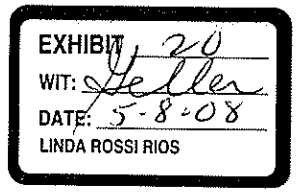
Id : i.m.ef999881864fd860e53326f80a60a9f2
CN : SQ1ED00428297
Date : Monday, September 18, 2000 10:23:59 PM GMT
From : Mailbox.OldNotes@astrapharmaceuticals.com
To : Wayne.Geller@astrazeneca.com
Subject : Re: FW: Quetiapine and glucose metabolism disorders Forward fromNotes
Attachments : SeroquelSERMDMDKAPositionPaper.doc
Custodians : Geller, Wayne



From: OldNotes Mailbox

Sent: Monday, September 18, 2000 11:24 PM

To: Geller Wayne

Subject: Re: FW: Quetiapine and glucose metabolism disorders Forward

from Notes

Attachments: Mac Word 3.0

CONFIDENTIAL

To: G=Dorothee/S=Wientjes/O=Astra Pharmaceutica BV/P=Astra/A=400NET/C=NL,

G=Liz/I=EH/S=Smith/OU=ALDERLEY/O=PHARMS/P=ZENECA/A=TMAILUK/C=GB@X400

cc: G=Safety/S=Mailbox/O=Astra Pharmaceutica BV/P=Astra/A=400NET/C=NL,

G=Joy/I=JA/S=Gulliford/OU=ALDERLEY/O=PHARMS/P=ZENECA/A=TMAILUK/C=GB,

G=Vikram/I=VJ/S=Dev/OU=PHWILM/P=ZENECA/A=TMAILUK/C=GB

From: Wayne Geller

Date: 09/18/2000 02:27 PM

Subject: Re: FW: Quetiapine and glucose metabolism disorders

This message contains 1 attachment(s).

Message

Dear Liz and Dorothee,

Attached is a position paper based upon my presentation at the last SERM meeting on diabetes mellitus, diabetic ketoacidosis, and non-ketotic hyperosmolar coma.

Please feel free to contact me if you have any additional questions.

Thanks and kind regards,

Wayne

(See attached file: SeroquelSERMDMDKAPositionPaper.doc)

Thanks,

Wayne

To: Wayne Geller/HQ/Astra Merck

cc: /G=Dorothee/S=Wientjes/O=Astra Pharmaceutica BV/P=Astra/A=400NET/C=NL,

/G=Safety/S=Mailbox/O=Astra Pharmaceutica BV/P=Astra/A=400NET/C=NL,

/G=Joy/I=JA/S=Gulliford/OU=ALDERLEY/O=PHARMS/P=ZENECA/A=TMAILUK/C=GB

From: Liz Smith @ X400

Date: 09/18/2000 11:51 AM GDT

Subject: FW: Quetiapine and glucose metabolism disorders

Message

Dear Wayne

Please find attached below a request from the Dutch regulatory authorities about Seroquel.

I would be grateful if you could reply direct to Dorothee since I am out of the office after tomorrow, and Mary O'Hare is also out of the office this week.

With many thanks and kind regards,

Liz

From: Wientjens, Dorothee (temp. employee)

Sent: 18 September 2000 08:53

To: Smith, Liz EH

Cc: O'Hare, Mary M; Hyde, Margaret EM; Gulliford, Joy JA; Whittaker, Denise D - R&D

Subject: FW: Quetiapine and glucose metabolism disorders

Dear Mailbox,

Please find enclosed a letter form the Duth authorities concerningQuetialpine and glucose metabolism.

I would be most grateful if you could address his request.

Thank you in advance

Dorothee PWM Wientjens

DSO

AstraZenecaNL

-----Oorspronkelijk bericht-----

Van: Meiners, dhr. drs. A.P. [mailto:ap.meiners@cbg-meb.nl]

Verzonden: dinsdag 5 september 2000 15:35

Aan: Wientjens Dorothee (temp. employee)

Onderwerp: Quetiapine and glucose metabolism disorders

Dear Dorothee,

At a recent pharmacovigilance working party a signal was raised for one of the other atypical antipsychotic drugs in relation to glucose metabolism disorders. Looking at our recent PSUR assessment reports we don-t seem to have recognised this with Seroquel, however, increases in weight and blood lipids are recognised, so it would not seem impossible. A formal request for an overview and assessment report on all reports of glucose metabolism disorders associated with quetiapine use is coming your way as part of conclusions of assessment of a type II variation application currently under review, but to expedite matters I am also already sending you this request by e-mail. Would it be possible to submit such a report on short notice. It probably doesn-t have to be very extensive as it only focusses on a single issue and it could well be that the number of reports is very limited(even if it would require searching your database for terms such as glucose metablism disorder, glucose incresased, hyperglycemia, diabetes, hypoglycemia, etc.)

Sincerely,

==========

Arthur P. Meiners, head of pharmacovigilance Medicines Evaluation Board Kalvermarkt 53 PoBox 16229 2500 BE The Hague Netherlands tel +31(70)3567492 fax +31(70)3567515 mailto:ap.meiners@cbg-meb.nl

ACCESSION NUMBER:

SAFETY POSITION PAPER

'SEROQUEL'

DIABETES MELLITUS, DIABETIC KETOACIDOSIS, NON-KETOTIC HYPEROSMOLAR COMA, AND HYPERGLYCAEMIA

AUTHOR:
Wayne K. Geller, MD
Global Drug Safety Physician
Wilmington, DE

SIGNATURE: .....

DATE: .....

SUMMARY AND CONCLUSIONS:

Currently, the Seroquel CDS does not include any references to diabetes mellitus, diabetic ketoacidosis, or hyperglycaemia associated with Seroquel therapy. Safety data derived from clinical trials and spontaneous reports often containing limited information may represent a weak signal linking Seroquel with impaired glucose regulation, including occasional reports of new onset diabetes mellitus. None of these reports are absolutely steadfast (i.e., there are no clear index cases and there were no reports of positive dechallenges/rechallenges) and most have either incomplete information or other explainable causes. Although the number of reports is fairly sizable, it was felt that there is insufficient evidence at present to warrant an amendment to the Seroquel CDS. However, it was agreed that this topic will be kept under ongoing review and will be reassessed at a later time. Additional clinical trials are planned in which baseline fasting blood glucose concentrations will be obtained as well as follow-up measurements on study drug.
Currently, no such signals exist for the complications of diabetes such as non-ketotic hyperosmolar coma or diabetic ketoacidosis.

1 INTRODUCTION

In May 2000 FDA notified AstraZeneca that, based upon review of postmarketing safety data for Seroquel and other atypical antipsychotics, they were further investigating a possible signal for new onset diabetes mellitus (NODM), non-ketotic hyperosmolar coma (NKHOC), and diabetic ketoacidosis (DKA). FDA expressed concern that increased market exposure could result in an increased number of reports of these events as has been observed with similar agents. In there correspondence (see attachment), they have requested "more extensive safety information" from all phases of clinical development to the present for Seroquel for their review. This discussion document will specifically address FDA's third item on their list of requests, "A review of spontaneous postmarketing reports for new-onset diabetes mellitus, hyperglycaemia, hyperosmolar coma, diabetic ketoacidosis, and weight gain".

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[1], several of these products have in their labels statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.
Frequent (>10%):
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

Clozapine: *Warnings and Precautions*:

Hyperglycaemia:

Severe hyperglycaemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL® (clozapine) treatment in patients with no prior history of hyperglycaemia. While a causal relationship to CLOZARIL® (clozapine) use has not been definitively established, glucose levels normalized in most patients after discontinuation of CLOZARIL® (clozapine), and a rechallenge in one patient produced a recurrence of hyperglycaemia. The effect of CLOZARIL® (clozapine) on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL® (clozapine) who develop symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycaemia, the discontinuation of CLOZARIL® (clozapine) should be considered.

Sertindole: Warnings and Precautions: *Diabetic patients:* Serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.
Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

2 BACKGROUND

The Seroquel core data sheet (CDS) last revised in March 2000 does not include listings for NODM, hyperglycaemia, NKHOC, or DKA. The following statement addresses the issue of weight gain with Seroquel:

"As with other antipsychotics, SEROQUEL may also be associated with limited weight gain, predominantly during the early weeks of treatment".

The Seroquel US package insert (PI) includes hyperglycaemia and diabetes mellitus as labeled events occurring infrequently (in 1/100 to 1/1000 patients) according to premarketing clinical trial safety data. The aforementioned complications of diabetes mellitus are not in the PI.

Patients with either impaired glucose tolerance (IGT) or frank diabetes mellitus have hyperglycaemia [2]. The term IGT represents a metabolic condition between normal glucose homeostasis and diabetes mellitus. This includes individuals with fasting glucose levels ≥110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l).

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The criteria for the diagnosis of DM are as follows:

1. Symptoms of DM (polyuria, polydipsia, and unexplained weight loss) plus random plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l); or
2. Minimum 8 hour fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l); or
3. Two hour plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test using a glucose equivalent of 75 g anhydrous glucose dissolved in water

Patients with diabetes mellitus are classified as having Type I or Type 2 disease. Patients with Type 1 disease are absolute insulin deficient with β-cell destruction and are at risk for developing DKA. Patients who develop Type 2 disease have both abnormal insulin secretion and insulin resistance in target tissues and are not at risk for developing DKA. It is felt that insulin resistance in these patients is the primary event and that obesity contributes to insulin resistance [3]. Type 2 diabetes mellitus is most prevalent and is thought to be a polygenic disease. The majority of patients with Type 2 disease are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2), but this is not thought to be the only factor that contributes to insulin resistance. Individuals with dyslipidemia and/or hypertension are at increased risk. There is a strong genetic predisposition to Type 2 disease. It is well known that a modest weight reduction in an obese individual with Type 2 DM frequently results in significant reduction in blood glucose levels. This is the cornerstone of therapy in patients with Type 2 diabetes mellitus, prior to and during treatment with pharmacologic agents.

Diseases and conditions that have been associated with diabetes mellitus include pancreatic diseases, acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma, congenital rubella, cytomegalovirus, pregnancy, and others. Drugs that are known to cause or contribute to hyperglycaemia include: pentamidine, nicotinic acid, glucocorticoids, thyroxine, diazoxide, β-agonists, thiazide diuretics, phenytoin, α-interferon, and others.

Criteria for testing for DM in otherwise asymptomatic, undiagnosed individuals are as follows:
Individuals ≥ 45 years of age, or younger in patients who:

- Are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2)
- Have a first degree relative with DM
- Belong to high-risk population
- Delivered a ≥ 9 pound baby or have been diagnosed with gestational DM
- Are hypertensive (≥140/90 mmHg)
- Have hyperlipidemia
- Have had abnormal IGT or IFG

3 THE LITERATURE

Wilson et al [4] presented a poster entitled, *New-Onset Diabetes and Ketoacidosis with Atypical Antipsychotics* at the American College of Neuropsychopharmacology Annual Meeting, December 12-16, 1999, in Acapulco, Mexico. They evaluated the risk of patients using atypical antipsychotics for developing new-onset diabetes mellitus and ketoacidosis. Their interest evolved from case reports in the literature describing altered glucose metabolism in patients receiving atypical antipsychotic agents (notably clozapine, olanzapine, and quetiapine). They conducted a retrospective analysis of the Ohio Department of Mental Health database searching for patients treated with an atypical antipsychotic agent who had also been evaluated or treated for diabetes mellitus. In 11 of 126 (8.7%) of patients receiving clozapine, olanzapine, or quetiapine were diagnosed with new-onset, acute, or market glucose intolerance. Six of these patients required insulin (4 short-term) and five developed DKA. Confounding these results are that only 21/126 patients studied had baseline fasting glucose and that only 14 patients had follow-up studies. Their findings were that:

1. The mean and median time to onset of diabetic ketoacidosis after starting treatment with atypical antipsychotic medications were 81 and 33 days, respectively (N=5).
2. Changes in glucose tolerance were not related to significant weight gain and often occurred during the first 6 weeks of treatment. Mean and median weight gains in patients with new-onset DM were 16 and 8 pounds, respectively.

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[4], several of these products have in their label statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.
Frequent (>10%):
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

Clozapine: *Warnings and Precautions*:
Undesirable effects: On rare occasions, hyperglycaemia has been reported in patients on Clozaril treatment.

Sertindole: Warnings and Precautions: *Diabetic patients:* Serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.
Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

4 CLINTRACE DATABASE (IN HOUSE SAFETY DATA)

A search was conducted for all cases in which diabetes mellitus, hyperglycaemia, diabetic ketoacidosis, and non-ketotic hyperosmolar coma were reported with Seroquel. The following are narratives for these 28 cases.

Case Number: 2000UW01164

KETOACIDOSIS, DIABETES MELLITUS, POLYURIA, POLYDIPSIA, WEIGHT LOSS, ELEVATED GLUCOSE LEVEL

A report has been received from a registered pharmacist, via sales rep, concerning a 43 year old male with a history of mental illness who started Seroquel 200mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 30 lbs. Fasting blood sugar showed glucose level over 700. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on Seroquel. More information will be sought.

Case Number: 2000UW01047

COUGH, ELEVATED CHOLESTEROL, WEIGHT GAIN, CONSTIPATION, ASTHMA, WORSENING FIBROMYALGIA, MUSCLE SPASMS, TENSENESS IN NECK, URINE ODOR, WORSENING ARTHRITIS, WORSENING ENDOMETRIOSIS, ELEVATED BLOOD SUGAR, EXCITABLE, DIFFICULTY IN WAKING, NEGATIVE MOOD, DECREASED SEX DRIVE, INABILITY TO HAVE ORGASMS

A report has been received from a nutritionist, who is also the patient, who has been receiving Seroquel, six 25 mg tablets at night, since September 1997 for psychotic episodes. She has been experiencing cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms in her neck and back, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, she is more excitable, has difficulty in waking, negative mood, decreased sex drive, and inability to have orgasms.

Case Number: 2000UW00266

DIABETES MELLITUS

A report has been received from a pharmacist concerning a 12 year old male patient who had been receiving Seroquel 300mg daily since 06 Dec 1999. On 26 Jan 2000, the patient experienced hyperglycaemia (blood sugar level of 863) and was hospitalized. Seroquel was discontinued and the patient was treated with insulin. His blood sugar level has decreased to 170. Concomitant medications include Zoloft, Klonopin, Haldol and Depakote. Follow-up 23 Feb 2000: Pharm D reports that "after further testing, the attending physicians did not feel that Seroquel was involved in the patient's hyperglycaemia. The patient was diagnosed with insulin dependent diabetes mellitus. The patient is currently being seen in the diabetic clinic."

Case Number: 1999UW03532

DIABETES MELLITUS, WEIGHT GAIN

A report has been received from a physician concerning a 45 year old female who has been receiving Seroquel and developed diabetes. Physician feels that Seroquel may possibly be responsible for the development of diabetes. Follow-up 11 Nov 1999: Physician reports that the 47 year old female (not 45) had been receiving Seroquel 600mg daily for schizoaffective disorder for a total of 12 months and experienced a severe 50 pound weight gain (date of onset unknown with no improvement). The patient was hospitalized in June 1999 due to the development of severe diabetes mellitus (difficult to control hyperglycemic). The patient is now receiving insulin and although the event continues, it has improved. Seroquel was tapered for discontinuation. Concomitant medications include Klonopin and Benadryl. The patient has a medical history of Hepatitis C, hypertension and arthritis. Physician states that he believes "Seroquel caused the weight gain which brought out diabetes in this patient likely predisposed for this condition."

Case Number: 1999UW03387

TYPE II DIABETES, DROWSINESS
A report has been received from a physician concerning a 17 year old Hispanic male patient who had been receiving Seroquel 100mg every evening since Jan 1999 for psychotic depression and auditory hallucinations. In March 1999, due to drowsiness in the daytime, the dosage of Seroquel was decreased to 50mg every evening. In July 1999, the patient was diagnosed with Type II diabetes. On 11 Sept 1999, Seroquel dosage was again decreased to 25mg every evening. The patient had been receiving Risperidol prior to Seroquel. Concomitant medications include Ritalin for attention disorder and Serzone for depression.

Case Number: 1999UW00969
COMPLICATIONS OF DIABETES MELLITUS
A report has been received from a physician concerning a 28 year old male patient who was taking Seroquel and Lithium (doses, duration, indications unknown). The patient presented to the emergency room following flu-like symptoms lasting for one week, as well as asthma, and weakness in the legs. There was no report of an increase or decrease in body temperature before presentation. His temperature at the emergency room was 107+ F (rectal probe 108 F), cardiac arrhythmias, liver enzymes were twice normal, blood glucose was 2240, potassium low, CPK normal, Lithium level was not elevated (0.4 or 0.6). The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. He died at 4:00 a.m., on 14-Mar-1999. The tentative diagnosis is neuroleptic malignant syndrome. Complete autopsy reports are pending.
*Follow-up received 22-Mar-1999: A pharmacist reports that the patient started Zithromax on 10-Mar-1999, to counter a suspected infection. She also reports that the patient had been bleeding from his eyes and nose.
*Follow-up received 14-Mar-1999: The patient presented on 14-Mar-1999 with focal twitching. He had increased tone, no doll's eyes or corneal responses. The pupils were mid-position and not reactive, and there was no reaction to noxious stimuli. Ativan was started, to a loading dose of 0.03 mg/kg. No further seizure activity was noted. The patient was started on Dantrium 2 mg/kg, with the dose of 150 mg. The patient developed cardiac arrhythmia requiring anti-arrhythmics. He continued to be acidotic and received bicarbonate and insulin. Split fibrins were ordered for the bleeding abnormalities, as well as whole blood. A pacemaker was placed and a rhythm obtained. The patient had been packed in ice from the onset. He died on 15-Mar-1999. The reporter attributed the event to a drug effect from multiple prescriptions.
*Follow-up received 05-May-1999: The county coroner reported the patient's cause of death as complications of diabetes mellitus. The patient did not have neuroleptic malignant syndrome. There had been a history of a 10-16 lb weight loss with flu-like symptoms, and blood glucose of 2240 on admission.

Case Number: 1999UW00967
DIABETES
A report has been received from a physician concerning a 17 year old male who is receiving Seroquel 200mg twice daily for schizophrenia. The patient was initially started on 100mg which was increased. While being hospitalized for his schizophrenia, routine lab work revealed diabetes which is being treated with Glucotrol 300mg daily. Patient also receives Paxil and Depakote. Patient continues on Seroquel.

Case Number: 1999UW00288
BLOOD SUGAR RISING
A report has been received from a 58-year-old diabetic female patient who has been receiving Seroquel since September 1997. In 1994 she was diagnosed with diabetes mellitus. In 1997 her blood sugar readings began rising and on 20 Jan 99 the reading was 321.

Case Number: 1999AP06660
LOSS OF DIABETIC CONTROL, TOOTH PAIN, INSOMNIA
A report has been received from a pharmacist concerning a 45 year old male patient who has been receiving Seroquel since April 1999 for treatment of schizophrenia. The patient began quetiapine therapy on 300-400 mg/day and increased to 750 mg/day in September/October 1999. For two years previously, the patient had a history non-insulin dependent diabetes mellitus. This was initially treated with metformin and then diet-controlled only until he started Seroquel in April 1999. After staring quetiapine therapy, the patient developed a loss of diabetic control,

particularly on the higher dosage. Blood glucose which was previously stable at 10 (units unknown) rose to 13 or greater. He was treated with glibenclamide 7.5mg/day. At the time of reporting the events were ongoing.
The reporter felt that the loss of diabetic control was related to quetiapine therapy due to the temporal relationship. It was noted that the patient had a history of non-insulin dependent diabetes mellitus that was previously diet controlled.

Case Number: 1999AP05757
DIABETES, KETOACIDOSIS.
A report has been received from a physician concerning a 25 year old male patient who has been receiving quetiapine fumarate 750mg daily for psychosis since November 1997. He was receiving acamprosate, Depixol and Priadel concomitantly. In August 1999, 1 year 9 months after starting quetiapine fumarate, the patient was hospitalised due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and quetiapine is continuing.
The reporter had no opinion regarding the causal relationship between the events and quetiapine fumarate, but commented that the weight gain may have been a contributing factor.

Case Number: 1999AP05218
DIABETES DURING PREGNANCY
Patient developed diabetes during pregnancy and started insulin on 30 Sept 99. Baby due 06 December 1999, but patient's water broke 30 Sept 99 and baby born in Oct 99. See case 1999AP06076.

Case Number: 1999AP02989
DIABETES MELLITUS
This patient started treatment with Seroquel on 13 Nov 1998 and with fluoxetine on 12 Nov 1998. Urine and blood tests on 26 Nov 1998 indicated that she had developed diabetes mellitus. Urinary sugar was raised and blood sugar was 17.1.

Case Number: 1999AP01985
NON INSULIN DEPENDENT DIABETES
A physician reported that a 44 year male patient was given Seroquel 250 mg BID for resistant schizophrenia. Treatment began on 27 August 1998. Concomitant medication included clonazepam, sodium valproate and cyproterone. The patient had no history of diabetes mellitus and was being treated with cyproterone for a disorder of sexual inhibition. Five months after starting Seroquel, the patient developed non-insulin dependent diabetes. Seroquel was stopped toward the end of January 1999. No follow-up is available.

Case Number: 1998UW49554
CEREBROVASCULAR ACCIDENT, DIABETIC ACIDOSIS, TRANSIENT ISCHEMIC ATTACK, COLLAPSE.
A report has been received from a physician concerning a 58-year old male patient who received Seroquel 800 mg daily for schizoaffective disorder. The patient has a history of diabetes and cerebrovascular accident. He also takes gabapentin. The patient experienced a transient ischemic attack and was unresponsive except for painful stimuli. Five minutes later, the patient recovered fully. The following day, he collapsed in the shower and died. An autopsy was performed and the primary cause of death was listed as diabetic acidosis and secondary to cerebrovascular accident. Additional information will be requested.

Case Number: 1998UW49081
HYPERGLYCAEMIA
Patient is an 83 year old female who was admitted to the hospital on 27 September 1998 with a diagnosis of hyperglycaemia. Past history and medical conditions include diabetes mellitus. The first patient completed the double-blind portion of the trial on 14 September 98. Open label medication started on 14 September 98 and ended on 26 September 98. This event took place on day 12 of study medication at a dose of 25 mg. In the opinion of the investigator, the elevated blood sugar was not related to the study medication.

Case Number: 1998UW48844
HYPERGLYCAEMIA, DIABETES.
A report has been received from a physician concerning a male patient in his early forties who has been receiving Seroquel for four weeks and is experiencing hyperglycaemia and diabetes. The patient, who has no previous history of diabetes, is now showing blood sugars of over 600 mg/dl.
NEW ONSET DIABETES MELLITUS ASSOCIATED WITH THE INITIATION OF QUETIAPINE TREATMENT, J OF CLINICAL PSYCHIATRY, 60: 556-557, AUG 99, USA, SOBEL, M., JAGGERS, ED, FRANZ, MA

Case Number: 1998UW48512
DIABETES MELLITUS
A report has been received from a pharmacist concerning a 42-year-old male patient who has taken Seroquel since July 1998. On 31 Aug 98 he was diagnosed with diabetes mellitus. Further information is being requested.
*Follow up 12 Oct 99: Further information reveals that the patient was receiving Seroquel 200 mg for a bipolar disorder since July 1998. On 31 Aug 99, patient was admitted to the hospital with a new-onset diabetes mellitus. Patient had no prior history of glucose intolerance or hyperglycaemia. Four months prior to admission blood glucose was 126 mg/dL and 107 mg/dL. At admission blood glucose was 607 mg/dL. Seroquel was tapered, then discontinued. Insulin requirements decreased markedly and insulin was eventually discontinued in January 1999. Patient was also receiving lithium carbonate, gabapentin, clonazepam, and venlafaxine.
SOBEL M, JAGGERS ED, FRANZ MA: NEW-ONSET DIABETES MELLITUS... J OF CLIN PSYCHIATRY; 1999;60(8):556-557.

Case Number: 1998AP50408
HYPERGLYCAEMIA (NON-SERIOUS)
A pharmacist and a nurse reported that a male patient taking Seroquel developed hyperlycaemia. The pharmacist considered the event unrelated to Seroquel; the nurse considered the event related to Seroquel. The patient was also taking Stelazine.

Case Number: 1998AP45979
LOSS OF DIABETIC CONTROL, AGGRESSIVE BEHAVIOUR, STROPPY BEHAVIOUR
Patient had actually been messing about with his insulin injections that weekend, the event therefore had nothing to do with Seroquel, Seroquel dosage has been reduced from 400 to 200mg. The physician is thinking of stopping Seroquel altogether.

Case Number: 1998AP18089
HYPERGLYCAEMIA.
A report has been received from a physician concerning a 32 year old male patient who has been receiving Seroquel from 21 May 1995 for psychosis as part of a clinical trial. The patient has a medical history of obesity, abdominal pain, indigestion, constipation, muscle stiffness, restlessness, depression, and hypertension. He was also taking valproate semisodium, benztropine mesylate and propranolol.
On 26 January 1998, 2 years 36 weeks after starting study medication, the patient was found to have hyperglycaemia and was hospitalised. At the time this report was received, the event was still ongoing. The study drug was stopped on 01 February 1998 due to the potential effect of unstable glucose levels on the patient's mood. The reporter considered that there was not a reasonable possibility that this event was related to the study therapy.

Case Number: 1997AP36803
DIABETIC KETOACIDOSIS
A report has been received from a physician concerning a 36 year old male who has been receiving Seroquel in a dose up to 500 mg daily for schizophrenia as part of a clinical trial. Seroquel started on 06 Sept 96. The patient had recently been diagnosed with diabetes mellitus which was controlled on Glucotrol. On 18 March 97, 28 weeks after starting Seroquel, he was admitted to hospital with decreased level of consciousness. He had not been taking his Glucotrol or Seroquel for 3-4 days prior to admission. He was given IV fluids and insulin but later developed severe

acidosis and an increased lipase of 1819 u/l(25-229)and amylase of 135u/l(27-92). Other abnormal laboratory findings were: sodium 130 mmol/l (135-146), chloride 99 mmol/l (100-107), bicarbonate 5mmol/l (22-32), creatinine 1.9 mg/dl (0.4-1.4), glucose 413mg/dl (70-160), uric acid 12.3mg/dl (2.2-7.2), White blood count 17,000 (4,000-11000), beta-hydroxy butyrate 182mg/dl(0.4-4). The patient was started on subcutaneous insulin & food was started once amylase and lipase were within normal range. At the time of reporting the patient had not restarted Seroquel. The event resolved on 01 April 97. The investigator felt that there was not a reasonable possibility that the event was related to Seroquel.

Case Number: 1997AP36246
UNCONTROLLED DIABETES
A report has been received from a physician concerning a 29-year old male who has been receiving Seroquel since 22 January 1997 in a clinical trial for schizophrenia. After 8 months treatment, the patient was attending a hospital trial visit on 23 September 1997 when he felt faint and collapsed. He was found to have elevated blood glucose, decreased blood pressure (70/50) and an abnormal ECG with cardiac enzymes raised. Seroquel treatment was put on hold and the patients diabetes treated with Humulin in Hospital. The event was ongoing at the time of the report. The physician felt that there was not a reasonable possibility that this event was related to the Seroquel therapy.

Case number: 1997AP35710
UNCONTROLLED DIABETES MELLITUS
A report has been received regarding a 45 year old male who has been receiving Seroquel as part of a clinical trial. He has a medical history of diabetes mellitus, insomnia, gonorrhoea, genital herpes, alcohol and heroin abuse. His concomitant medications were clonazepam, amitriptyline, famotidine and lisinopril. On 10 Aug 97, 163 days after starting Seroquel, he had a moderately severe episode of uncontrolled diabetes mellitus requiring hospital treatment. He recovered after IV fluids and a 2200 calorie diabetic diet. He remains in the trial.
The investigator considered the event not related to trial therapy.

Case Number: 1996AP19874
PNEUMONIA, DIABETES, HYPERTENSION
This 65-year old male patient with Parkinsons disease, anaemia of chronic disease, obsessive compulsive disorder, penile implant, and peptic ulcer disease was being treated with Seroquel as part of a clinical trial. The patient was receiving gastric tube nutrition secondary to poor gag reflex. Treatment began on 21 September 1995. Earlier in the year the patient had been hospitalised suffering from pneumonia. On 28 March 1995, the patient complained of chest congestion. X-ray confirmed that he had pneumonia. He was treated with antibiotic in his nursing home but was later admitted to hospital for further antibiotic treatment. During his admission, he was noted to have elevated blood sugar and blood pressure. Discharge diagnoses were right lower lobe pneumonia, possible nasotracheal aspiration, new onset diabetes and hypertension. The diabetes and hypertension were considered to be not regulatory serious and not related to trial therapy.
The investigator considered the pneumonia was not related to trial therapy.

Case Number: 1995AP10737
DIABETES MELLITUS
This 52 year-old-female with schizophrenia was taking Seroquel 400 mg from 28 January 95 as part of a clinical trial. On 31 January 95 this patient was hospitalised with diabetes mellitus. She was not withdrawn from the trial. When first reported 3rd April '95, this event was considered probably not related. However, further information now reveals that elevated sugar levels have been detected in this patient for two years. Therefore it is considered that her diabetes was definitely not related to the study medication.
This event is now regarded as non-serious by the investigator as it was symptoms of the patient's schizophrenia which led to prolonged hospitalisation and not the diabetes.

Case Number: 1994AP04544
AGITATION, UNREST, INCOMMUNICATIVE, DISINHIBITION, PARANOIA, DIABETES, INCREASED TRIGLYCERIDES

Patient with impaired glucose metabolism pre-trial. Entered in Seroquel trial on 26th September. On study day 8 this patient developed an acute psychosis, suggesting lack of efficacy, which led to withdrawal from the trial. On 4th November, the patient developed symptoms of diabetes. Physician assessment is that there is no reason to suspect that development of diabetes is related to treatment with Seroquel.

Case Number: 1994AP03286
HYPERGLYCAEMIA
An investigator reported that a 53 year old female patient started taking Seroquel on 22 July 1994. The patient had a history of insulin-treated diabetes and had been taking several concomitant medications. On 8 August 1994, the patient was noted to be hyperglycaemic. The investigator reported that the patient had the same level of hyperglycaemia that she had prior to study entry.

Case Number: 1994AP00893
HYPERGLYCAEMIA
An investigator reported that a 45 year old male was treated with Seroquel beginning on 4 March 1994. Concomitant medications included Zantac and Haldol. The patient had no history of diabetes mellitus. He had recently stopped taking a n unblinded Seroquel study drug. On 3 March, the fasting blood sugar was 393. The following day, it rose slightly before increasing to 1104 on 13 March. Seroquel was stopped that day. No treatment was reported but the blood glucose on 14 March was 200.

5 DISCUSSION

There were 27 reports of diabetes mellitus and 2 reports of hyperglycaemia received by AstraZeneca to date. New onset diabetes mellitus was described in 19 of these 27 reports and exacerbation of preexisting diabetes mellitus accounted for 8 reports. Four reports described patients who developed diabetic ketoacidosis (2000UW01164, 1999AP05757, 1998UW49554, and 1997AP36803). Two of these were new onset reports and the other two involved worsening of preexisting diabetes mellitus. There have been no reported cases of non-ketotic hyperosmolar coma received to date. Of these total 28 reports, 16 were spontaneous reports, 10 were from clinical trials, and 2 were literature reports. The investigator attributed none of the cases reported from clinical trials to Seroquel.

New onset diabetes mellitus: There have been 19 cases of new onset diabetes mellitus reported to date. The age range for patients with new onset diabetes mellitus is 12 to 65 with an average age at onset of 37.5 years (median = 41 years). There is a male predominance with males constituting 74% of all reports. Daily Seroquel dosages ranged from 50 mg to 800 mg, with an average daily dose of 419 mg (median = 400 mg). The average time interval between initial therapy and the date of the reported event was 6.2 months with a range of 3 days to 27 months (median = 2.5 months). Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Blood glucose concentrations at clinical presentation averaged 833 mg/dl and ranged from 311 to 2240 mg/dl.

Two patients who developed new onset diabetes mellitus also experienced weight gain (1999UW03532 and 1999AP05757). The latter patient also had diabetic ketoacidosis. One patient who developed hyperglycaemia also experienced weight gain (2000UW01047). Weight gain was not reported in any other cases.

Two patients with new onset diabetes mellitus experienced dose related loss of glycemic control as reported by their physicians (1999UW00969 and 1998UW48512).

Diabetic ketoacidosis: There have been 4 cases of diabetic ketoacidosis reported to date all involving males. The age range for patients with diabetic ketoacidosis is 25 to 58 with an average age at onset of 40.5 years. Daily Seroquel dosages ranged from 200 mg to 800 mg, with an average daily dose of 562 mg (median = 625 mg). The average time interval between initial therapy and the date of the reported event was 9.7 months with a range of 1 to

21 months. Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Only one case (1997AP36803) reported the blood glucose concentration at clinical presentation, which was 413 mg/dl. One patient died of complications of diabetes mellitus (1998UW49554). A second patient (1997AP36803) recently diagnosed with diabetes mellitus, discontinued taking his oral hypoglycemic agent three days before being hospitalized with DKA. A third patient (1999AP05757) with new onset diabetes mellitus also experienced weight gain (unspecified) and at last word required insulin therapy.

Non-ketotic hyperosmolar coma: There have been no reported cases of non-ketotic hyperosmolar coma.

Hyperglycaemia: There have been two reports of hyperglycaemia reported to date (2000UW01047 and 1998AP50408). Blood glucose concentrations were not provided for either patient. The former report involved a 47-year-old female who developed weight gain and hyperglycaemia after taking Seroquel 150 mg daily for 30 months. The latter report contains scant information, except the daily Seroquel dose which was 750 mg.

Confounding factors: Few, if any, of these patients had baseline fasting glucose levels. Seven patients with new onset diabetes mellitus were using concomitant medications known to impair glucose tolerance and cause diabetes mellitus including risperidone, fluoxetine, albuterol, and venlafaxine (2000UW01164, 1999UW03387, 1999AP02989, 1999AP05218, 1998UW48512, 1999UW00969, and 1998AP18089). This last patient was also reportedly obese. One patient developed Type 1 diabetes mellitus (2000UW00266). Several reports contained only scant information which precluded detailed analysis of these cases.

While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest that Seroquel therapy can cause impaired glucose regulation including diabetes mellitus in certain individuals. Consideration should be given to adding diabetes mellitus to the core data sheet based upon postmarketing and clinical trial safety data.

6 REFERENCES

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