanzapine, triglycerides were 149mg/dl, fasting blood glucose was 116mg/dl and HDL was 23mg/dl. Family history of diabetes

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			haemoglobin increased Blood cholesterol increased							
26	USA020515251	20, M	Diabetic ketoacidosis Blood triglycerides increased Ketonuria Blood cholesterol increased Weight increased Blood glucose increased Respiratory failure	15/1643	Unknown	4.5 kg over 1 year/ BMI = 29.9	3189 (units not provided)	26/539 (units not provided)	736 (units not provided)	After 18 months of olanzapine, urine ketones were 3+ and BUN was 23. Olanzapine was discontinued. Patient experienced diabetic ketoacidosis one month after discontinuation of olanzapine and **died.** Cause of death was considered respiratory failure. Patient had a history of hypercholesterolemia and mild elevation of amylase and lipase, but no history of pancreatitis or alcoholism. He had a family history of diabetes, pulmonary disease, and chronic renal insufficiency.
27	USA020617403	50, F	Weight increased Diabetes mellitus Blood cholesterol increased Blood triglycerides increased	20/2280	Unknown	13.6 kg over 6.25 years/ BMI = 36.9	Unknown	Unknown/ Unknown	Unknown	No lab values were provided. Olanzapine was discontinued.
28	USA020718365	37, M	Diabetes mellitus Hypertension Blood cholesterol increased Anemia Thyroid disorder Hallucination, auditory	30/1715	Unknown	Unknown/ BMI = 34.9	Unknown	Unknown/ Unknown	Unknown	After 4.7 years of olanzapine treatment, the patient experienced diabetes. Three months later, he experienced anemia, thyroid problems, high blood pressure and high cholesterol. All events and olanzapine have continued.
29	USA020718994	56, M	Hyperglycaemia Blood triglycerides increased Blood cholesterol increased Weight increased	15/8	Unknown	0.9 kg over 15 days/ BMI = 29	235	Unknown/298	325 (fasting)	Olanzapine was discontinued. Follow-up fasting glucose levels were still elevated. Patient had a history of hyperglycaemia on high dose quetiapine and a family history of diabetes mellitus.
30	USA020819832	73, M	Diabetes mellitus Weight increased Diabetic ketoacidosis Hypoglycaemia Blood triglycerides increased Urinary incontinence Hypotension Heart rate increased	25/1278	97/80 (during hypoglycemic episode 2 months after olanzapine discontinued)	22.7kg over 1 year/ BMI = 31.5	492	Unknown/159	425 (fasting)	Patient developed diabetes mellitus including diabetic ketoacidosis after 1 year of olanzapine treatment. The patient was treated with Insulin and metformin. Olanzapine was continued for another 18 months and was then discontinued. Insulin was also discontinued and the blood glucose range was 90-105mg/dl. Patient also lost 41 pounds.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

31	USA020920690	56, F	Blood glucose increased Blood cholesterol increased Hypertension Weight increased Cystitis Somnolence Apathy Blood iron decreased	15/730	Unknown	22.7 kg over 2 years/ BMI = 32.4	Unknown	Unknown/ Unknown	Up to 300	**Pre-existing diabetes.** After 2 years of olanzapine treatment, the patient was hospitalized for a bladder infection. While hospitalized, the olanzapine dose was “tripled” for 3 doses, and experienced high blood sugars Treatment included insulin, simvastatin, iron sulfate and an unnamed medication for blood pressure. Olanzapine was continued. The patient had a history of diabetes.
32	USA020920944	37, F	Diabetes mellitus Weight increased Blood triglycerides increased	25/300	Unknown	19 kg over 10 months/ Unknown	335	Unknown/ Unknown	278	Patient received unspecified treatment for increased glucose and triglycerides. Olanzapine and fluoxetine were continued.
33	USA030434649	32, F	Weight increased Blood glucose increased Blood cholesterol increased Back pain Panic attack Anxiety	Unknown/90	Unknown	11.4 kg over 3 months/ Unknown	Unknown	Unknown/240	141 (fasting)	Olanzapine was discontinued and weight stabilized. Rechallenge 2 months later resulted in another weight gain (9 kg). Olanzapine was again discontinued. Two months after olanzapine was discontinued, the patient had increased fasting blood glucose and cholesterol. Event outcomes are unknown.
34	USA030435246	48, F	Diabetes mellitus inadequate control Weight increased Blood cholesterol increased	15/912	Unknown	Unknown/ Unknown	Unknown	Unknown/ Unknown	Unknown	**Pre-existing diabetes.** Events occurred over the course of therapy. No values were provided. Dose was decreased to 10mg. Outcome of events was unknown. The patient had a history of diabetes
35	USA030639574	45, F	Diabetes mellitus Hyperlipidemia	10/>365	Unknown	Unknown/ Unknown	Unknown	Unknown/ Unknown	Unknown	Patient gained weight and developed diabetes and hyperlipidemia while on olanzapine (over 1 year). No values were provided. Olanzapine was discontinued and patient was being treated with metformin for diabetes.
36	USA030741569	35, M	Hypertriglyceridaemia Hypercholesterolaemia Diabetes mellitus Weight increased	15/60	Unknown	6.4 kg over 2 months/ Unknown	3030	57/771	297	Upon discontinuation of olanzapine, blood glucose, cholesterol, and triglycerides normalized.
37	USA031152021	52, F	Diabetes mellitus Weight increased Hypertension Increased appetite Food craving	30/2098	Unknown	36.4 kg over 5.7 years/ Unknown	Unknown	Unknown/ Unknown	Unknown	With diet and exercise, the patient has lost 30 pounds and is recovering from diabetes. The hypertension has not resolved.
38	USA031153125	32, M	Diabetic ketoacidosis Blood triglycerides increased	15/540	Unknown	9 kg over 4 months/ BMI = 38	2458	30/374	294 (fasting)	The patient experienced possible diabetic ketoacidosis. Olanzapine was discontinued. The events continued.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			Blood glucose increased Blood cholesterol increased Weight increased							
39	USA031153505	48, M	Blood triglycerides increased Hypertension Glucose tolerance impaired	20/ Unknown	Unknown	Unknown/ Unknown	700	Unknown	Unknown	Patient experienced an elevated triglyceride level and was hypertensive and borderline diabetic since starting olanzapine. Olanzapine was discontinued. Outcome of events was unknown.
40	US_000235844	43, M	Diabetes mellitus non-insulin dependent Blood cholesterol increased Weight increased	15/180	Unknown	8.6 kg over 8 months BMI = 22.4	Unknown	Unknown/350	340	Olanzapine was continued with glyburide and gemfibrizol. Serum glucose was 106mg/dl and cholesterol was 209. The patient had a family history of diabetes.
41	Us_00236410	14, M	Hyperglycaemia Hypertriglyceridaemia Weight increased Weight decreased Polyuria Polydipsia Anxiety Aggression Affect lability	20/365	Unknown	17.7 kg over 8 months/ BMI = 33.3	298	Unknown/ 173	368	Olanzapine was discontinued. Serum glucose, triglycerides and weight normalized. The patient had a history of mild obesity, and a family history of adult onset diabetes.
42	US_000338149	46, M	Weight increased Diabetes mellitus Blood cholesterol increased Hypertension Muscle cramp	20/1095	Unknown	36.4 kg over 1 year/ Unknown	Unknown	Unknown/ Unknown	Unknown	Patient was diagnosed with diabetes after 18 months of olanzapine treatment, and is receiving treatment with insulin, simvastatin, lisinopril and atenolol. Olanzapine was continued.
43	US_000642765	48, M	Diabetic ketoacidosis Blood triglycerides increased Weight increased Weight decreased Pancreatitis Mental status changes Blood creatinine increased	20/912	Unknown	16.4 kg **loss** over previous year, but gained 5.5 kg over last 2.5 months/ BMI = 33.2	773	Unknown/ Unknown	1069	Olanzapine was discontinued and glucose was 229 mg/dl. Patient had a history of hypertension, chronic renal insufficiency, seizures, coronary artery disease, pancreatitis, and a family history of diabetes.
44	US_000643672	57, M	Weight increased Hypercholesterolaemia Hyperlipidaemia Diabetes Mellitus non-insulin dependent Hypertension	15/1277	Unknown	15.9 kg over 3.5 years/ BMI = 30.8	922	Unknown/299	132 (fasting)	Patient developed diabetes 2 years after starting olanzapine treatment Olanzapine was continued Patient had a history of obesity.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

45	US_000847394	33, M	Weight increased Blood cholesterol increased Blood glucose increased Blood triglycerides increased Hepatic enzyme increased	15/180	Unknown	11.4 kg over over 6 months/ BMI = 28.3	638	Unknown/282	227 (non-fasting)	Patient also experienced increased liver enzymes after 6 months of olanzapine treatment. Olanzapine was discontinued. The patient had a family history of diabetes.
46	US_001052548	56, F	Blood triglycerides increased Blood cholesterol increased Weight increased Arterial occlusive disease Chest pain Blood glucose abnormal Hypoglycaemia White blood cell count increased Blood thyroid stimulating hormone increased Neutrophil count increased	15/810	Unknown	30 kg over 27 months/ Unknown	658	Unknown/288	51 (non-fasting)	The patient had angioplasty and open-heart surgery. The patient had a history of coronary artery disease.
47	US_001052572	48, M	Blood cholesterol increased Blood triglycerides increased Weight increased Blood glucose increased	20/540	Unknown	6.8 kg over 18 months/ BMI = 33	5873	Unknown/582	323	**Pre-existing diabetes.** The patient was treated with atorvastatin. Olanzapine was discontinued and his blood sugar and cholesterol normalized. Triglycerides decreased to 207mg/dl. The patient had a history or alcohol abuse, type II diabetes mellitus, hypercholesterolemia, and hyperlipidemia
48	US_001152687	52, M	Glucose tolerance impaired Weight increased Blood pressure increased Fluid retention	5/180	Unknown	17/3 kg over 6 months/ Unknown	Unknown	Unknown/ Unknown	Unknown	After 6 months of olanzapine treatment, the patient's hypertension was difficult to control. Olanzapine was discontinued. Borderline diabetes was diagnosed 17 months later. The patient had a history of hypertension.
49	US_001254588	49, M	Diabetes mellitus Hyperlipidaemia Body Mass Index increased	20/730	Unknown	10 kg over 5 months BMI = 29	995	Unknown/ Unknown	276	**Literature case.** After 24 months of olanzapine therapy, the patient developed diabetes. Olanzapine was discontinued and blood glucose normalized.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			Hyperinsulinaemia Hormone level abnormal Increased appetite Psychotic disorder Depression Blood prolactin increased							The patient had a history of being overweight.
50	US_001254605	53, F	Hyperlipidaemia Body Mass Index increased Hyperinsulinemia Hormone level abnormal	Unknown/ 75	Unknown	5 kg over 2.5 months BMI - 29	374	Unknown/ 321	119	**Literature case.** Olanzapine status and event outcomes are unknown.
51	US_001254607	57, F	Diabetes mellitus Hyperlipidaemia Body Mass Index increased Hyperinsulinaemia	Unknown/120	Unknown	10 kg over 4 months BMI = 30	361	Unknown/302	124	**Literature case.** After 4 months of olanzapine treatment, the patient also experienced hyperinsulinemia. Olanzapine status and event outcomes are unknown.
52	US_010259222	28, F	Weight gain Blood glucose increased Blood triglycerides increased Fatigue Increased appetite	20/730	Unknown	53.2 kg over 24 months/ BMI = 48.3	335	Unknown/212	153 (fasting)	The 2-hour glucose was 218mg/dl. Metformin therapy was started. Olanzapine was continued.
53	US_010769819	30, M	Weight increased Hypertension Blood cholesterol increased	10/1277	Unknown	27.3 kg over 3.5 years/ BMI = 38	Unknown	Unknown/ Unknown	Unknown	After 3-3.5 years of olanzapine treatment, the patient developed high blood pressure and increased cholesterol level. He was treated with valsartan and simvastatin. Olanzapine was continued.
54	US_011076520	34, M	Blood glucose increased Blood cholesterol increased Weight gain	Unknown/ 1095	Unknown	16.4 kg over 3 years/ BMI = 26.6	Unknown	Unknown/ Unknown	Unknown	Patient also received fluoxetine. In the 3 years after starting olanzapine, the patient's blood glucose and blood cholesterol were increased (no values provided). Olanzapine was continued.
55	US_020281559	38, M	Diabetes mellitus Hypertriglyceridaemia Weight increased	20/105	Unknown	4.5 kg over 3.5 months BMI = 34.48	966	Unknown/183	393	**Literature case.** After 3.5 months of olanzapine treatment, the patient was diagnosed with new onset diabetes mellitus.
56	US_020281563	44, M	Diabetes mellitus Hypertriglyceridaemia Blood cholesterol increased Weight increased	30/95	Unknown	9 kg over 6.5 months BMI = 39.14	7668	Unknown/856	131	**Literature case.** After 6.5 months of olanzapine treatment, the patient was diagnosed with new onset diabetes mellitus.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

57	US_020281594	38, M	Hypertriglyceridaemia Blood cholesterol increased Weight increased Blood glucose increased	15/270	Unknown	9.5kg over 9 months BMI = 37.10	669	Unknown/398	135	**Literature case.** Event outcomes are unknown. The patient had a history of hyperlipidemia.
58	US_020483478	-, M	Diabetes mellitus Weight increased Blood cholesterol increased Blood triglycerides increased	2.5/180	Unknown	Unknown/ Unknown	400	Unknown/260	Unknown	After therapy of unknown duration, the patient was diagnosed with moderate diabetes mellitus. Olanzapine was discontinued. Outcomes of the events are unknown.
59	US_020584499	32, M	Diabetic ketoacidosis Diabetic coma Hypercholesteraemia Blood glucose increased Obesity Glucose urine present Hepatic function abnormal	10/270	Unknown	Unknown/ Unknown	449	Unknown/345	1225	**Pre-existing diabetes.** After 9 months of olanzapine treatment, the patient developed diabetic ketoacidosis and diabetic coma. The diabetic ketoacidosis resolved and the olanzapine was discontinued. One month later, blood sugar was 174, cholesterol was 188 and triglycerides were 191. The patient had a history of diabetes mellitus and hyperlipidemia.
60	US_020584526	40, M	Diabetes mellitus Hyperlipidemia Hepatic steatosis Weight increased Blood pressure increased	20/210	Unknown	17 kg over 7 months/ BMI = 30.1	1214 (reported as acylglycerol)	Unknown/240	517	After 7 months of olanzapine treatment, patient was diagnosed with diabetes mellitus and moderate hyperlipidemia. Olanzapine was discontinued and the events resolved. The patient had a history of autism and liver damage from bromperidol and hepatic function disorder.
61	US_020584604	36, F	Hyperglycaemia Hyperlipidaemia Obesity Hyperphagia	10/270	Unknown	Unknown/ BMI = 25.6	2324	Unknown/481	254	After 10 weeks of olanzapine treatment, the patient's triglyceride level increased from 356 to 903mg/dl and she developed obesity. Nine months after starting olanzapine, triglycerides were 2324mg/dl. Olanzapine was discontinued and the hyperglycemia and hyperlipidemia abated (glucose 132mg/dl; triglyceride 280mg/dl) The patient had a history of mild hyperlipidemia and mild fatty liver.
62	US_020584623	66, M	Hyperglycaemia Weight increased Blood triglycerides increased Hyperphagia	20/300	Unknown	7 kg over 6.5 months/ BMI = 29.4	236	Unknown/144	778	Ten months after starting therapy, blood glucose was 778mg/dl. Olanzapine was discontinued. The hyperglycaemia and increased triglycerides resolved. Outcome of weight gain is unknown.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			Blood alkaline phosphatase increased Blood cholesterol decreased Protein total decreased Persecutory delusion Hallucination, auditory Hallucination, visual							The patient had a history of cerebral infarction, chronic hepatitis, hypertension, and chronic gastritis.
63	US_020684886	32, M	Hyperglycaemia Hyperlipidaemia Weight increased Convulsion	5/285	Unknown	Unknown/ BMI = 25.4	672	Unknown/262	406 (2 hour post-prandial)	**Pre-existing diabetes.** After 5 months of olanzapine treatment, the patient had a seizure and experienced a moderate weight increase (value not provided). Two weeks after the olanzapine was discontinued, the triacylglycerol was 672mg/dl, and the hyperglycemia and increased weight resolved. The patient had a history of non-insulin dependent diabetes mellitus, moderate epilepsy, and a family history of diabetes.
64	US_020887393	56, F	Hyperglycaemia Hyperlipidaemia Hepatic function abnormal Weight increased	10/210	Unknown	8 kg over 7 months/ BMI = 21.3	419	Unknown/298	584	Olanzapine was discontinued and the hyperlipidemia abated (cholesterol 258mg/dl from 298mg/ml; triglycerides 206mg/dl from 419mg/dl)
65	US_020988025	42, M	Hyperglycaemia Blood triglycerides increased Blood cholesterol increased Obesity	15/34	Unknown	6 kg over 1 month/ BMI = 26.6	253	Unknown/280	125 (fasting)	Olanzapine was discontinued and event outcomes were unknown.
66	US_030594564	36, M	Diabetes mellitus Blood triglycerides increased Weight increased Confusional state Thinking abnormal Mood swings	10/358	Unknown	29 kg over 6 months/ BMI = 28.7	345	Unknown/ Unknown	439	Patient was diagnosed with diabetes mellitus after 11 months of olanzapine treatment. Olanzapine was discontinued 36 days later. Diabetes was well controlled with metformin and triglycerides were 130mg/dl. The patient had a history of smoking, cocaine, marijuana and methamphetmine use, medication non-compliance, and head injury.
67	US_030695383	15, F	Hyperglycemia Obesity Blood cholesterol	20/2	Unknown	9 kg over 24 days/ Unknown	Unknown	Unknown/246	148 (fasting)	**Literature case.** Olanzapine was discontinued and the blood glucose decreased to 94mg/dl.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			increased Glycosylated haemoglobin increased							
68	US_030695387	17, F	Hyperglycaemia Obesity Blood cholesterol increased Mental impairment	20/56	Unknown	24 kg over 56 days/ Unknown	Unknown	Unknown/138	178	**Literature case.** Dietary restrictions were implemented and fasting glucose decreased to 102mg/dl. Patient had a history of attempted suicide related to a depressive exacerbation.
69	US_030695410	14, F	Hyperglycaemia Obesity Blood cholesterol increased Glycosylated haemoglobin increased	Unknown/84	Unknown	20.5 kg over 84 days/ Unknown	Unknown	Unknown/172	288	**Literature case.** The hyperglycaemia was controlled by dietary restrictions. The patient had a history of seizures.
70	US_0403101879	32, M	Weight increased Blood glucose increased Blood triglycerides increased Blood cholesterol increased	10/90	Unknown	5 kg over 3 months/ BMI = 27.5	233	Unknown/197	97	No baseline lab values were available. Olanzapine and the events continued.
71	US_980809227	20, M	Diabetes mellitus Hypertension Weight increased Increased appetite Sedation Anger Headache Delusion of grandeur	20/1460	Unknown	11.4 kg over 4 years/ Unknown	Unknown	Unknown/ Unknown	Unknown	Patient was diagnosed with Type I diabetes after 2 years of olanzapine treatment. Olanzapine was continued.
72	US_980910955	57, M	Blood glucose increased Blood cholesterol increased Weight increased Cerebrovascular accident Asthenia Anaemia Fatigue Sedation	15/1350	Unknown	23.6 kg over unknown period/ BMI = 30.3	Unknown	Unknown/ Unknown	Unknown	**Pre-existing diabetes.** Patient suffered a minor stroke and was hospitalized. All medications were discontinued. Olanzapine was not restarted. Patient has fully recovered. The patient had a history of diabetes, hypercholesteremia, and hypothyroidism.
73	US_990319390	24, M	Diabetes mellitus Weight increased Blood triglycerides	15/	Unknown	18.2 kg over 1 year/	Unknown	Unknown/ Unknown	340	Patient developed diabetes after 15 months of olanzapine treatment. Diet resulted in a 13.6 kg weight loss and blood glucose levels were

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			Blood triglycerides increased Blood cholesterol increased Weight decreased Alopecia Mononucleosis syndrome Aspartate aminotransferase increased Alanine aminotransferase increased			BMI = 30.3				weight loss and blood glucose levels were normal, glyburide was discontinued. Five months later, the blood glucose increased again. He was switched to quetiapine, but it did not work for him and olanzapine was restarted. Also, his cholesterol and triglyceride levels were reported as very high but no values were provided. The olanzapine was continued because of its effectiveness for him. Event outcomes were unknown. Concomitant medication: lithium.
74	US_990319516	28, F	Hyperglycaemia Blood triglycerides increased Blood cholesterol increased Urinary tract infection Glycosuria Polyuria Polydipsia	30/270	Unknown	Unknown/ BMI = 35.4	1019	Unknown/273	189 (fasting)	Blood sugar was regulated with diet and exercise. Outcomes of other events are unknown. The patient had a history of obesity.
75	US_990725007	45, M	Hyperglycaemia Weight increased Blood cholesterol increased Blood triglycerides increased Pitting oedema Bilantis candida	10/30	Unknown	11.4 kg over 1 month/ BMI = 32.5	2337	Unknown/325	400	**Pre-existing diabetes.** **Literature case.** Patient had been taking fluoxetine, haloperidol and thioridazine prior to olanzapine therapy. Patient experienced 3+pitting oedema and weight gain 1 day after starting olanzapine. Olanzapine was discontinued after 3 months of therapy. Within 1 week, his blood glucose returned to normal with glyburide 5 mg BID only. Other event outcomes were unknown. The patient had a history of hypertension and diabetes.
	Total 75 cases									

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Cases identified by second MedDRA Preferred Term search and/or Textstring search for metabolic syndrome/ Insulin resistance / Syndrome X phrases

Case No	Case ID	Age, Sex	MedDRA Preferred Terms	Olanzapine dosing/ duration (mg/ days)	Blood Pressure (mmHg)	Weight Gain/ BMI	Peak serum triglyceride (mg/dL)	Cholesterol HDL/Total (mg/dL)	Blood Glucose (mg/dl)	Comments
1	CA_010503671 **(found with "insulin resistance" term)**	31, M	Diabetes mellitus Diabetic hyperosmolar coma Psychotic disorder Weight increased	20/30 History of intermittent olanzapine use x 240-days	Unknown	12 kg / Unknown	Unknown	Unknown/ Unknown	268 (fasting) 15 days prior to death. 898 (on autopsy)	**Fatal outcome.** Found dead in bed at home. **Literature case: patient noted to have insulin resistance.** Paranoid schizophrenic with bizarre delusions. Had medication compliance issue but was noted to have been compliant for 30-days prior to death. Autopsy ruled cause of death: hyperosmolar non-ketotic diabetic coma.
2	CA_030305793 **(found with "insulin resistance" term)**	28, M	Diabetic ketoacidosis Coma	10/540	Unknown	Unknown/ BMI = 38.1	Unknown	Unknown/ Unknown	1020 (upon admission)	**Considered as insulin resistance case by reporter**. Olanzapine stopped /patient recovered. Lipid value not provided.
3	DE_000602613 (**found with "metabolic syndrome" term)- also found in lipid table.**	36, M	Diabetes mellitus non-insulin dependent Weight increased	10/ 90	Unknown	Unknown/ BMI = 37.8	508	Unknown / 384	342	**Literature case. Classified as metabolic syndrome by reporter.** Olanzapine continued. Metformin & repaglinide started for diabetes diagnosis. Had history of lipid elevation and hyperglycemia prior to olanzapine.
4	EWC000606856 **(found with "insulin resistance" term)**	51, F	Diabetic coma	15/56	140/60	Unknown/ BMI = 32.1	198	29/197	371	Patient considered as hyperosmolar with severe ketoacidosis. Insulin therapy started with improvement. Hemoglobin A1c: 14.2%. Olanzapine dose reduced and stopped. Insulin withdrawal tried and failed.
5	GBS030513113 **(from PT search-insulin resistance)**	61, F	**Insulin resistance** Glycosylated haemoglobin increased Hyperosmolar state	Unknown/ Unknown	Unknown	Unknown/ BMI = 39.0	529	Unknown/304	Unknown (HgbA1c:: 10-13%).	**Literature case.** Newly diagnosed diabetic patient with dyslipidemia and glucose control problems. Placed on metformin and a statin medication. Admitted to hospital with BS control issues in a hyperosmolar state. Started on insulin therapy and olanzapine was dechallenged. Six months later HgbA1c: 6.1% and insulin requirements had reduced. No comment regarding lipids.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

6	USA020515135 **(found with "syndrome X" term)**	45, M	Blood glucose increased Weight increased Fatigue Polydipsia Polyuria Hallucinations visual	15/210	History of hypertension (no values)	Unknown amount/ Unknown	History of lipid elevations. No values provided.	Unknown/ Unknown lipids elevated	400	**Reporter termed the case syndrome X.** Developed diabetes along with weight gain. Change in lipids not noted. History of hypertension/lipid elevation and alcohol dependence.
7	USA020616842 **(found with "syndrome X" term)**	-, M	Lipids increased Angina pectoris Prescribed overdose	40/Unknown	Unknown	Unknown/ Unknown	Increased lipids (no values provided)	Unknown/ Increased (no value)	Unknown	**Reporter considered patient to have syndrome X.** Case coded in error to angina pectoris ! Olanzapine dose reduced and therapy continued. Other intervention not provided.
8	USA030947448 **(found with "metabolic syndrome" and "insulin resistance" terms)**	65, F	Diabetes mellitus Blood triglycerides increased	5/300	Unknown	Unknown/ BMI = 25.5	706	Unknown/ Unknown	299	**Olanzapine noted by reporter to exacerbate the markers of metabolic syndrome.** Patient had baseline high triglycerides (400mg/dl) and fasting blood glucose of 115mg/dl. Diagnosed with non-insulin dependent diabetes Pioglitazone therapy started. Olanzapine underwent a positive dechallenge.
9	USA030947450 **(from PT search – insulin resistance)**	33, M	**Insulin resistance** Blood glucose increased Blood glucose decreased Prescribed overdose Bipolar disorder Incoherent Dizziness	40/Unknown	Unknown	Unknown/ Unknown	300	Unknown/ Unknown	495 160 (fasting)	Patient blood glucose control issues. Pioglitazone and metformin therapy started. Patient had fluctuating blood glucose. Olanzapine, metformin and pioglitazone were all stopped. Olanzapine underwent a negative dechallenge as blood glucose remained elevated (137mg/dl). **Case can also be found in triglyceride elevation table.**
10	US_011278580 **(found with "metabolic syndrome" term)**	27, M	Diabetes mellitus Hyperglycaemia Ketonuria Acidosis Agitation Aggression Blood potassium increased Blood urea nitrogen increased Thrombocytopenia Folliculitis Hypoglycemia Incontinence	15/570	Unknown	Unknown/ BMI = 27.0	Unknown	Unknown/ Unknown	1240	**Literature case. Reporters considered patient at high risk for metabolic syndrome.** Black male hospitalized with blood glucose of 1240 mg/dl and arterial blood pH of 7.3. Insulin infusion started. Olanzapine continued and valproic acid stopped. Insulin requirement did not change after stop of valproic acid.
11	US_020483750 **(from PT search – insulin resistance)**	39, M	**Insulin resistance** Diabetes mellitus Hypertriglyceridaemia Type IIB hyperlipidaemia	15/42	Unknown	Unknown/ Unknown	2087	Unknown/ Unknown	578	**Literature case.** Severe insulin resistance noted by reporter. Patient developed diabetes mellitus and hyperlipidemia and started insulin therapy. Olanzapine was dechallenged. Blood glucose did not normalize.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			Polydipsia							
12	US_020584425 **(found with "insulin resistance" term)**	46, M	Diabetes mellitus Glucose tolerance impaired Hyperlipidaemia	5/11	Unknown	Unknown/ BMI = 24.8	321	38 /286	227l	History of mild lipid elevation. Treated for elevated lipids prior to olanzapine. Developed increased lipids and blood glucose elevation after start of olanzapine. Diagnosed with diabetes. Olanzapine underwent a positive dechallenge. (blood glucose lowered to normal limits and lipids lowered)
13	US_990319397 **(found with "insulin resistance" term)**	32, M	Hyperglycaemia	20/42	History of hypertension	Unknown/ BMI = 34.4	Unknown	Unknown/ Unknown	402	Black male with normal baseline blood glucose. Blood glucose values elevated-diabetes diagnosed and insulin therapy started. Olanzapine underwent a positive dechallenge-however, insulin continued throughout. Over next 60-days blood glucose averaged 103mg/dl-insulin stopped. Eight months later, olanzapine **underwent a positive rechallenge** (blood glucose: 254mg/dl.
	Total **13 cases**									

	Total **88 cases**									

Insert Table 4X: i.e. Metabolic Syndrome MedWatch Reports from GPS

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

4. Lipids and Cholesterol Appendix (listing of tables referenced in Section 2)

Table 5X. Frequency table to reports with elevated Triglycerides

Cases (n= 173) with Triglyceride Values greater than or equal to 500mg/dl
Preferred Terms (non-searched) by Decreasing Frequency

Adverse Events by Preferred Term	# Events
Diabetic ketoacidosis	**7**
Hepatic steatosis	**6**
Pancreatitis	**6**
Pancreatitis acute	**5**
Alanine aminotransferase increased	4
Aspartate aminotransferase increased	4
White blood cell count increased	4
Chest pain	**3**
Depression	3
Gamma-glutamyltransferase increased	3
Headache	3
Hepatic function abnormal	3
Ketoacidosis	**3**
Xanthoma	**3**
Abdominal pain upper	2
Blood alkaline phosphatase increased	2
Blood creatinine increased	2
Cataract	2

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Convulsion	**2**
Diabetic hyperosmolar coma	**2**
Diarrhoea	2
Hallucination auditory	2
Hepatic enzyme increased	2
Ketonuria	2
Liver function test abnormal	2
Proteinuria	2
Psychotic disorder	2
Respiratory Failure	2
Tachycardia	2
Abdominal pain	1
Acanthosis nigricans	1
Aggression	1
Agitation	1
Amenorrhoea	1
Angina pectoris	1
Anxiety	1
Arterial occlusive disease	**1**
Balanitis candida	**1**
Blood LDH increased	1
Blood prolactin increased	1
Blood thyroid stimulating hormone increased	1
BUN increased	1
Cardio-respiratory arrest	**1**
Cerebrovascular accident	**1**
Confusional state	1
Dehydration	1
Delirium	1
Delusion	1
Dilatation atrial	1

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Diverticulum	1
Dizziness	1
Dyskinesia	1
Electrocardiogram T wave abnormal	1
Eye disorder	**1**
Fatigue	1
Gastrointestinal haemorrhage	1
Haemoglobin increased	1
Haemorrhoidal haemorrhage	1
Hallucination visual	1
Hallucinations	1
Healing impaired	1
Hepatitis granulomatous	**1**
Hepatocellular damage	**1**
Hip fracture	1
Hormone level abnormal	1
Hyperosmolar state	**1**
Hypertension	1
Ingrown toenail	1
Insomnia	1
Leukocytosis	1
Lipid metabolism disorder	1
Liver disorder	1
Macular degeneration	1
Malaise	1
Mood altered	1
Nausea	1
Nervousness	1
Neutrophil count increased	1
Ocular icterus	1
Oedema	**1**

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Oedema peripheral	1
Pancreatic necrosis	**1**
Pancreatic pseudocyst	**1**
Photophobia	1
Pitting oedema	**1**
Platelet count increased	1
Pneumonia	1
Pneumonia mycoplasmal	1
Psychiatric symptom	1
Pulmonary embolism	**1**
Rash	1
Reflux oesophagitis	1
Renal insufficiency	1
Retching	1
Sedation	1
Sensory loss	1
Somnolence	1
Stomatitis	1
Syncope	1
Testis cancer	1
Thrombosis	1
Tremor	1
Triple vessel bypass graft	**1**
Upper respiratory tract infection	1
Urinary tract infection	1
Ventricular hypertrophy	**1**
Vertigo postural	1
Vision blurred	1
Visual disturbance	1
Vomiting	1

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Table 5.5X: Overview of Elevated Triglycerides Cases > 500 mg/dL

OVERVIEW OF ELEVATED TRIGLYCERIDE CASES ≥ 500mg/dl

All cases found with the LIPID search methodology were examined for the peak serum triglyceride level regardless of whether the blood draw was fasting, random or postprandial. The vast majority of cases did not describe the timing of the blood draw and therefore all values were assumed to be fasting serum triglyceride values.

Demographics:

Triglyceride Category	***Male***	***Female***	***Unknown***	***Total***
≥ 500mg	131	37	5	173
Percentage	**76%**	**21%**	**3%**	**100%**

- 76% of all patients with serum triglyceride ≥ 500mg/dl were males
- 78% of all patients with a stated gender (n= 168) were males

Triglycerides ≥ 500mg/dl	**Mean age in years**	**Age range in years**	**Cases with gender and age**
Male	36.3	10 to 64	121
Female	43.7	15 to 80	33
Overall	**37.9**	**10 to 80**	**154**

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

- There were 19 cases of 173 whereby both gender and age could not be determined
- Eight patients among the 173 reports were age ≤ 19 years of age

Triglyceride elevations:

Serum triglyceride level	**Number of cases**	***Mean serum level***	**Range of serum elevation**
Reports ≥ 500mg/dl	173	1820mg/dl	500mg/dl to 12,000mg/dl

Serum triglycerides ranges	**Number of case reports**	**Percentage of total**
≥ 500mg to 999mg/dl	79	45.7%
≥ 1,000mg to 5,000mg/dl	81	46.8%
>5,000mg to 10,000mg/dl	12	6.9%
> 10,000 mg/dl	1	0.6%
Total	**173**	**100%**

- 12,000mg/dl is the highest triglyceride serum level in the database- patient developed diabetes but no other clinical events described at time of peak triglyceride level
- Pancreatitis seen in 14 of the 173 case reports with serum triglycerides ≥ 500mg/dl
- Four cases among the 173 reports had a fatal outcome

Overview of fatal outcome cases:

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Case **(USA020515251)** concerned a 20-year-old African American male with a body mass index of 29.8 that died from respiratory failure. It is case #14 in Appendix A. The patient had a history of elevated cholesterol, renal insufficiency, pulmonary disease, mild amylase elevations and mild lipase elevations. The patient had no history of diabetes mellitus or diagnosed pancreatitis. The patient had a family history of diabetes mellitus. The patient was not considered to be an alcoholic. Olanzapine had been administered for approximately 4 ½ years in the treatment of schizophrenia. Concomitant medications included clonazepam, haloperidol decanoate, risperidone and trazodone. The baseline laboratory values prior to the start of olanzapine were serum cholesterol 242mg/dl, serum triglycerides 56mg/dl and fasting blood sugar 101mg/dl. No other baseline laboratories were provided. Upon admission to the hospital, the patient laboratory values were non-fasting blood sugar 736mg/dl, serum cholesterol 539mg/dl, HDL cholesterol 26mg/dl, serum triglycerides 3189mg/dl, urinary ketones 3+, plasma osmolality 287.5, blood urea nitrogen 23mg/dl and arterial blood pH of 7.148. The patient was diagnosed with diabetic ketoacidosis. Respiratory failure ensued leading to death.

Assessment and comments of Eli Lilly: The patient had a significant elevation of serum triglycerides (3189mg/dl). Four of the 5 factors of metabolic syndrome were present (hyperglycemia, hypertriglyceridemia, elevated body mass index and lowered HDL cholesterol). Values for the fifth factor (blood pressure) were not provided. The elevations in amylase and lipase during olanzapine therapy may be suggestive of an underlying undiagnosed pancreatitis. Diabetic ketoacidosis and the acid-base imbalance are the most important components in the patient outcome. The obesity and family history of diabetes mellitus are notable.

Case **(USA031050393)** concerned a 24-year-old male weighing 116 kilograms (no BMI) that died due to nonketotic hyperosmolar coma and pancreatitis. A blood sugar measured 2-years prior to death was 101mg/dl. The patient had taken olanzapine intermittently for about 6-years. Olanzapine had been discontinued and restarted 3-times over the course of therapy. Patient had received olanzapine consistently for about 2 ½ years prior to the hospital admission. Concomitant medications included trazodone, paroxetine and quetiapine. The patient had a 3-day history of nausea, emesis and abdominal pain along with excessive soda intake prior to hospital admission. Laboratory values were blood sugar 1214mg/dl, serum triglycerides 2195mg/dl, lipase 414 and white blood cell count 18,400. An enlarged pancreas was discovered. The patient according to the reporter did not have any known medical conditions at the time of hospital admission other than mental disease.

Assessment and comments of Eli Lilly: The patient had a significant elevation of serum triglycerides (2195mg/dl) upon hospital admission. No history of diabetes or other medical conditions according to reporter. Patient had suffered from chronic paranoid schizophrenia as the only known medical condition. It is not possible in this case to determine the sequence of the pancreatitis and DKA. It is conceivable that the DKA developed leading to the pancreatitis. The elevation of triglycerides might have placed the patient at risk leading to the pancreatitis. The patient does have factors suggesting metabolic syndrome may have taken place (weight: 116 kg, triglyceride elevation, blood sugar elevation in a non-diabetic).

.

Case **(FR_020100595)** was a 35-year-old male with a body mass index of 23.1 and a history of Klinfelter's syndrome, brucellosis along with chronic complaints of leg pain and fatigue that died while on olanzapine. The patient had taken olanzapine for approximately 15-months when the patient underwent a "biological" check-up and the following laboratory values were discovered: blood sugar: 478mg/dl, serum triglycerides: 895mg/dl, hemoglobin A1c: 13.3%, acetone and

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

protein in urine. The patient was diagnosed with diabetes mellitus. Olanzapine was discontinued the same day as the laboratory abnormalities were discovered. Ten days later the patient was found dead by his mother. The reporting physician determined the cause of death was ketoacidosis. It was observed by the reporter that the patient had no history of suicidal ideation or history of alcohol ingestion. The reporter could not provide evidence of ketoacidosis at the time of death. No autopsy was performed. The patient had not been taking any concomitant medications.

Assessment and comments of Eli Lilly:

The patient did not fit the criteria for metabolic syndrome. Only elevated triglycerides and elevated blood sugar with a diagnosis of diabetes were noted. The patient had experienced a weight gain (amount not provided) but had a BMI of 23.1. The patient had not taken olanzapine for 10-days at the time of his death. The case does not provide sufficient evidence that any acute changes had taken place in the direction of an acid-base imbalance at the time of death. The examination that determined lab abnormalities was 10-days prior to the death. The death occurring on an outpatient basis and the lack of an autopsy severely limits the ability to assess this case.

Case **(US_011178209)** involved a 29-year-old Asian male with a BMI of 31.1, baseline blood sugar: 137mg/dl, baseline triglycerides: 547mg./dl and baseline cholesterol: 278mg/dl prior to starting olanzapine. In addition, the patient had a history of liver enzyme elevations (ALT, AST, GGT), drug-induced Parkinsonism, schizophrenia and autistic tendencies. Concomitant medications included timiperone, biperiden, cloxazolam and fenofibrate. The patient had no history of diabetes but had displayed hyperglycemia as evidenced by the baseline blood sugar of 137mg/dl. In addition, 30-days after the start of olanzapine the blood sugar was 230mg/dl. Olanzapine had been administered for approximately 40-days when a blood sugar of 723mg/dl, cholesterol of 362mg/dl, serum triglyceride of 960mg/dl, glycosuria, ketonuria and a hemoglobin A1c of 15.4% were discovered and the patient went into cardio-respiratory arrest. The patient was resuscitated and admitted to the hospital. A diagnosis of diabetic coma was made and the blood sugar had peaked at 854mg/dl upon admission. Treatment was initiated and the patient died some 72-hours later. The patient had suffered hypoxia due to the cardio-respiratory arrest and did not display normal brain activity after admission. The diabetic coma was considered to be a hyperosmolar hyperglycemic nonketotic coma.

Assessment and comments of Eli Lilly:

The patient had elevated triglycerides and blood sugar prior to olanzapine therapy. In addition, the patient had a recent weight loss yet the BMI still remained greater than 30. It would appear the patient had metabolic syndrome prior to olanzapine. The patient may have had an undiagnosed diabetes mellitus prior to the start of olanzapine. However, it is acknowledged that the blood sugar values worsened after the start of olanzapine. A positive patient outcome was severely compromised by the cardio-respiratory arrest and resultant brain hypoxia.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Table 6X: Triglycerides line listings

LIPID ANALYSIS- Case Reports within Clintrace with Serum Triglycerides ≥ 500mg/dl (n = 173)

#	Case ID	Age/ Sex	MedDRA preferred term(s)	Olanzapine dosing	Concomitant Medications	Medical history	Peak serum triglyceride value / Metabolic syndrome	Acute clinical issues/ Comments
1	AU_011004259	Unk/M	Blood triglycerides increased, Blood cholesterol increased	Unknown dosing	Sertraline	Baseline cholesterol: 267mg/dl & triglyceride: 226mg/dl. Other history not provided.	1418mg/dl Metabolic syndrome: serum triglyceride increase only.	Patient has not had any significant weight gain. Cholesterol increased to 553mg/dl and serum triglyceride from 226 to 1418mg/dl. Olanzapine disposition unknown.
2	DE_010205189	43/ F	Blood triglycerides increased, Blood cholesterol increased, ALT increased, AST increased, GGT increased	10mg daily x 22-days	None	Unknown medical history. BMI: 30.6. No family history hyperlipidemia.	1500mg/dl Metabolic syndrome: (3 of 5 factors) 1. HDL decreased, 2. BMI > 30 and 3. triglyceride increased even at baseline !	Baseline serum triglyceride: 188mg/dl. Baseline cholesterol 188mg/dl. Olanzapine given 3 days: triglyceride: 1486mg/dl / cholesterol 361mg/dl / HDL cholesterol: 39mg/dl. Olanzapine stopped/ status of lipids unknown.
3	DE_991001623	55/ F	Blood triglycerides increased	15mg daily x 42-days	Mirtazapine	Baseline triglycerides: 267mg/dl. BMI:	1440mg/dl.	Blood sugar and body weight remained unchanged on

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

						25.6. Cholesterol listed as pathologically elevated (no values).	Metabolic syndrome: BMI > 25 and triglycerides: 1440mg./dl. Only 2 of 5 factors.	olanzapine. Serum triglycerides: 864mg/dl 2-days into therapy. Dechallenge of olanzapine: triglycerides: 640mg/dl. Negative dechallenge. Cholesterol unchanged throughout olanzapine therapy.
4	EWC021233288	42/ M	Blood triglycerides increased	10mg daily x 750-days	Verapamil, lithium	BMI: 34.4 , hypertension, Baseline triglyceride: 1148mg/dl.	4430mg/dl Metabolic syndrome (3 of 5 factors) hypertension, BMI: >30 and triglycerides: 1148mg/dk and higher. Preexisting metabolic syndrome.	Serum triglyceride level increased on olanzapine. Olanzapine stopped/ simvastatin started/ triglycerides within normal range (no value).
5	GBS031214219	60/ M	Blood triglycerides increased, Blood cholesterol increased	30mg daily 540-days	Pantoprazole, atenolol	Hypertension, BMI: 24.6	5269mg/dl Metabolic syndrome: (2 of 5 factors) hypertension and elevated triglycerides.	Cholesterol and triglycerides elevated. Cholesterol: 813mg/dl. No baseline values. Olanzapine discontinued and statin therapy started. No outcome.
6	JP_030901751	25/ M	Blood triglycerides increased, Hyperglycaemia, Weight increased,	10mg daily x 180-days	Brotizolam	Baseline triglycerides: 327mg/dl. BS: 220mg/dl non-	1041mg/dl Metabolic syndrome:	Had 35-lb weight gain. Unknown BMI. Serum triglycerides elevated from 327 to

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			hepatic function abnormal, Headache, Abdominal pain, Diarrhoea			fasting.	(2 of 5 factors) serum triglycerides: 327mg/dl baseline and BS 220mg/dl.	1041mg/dl. Olanzapine stopped.
7	US97011894A	33/ M	Blood triglycerides increased	10mg daily x 45-days	None	Baseline serum triglycerides: 700mg/dl. BMI: 20.9 (thin). Family history of elevated triglycerides.	3000mg/dl Metabolic syndrome: (1 of 5 factors) elevated serum triglycerides.	Olanzapine therapy discontinued and lipid lower agent started. Triglycerides increased 4.5-fold.
8	US97051090A	44/ M	Blood triglycerides increased	20mg daily x unknown duration	Benztropine, carbamazepine, lithium, lorazepam, chloral hydrate	BMI: 25.8. No medical history provided.	2000mg/dl Metabolic syndrome: (1 of 5 factors) triglycerides increased.	Triglyceride levels have been steadily rising since olanzapine therapy. No baseline values. Olanzapine disposition unknown.
9	US97061336A	24/ M	Blood triglycerides increased, **Pancreatitis acute**	15mg daily x 180-days	Fluoxetine, gemfibrozil, benztropine	BMI: 30.4. Serum triglycerides: 609mg/dl while on clozapine.	1627mg/dl Metabolic syndrome: (2 of 5 factors) BMI: 30.4 and triglycerides elevated.	Patient had 2 bouts of acute pancreatitis while on olanzapine. Olanzapine dechallenged: triglycerides 155mg/dl.
10	US97092872A	15/ F	Blood triglycerides increased, Liver function test abnormal	10mg daily x unknown duration	Clonidine, loratadine, chlorpromazine	BMI: 21.2 behavior problems along with mood disorder, Other history unknown.	1500mg/dl Metabolic syndrome: (1 of 5 factors) triglycerides	Minimal information. Noted to have had large increase in triglycerides (baseline unknown) along with increase in liver function tests (no

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

							elevated.	values).
11	US97114114A	Unk	Blood triglycerides increased	Unknown dosing	Unknown	No medical history provided. No baseline values of lipids provided.	1200mg/dl Metabolic syndrome: (1 of 5 factors) Serum triglycerides 1200mg/dl	Lack of information does not allow an assessment of this case. Olanzapine treatment duration unknown.
12	USA020110568	53/ M	Blood triglycerides increased, Weight increased, Diabetes mellitus	7.5mg daily x 365-days	Perphenazine (tapered and stopped while on olanzapine), paroxetine, sertraline, minocycline, docusate sodium (paroxetine and sertraline not used concurrently-paroxetine switched to sertraline)	Cholesterol: 116mg/dl. However, medical history not provided. Reporter stated medical history was negative for significant medical problems.	1220mg/dl Metabolic syndrome: (3 of 5 factors) BS: 800mg/dl, triglycerides elevated, obesity (224lbs)	Blood sugar: 800mg/dl. Glycosylated hemoglobin: 20. African-American. First BS screening 6-months into therapy: 557mg/dl. No history of diabetes. Olanzapine discontinued.
13	USA020211675	29/ M	Blood triglycerides increased, Blood cholesterol increased, Blood glucose increased, HDL cholesterol decreased, Glycosylated hemoglobin increased	5mg daily x 90-days	Bupropion, lansoprazole	BMI: 25.8. History of obesity and family history of diabetes. BS: 301mg/dl. HDL cholesterol: 5mg/dl.	7067mg/dl Metabolic syndrome: (4 of 5 factors) 1.BMI > 25 2. triglycerides elevated 3.HDL choles lowered 4.BS elevated.	Olanzapine administered for 90-days when fasting blood sugar: 301mg/dl and serum triglycerides 7067mg/dl, HDL: 5mg/dl, HgbA1c: 9.4. . Total cholesterol listed as 614mg/dl. Olanzapine underwent dechallenge. Metformin and atorvastatin started. 30-days later

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

								triglycerides 149mg/dl and fasting BS 116mg/dl.
14	USA020515251	20/ M	Blood triglycerides increased, Blood cholesterol increased, **Diabetic ketoacidosis**, Ketonuria, **Respiratory failure**	15mg daily x 1640-days	Clonazepam, trazodone, risperidone, haloperidol	BMI: 29.8. Family history of diabetes. Elevated cholesterol history. History of renal insufficiency and mildly elevated lipase/amylase.	3189mg/dl Metabolic syndrome (4 of 5 factors) 1. BMI> 25, 2. BS 736mg/dl 3. HDL choles: 26mg/dl 4.triglycerides: 3189mg/dl	**Fatal outcome.** African-American with baseline cholesterol 242mg/dl, fasting BS: 101mg/dl and. triglycerides 56mg/dl prior to olanzapine. Long term olanzapine-upon acute changes: BS 736mg/dl. Cholesterol 539mg/dl., triglycerides 3189mg/dl, HDL cholesterol: 26mg/dl. DKS ensued with respiratory failure.
15	USA020515701	Unk/ F	Blood triglycerides increased	Unknown dosing	Unknown	Medical history was not provided.	1000mg/dl Metabolic syndrome: (1 of 5 factors) elevated serum triglycerides	Information is not sufficient in the case to make an assessment.
16	USA020718851	42/ F	Blood triglycerides increased, **Pancreatitis,** Prescribed overdose, Drug interaction, Pneumonia	30mg daily x unknown duration	Valproic acid, insulin, metformin, omeprazole, simvastatin	History of elevated triglycerides (1200mg/dl), history of diabetes and gallstones.	8000mg/dl Metabolic syndrome: (3 of 5 factors) existing diabetes + BS 300mg/dl, elevated	Patient admitted to hospital with pancreatitis thought to be induced by elevated triglycerides. Amylase: 517. CT scan was diagnostic. Both valproic acid and olanzapine were stopped. Triglycerides

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

							triglycerides, BMI: unknown but is 194 lb female.	225mg/dl and amylase: 60 some 6-weeks later. Reporter proposed drug interaction: olanzapine with valproic acid leading to pancreatitis.
17	USA030330760	50/ M	Blood triglycerides increased, Blood cholesterol increased, HDL cholesterol decreased	Unknown daily dose x 90-days	None	Unknown medical history. Cholesterol: 360mg/dl, HDL choles: 33mg/dl	2521mg/dl Metabolic syndrome: (2 of 5 factors) HDL choles reduced and elevated triglycerides.	Olanzapine dose reduced but not withdrawn. Cholesterol and triglycerides elevated. HDL cholesterol lowered. Outcome of dose reduction unknown.
18	USA030536235	Unk/ M	Blood triglycerides increased, Weight increased	Unknown daily dosing x 30-days	None	Medical history nor provided.	1100mg/dl Metabolic syndrome: (2 of 5 factors) elevated triglycerides and potentially high BMI	Patient experienced a 30-lb weight gain over 30days. BMI unknown. Olanzapine dechallenged. Outcome unknown.
19	USA030538206	Unk	Blood triglycerides increased	Unknown dosing	None	No medical history.	3000mg/dl Metabolic syndrome: (1 of 5 factors) elevated serum triglycerides	Serum triglycerides elevated and olanzapine dechallenged. The triglycerides reportedly lowered but value not provided.
20	USA030741079	34/ M	Blood triglycerides increased, Blood cholesterol increased	Unknown dosing	Paroxetine	No medical history. Social history: non-smoker and non-drinker.	1000mg/dl Metabolic syndrome: (1 of 5 factors)	Patient on olanzapine experienced elevated cholesterol: 500mg/dl and elevated triglycerides. Olanzapine was

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

							elevated triglycerides	continued.
21	USA030946310	Unk/ M	Blood triglycerides increased, Glycosylated hemoglobin increased, Diabetes mellitus, Abnormal behaviour	15mg daily x unknown duration	Glimepiride, aspirin, amlodipine, metoprolol, quinapril	Alcohol use and history of enlarged abdomen. Ascites? Consumer reporter.	1300mg/dl Metabolic syndrome (2 or 3 of 5 factors) Blood sugar: elevated and elevated triglycerides. Possible elevated blood pressure.	Glycosylated hemoglobin: 13. Blood sugar: 600mg/dl. Patient diagnosed with diabetes. Olanzapine continued. Concomitant medications suggest hypertension.
22	USA030948449	45/ M	Blood triglycerides increased, Blood glucose increased	Unknown dosing	Gemfibrozil	History of diabetes. Considered borderline obese. BMI: unknown.	3600mg/dl Metabolic syndrome: (2 of 5 factors) elevated triglycerides and obesity ?	African-American male developed increased serum triglycerides. Placed on gemfibrozil (reduction to 607mg/dl). Measured sometime later and triglycerides were 2300mg/dl. Olanzapine continued throughout.
23	USA031153125	32/ M	Blood triglycerides increased, Blood glucose increased, **Diabetic ketoacidosis**, Weight increased, Blood cholesterol increased DKA listed as possible with only symptoms	15mg daily x 570-days	Escitalopram	No medical history. BMI: 38.3	2458mg/dl Metabolic syndrome: (4 of 5 factors) 1. BMI: 38.3 2. BS: 249mg/dl 3. HDL choles:	Olanzapine administered for 19-months when labs checked. Cholesterol: 374mg/dl, HDL cholesterol: 30mg/dl, fasting glucose: 249mg/dl. Olanzapine underwent a negative dechallenge. Diagnosis of

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			described as polyuria and polydipsia.				30mg/dl 4. elevated triglycerides	DKA not supported by information.
24	USA040156734	45/ F	Blood triglycerides increased, Diabetes mellitus, Blood cholesterol increased, Prescribed overdose	30mg daily x 1460-days	Venlafaxine, quetiapine	History of hepatitis C and hyperlipidemia. No history of diabetes.	1650mg/dl Metabolic syndrome: (2 of 5 factors) increased blood sugar and elevated triglycerides.	Patient developed increased fasting BS (322mg/dl), elevated cholesterol (288mg/dl) and triglycerides (1650mg/dl) on olanzapine. Olanzapine discontinued and values decreased slightly. Olanzapine rechallenged and BS went to 475mg/dl. Patient diagnosed with Type-II diabetes.
25	USA040259311	Unk/ M	Blood triglycerides increased	Unknown dosing	Unknown	No medical history	1000mg/dl Metabolic syndrome: (1 or 5 factors) elevated triglycerides	Olanzapine administered for unknown period and triglycerides elevated. Baseline triglycerides were unknown. Same reporter as case #26.
26	USA040259321	Unk/ M	Blood triglycerides increased, Weight increased	Unknown dosing	Unknown	Medical history not provided.	1000mg/dl Metabolic syndrome: (1 of 5 factors) elevated triglycerides	Olanzapine associated with weight gain and elevated triglycerides. Baseline weight and triglycerides unknown. Same reporter as case #25.
27	USA040260217	27/ M	Blood triglycerides increased, Blood cholesterol increased,	20mg daily x unknown duration	Quetiapine, escitalopram, valproic acid	Infantile seizures, functioning autistic patient, depression and	1000mg/dl Metabolic syndrome:	Patient experienced elevated cholesterol (380mg/dl), elevated triglycerides, and 60-lb

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			Weight increased, **Oedema,** Sensory loss, Healing impaired, Ingrown toenail, Cataract			psychosis. Asperger's syndrome. Baseline weight and/or BMI not known.	(1 or 2 of 5 factors) elevated triglycerides and potential obesity.	weight gain. Olanzapine had been given for unknown period. Also experienced hand, face and feet swelling. Fasting blood sugars were normal. Olanzapine was continued.
28	USA040362893	37/ M	Blood triglycerides increased, Blood cholesterol increased, Weight increased	5mg daily x 210-days	Perphenazine, carbamazepine, propranolol, citalopram	No baseline lipid values. Medical history not provided. Upon olanzapine dechallenge: triglycerides 223mg/dl and total cholesterol 268mg/dl.	3930mg/dl Metabolic syndrome: (2 of 5 factors) elevated triglycerides, HDL choles: decreased 30mg/dl)	Patient experienced a 30-lb weight gain along with elevated cholesterol (554mg/dl), and elevated triglycerides. Olanzapine was discontinued. Lipids lowered but did not reach normal. HDL lowered (30mg/dl). Used low fat diet and atorvastatin with dechallenge of olanzapine.
29	US_000336807	50/ M	Blood triglycerides increased, **Ketoacidosis**	10mg daily x 180-days	.Doxepin, gabapentin, bupropion	BMI: 35.3. Family history of diabetes. No personal history of diabetes. Case probably a DKA rather than ketoacidosis.	7310mg/dl Metabolic syndrome: (4 of 5 factors) BMI > 30, elevated triglycerides, elevated blood sugar and decreased	Olanzapine started & baseline fasting BS: 110mg/dl. Fasting BS elevated to 479mg/dl. Olanzapine dechallenged. Patient has HgbA1c : 17, blood pH: 7.21 and elevated serum triglycerides. Amylase/lipase within normal limits. Lab values after

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

							HDL cholesterol: 22mg/dl.	dechallenge: cholesterol: 269mg/dl, HDL choles: 22mg/dl, triglycerides: 361mg/dl.
30	US_001052563	35/ M	Blood triglycerides increased, Blood cholesterol increased, Increased appetite, Delusion	15mg daily x 120-days	Nefazodone	History of substance abuse and mood disorder.	1817mg/dl Metabolic syndrome: (2 of 5 factors) Weight gain (122-lbs to 166-lbs and elevated triglycerides	Patient gained 44-lbs after 120-days therapy. Cholesterol : 275mg/dl and elevated triglycerides. Olanzapine discontinued and gemfibrozil started. Triglyceride levels began to decrease (value not provided). Same reporter as case #31.
31	US_001052572	48/ M	Blood triglycerides increased, Blood cholesterol increased, Weight increased, Blood glucose increased	20mg daily x 730-days	Lithium, venlafaxine, atorvastatin, glyburide, metformin, simvastatin	Medical history includes diabetes, elevated lipids and alcohol abuse. Baseline cholesterol: 225mg/dl and triglycerides: 389mg/dl.	5873mg/dl Metabolic syndrome: (3 of 5 factors) BMI > 30, elevated triglycerides and elevated BS.	Hispanic male with BMI of 33 with elevated baseline lipids had exacerbation of lipid values. Cholesterol increased to 582mg/dl. BS out-of-control with value of 315mg/dl. Olanzapine stopped. Lab values 1-yr later: choles: 157mg/dl, BS: 117mg/dl & triglycerides: 207mg/dl Same reporter as case #30.
32	US_010973033	19/ M	Blood triglycerides increased, **Diabetic ketoacidosis**, BUN increased,	12.5 mg daily x unknown duration	None	Medical history not provided. Reporter considered history	2533mg/dl Metabolic syndrome: (2 of 5 factors)	African-American male developed DKA, elevated triglycerides and altered renal

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			Blood creatinine increased			not relevant to DKA.	elevated BS (no value), elevated triglycerides.	function. Baseline values not provided.
33	US_011075452	46/ M	Blood triglycerides increased, Prescribed overdose	25mg daily x unknown duration	Lithium, citalopram, clonazepam, vitamin E	History of elevated cholesterol.	1009mg/dl Metabolic syndrome: (1 of 5 factors) elevated triglycerides.	Patient experienced elevated triglycerides and cholesterol: 240mg/dl. Olanzapine disposition unknown.
34	US_011076376	40/ M	Blood triglycerides increased, Blood glucose increased, Blood cholesterol increased	15mg daily x unknown duration	Bupropion	Family history of diabetes. No other medical history known.	2000mg/dl Metabolic syndrome: (2 of 5 factors) elevated blood sugar, elevated triglycerides.	Patient experienced elevated BS: 600mg/dl, cholesterol: 654mg/dl and elevated triglycerides. Olanzapine discontinued.
35	US_011177698	55/ M	Blood triglycerides increased	15mg daily x unknown duration	Milnacipran, haloperidol, sulpiride	Medical history not provided.	1390mg/dl Metabolic syndrome: (1 of 5 factors) elevated triglycerides	Asian male experienced elevated triglycerides. Diet initiated and triglyceride level decreased to 400mg/dl. Level increase had resolved according to reporter within 5-weeks. Disposition of olanzapine unknown.
36	US_020281705	Unk/ M	Blood triglycerides increased, Blood cholesterol increased, Weight increased, Testis cancer	Unknown daily dosing x 180-days	Unknown	Medical history not provided. Baseline weight: 160-lbs, triglycerides: 83mg/dl,	1954mg/dl Metabolic syndrome: (2 of 5 factors) BMI:	Patient experienced wt gain, elevated cholesterol: 266mg/dl and elevated triglycerides. Olanzapine underwent

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

						cholesterol: 132mg/dl.	increased-wt increased from 160-lbs to 236-lbs, elevated triglycerides.	a positive dechallenge. Triglycerides decreased: 178mg/dl & cholesterol: 137mg/dl.
37	US_020281845	42/ M	Blood triglycerides increased, Blood glucose increased, Hypoglycemia, Hallucination auditory, Hallucination visual, Weight decreased	15mg daily x 30-days	Valproic acid, propranolol, gemfibrozil, thioridazine, pravastatin	BMI: 28.1. Alcohol abuse history along with other illicit drug abuse.	5093mg/dl Metabolic syndrome: (5 of 5 factors) BMI > 25, hypertension (no BP readings), HDL choles: 27mg/dl, BS increased & elevated triglycerides.	African-American male hospitalized for schizophrenia. Cholesterol: 227mg/dl, triglycerides: 313mg/dl & fasting BS: 82mg/dl. Diagnosed with hypertension upon admission. Olanzapine started after hospital admission. Cholesterol elevated to 375mg/dl, BS to 394mg/dl & triglycerides to 5093mg/dl. Medication regimen was changed (olanzapine continued) Atorvastatin and fenofibrate started. Lipids and blood sugar normalized. Literature case.
38	US_021291011	23/ M	Blood triglycerides increased, Weight increased	5mg daily x 390-days	Sulpiride, trazodone, Phenobarbital	History of brain disorder with organic mental disorder. Baseline triglycerides: 72mg/dl.	1053mg/dl Metabolic syndrome: (1 of 5 factors) increased triglycerides	Asian male developed elevated triglycerides. Olanzapine underwent a positive dechallenge. Triglycerides returned to 62mg/dl.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

39	US_030897285 **(see case #80 and #81)**	21/ M	Blood triglycerides increased, Blood cholesterol increased, **Xanthoma**, Diabetes mellitus non-insulin dependent	Unknown daily dosing x 60-days	Buspirone, bupropion, gabapentin, fluoxetine	No personal or family history of diabetes. Hemoglobin A1c: 16.4 suggests blood sugar issue prior to start of olanzapine.	5907mg/dl Metabolic syndrome: (2 of 5 factors) elevated BS: 358mg/dl & elevated triglycerides.	Biopsy found lipid-laden macrophages. Literature case. Eruptive xanthoma diagnosed along with diabetes. Cholesterol was 544mg/dl. Olanzapine continued. Started metformin, gemfibrozil and fenofibrate. No improvement noted.
40	US_0403101321	32/ M	Blood triglycerides increased, Blood cholesterol increased, Blood glucose increased	20mg daily x 120-days	Escitalopram, atorvastatin, enalapril, gabapentin, valproic acid, clonazepam	Medical history not provided. BMI: 38.9. Medication history suggests preexisting lipid disorder.	2548mg/dl Metabolic syndrome: (3 of 5 factors) BMI: >30, elevated BS: 249mg/dl & elevated triglycerides.	Olanzapine underwent a negative dechallenge. Triglycerides, cholesterol and glucose remained elevated. Same reporter as case #41.
41	US_0403101322	36/ M	Blood triglycerides increased, Blood cholesterol increased,	15mg daily x 150-days	Benztropine, clonazepam	BMI: 25.3. Quetiapine added to regimen after lipid elevations. Reporter did not provide medical history but considered history not remarkable regarding lipid issue.	1183mg/dl Metabolic syndrome: (1 of 5 factors) elevated triglycerides.	Patient experienced elevated cholesterol: 356mg/dl and elevated triglycerides. Olanzapine dose reduced. Not discontinued. Outcome not provided on lipids. Same reporter as case #40.
42	US_990319516	28/ F	Blood triglycerides increased, Blood cholesterol	30mg daily x 270-days	Venlafaxine, bupropion	BMI: 35.5. Patient noted to have undergone	1019mg/dl Metabolic	Patient hospitalized for psychiatric problems. Upon admission fasting

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			increased, Urinary tract infection, Polydipsia, Polyuria, Weight increased, Glycosuria, Hyperglycemia, Overdose			dehydration and starvation prior to lipid and BS measurements.	syndrome: (3 of 5 factors) BMI > 30, elevated triglycerides, blood sugar: 189mg/dl.	BS: 189mg/dl, cholesterol: 273mg/dl and triglycerides: 1019mg/dl. No baseline values. Olanzapine continued.
43	US_990623649	22/ M	Blood triglycerides increased, Overdose	30mg daily x 60-days	Valproic acid, lactulose, clonazepam, carbamazepine	Bipolar disorder and elevated cholesterol history. Baseline triglycerides: 287mg/dl.	1068mg/dl Metabolic syndrome: (1 of 5 factors) elevated triglycerides	Patient experienced elevated lipids. Atorvastatin therapy started. Olanzapine continued. Patient had baseline lipid elevations.
44	US_990725007	45/ M	Blood triglycerides increased, Blood cholesterol increased, Weight increased, **Pitting oedema**, **Balanitis candida**	10mg daily x 90-days	redacted insulin, glyburide, nifedipine	BMI: 32.6. History of hypertension and diabetes. Baseline cholesterol: 240mg/dl.	2337mg/dl Metabolic syndrome: (4 of 5 factors) hypertension, elevated triglycerides, elevated blood sugar, BMI > 30	African-American male presented to emergency room with 3+ pitting edema after 2-days of olanzapine. In addition, had a profound weight gain (25-lbs). Blood sugar ranged from 180 to 260mg/dl. Olanzapine underwent a positive dechallenge regarding blood sugar. Literature case.
45	US_991029245	25/ M	Blood triglycerides increased, Weight increased, **Chest pain**	10mg daily x 365-days	redacted	BMI: 30.2. Family history of diabetes and lipid elevations.	3240mg/dl Metabolic syndrome: (2 of 5 factors) BMI >30, elevated	Patient experienced weight gain, elevated cholesterol: 680mg/dl and elevated triglycerides. Olanzapine was discontinued and atorvastatin/gemfibrozil

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

							triglycerides	were started. Triglycerides: 377mg/dl / cholesterol: 210mg/dl were the result.
46	US_991029546	Unk/ M	Blood triglycerides increased	Unknown daily dosing x 150-days	Paroxetine, carbamazepine	Medical history not provided.	2000mg/dl Metabolic syndrome: (1 of 5 factors) elevated triglycerides	Patient experienced an elevated serum triglyceride level. Olanzapine continued. No other information was available.
47	DE_001103574	56/ F	Hypertriglyceridaemia	5mg daily x 60-days	Citalopram	BMI: 25.2. Medical history not provided. No baseline triglyceride values provided.	1605mg/dl Metabolic syndrome (2 of 5 factors) elevated triglycerides & BMI > 25	Elevated triglycerides. Olanzapine stopped and level decreased to 603mg/dl. No cholesterol values. No blood sugar values.
48	DE_030711769	28/ F	Hypertriglyceridaemia, Hypercholesterolaemia, Insulin requiring Type-II diabetes mellitus	15mg daily x 5-years. Drug stopped. Rechallenged: 15mg daily x 90-days	Perazine , birth control (ethinyl estradiol and levonorgestrel)	BMI: 32.7. Developed diabetes.	12,000mg/dl (triglycerides elevated at baseline) Metabolic syndrome: (3 of 5 factors) BMI > 30, elevated blood sugars (no value) & serum triglyceride elevation.	**Highest triglyceride level in database.** Dramatic Increase noted after 90-day regimen. Patient noted to have had a "prediabetic" condition since age 5. Prediabetic condition not defined. History elevated triglycerides. Cholesterol: 1200mg/dl. No HDL value. Olanzapine discontinued. Triglycerides reduced

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

								to 6250mg/dl.. Reporter considering a genetic predisposition to lipid change.
49	DE_990401100	38/ M	Lipid metabolism disorder, Diabetes mellitus	7.5mg daily x unknown duration	Medications not provided.	BMI: 32.2. Elevated triglycerides (1527mg/dl) before olanzapine., hepatic steatosis	5000mg/dl Metabolic syndrome: (3 of 5 factors) BMI > 30, Blood sugar: 165mg/dl, elevated triglycerides.	Chronic alcohol abuse and hepatic steatosis (hepatic issue 1-yr prior to olanzapine). Developed diabetes while on olanzapine. Olanzapine continued. Cholesterol: 580mg/dl (No HDL value). BS: 165mg/dl. Olanzapine continued.
50	DE_990401116	58/ M	Hypertriglyceridaemia, Hypercholesterolaemia	20mg daily x 180-days	Fluvastatin	BMI: not known. BS: not provided. History of clozapine and normal lipids after dechallenge of clozapine.	1523mg/dl Metabolic syndrome: (2 of 5 factors) HDL choles: 33mg/dl and triglycerides elevated.	Olanzapine continued. Patient experienced elevated triglycerides and lowered HDL cholesterol (33mg/dl). May have had baseline elevated lipids.
51	EWC010225371	52/ M	Hypertriglyceridaemia	15mg daily x 60-days	Prazepam, zopiclone	Alcohol use, food intake disorder.	1060mg/dl Metabolic disorder: (2 of 5 factors) BS: 142mg/dl) and elevated triglycerides. BMI not known.	Post marketing study patient with alcohol intake (amount unknown) and food intake disorder. Elevation of blood sugar (142mg/dl), cholesterol (291mg/dl and serum triglycerides. Olanzapine stopped. Outcome not known.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

								45-days later olanzapine rechallenged. (outcome not known).
52	EWC020631303	36/ F	Hypertriglyceridaemia, Blood cholesterol increased, Weight increased, **Pancreatic pseudocyst**	15mg daily x 180-days	Lithium, redacted	Medical history and BMI not known.	3003mg/dl Metabolic syndrome: (1 of 5 factors) elevated triglycerides. Blood sugar and weight not provided.	Considered possibly pancreatitis. Patient admitted with abdominal pain. Diagnostics suggested pancreatic pseudocyst. Elevated cholesterol (402mg/dl) and triglycerides noted. HDL chol not known. Blood sugar value not provided. Olanzapine continued.
53	EWC020932267	36/ M	Hypertriglyceridaemia, Hyperglycaemia	15mg daily x 60-days	Phenytoin, redacted clomipramine	Epilepsy. No BMI. Other history not known	10,000mg/dl Metabolic syndrome: (2 of 5 factors) elevated triglycerides and start of metformin (indication blood sugar problems)	Patient noted to have been critically ill with elevated blood sugar and lipids. No blood sugar value provided. Olanzapine stopped. Atorvastatin, metformin and ramipril added to drug regimen. Ramipril: Hypertension ?
54	EWC030334389	35/ M	Hypertriglyceridaemia, **Pancreatitis, Hepatic steatosis**, Diabetes mellitus non-insulin dependent, Abdominal pain upper, Dehydration	15mg daily x 365-days (diabetes diagnosed) 450-days later other issued developed.	Metformin	BMI: 31.1. Smoking history.	2658mg/dl Metabolic syndrome: (3 of 5 factors) BMI > 30,	Patient diagnosed with diabetes while on olanzapine. Some 15-months later hospitalized for pancreatitis. Discovered elevated

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

							elevated blood sugar and elevated triglycerides.	triglycerides. Patient recovered. Discharged on atorvastatin, olanzapine, ranitidine and metformin. Olanzapine later discontinued.
55	EWC980400467	50/ M	Hypertriglyceridaemia, Hyperglycaemia	Unknown dosing	Atenolol, amiodarone, aspirin, fenofibrate	Obesity and alcohol abuse history. No BMI provided. Fasting BS: 582mg/dl	1625mg/dl Metabolic syndrome: (3 of 5 factors) Obesity (no BMI value), elevated fasting BS: 582mg/dl, elevated triglycerides.	Patient experienced a 45-lb weight gain on olanzapine. In addition, experienced elevation of fasting blood sugars. Started on metformin and sulfonyl urea for diabetes. Olanzapine continued.
56	EWC980701207	38/ F	Hypertriglyceridaemia	20mg daily x 30-days	Medication not provided.	Vegetarian diet. No weight gain. No other history provided.	4000mg/dl Metabolic syndrome: (1 of 5 factors) elevation of triglycerides.	Patient is a vegetarian with unusual dietary habits. Serum triglycerides began to elevate about 500mg/dl every 3 to 4 days. Reached a maximum of 4000mg/dl. No weight gain on olanzapine. Olanzapine discontinued. Olanzapine under went a positive dechallenge. Triglyceride level listed as within normal range after dechallenge. Value not provided.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

57	FR_020400872	51/ M	Hypertriglyceridaemia, Hyperglycaemia	7.5mg daily x 365-days	Levothyroxine	Hypothyroidism. BMI: no value. No other history provided..	1325mg/dl Metabolic syndrome: (2 of 5 factors) elevation of blood sugar (129mg/dl), elevation of triglycerides.	Patient developed elevation of blood sugar and triglycerides. Blood sugar: 129mg/dl and triglycerides elevated over 1-yr on olanzapine. Disposition of olanzapine unknown.
58	FR_030502479	36/ M	Hypertriglyceridaemia, Hypercholesterolaemia, Diabetes mellitus insulin-dependent, Psychiatric symptom	10mg daily x 1095-days	Valproic acid, clonazepam	BMI: 27.8 at time of diabetes diagnosis. BMI was 34.2. Family history of diabetes.	1350mg/dl Metabolic syndrome: (3 of 5 factors) BMI peaked at 34.2, elevated blood sugar: 400mg/dl), elevated triglycerides	Patient initially developed significant weight gain. (BMI: 34.2). Weight reduction took place. Patient considered normotensive (BP: 105/60). Total cholesterol elevated (411mg/dl). Blood sugar elevated and insulin started. Hemoglobin A1c: 15.7%. Diabetes diagnosis made and insulin therapy started. Olanzapine discontinued. Long-term outcome not known.
59	DE_000302118	31/ M	Hyperlipidaemia, **Pancreatitis**, Diabetes mellitus, Hypercholesterolaemia, Liver function test abnormal	10mg daily x 100-days	Fluphenazine depot (had been stopped but long duration continued)	BMI: 34.6. Catatonic schizophrenic history. No history of	3167mg/dl Metabolic syndrome: (3 of 5 factors) elevated BS:	Post marketing study patient converted from fluphenazine depot to olanzapine. Admitted to hospital with pancreatitis. Recovered

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

						diabetes or pancreatitis	(740mg/dl), elevated triglycerides and BMI > 30.	and discharged on olanzapine with dose reduction. Olanzapine continued. Atorvastatin and captopril added to regimen. Upon admission noted elevated cholesterol (627mg/dl), elevated blood sugar (740mg/dl), Hemoglobin A1c: 15.3%.
60	JP_030701347	53/ F	Hyperlipidaemia, **Hepatic steatosis**, Weight increased, Hyperuricaemia, Increased appetite	15mg daily x 28-days	Lithium, etizolam, levomepromazine	BMI 23.7 (normal). Manic disorder and sleep loss history. .	1444mg/dl Metabolic syndrome: (1 of 5 factors) elevated triglycerides	Patient diagnosed with hepatic steatosis and hyperlipidemia (elevated cholesterol: 306mg/dl), no HDL value, elevated triglycerides), no mention of blood sugar value. Noted elevated uric acid levels (8.3mg/dl). Olanzapine was discontinued. Triglyceride value reduced to 422mg/dl but did not normalize. Also started on benzafibrate therapy.
61	JP_030801682	37/ M	Hyperlipidaemia, **Diabetic ketoacidosis**, Haemoglobin increased, Liver disorder	10mg daily x unknown duration	Information not provided but on other drugs.	BMI: 29.2. History of hepatic steatosis.	1237mg/dl Metabolic syndrome: (3 of 5 factors) BMI > 25,	Patient developed diabetes / diabetic ketoacidosis and elevated lipids while on olanzapine. Total choles (398mg/dl). No HDL value. Insulin

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

							elevated blood sugar (349mg/dl), elevated triglycerides.	therapy started. Had preexisting hepatic impairment. Olanzapine discontinued.
62	US_020584604	36/ F	Hyperlipidaemia, Obesity, Hyperphagia, Hyperglycaemia	10mg daily x 70-days	Lorazepam, fluvoxamine, paroxetine, trazodone	Baseline BMI: 25.6. BMI increased to 30.8 on olanzapine. Baseline lipid elevations: triglycerides: 356mg/d. Baseline blood sugar: 120mg/dl. History of fatty liver. Patient wt increased from 60kg to 72kgs.	2324mg/dl Metabolic syndrome: (3 of 5 factors) BMI > 30, elevated BS: 254mg/dl), elevated triglycerides.	Patient developed exacerbation of lipid elevations. Total cholesterol: 481mg/dl. No HDL value. Triglycerides increased from 356 to 2324mg/dl. Developed diabetes and obesity while on olanzapine. Had preexisting fatty liver and elevated triglycerides. Olanzapine was discontinued. BS and triglycerides improved but still outside of normal limits.
63	US_980605251	44/ M	Hyperlipidaemia, Hyperglycaemia, Hypercholesterolaemia, Overdose	30mg daily x 180-days	Lithium, valproic acid, nicotinic acid, gemfibrozil	BMI: 36.9. No history of hyperglycemia. Had baseline lipid elevation (cholesterol: 228mg/dl and triglycerides: 189mg/dl)	7668mg/dl Metabolic syndrome: (3 of 5 factors) BMI > 30, elevated triglycerides, elevated blood sugar (no value)	Patient with no history of hyperglycemia and a history of cholesterol and triglyceride mild elevations developed dramatic cholesterol changes (856mg/dl), hyperglycemia (no value) and pronounced triglyceride elevation (7668mg/dl). Disposition of olanzapine unknown.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

64	US97093754A	21/ M	Hyperlipidaemia, Weight increased, Diabetes mellitus, Reflux oesophagitis, Hyperglycaemia, Polyuria, Polydipsia, Nausea, Vomiting, Tachycardia	10mg daily x 150-days	Haloperidol, paroxetine	BMI: 46.6. No family history of diabetes. History of obesity. Baseline BMI: 41.7	1575mg/dl Metabolic syndrome: (3 of 5 factors) BMI> 30, elevated BS: 475mg./dl, elevated triglycerides.	Alcoholic patient develop hyperglycemia and lipid elevations on olanzapine. Cholesterol:646mg/dl), blood sugar: 475mg/dl, triglycerides > 1575mg/dl. Olanzapine continued.
65	US_990217774	50/ M	Hyperlipidaemia	20mg daily x 90-days	Lovastatin	BMI: no value. No medical history known. Lovastatin therapy suggests preexisting problem.	1300mg/dl Metabolic syndrome: (1 of 5 factors) elevated triglycerides	Patient developed elevation of triglycerides while on olanzapine. Medical history not provided. Olanzapine underwent a negative dechallenge. Triglyceride level after dechallenge: > 1000mg/dl.
66	DE_010104555	31/ M	Hyperlipidaemia, **Pancreatitis,** Diabetes mellitus non-insulin dependent, Drug interaction	10mg daily x 365-days	Clozapine, paroxetine, pirenzepine	BMI: no value. Wt: 114 kg. Long-term use of clozapine without adverse event issues.	1147mg/dl Metabolic syndrome: (4 of 5 factors) Wt: 114 lbs, HDL decreased: 39mg/dl, elevated BS: 372mg/dl, elevated triglycerides.	Patient experienced pancreatitis, elevated blood sugar and elevated lipids. Total cholesterol: 387mg/dl-HDL: 39mg/dl. Patient diagnosed with diabetes. All drugs stopped including olanzapine. Clozapine had been administered for 11-years without adverse events involving pancreas and blood sugar. Long-term outcome unknown.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

67	US97010475A	34/ M	Lipids increased	10mg daily x unknown duration	Medications not provided	BMI: 20.9 (thin). Baseline triglycerides: 819mg/dl. No other medical history.	2850mg/dl Metabolic syndrome: (1 of 5 factors) elevated triglycerides	Case with limited information. Cholesterol and triglycerides elevated while on olanzapine. Total cholesterol: 413mg/dl.- HDL cholesterol: 83mg/dl.
68	USA021023203	70/ F	Hypertriglyceridaemia, Blood cholesterol increased, Weight decreased, Prescribed overdose	25mg daily x 540-days	Gemfibrozil, alprazolam, trazodone, bupropion	BMI: 28.4. History of elevated lipids. Multiple personality disorder.	1877mg/dl Metabolic syndrome: (1 of 5 factors) elevated triglycerides	Patient with history of elevated triglycerides (422mg/dl) had increased levels. Had baseline cholesterol elevation (210mg/dl) that elevated to 325mg/dl while on olanzapine.
69	USA030741569	35/ M	Hypertriglyceridaemia, Hypercholesterolaemia, Diabetes mellitus, Weight increased	10-15mg daily x 90-days	Venlafaxine	BMI: no value. Wt increased to 224lbs. No history of diabetes or lipid elevations. Baseline cholesterol: 185mg/dl.	3030mg/dl Metabolic syndrome: (3 of 5 factors) Wt: 224 lbs, elevated BS: 296mg/dl, elevated triglycerides.	Patient experienced elevated BS with diagnosis of diabetes. Metformin treatment started. Also elevated cholesterol: 771mg/dl – HDL choles: 57mg/dl and elevated triglycerides. Had gained 14lbs in first 5-weeks on olanzapine. Olanzapine underwent a positive dechallenge. BS, cholesterol and triglycerides normalized. Metformin stopped.
70	US_010361882	44/ M	Hypertriglyceridaemia, Blood glucose increased	5mg daily x 60-days	Trichloroacetic acid, oxaprozin, valproic acid,	BMI: 34.4. Sleep apnea and obesity history.	3410mg/dl Metabolic	Patient developed hyperglycemia (BS 306mg/dl and elevated

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

					cerivastatin		syndrome: (3 of 5 factors) BMI > 30, blood sugar elevated: 306mg/dl and elevated triglycerides	lipids while on olanzapine. Cholesterol baseline: 205mg/dl and baseline triglycerides: 100mg/dl. Cholesterol value not provided. Triglycerides elevated. Metformin and insulin therapy started. Cerivistatin start undetermined:. Intervention or concomitant medication. Olanzapine therapy continued.
71	US_020281563	44/ M	Hypertriglyceridaemia, Diabetes mellitus, Blood cholesterol increased, Weight increased	30mg daily x 95-days	Lithium, valproic acid	BMI: 39.1. No history of diabetes. Baseline lipids were choles: 228mg/dl & triglycerides: 198mgd/dl	7668mg/dl Metabolic syndrome: (3 of 5 factors) BS elevation: 131mg/dl. BMI > 30, elevated triglycerides	**Literature case**. Patient gained 9 kg and BMI increased from 35.9 to 39.1 while on olanzapine. Diagnosed with diabetes. Triglyceride level peak 195-days into therapy. Cholesterol peaked at 856mg/dl. Had history of slight lipid elevations. Olanzapine disposition unknown.
72	US_020281564	39/ M	Hypertriglyceridaemia, Diabetes mellitus, Blood cholesterol increased	20mg daily x 585-days	Valproic acid	BMI: 36.2. History of BMI: 38.4. Recent wt loss. Baseline choles: 169mg/dl and triglycerides: 120mg/dl. Baseline BS: 86mg/dl	2811mg/dl Metabolic syndrome: (3 of 5 factors) BMI> 30, elevated BS: 277mg/dl,	**Literature case.** Patient with normal lipids and blood sugar developed diabetes and elevated lipids. Cholesterol elevated to 445mg/dl and glycosylated hemoglobin was

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

							elevated triglycerides.	11.3%. Disposition of olanzapine was unknown.
73	US_020281585	14/ F	Hypertriglyceridaemia, Blood cholesterol increased, Weight increased	12.5mg x 75-days	Lithium, valproic acid	BMI: 29.9. Had history of elevated lipids. Baseline triglycerides: 359mg/dl.. Choles baseline: 199mg/dl	2061mg/dl Metabolic syndrome: (2 of 5 factors) BMI > 25, elevated triglycerides.	**Literature case.** Patient experienced wt gain, cholesterol elevation (268mg/dl), elevated triglycerides and normal blood sugar (92mg/dl). Olanzapine disposition unknown.
74	US_020281587	31/ M	Hypertriglyceridaemia, Blood cholesterol increased, Weight increased	10mg daily x 180-days	Medications not provided.	BMI: 32.9. History of lipid elevations. Baseline triglycerides: 219mg/dl and choles: 265mg/dl.	1421mg/dl Metabolic syndrome: (2 of 5 factors) BMI > 30, elevated triglycerides.	**Literature case.** Patient with baseline lipid elevations had worsening of lipid values. Blood sugar remained normal: 86mg/dl. Cholesterol peak: 570mg/dl. Olanzapine therapy status not provided..
75	US_020281597	33/ F	Hypertriglyceridaemia, Blood cholesterol increased, Weight decreased	20mg daily x 330-days	Medications not provided.	BMI: 23.7. Baseline BMI: 25.7. Lost 13-lbs Had history of lipid elevations.	1022mg/dl Metabolic syndrome: (1 of 5 factors) elevation of triglycerides.	**Literature case.** Patient with baseline triglycerides of 64mg/dl and cholesterol baseline: 84mg/dl experienced elevations. Choles: 198mg/dl. BS: 91mg/dl. Olanzapine therapy status unknown.
76	US_020281605	41/ F	Hypertriglyceridaemia, Blood cholesterol increased, Weight increased	15mg daily x 540-days	Medications not provided.	BMI: 26.4. Gained 18-lbs. History of lipid elevations.	1305mg/dl Metabolic syndrome:	**Literature case.** Patient experienced worsening of triglycerides and

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

						Baseline triglycerides: 279mg/dl/ Choles: 222mg/dl	(2 of 5 factors) BMI > 25, elevated triglycerides.	cholesterol values. BS value not provided after therapy. Baseline BS: 82mg/dl. Olanzapine disposition not known.
77	US_020483750	39/ M	Hypertriglyceridaemia, Diabetes mellitus, Type-IIB hyperlipidaemia, Insulin resistance, Polydipsia	15mg daily x 42-days	Risperidone, biperiden, brotizolam, atorvastatin, bezafibrate	BMI: not provided. History of fatty liver, hyperglycemia and elevated lipids (type IIB). Baseline triglycerides:: 88mg/dl with atorvastatin.	2087mg/dl Metabolic syndrome: (2 of 5 factors) BS elevated: 578mg/dl, triglycerides elevated.	**Literature case.** Had history of excessive drinking. Patient developed severe insulin resistance. Diagnosed with diabetes and insulin therapy started. Hyperlipidemia worsened. Olanzapine underwent a negative dechallenge.
78	US_020584272	37/ M	Hypertriglyceridaemia, Diabetes mellitus non-insulin dependent	20mg daily x 150-days	Quetiapine	BMI: not provided. Baseline triglycerides: 384mg/dl.	1543mg/dl Metabolic syndrome: (2 of 5 factors) Blood sugar: 630mg/dl, elevated triglycerides	Patient reportedly experienced elevated BS from baseline BS of 116mg/d. Worsening of triglycerides. Olanzapine discontinued. Oral hypoglycemic / diet therapy started. Events resolved..
79	US_020987964	48/ M	Hypertriglyceridaemia, Hyperglycaemia, Blood cholesterol increased	20mg daily x 105-days	Perospirone, zopiclone	BMI: 23.9. Baseline BS elevation: 153mg/dl. Lipids elevated at baseline. choles: 245mg/dl.	1113mg/dl Metabolic syndrome: (2 of 5 factors) BS elevated: 628mg/dl, elevated triglycerides.	Experienced elevated blood sugar, cholesterol worsening and elevated triglycerides. Diabetes therapy started (non-specified). Olanzapine stopped. Improvement noted: BS: 119mg/dl triglycerides: 177mg/dl. Cholesterol did not

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

								improve.
80	US_030897250 **(see case #81 and #39)**	31/ M	Hypertriglyceridaemia, Blood cholesterol increased, Diabetes mellitus, **Xanthoma,** Acanthosis nigricans	10mg x 56-days	Clomipramine, methylphenidate, buspirone, citalopram, trihexyphenidyl	BMI: not provided. Family history of diabetes.	3220mg/dl Metabolic syndrome: (2 of 5 factors) Blood sugar: 370mg/dl, elevated triglycerides.	**Literature case.** Considered a dyslipidemia leading to xanthoma. Eruptive xanthoma confirmed by punch biopsy. New onset diabetes. BS peaked at 370mg/dl and cholesterol peaked at 607mg/dl. Insulin and glyburide started. Olanzapine continued - blood sugar and triglycerides normalized, No values provided.
81	US_030897307 **(see case #80 and #39)**	50/ F	Hypertriglyceridaemia, Hyperglycaemia, Blood cholesterol increased, **Xanthoma**	10mg daily x unknown duration	Trihexyphenidyl, diphenhydramine	BMI: not provided. No family history of diabetes.	7210mg/dl Metabolic syndrome: (2 of 5 factors) elevated blood sugar: no value, elevated triglycerides.	Literature case. Eruptive xanthoma diagnosed with punch biopsy. Cholesterol elevated: 1090mg/dl and triglycerides elevated. Severe hyperglycemia noted (no value). Simvastatin started. Olanzapine continued. No follow-up obtained.
Cases #82 through #94 (n= 13) were found with textstring search methodology:								
82	DE_981100567	35/ F	Hyperglycaemia	7.5mg daily x unknown duration	Chlorprothixene	BMI: 28. History of elevated fasting BS: 130mg/dl and elevated lipids (no values)	3800mg/dl Metabolic syndrome: (3 of 5 factors) BMI > 25, BS:	Patient with baseline blood sugar and triglyceride problems experienced worsening triglyceride levels. Patient hospitalized with BS of 600mg/dl

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

							600mg/dl, elevated triglycerides	and cholesterol: 440mg/dl. Insulin and metformin therapy started. Status of olanzapine therapy unknown.
83	DE_990200903	24/ M	***Pancreatitis acute***	10mg daily x 5-days	Levomepromazine	BMI: no value. Classified as obese by reporter. Alcohol abuse, elevated lipids at baseline (no values), elevated cholesterol (no value)	3399mg/dl Metabolic disorder: (2 of 5 factors) Obesity (no BMI), elevated triglycerides	Patient admitted to hospital with pancreatitis. Alcohol abuse history and lipometabolic disorder. Blood sugar values not provided. Olanzapine stopped along with levomepromazine.
84	EWC020230150	44/ M	Hyperglycaemia	10mg daily x 50-days	Clorazepate, lormetazepam, mianserin, venlafaxine, lithium	BMI: no value. History elevated triglycerides (1242mg/dl). No history of hyperglycemia.	1242mg/dl Metabolic syndrome: (2 of 5 factors) BS elevated, elevated triglycerides.	Patient with preexisting lipid disorder (triglycerides elevated and cholesterol: 498mg/dl) experienced elevated blood sugar. Fasting BS: 111mg/dl. Metformin/sulfonyl urea and atorvastatin started. Olanzapine continued.
85	GBS020110070	24/ M	Diabetes mellitus, **Eye disorder**, Blood alkaline phosphatase increased, GGT increased, ALT increased	10mg daily x 690-days	Acetaminophen, dihydrocodeinone	BMI: no value. Alcohol ingestion history..	1967mg/dl Metabolic syndrome: (3 of 5 factors) HDL choles decreased (30mg/dl), elevated BS:	Patient experience elevated blood sugar along with triglyceride elevation. In addition, total cholesterol was elevated: 281mg/dl and HDL cholesterol decreased: 30mg/dl. Olanzapine was stopped.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

							294mg/dl, elevated triglycerides.	
86	USA020211401	19/ M	**Diabetic ketoacidosis, Pancreatitis**, Schizophrenia	12.5mg daily x 120-days	None	BMI: no value. No history of pancreatitis or diabetes.	1441mg/dl Metabolic syndrome: (2 of 5 factors) BS: 517mg/dl elevated, elevated triglycerides.	African-American patient experienced elevated blood sugar: 517mg/dl along with elevated triglycerides. Lipase and amylase strongly elevated: large edematous pancreas. Olanzapine was stopped.
87	USA031050393	24/ M	**Diabetic hyperosmolar coma, Pancreatitis acute**, White blood cell count increased, Polydipsia, Pollakiuria, Confusional state	10mg daily intermittently x 2190-days	Quetiapine, paroxetine, trazodone	BMI: no value but wt: 116-kgs. No known medical conditions.	2195mg/dl Metabolic syndrome: (3 of 5 factors) Wt: 116kgs, elevated BS: 1214mg/dl, elevated triglycerides.	**Fatal outcome.** Blood sugar: 1214mg/dl. Death attributed to nonketotic hyperosmolar coma and pancreatitis. Baseline blood sugar 2-yrs prior to death: 101mg/dl.
88	US_000338297	80/ F	Hip fracture	5mg daily x 390-days	Gemfibrozil, gluburide redacted	BMI: 21 (thin). History of lipid elevations and diabetes. No baseline values.	1251mg/dl Metabolic syndrome: (2 of 5 factors) BS: 317mg/dl, elevated triglycerides.	**Clinical trial patient.** Diabetic with history of lipid elevations fell and broke hip. Admission lab values showed blood sugar: 317mg/dl, cholesterol: 298mg/dl, elevated triglycerides. Olanzapine continued.
89	US_010463717	41/ M	Hyperglycaemia, Dizziness, Vision blurred, Vertigo postural	6mg daily with redacted 25mg daily x	aspirin, acetaminophen, ibuprofen,	BMI: 44. Obesity. Trial for depression. History of sleep	1947mg/dl Metabolic syndrome:	**Clinical trial patient.** Patient being treated for depression presented to clinic with

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

				135-days	hydrochlorothiazide budesonide	apnea and liver enzyme elevations.	(4 of 5 factors) BMI > 30, blood sugar elevated, HDL choles: 30mg/dl, elevated triglycerides	blood sugar: 880mg/dl. Glycosylated hemoglobin: 10.5%. Also noted elevated lipids including total cholesterol: 320mg/dl. Olanzapine/ combination continued. Added pioglitazone, metformin and fenofibrate to drug regimen. .
90	US_010872076	38/ M	**Diabetic ketoacidosis**, Headache, Weight increased, Upper respiratory tract infection, Insulin-requiring Type-II diabetes mellitus	20mg daily x 365-days	Venlafaxine, valproic acid, atorvastatin, propranolol, paroxetine, ibuprofen	BMI: 31. Baseline blood sugar: 170mg/dl. History of lipid elevations and hepatitis A.	6589mg/dl Metabolic syndrome: (3 of 5 factors) BMI > 30, blood sugar: 765mg/dl, elevated triglycerides.	**Literature case.** Patient admitted to hospital with DKA. Blood sugar: 765mg/dl, elevated triglycerides, hemoglobin A1c: 13.4%. Started on insulin. Olanzapine continued.
91	US_980909827	42/ M	Diabetes mellitus, Proteinuria, Polyuria, Polydipsia, Tachycardia, Weight decreased	15mg daily x 365-days	Doxepin, ranitidine	BMI: 27.9. Family history of diabetes. Personal history of hepatitis C.	2884mg/dl Metabolic syndrome: (3 of 5 factors) BMI > 25, blood sugar elevated, triglycerides elevated.	African-American patient diagnosed with diabetes while on olanzapine. Blood sugar: 796mmg/dl. Also noted elevated triglycerides. Olanzapine continued. Glipizide, metformin and insulin started.
92	EWC010125164	53/ M	Diabetes mellitus, Dyskinesia	20mg daily x 365-days	Simvastatin	BMI: 32.3. Family history of diabetes. Some	1056mg/dl Metabolic	Diagnosed with diabetes. Blood sugar: 298mg/dl. Started on

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

						history of lipid disorder based upon simvastatin therapy.	syndrome: (3 of 5 factors) BMI > 30, elevated blood sugar, elevated triglycerides.	metformin and gliclazide. Olanzapine continued. Simvastatin started 2-years prior to olanzapine.
93	US_010769645	42/ M	Blood glucose increased	20mg daily x 1100-days	Risperidone, valproic acid, citalopram, anti-lipid meds (two agents)-not known	BMI: 33. History of alcoholism, methamphetamine abuse and elevated cholesterol.	4000mg/dl Metabolic syndrome: (3 of 5 factors) BMI> 30, elevated blood sugar (no value), elevated triglycerides.	Hispanic patient with history of normal hemoglobin A1c values developed diabetes. Olanzapine continued. Metformin started.
94	US_020684932	48/ M	Hepatic function abnormal	15mg daily x 165-days	Multiple meds:	BMI: 30. History of elevated triglycerides: 1005mg/dl, cholesterol: 268mg/dl. No comment regarding blood sugar history.	1005mg/dl Metabolic syndrome: (2 of 5 factors) BMI > 25, elevated triglycerides.	Patient with history of multiple problems including liver function and lipid issues developed altered liver enzymes. Triglyceride values did not alter. Baseline was peak value. Olanzapine stopped due to liver not lipid issues.
	94 case reports ≥ 1000mg/dl serum triglycerides							

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Table 6X continued: Triglycerides line listings (500 to 999 mg/dL)

Case reports with serum triglyceride values from 500mg/dl to 999 mg/dl (n = 79)

#	Case ID	Age/ Sex	MedDRA preferred term(s)	Olanzapine dosing	Concomitant Medications	Medical history	Peak serum triglyceride value / Metabolic syndrome	Acute clinical issues/ Comments
1	DE97122476A	Unk/F	Blood triglycerides increased				580mg/dl	
2	DE_031112325	28/M	Blood triglycerides increased, thrombosis, **pulmonary embolism**				900mg/dl	
3	EWC030534966	34/M	Blood triglycerides increased, lipids increased, weight increased				956mg/dl	
4	EWC031036535	33/M	Blood triglycerides increased, prescribed overdose				551mg/dl	
5	JP_040302825	32/M	Blood triglycerides increased				507mg/dl	
6	US97015881A	23/M	Blood triglycerides increased, blood cholesterol increased, liver function test abnormal			Baseline triglycerides: 257mg/dl	810mg/dl	
7	US98011711A	14/M	Blood triglycerides				587mg/dl	

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			increased, blood glucose increased, HDL cholesterol decreased, blood alkaline phosphatase increased, blood LDH increased, blood creatinine increased, **hepatic steatosis**, aspartate aminotransferase increased, aggression				Metabolic syndrome: (3 of 5 factors)	
8	USA020110313	30/M	Blood triglycerides increased, blood glucose increased, weight increased, sedation, insomnia, headache				600mg/dl Metabolic syndrome: (3 of 5 factors)	
9	USA020616863	45/F	Blood triglycerides increased, **pancreatic necrosis**, hyperglycaemia, depression, diabetes mellitus				500mg/dl	
10	USA020920945	42/M	Blood triglycerides increased, weight increased				Baseline triglycerides: 519mg/dl	817mg/dl
11	USA030125831	24/M	Blood triglycerides increased, blood cholesterol increased,					982mg/dl
12	USA030228959	30/F	Blood triglycerides increased,					940mg/dl

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			blood glucose increased, weight decreased, visual disturbance					
13	USA030434291	23/M	Blood triglycerides increased, weight decreased, alanine aminotransferase increased			Baseline triglycerides: 332mg/dl	601mg/dl	
14	USA030536076	Unk/M	Blood triglycerides increased			Baseline triglycerides: 200mg/dl	900mg/dl	
15	USA030946235	70/F	Blood triglycerides increased, weight increased				>500mg/dl	
16	USA030947448	65/F	Blood triglycerides increased, diabetes mellitus				706mg/dl	
17	USA031153505	48/M	Blood triglycerides increased, glucose tolerance impaired, hypertension			Baseline triglycerides: 300mg/dl	700mg/dl Metabolic syndrome: (3 of 5 factors)	
18	US_000642765	48/M	Blood triglycerides increased, **pancreatitis, diabetic ketoacidosis**, mental status changes, blood creatinine increased, weight increased, weight decreased				773mg/dl Metabolic syndrome: (3 of 5 factors)	
19	US_000644425	12/M	Blood triglycerides increased				970mg/dl	

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

20	US_000847394	33/M	Blood triglycerides increased, weight increased, blood glucose increased, hepatic enzyme increased, blood cholesterol increased				638mg/dl Metabolic syndrome: (3 of 5 factors)	
21	US-001052548	56/F	Blood triglycerides increased, blood cholesterol increased, **arterial occlusive disease**, weight increased, chest pain, blood glucose abnormal, hypoglycaemia, white blood cell count increased, blood thyroid stimulating hormone increased, neutrophil count increased				658mg/dl Metabolic syndrome: (3 of 5 factors)	
22	US_001152667	30/M	Blood triglycerides increased, blood glucose increased, nervousness				548mg/dl	
23	US-001152674	39/M	Blood triglycerides increased, white blood cell count increased, mania,				502mg/dl	

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			delirium, mood altered, depression					
24	US_001152798	56/F	Blood triglycerides increased, **hepatitis granulomatous**				536mg/dl	
25	US_001152994	49/M	Blood triglycerides increased, blood cholesterol increased, diabetes mellitus				575mg/dl	
26	US_001153632	30/F	Blood triglycerides increased, weight increased, hypercholesterolaemia				800mg/dl	
27	US_010565372	39/M	Blood triglycerides increased, blood cholesterol increased, weight increased, overdose, psychotic disorder, aspartate aminotransferase increased, alanine aminotransferase increased				823mg/dl	
28	US_010973247	10/M	Blood triglycerides increased, blood cholesterol increased, lipids abnormal			Baseline triglycerides: 450mg/dl	>900mg/dl	
29	US_011177903	Unk/M	Blood triglycerides increased, blood cholesterol				500mg/dl	

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			increased,					
30	US_020382427	25/M	Blood triglycerides increased, **pancreatitis acute, diabetic ketoacidosis**				514mg/dl	
31	US_020584602	24/M	Blood triglycerides increased, weight increased, blood cholesterol increased				818mg/dl	
32	US_021088562	35/M	Blood triglycerides increased				500mg/dl	
33	US_981112774	Unk/F	Blood triglycerides increased, weight increased, blood cholesterol increased				900mg/dl	
34	US_981214658	51/F	Blood triglycerides increased, oedema peripheral, **triple vessel bypass graft**				700mg/dl	
35	US_981215124	26/Unk	Blood triglycerides increased, overdose				925mg/dl	
36	US_981215147	48/Unk	Blood triglycerides increased				669mg/dl	
37	US_981215171	40/Unk	Blood triglycerides increased				705mg/dl	
38	US_990420639	Unk/F	Blood triglycerides increased, **convulsion,** hallucinations auditory, anxiety				700mg/dl	
39	US_990826458	64/M	Blood triglycerides increased, tremor,				>800mg/dl	

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			muscle rigidity					
40	US_990826672	16/M	Blood triglycerides increased				780mg/dl	
41	DE_030811817	40/F	Hypertriglyceridaemia, blood cholesterol increased				781mg/dl	
42	EWC001108585	22/F	Hypertriglyceridaemia, hypercholesterolaemia, hyperglycaemia, weight increased, overdose				660mg/dl	
43	EWC990703852	39/F	Hypertriglyceridaemia, weight increased, amenorrhea, hypercholesterolaemia				733mg/dl	
44	FR_020100595	35/M	Hypertriglyceridaemia, **ketoacidosis,** ketonuria, proteinuria, weight increased, agitation, diabetes mellitus				829mg/dl	**Fatal outcome.**
45	FR_030101871	36/F	Hypertriglyceridaemia, hyperglycaemia, hypercholesterolaemia, weight increased				744mg/dl	
46	FR_031103127	38/M	Hypertriglyceridaemia, hyperglycaemia				685mg/dl	
47	USA030127266	31/M	Hypertriglyceridaemia				700mg/dl	
48	US_020281559	28/M	Hypertriglyceridaemia, weight increased, diabetes mellitus				966mg/dl	
49	US_020281582	59/M	Hypertriglyceridaemia, blood cholesterol increased, weight increased				735mg/dl	

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

50	US_020281592	34/M	Hypertriglyceridaemia, weight increased, blood cholesterol increased,				681mg/dl	
51	US_020281594	38/M	Hypertriglyceridaemia, blood glucose increased, weight increased, blood cholesterol increased				669mg/dl	
52	US_020281603	32/M	Hypertriglyceridaemia, weight increased, blood cholesterol increased,				760mg/dl	
53	US_020281610	40/M	Hypertriglyceridaemia, blood cholesterol increased				746mg/dl	
54	DE_011107356	39/M	Hypertriglyceridaemia			Baseline triglycerides: 407mg/dl	839mg/dl	
55	EWC030334049	26/M	Hyperlipidaemia, weight increased				706mg/dl	
56	EWC040338570	33/M	Hyperlipidaemia, prescribed overdose				551mg/dl	
57	GBS000505970	52/M	Hyperlipidaemia				964mg/dl	
58	JP_030200417	27/M	Hyperlipidaemia, hyperglycaemia, weight increased, increased appetite, polydipsia				702mg/dl Metabolic syndrome: (3 of 5 factors)	
59	US_001254588	49/M	Hyperlipidaemia, diabetes mellitus, body mass index increased, hyperinsulinaemia, hormone level				824mg/dl	

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			abnormal, increased appetite, psychotic disorder, depression, blood prolactin increased					
60	US_011178209	29/M	Hyperlipidaemia, **diabetic hyperosmolar coma, cardio-respiratory arrest,** hyperglycaemia, **hepatocellular damage**, increased appetite				960mg/dl	**Fatal outcome.**
61	US_020584526	40/M	Hyperlipidaemia, diabetes mellitus, weight increased, **hepatic steatosis**, blood pressure increased				944mg/dl Metabolic syndrome: (4 of 5 factors)	
62	US_020684886	32/M	Hyperlipidaemia, weight increased, **convulsion,** hyperglycaemia				672mg/dl	
63	US_020887033	34/M	Hyperlipidaemia, weight increased, blood cholesterol increased, hepatic function abnormal, white blood cell count increased, malaise, **hepatic steatosis**, ocular icterus, retching				523mg/dl	

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

64	DE_000602573	27/M	Lipids increased, hepatic enzyme increased				825mg/dl	
65	US_030695010	42/M	Lipids increased				709mg/dl	
Cases #66 through #79 (n = 14) were found with textstring search methodology								
66	CA_021205584	45/F	Diabetes mellitus non-insulin dependent, rash, hallucinations, diarrhea			BMI: 32.2	754mg/dl	
67	DE_000602613	36/M	Diabetes mellitus non-insulin dependent				508mg/dl	
68	DE_030511252	37/M	**Pancreatitis acute**, diabetes mellitus insulin dependent				808mg/dl	
69	EWC010426225	52/M	Diabetes mellitus, weight increased				988mg/dl	
70	GBS030513113	61/F	Insulin resistance, glycosylated haemoglobin increased, hyperosmolar state				529mg/dl	
71	US_001255078	24/M	Diabetes mellitus non-insulin dependent				659mg/dl	
72	US_020281531	47/M	Syncope, abdominal pain upper, chest pain				660mg/dl	
73	DE_001103382	36/M	Diabetes mellitus, hyperglycaemia, weight increased				541mg/dl	
74	DE_030110456	39/M	Leukocytosis, weight increased				507mg/dl	
75	EWC010727733	35/M	Diabetes mellitus insulin dependent, **hepatic steatosis**, weight increased, renal insufficiency,				988mg/dl	

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

			platelet count increased, gamma-glutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased					
76	JP_030901854	38/M	Diabetes mellitus				631mg/dl	
77	US_000133560	25/M	Weight increased				635mg/dl	
78	US_030795917	54/M	**Pancreatitis,** ketoacidosis, **cerebrovascular accident,** Diabetes mellitus non-insulin dependent, weight increased **Plus** 13 other preferred terms !				567mg/dl	
79	US_981214997	Unk/M	Electrocardiogram T wave abnormal				569mg/dl	

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Table 7X: Frequency Table of Elevated Cholesterol

Cases (n=94) with Elevation of Serum Cholesterol:
Preferred Terms (non-searched) by Decreasing Frequency

Adverse Events by Preferred Term	# Events
Gamma-glutamyltransferase increased	6
Alanine aminotransferase increased	**5**
Aspartate aminotransferase increased	**4**
Blood alkaline phosphatase increased	4
Blood creatine phosphokinase increased	3
Blood creatinine increased	3
Blood prolactin increased	3
Insomnia	3
Panic attack	3
Aggression	2
Blood lactate dehydrogenase increased	2
Buccoglossal syndrome	2
Dry mouth	2
Hepatic enzyme increased	2
Nephrotic syndrome	**2**
Somnolence	2
Abdominal distension	1
Acne	1
Agitation	1
Allergic rhinitis	1
Amenorrhea	1
Anxiety	1
Asthma	1
Back pain	1

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Binge eating	1
Blood amylase increased	1
Blood bilirubin increased	1
Blood phosphorus increased	1
Blood thyroid stimulating hormone increased	1
Cardiorespiratory arrest	**1**
Chest discomfort	1
Chest pain	**1**
Constipation	1
Convulsion	**1**
Coronary artery surgery	1
Death	**1**
Diabetic coma	**1**
Dilatation atrial	1
Drug hypersensitivity	1
Dysphagia	1
Dyspnoea	1
Dysuria	1
Eating disorder	1
Electrocardiogram abnormal	1
Euphoric mood	1
Eye infection	1
Facial palsy	1
Feeling hot	1
Gait abnormal	1
Gallbladder disorder	1
Granulocytopenia	1
Haematuria	1
Hallucination	1
Hallucination, auditory	1
Hallucinations, mixed	1

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Hangover	1
Headache	1
Heart rate increased	1
Hepatic steatosis	**1**
Hepatitis B	1
Hepatocellular damage	**1**
Hormone level abnormal	1
Hunger	1
Hyperinsulinaemia	1
Hyperkinesia	1
Hypersomnia	1
Hypertension	1
Hypoproteinaemia	1
Incoherent	1
Incontinence	1
Joint swelling	1
Leukocytosis	1
Liver function test abnormal	1
Malaise	1
Mouth ulceration	1
Movement disorder	1
Musculoskeletal stiffness	1
Myocardial infarction	**1**
Nausea	1
Oedema	**1**
Pain	1
Pain in extremity	1
Pancreatic enzymes increased	1
Pancreatitis acute	**1**
Pancreatitis necrotising	**1**
Periodontitis	1

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Periorbital oedema	1
Pitting oedema	**1**
Platelet count decreased	1
Prostatitis	1
Protein urine	1
Psychotic disorder	1
Pyrexia	1
Rash	1
Renal failure acute	1
Renal pain	1
Respiratory arrest	**1**
Respiratory rate increased	1
Restlessness	1
Rhabdomyolysis	1
Salivary hypersecretion	1
Sedation	1
Skin striae	1
Sleep apnea syndrome	1
Social avoidant behaviour	1
Suicidal ideation	1
Swelling	1
Systemic lupus erythematosus	1
Systemic lupus erythematosus rash	1
Thinking abnormal	1
Tobacco abuse	1
Toothache	1
Tremor	1
Urinary incontinence	1
Visual disturbance	1

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Table 8X: ELEVATION OF SERUM CHOLESTEROL- Case reports in Clintrace

ELEVATION OF SERUM CHOLESTEROL- Case reports in Clintrace

Table excludes case reports with elevated triglycerides – These cases are captured elsewhere

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
1	AU_010804079	F	Blood cholesterol increased	Unk	Yes, but unknown	Unk	Unk	Olz continuing, not yet recovered	Olz or con meds
2	AU_030806552	25/M	"	10	Sertraline	OCD, psychosis	Unk	Acute pancreatitis, **wt gain**; **olz D/C, abate-no**	Y
3	AU_040207417	50/F	"	Unk	Unk	nl TC	Unk	Olz continuing, OUNK	DNK
4	CA_000301339	13/M	LDL increased	20	NONE	Mild sleep apnea	Unk	**Wt gain**, sleep apnea, SOB; D/C unk study prior to olz tx, **olz D/C, abate-no**	UA
5	DE_010204976	56/M	Hypercholesterolaemia	15	Fluphenazine, melperone	Suspect type 2 DM	238/Unk/Unk	DM; **olz D/C, recovering**	DNK
6	DE_011006948	57/F	"	15	NONE	NONE	Baseline: **300**/Unk/Unk **400/193**/Unk 200	**Wt gain**; olz continuing, not yet recovered, + lipid-lowering med & diet	Y

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
7	DE_011107335	38/M	Blood cholesterol increased	5	Tiapride	NONE	**335**/Unk/Unk	SGOT & SGPT ↑, hep B; **olz D/C, abate-YD**	N
8	DE_020609022	72/M	Blood cholesterol increased, LDL increased, HDL increased	5	Mirtazapine, sertraline, valproic acid	Depressive state	239/Unk/Unk Unk/**189**/Unk Unk/**250**/Unk **306**/Unk/Unk	Toxic liver damage; valproic acid D/C & liver damage resolved, **olz dose ↓ to 2.5 mg, + lipid-lowering med, abate-no**	Suspects sertraline
9	DE_031112373	50/F	Blood cholesterol increased, LDL increased	20	Levothyroxine, lithium, venlafaxine	Thyroid disease, glaucoma	230/Unk/Unk 194	Butterfly rash, suspected lupus, ↑ blood glucose; olz continuing, OUNK	UA
10	DE_031112378	20/M	LDL increased	15	Benperidol, diazepam	CK 200 U/L with benperidol, NO drug or EtOH misuse or convulsions, olz with no AEs	Unk	CK ↑, GOT & GPT ↑, GGT ↑, creatinine ↑; **olz D/C, not recovered for all events, abate-no**	UA
11	DE_040313229	38/M	Blood cholesterol increased	30	Risperidone	CK ↑ with clozapine, EPS with risperidone	**246**/Unk/Unk	OD, CK ↑, creatinine ↑; olz continuing, not yet recovered	Y

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
12	DE_981000506	51/F	Hypercholesterolaemia	10	Lorazepam	Unk	Unk	Nephrotic syndrome, **wt gain**, hypoproteinemia, edema; **olz D/C, little bit improving; + furosemide, captopril, imurek, dytide H, & diet**	N
13	DE97063094A	24/M	"	20	Unk	No organic disorder	Baseline: nl/Unk/Unk **280/185**/Unk		UA
14	EWC010928453	37/M	Blood cholesterol increased	12.5	NONE	nl TC	Baseline: nl/Unk/Unk **278/193/36** 204		NHCP
15	EWC011229379	26/M	"	20	Gliclazide, metformin, salbutamol, triamcinolone	Poorly controlled diabetes, asthma, eczema, hep B immune, keratosis, viral warts; NO smoking or EtOH	Unk	Bili ↑, Alk Phos ↑, GGT ↑, ALT & AST ↑; **olz dose ↓ to 17.5 mg/day, not yet recovered**	Y
16	EWC020430724	M	LDL increased, HDL increased	5	Unk	Unk	Unk	Olz D/C considered	NHCP
17*	EWC040338369	33/M	Hypercholesterolaemia ***SERIOUS***	5	Clorazepate	LFTs ↑ with olz, possible EtOH abuse	**294**/Unk/Unk	ALT & GGT ↑, LDH ↑; **YD with (+) rechallenge**	UA

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
18	FR_011000265	20/F	"	10	Chlorpromazine	Unk	Unk	**Wt gain**; **olz D/C**, OUNK	Y
19	FR_021001548	56/F	"	Unk	Ferrous fumarate, glibenclamide, metformin, tiapride, valpromide	Type 2 DM, hypercholesterolemia, obesity, hep A, psychosis, food behavior disorder	**268**/Unk/Unk **278**/Unk/Unk	GGT ↑, leucocytosis, granulocytopenia, DM aggravated; **olz D/C, events continue, abate-no**	DNK
20	FR_021201823	16/M	"	10	NONE	Untx acne	**313**/Unk/Unk	Acne aggravated, **wt gain**; olz continued, not yet recovered	Y
21	FR_030602523	F	"	Unk	Unk	Unk	**250**/Unk/Unk		UA
22	FR_030702672	55/F	"	10	Antidepressant, valproate	Psychosis	Unk	**Wt ↑;** olz continued, not yet recovered, no corrective tx	Y
23	FR_031203318	33/F	Blood cholesterol increased	7.5	Unk	Unk	Unk	Amenorrhea	NHCP
24	FR_031203323	60/F	Hypercholesterolaemia	20	Carbamazepine, citalopram, diazepam	Manic depressive psychosis, hypercholesterolemia w/o obesity or DM	**328**/Unk/115 F/U: **309**/Unk/Unk	Hyperglycemia, olz D/C, abate-no	N
25	GBS000105268	61/M	Blood cholesterol increased	5	Lithium, paroxetine, trifluoperazine	Unk	Unk	Periorbital oedema, swollen wrist, low plts; olz continuing	UA
26*	GBS011009654	64/M	" SERIOUS	10	ASA, atenolol, lithium, **pravastatin**	Raised TC	Baseline: 155/Unk/Unk 236/Unk/Unk	Olz D/C, not recovered	Y

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
27	GBS980600804	M	LDL increased, HDL increased	20	Unk	Unk	Unk/**309**/Unk	**Olz D/C**, OUNK	UA
28	IL98021708A	40/M	Blood cholesterol increased	15	Clonazepam, clotiapine	Unk	**361**/Unk/Unk **375**/Unk/Unk 174	LDH ↑, CK↑, Phosphorus ↑, Alk Phos ↑, amylase ↑; **olz D/C**	UA
29	JP_030400647	26/M	"	5	Unk	Unk	Unk	Olz continued, event continued	Y
30	JP_030400780	31/M	"	20	Risperidone	Unk	Unk (mild)	Prolactin ↑; olz continued, OUNK	N
31	JP_030400788	37/F	"	10	Risperidone	Unk	Unk (mild)	Prolactin ↑; olz continued, OUNK	N, suspect risperidone
32	JP_030400798	22/F	"	20	Chlorpromazine	Unk	Unk (mild)	Olz continued, OUNK	N
33	JP_030400799	60/F	"	20	Levomepromazine, quetiapine	Unk	Unk (mild)	Olz continued, OUNK	N
34	JP_030400804	34/M	"	20	Unk	Unk	Unk (mild)	Olz continued, OUNK	N
35	JP_030400806	32/M	"	5	Chlorpromazine	Unk	Unk (mild)	Olz continued, OUNK	N
36	JP_030400811	57/F	"	15	Periciazine, risperidone	Unk	Unk (mild)	Prolactin ↑; olz continued, OUNK	N, suspect con meds
37	JP_030400813	33/F	"	10	Unk	Unk	Unk (mild)	Olz continued, OUNK	N
38	JP_030400832	37/M	"	10	Bromperidol, sulpiride	Unk	Unk (mild)	Olz continued, OUNK	N, suspect con meds

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
39	JP_030400836	42/M	"	10	Chlorpromazine, quetiapine, risperidone	Unk	Unk (mild)	Olz continued, OUNK	N, suspect con meds
40	US_000134900	41/F	"	20	Amitriptyline, citalopram, clonazepam	fluvoxamine	Baseline: 168[b]/Unk/Unk 238[a]/**175**/53 48 F/U: 203[b]/146[b]/47[b] 52[b]	***Wt gain**, olz continued*	DNK
41	US_000542556	15/M	"	Unk	Carbamazepine, paroxetine, valproate	Unk	Unk	Literature: **Death** (necrotizing pancreatitis), DM	DNK
42	US_000745997	60/F	"	7.5	NONE	Unk	**265**/Unk/Unk	Dry mouth, excessive salivation, excessive thirst, euphoria, abnl gait, malaise, insomnia, tobacco misuse, dental pain, mouth ulceration, abd distention, dysphagia, facial paralysis, high BP; olz continued	NHCP
43	US_000948716	43/M	Hypercholesterolaemia	10	Fluphenazine, lisinopril	Hx of DM	**280**/Unk/Unk	**Wt gain**, socially withdrawn; olz continued	NHCP

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
44	US_001254576	M	"	15	NONE	Unk	Unk	Panic attack, hyperglycemia; **olz D/C, AEs continued**	UA
45	US_001254594	30/F	Blood cholesterol increased	Unk	Unk	Family hx of DM	212/Unk/Unk	Literature: **wt gain,** BMI ↑	Y
46	US_001254596	31/F	"	Unk	Unk	Classical antipsychotic use, family hx of DM	220/Unk/Unk	Literature: **wt gain**, BMI ↑, hyperinsulinemia, leptin ↑	Y
47	US_001254603	46/F	"	Unk	Unk	Family hx of DM	196/Unk/Unk	Literature: **wt gain**, BMI ↑	Y
48	US_001255487	13/M	"	15	Benzatropine, citalopram, lithium	Admission to a LTCF while on olz & benzatropine, multiple previous outpt & short-term tx with hx of self-abuse, dangerous to siblings, elopement, chaotic family structure, med noncompliance	**282/168/**42 **287/174/**47 358, 332	Borderline high liver enzyme levels, TSH ↑	DNK

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
49	US_010463418	23/M	"	15	NONE	Learning disabled, delayed milestones, borderline IQ, premature birth with jaundice, cyanosis, respiratory distress, anatomic chest defect, hyperbilirubinemia, seasonal rhinitis, constipation, scrofula (atypical mycobacterial lymphadenitis)	**280**/Unk/Unk	Interaction with ciprofloxacin, prostatitis, rxn to ciprofloxacin, incontinence, fatty liver, microscopic hematuria, **wt gain**, oversedation; olz dose dec'd, AE continued	Y, due to wt gain
50	US_010667081	50/M	"	20	NONE	NONE	228/Unk/Unk	SGPT & SGOT ↑; olz continued	UA
51	US_010667085	F	"	10	Unk	Unk	**327**/Unk/Unk	Olz continued	NHCP
52	US_010667251	22/M	Hypercholesterolaemia	20	**Levothyroxine**, valproate, ziprasidone	Unk	Unk	**Wt gain**, thinking abnl; **olz D/C but restarted because pt "went downhill"**	NHCP
53	US_011076380	42/M	Blood cholesterol increased	20	Biperiden, haloperidol, levomepromazine, promethazine, risperidone, zotepine	Sinus tachycardia	Baseline: 217/Unk/Unk **242**/Unk/Unk	Convulsive Sz, respiratory arrest, Alk Phos ↑, blood sugar ↑; NO abnl electrolyte, liver damage, or renal failure; **olz D/C, event resolved**	DNK

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
54	US_011176908	36/M	"	15	Alprazolam, estazolam, paroxetine, quazepam	NONE (allergic rxns unk)	**281**/Unk/Unk	**Wt gain**; **olz D/C; TC 185 (YD) with atorvastatin**	UA
55	US_020483294	39/M	"	Unk	Unk	Unk	Unk	Olz continued, OUNK	DNK
56	US_020685237	62/F	"	15	Chlorpromazine, etizolam, flunitrazepam, haloperidol, levomepromazine, prometazine, trihexyphenidyl; NO OC	Orthostatic hypotension, hyperlipidemia; NO hx of AEs, CAD, Vfib, bradyarrhythmia, other cardiac arrhythmia, acute MI, other heart collapse, recurrent angina pectoris, EtOH intox, cerebral vascular disturbance, asthma, epilepsy, or other illnesses; ECG nl, asymptomatic; allergic rxns unk	**250**/Unk/Unk	**Death**, cardiorespiratory arrest, mental condition aggravated, Alk Phos ↑	UA, due to tx with inj
57	US_020987609	F	"	15	Perospirone	Unk	**290-300/** Unk/Unk	**Olz D/C, AE persisting**	DNK
58	US_021089321	12	"	Unk	Unk	Unk	Unk	Olz continued, OUNK	UA
59	US_030695366	14/M	"	10	Risperidone	Prader-Willi syndrome with extreme obesity; NO family hx of DM	Baseline: 143/Unk/Unk 154/Unk/Unk	Literature: DM, olz continued	UA

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
60	US_030695368	17/M	"	Unk	Clozapine, lithium	Schizoaffective disorder, severe obesity due to clozapine; family hx of type 2 DM (mom)	Baseline: 136/Unk/Unk 138/Unk/Unk 145/Unk/Unk	Literature: DM, wt loss, psychotic exacerbation, severe acts of violence, gradual ↑ in violence; **olz D/C, partial remission**	UA
61	US_990217073	40/M	Hypercholesterolaemia	5	Diclofenac, glimepiride, lisinopril, metformin, **simvastatin**, vit C	Overweight, family hx of DM (both sides)	Unk	DM, polyuria, polydipsia	DNK, suspect wt & family hx
62	US_990421252	M	Blood cholesterol increased, lipids increased	Unk	Buspirone, clomipramine, paroxetine	Pancreatitis & elevated TC & lipid levels while on clozaril and risperidone	Unk	Olz continued	Y
63	US_990624089	57/F	Blood cholesterol increased	15	Amlodipine, phenobarbital, phenytoin	Sz disorder, HTN; NO hx of EtOH use	Baseline: 172/Unk/Unk **263**/Unk/Unk	Suicidal, hallucinations, ↑ pancreatic enzymes; asymptomatic; **olz D/C**	DNK, consider phenobarb also
64	US_991131539	56/F	"	Unk	Unk	Unk	**260**/Unk/Unk	EKG abnl, enlarge right atrium, **wt gain**; asymptomatic; olz continued	N
65	US_991232925	43/M	"	Unk	Lithium	Resident at state hospital	↑ by 53/ Unk/Unk	Literature: prospective MUE	Y

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
66	US96114975A	39/M	Hypercholesterolaemia	10	Diazepam, loperamide, **lovastatin**, nicotine	Panic attacks; dad died young of heart attack	Unk	Study: **Death** (acute cardiac arrhythmia), heart attack, ↑ liver enzymes, arm pains; severe CAD	N
67	US97014882A	33/M	Blood cholesterol increased	10	Clonazepam, felodipine, **fluvastatin**, indapamide, mirtazapine, potassium, zolpidem	HTN, obesity, hyperlipidemia	Baseline: **240**/Unk/Unk **700**/Unk/Unk	↑ blood sugar, nausea	Y
68	US97023562A	22/M	Blood cholesterol abnormal	10	Unk	Unk	Unk/141/**26**		UA
69	US97044960A	23/M	Blood cholesterol increased	20	Clonazepam, perphenazine, valproate	Rash with Tegretol	**483**/Unk/Unk	Nephrotic syndrome, high protein in urine, ↑ creatinine, **wt gain,** swelling, rash	Y, consider valproate also
70	US97045527A	28/M	"	20	Unk	Thioridazine, risperidone, divalproex	Unk	Auditory hallucinations, **wt gain**, hungry	NHCP
71	USA020211618	40/M	Hypercholesterolaemia	15	redacted	NO family hx of hypercholesterolemia	Baseline: 200-210/ Unk/Unk **600**/Unk/Unk	**Wt gain**; olz continued	UA, consider [redacted] also
72	USA020312308	23/M	Blood cholesterol increased	5	redacted valproate	Unk	**320**/Unk/Unk	↑ blood sugar	Y, consider [redacted] also

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
73	USA020312719	32/M	"	10	Unk	Unk	Unk	**Wt gain**; olz continued, OUNK	NHCP
74	USA020313006	41/F	"	15	Amlodipine/ benazepril, propranolol, triamterene	High BP		Facial contortions, vision damage, painful urination, tremor, urinary incontinence, **wt gain**, compulsive eating; olz continuing, AEs continuing	NHCP
75	USA020414710	54/M	"	Unk	Unk	Unk	Baseline: 200/Unk/Unk **320**/Unk/Unk F/U: 194/Unk/Unk	**Olz D/C, AE resolved**	Y
76	USA020515348	20/M	"	15	**Atorvastatin**, quetiapine	Paranoid schizo, AEs with risperidone	4x nl/ Unk/Unk	**Wt gain**, permanent stretch marks; atorvastatin D/C; **olz D/C but psychotic Sx returned, restarted**	NHCP
77	USA020920732	37/F	Blood cholesterol increased, LDL increased	15	Unk	Unk	**284/213**/Unk	**Wt gain**; **olz D/C**, OUNK	NHCP

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
78	USA020920769	47/F	Blood cholesterol increased	30	Benzatropine, **fluvastatin**, furosemide, ibuprofen, topiramate, valproate	Bipolar disorder with psychotic features, hypercholesterolemia, hypertriglyceridemia	**260/161/34** 325	OD, pitting edema of lower extremities, **wt gain; olz D/C, lipids improved**	Y
79	USA021022302	39/M	"	15	Lithium, venlafaxine	Schizoaffective disorder, suicidality	**287**/Unk/Unk	**Death** (ARF), hyperglycemia, acute rhabdo, diabetic coma, constipation; **olz D/C**	UA
80	USA021124027	49/M	"	10	Gabapentin, trazodone, venlafaxine	Obesity, depression, poor impulse control, noncompliant with DM meds	Unk	CABG, DM, chest pain, high blood glucose; **olz dose ↓ to 7.5**, recovering from surgery	UA
81	USA021124187	20/M	"	10	NONE	Unk	**254**/Unk/Unk	Chest discomfort, **wt gain**; olz continued, OUNK	NHCP
82	USA030125560	34/M	"	10	Topiramate	Psychosis	230, **250**/ Unk/Unk	Appetite ↑; **olz D/C,** OUNK	NHCP
83	USA030536259	30/M	"	Unk	Quetiapine	Paranoid schizo, intermittent med noncompliance	Unk	Blood sugar ↑, LFTs ↑, incoherent, wt loss, thirst ↑	Y

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
84	USA030639685	40/F	"	Unk	Unk redacted	Unk	Unk	Blood sugar ↑; **levels returned to nl when olz D/C**, rechallenge unk	UA
85	USA030740932	51/F	Hypercholesterolaemia	10	gabapentin	Depression, anxiety, multiple psychiatric hospital admissions, suicide attempts	Unk	**Wt gain**, appetite ↑, heating sensation in brain, ache in ctr of brain, binge eating, chronic periodontitis, allergic rhinitis, asthma, difficulty sleeping, audio & visual hallucinations; **olz D/C**, OUNK	UA
86	USA030947969	7/M	Blood cholesterol increased	7.5	Unk	Family hx of obesity (mom)	224/Unk/Unk		N

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
87	USA030948566	45/M	"	5	Clonazepam, haloperidol, quetiapine, risperidone, thioridazine, valproate	Low BP, sensitivity to meds, depression with valproate; NO hx of Sz	Baseline: 170/Unk/Unk 201/Unk/Unk	**Wt gain**, rapid heart rate, buccoglossal syndrome, fever, eye infection, back stiffness, back pain, breathing fast, sleep excessive, panic attacks, hyperkinesias, anxiety, agitation, restlessness, dry mouth, unable to sleep, sleepy; **olz D/C,** OUNK	NHCP
88	USA030948579	44/F	Blood cholesterol increased, LDL increased, HDL increased	10	Levothyroxine, zolpidem	Unk	206, **308/** Unk/Unk	Acute gall bladder events, pain in kidney, radiating pain around femoral artery, GGT ↑, **olz D/C**	NHCP
89	USA031050436	F	Blood cholesterol increased	20	Bupropion, clonazepam, venlafaxine	Unk	**259**/Unk/Unk	Olz continues, OUNK	NHCP
90	USA031151635	M	"	10	Unk	Schizo, schizoaffective disorder	Baseline: negligible Borderline bad	Olz continues, OUNK	NHCP

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

#	Case ID	Age (yrs)/ Sex	MedDRA preferred term(s)	Olanzapine dosing (mg/day)	Concomitant Medications	Medical history	Total cholesterol / LDL / HDL (mg/dL), TG	Acute clinical issues[c]/ Comments	HCP Rel
91	USA031253801	39/M	LDL increased, HDL decreased	10	Clonazepam	Panic attacks	Unk	↑ frequency panic attacks, frequent urination, wt loss, olz continues, OUNK	NHCP
92	USA040157726	54/M	Blood cholesterol increased	20	Clonazepam, gabapentin, nefazodone, pravastatin	Poor diet, lack of exercise; family hx of high TC (bro)	Baseline: 150-160/ Unk/180(?) **265**/Unk/Unk 299	**Wt gain**; olz continues, AEs not resolved	NHCP
93	USA040361451	51/F	"	10	Citalopram	Schizo	Unk	**Wt gain**; olz continues, AE recovering	NHCP
94	USA040363025	56/F	"	10	Alprazolam, bupropion, dexamfetamine, levothyroxine, metoprolol, quetiapine, risperidone	Insomnia, hypothyroidism, addiction NOS, depression, BP probs, allergies NOS, menopause, obesity/wt gain; family hx of gallstones, HTN, COD: heart attack, DM, obesity; risperidone	222/Unk/Unk	Lack of drug effect, GGT ↑, hangover effect, **wt gain**, drowsy; AEs not resolved	NHCP

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Table 9X:
Number of Cases with a MedDRA Preferred Term of Weight Increased

Table	**# Cases with Weight Increased**	**Total Cases**	**% of Cases with Weight Increased**
Triglycerides cumulative (all cases)			
Preferred terms			
Hyperlipidaemia	20	50	40%
Hypertriglyceridaemia	31	76	40.8%
Blood triglycerides increased	61	210	29.0%
Textstring search cases	20	88	22.7%
Miscellaneous terms (Lipids abnormal, Lipids increased, Lipid metabolism disorder, Dyslipidaemia)	7	23	30.4%
Total	**139**	**447**	**31.1%**
Triglycerides (≥ 500mg/dl)			
500 - 999 mg/dl	29	79	36.7%
≥1000 mg/dl	20	94	21.3%
Total	**49**	**173**	**28.3%**
Metabolic Syndrome			
Preferred Term Search	58	75	77.3%
Textstring Search	3	13	23.1%
Total	**61**	**88**	**69.3%**
Cholesterol			
Preferred term search			
Total	**27**	**93**	**29.0%**

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Table 10X: Review of Olanzapine LIPID cases regarding Dechallenge /Rechallenge Information with Emphasis upon those with Serum Triglyceride values ≥ 500mg/dl

Case categorization:

Global Product Safety (GPS) examined the olanzapine safety database (Clintrace) for all cases that involved the reporting of lipid abnormalities. The overall review of case reports had placed them into 4 general categories. Those categories were 1) elevation of serum triglyceride of ≥ 500mg/dl; 2) elevation of serum cholesterol that did not document a triglyceride elevation; 3) potential metabolic syndrome (≥ 3 of 5 risk factors present) based upon the adult treatment panel (ATP-III) guidelines; and 4) all serum triglyceride elevations ≥ 150mg/dl.

It is acknowledged that there would be some overlapping of cases within 3 of the categories. The only category that would not have overlap would be category 2) elevation of serum cholesterol that did not document a triglyceride elevation.

Table 1displays the 4 categories with the number of cases found with the search methodology.

Table A

Case Category	**# of case reports**
Elevation of serum triglycerides ≥ 500mg/dl	173
Elevation of serum cholesterol	93
Potential metabolic syndrome	88
Elevation of serum triglycerides ≥150mg/dl	447

The assessment on LIPIDS focused on the case category with the 173 reports. Those were the reports with "very high" triglyceride values.

Dechallenge / Rechallenge working definitions:

Dechallenge would refer to a decrease in dosing or a discontinuation of the drug.

Rechallenge would refer to an increase in dosing or a restart of the drug that followed a dechallenge.

For the purpose of this review, interest in dechallenge and rechallenge information is focused towards olanzapine in regards to lipids and metabolic syndrome only. It is not focused towards any other adverse events involved in the case such as headache. The application of the information is most useful when the following have taken place:

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Olanzapine is the only drug discontinued (dechallenged) and is not one of several drugs stopped simultaneously
Pharmacological intervention (antilipemics) has not taken place at the time of olanzapine dechallenge. Antilipemics such as atorvastatin, gemfibrozil and others added with the discontinuation of olanzapine cannot be interpreted.
Olanzapine has been restarted as the only drug and not in a combination of drugs and the restart has followed a positive dechallenge.

Each category would be assessed through the placement into one of four primary groups. Those groups would be the following:

Olanzapine continuation
Olanzapine disposition unknown
Olanzapine stopped due to patient death
Olanzapine dechallenged (stopped or dose reduced)

The group with olanzapine dechallenge would be further subdivided through assessing the outcome on serum triglyceride levels. The cases would be placed into one of the following:

Dechallenge- outcome unknown
Dechallenge - negative (triglycerides did not lower)
Dechallenge - positive (triglycerides lowered)

Serum triglycerides ≥ 500mg/dl (n = 173 reports)

The 173 were examined and subdivided as displayed in table 2.

Table B

Olanzapine disposition groups	**# of reports**	Comments
Continuation	49	
Unknown	41	
Deaths	4	FR_020100595 USA020515251 USA031050393 US_011178209
Dechallenge - positive	33	**79 total dechallenge cases. 41 had no discussion of outcome**
Dechallenge - negative	5	
Dechallenge - unknown	41	
Total	**173**	

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

Nineteen percent of the cases (33/173) were classified as a positive dechallenge to olanzapine. A significant number of the positive dechallenge cases are not well developed. However, there are 12 notable case reports provided in table 3.

Strongest positive dechallenge cases:

Table C

Case ID	Comments
JP_040302825	32-year old male without co-morbidities had a triglyceride level of **507mg/dl.** Olanzapine stopped. Serum triglycerides reduced to within normal limits **(107mg/dl)** No baseline triglycerides mentioned. No drugs to lower lipids added.
USA020616863	45-year-old male with a baseline triglyceride of **213mg/dl** received olanzapine 8-days. Serum triglyceride level was **500mg/dl** after 8-days. Olanzapine stopped. Fenofibrate started. Serum triglycerides were **176mg/dl** 1-year later.
FR_031103127	38-year-old male without a baseline triglyceride value received olanzapine for 90-days. Serum triglycerides were **685mg/dl** after 90 days. Olanzapine stopped. 30-days later serum triglycerides were **139mg/dl.** Metformin started with olanzapine dechallenge. No antilipemics started.
JP_030200417	27-year-old male without a baseline serum triglyceride value had taken olanzapine for 6-months. Serum triglyceride was **702mg/dl**. Olanzapine was discontinued. No other drugs were stopped. No new drugs started. Serum triglycerides reduced to **48mg/ml** within 30-days of dechallenge.
US_030695010	42-year-old male without a baseline serum triglyceride value had taken olanzapine for > 5-years. Serum triglycerides were **709mg/dl**. Olanzapine stopped. Serum triglycerides decreased to **128mg/dl** in less than 6-months. Patient also lost 40-lbs over same time frame.
US97061336A	24-year-old male with baseline serum triglyceride of 609mg/dl started olanzapine. Olanzapine administered less than 60-days when serum triglycerides were **1627mg/dl**. Olanzapine stopped. In less than 30-days serum triglycerides were **155mg/dl** Gemfibrozil therapy had been started.
USA020211675	29-year-old male without a baseline serum triglyceride value took olanzapine for 90-days and the serum triglyceride value was **7067mg/dl.** Olanzapine discontinued. Patient started on metformin and atorvastatin. Serum triglyceride level was **149mg/dl** 28-days later.
USA020718851	42-year-old male with a baseline triglyceride of **1200mg/dl** received olanzapine for an unknown duration and developed pancreatitis. Serum triglycerides were **8000mg/dl**.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

	Olanzapine and valproic acid stopped. Atorvastatin started. Serum triglycerides were **225mg/dl** 19-days later.
US_001052572	48-year-old male with a baseline serum triglyceride of **389mg/dl** took olanzapine for an undetermined time period and the serum triglycerides were **5873mg/dl**. Olanzapine stopped. Metformin and atorvastatin started. Serum triglycerides were **207mg/dl** 1-year later.
US_020281705	Male of unknown age with a baseline serum triglycerides of **83mg/dl** took olanzapine for 180-days and had a serum triglyceride value of **1954mg/dl.** Olanzapine stopped. Serum triglycerides were **178mg/dl** 4-weeks later.
US_021291011	23-year-old male had taken olanzapine for 5-months and serum triglyceride level was **72mg/dl.** Serum triglycerides were **1053mg/dl** 8-months later. Olanzapine stopped. Serum triglycerides were listed as **normal (no value)** 10-days later.
US_020987964	48-year-old male without a baseline serum triglyceride value had taken olanzapine for 3 ½ months. Serum triglycerides were **1113mg/dl.** Olanzapine stopped. Oral hypoglycemics started. 5-months later serum triglycerides were **177mg/dl.**

All of the dechallenge cases (n = 79) were examined for rechallenge information concerning the elevated triglyceride values. The emphasis among the dechallenge cases would be those with a documented positive dechallenge. There were 5 cases that discussed a rechallenge of olanzapine. In some cases the discussion did not focus on serum triglycerides but rather another clinical issue. The cases are displayed in table 4.

<u>Rechallenge cases among the dechallenge reports:</u>

Table D

Case ID	Comments
USA040156734	45-year-old female with a peak serum triglycerides of **1650mg/dl** underwent dechallenge. Serum triglycerides noted to have decreased slightly (**value not provided**). BS also decreased. Olanzapine restarted. Olanzapine again dechallenged. BS improved. Triglycerides did not improve upon second dechallenge.
EWC0010225371	52-year-old male with a peak serum triglyceride level of **1060mg/dl** underwent dechallenge. Serum triglyceride value **change not noted**. 45-days later olanzapine restarted. Outcome of rechallenge on triglycerides not provided.
USA020110313	30-year-old male with a peak serum triglyceride of **600mg/dl** while on olanzapine started metformin.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

	Triglycerides decreased to mid 200mg/dl level. Olanzapine underwent dechallenge. Values not provided but an improvement noted. Olanzapine restarted. No outcome on triglyceride level provided.
USA030947448	65-year-old female with a peak serum triglyceride of **706mg/dl** underwent dechallenge. Serum triglycerides decreased (**no value**). Olanzapine restarted and outcome on triglycerides not provided.
US_010565372	39-year-old male with a peak serum triglyceride of **823mg/dl** underwent dechallenge. Change in serum triglycerides **not noted**. Olanzapine restarted due to exacerbation of psychosis. Outcome on triglycerides not provided.

There were not any cases among the 173 triglycerides ≥ 500nmg/dl reports whereby a positive dechallenge took place followed by a well documented positive rechallenge.

Case reports with serum triglycerides ≤ 500mg/dl (n = 274)

The cases within this group were examined for placement into the same categories used for the "very high" serum triglycerides. Table 5 displays the results of the assessment.

Table E

Olanzapine disposition groups	**# of reports**	Comments
Continuation		
Unknown		
Deaths		
Dechallenge - positive		
Dechallenge - negative		
Dechallenge - unknown		
Total	**274**	

Case reports with elevated cholesterol without reference to elevated triglycerides:

There were 93 case reports that involved an elevation of serum cholesterol without the mention of altered triglycerides. When a case discussed both an elevation of cholesterol and triglycerides it was captured in one of the other tables

INSERT TABLE 10X: MedWatch Forms for Elevated Triglycerides and Cholesterol Reports.

[a]Fasting
[b]Non-fasting
[c]Concomitant AEs

[GAB1]IMO, I don't think it is necessary to provide extensive discussion on each case of interest. Our goal to make sure that the agency understands the search and then provide examples. However, all cases that we reviewed in be listed in an appendix. Also, I think the narrative text for all cases need to be supplied, either on AE reports or you could pdf the clintrace files – I wouldn't recommend the latter approach.

There is also no way to make judgments about causality except for identifying rechallenges. Since one would expect to observe these events in the population, many cases would be expected. I hope one section in the report that reviews the epi of this issue is going to take the estimated O use and then extrapolate the background rates to this use showing the many cases we would expect.

The summary for the post-marketing should go with the summary for the rest of the document. The summary should be that, as expected, there are cases of MS that occur during o treatment. Likewise patients treated with olanzapine can have large increases in tri. Given the background rate of these events, it is not possible to reach conclusions about attribution on individual cases, but given that olanzapine causes weighty gain, which itself can be associated with elevations in triglycerides, and increases in blood sugar, some cases are likely to have been caused by O.

Nothing that we have found is unexpected.
[GAB2]I don't understand where the 88 came from. 75, 1 and 1 from the 3 search strategies?????

[GAB3]It would be great to include the seriousness and codes for dechallenge and rechallenge in the table.
[GAB4]It would be helpful to have a summary table before this for the 88 cases that includes dechall and rechall info.
[GAB5]What about oral hypoglycemis?
[GAB6]Correct?
[GAB7]Did his weight change at all? If no change, then you have to wonder about an independent effect of O on lipids and glucose.
[GAB8]???
[GAB9]I assume he is not on any other oral diabetic agents – right?
[GAB10]Any values??
[GAB11]Did they measure fasting insulin levels – is that what this is. ??? How relevant is the increase given the other findings. If this is highly variable, I would delete the comment.
[GAB12]Not sure how these case reports will go in or if they will.
[GAB13]If we add the summary table for all 88 cases, we will not need this table.
[GAB14]I don't understand where the 88 came from. 75, 1 and 1 from the 3 search strategies?????

[GAB15]The frequency table doesn't have 14???????
[GAB16]Not sure we will need this
[GAB17]You could compare the odds of pancratitis in the 173 against the odds of pancreatic in the remaining olan events.
[GAB18]Correct???