Id : i.m.2aaf56bac507dc10b85fe7c2d5911379
CN : SQ1ED00367420
Date : Tuesday, September 30, 2003 11:38:00 PM GMT
From : Melville, Margaret G
To : Grafford, Kerstin; Melville, Margaret G
Cc : Bertelsen, Darci L; Bj÷rk, Susanna; Blythe, Louise; Boorstein, John; Cockhill, John; Cronin, Kathryn E; DeFeo, Pat A; Ealer, Norbert R; Grafford, Kerstin; Groves, Angela J; Horowitz, Anne M; Jonsson, Marianne; Koomen, Oscar; Limp, Gerald L; McCleary Claire; McKeown, Debra; Nakajo, Hirochika; Nemeth, Paul; Ratcliffe, Chris; Rullo, Greg G; Sparco, Joseph J; Street, Paul R; Trumble, Sharon M
Subject : RE: UPDATED COMMUNICATIONS ON DIABETES
Attachments : Seroquel CDS text deviations glucose dysregulations.xls
SeroqGlucosePP.doc
Atypical antipsychotics - glucose intolerance.doc
Seroquel and glucose dysregulation
Custodians : Melville, Margaret

From: Melville, Margaret G
Sent: 9/30/2003 4:55:01 PM
To: Melville, Margaret G; Grafford, Kerstin
CC: Grafford, Kerstin; Groves, Angela J; Cronin, Kathryn E; Street, Paul R; Trumble, Sharon M; Limp, Gerald L; Björk, Susanna; DeFeo, Pat A; Ealer, Norbert R; Boorstein, John; Sparco, Joseph J; Rullo, Greg G; Koomen, Oscar; McKeown, Debra; McCleary Claire; Ratcliffe, Chris; Bertelsen, Darci L; Jonsson, Marianne; Nemeth, Paul; Nakajo, Hirochika; Horowitz, Anne M; Blythe, Louise; Cockhill, John
BCC:
Subject: RE: UPDATED COMMUNICATIONS ON DIABETES

Dear All,

In addition, please find below a very helpful table and summary by Marianne Jonsson on the issue of diabetes.

Best Regards,

Margaret (Meg) Melville
Seroquel Global Regulatory Affairs Director
((302) 886-2118 or 1(800) 456-3669 X 62118
mobile REDACTED

CONFIDENTIAL

fax (302) 886-1400
: margaret.melville@astrazeneca

> -----Original Message-----
>From: Melville, Margaret G
>Sent: Tuesday, September 30, 2003 4:08 PM
>To: Grafford, Kerstin
>Cc: Grafford, Kerstin; Groves, Angela J; Cronin, Kathryn E; Street, Paul R; Trumble, Sharon M; Limp, Gerald L; Björk, Susanna; DeFeo, Pat A; Ealer, Norbert R; Boorstein, John; Sparco, Joseph J; Rullo, Greg G; Koomen, Oscar; McKeown, Debra; McCleary Claire; Ratcliffe, Chris; Bertelsen, Darci L; Jonsson, Marianne; Nemeth, Paul; Nakajo, Hirochika; Horowitz, Anne M; Blythe, Louise; Cockhill, John
>Subject: RE: UPDATED COMMUNICATIONS ON DIABETES
>Sensitivity: Confidential
>
>Dear Kerstin,
>
>I have copied others on your request for information as this seems something worth updating the Regulatory Team...
>
>There is nothing specific to say from a regulatory perspective regarding recent events in the US. In the communications from the Business, it is AZ's opinion that there is no causal association between glucose dysregulation and Seroquel. The CDS adequately communicates the risks and benefits of Seroquel therapy. Aside from addressing the FDA request for class labelling, I do not see any further regulatory action required. As always, any future HA queries should be handled by filing defence documents. We have one available for glucose dysregulation, and it is to my knowledge it is going to be updated for FDA's needs.
>
>For information only, those major territories that have labelling that varies from the CDS, due to HA imposition of labelling, include:
>
>EU MR SPC
>Italy
>New Zealand
>Japan
>
>and the Australian TGA have proposed language, and our currently reviewing our response. Canada have received a similar request to provide labelling in their Precaution section of the Canadian Monograph.
>
>Does this help you at all?

>
>Best Regards,
>
>Margaret (Meg) Melville
>Seroquel Global Regulatory Affairs Director
>((302) 886-2118 or 1(800) 456-3669 X 62118
>mobile REDACTED
>fax (302) 886-1400
>: margaret.melville@astrazeneca
>
> -----Original Message-----
> From: Grafford, Kerstin
> Sent: Monday, September 29, 2003 10:53 AM
> To: Melville, Margaret G
> Subject: FW: UPDATED COMMUNICATIONS ON DIABETES ISSUE
> Importance: High
> Sensitivity: Confidential
>
> Hi Meg,
> I hope you are well - I can imagine "the piles" on your desk.
>
> Sorry to have to ask you about this - the US diabetes issues. As you can see from the correspondence RA collegues (eg Argentina) are asking for comments on communication sent out recently - but not to regulatory. They like to know if any action is expected from them. I spoke with Paul Street some weeks ago following similar early communication on the uS situation but Paul had nothing to add at that time.
>
> I anticipate similar questions from other markets. Could you give me some direction?
> Kind regards,
> Kerstin
> -----Original Message-----
> From: Williams, Kathy A
> Sent: den 29 september 2003 13:48
> To: Grafford, Kerstin
> Cc: Short, Claire
> Subject: FW: UPDATED COMMUNICATIONS ON DIABETES ISSUE
> Importance: High
> Sensitivity: Confidential
>
> hej Kerstin,

>
> Is there anything specific that we should do regarding the attached communication....it has gone out directly to MCPs, product managers etc but not to Regulatory..>
>
> cheers
> Kathy
>
> -----Original Message-----
> From: Blanc, Jose
> Sent: 22 September 2003 18:15
> To: Gill, John
> Cc: Williams, Kathy A
> Subject: RV: UPDATED COMMUNICATIONS ON DIABETES ISSUE
> Importance: High
> Sensitivity: Confidential
>
> Dear Colleagues
>
> I didn't receive any news from the Regulatory corner. Have you any comment on this issue?
>
> There are a lot of Departments involve in this topic but we are not aware on it.
>
> Best regards
>
> José
> -----Mensaje original-----
> De: Replenski, Lois En nombre de Doran, Nigel M>
> Enviado el: Lunes, 22 de Septiembre de 2003 09:53 a.m.
> Para: +ISMO MCPs; +ISMO SMT Members; Collins, Andy J (Alderley Park); Milton-Edwards, Mark; Allman, Debbie; Parsons, Noreen E; +Seroquel Product Managers; +Seroquel Medical Managers; +Seroquel Marketing Managers; +SEROQUEL GLOBAL BRAND TEAM; +Seroquel Global Product Team; +Seroquel PR Contacts
> CC: Minnick, Jim G
> Asunto: UPDATED COMMUNICATIONS ON DIABETES ISSUE
> Importancia: Alta
>
> SENT ON BEHALF OF NIGEL DORAN
>
> All,
>

> Please find attached updated communications on the diabetes issues including the lawsuit and FDA letter previously sent to your attention. Please replace all these updated versions with all documents on these topics previously sent to you.
>
> FDA Label Change Reserved Press Statement and Q&A
>
> << File: RS&QA re pancreatitis.doc >>
>
> Reserved Press Statement and Q&A on Pancreatitis following articles in the Wall Street Journal (WSJ) and New York Times. These documents were not previously sent to you as Seroquel was not involved in the study identified in the articles. However, we are providing this to you now "for your information."
>
> << File: RS&QA re pancreatitis.doc >> << File: WSJ.september 2.doc >> << File: NYT9.2a4.doc >>
>
> Revised versions of the Reserved Press Statement on the media coverage of the VA Study that first appeared in the WSJ.
>
> << File: WSJ RS_QAfinal.doc >>
>
> Apologies for re-sending this information, however, it is important that all global communications on these issues be consistent.
>
> Regards,
>
> Nigel
>
> Lois Replenski
> AstraZeneca
> 1800 Concord Pike
> PO Box 15437
> Wilmington, DE 19850-5437
> Tel: 302-886-3526
> Fax: 302-886-8010
> lois.replenski@astrazeneca.com <mailto:lois.replenski@astrazeneca.com>
>
>
>
>

>

Seroquel™ CDS Deviations regarding Glucose Dysregulation

Text section	CDS text	USA	Japan	EU	UK	Italy	New Zealand
Adverse Reactions/Undesirable Effects	N.A.	Other adverse events observed during the premarketing evaluation of Seroquel. In this section of the US PI it is clearly emphasized that although the events reported occured during treatment with Seroquel, they were not necessarily caused by it. **Metabolic and Nutritional System:** Infrequent: hyperglycemia, hypoglycemia. Rare: glucosuria. **Endocrine System:** Infrequent: diabetes mellitus	**Clinically significant adverse reactions:** (only in Japanese patients? needs to be confirmed!) hyperglycemia, diabetic ketoacidosis, diabetic coma.	Very rare: hyperglycemia, diabetes mellitus, including a footnote: Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases.	Recently imposed from the authorities in UK - discussions still ongoing: Hyperglycemia and exacerbation of pre-exicting diabetes have been reported in very rare cases during quetiapine treatment.	Recently imposed by the HA: Hyperglycemia or exacerbation of pre-existing diabetes mellitur during treatment with quetiapine has been reported in very rare cases (see also paragraph 4.4 Special Warnings and Special Precautions for Use).	Imposed about 1 year ago by the HA: Hyperglycemia, diabetes mellitus, exacerbation of pre-existing diabetes mellitus and diabetic ketoacidosis have occurred very rarely with quetiapine therapy. The causal association with quetiapine has not been established.
Front page of the label	N.A.		**A boxed warning:** 1. During administration of this drug, patients must be carefully observed with measurement of blood glucose levels, because marked elevation of blood glucose after administration may cause clinically significant adverse reactions such as diabetic ketoacidoses and diabetic coma, which may be fatal. 2. Prior to administration of the drug, patients and their families should be sufficiently explained that the above adverse reactions may occur. They should be advised to note abnormalities such as thirst, excessive drinking, polyuria and urinary frequency and also instructed to stop administration of the drug and consult a doctor if any of these symptoms appear (see Important Precautions).				
Contraindications	N.A.		Patients with diabetes mellitus or a history of diabetes mellitus.				

Seroquel™ CDS Deviations regarding Glucose Dysregulation							
Text section	CDS text	USA	Japan	EU	UK	Italy	New Zealand
Precautions	N.A.		1. Careful Administration: Patients with a family history of diabetes mellitus or the risk factors of diabetes mellitus such as hyperglycemia or obesity (see Important Precautions). 2. Important Precautions: Administration of this drug may cause markedly increased blood glucose leading to fatal clinical course including diabetic ketoacidosis or diabetic coma. During administration of the drug, blood glucose levels should be measured, and thirst, excessive drinking, polyuria, urinary frequency and others should be carefully monitored. Especially in the patients with risk factors of diabetes mellitus such as hyperglycemia or obesity, blood glucose levels may be increased an thereby metabolic condition rapidly aggravated. Prior to starting therapy with this drug, provide sufficient explanation to patients and their families that the adverse reactions as mentioned may occur. Also, advise them to pay attention to such abnormalities as thirst, excessive drinking, polyuris and urinary frequency, and instruct to discontinue the drug and consult a physician if such symptoms a observed.	Hyperglycemia: Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with quetiapine. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable Effects).		Recently imposed by the HA: Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with quetiapine. Appropriate clinical monitoring, following medical opinion, is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.	

AstraZeneca

Drug Name SEROQUEL® (quetiapine fumarate)

Date 24 July 2003

Position Paper
SEROQUEL
GLUCOSE DYSREGULATION

<<Actions>>

AUTHOR(S):

Linda Warner MS, RN SIGNATURE:

Safety Surveillance TA Team Leader

Drug Safety, Wilmington DE DATE:

Ronald Leong MD SIGNATURE:

Global Drug Safety Physician

Drug Safety, Wilmington DE DATE:

AstraZeneca

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AUTO PAGE (AUTO NUMPAGES)

SUMMARY AND CONCLUSIONS

Glucose disorders including diabetes mellitus (DM), diabetic ketoacidosis (DKA), hyperglycemia, and exacerbation of DM were reviewed by AstraZeneca to assess whether there is a causal association between treatment with SEROQUEL (quetiapine fumarate; quetiapine) and glucose disorders.

As of 25 April 2003, worldwide post-marketing reports received by AstraZeneca (AZ) comprised 153 cases of new-onset DM, exacerbation of pre-existing DM, DKA or hyperglycemia in patients taking SEROQUEL. Assessment of causality was difficult in most of these cases because of either scant clinical detail, unclear temporal sequence of exposure and outcome, confounding by concomitant medications for which DM or related events have been reported, risk factors for DM (obesity or family history of DM), documented dietary non-compliance, or combinations of these factors.

In clinical trials with SEROQUEL, there were no reports of DKA or hyperosmolar coma. There were no statistically significant differences between SEROQUEL compared to placebo, chlorpromazine, or haloperidol in mean change of glucose from baseline. There was no consistent or clinically significant effect on random glucose levels. There was no increase in adverse events (AE) associated with disturbances in glucose metabolism for SEROQUEL when compared to placebo, chlorpromazine, risperidone, and haloperidol. There were five reports of DM in the open-label extension, but none were considered drug related or led to drug withdrawal.

The medical/scientific literature was inconclusive regarding evidence to suggest that SEROQUEL negatively influences glucose regulation causing new onset DM or worsening of pre-existing DM. In addition, according to the literature, the prevalence of DM in the schizophrenic population (up to 15.8% in one study (Mukherjee et al. 1996) and 11.1-14.9% in another study (Dixon et al. 2000) is noted to exceed that in the general population (10%/United States (US)) even prior to the introduction of atypical antipsychotic medications (Dixon et al. 2000, Mokdad et al, 2001). Furthermore, a recent study (Ryan et al. 2003) showed impaired fasting glucose tolerance in drug-naïve schizophrenic patients.

Diabetes is a progressive disease that begins sub-clinically and progresses to an impaired fasting glucose with glucose intolerance, and then to full-blown DM. In published epidemiology studies and other research studies comparing various antipsychotic drugs, an association between DM and olanzapine, but not the other atypical antipsychotics, was consistently shown. The weight of the evidence is insufficient for a causal association between SEROQUEL and DM.

Taken together, there is currently inconclusive evidence to suggest that Seroquel negatively influences glucose regulation causing new-onset DM or worsening of preexisting DM.

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1. INTRODUCTION

The purpose of this document was to review and analyze all information (pre-clinical and clinical data, the scientific/medical literature, and post-marketing reports received by AstraZeneca through 25 April 2003) regarding glucose related disorders associated with SEROQUEL therapy, and to assess whether SEROQUEL has a causal relationship to glucose disorders.

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2. BACKGROUND

2.1 SEROQUEL

SEROQUEL™ (quetiapine fumarate, quetiapine) was first approved for marketing in the United Kingdom on 31 July 1997 and was first launched in the United Kingdom on 22 September 1997. As of 31 July 2002 (the data lock point for the most recent Periodic Safety Update Review (PSUR)), SEROQUEL had been approved in more than 78 countries.

SEROQUEL is indicated for the treatment of acute and chronic psychoses, including both positive and negative symptoms of schizophrenia. Quetiapine fumarate is presented as tablets delivering a dose of 25 mg, 100 mg, 150 mg, 200 mg, or 300 mg of SEROQUEL free-base. It is an atypical antipsychotic agent, which interacts with a broad range of neurotransmitter receptors. SEROQUEL exhibits affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors. SEROQUEL also has high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

2.2 Schizophrenia

Schizophrenia is a disorder that has a lifetime risk of approximately 1%, and it is one of the most debilitating and persisting diseases with 50 to 80% of initially discharged patients requiring re-hospitalization (Eaton et al. 1992, Westermeyer and Harrow et al.1988).

Gastrointestinal cancer, cardiovascular disease, and infectious disease occur more often in the schizophrenic population than in the general population (Tsuang et al. 1983). In addition, substance abuse is more common with a lifetime prevalence of alcoholism of 33.7% in people with schizophrenia compared to 13.5% in the general population (Vieweg et al. 1995). While 30 to 35% of the general population now smoke, the prevalence among schizophrenic patients is 75 to 95%. This high frequency may contribute to the increases in cancer and cardiovascular disease seen in schizophrenia (Gopalaswamy and Morgan et al. 1986, Hughes et al. 1986, Masterson and O'Shea et al. 1984). Likewise, the prevalence of DM is higher in the schizophrenic population (11.2 – 14.9%/US) than it is in the general population (10%/US) (Mokdad, et al. 2001).

The mortality rate in schizophrenia is at least twice that of the general population, with suicides and accidental death being the most common causes of excess death (Vieweg et al. 1995, Black et al. 1985). More detailed epidemiological work has shown that there is a higher death rate due to infections (with tuberculosis being a major factor) and from cardiovascular disease, which may be in part related to the high prevalence of smoking in people with schizophrenia (Buda et al. 1988).

Hussar studied autopsy reports in 1275 chronic schizophrenic patients (95% of whom were men) between 1954 and 1959. The causes of death were heart disease 17.3%, cancer 13.1%, gastrointestinal disease 6.1%, vascular disease 5.3%, stroke 3.9%, urinary tract disease 1.6%, nervous system disease 1.3%, and other 10.1%. Thirty-one percent of the reviewed fatalities were diagnosed as experiencing "sudden death", mainly from myocardial infarction (Hussar et al. 1966).

Buda et al. (1988) followed up 332 people with schizophrenia from first identification in the period 1934 to 1945 until 1974. In 1974, 124 (37%) were deceased. The cause of death was taken from the death certificate; 46 (37%) died of cardiovascular causes, 17 (14%) died of infections, 14 (11%) died of neoplasms, 6 (5%) committed suicide, 15 died of unnatural causes, and 32 died of other causes (unspecified).

The pattern of mortality and morbidity seen with patients with schizophrenia means that it can be predicted that AstraZeneca is likely to receive reports of cardiovascular, psychiatric (including suicides and sudden deaths), infectious and oncological adverse events (AE) reports, due to the patient population that will be receiving the drug.

2.3 Patient Exposure

It was estimated that about 4.5 million patients have been exposed to SEROQUEL as of 31 December 2002 (an estimate of almost 4 million patients in the United States (US) and 0.5 million patients ex-US).

2.4 Diabetes

Diabetes mellitus is common in the general population, with a prevalence of approximately 10% in the US (Mokdad et al. 2001). Diabetes is even more common in the schizophrenic population. One study reports the prevalence of DM to be up to 15.8% (Mukherjee et al. 1996). Another source reports the prevalence to be 11.1-14.9% in the United States (Dixon et al. 2000).

Diabetes is a progressive disease, which begins sub-clinically, progressing to impaired fasting glucose or glucose intolerance, and then to full-blown DM. Furthermore, Type II diabetics may progress from insulin resistance and impaired insulin secretion to pancreatic beta cell failure. This means Type II diabetics may be initially successfully treated with oral hypoglycemic medications, but may eventually require insulin. It is important to note that Type I diabetics may initially present as DKA, precipitated by an infection. For example, a

patient may have undiagnosed Type I DM, and develop an infection that precipitates DKA, which may be the first manifestation of the DM.

The epidemiology of DM demonstrates that a schizophrenic patient may develop DM, because it is common. Likewise, a schizophrenic patient with DM may experience exacerbation of DM, because DM is a progressive disease.

2.4.1 Type I Diabetes

Although it may occur at any age, Type I DM most commonly develops in childhood or adolescence and is the predominant Type of DM diagnosed before age 30. This type of DM accounts for 10 to 15% of all cases of DM and is characterized clinically by hyperglycemia and a propensity to DKA. DKA is a life-threatening complication of DM, which is characterized by increased glucose levels and acidosis. Frequently DKA is precipitated by other medical illnesses ranging from mild (e.g. flu) to serious (e.g. myocardial infarction). In type I DM, the pancreas (via β cells) produces little or no insulin. The disease results in a genetically susceptible individual, from an immune-mediated, selective destruction of > 90% of their insulin-secreting β cells. Their pancreatic islets exhibit insulitis, which is characterized by an infiltration of T lymphocytes accompanied by macrophages and B-lymphocytes, and by the loss of most of the β cells, without involvement of the glucagon-secreting α cells. Cell-mediated immune mechanisms are believed to play the major role in the β cell destruction. The antibodies present at diagnosis usually become undetectable after a few years. They may be primarily a response to β cell destruction, but some are cytotoxic for β cells and may contribute to their loss. The clinical onset of Type I DM may occur in some patients, years after the insidious onset of the underlying autoimmune process. (Beers, 1999)

2.4.2 Type II Diabetes

Type II DM is more commonly diagnosed in patients > 30 years, but it also occurs in children and adolescents. Hyperglycemia and insulin resistance are the clinical characteristics of Type II DM. DKA is rare. Although most patients are treated with diet, exercise, and oral drugs, some patients intermittently or persistently require insulin to control symptomatic hyperglycemia and prevent non-ketotic hyperglycemic-hyperosmolar coma (NKHHC). Type II DM is commonly associated with obesity, especially of the upper body (visceral/abdominal), and often presents after a period of weight gain. Impaired glucose tolerance associated with aging is closely correlated with the typical weight gain. Type II DM patients with visceral/abdominal obesity may have normal glucose levels after losing weight.

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3. THE LITERATURE

3.1 Search Strategy

A thorough search of medical databases (including Medline, Embase, Biosis, Current Contents) through 25 April 2003 was conducted to obtain information on literature articles

about DM in patients receiving SEROQUEL. In addition, the medical/scientific literature was searched for prevalence and incidence of DM in the schizophrenic patient population.

3.2 Search Results

A summary of information obtained from the scientific/medical literature databases is provided below.

3.2.1 Prevalence in the Schizophrenic Population

Within the psychiatric community there is a great deal of concern about DM as a potential side effect of anti-psychotic agents. Before the contributions of pharmacotherapy can be assessed, it is important to understand the prevalence and characteristics of DM. Diabetes is a progressive disease that begins sub-clinically and progresses to an impaired fasting glucose with glucose intolerance, and then to full-blown DM. The American Diabetic Association reported that 20 million people have impaired glucose tolerance (IGT) defined as fasting plasma glucose >110 mg/dL and <126 mg/dL or two hour post load glucose >140 mg/dL and <200 mg/dL. An additional 16 million people in the United States (US) have DM and the World Health Organization estimated that the worldwide prevalence of DM will more than double from 1995 to 2025 (Buse et al. 2002). According to the 1995 National Health Interview Survey, the prevalence of DM in the general population of individuals between the ages of 18 and 44 years old is 1.2% and in those between 45 and 64 years old is 6.3% (Lindenmayer et al. 2001). As cited previously, in a survey of 2000 data, Mokdad determined the prevalence of DM in the general population to be approximately 10% (Mokdad et al. 2001)

Abnormalities in glucose regulation were first reported in schizophrenia prior to the introduction of antipsychotic medications (Haupt et al. 2002). A number of early reports of impaired glucose metabolism suggested an association with various mental illnesses, independent of medication effects. The number and the relative consistency of observation of increased rates of insulin resistance and Type II, rather than Type I DM, in un-medicated patients have suggested that disease-related disturbance in whole-body glucose metabolism can occur more frequently in schizophrenia patients than in control subjects. Studies involving large populations of persons receiving medications for schizophrenia (from the Schizophrenic Patient Outcomes Research Team) concluded that rates of diagnosed DM in the US exceeded general population statistics well before the widespread use of the newer atypical antipsychotic drugs (Dixon et al. 2000). They determined that the risk factors for DM were similar to those observed in the general population, and that people with schizophrenia may have poorer overall physical health, less healthy lifestyles, and poorer health care than the general population.

Studies conducted in different countries indicated that DM is more common among schizophrenic patients than among the general population. For example, one study in Canada (Curkendall et al. 2001) determined that there was an increased prevalence of DM (1994-1995) and an increased relative risk for DM (1996-1999) in schizophrenic patients compared to controls in their retrospective study of 3022 schizophrenic patients. An Italian study

demonstrated similar findings (overall prevalence of DM among long-term care facility schizophrenic patients was 15.8% (95% confidence interval 12.1% to 19.5%)) in that the rates of DM among the schizophrenic population was considerably higher than those reported from population surveys in Italy (Mukherjee et al. 1996). The Schizophrenic Patient Outcomes Research Team study (Dixon et al. 2000) showed the prevalence of diabetes among schizophrenic patients in the US to be 11.1- 14.9%. Lastly, a recent publication (Ryan et al. 2003) showed impaired fasting glucose tolerance in drug-naïve schizophrenic patients. Thus, the patient population treated with SEROQUEL is at a higher risk for DM than the general population.

3.2.2 Diabetes and Antipsychotic Treatment

There were five large epidemiologic studies conducted to evaluate the relationship between DM and antipsychotic medications. Gianfrancesco et al. (2002) showed an association between Type II DM and olanzapine, but not for SEROQUEL, risperidone, or typical anti-psychotics, by an analysis of claims data for patients with psychosis within a large health plan database. A second study (Sernyak et al. 2002) showed an association between DM and clozapine, olanzapine, and SEROQUEL, but not risperidone, compared to typical antipsychotics. The authors acknowledged limitations of this study that could have confounded the results, including the following five points: 1.) the populations were significantly different in age, sex, presence of other psychiatric diagnosis(s), economic status, distance from medical care, and inpatient/outpatient status, 2.) the narrow time frame (four months) yielded a virtual cross-sectional sample, precluding determination of the temporal relationship between the prescription of neuroleptics and the development of DM, 3.) data on changes in weight gain (one potential mechanism of action for the development of DM) were unavailable to the study investigators, 4.) the patients who received typical neuroleptics may have been less likely to take the medication because of their side effect profile, and 5.) it is possible that patients with pre-existing DM were selectively switched to atypical neuroleptics, or that clinicians chose to monitor blood sugars more carefully in patients taking atypical neuroleptics, thereby identifying additional cases of DM and inflating the effect size.

A third study (Lambert et al. 2002) showed an association between olanzapine, clozapine, and SEROQUEL, and Type II DM compared to conventional antipsychotics. It also showed a trend for an association between risperidone and Type II DM compared to conventional antipsychotics (odds ratio > 1, but the confidence interval included 1). Details concerning the methodology were not available in this abstract, so it is possible some of the limitations of the Sernyak study could also apply to this study. For example, it could not be determined whether patients who had been receiving typical antipsychotics were less likely to take the medication because of their side effect profile, or were recently switched to an atypical antipsychotic.

A fourth study (Buse et al. 2003) of another large US prescription database (AdvancePCS) showed an association between both typical and atypical antipsychotic drugs and DM, compared to a control group of non-users of antipsychotics. Interestingly, SEROQUEL had the weakest association among both typical and atypical antipsychotics. The data showed no difference from control in the 45-64 year old group, and a lower risk overall than haloperidol.

The authors acknowledge that the study does not account for other factors, such as the possibility that DM may be linked to the underlying disorder.

The fifth study was a nested case-control study that included all patients (age 18 to 64 years) in the United Kingdom (UK) General Practice Research Database (GPRD) treated with antipsychotic drugs between January 1994 and December 1998 (n = 73,428). It concluded that there was an increased risk of DM among current users of atypical and conventional antipsychotic medications (Kornegay et al. 2002). It should be noted however, that the data for atypical anti-psychotics included only eight cases of DM; five for risperidone, three for olanzapine, and none for SEROQUEL.

These five epidemiology studies showed inconsistent results. One of them (Sernyak et al. 2002) used the typical antipsychotics as a control group. Another one (Lambert et al. 2002) also appeared to use the typical antipsychotics as a control group, but a lack of details did not allow a complete determination. Of the other three, one showed no association between DM and typical antipsychotics (Gianfresco et al. 2002), while the other two showed an association (Kornegay et al. 2002 and Buse et al. 2003). Regarding the atypical antipsychotics, all five showed an association between olanzapine and DM, but the results for the other atypical anti-psychotics were inconsistent. Two (Gianfresco et al. 2002 and Kornegay et al. 2002) showed no association between SEROQUEL and DM, and one (Buse et al. 2003), which showed an association for both typical antipsychotics and atypical antipsychotics, showed SEROQUEL had the weakest association of any antipsychotic, typical or atypical.

A retrospective review of 215 charts, (which had baseline and follow-up laboratory data available), showed a statistically significant increase in glucose for olanzapine, clozapine, and haloperidol, but not for risperidone or SEROQUEL (Wirshing et al. 2002).

In a cross-sectional study of antipsychotic medication use involving pharmacy records for 213 long-term psychiatric inpatients, the following parameters were evaluated: smoking, body weight, height, fasting blood sugar, fasting total cholesterol, triglycerides, HDL and LDL, and medication use. The authors did not reported any cases of DM or elevated fasting blood sugar, or hypertriglyceridemia for the SEROQUEL (n=20) or risperidone (n=24) treated patients, although these were reported for patients receiving clozapine (n=68), olanzapine (n=57), or Depot Zuclopenthixol (n=43) (Cohn et al. 2000).

In a prospective, randomized, double blind 14-week trial; patients receiving clozapine, olanzapine, and haloperidol, but not risperidone, experienced significant increases in plasma glucose levels (Lindenmayer et al. 2003).

A retrospective survey of clinical records of schizophrenic patients identified those with a concurrent diagnosis of DM, and noted which antipsychotic agents they were on at the time. (Casey et al. 2001) The percentage of patients who had a concurrent diagnosis of DM ranged from 6.4% (3/47) for haloperidol to 20% (4/20) for thioridazine among the typical antipsychotics, and from 8.2% (6/73) for risperidone to 17.0% (33/194) for olanzapine. The figure for quetiapine was 12.5% (2/16). The methodology of the study does not permit conclusions regarding causal association between DM and antipsychotic drugs, since the cases

identified may simply reflect prevalence of diabetes among schizophrenics. The percentages cited are in the 15% prevalence range of DM among schizophrenics discussed above (Mukherjee et al. 1996; Dixon et al. 2000). In addition, the numbers of patients are small. Thus, differences of percentages among different drugs may not be statistically meaningful. In addition, the methodology does not allow for assessment of temporal relationship between drug and DM, i.e. the DM could have preceded the prescription for a particular drug.

One case report identified in the literature (Saito et al. 2002) described a patient who initiated treatment with divalproex and SEROQUEL and shortly thereafter developed DM. The authors questioned if atypical antipsychotic medication can contribute/hasten the development of DM in an otherwise pre-diabetic patient. This patient was African American, morbidly obese (BMI of 35 – 44 kg/m^2) and had a family history of DM. Thus, causality assessment for SEROQUEL was difficult with three risks factors confounding the case.

The literature regarding DM and antipsychotic treatment shows generally inconsistent results, except for the consistent result of an association between olanzapine and DM. The weight of the evidence does not support a causal association between SEROQUEL and DM.

Since there is some data suggesting an association between schizophrenia itself and DM (see Section 3.2.1), one possible explanation for what is being observed is a manifestation of the underlying disease. Following a review of the literature on DM and antipsychotic treatment, Meltzer pointed out that DM cannot be avoided by not using an atypical antipsychotic medication, as schizophrenia itself is associated with a relatively high risk for DM (Meltzer et al. 2001).

3.2.3 Weight Gain Related to Incidence of Diabetes and Hyperglycemia

Some of the morbidities seen with schizophrenia constitute a syndrome called the Metabolic Syndrome, which is characterized phenotypically by excessive visceral fat distribution (Ryan et al. 2002). It is unclear why this syndrome occurs in schizophrenia, although factors such as life style, poor diet, and lack of exercise may contribute to its development. An increase in body weight gain increases the risk for developing DM and cardiovascular disease as well as being detrimental to the patient's quality of life.

A review of the literature demonstrated that there is no consensus on the definition of a clinically significant increase in body weight. In a review of three SEROQUEL studies, which assessed weight gain, Russel (2001) reported that 16-25% of patients experienced clinically significant weight gain (0.09 – 5.6 kg, and > 7% baseline) compared to 4-6% of placebo treated patients, in two out of three studies. In the third study, a total body weight loss of 0.45 – 18.6 kg in patients initially treated with clozapine for six months followed by treatment with a combination of clozapine and SEROQUEL for 10 months was demonstrated (see 3.2.4 below).

In an analysis of the long term weight changes observed in a cohort of 427 patients with schizophrenia from controlled and open-label extension (OLE) trials with SEROQUEL, it was concluded that there was no overall effect on weight across the body mass index (BMI)

spectrum. There were no dose-related effects on weight and SEROQUEL appeared to have a weight-neutral or 'normalizing' effect, with a tendency towards favourable shifts in bodyweight in underweight patients (BMI < 18.5 kg/m2) and severely obese patients (BMI ≥ 35 kg/m2) (Brecher et al. 2000). An anonymous (Anonymous 2002) review of body weight gain and antipsychotic medications concluded that the available data indicated that clozapine and olanzapine are associated with more body weight gain than the other atypical antipsychotics.

3.2.4 SEROQUEL/Clozapine Combination

Two papers (Reinstein MJ et al. 1999, Liebzeit KA et al. 2001) discussed an open-label, non-randomized, retrospective study designed to assess changes in weight and DM status for patients (n = 65) initially treated with clozapine who developed DM (n = 13) and then switched to clozapine-SEROQUEL combination therapy over a 10-month period. All patients showed weight loss with a mean loss of 3.98 pounds in the first month, and 9.2 pounds over the 10-month study period. Serum glycosylated hemoglobin A (HbA1c) and glucose levels had returned to normal by the end of the study. The authors concluded that SEROQUEL shows an unusual propensity to induce weight loss and helps manage the DM that may develop during clozapine monotherapy. They further concluded that the data supports the safety and tolerability of clozapine-SEROQUEL combination therapy.

3.3 Summary of Literature

Diabetes is a progressive disease that begins sub-clinically and progresses to an impaired fasting glucose with glucose intolerance, and then on to full-blown DM. The literature revealed that patients with schizophrenia are at a higher risk for developing DM given some of the risk factors that are commonly seen in this patient population (i.e. obesity, sedentary lifestyle, poor diet, and dyslipidemia). The prevalence of DM in the schizophrenic population (approximately 15%) is higher than in the general population (approximately 10%). Indeed, a recent publication (Ryan et al. 2003) showed impaired fasting glucose tolerance in drug-naïve schizophrenic patients.

There were five large retrospective studies conducted to evaluate the relationship between DM and antipsychotic medications. These five epidemiology studies showed inconsistent results. One of them (Sernyak et al. 2002) used the typical antipsychotics as a control group. Another (Lambert et al. 2002) appeared also to use the typical antipsychotics as a control group. Of the other three, one showed no association between DM and typical antipsychotics (Gianfresco, 2002), while the other two showed an association (Kornegay et al. 2002 and Buse et al. 2003). Regarding the atypical antipsychotics, all five showed an association between olanzapine and DM, but the results for the other atypical antipsychotics were inconsistent. Two (Gianfresco et al. 2002 and Kornegay et al. 2002) showed no association between SEROQUEL and DM, and one (Buse et al. 2003), which showed an association for both typical antipsychotics and atypical antipsychotics, showed SEROQUEL had the weakest association of any antipsychotic, typical or atypical.

An open-label, non-randomized, retrospective study conducted to assess changes in weight and DM status for patients initially treated with clozapine who developed DM and then switched to clozapine-SEROQUEL combination therapy (over a 10 month period) demonstrated that SEROQUEL induced weight loss and improved glycemic control in those patients that gained weight and had developed DM on clozapine.

In published epidemiology studies and other research studies comparing various antipsychotic drugs, the only consistent finding is an association between DM and olanzapine, but not the other atypical antipsychotics. The results for the other atypical and typical antipsychotic drugs are inconsistent. The weight of the evidence is insufficient for a causal association between SEROQUEL and DM.

4. REVIEW OF PRE-CLINICAL DATA

4.1 Summary of Pre-clinical Data

There is no evidence from pre-clinical data that SEROQUEL treatment in humans may be associated with DM. The only salient observation was small changes in glucagon secreting cells (hyperplasia) after 12 months administration of SEROQUEL in one rat study. These changes were minimal and were not seen in another rat study after two years of SEROQUEL dosing. No such changes were observed in the pancreatic islets of mice, dogs, or primates in studies of up to one year.

No changes in serum glucose levels and no degenerative pathology that would indicate the induction of a diabetic state were observed in any species throughout the pre-clinical toxicology program. Thus, the changes observed in the single rat study are considered to be of minimal pathological significance and would not be expected to have any clinical significance in humans.

5. REVIEW OF CLINICAL DATA

AstraZeneca has thoroughly reviewed AE data and plasma glucose data from the clinical trials database for evidence of an association between SEROQUEL treatment and disturbances in glucose metabolism.

5.1 Source Material

5.1.1 Adverse Event Data

5.1.1.1 Incidence of AE Possibly Associated With Disturbances in Glucose Metabolism

AstraZeneca has analyzed the incidence of AEs possibly associated with disturbances in glucose metabolism in the integrated safety database of the original registration dossier. In

this database, AEs were categorized using an in-house dictionary based on the FDA Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). For the purpose of this review, a list of COSTART terms for AEs that could possibly be associated with disturbances in glucose metabolism included *thirst, polyuria, urinary frequency, weight gain, hyperglycemia, DM, DKA, and hyperosmolar coma.*

A summary of exposure to treatment in the integrated safety database prepared for the original Mutual Recognition registration dossier is presented in Table 1.

Table 1 Summary of treatment exposure in the Mutual Recognition integrated safety database

Pools by trial design	Treatment group and number of patients				
	Seroquel	**Placebo**	**Haloperidol**	**Chlorpromazine**	**Risperidone**
Phase 1	553	0	0	0	0
Controlled Phase II/III	2185	206	320	230	208
Short-term (≤ 6 weeks duration)	1925	206	279	230	208
Long-term (> 6 weeks duration)	260	0	41	0	0
Uncontrolled	1640	0	0	0	0
New exposures	768	0	0	0	0
Patients already counted under previous headings[a]	872	0	0	0	0
All trials[b]	**3506**	**206**	**320**	**230**	**208**

[a]Previously took part in controlled Phase II/III trials. [b]Only includes the new exposures in the uncontrolled trials.

In order to observe the effect of an increased duration of exposure to SEROQUEL on the incidence of the adverse events (AE) listed above, the adverse data in this report have been divided into the following trial pools:

- Phase I trials (SEROQUEL; N=553)
- Short-term controlled Phase II/III trials (≤ 6 weeks duration: SEROQUEL; N=1925, placebo; N=206, haloperidol; N=279, chlorpromazine; N=230, risperidone; N=208)
- Long-term controlled Phase II/III trials (> 6 weeks duration: SEROQUEL; N =260, haloperidol; N=41)
- Uncontrolled Phase II/III trials (SEROQUEL; N=1640)

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As the time-on-study in each treatment group will have varied, overall *incidence density* rates, as well as normal cumulative incidence rates, are presented in this report. (Incidence density is defined as the total number of patients with an event, divided by the total patient year exposure).

5.1.2 Plasma Glucose Data

Plasma glucose data were collected in the following trials in the SEROQUEL Mutual Recognition integrated database:

- three short-term placebo controlled trials (204636/0008, 5077IL/0004, 5077IL/0006) (SEROQUEL; N=230, placebo; N=143)
- one short-term comparator controlled trial (204636/0007) (SEROQUEL; N=93, chlorpromazine; N=92)
- one long-term comparator controlled trial (5077IL/0015) (SEROQUEL N=170, haloperidol; N=35)

(N is the number of patients with both baseline and end of treatment glucose data).

5.1.2.1 Mean Change From Baseline in Plasma Glucose Levels

Mean changes from baseline to end of treatment in plasma glucose levels have been presented for the three trial pools indicated in Section 5.1.2. To observe any statistically significant differences between the treatment groups in each trial pool, the data were analyzed using analysis of covariance, including the baseline score, treatment, center and center-by-treatment interaction as factors. Differences between the treatments were estimated and 95% confidence intervals and p values have been presented.

5.1.2.2 Patients Meeting Criteria For a Markedly Abnormal Plasma Glucose Level

The Expert Committee on the Diagnosis and Classification of DM (1998) have defined the diagnostic criteria for DM as follows: symptoms of DM plus a casual plasma glucose concentration ≥ 200 mg/dl; or a fasting blood glucose level equal to or > 126 mg/dl or a 2-hour blood glucose level ≥ 200 mg/dl during an oral glucose tolerance test (Diabetes Care 1997; 20:1183–1197).

In the SEROQUEL clinical trials, the investigators were not instructed when to take plasma samples for assessment of glucose levels, and thus the glucose values obtained were *random* values. Therefore, based on the criteria defined by the Expert Committee above, AstraZeneca has defined a markedly abnormal plasma glucose concentration as ≥ 200 mg/dl, at any time.

The number of patients with a plasma glucose concentration of ≥ 200 mg/dl at any time will be summarized by baseline glucose level, as follows:

- patients with a baseline glucose < 200 mg/dl

- patients with a baseline glucose ≥ 200 mg/dl
- all patients, irrespective of the baseline value

To observe the effect of an increased duration of exposure to trial treatment on the number of patients with a markedly high glucose level, the above data will be summarized in two trial pools: short-term trials and long-term trials. As with the AE event data, in order to adjust for time-on-study, the overall incidence density rates, as well as the normal cumulative incidence rates, will be presented for the proportion of patients with a plasma glucose level ≥ 200 mg/dl at any time.

In order to analyze plasma glucose values over the course of treatment, and to obtain details on whether the patients had any symptoms of DM, detailed profiles of each patient with a plasma glucose level ≥ 200 mg/dl at any time have been obtained and assessed in this report.

5.1.3 Long-term Effect of SEROQUEL on Weight

As obesity can be a risk factor for DM, the effect of SEROQUEL on weight change in the long-term has been analyzed in some detail.

To assess the long-term effects of SEROQUEL on weight gain, a cohort of schizophrenic patients who provided weight data at least 52 weeks after the start of SEROQUEL treatment (N=453) and a subset of monotherapy SEROQUEL treatment (n=387) were analyzed. The change from baseline to their final weight on SEROQUEL treatment was examined. In order to analyze the effect of baseline status on weight change with SEROQUEL, patients were stratified into the following 5 categories according to their body mass index (BMI) at baseline: <18.5 kg, 18.5 to <25 kg, 25 to <30 kg, 30 to <35 kg and ≥ 35 kg.

The effect of dose on weight change with SEROQUEL has also been assessed. Three SEROQUEL dose groups were selected: <200 mg, 200 to 399 mg and 400 to 599 mg, and >600 mg. For each dose group, the absolute mean weight data were obtained from the same cohort of patients at baseline and at endpoint. Endpoint was defined as the final weight value that was taken for each patient. Dose groups were calculated using the modal dose value for the time period when the last weight value was recorded.

5.2 Results

5.2.1 Adverse Event Data

5.2.1.1 Incidence of All AEs Possibly Associated With Disturbances in Glucose Metabolism

Phase I trials

The number (%) of patients with AE possibly associated with disturbances in glucose metabolism across the Phase I trials are presented in Table 2.

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Table 2 **Number (%) of patients with AE possibly associated with disturbances in glucose metabolism in the Phase I trials**

COSTART term[a]	Number (%) of patients
	SEROQUEL (N=553)
Thirst	0
Polyuria	2 (0.4)
Urinary frequency	3 (0.5)
Weight gain[b]	1 (0.2)
Hyperglycemia	3 (0.5)
DM	0
DKA	0
Hyperosmolar coma	0
Total number of patients with events	**9 (1.6)**
Total number of events	**9**
Total patient year exposure[c]	**22.6**
Incidence density[d]	**0.4**

[a]Each patient may have more than 1 AE. [b]Any weight gain event, irrespective of the magnitude of the gain. [c]Total patient year exposure = sum of days on treatment for each patient, divided by 365. Note that exposure data was only available for 549 patients. [d]Incidence density = total number of patients with events divided by the total patient year exposure.

Nine patients (1.6%) had AE possibly associated with disturbances in glucose metabolism in the Phase I trials. No cases of DM, DKA or hyperosmolar coma were reported. Urinary frequency and hyperglycemia were the most commonly reported events in these trials. None of the events in Table 2 were considered serious by the investigator, or led to withdrawal from treatment.

CONTROLLED PHASE II/III TRIALS

Short-term trials

The number (%) of patients with AE possibly associated with disturbances in glucose metabolism across the short-term controlled Phase II/III trials (≤ 6 weeks duration) is presented in Table 3.

Table 3 **Number (%) of patients with AE possibly associated with disturbances in glucose metabolism in the short-term controlled Phase II/III trials**

COSTART term[a]	Number (%) patients				
	SEROQUEL (N=1925)	Placebo (N=206)	Haloperidol (N-279)	Chlorpromazine (N=230)	Risperidone (N=208)
Thirst	4 (0.2)	0	0	0	1 (0.5)
Polyuria	2 (0.1)	0	0	1 (1.0)	0
Urinary frequency	2 (0.1)	0	1 (0.4)	0	2 (1.0)
Weight gain[b]	25 (1.3)	0	3 (1.1)	2 (0.9)	3 (1.4)
Hyperglycemia	0	0	0	0	
DM	0	0	0	0	
DKA	0	0	0	0	
Hyperosmolar coma	0	0	0	0	
Total number of patient with events	**30 (1.6)**	**0**	**4 (1.4)**	**3 (1.3)**	**6 (2.9)**
Total number of events	**33**	**0**	**4**	**3**	**6**
Total patient year exposure[c]	**171.3**	**14.6**	**24.8**	**29.0**	**32.4**
Incidence density[d]	**0.2**	**0**	**0.2**	**0.1**	**0.2**

[a]Each patient may have more than 1 AE. [b]Any weight gain event, irrespective of the magnitude of the gain. [c]Total patient year exposure = sum of days on treatment for each patient, divided by 365. [d]Incidence density = total number of patients with events divided by the total patient year exposure.

Thirty patients (1.6 %) treated with SEROQUEL had AE possibly associated with disturbances in glucose metabolism in the short-term controlled trials. The incidence density was 0.2, which is similar to that observed in the comparator groups.

Three patients each had two events in the SEROQUEL group; one patient had thirst and weight gain, and two patients had thirst and polyuria.

No cases of DM, DKA or hyperosmolar coma were reported.

The most frequently reported event in patients treated with SEROQUEL was weight gain (25 patients, 1.3%); this occurred at a similar incidence as that in the haloperidol (1.1%) and risperidone (1.4%) groups. (Note: the AE event of 'weight gain' refers to *any* weight gain, irrespective of the magnitude of the gain).

One patient was withdrawn from treatment due to weight gain (5077IL/0012/0007/0708). The Investigator did not considered this event to be serious. A review of this patient's details revealed that, in addition to weight gain (2.0 kg over two weeks), this patient also withdrew for reasons of somnolence and abdominal distension.

Apart from the one case of weight gain discussed above, none of the other events in Table 3 led to a patient being withdrawn from treatment, or were considered serious by the investigator.

Long-term trials

The number (%) of patients with AE possibly associated with disturbances in glucose metabolism across the long-term controlled Phase II/III trials (> 6 weeks duration) is presented in Table 4.

Table 4 Number (%) of patient with AE possibly associated with disturbances in glucose metabolism in the long-term-controlled Phase II/III trials

COSTART term[a]	Number (%) of patients	
	SEROQUEL (N=260)	Haloperidol (N=41)
Thirst	1 (0.3)	0
Polyuria	0	0
Urinary frequency	0	0
Weight gain[b]	12 (4.6)	0
Hyperglycemia	0	0
DM	0	0
DKA	0	0
Hyperosmolar coma	0	0
Total number of patient with events	**13 (5.0)**	**0**
Total number of events	**13**	**0**
Total patient year exposure[c]	**84.5**	**17.8**
Incidence density[d]	**0.2**	**0**

[a]Each patient may have more than 1 AE. [b]Any weight gain event, irrespective of the magnitude of the gain. [c]Total patient year exposure = sum of days on treatment for each patient, divided by 365. [d]Incidence density = total number of patients with events divided by the total patient year exposure.

Thirteen patients (5.0%) treated with SEROQUEL had AE possibly associated with disturbances in glucose metabolism in the long-term controlled trials. The incidence density was 0.2, which is the same as that observed in the short-term trials (Table 3), indicating that the incidence of AE possibly associated with disturbances in glucose metabolism does not increase as duration of exposure to SEROQUEL increases.

No cases of DM, DKA or hyperosmolar coma were reported in either treatment group. Weight gain was the most frequently reported event in the SEROQUEL group.

None of the events in Table 4 were considered serious by the investigator, or led to withdrawal from treatment.

Uncontrolled Phase II/III trials

The numbers (%) of patients with AE possibly associated with disturbances in glucose metabolism across the uncontrolled Phase II/III trials are presented in Table 5

Table 5 Number (%) of patients with AE possibly associated with disturbances in glucose metabolism in the Phase II/III trials

COSTART term[a]	Number (%) of patients
	SEROQUEL (N=1640)
Thirst	2 (0.1)
Polyuria	1 (0.1)
Urinary frequency	7 (0.4)
Weight gain[b]	48 (2.9)
Hyperglycemia	8 (0.5)
DM	5 (0.3)
DKA	0
Hyperosmolar coma	0
Total number of patients with events	**66 (4.0)**
Total number of events	**71**
Total patient year exposure[c]	**894.4**
Incidence density[d]	**0.1**

[a]Each patient may have more than 1 AE. [b]Any weight gain event, irrespective of the magnitude of the gain. [c]Total patient year exposure = sum of days on treatment for each patient, divided by 365. Note that exposure data was only available for 549 patients. [d]Incidence density = total number of patients with events divided by the total patient year exposure.

In total, 4.0 % of patients had AE possibly associated with disturbances in glucose regulation in the uncontrolled trials.

Five patients each reported two events: one patient had hyperglycemia and urinary frequency, one patient had thirst and polyuria, one patient had DM and weight gain, one patient had hyperglycemia and weight gain and one patient had DM and urinary frequency. Weight gain was the most frequently reported event in these trials.

No cases of DKA or hyperosmolar coma were reported. Five cases (0.3%) of DM were reported. In two cases (5077IL/0012/0046/4603 and 5077IL/0015/0005/0509), the patients had a history of DM. In a third case (5077IL/0014/0036/3605), the patient is reported to have 'recovered' from the DM whilst on SEROQUEL treatment following treatment with

glibenclamide. None of the five cases of DM were considered by the investigator to be related to trial therapy. In addition, none of the five cases were considered by the investigator to be serious, or led to withdrawal of treatment.

Three patients were withdrawn from treatment in this trial pool; all three were withdrawn due to hyperglycemia. One of the three patients (5077IL/0048/0003/0310) died of myocardial infarction. Hyperglycemia, as well as severe pancreatitis, dehydration, pneumonia, hyponatremia and hyperkalemia, were all noted in concurrence with the myocardial infarction. The patient in question was 77 years old and had a history of borderline DM. In the remaining two cases, both patients had significant confounding factors: one patient (5077IL/0012/0093/9304) had a history of hyperglycemia and DM and the other patient (5077IL/0013/0001/0109) had a history of borderline elevated glucose levels. In all three cases, the investigator considered the hyperglycemia events to be serious, but unrelated to treatment with SEROQUEL.

Apart from the three events of hyperglycemia discussed above, none of the other events in Table 5 were considered to be serious by the investigator, or led to withdrawal from treatment.

5.2.2 Plasma Glucose Data

5.2.2.1 Short Term Effect of SEROQUEL on Plasma Glucose Levels

Plasma glucose levels (random values) were evaluated in three studies comparing SEROQUEL versus placebo, SEROQUEL versus chlorpromazine, and SEROQUEL versus haloperidol. See Tables 6, 7, and 8, respectively. In addition, Table 9 shows the mean change in plasma glucose levels in elderly patients.

Table 6 Mean change from baseline to end of treatment in plasma glucose levels (random values) in short-term placebo-controlled trials

Treatment	N	Mean change from baseline (mg/dL)		Difference between treatments				
		LS Mean	SE	Diff (mg/dL)	SE	LCL	UCL	p-value
SEROQUEL	230	3.60	1.52					
Placebo	143	-0.26	1.93					
SEROQUEL versus placebo				3.87	2.46	-0.97	8.71	0.1173

LS = least square mean, SE = standard error, Diff = difference between treatments, LCL = lower 95% confidence limit, UCL = upper 95% confidence limit, N = number of patients with both baseline and end of treatment glucose data.

Table 7 Mean change from baseline to end of treatment in plasma glucose levels (random values) in short-term comparator-controlled trials

Treatment	N	Mean change from baseline (mg/dL)		Difference between treatments				
		LS Mean	SE	Diff (mg/dL)	SE	LCL	UCL	p-value
SEROQUEL	93	-1.30	1.98					
Chlorpromazine	92	-1.20	1.99					
SEROQUEL versus chlorpromazine				-0.10	2.81	-5.64	5.44	0.9721

LS = least square mean, SE = standard error, Diff = difference between treatments, LCL = lower 95% confidence limit, UCL = upper 95% confidence limit, N = number of patients with both baseline and end of treatment glucose data.

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Table 8 Mean change from baseline to end of treatment in plasma glucose levels (random values) in long-term trials

Treatment	N	Mean change from baseline (mg/dL)		Difference between treatments				
		LS Mean	SE	Diff (mg/dL)	SE	LCL	UCL	p-value
SEROQUEL	170	4.53	2.57					
Haloperidol	35	4.01	5.68					
SEROQUEL versus haloperidol				0.52	6.24	-11.79	12/83	0.93333

LS = least square mean, SE = standard error, Diff = difference between treatments, LCL = lower 95% confidence limit, UCL = upper 95% confidence limit, N = number of patients with both baseline and end of treatment glucose data.

Table 9 Mean change from baseline to end of treatment in plasma glucose levels (random values) in long-term open, uncontrolled trial in elderly subjects

Treatment	N	Mean change from baseline (mg/dL)	
		Mean	Std. Dev.
SEROQUEL	153	9.53	51.74

From Trial 5077IL/ 0048; N = number of patients with both baseline and end of treatment glucose data.

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The differences between the treatment groups within each trial pool were small. There was a wide variability in the results, as expected from blood samples collected at unspecified times after meals. There were no statistically significant differences between any of the treatment groups in each trial pool (SEROQUEL versus placebo, SEROQUEL versus chlorpromazine or SEROQUEL versus haloperidol).

5.2.2.2 Patients Meeting the Criteria For a Markedly Abnormal Plasma Glucose Level

The number of patients with a plasma glucose level ≥ 200 mg/dl at any time post baseline has been summarized in Table 10 (short-term trials), Table 11 (long-term trials) and Table 12 (long-term trial in elderly subjects), according to the baseline glucose level.

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Table 10 Number (%) of patient with glucose ≥ 200 mg/dL (random values) in short-term trials[a]

Baseline glucose level	Treatment group		
	SEROQUEL (N=323)	Placebo (N=143)	Chlorpromazine (N=92)
Number of patients with baseline glucose < 200 mg/dL	322	142	92
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	10 (3.1)	1 (0.7)	0
Number of patients with baseline glucose >200 mg/dL	1	1	0
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	1 (100%)	0 (0)	0
All patients, irrespective of baseline glucose value	**323**	**143**	**92**
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	**11 (3.4)**	**1 (0.7)**	**0**
Total patient year exposure[c]	**28.1**	**10.6**	**8.8**
Incidence density[d]	**0.4**	**0.1**	**0**

a from Trials 204636/0007, 204636/0008, 5077IL/0004, 5077IL/0006. b % uses total number of patients in baseline sub-group as a denominator. c Total patient year exposure = sum of days on treatment for each patient, divided by 365. d Incidence density = total number of patients with glucose ≥ 200 mg/dL at any time divided by the total patient year exposure. N = number of patients with both baseline and end of treatment glucose data.

Table 11 Number (%) of patient with glucose ≥ 200 mg/dL (random values) in long-term trials[a]

Baseline glucose level	Treatment group	
	SEROQUEL (N=170)	Haloperidol (N=35)
Number of patients with baseline glucose < 200 mg/dL	167	32
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	2 (1.2)	1 (3.1)
Number of patients with baseline glucose >200 mg/dL	3	3
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	3 (100)	2 (66.7)
All patients, irrespective of baseline glucose value	**170**	**35**

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Table 11 Number (%) of patient with glucose ≥ 200 mg/dL (random values) in long-term trials[a]

Baseline glucose level	Treatment group	
	SEROQUEL (N=170)	Haloperidol (N=35)
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	**5 (2.9)**	**3 (8.6)**
Total patient year exposure[c]	**68.1**	**16.4**
Incidence density[d]	**0.1**	**0.2**

a from Trials 204636/0007, 204636/0008, 5077IL/0004, 5077IL/0006 b % uses total number of patients in baseline sub-group as a denominator. c Total patient year exposure = the sum of days on treatment for each patient, divided by 365. d Incidence density = the total number of patients with glucose ≥ 200 mg/dL at any time divided by the total patient year exposure. N = number of patients with both baseline and end of treatment glucose data.

Table 12 Number (%) of patients with glucose ≥ 200 mg/dL (random values) in long-term trials in elderly subjects[a]

Baseline glucose level	SEROQUEL
Number of patients with baseline glucose < 200 mg/dL	148
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	2 (1.4)
Number of patients with baseline glucose >200 mg/dL	5
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	5 (100)
All patients, irrespective of baseline glucose value	**163**
Number (%[b]) of patients with glucose ≥ 200 mg/dL post-baseline	**8[c] (4.9)**
Total patient year exposure[d]	**127.6**
Incidence density[e]	**0.1**

a from Trials 25077IL/0048; total number of patient 184, glucose data available from 163 patients. b % uses total number of patients in baseline sub-group as a denominator. c Baseline glucose value is missing for one patient with glucose >200 mg/dL post-baseline. d Total patient year exposure = sum of days on treatment for each patient, divided by 365. e Incidence density = total number of patients with glucose ≥ 200 mg/dL at any time divided by the total patient year exposure. N = number of patients with both baseline and end of treatment glucose data.

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The proportion of patients with a post baseline glucose value ≥ 200 mg/dl in the short-term trials was low in all treatment groups (an incidence density of 0.4, 0.1 and 0 in the SEROQUEL, placebo and chlorpromazine groups, respectively). Similarly, the proportion of patients with a post baseline glucose value ≥ 200 mg/dl in the long-term trials was low in both treatment groups (an incidence density of 0.1 and 0.2 in the SEROQUEL and haloperidol groups, respectively), and in the long-term trial in elderly subjects (incidence density 0.1).

The proportion of patients with a post baseline glucose value ≥ 200 mg/dl did not increase as duration of exposure to SEROQUEL increased (an incidence density of 0.4 in the short-term trials, compared with 0.1 in the long-term trials).

The patient profile data were based on random plasma glucose assessments and are therefore expected to fluctuate depending on the interval since the last meal, glucose content of the last meal, the state of hydration of the patient and many other factors. In order to make a thorough assessment on the effect of SEROQUEL treatment on plasma glucose levels, narratives of all patients with a glucose value ≥ 200 mg/dl at any time have been prepared and analyzed to assess whether the elevated levels were consistent or sporadic, whether they were extreme, and whether any of the patients concerned had symptoms of DM. Full details are provided below.

In total, 20 patients had a plasma glucose level ≥ 200 mg/dl. Of these, three patients received haloperidol, one patient received placebo, and 16 patients received SEROQUEL.

Three patients who received haloperidol (0012/1205,0021/2105, 0035/3502) had post baseline glucose values >200 mg/dl. Two of these three had baseline glucose values >200mg/dl and all three had a history of hyperglycemia or DM.

The single placebo patient with post baseline hyperglycemia, had a baseline glucose of 142 mg/dl. Four of six post baseline assessments including the final assessment were in excess of 200 mg/dl.

A review of the 16 patients who received SEROQUEL did not suggest a diabetogenic effect of SEROQUEL. Twelve of the 16 patients treated with SEROQUEL had a baseline glucose value < 200 mg/dl and at least one post-baseline glucose value ≥ 200 mg/dl. In five of the 12 patients, the last glucose value was >200 mg/dl. In three of these five patients (0001/0021,0026/2607 and 0034/3411) the baseline value was elevated and slightly less than 200 mg/dl (178 mg/dl, 192 mg/dl and 186 mg/dl, respectively). In the remaining two patients, repeated hyperglycemia was not observed since only the last glucose determination was >200 mg/dl.

Seven of the 12 patients had baseline glucose values <200 mg/dl, a last glucose of <200 mg/dl and at least one post baseline assessment of >200 mg/dl. In six of these seven patients, only one of several post-baseline assessments was >200 mg/dl. In the seventh of these patients three of six determinations were >200 mg/dl, but the last glucose value was 149.5 mg/dl, only 7.2 mg/dl greater than the baseline value.

Thus in these 12 patients, sustained hyperglycemia was not observed and the sporadic glucose elevations were not extreme. Further, *none* of the patients had classic symptoms of DM, such as

polyuria, polydipsia, and unexplained weight loss. The glucose values observed are plausibly understood as variations in a parameter that is strongly influenced by the interval since the last meal, glucose content of the last meal, state of hydration and many other factors.

The remaining four of the 16 patients treated with SEROQUEL had a baseline glucose value ≥ 200 mg/dl and at least one post-baseline glucose value ≥ 200 mg/dl. Two of the four patients (0019/1903, 0023/2310) had a history of DM. A third had a history of hypothyroidism (0013/1309). The fourth patient's (0020/0005) final blood glucose was lower than baseline.

5.2.3 Long-term Effect of SEROQUEL on Weight

Results of weight change for all patients treated with SEROQUEL and patients receiving SEROQUEL monotherapy for 52 weeks are presented in Tables 13, 14, and 15 and Figures 1 and 2 below.

Table 13 Weight change over 52 weeks in all patients receiving SEROQUEL

Number of weeks since first dose	Label	N	Mean	Std Dev	Median
Baseline	Weight (kg)	453	76.05	18.60	73.71
	Wt_chg	453	0.00	0.00	0.00
2 weeks +/-2 days	Weight (kg)	81	70.97	17.57	68.86
	Wt_chg	81	0.80	1.63	0.91
4 weeks +/-3 days	Weight (kg)	86	70.39	16.20	68.00
	Wt_chg	86	1.07	2.11	1.02
8 weeks +/-4 days	Weight (kg)	78	70.47	15.91	67.50
	Wt_chg	78	2.26	4.35	1.60
12 weeks +/-4 days	Weight (kg)	173	72.63	16.97	70.76
	Wt_chg	173	2.12	4.97	1.59
26 weeks +/-14 days	Weight (kg)	276	76.44	18.49	73.26
	Wt_chg	276	1.95	6.44	1.81
52 weeks +/-30 days	Weight (kg)	453	78.91	19.13	77.38
	Wt_chg	453	2.86	8.48	2.27

Std =standard, dev = deviation, kg = kilograms, Wt_chg = weight change (kg) since start of Seroquel

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Table 14 Weight change over 52 weeks in patients receiving SEROQUEL monotherapy

Number of weeks since start of first dose	Label	N	Mean	Std Dev	Median
Baseline	Weight (kg)	387	76.81	18.99	74.00
	Wt_chg	387	0.00	0.00	0.00
2 weeks +/-2 days	Weight (kg)	55	73.25	18.68	69.50
	Wt_chg	55	0.85	1.66	0.91
4 weeks +/-3 days	Weight (kg)	63	72.07	16.60	68.04
	Wt_chg	63	1.25	2.10	1.36
8 weeks +/-4 days	Weight (kg)	54	71.38	16.61	67.00
	Wt_chg	54	3.06	4.59	2.61
12 weeks +/-4 days	Weight (kg)	135	74.41	17.45	72.00
	Wt_chg	135	2.86	4.59	2.00
26 weeks +/-14 days	Weight (kg)	236	77.95	18.39	74.45
	Wt_chg	236	2.34	6.34	2.00
52 weeks +/-30 days	Weight (kg)	387	80.03	19.42	78.00
	Wt_chg	387	3.22	8.50	2.72

Std =standard, dev = deviation, kg = kilograms, Wt_chg = weight change (kg) since start of Seroquel

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As can be seen in Table 13, the mean weight change at 52 weeks in all patients treated with SEROQUEL was 2.86 kg (median = 2.27 kg). Most of the weight gain was seen at eight weeks (mean =2.26 kg, median = 1.60). From eight weeks through 26 weeks, the mean weight gain fluctuated between 1.95 and 2.26 kg and the median weight gain fluctuated between 1.60 and 1.81 kg.

The weight change at 52 weeks of patients receiving SEROQUEL monotherapy (Table 14) was slightly higher than the group of all patients treated with SEROQUEL (mean = 3.22 compared to 2.86 kg and median = 2.72 compared to 2.27 kg). Most of the mean weight gain was also seen at eight weeks (mean = 3.06 kg, median = 2.61 kg). From eight weeks through 26 weeks, the mean weight gain fluctuated between 2.34 and 3.06 kg and the median weight gain fluctuated between 2.00 and 2.61 kg.

The observations regarding weight gain were similar whether analyzing all SEROQUEL patients or SEROQUEL monotherapy patients, or using mean or median values.

Figure 1 shows mean weight change by Body Mass Index (BMI) at 52 weeks of all patients receiving SEROQUEL and Figure 2 shows mean weight change by BMI at 52 weeks of patients receiving SEROQUEL monotherapy.

Figure 1 **Mean Weight Change After 52 Weeks on SEROQUEL For All Patients Receiving SEROQUEL**

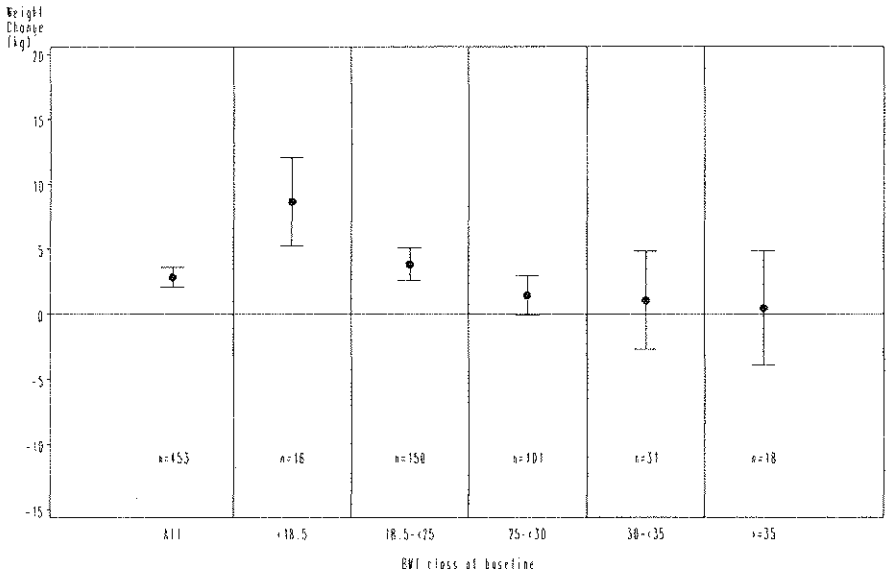

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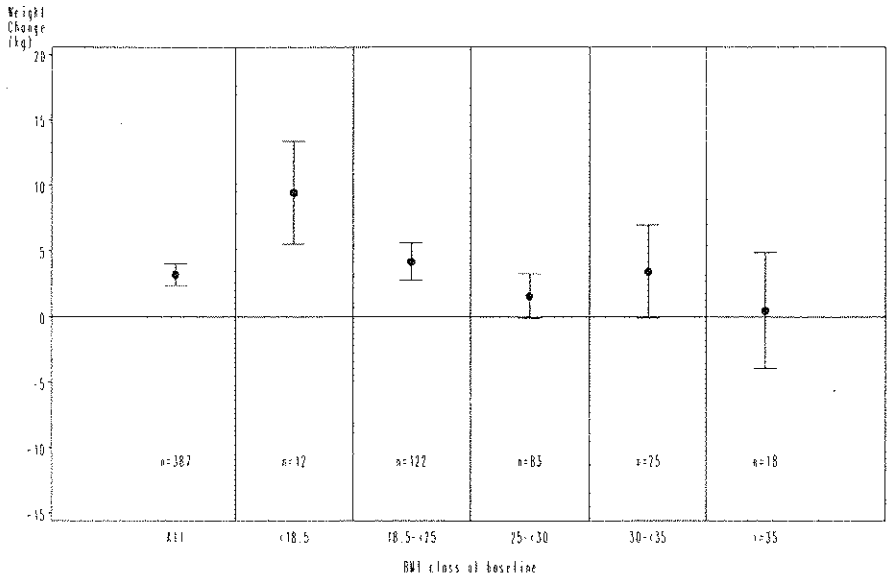
Figure 2 **Mean Weight Change After 52 Weeks on SEROQUEL For Patients Receiving SEROQUEL Monotherapy**



As can be seen in all patients receiving therapy with SEROQUEL, as well as patients receiving SEROQUEL monotherapy, there was a general trend for greater mean weight gain in lower BMI patients, and lower mean weight gain in higher BMI patients. The leanest patients (BMI < 18.5) had the greatest mean weight gain, and the most obese patients (BMI > 35) had virtually no mean weight change in both groups.

Table 15 shows weight change by modal dose.

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Table 15 Weight change by Modal dose of SEROQUEL

Modal daily dose	N Obs	Variable	N	Mean	Std Dev	Median
<200	75	wt_bas	75	72.57	19.79	67.00
		wt_chg	75	0.71	7.49	0.91
200-399	129	wt_bas	129	73.29	18.69	71.00
		wt_chg	129	3.58	8.27	3.18
400-599	90	wt_bas	90	79.58	19.64	76.00
		wt_chg	90	2.09	7.89	2.00
>600	159	wt_bas	159	77.93	16.85	77.57
		wt_chg	159	3.71	9.23	3.50

Std = standard, dev = deviation, kg = kilograms, obs = observed, wt_bas = weight (kg) at baseline of trial, wt_chg = weight change (kg) since start of Seroquel

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There was an inconsistent relationship between modal daily dose and mean weight change. Although the lowest mean/median weight gain (0.71 kg/0.91 kg) was in the lowest daily dose group (<200 mg), and the highest mean/median weight gain (3.71 kg/3.50 kg) was in the highest daily dose group (>600 mg), the mean/median weight change decreased from 3.58 kg/3.18 kg (200-399 mg daily dose) to 2.09 kg/2.00 kg (400-599 mg daily dose), as the daily dose increased.

5.3 Discussion

5.3.1 Adverse Event Data

A total of 3506 patients were exposed to SEROQUEL across the Phase I, short- and long-term controlled Phase II/III, and uncontrolled trials in the integrated safety database prepared for the original Mutual Recognition registration dossier.

The incidence of patients with AE possibly associated with disturbances in glucose regulation in patients treated with SEROQUEL was low across all the trial pools analyzed (1.6% in the Phase I trials, 1.6% in the short-term Phase II/III trials [≤ 6 weeks duration], 5.0% in the long-term controlled [> 6 weeks duration] and 4.0% in the uncontrolled trials) and, after adjusting for time-on-study, the incidence of AE possibly associated with disturbances in glucose metabolism did not increase as the duration of exposure to SEROQUEL increased (incidence density of 0.4 for the Phase I trials, 0.2 for the short-term Phase II/III trials, 0.2 for the long-term controlled trials, and 0.1 for the uncontrolled trials).

No cases of DKA or hyperosmolar coma were reported. DM was reported in five of 3506 patients (0.1%). All five cases were reported in the uncontrolled trials. Two of the five patients had a history of DM. A third patient is reported to have 'recovered' from the DM following treatment with glibenclamide and continued treatment with SEROQUEL. None of the five cases of DM were considered by the investigator to be related to trial therapy. Further, none of the cases were considered serious by the investigator or led to withdrawal of treatment.

The most frequently reported event in patients treated with SEROQUEL (in this class of events) was weight gain (a total of 86 of 3506 patients, 2.5 %). (Note: this refers to patients with *any* weight gain, irrespective of the magnitude of the gain). Only one of the 3506 patients with weight gain in the clinical trial program had DM. This patient had DM at baseline (for which they were receiving treatment) and subsequently had 'poorly controlled' DM recorded as an adverse event.

There was one death due to AE possibly associated with disturbances in glucose dysregulation. The patient concerned is noted to have died of myocardial infarction. Hyperglycemia, as well as severe pancreatitis, dehydration, pneumonia, hyponatremia and hyperkalemia, were all noted in concurrence with the myocardial infarction. The patient in question was 77-year-old and had a history of borderline DM.

A total of four of 3506 patients (0.1%) were withdrawn from treatment due to events possibly associated with glucose dysregulation. Three patients were withdrawn due to hyperglycemia.

One of the three patients died; this patient is described above. Of the remaining two patients, one was a known diabetic with a history of hyperglycemia before entering the trial, and the other had a history of borderline elevated glucose levels. In all three cases, the investigator considered the hyperglycemia events to be serious, but unrelated to treatment with SEROQUEL. A further patient was withdrawn due to weight gain. Somnolence and abdominal distension were also documented as reasons for withdrawal in this patient. The weight gain was not considered serious by the investigator.

Apart from the three cases of hyperglycemia mentioned above, none of the other events possibly associated with disturbances in glucose regulation were considered serious by the investigator.

Obesity can be a risk factor for DM. The latest analyses (from Trial 5077IL/0051) have shown that SEROQUEL has a minimal effect on weight gain in the long-term, at all doses.

5.3.2 Plasma Glucose Data

The differences between the treatment groups in the *mean change from baseline in plasma glucose* data in short-term trials and long-term trials were small. There was a wide variability in the results, as expected from blood samples collected at unspecified times after meals. There were no statistically significant differences between any of the treatment groups in each trial pool (SEROQUEL versus placebo, SEROQUEL versus chlorpromazine [short-term trial] or SEROQUEL versus haloperidol [long-term trial]).

The proportion of patients with a glucose value ≥ 200 mg/dl at any time was low and did not increase as the duration of exposure to SEROQUEL increased (an incidence density of 0.4 in the short-term trials, compared with 0.1 in the long-term trials).

5.3.3 Long-term Effect of SEROQUEL on Weight

The mean weight change at 52 weeks in all patients treated with SEROQUEL was 2.86 kg (median = 2.27 kg). The weight change at 52 weeks of patients receiving SEROQUEL monotherapy was slightly higher than the group of all patients treated with SEROQUEL (mean = 3.22 compared to 2.86 kg and median = 2.72 compared to 2.27 kg). Most of the weight gain was seen at eight weeks for both treatment groups.

The observations regarding weight gain were similar whether analyzing all SEROQUEL patients or SEROQUEL monotherapy patients, or using mean or median values

There was a general trend for greater mean weight gain in lower BMI patients, and lower mean weight gain in higher BMI patients, in all patients receiving therapy with SEROQUEL, as well as patients receiving SEROQUEL monotherapy. The leanest patients (BMI < 18.5) had the greatest mean weight gain, and the most obese patients (BMI > 35) had virtually no mean weight change in both groups.

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The clinical trial data indicate that SEROQUEL has a minimal effect on weight gain in the long-term, at all doses.

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5.4 Conclusion

In conclusion, a thorough review of all the adverse event data and plasma glucose data in the clinical trial program has revealed no clear evidence of a causal association between SEROQUEL treatment and disturbances in glucose regulation. In addition the clinical trial data indicate that SEROQUEL has a minimal effect on weight gain in the long-term, at all doses.

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6. CLINTRACE DATABASE (IN HOUSE SAFETY DATA)

6.1 General

The AstraZeneca safety database (Clintrace) contains global AE reports, from consumers, health care professionals, registries, clinical trials, and literature articles for SEROQUEL. For clinical studies, only reports that have a serious AE associated with them are stored in Clintrace. The following summary is based on information in Clintrace through 25 April 2003.

6.2 Clintrace Search Strategy

A comprehensive search of Clintrace was performed to identify reports that contained the following MedDRA preferred terms: "Blood glucose abnormal", "Blood glucose fluctuation", "Blood glucose increased", "Diabetes mellitus aggravated", "Diabetes mellitus inadequate control", "Diabetes mellitus insulin-dependent", "Diabetes mellitus non-insulin-dependent", "Diabetes mellitus NOS", "Diabetic coma NOS", "Diabetic complication NOS", "Diabetic ketoacidosis", "Gestational diabetes", "Glucose tolerance impaired", "Hyperglycaemia NOS", "Nonketotic hyperglycaemic-hyperosmolar coma", and "Ketoacidosis".

6.3 Database Search Results Overview (153)

A total of 153 reports were identified from the safety database search as of 25 April 2003. Of these 153 reports, 24 reports described DKA, 11 reports described coma (however, one of these was also counted in the DKA group), 118 reports described new onset DM, hyperglycemia, or exacerbation of DM, and one report described urinary glucose abnormality.

6.4 Diabetic Ketoacidosis (24)

6.4.1 Search Results

Twenty-one reports containing the MedDRA preferred term "Diabetic ketoacidosis" and three reports containing the MedDRA preferred term "Ketoacidosis" were identified. Seven of

these reports (2002AP01772, 2002AP02883, 2001UW12078, 2002UW08229, 2002AP01163, 2001UW05726, 1998UW49554) had an outcome of death.

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6.4.2 Report Descriptions: DKA

In Table 16 below, the first eight reports described patients with a history of DM and the remaining 16 reports described patients with no reported history of DM. Detailed report narratives for these reports can be found in Appendix A.

Table 16 DKA Reports

Report #	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	Comments
2003AP00312	32/F	100 mg/day; 6 ½ months	Type II DM (diet-controlled), BMI =45.7 kg/m^2	No other meds taken	Events of hyperglycemia + DKA occurred one month after Seroquel d/c'd and after taking chlorpromazine[1] for one month. Pt outcome ?
2002AP01163 (in coma section also)	36/M	25 mg/day; 12 days	Type II DM, drinks excessive soft drinks, non-compliance w/ oral diabetic med	sennoside	Pt taken Seroquel previously + D/c'd for ? reason. 5 mos later restarted. Seroquel x12 days: Pt had DKA + NKHHC. (Glucose: 420 mg/dl + HbA1c: 8.2% 3 days before starting Seroquel.) HbA1c ↑ (11.8%) after 12 days. Pt had suspected infection. Pt died
2002AP02329	21/F	600 mg/day; 8 weeks	Type I DM (since age 5)	Pt d/c'd all meds 3 days prior to event.	Pt had vomiting + D/c'd all oral meds and insulin. 3 days later: glucose = 745 mg/dl, dehydration, DKA, WBC = 29200/mm^3. Pt rec'd w/ tx after 7 days.
2000AP03612	64/M	50-400 mg/day; unknown time	DM, prostate cancer, COPD	No other meds taken	2 months after dose at 400 mg/day Pt found unresponsive after breakfast. DKA (no lab data reported). No other info. Pt outcome ?
2001UW05726	43/M	Dose unknown; 6 months	DM, obesity	haloperidol[6], lithium[1], pimozide[6], clonidine[7], chlorpromazine[1,2]	Pt died from possible DKA. Lab values changed drastically (no values reported). No other info
1998UW49554	58/M	800 mg/day; time unknown	DM, CVA	gabapentin[5]	Pt had TIA + rec'd. Next day Pt collapsed + died. Cause of death = diabetic acidosis + 2^0 cause CVA
2001UW16478	32/M	800 mg/day; 2 weeks	Borderline DM (diet-controlled)	risperidone[2], valproic acid[1]	Pt c/o upper respiratory sxs + dizziness. 3 days later had DKA. Peak glucose = 700 mg (no other units). Outcome ?
2000AP04688	24/M	300 mg/day;	IDDM, questionable med compliance	"Ecstasy" + alcohol	Pt took 5 ecstasy tablets + ? amount of alcohol. Pt had n/v, hypokalemia, metabolic acidosis, DKA. Developed ARF. ? if Pt took an OD of Seroquel. Pt rec'd.

Table 16 DKA Reports

Report #	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	Comments
2002UW14814	??/F	400 mg/day; 17 months	Obesity, ↑glucose on olanzapine	lithium[1], clonazepam	Pt experienced DM, DI, DKA, Pancreatitis, glucose = 1400 (no units). All meds d/c'd. Outcome ? No baseline labs.
2002GB02627	44/M	400 mg/day; 3 months	Not provided	lactulose	Pt had DM + "early DKA." Tx = insulin. Weight gain of 32 kg. Seroquel contd. Event ongoing.
2002AP01772	51/M	300 mg/day; 42 weeks	Hepatic failure, chronic hepatitis	risperidone[2], nitrazepam	Pt had disturbed consciousness, glucose =1179 mg/dl, Na+ = 116 mmol/L. Dx = DKA. Tx = insulin, normal saline, bicarb, all previous meds D/c'd,. Next day glucose = 233 mg/dl but Pt still comatose. Later that day glucose = 545 mg/dl + shock occurred. Tx = dopamine. Pt died from circulatory failure. Pt's sister stated "Pt drank 4 liters of Coca-cola daily for 5 weeks before death". No autopsy.
2002AP02304	31/M	100 mg/day; 15 months 600 mg/day; 3 months	Obesity, excessive consumption of sweetened drinks	chlorpromazine[1,2], haloperidol, biperiden, trihexyphenidyl, levomepromazine	Blood sugar = 1348 mg/dl, Pt "almost conscious." Tx = insulin, infusion. Event resolved next day; then Seroquel dose ↓. "PET bottle syndrome".
2002AP02883	30/F	200 mg/day; 1 yr 3 months	Unknown family history of DM	haloperidol	Sxs of common cold. Tx = infusion for dehydration. Later that night Pt experienced possible cardiac arrest + died. Cause of death ARF. No labs to support DKA. Sxs (n/v, diarrhea) associated with distigmine.
2001UW12078	57/?	Dose and TTO unknown	Not provided	risperidone[2]	Pt had DKA + died. No other info.
2002UW08229	40/F	200-300 mg/day; >9 months	Smoking, obesity, cocaine/crack/marijuana abuse	buspirone, sertraline, gatifloxacin	Pt found dead. Cause of death = DKA w/ contributing diabetic renal failure. Autopsy revealed fatty liver, cholelithiasis, congestion of viscera, urine + for cocaine; heart blood + for cocaine, ethanol, acetone, sertraline.
2002UW09406	36/M	400 mg/day; one month	GERD, no family hx of DM	lansoprazole, ibuprofen, Metamucil	Hospitalized for DKA. Glucose = 1544mg/dl. Tx = insulin. Seroquel d/c'd. Pt rec'd, ? if Seroquel restarted.
2002GB01741	50/M	800 mg/day; > 3 years	BMI = "70", no family hx of DM	nifedipine[1]	Pt developed ketoacidosis. Seroquel d/c'd. Outcome ?

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Table 16 DKA Reports

Report #	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	Comments
2002GB01254	??/M	300 mg/day; 1 year 2 months	Obesity (BMI = 48.7 kg/m^2).	clozapine[1,3], olanzapine[2,3]	Hospitalized w/ DKA. Glucose = 46.6 (no units), HbA1c = >12%. Dehydration. Type I or II DM suspected. Tx = insulin. Event ongoing.
2001UW14447	13/M	300 mg/day; one month	Morbid obesity, possible family hx of DM	valproic acid[1]	Pt hospitalized w/ DKA. Tx = insulin. Outcome ? No other info
2001UW12263	30/M	300 mg/day; unknown TTO	Not provided	olanzapine[1,2,3]	Pt had polydipsia, polyuria. Later that month had hyperglycemia + DKA. Tx = glyburide + insulin. Seroquel contd. Outcome?
2001UW02143	48/M	Unknown dose + TTO	Hyperlipidemia	lorazepam	Pt had DKA. Glucose = 630 mg/dl, ketones in urine. Tx = insulin, IV fluids. Seroquel D/c'd. Glucose remained ↑. Outcome ?
2000UW02905	18/?	Unknown dose + TTO	Not provided	sertraline	Hospitalized w/ DKA, acute Pancreatitis, ↑ lipids. Glucose = 1200 (no units). Outcome ? No other info
2000UW01164	43/M	200 mg/day; "few weeks"	Not provided	venlafaxine	Pt had polyuria, polydipsia, 30 lbs weight loss. Glucose > 700 (no units). Dx = new onset DM. Outcome ?
1999AP05757	25/M	750 mg/day; 1 yr 9 months	Not provided	lithium[1], flupenthixol[6], acamprosate	Pt hospitalized d/t new DM + ketoacidosis. Pt also had weight gain. Tx = insulin. Pt rec'd. Seroquel contd.

[1]for which hyperglycemia reported, [2] = for which DM reported, [3] = for which DKA reported, [4] = for which coma (diabetic or hyperosmolar) reported, [5] = for which blood sugar fluctuation in diabetic patients reported, [6] = for which interaction w/ lithium resulting in hyperglycemic reaction reported, [7] = for which hyperglycemia in Pt w/ NIDDM or IDDM reported, TTO = time to onset, BMI = body mass index, meds = medications, d/c'd = discontinued, Pt = patient, ? = unknown, w/ = with, NKHHC = nonketotic hyperglycemic hyperosmolar coma, WBC = white blood cells, rec'd = recovered, tx = treatment, COPD = chronic obstructive pulmonary disease, info = information, CVA = cerebrovascular accident, TIA = transient ischemic attack, c/o = complained of, sxs = symptoms, IDDM = insulin dependant DM, n/v = nausea/vomiting, ARF = acute renal failure, OD = overdose, DI = diabetes insipidus, contd. = continued, Hx = history, GERD = gastroesophageal reflux disease, IV = intravenous, d/t = due to, bicarb = bicarbonate

6.4.3 Summary of Reports of DKA With Previous History of Diabetes (8)

Of the twenty-four reports of DKA, eight had pre-existing DM reported. Three of these eight reports were confounded by the following concomitant medications: 1998UW49554 (gabapentin; for which blood sugar fluctuations in diabetic patients has been reported), 2001UW16478 (Risperdal; for which DM has been reported, Depakote; for which hyperglycemia has been reported), and 2001UW05726 (chlorpromazine; for which hyperglycemia has been reported, Lithium; for which hyperglycemia and a drug interaction known to induce hyperglycemic reaction in combination with Haldol and/or pimozide has been reported). This last report (2001UW05726) was also confounded by obesity.

The fourth report (2002AP01163) contained an HbA_{1C} level that indicated that the patient's DM was poorly controlled prior to receiving SEROQUEL. This patient also had a suspected infection and a history of non-compliance with both diet and medication. The fifth report (2002AP02329) described a patient with a possible infection (WBC elevated) and a history of non-compliance with diabetic medication. The sixth report (2000AP04688) was confounded by alcohol consumption, which can cause DKA. The seventh report (2000AP03612) contained scant clinical detail and did not lend itself to analysis. The last report (2003AP00312) described a patient who experienced DKA and hyperglycemia two months after discontinuing SEROQUEL and while taking chlorpromazine (for which hyperglycemia has been reported). This patient did experience an elevation in her HbA1c, however her DM was noted to be diet controlled only and an elevation in HbA1c could signify dietary non-compliance.

6.4.4 Summary of Reports of DKA With No History of Diabetes Reported (16)

Of the 24 reports of DKA, 16 had no prior history or family history of DM reported. Four of these 16 reports were confounded by both obesity (a known risk factor for DM) and the following concomitant medications: 2002GB01741 (nifedipine; for which hyperglycemia has been reported), 2002GB01254 (clozapine; for which hyperglycemia has been reported, olanzapine; for which DM has been reported), 2002UW14814 (lithium for which hyperglycemia has been reported), and 2001UW14447 (Depakote; for which hyperglycemia has been reported). Another two of the 16 reports (2002AP01772, 2002AP02304) were confounded by dietary practices, that is the patients were drinking large amounts of sugar-containing beverages; one of these (2002AP01772) was also confounded by a concomitant medication for which DM (Risperdal) has been reported. Another of the 16 reports (1999AP05757) was confounded by medications (lithium and Depixol) that are known to cause a hyperglycemic reaction when combined. Another of the 16 reports (2002UW08229) described a patient who died from DKA and diabetic renal failure, whereby the diabetic renal failure suggests some degree of chronicity of the DM (although DM was not reported as part of the patient's medical history).

Of the remaining eight reports of DKA with no prior history or family history of DM; one report (2002AP02883) reported possible DKA, however, there was no laboratory data to support a diagnosis of DM or DKA, and a viral illness could have accounted for many of the symptoms or precipitated a possible DKA. Another report (2002GB02627) was confounded

by obesity (a known risk factor for DM) and also contained little information (there was no laboratory data to support a diagnosis of DM or DKA) such that assessment was difficult.

Five other reports (2001UW12078, 2001UW12263, 2002UW02143, 2000UW02905, 2000UW01164) contained scant clinical detail and did not lend themselves to analysis. Two of these six reports were confounded by the following concomitant medications: 2001UW12078 (Risperdal; for which DM has been reported) and 2001UW12263 (olanzapine; for which DKA has been reported), and another of the six was confounded by the patient's weight gain of 32 kg. The last report (2002UW09406) described a 36-year-old male patient who experienced DKA after about a month of SEROQUEL therapy. This report had no obvious confounders, and follow-up information had been requested.

6.4.5 Conclusion for DKA (24)

Following a review of these reports of DKA, it was determined that there is insufficient evidence to suggest a causal role for SEROQUEL and DKA.

6.5 Coma (11)

6.5.1 Search Results

Eleven reports of coma were identified. Four contained the MedDRA preferred term "Diabetic Coma NOS", five contained the MedDRA preferred term "Nonketotic hyperglycaemic hyperosmolar coma", one contained the MedDRA preferred term "Coma", and one contained the MedDRA preferred term "Consciousness disturbed". Three of these eight reports (2002UW05916, 1999UW00969, 2002AP01163) contained an outcome of death. One of these reports (2002AP01163) also contained the MedDRA preferred term "Diabetic ketoacidosis" and is discussed (and counted) in Section 6.4.3 (Reports of Diabetic Ketoacidosis With Previous History of Diabetes) above. The reports of coma are described below in section 6.5.2.

6.5.2 Report Descriptions: Coma

In Table 17, the first three reports described patients with a history of DM and the remaining eight reports described patients with no reported history of DM. Detailed report narratives for these reports can be found in Appendix A.

Table 17 Reports of Coma

Report #/ PT	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	Comments
2002AP04514 NKHHC	57/F	75 mg/day; 27 weeks	DM, ovarian cancer, ITP	chlorpromazine[1], prednisilone[1,2,3,4] bromisoval, amobarbital, haloperidol	Pt started prednisilone. One month later Pt developed hyperglycemia (417-649 mg/dl). Seroquel d/c'd. Tx = diet control. Nine days later Pt developed NKHHC. Tx = chlorpromazine/risperidone d/c'd, insulin started, prednisone tapered down + then d/c'd. Pt rec'd.
2002AP01163# Diabetic coma and DKA	36/M	25 mg/day; 12 days	Type II DM, drinking excessive soft drinks, non-compliance w/ oral diabetic med	sennoside	Pt taken Seroquel previously + D/c'd for ? reason. 5 mos later restarted. Seroquel x12 days: Pt had DKA + NKHHC. HbA1c ↑ (11.8%) after 12 days. Pt had suspected infection. Pt died. (Glucose: 420 mg/dl + HbA1c: 8.2% 3 days before starting Seroquel.)
2002SE05071 Diabetic coma NOS	51/F	50-100 mg/day;	DM, non-compliance w/ diet control, Alzheimer's type dementia	phenytoin[1], rivastigmine[8], sertraline, acarbose	Pt previously on olanzapine [1,2,3]. Olanzapine D/c'd; Seroquel started. Day 1 of Seroquel: fever, unconsciousness, urinary incontinence, ↑glucose (700 mg/dl). On Day 3 of Seroquel: diabetic coma, UTI, leucocytosis. Tx = insulin + abx. Fever resolved + Seroquel d/c'd. Pt rec'd 1 week after start of events. Pt had ↑HbA1c (11.02%) prior to Seroquel.

Table 17 Reports of Coma

Report #/ PT	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	Comments
2003AP01289 NKHHC	70s/ M	25-75 mg/day; 12 days	Rectal carcinoma, alcoholic liver disease, chronic Pancreatitis	loperamide[1], distigmine	Glucose = 120 mg/dl on day 4 of therapy. 3 days later Seroquel d/c'd for ? reason. 1 week later Pt became comatose, glucose = 500 mg/dl. Dx = Nonketotic acidosis, DIC. Pt was recovering.
2002AP04136 NKHHC	74/F	75 mg/day; 6 months	Stage II breast cancer, respiratory infection, dehydration	furosemide[9], spironolactone, haloperidol, trihexyphenidyl, levomepromazine	Pt had ↓ consciousness, trembling, temp = 37 -38°C, ↓O_2 saturation, ↑heart rate. Pt became unresponsive, FBS = 1100 mg/dl. Dx = left pneumonia, NKHHC. Tx = insulin, abx, IV fluid. All meds d/c'd. Next day glucose = 82-280 mg/dl. Insulin d/c'd. Following day FBS = 284 mg/dl, WBC = 16200/mm^3. Outcome ?
2002GB02176 Diabetic coma NOS	50s/F	Up to 400 mg/day; 2 years	Not provided	lithium[1]	Pt developed "Type I DM" and was admitted to the hospital in a diabetic coma. No other info. Pt improving.
2002UW05916 NKHHC	12/F	400-600 mg/day; unknown time	Seizure disorder, obesity, medical neglect	albuterol[1,3], citalopram, desmopressin, oxybutynin	On 600 mg/day Seroquel x 1month; Hospitalized w/ mental status changes, polyuria, polydipsia, ↑BP, n/v, sore throat, abdominal pain. Glucose = 1779 mg/dl, WBC = 18.3K. Tx = abx + acetaminophen. Pt unconscious; died 12 hours later w/ temp of 111°F. Cause of death = NKHHC 2^0 to newly diagnosed DM + unspecified infectious process.

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Table 17 Reports of Coma

Report #/ PT	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	Comments
1999UW00969 NKHC	28/M	Dose unknown; time unknown	Hallucinations, asthma	albuterol[1,3], lithium[1], omeprazole	Pt had flu like S/S; (tx: zithromax), hospitalized 3 days later w/ fever (107°F), arrhythmias, non-reactive pupils, bleeding from eyes/nose, glucose = 2240 (no units), ↓K+ (no units). Then developed DIC, v-fib. Tx = dantrolene, anti-arrhythmics, bicarb, insulin, FSP, whole blood, packed in ice. Pt died. Autopsy = new onset DM w/ NKHC, NMS, metabolic acidosis, DIC, respiratory failure.
2002AP02699 Consciousness disturbed, blood glucose increased	63/F		Hallucinations, delusions, NMS, pneumonia	timiperone, biperiden, promethazine, estazolam, nitrazepam	3 hours after taking Seroquel, estazolam, +nitrazepam. Pt had ↓BP, cyanosis of lips, deep coma. All meds D/c'd. Tx = LR, electrolytes/glucose solution, K+. After tx began, glucose = 360 mg/dl. Tx stopped; 8 hours later glucose = 134 mg/dl. Pt rec'd all events.
2003UW02826 Coma, blood glucose increased	35/M	1200 mg/day; 3 months	Depression, hyperlipidemia, alcohol/cocaine/marijuana/ mushroom use	paroxetine, haloperidol	Pt w/o meds for 12 days while incarcerated. Upon return to hospital, Pt given paroxetine (20 mg) + Seroquel (1200 mg) without titration; had delirium, ↓BP, ↑pulse, pinpoint pupils. K^+ = 3.1 mmol/L, glucose = 203 mg/dl. Tx = IV fluids, K+. Seroquel ↓ to 900 mg/day. Pt rec'd.

Table 17 Reports of Coma

Report #/ PT	Age/ Sex	Dose/ TTO	Medical history	Concomitant medications	Comments
2002AP02947 Coma, Hyperglycaemia NOS	44/F	100 mg/day; 35 weeks	No hx of obesity or DM	carbamazepine, tiapride, sofaloconc, biperiden	Pt had fever + aggravation of mental state. Tx = IM diazepam, haloperidol, fluphenazine. 6 days later Pt had not eaten/drank. Tx = infusion solution w/ haloperidol. Next day BP ↓, glucose = 300 mg/dl. Next day Pt improved but creatinine = 5.1 mg/dl, BUN = 114 mg/dl, consciousness ↓, WBC = 13300/mm^3. Dx = dehydration, ↓consciousness. Pt had deep coma, glucose = 1057 mg/dl, acidosis, CPK = 2124 u/L, hypernatremia. Tx = hemodialysis. CPK = 15215 u/L, glucose 535 mg/dl. DIC noted. Next day hyperglycemia, acidosis, dehydration, hypernatremia resolved. CPK peaked 78690 u/L. Tx = dantrolene. Pt rec'd. Physician stated "Pt hyperglycemia chronic"

[1] for which hyperglycemia reported, [2] = for which DM reported, [3] = for which DKA reported, [4] = for which coma (diabetic or hyperosmolar) reported, [5] = for which blood sugar fluctuation in diabetic patients reported, [6] = for which interaction w/ lithium resulting in hyperglycemic reaction reported, [7] = for which hyperglycemia in Pt w/ NIDDM or IDDM reported, [8] = precaution for use with diabetic Pt, [9] = for which hyperglycemia w/ dehydration reported, [#] = report also contained in DKA section, TTO = time to onset, NKHHC = nonketotic hyperglycemic hyperosmolar coma, ITP = idiopathic thrombocytopenic purpura, Pt = patient, d/c'd = discontinued, Tx = treatment, w/ = with, UTI = urinary tract infection, abx = antibiotics, rec'd = recovered, ? = unknown, dx = diagnosis, DIC = disseminated intravascular coagulation, temp = temperature, FBS = fasting blood sugar, IV = intravenous, WBC = white blood cell, info = information, BP = blood pressure, n/v = nausea/vomiting, K^+ = potassium, v-fib = ventricular fibrillation, FSP = fibrin split products, NKHC = nonketotic hyperosmolar coma, NMS = neuroleptic malignant syndrome, LR = lactated ringers, w/o = without, meds = medications, hx = history, IM = intramuscularly, BUN = blood urea nitrogen, CPK = creatine phosphokinase, bicarb = bicarbonate

6.5.3 Summary of Coma Reports With Previous History of Diabetes Reported (3)

The first report (2002AP04514) described a patient who was taking multiple medications for which hyperglycemia, DM, DKA, and hyperosmolar coma have been reported. The second report of coma (2002AP01163) was discussed in section 6.4.3. The HbA_{1C} level on the day SEROQUEL therapy was initiated was 8.2%; indicating that the patient's DM was poorly controlled prior to receiving SEROQUEL. This patient also had a suspected infection and a history of non-compliance with both diet and medication. The last report (2002SE05071) indicated that the patient's DM was poorly controlled prior to receiving SEROQUEL. This patient also had an infection and a history of non-compliance with diet.

6.5.4 Summary of Reports With no Previous History of Diabetes Reported (8)

The first report (2002AP04136) described a patient who was taking a medication for which hyperglycemia with dehydration has been reported, and who developed an infection and dehydration at the time of the event. The next three reports (2002GB02176, 2002UW05916, 1999UW00969) described new onset DM, which can present itself as diabetic coma or non-ketotic hyperosmolar coma. Two of these three (2002UW05916, 1999UW00969) presented a clinical picture consistent with infection precipitating the hyperosmolar coma. The other report (2002GB02176) contained scant clinical detail. In addition, these three reports were confounded by concomitant medications (2002UW05916: albuterol, for which DKA and hyperglycemia have been reported, 1999UW00969: albuterol; for which DKA and hyperglycemia have been reported, lithium; for which hyperglycemia has been reported, 2002GB02176: lithium; for which hyperglycemia has been reported).

The fifth report of coma (2002AP02699) described an isolated elevated blood glucose that normalized within a few hours, without any treatment reported that was directed specifically towards the elevated glucose; which raises the possibility of a false elevated blood glucose level. In addition, this report was confounded by concomitant medications (timiperone, promethazine, estazolam, nitrazepam) for which CNS depression has been reported. The sixth report (2003UW02826) described a patient with a history of hyperlipidemia who experienced a coma after receiving a 1200 mg dose of SEROQUEL. Blood work taken during the coma revealed blood glucose at 203 mg/dl. It was not reported that the patient's coma was related to the elevation in glucose, rather the coma could have been due to the large dose of SEROQUEL that was received (SEROQUEL CDS contains coma with overdose; maximum dose as per the CDS is 800 mg/day). Additionally, it is unknown at what point during the patient's treatment of coma the blood was drawn. It is possible that the patient may have been treated with intravenous fluids containing glucose. The patient recovered.

The seventh report (2002AP02947) described a patient whose hyperglycemia was likely to be pre-existing based on the HbA1c and input from one physician. This patient may have experienced an infection (fever, increased WBC) that precipitated an acute increase in blood glucose (infections are common precipitators on non-ketotic hyperosmolar coma or DKA in DM. The eighth report (2003AP01289) described a patient who had discontinued SEROQUEL one week prior to the event and who was receiving a concomitant medication (loperamide) associated with hyperglycemia.

6.5.5 Conclusion for Coma (11)

Taken together, the evidence for causality regarding the use of SEROQUEL and coma was insufficient in these reports.

6.6 New Onset Diabetes Mellitus, Hyperglycemia, and Exacerbation of Diabetes (118)

6.6.1 Search Results

One hundred and eighteen reports of new onset DM, hyperglycemia, or exacerbation of DM were identified and can be divided into the following sections: 1.) new onset DM (45), 2.) hyperglycemia in patients with no prior history of DM (45), and 3.) exacerbation of DM (28). A summary for each section is presented below.

6.6.2 New Onset Diabetes Mellitus (45)

6.6.2.1 Search Results

Forty-five reports of new onset DM were identified. One (2002GB00282) contained an outcome of death.

6.6.2.2 Report Descriptions or Narratives

Of these 45 reports, four patients developed insulin dependent DM (IDDM) (2001UW00363, 2001GB00094, 2000UW00266, 2002GB00282), which is considered not to be drug related, and two patients (1999AP05218, 2002GB00947) developed gestational DM. These six cases are summarized below.

Of the four reports of IDDM; 2000UW00266 described a 12-year-old patient who developed type I DM while receiving SEROQUEL, haloperidol, and valproic acid (for which hyperglycemia has been reported); 2001UW00363 described a 5-year-old male patient with a family history of DM (grandfather) who was diagnosed after six months of SEROQUEL therapy (12.5 to 37.5 mg/day); 2001GB00094 described a 66-year-old patient who was receiving a concomitant medication for which hyperglycemia (lithium) has been reported, thus confounding the report; and 2002GB00282 described a 19-year-old male patient with a history of obesity. This patient was diagnosed with Type I DM after four months of SEROQUEL therapy. The patient's DM was controlled with insulin and SEROQUEL was discontinued for an unspecified reason four months later. Four months after discontinuing therapy with SEROQUEL the patient died from an unknown cause. No information was provided about this patient's concomitant medications.

The two reports of gestational DM described two female patients (age 27 and 32 years) who each developed DM during their pregnancies. The first report (1999AP05218) was confounded by a concomitant medication for which DM (chlorpromazine) has been reported. The second report (2002GB00947) described a patient who was treated with olanzapine and then switched to SEROQUEL because of excessive weight gain. The patient became pregnant and developed gestational DM in the third trimester.

An additional 16 reports of new onset DM were confounded by concomitant medications for which hyperglycemia or DM has been reported. These reports and the relevant confounding medication(s) are listed in Table 18 below:

Table 18 Reports of New Onset Diabetes Mellitus Confounded by Medications (16)

Report number	Concomitant medication for which diabetes/hyperglycemia have been reported
2003UW02110	risperidone[1], buproprion[2].
2003AP00095	chlorpromazine[2], risperidone[1]
2003GB00857	medroxyprogesterone[1] *Also confounded by diet non-compliance; the reporting physician stated "the patient would not stop eating sugar".
2002AP04001	valproic acid[2]
	*Also risk factors of: family hx of DM, BMI 35 kg/m^2; obesity.
2002AP04184	mianserin[2], sulpiride[2]
	*Also risk factors of: obesity and hyperlipidemia
2002AP01607	valproic acid[2]
2002AP00323	olanzapine[1,2], valproic acid[2]
2001UW07693	prednisone[1,2]
2001UW00231	mirtazapine[1] (history of increased blood glucose with Zyprexa)
2001SE07046	mirtazapine[1]
2001AP03248	mirtazapine[1]
2000UW02019	Ziac (bisoprolol/ hydrochlorothiazide)[1,2], lithium[2]
	*Also risk factors of: family history of DM-(father)
2000AP05293	valproic acid[2]
1999UW00967	valproic acid[2]
1999AP01985	valproic acid[2]
1998UW48512	lithium[2]

1 = for which reported, DM, 2 = for which hyperglycemia reported.

Another seven reports contained risk factors for DM: 2002AP04524 (family history of DM-father), 2002AP00269 (obesity; also this patient contained an HbA_{1C} level (8.6%; after four weeks of SEROQUEL) that indicated that the patient was experiencing hyperglycemia prior to receiving SEROQUEL), 2002GB01293 (family history of DM), 2001AP05019 (obesity), 2000AP02609 (family history of DM), 2003AP00844 (two sisters and an uncle had DM, patient was obese (93.5kg), and patient had positive urine glucose one month prior to starting SEROQUEL and an HbA1c of 6.7% 39 days after starting SEROQUEL), and 2003GB00633 (family history of DM and obesity).

Another 14 reports (2002UW16583, 2002UW03965, 2001UW13414, 2001SE08506, 2000UW04533, 2000UW04346, 1998UW48844, 2001UW13180, 1999AP02989, 2003UW01302, 2003UW03250, 2003UW03853, 2003UW03648, 2003AP01273) contained scant clinical detail and did not lend themselves for analysis. One of these reports (2001UW13180) also reported that the patient had a family history of DM. Another of these reports (2002UW16583) indicated that the patient had a history of hyperglycemia with risperidone. Another of these reports (2003UW01302) indicated that the patient had a history of "borderline DM".

Another two reports described new onset-DM and are described below.

1999UW03532: This serious report of "Diabetes mellitus NOS" and "Weight increased" described a 47-year-old female patient receiving SEROQUEL (600 mg/day for 12 months) for schizoaffective disorder. She experienced a severe 50-pound weight gain (date of onset unknown) and developed DM. The patient was hospitalized in June 1999 because the DM was difficult to control. Treatment included insulin and the patient's condition improved. SEROQUEL was tapered and discontinued. Concomitant medications included Klonopin (clonazepam) and Benadryl (diphenhydramine). The patient has a medical history of hepatitis C, hypertension, and arthritis. The DM continued. No further information was provided.

Comment: This report demonstrated a negative de-challenge. The source documents did not specify Type I or Type II DM.

1999UW03387: This non-serious report of "Diabetes mellitus non-insulin-dependent" described a 17-year-old Hispanic male patient receiving SEROQUEL (100 mg/day) since January 1999 for psychotic depression and auditory hallucinations. In March 1999, due to drowsiness in the daytime the dosage of SEROQUEL was decreased to 50 mg every evening. In July 1999, the patient was diagnosed with type II DM. On 11 Sept 1999, SEROQUEL dosage was again decreased to 25 mg every evening. The patient had been receiving Risperdal (risperidone) prior to SEROQUEL. Concomitant medications include Ritalin (methylphenidate) for attention disorder and Serzone (nefazodone) for depression. Medical history included auditory hallucination, psychotic depression and attention disorder. No further information was provided.

Comment: The patient developed Type II DM while receiving decreasing doses of SEROQUEL. This report did not contain any obvious confounders, or information about the outcome.

6.6.2.3 Summary of Reports of New Onset Diabetes (45)

Of the 45 reports of new onset DM, four described patients who developed IDDM (2001UW00363, 2001GB00094, 2000UW00266, 2002GB00282), which is considered not to be drug related, two described patients who developed gestational DM (1999AP05218, 2002GB00947), 16 (see Table 17 above) were confounded by concomitant medications for which hyperglycemia or DM have been reported, seven (200AP04524, 2002GB01293, 2001AP05019, 2000AP02609, 2003AP00844, 2003GB00633, 2002AP00269) contained risk

factors including a family history of DM or obesity, and 14 (2002UW16583, 2002UW03965, 2001UW13414, 2001SE08506, 2000UW04533, 2000UW04346, 1998UW48844, 2001UW13180, 1999AP02989, 2003UW01302, 2003UW03250, 2003UW03853, 2003UW03648, 203AP01273) were scant reports and did not lend themselves to analysis.

Of the remaining two reports, one (1999UW03532) described a patient who developed DM after a 50 pound weight gain and experienced a negative de-challenge with SEROQUEL, and one (1999UW03387) developed type II DM while on decreasing doses of SEROQUEL. This last report also contained little information with regards to the event of DM.

6.6.2.4 Conclusion for New Onset Diabetes Mellitus (45)

Following a review of the reports describing patients who experienced new onset DM, it was determined that the available safety information was insufficient to establish a causal relationship between SEROQUEL and DM.

6.6.3 Hyperglycemia (45)

6.6.3.1 Search Results

There were 45 reports containing the MedDRA preferred term "Hyperglycaemia NOS" or "Blood glucose increased", which described patients that had no prior history of DM, or contained no information about pre-existing DM or hyperglycemia.

6.6.3.2 Report Descriptions or Narratives (45)

Nineteen of the 45 reports were confounded by concomitant medications for which hyperglycemia or DM has been reported. These 19 reports are listed in Table 19 below.

Table 19 Reports of Hyperglycemia with no history of diabetes confounded by medications (19)

Report number	Confounding concomitant medications
2003AP00033	risperidone[2]
2003AP00109	chlorpromazine[1], lithium[1], mianserin[1]
2003AP01545	olanzapine[1,2,3]
2003AP01546	lithium[1]
2003GB00473	valproic acid[1]
2003UW03989	indapamide[1], nifedipine[1]
2002AP04011	chlorpromazine[1]
2002AP04183	mianserin[1]
2002AP04278	chlorpromazine[1]
2002UW01476	metoprolol[1]
2002UW09024	lithium[1]
2002UW09743	valproic acid[1]

Table 19 Reports of Hyperglycemia with no history of diabetes confounded by medications (19)

Report number	Confounding concomitant medications
2002UW10490	lisinopril/HCTZ[1]
2002UW14620	timolol[1,2]
2002UW16205	clozapine[1,2,3]
2002UW16580	risperidone[2]
2001AP02034	chlorpromazine[1]
2001AP04330	lithium[1]
2001SE02468	mirtazapine[2]

[1]for which hyperglycemia reported, [2] = for which DM reported, [3] = for which DKA reported.

Of these 19 reports, two (2001SE02468 and 2002AP04011) are also confounded with a risk factor of obesity, one (2002UW09743) is also confounded with a family history of DM (brother, grandmother, aunt, and nephew), one (2002AP04183) is also confounded with obesity and a family history of DM (father), one (2002UW01476) is confounded with a history of hyperlipidemia and obesity, and one (2002UW09024) is also confounded with a family history of hyperglycemia. Another of the 19 reports (2003AP00033) contained an increased HbA1c, which implied the patient's blood glucose was increased before SEROQUEL was initiated.

Eighteen reports (2003AP00090, 2002UW15836, 2002UW16588, 2002UW13371, 2002UW14319, 2002UW14549, 2002UW05977, 2002UW02227, 2001UW02046, 2001AP04437, 2000UW01047, 2002UW14927, 2002UW11778, 1998AP50408, 2003UW00329, 2003GB00465, 2003SE02056, 2003GB00705) contained scant clinical detail and did not lend themselves to analysis. One of these reports (2003GB00465) also contained the risk factor of a family history of DM.

Four additional reports described patients with risk factors for DM including 2002UW15932 (family history of DM), 2003AP00040 (obese patient had marked weight gain prior to SEROQUEL, and had polydipsia and promiscuous eating habits), 2002AP04245 (fatty liver), and 2002UW15169 (history of hyperglycemia prior to receiving SEROQUEL). One of these (2002AP04245) described a patient who experienced an increased FBS and HbA1c after nine months of SEROQUEL therapy, which did not resolve two weeks after SEROQUEL was discontinued.

One additional report (1998UW49037: literature report) described a patient who took an overdose of SEROQUEL (9600 mg) and had "mildly elevated" serum glucose (137 mg/dl). No baseline glucose or concomitant medications were reported in this case.

The remaining three reports are discussed below:

2002GB02591: This report of "Glucose tolerance impaired" described a 31-year-old female patient who was receiving SEROQUEL (650 mg/day) for the treatment of schizoaffective disorder. The patient had no relevant medical history and was not receiving concomitant medications. Following SEROQUEL treatment, the patient's weight had increased from 57 kg to 77 kg. Approximately 14 months after starting SEROQUEL the patient developed severe hypothyroidism (no specifics provided). Thyroid tests were reported to be normal 13 days prior to the initiation of SEROQUEL. The physician commented that the patient was noted to be very psychotic, giddy with poor concentration, as a result of the hypothyroidism. The patient's thyroid profile continued to deteriorate. One year after the hypothyroidism was noted the patient developed mild impaired glucose tolerance (FBS = 6.7; no units) and hyperlipidemia (approximately two years and one month after starting SEROQUEL). No action was taken with SEROQUEL, and the hypothyroidism, impaired glucose tolerance (FBS = 7.4; no units, four months after initial event), and hyperlipidemia had not resolved. The physician was continuing to monitor and treat the events. Approximately eight weeks later, further lab tests indicated that the patient's thyroxine levels were within normal limits. No further information was available.

Comment: The patient had a 20 kg weight gain and developed hypothyroidism and hyperlipidemia; all of which are risk factors for DM.

2003AP00035: This report of "Blood glucose increased" described a 50-year-old male who was receiving SEROQUEL for the treatment of schizophrenic psychosis. The patient had no history of DM, overeating, or polydipsia. Concomitant medications were not provided. Prior to starting SEROQUEL the patient had a FBS of 131 mg/dl, an HbA1c of 6.3%, and negative urine glucose. After about five months of SEROQUEL therapy, the FBS (234 mg/dl) and HbA1c (8.1%) increased further and the patient's urinary glucose was 3+. SEROQUEL was discontinued. One month later, the patient's FBS (145 mg/dl) and HbA1c (7.8%) had decreased.

Comment: It is unknown if the patient was taking any concomitant medications at the time of SEROQUEL therapy. Additionally, the patient had an elevated FBS and HbA1c prior to SEROQUEL and there is no information regarding what treatment measures were taken in response to the increased FBS and HbA1c. After discontinuation of SEROQUEL, the FBS and HbA1c decreased, although they were still above the normal ranges.

2003UW01256: This report of "Blood glucose increased" described a 49-year-old male patient who was receiving SEROQUEL (500 mg/day) for the treatment of bipolar disorder. Medical history included depression, alcohol dependency (sober for two years) and questionable hepatitis (currently liver function tests were normal). Concomitant medication included Serzone (nefazodone) and Effexor (venlafaxine). On the day that SEROQUEL therapy was initiated an elevated blood sugar level (28 mmol/L; ~ 504 mg/dL) was reported. The patient remained on SEROQUEL for two months and was treated with an oral hypoglycemic (metformin). The elevation in blood sugar was reported to have decreased by 6-10 mmol/L during this time. SEROQUEL was discontinued (reason unspecified), however the patient remains on therapy with metformin. No further information was available.

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Comment: The hyperglycemia was identified on the day that SEROQUEL was commenced; therefore, the hyperglycemia was not causally related to SEROQUEL. Following discontinuation of SEROQUEL, treatment with metformin was still needed.

6.6.3.3 Summary of Reports of Hyperglycemia (45)

Of the 45 reports of hyperglycemia, 19 were confounded by concomitant medications for which hyperglycemia or DM has been reported (2003AP01546, 2002UW01476, 2002AP04011, 2002UW16205, 2002AP04183, 2002AP04278, 2003AP00033, 2002UW16580, 2002UW10490, 2002UW09743, 2001SE02468, 2001AP04330, 2001AP02034, 2002UW14620, 2003AP00109, 2002UW09024, 2003UW03989, 2003GB00473, and 2003AP01545).

Of these 19 reports, two (2001SE02468, 2002AP04011) also described patients with a risk factor of obesity, one (2002UW09743) described a patient with a family history of DM, one (2002UW01476) described a patient with a history of hyperlipidemia and obesity, and one other (2002AP04183) described a patient with obesity and a family history of DM.

Another 18 (2003AP00090, 2002UW15836, 2002UW16588, 2002UW13371, 2002UW14319, 200214549, 2002UW05977, 2002UW02227, 2001UW02046, 2001AP04437, 2000UW01047, 2002UW14927, 2002UW11778, 1998AP50408, 2003UW00329, 2003GB00465, 2003SE02056, 2003GB00705) contained scant clinical detail and did not lend themselves to analysis. One of these patients (2003GB00465) also contained a family history of DM (risk factor).

Four additional reports described patients with risk factors for DM (2002UW15932; family history of DM, 2003AP00040; obese patient that had marked weight gain prior to SEROQUEL, and had polydipsia and promiscuous eating habits), 2002AP04245; fatty liver, and 2002UW15169; history of hyperglycemia prior to receiving SEROQUEL).

Another report (1998UW49037) described an overdose of SEROQUEL (9600 mg) with subsequent "mildly elevated" serum glucose (137 mg/dl). Another report (2002GB02591) described a patient who developed hypothyroidism, hyperlipidemia, and a 20 kg weight gain while receiving SEROQUEL. Another report (2003AP00035) described a patient with an increased FBS and HbA1c prior to commencing SEROQUEL, which both increased while on SEROQUEL, and then both decreased (but remained above normal) when SEROQUEL was discontinued.

The last report (2003UW01256) described a 49-year-old male patient with a history of alcohol dependency who experienced a blood sugar of 28 mmol/L (~ 504 mg/dL) on the day that SEROQUEL therapy commenced. The patient began treatment with metformin, continued on SEROQUEL for two months, and experienced an improvement in blood sugar readings (decreased by 6-10 mmol/L) during that time. The patient remained on metformin after SEROQUEL was discontinued.

6.6.3.4 Conclusion for Reports of Hyperglycemia (45)

Following a review of all the reports of hyperglycemia, it was determined that the evidence to establish a causal relationship for SEROQUEL and hyperglycemia was insufficient.

6.6.4 Exacerbation of Pre-existing Diabetes Mellitus (28)

6.6.4.1 Database Results

Twenty-eight reports were identified that reflected an exacerbation of the clinical status of a diabetic patient. Twelve of these reports contained the MedDRA preferred terms "Diabetes mellitus inadequate control", "Diabetes mellitus NOS", or "Diabetes mellitus aggravated", and described an exacerbation of pre-existing DM. Sixteen of these reports contained the MedDRA preferred terms "Hyperglycaemia NOS" or "Blood glucose increased" and although it was not reported that there was an exacerbation of the diabetic status, these patients all had pre-existing DM.

6.6.4.2 Report Descriptions or Narratives

Of the 12 reports describing an exacerbation of pre-existing DM, five were confounded by concomitant medications. These five reports and the confounding medication are listed in Table 20 below.

Table 20 Reports where an Exacerbation of diabetes was reported—confounded by medications (5)

Report number	Confounding concomitant medication
2003AP00123	fenoterol[1,3], procaterol[1,3], salmeterol[1,3], fluticasone[1]
2002AP00855	olanzapine[1,2,3]
2002SE03085	olanzapine[1,2,3]
2001GB00231	beclomethasone[1] (oral inhalation), fluticasone[1] (nasal inhalation)
2000UW04457	nortriptyline[1]

[1] for which hyperglycemia reported, [2] = for which DM reported, [3] = for which DKA reported.

Another four of the 12 reports (2002UW12946, 2001UW08041, 2001UW07793, 1998AP45979) contained scant clinical detail and thus did not lend themselves to analysis.

Another one (2002AP02570) of the 12 reports was confounded by the patient drinking large volumes of juice; the patient continued on SEROQUEL and became better controlled with diet, weight reduction, and initiation of an oral hypoglycemic medication. Another report (2002AP03075) exhibited a negative de-challenge when SEROQUEL was discontinued. The 12th report (1999AP06660) described a patient with NIDDM who experienced an exacerbation while receiving SEROQUEL. The three reports listed immediately above are described in Table 21 below.

Table 21 Other reports of exacerbation of diabetes

Report#	Age/ Sex	Dose/ TTO	Medical history	Con meds	Comments
2002AP02570	26/F	600 mg/day; 14 months	NIDDM, bulimia nervosa, obesity, drinking large amounts of juice	flunitrazepam, quazepam, bromocriptine, levomepromazine, zotepine	FBS = 170 mg/dl, HbA1c = 6.6 %: valproic acid[1] D/c'd, started Seroquel. After 14 mos: glucose = 300 mg/dl, HbA1c = 10%. Admitted drinking large volumes of juice. Tx = oral hypoglycemic, diet + weight control, Seroquel continued: Pt improved.
2002AP03075	66/F	125 mg/day; 3 weeks	NIDDM	biperiden, acarbose, brotizolam, carbamazepine, atorvastatin	Baseline FBS = 179 mg/dl. Seroquel x3weeks: FBS = 300 mg/dl. Tx = glibenclamide. 1 month later FBS = 205 mg/dl. 1 week later Seroquel ↓ (100 mg/day). 7 days later FBS = 200 mg/dl, glibenclamide↑. After 9 weeks Seroquel d/c'd. 1 mo later FBS = 281 mg/dl. Tx = insulin. Restarted oral hypoglycemics w/o insulin: FBS = 160-293 mg/dl. Tx = insulin
1999AP06660	45/M	300-400 mg/day; time unknown	NIDDM (diet controlled)	Not provided	During Seroquel therapy (duration unknown) glucose ↑ 10 to 13 (no units). Tx = glibenclamide, Seroquel contd. Pt not rec'd,

TTO = time to onset, NIDDM = non-insulin dependant DM, d/t = due to, FBS = fasting blood sugar, Pt = patient, tx = treatment, contd. = continued, d/c'd = discontinued, w/o = without, info = information, rec'd = recovered, mo(s) = month(s).

An additional 16 reports contained the MedDRA preferred terms "Hyperglycaemia NOS" or "Blood glucose increased" and although it was not reported that there was an exacerbation of the diabetic status, these patients all had pre-existing DM. Eight of these reports were confounded by concomitant medications and are listed in Table 22 below.

Table 22 Reports of hyperglycemia in patients with a history of diabetes confounded by medications (8)

Report number	Confounding concomitant medication
2003UW03539	chlorpromazine[1]
2002AP03102	risperidone[2]
2002UW08675	Bupropion[3]
2002UW08863	lisinopril[1]
2002UW10887	metoprolol[1, 4]
2002AP04372	Lithium[1], amoxapine[1]

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Table 22 Reports of hyperglycemia in patients with a history of diabetes confounded by medications (8)

Report number	Confounding concomitant medication
2001AP04784	olanzapine[1,2,5]
2000UW04142	valproic acid[1]

[1] for which hyperglycemia reported, [2] = for which DM reported, [3] = precaution for use with diabetic Pt, [4] = for which interaction w/ anti-diabetic drugs resulting in hyperglycemia reported, [5] = for which DKA reported.

Report 2002AP03102 (in Table 21 above) described a negative de-challenge based on the lack of recovery three weeks after discontinuation of SEROQUEL. Another case (2002AP04372; in Table 21) was confounded with dietary non-compliance because the patient "found it difficult to control his diet due to his personality and expenditure problems".

Another two (of the 16) reports were confounded by the patient's dietary non-compliance. The first of these (2000UW03255) described a 58-year-old diet controlled diabetic female patient who had been receiving SEROQUEL (300 mg/day x 4 months) and experienced an elevated glucose (564; no units). This patient was evaluated in the emergency room and the reporter stated "she wondered if this increase was related to SEROQUEL or the large amount of regular root beer ingested by the patient that day". Additional information was requested but no follow up was received. The second of these (2002AP01913) stated the patient "was unable to follow, and resisted, dietary therapy for DM" and that the "patient's body weight gradually increased again due to consumption of soft drinks, and eating after scheduled meals". This report is also confounded by a medication (chlorpromazine) for which hyperglycemia as been reported.

Four more reports (2003AP00038, 1999UW00288, 2002UW14424, 2002GB03159) contained scant clinical detail and thus did not lend themselves to analysis.

Another report (2002SE06379) described a patient with a 15-year history of DM who was receiving insulin and experienced two episodes of hypoglycemia and then one episode of hyperglycemia (387 mg/dL). The physician stated "the hypo and hyperglycemic attacks might be induced by inadvertent insulin dose changes". No additional information was provided.

The last report (2001AP04051) is described below.

2001AP04051: This report described a 44-year-old male patient receiving SEROQUEL for schizophrenia. Prior to treatment with SEROQUEL, the patient's DM was well controlled with an HbA_{1C} of 6.5 %. Four weeks and three days after the first dose of SEROQUEL, the patient experienced hyperglycemia (HbA_{1C} was 9.2 % and blood glucose was 486 mg/dl). One month later, the patients HbA_{1C} increased to 12 % and his blood glucose level was increased to 226 mg/dl. The patient admitted drinking large volumes of fruit juice. The physician initially considered the laboratory findings due to the ingestion of the fruit juice. However, the patient was hospitalized three days later and dietary controls were introduced

but laboratory values remained increased with an HbA_{1C} of 12 % and blood sugar of 226 mg/dl. The patient began treatment with Euglucon (glibenclamide; 2.5 mg/day), without improvement. SEROQUEL was discontinued six weeks and three days after the onset of the event. The patient's blood glucose level began to decrease and glibenclamide was stopped one month later. Seventeen weeks and three days after the onset, the patient recovered. His HbA_{1C} returned to 6.9% and his blood sugar level was 122 mg/dl. Medical history included hyperlipemia, DM, and an adverse drug reaction to risperidone (mania). Concomitant medications included Amoxan (amoxapine; for which hyperglycemia has been reported), sulpiride, Cerekinon (trimebutine maleate), Seniran (bromazepam), Akineton (biperidin), Ledolper (brotizolam), Atarax (hydroxyzine), Rohypnol (flunitrazepam), Myslee (zolpidem tartrate), Cremin (mosapramine), Bezatate (bezafibrate) and Telesmin (carbamazepnie).

Comment: Although this report described a temporal relationship to the initiation of SEROQUEL and a positive de-challenge, it is difficult to assess causality due to confounding with dietary non-compliance, and a concomitant medication associated with hyperglycemia (amoxapine).

6.6.4.3 Summary of Reports of Exacerbation of Pre-existing Diabetes Mellitus (28)

Of the 28 reports reflecting an exacerbation of DM, 13 reports are confounded with concomitant medications (2002SE03085, 2002AP00855, 2001GB00231, 2000UW04457, 2002UW08675, 2001AP04784, 2002UW10887, 2002UW08863, 2000UW04142, 2002AP03102, 2003UW03539, 2003AP00123, 2002AP4372), eight contained scant clinical detail (2003AP00038, 2002UW12946, 2001UW08041, 2001UW07793, 1998AP45979, 1999UW00288, 2002UW14424, 2002GB03159), three are confounded with dietary non-compliance (2002AP02570, 2000UW03255, 2002AP01913), and one (2002AP03075) described a negative de-challenge (no recovery after SEROQUEL discontinued). One other report (1999AP06660) described a patient who experienced an exacerbation that was being treated with glibenclamide while SEROQUEL continued. The patient had not recovered at the time of the report. Another (2002SE06379) described a patient who was receiving insulin and experienced two episodes of hypoglycemia and then one episode of hyperglycemia while on SEROQUEL therapy. The physician stated "the hypo and hyperglycemic attacks might be induced by inadvertent insulin dose changes". No additional information was available. The last report (2001AP04051) described a temporal relationship to the initiation of SEROQUEL and a positive de-challenge, however, it was confounded with dietary non-compliance, and a concomitant medication associated with hyperglycemia.

6.6.4.4 Conclusion for Exacerbation of Pre-existing Diabetes Mellitus (28)

Following a review of the reports of exacerbation of diabetes, and of hyperglycemia or increased blood glucose in patients with pre-existing DM, it was determined that the evidence to establish a causal relationship for SEROQUEL and exacerbation of diabetes (or hyperglycemia in patients with pre-existing diabetes) was insufficient.

6.7 Reports of Urinary Glucose Abnormality (1)

AstraZeneca received one non-serious report regarding urinary glucose abnormality. This report is described below.

6.7.1 Report Narratives

2003AP00034: This report of "Glucose urine present" described a 35-year-old male patient who was receiving SEROQUEL (600 mg/day) for the treatment of schizophrenia and persecutory delusions. Medical history included obesity (BMI = 36.1), hyperlipidemia, hyperorexia (bulimia), head injury, rib fracture, and toe fracture. Concomitant medications included Wintermin (chlorpromazine; for which hyperglycemia has been reported), Tegretol (carbamazepine), Depakene (valproic acid; for which hyperglycemia has been reported), Artane (trihexyphenidyl), Mobic (meloxicam), magnesium oxide, Rohypnol (flunitrazepam), and Landsen (clonazepam). Twenty-six weeks and one day after starting SEROQUEL the patient experience positive (+++) urine glucose. At the time of the AE, the patient did not experience malaise or thirst. One week later blood work revealed an HbA1c of 5.7% and blood glucose of 93 mg/dl (unknown if random or fasting). The patient's urine glucose one month prior to the event had been negative and repeat urine glucose 18 days after the event was also negative. The patient was a "sweet/juice" consumer. The AE resolved without treatment and SEROQUEL was continued.

6.7.2 Summary of the Non-serious Report of Urinary Glucose Abnormality (1)

This patient had a normal HbA1c and a repeat urine test that was negative for glucose. These data indicate the patient did not have DM.

6.7.3 Conclusion for Urinary Glucose Abnormality Report (1)

This report (positive urine glucose test) did not contribute any significant information to suggest that SEROQUEL has a causal role in glucose dysregulation.

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7. DISCUSSION/CONCLUSION

As of 25 April 2003, worldwide post-marketing reports received by AstraZeneca comprised 153 cases of new-onset DM, exacerbation of pre-existing DM, DKA or hyperglycemia. The majority of reports of DM did not include baseline fasting blood glucose levels, to rule-out preexisting disease in new-onset diabetics or to indicate the degree of glycemic control in patients with preexisting DM. Regarding the latter cohort, patients with schizophrenia are frequently noncompliant with treatment regimens including medications and lifestyle modifications used to achieve glycemic control. Assessment of causality was difficult in most of these cases because of either scant clinical detail, unclear temporal sequence of exposure and outcome, confounding by concomitant medications for which DM or related events have been reported, risk factors for DM (obesity or family history of DM), and documented dietary non-compliance.

It was estimated that about 4.5 million patients have been exposed to SEROQUEL as of 31 December 2002 (an estimate of almost 4 million patients in the US and 0.5 million patients ex-US). Given this exposure, the number of post-marketing reports (153) of glucose dysregulation in patients using SEROQUEL is very small.

In clinical trials with SEROQUEL, there were no reports of DKA or hyperosmolar coma. There were no statistically significant differences between SEROQUEL compared to placebo, chlorpromazine, or haloperidol in mean change of glucose from baseline. There was no consistent or clinically significant effect on random glucose levels. There was no increase in adverse events (AE) associated with disturbances in glucose metabolism for SEROQUEL when compared to placebo, chlorpromazine, risperidone, and haloperidol. There were five reports of DM in the open-label extension, but none were considered drug related or led to drug withdrawal.

There was inconclusive evidence in the medical/scientific literature to suggest that SEROQUEL negatively influences glucose regulation causing new-onset DM or worsening of pre-existing DM. Furthermore, according to the literature, the incidence of DM in the schizophrenic population (~15%) is noted to exceed that in the general population (10%/US) even prior to the introduction of atypical antipsychotic medications (Dixon et al. 2000, Mokdad et al. 2001).

Diabetes is a progressive disease that begins sub-clinically and progresses to an impaired fasting glucose with glucose intolerance, and then to full-blown DM. In published epidemiology studies and other research studies comparing various antipsychotic drugs, an association between DM and olanzapine, but not the other atypical antipsychotics, was consistently shown. The weight of the evidence is insufficient for a causal association between SEROQUEL and DM.

Following a review of all the available relevant pre-clinical, clinical and safety information, as well as the medical/scientific literature, it was determined that there is currently inconclusive evidence to suggest that SEROQUEL negatively influences glucose regulation causing new-onset DM or worsening of preexisting DM.

AstraZeneca will continue to keep reports of DM and related disorders under careful review.

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8. REFERENCES

Anonymous. Atypical antipsychotics and body weight gain: how serious is the problem? Drugs & Therapy Perspectives 2002;18(8):23-6.

Beers MH, and Berkow R. The Merck Manual of Diagnosis and Therapy Seventeenth Edition. Merck Research Laboratories, June 1999.

Bettinger TL, Mendelson SC, Dorson PG, et al. Olanzapine-induced glucose dysregulation. Ann Pharacother 2000;34:865-7. (2002AP00855)

AUTO PAGE (AUTO NUMPAGES)

Black DW, Warrack G, Winokur G. Excess mortality among psychiatric patients. The Iowa Record-Linkage Study. JAMA 1985;253:58-61.

Brecher M, Rak IW, Melvin K, and Jones AM. The long-term effect of quetiapine (SeroquelTM) monotherapy on weight in patients with schizophrenia. International Journal of Psychiatry in Clinical Practice. 2000;4:287-291.

Buda M, Tsuang MT, Fleming JA. Causes of death in DSM-III schizophrenics and other psychotics (atypical group). A comparison with the general population. Arch Gen Psychiatry 1988;45:283-5.

Buse JB, Cavazzoni P, Hornbuckle K, Hutchins D, Breier A, Jovanovic L. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. Journal of Clinical Epidemiology. 2003;56:164-170.

Buse, JB. Metabolic side effects of antipsychotics: Focus on hyperglycemia and diabetes. Journal of Clinical Psychiatry 2002;63(4):37-41.

Casey DE. Danielson EM, Fishman NB. Prevalence of diabetes in schizophrenia patients treated with antipsychotics. Proceedings of the Amer Psychiatric Assoc. 2001;No. NR 315.

Chue PS. Are atypical antipsychotics associated with an increased risk of diabetes, and is this associated with weight gain? Journal of Psychiatry and Neuroscience 2001;26(4):360.

Cohn T, Remington G. Changing times, changing concerns-a cross-sectional study of antipsychotic medication use and cardiac risk factors in 213 long-term psychiatric inpatients. International Journal of Neuropsychopharmacology 2000;3 Suppl:S153, Abs P.01.225.

Curkendall SM, Mo J, Jones JK, Glasser D. Increased cardiovascular disease in schizophrenia. World Journal of Biological Psychiatry 2001;2 Suppl 1:207S Abs P001-4.

Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20:1183-1197.

Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A, Lehman A. Prevalence and Correlates of Diabetes in National Schizophrenia Samples. Schizophrenia Bulletin, Vol. 26 (4):903-912, 2000.

Eaton WW, Mortensen PB, Herrman H, Freeman H, Bilker W, Burgess P, et al. Long-term course of hospitalization for schizophrenia. Part I, Risk for rehospitalization. Schizophr Bull 1992;18:217-28.

Gianfrancesco F, White RE, Yu E. NR 400: antipsychotics-induced type 2 diabetes: evidence from a large health plan database. Presented at the annual meeting of the American Psychiatric Association—Institute on Psychiatric Services, Chicago, IL, October 10, 2002.

AUTO PAGE (AUTO NUMPAGES)

Gopalaswamy AK, Morgan R. Smoking in chronic schizophrenia. Br J Psychiatry 1986;149:523.

Haupt DW, Newcomer JW. Abnormalities in glucose regulation associated with mental illness and treatment. Journal of Psychosomatic Research 2002;53:925-933.

Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA. Prevalence of smoking among psychiatric outpatients. Am J Psychiatry 1986;143:993-7.

Hussar AE. Leading causes of death in institutionalized chronic schizophrenic patients: a study of 1275 autopsy protocols. J Nerv Ment Dis 1966;142:45-57.

Hustey FM. Acute quetiapine poisoning. [Article, Case report] Journal of Emergency Medicine 1999;17(6):995-997. (1998UW49037)

Kornegay CJ, Vasilakis-Scaramozza C, Jick H. Incident Diabetes Associated With Antipsychotic Use in the United Kingdom General Practice Research Database. J Clin Psychiatry 63(9):758-762, September 2002.

Lambert B, Chou C.-H., Chang K.-Y., Iwamoto T, Tafesse E. Assessing the risk of antipsychotic-induced Type II diabetes among schizophrenics: A matched case-control study. European Neuropsychopharmacology 2002, 12 (Suppl 3): 307S-308S.

Liebzeit KA, Markowitz JS, Caley CF. New onset diabetes and atypical antipsychotics. European Neuropsychopharmacology 2001;11(1):25-32.

Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman B, McEvoy JP, Cooper TB, Chakos M, Lieberman JA. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical and atypical antipsychotics. Amer Jr Psychiatry 160(2):290-296, 2003.

Lindenmayer JP, Nathan AM, Smith RC. Hyperglycemia associated with the use of atypical antipsychotics. Journal of Clinical Psychiatry 2001;62 Suppl 23:30-8.

Masterson E, O'Shea B. Smoking and malignancy in schizophrenia. Br J Psychiatry 1984;145:429-32.

Meltzer HY. Putting metabolic side effects into perspective: Risks versus benefits of atypical antipsychotics. Journal of Clinical Psychiatry 2001;62 Suppl 27:35-9.

Meyer JM. A retrospective comparison of lipid, glucose, and weight changes at one year between olanzapine and risperidone treated inpatients. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology; Dec 10-14, 2000; San Juan, Puerto Rico. (2001AP04330)

AUTO PAGE (AUTO NUMPAGES)

Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The Continuing Epidemics of Obesity and Diabetes in the United States. Journal of the American Medical Association 2001: 286(10);1195-1200.

Mukherjee S, Decina P, Bocola V, Saraceni F, Schapicchio PL. Diabetes Mellitus in Schizophrenic Patients. Comprehensive Psychiatry 1996;7(1):68-73.

Procyshyn RM, Pande S, Tse G. New-Onset Diabetes Mellitus Associated With Quetiapine. (Letter). Canadian Journal of Psychiatry 2000;45(7):668-669. (2000AP05293)

Reinstein MJ, Sirotovskaya LA, Jones LE, Mohan S, Chasanov MA. Effect of Clozapine-Quetiapine Combination Therapy on Weight and Glycaemic Control: Preliminary Findings. Clinical Drug Investigation 1999;18(2):99-104.

Russel JM, Mackell JA. Body weight gain associated with atypical antipsychotics – Epidemiology and therapeutic implications. CNS Drugs 2001;15(7):537-51.

Ryan MCM, Collins P, Thakore JH. Impaired Fasting Glucose Tolerance in First-Episode, Drug-Naïve Patients With Schizophrenia. Am J Psychiatry 160:2, Feb 2003.

Ryan MCM, Thakore JH. Physical consequences of schizophrenia and its treatment – The metabolic syndrome. Life Sciences 2002;71(3):239-57.

Saito E, Kafantaris V. Can diabetes mellitus be induced by medication? Jr Child and Adolescent Psychopharm 2002;12(3):231-6. (2002AP01607)

Sernyak MJ, Leslie DL, Alarcon RD, Losonczy MF, Rosenheck R. Association of Diabetes Mellitus With Use of Atypical Neuroleptics in the Treatment of Schizophrenia. Am J Psychiatry 2002; 159:561–566.

Sobel M, Jaggers ED, Franz MA. New-Onset Diabetes Mellitus Associated With the Initiation of Quetiapine Treatment. (Letter). Journal of Clinical Psychiatry 1999;60(8):556-557. (1998UW48844) (1998UW48512)

Tsuang MT, Perkins K, Simpson JC. Physical diseases in schizophrenia and affective disorder. J Clin Psychiatry 1983;44:42-6.

Van Meter SA, Seaburg H, McLendon B, Doraiswamy PM. Olanzapine, new-onset diabetes mellitus, and risk for insulin overdose. [Letter, Case report] Journal of Clinical Psychiatry 2001;62(12):993-4. (2002AP00323)

Vieweg V, Levenson J. Pandurangi A, Silverman J. Medical disorders in the schizophrenic patient. Int J Psychiatry Med 1995;25(2):137-72.

Westermeyer JF, Harrow M. Course and outcome in schizophrenia. In: Tsuang MT, Simpson JC, editors. Nosology, epidemiology, and genetics of schizophrenia. Handbook of Schizophrenia vol 3. Amsterdam: Elsever, 1998;205-44.

AUTO PAGE (AUTO NUMPAGES)

Wilson DR, D'Souza L, Sarkar N, Newton M, Hammond C. New-Onset Diabetes and ketoacidosis with atypical antipsychotics. Schizophr Res 2003 Jan 1(59): 1-6. (2000AP03612)

Wirshing DA, Boyd JA, Meng LR, Ballon JS, Marder SR, Wirshing WC. The Effects of Novel Antipsychotics on Glucose and Lipid Levels. J Clin Psychiatry 2002, 63:856-865.

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APPENDIX A

NARRATIVES FOR REPORTS IN CLINTRACE

Diabetic ketoacidosis (DKA) (24)

Report Narratives

Reports of diabetic ketoacidosis with previous history of diabetes (8)

2003AP00312: This report of "Diabetic ketoacidosis" and "Hyperglycemia NOS" described a 32-year-old female patient who was receiving SEROQUEL (100 mg/day) for the treatment of panic disorder, dissociated disturbance, dysthymia, and post-traumatic stress disorder. Medical history included DM (type II—diet controlled), and height and weight of 163.9 cm and 123 kg, respectively (BMI = 45.7). The patient has weighed over 80kg since high school. The patient was not receiving any concomitant medications while on SEROQUEL therapy. The patient had been receiving Zyprexa (olanzapine) for three months but was discontinued due to a 'Dear Doctor' letter regarding diabetes. Treatment with SEROQUEL (100mg/day) was then commenced (no other antipsychotics were used at this time). Three months prior to starting SEROQUEL the patient's HbA1c was 5.3%. Eight days after starting SEROQUEL the patient's fasting blood sugar and HbA1c were 134 mg/dl and 6.4%, respectively. Six and one-half months after starting SEROQUEL the patient's HbA1c was 7.7% and SEROQUEL was discontinued due to a 'Dear doctor' letter issued regarding SEROQUEL and hyperglycemia. The patient was then switched to therapy with chlorpromazine (for which hyperglycemia has been reported). Two months later the patient experienced dry mouth and general malaise. Later that month the patient went to the emergency department and an acute aggravation of diabetes was observed. It was reported that the patient had polydipsia and polyuria two weeks before she was hospitalized. Infection was excluded due a CRP (C-reactive protein) of 0.26 (normal range <0.3 mg/dL. The patient's HbA1c was 12.4% at this time and fasting blood sugar was 487 mg/dl. The patient's blood sugar gradually decreased with insulin treatment and her fasting blood sugar was reported to be less than 100 mg/dl.

Comment: The patient's HbA1c increased while receiving SEROQUEL, however the start dates of the hyperglycemia and DKA occurred two months after discontinuing SEROQUEL. Previously in 1998 the patient's HbA1c was noted to be "around 10". Additionally, the patient's diabetes was diet controlled and a fluctuation of HbA1c could indicate dietary non-compliance.

2002AP01163: This serious report of "Diabetic ketoacidosis" and "Diabetic coma NOS" described a 36-year-old male patient who had a medical history of type II DM and drinking excessive amounts of soft drinks and coffee. The patient had been drinking large volumes of soft drink and his blood glucose level and HbA_{1C} were 776 and 10.7 %, respectively.

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Treatment included a drip infusion with added insulin and eventually oral pioglitazone. After six months of pioglitazone therapy, the blood glucose level was 109 (2 hr value) and HbA_{1C} was 5.3%. On 18 July 2001, his blood glucose was increased to 331 (4 hr value) due to drinking excessive amounts of coffee and his HbA_{1C} was 13.9%. On 28 January 2002, the patient reported that he stopped taking pioglitazone but his blood glucose was 117 (4 hr value); HbA_{1C} was 4.9% and body weight was 59 kg. On 15 April 2002, blood glucose was 420 (2 hr value) and HbA_{1C} was 8.2%. The patient was being treated with Clofekton (clocapramine) and on 15 May 2001, SEROQUEL (25 mg/day) was added. The dosage of SEROQUEL was increased and decreased over the next few months until it was discontinued on 07 September 2001 when it was switched to clocapramine. On 18 April 2002, clocapramine (75mg/day) was switched to SEROQUEL (75 mg/day). Two days later the patient's mental status was unchanged and he had no physical complaints. On 25 April 2002, his mental status was unchanged, though he felt terribly unwell. On REDA 2002, the patient was admitted to the hospital in a deep coma. Blood pressure was 60/36 mmHg, pulse was 120 bpm, and blood glucose was 1570. Renal failure developed secondary to severe dehydration and right heart collapse or shock. Treatment included continuous large volume infusion with a drip infusion of insulin and noradrenaline; which resulted in systolic BP of 90-100 mmHg. Immediately after, a fever (~ 40 $^{\circ}C$) was recorded and antibiotic therapy of ampicillin, sulbactam, and clindamycin started. FOY (gabexate mesylate) was started for disseminated intravascular coagulation (DIC) and L-Aspartate potassium was given for hypokalemia. "The condition was almost hyperglycemic hyperosmolar nonketotic coma (NKHHC)." On hospital day two, his respirations were weak. Blood gas analysis revealed carbon dioxide narcosis. Urinary ketone body (-), pH 5, microbial tests showed urinary test was negative, however, sputum test result revealed suspected BLNAR (beta-lactamase negative ampicillin resistant), haemophilus influenza (1+), streptococcus a-haemolyticus (1+), and candida albicans (1+). The patient was intubated and put on a respirator. The fever continued. Antibiotics were changed to imipenem and cilastatin. Abdominal CT scan and echography were carried out to detect the cause of the fever, but infection could not be detected. Blood analysis also excluded the possibility of infection. CNS disorder was suspected due to anisocoria and weak/absent spontaneous respiration. Brain stem lesion was suspected, since brain edema, hemorrhage, and major infarction were not recognized on brain CT. Concerning the fever, hypermyoglobinemia was recognized on blood gas analysis data, and it was considered necessary to rule out neuroleptic malignant syndrome (NMS) since he was taking SEROQUEL, though muscle findings were few. Dantrolene was given with injection for diagnostic treatment. Acute renal failure occurred due to the hypermyoglobinemia, but dialysis could not be started, since BP was decreased (around 60-70 mmHg) and gastrointestinal (GI) bleeding occurred due to disseminated intravascular coagulation (DIC). Catecholamine resistant hypotension (shock) occurred and the patient subsequently died. The cause of death was DKA. The physician commented that the patient had not been compliant with his diet. NMS was suspected to have caused the hypermyoglobinemia but there were few clinical or physical findings. Rhabdomyolysis may have occurred after peripheral circulatory failure, dehydration severe enough to cause shock in the condition of ketoacidosis, and central fever. No further information was provided.

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Comment: A detailed review of the laboratory data indicated that the HbA_{1C} was markedly elevated at 11.8% on REDA 2002, twelve days after starting SEROQUEL. Since the HbA_{1C} indicates glucose control for the previous two to three months, this elevated level suggested that the patient had poor diabetic control for a couple of months before SEROQUEL was initiated. The patient's history of non-compliance with diet (excessive consumption of soft drinks) and medication (stopped oral hypoglycemic pioglitazone) would account for poor diabetic control. In addition, infection, which was suspected in this case, is a common precipitator of DKA. Thus, this case is confounded.

2002AP02329: This serious report of "Diabetic ketoacidosis" described a 21-year-old female who was receiving SEROQUEL (600 mg/day) for the treatment of schizophrenia. The patient stopped oral medications and insulin, as her psychiatric symptoms were aggravated and vomiting occurred. Three days later (about eight weeks after starting SEROQUEL) the patient was hospitalized with vomiting, "deterioration of consciousness", blood sugar level of 745 mg/dl, WBC of 29,2000/mm3, C-reactive protein (CRP) of 1.28 mg/dl, and moderate dehydration. DKA was diagnosed. Treatment included drip infusion of normal saline, electrolytes with glucose drip infusion, and insulin infusion. Blood sugar, blood gases and mental status all improved. The next day the blood sugar was 276 mg/dl. The following day oral drugs (risperidone, biperiden, carbamazepine, flunitrazepam, and levomepromazine) were started. The day after that, auditory hallucinations and delusion "continued". Blood sugar was stable with a mean blood sugar of 200-300 mg/dl; urine ketones and sugar were both negative. Two days later the blood sugar again improved with a mean of 100-200 mg/dl. Auditory hallucinations and delusions still continued but insomnia did not occur. On the seventh day of admission the event had improved. Medical history included insulin dependent DM (IDDM) since age five. Concomitant medication included trihexyphenidyl, carbamazepine, haloperidol, clonazepam, flunitrazepam, zotepine, levomepromazine, and human insulin.

Comment: This patient had a history of insulin dependent DM since the age of five, and had a history of medication non-compliance (stopped her insulin). The high WBC may also have indicated an infection. Infections can precipitate DKA.

2000AP03612: This serious literature report of "Diabetic ketoacidosis" described a 64-year-old male patient with schizophrenia, who was switched from risperidone to SEROQUEL monotherapy (50 mg/day) 12 days after admission to the hospital (reason unknown). SEROQUEL was then increased to 100 mg in the morning and 300 mg at night. Two months later the patient was found unresponsive after breakfast and was transferred to a tertiary care center with a diagnosis of acute DKA. The patient was then lost to follow-up. The authors commented that the basal rate of DM in the Cincinnati area and among psychotic persons is higher than the national median. Medical history included chronic obstructive airways disease, prostate cancer, and DM. Concomitant medications included propranolol. Fasting blood sugar on an unknown date was 120 mg/dl.

Comment: This report did not contain information about what treatment measures this diabetic patient followed for the pre-existing diabetes. Assessment of causality is difficult due to scant clinical detail.

2001UW05726: This serious report of "Diabetic ketoacidosis" described a 43-year-old male patient who was receiving SEROQUEL (dose unknown) for the treatment of atypical psychosis. After six months of SEROQUEL therapy the patient died from possible DKA. Medical history included obesity, DM, Tourette's syndrome, borderline personality, and mild manic-depressive disorder. Concomitant medications included Haldol (haloperidol; for which a drug interaction with lithium resulting in a hyperglycemic reaction has been reported), lithium (for which hyperglycemia has been reported), pimozide (for which a drug interaction with lithium resulting in a hyperglycemic reaction has been reported), tetrabenazine, clonidine (for which hyperglycemia in NIDDM and IDDM has been reported), Tegretol (carbamazepine), clomipramine, Ativan (lorazepam), clonazepam, propranolol, Zoladex (goserelin), chlorpromazine (for which hyperglycemia has been reported), and chloral hydrate. It was also noted that the patient had been on Risperdal at the same time that SEROQUEL was started; Risperdal was discontinued three to four months prior to the patient's death. The reporter also stated that the patient's lab values, in reference to diabetes, changed drastically (not indicated if they improved or worsened) once the patient started SEROQUEL (no values given). Additional information was requested.

Comments: It was unknown how well controlled the diabetes was prior to or during treatment with SEROQUEL. This report is confounded by multiple concomitant medications for which hyperglycemia has been reported. Thus, assessment of causality for SEROQUEL is difficult.

1998UW49554: This serious report of "Diabetic ketoacidosis" described a 58-year-old male patient who was receiving SEROQUEL (800 mg/day; duration unknown) for the treatment of schizoaffective disorder. The patient experienced a transient ischemic attack (TIA) 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 cerebrovascular accident (CVA). Medical history included diabetes and CVA. Concomitant medications included gabapentin (for which blood sugar fluctuation in diabetic patients has been reported).

Comment: This patient had a history of diabetes and CVA, and was taking a medication for which blood sugar fluctuation in diabetic patients has been reported, thus confounding the report. The patient experienced a TIA followed the next day by a CVA and died. Significant medical illness can precipitate DKA. Therefore, it is difficult to assess causality to SEROQUEL.

2001UW16478: This serious report of "Diabetic ketoacidosis" described a 32-year-old male patient who was receiving SEROQUEL (800 mg/day x 2 weeks) for the treatment of schizophrenia and mental retardation. The patient experienced DKA. Three days prior to the incident the patient complained of upper respiratory symptoms and dizziness. On the day of the event the patient had an episode of urinary incontinence, confusion, and an abnormal heart rate. The blood glucose on chemstrip was abnormal (no value given). The peak glucose level

was 700 mg (no other unit). It was not reported whether SEROQUEL therapy continued. The patient remained hospitalized at the time of the report. Medical history included borderline diabetes (diet controlled). Concomitant medications included Risperdal (risperidone; for which DM has been reported), Serentil (mesoridazine), Depakote (valproic acid; for which hyperglycemia has been reported), and Ativan (lorazepam). Additional information has been requested.

Comment: If the upper respiratory symptoms represented an infection, the infection could have precipitated DKA. This report is confounded with the use of concomitant medications for which DM and hyperglycemia have been reported. Thus, assessment for a causal relationship to SEROQUEL is difficult.

2000AP04688: This serious report of "Diabetic ketoacidosis" described a 24-year-old male patient who was receiving SEROQUEL (300 mg/day) for the treatment of schizophrenia. It was reported that the patient took five "ecstasy" tablets and then consumed an unknown amount of alcohol on a Saturday evening. The patient was admitted to the hospital on Sunday with nausea, vomiting, hypokalemia, metabolic acidosis and was treated for DKA. The patient was admitted to the high dependency unit with worsening renal function, increasing aggression, and possible aspiration pneumonia. He aspirated and was therefore intubated and transferred to the intensive care unit. The patient developed acute renal failure with increased creatinine levels, reaching a maximum of 327 μmol/L (normal range = 55-150 μmol/L) ten days after admission. Treatment included hemodiafiltration, and alfentanil, midazolam, propofol, haloperidol, epoprostenol, and metronidazole. Vancomycin and ciprofloxacin were initiated after methicillin-resistant Staphylococcus aureus (MRSA) and coliform were identified. The acute renal failure resolved after two weeks and two days but the metabolic acidosis and hypokalemia were resolving slowly at the time of this report. The patient was unable to take his SEROQUEL and paroxetine after taking "ecstasy" due to the initial symptoms of nausea and vomiting. There is a possibility that the patient took an overdose of SEROQUEL but this was not confirmed. Follow-up information revealed that the patient was regularly prescribed SEROQUEL and paroxetine but his compliance was questionable. Medical history included insulin dependent DM, depression, and learning difficulties.

Comment: This report is confounded by alcohol consumption (alcohol can cause DKA). Therefore, assessment of causality for SEROQUEL is difficult.

Reports of diabetic ketoacidosis with no history of diabetes reported (16)

2002UW14814: This report of "Diabetic ketoacidosis" and "Diabetes mellitus NOS" described a female patient who was receiving SEROQUEL (400 mg/day) for irritability, insomnia, and mania. Medical history included obesity since treatment with atypical antipsychotics and increased blood glucose while taking Zyprexa (olanzapine). Concomitant medications included lithium (for which hyperglycemia has been reported), Klonopin (clonazepam), and Neurontin (gabapentin). Zyprexa was discontinued on the day that SEROQUEL therapy was started. After seventeen months of SEROQUEL therapy the patient experienced pancreatitis, DM, diabetes insipidus, DKA, apnea, and dyspnea. The patient's

glucose was reported to be 1400 (no units) on an unknown date. SEROQUEL, Klonopin, and lithium were all discontinued. The patient recovered from the pancreatitis. The outcome for the other events was unknown at the time of the report.

Comment: This report was confounded with a concomitant medication (lithium) for which hyperglycemia has been reported and by a risk factor (obesity). In addition, it appears that the patient experienced increased blood glucose while taking olanzapine prior to this event. No pre-SEROQUEL blood glucose values were reported.

2002GB02627: This serious report of "Diabetes Mellitus" described a 44-year-old male who began SEROQUEL therapy (200 mg 2x/day) on 05-Jul-2002 for the treatment of schizophrenia and experienced DM three months later. The patient was hospitalized with "early DKA" and was treated with insulin. A hemoglobinopathy screen about three weeks prior to commencing SEROQUEL "detected HbA and HbA4" (no values provided). No evidence of sickle cell or thalassemia was observed. The patient's weight had also increased from 90.3 kg on 26-Nov-2001 to 122.5 kg on 19-Oct-2002. SEROQUEL was continued and the event was ongoing at the time of the report. Concomitant medication included lactulose and orphenadrine "for schizophrenia", which was discontinued two months prior to the event. No further information was provided.

Comment: This report contains scant clinical detail (i.e. no glucose, baseline or otherwise, or pH levels provided). In addition, the significant weight gain is a risk factor for diabetes.

2002AP01772: This serious report of "Diabetic ketoacidosis" described a 51-year-old male patient who was receiving SEROQUEL and Risperdal (risperidone; for which DM and hyponatremia have been reported) for schizophrenic psychosis, and developed DKA. The patient was hospitalized for four months for an unspecified reason. Urinary glucose levels were analyzed monthly and remained negative during this time. Risperdal (2 mg/day) was initiated upon hospitalization and increased to 4 mg/day by two months. About six weeks later, SEROQUEL (200 mg/day) was initiated and titrated to 300 mg/day within eight days. About six weeks after discharge blood tests revealed mild anemia, slightly increased triglycerides, and normal glucose (not fasting) and HbA_{1C} values (123 mg/dl and 4.8 %, respectively). About six months later, the patient's condition seemed uneventful except for a complaint of insomnia, for which his nitrazepam dose was increased (as outpatient). Fifteen days later (42 and 48 weeks after beginning SEROQUEL and Risperdal, respectively) the patient experienced "disturbed consciousness" and was hospitalized. Laboratory results included blood sugar level (1179 mg/dl), HCO3 (3.0 mmol/L), sodium (116.3 mmol/L), and potassium (6.55 mmol/L). Results of the blood gas analysis were; BE (base excess) -25.2, and pH 7.055. DKA was diagnosed. Hydration status prior to hospitalization was unknown. All medications were discontinued and the patient was given normal saline, Myelon (sodium bicarbonate), and Novolin-R (insulin). The following day, blood glucose improved (233 mg/dl) but the patient remained comatose. Potassium levels had decreased (2.73 mmol/L) before increasing again (3.98 mmol/L) by the evening. During the evening, the patient's blood sugar increased to 545 mg/dl. Shock occurred and was unsuccessfully treated with a large volume of dopamine. The following day the patient died of circulatory failure (not confirmed

that the patient died from a hyperosmolar coma). An autopsy was not performed. The patient's sister confirmed that the patient drank about 4 liters of Coca-Cola (regular formula) every day for the last five weeks, and that the patient had lost weight rapidly in the last few weeks. Medical history included hepatic failure and acute hepatitis, which were suspected to be drug induced (drug not identified), prior to the DKA. Concomitant medications included Meilax (ethyl loflazepate; 4 mg/day) and Benzalin (nitrazepam; 20 mg/day). Family history for DM was unknown.

Comment: The blood glucose and HbA_{1C} levels taken months after starting Risperdal and SEROQUEL were normal. The DKA occurred after almost a year of therapy with Risperdal and SEROQUEL and several weeks after drinking four liters of Coca-Cola daily. Thus, this report is confounded both by diet (drinking large amounts of Coca-Cola) and a concomitant medication (risperidone).

2002AP02304: This serious report of "Diabetic ketoacidosis" described a 31-year-old male patient who was receiving SEROQUEL for treatment of schizophrenia. Three months after SEROQUEL was increased to 600 mg/day, the patient complained of limb weakness and a limp, which were not recognized objectively. Two days later the dysarthria and limb weakness worsened. The next day, approximately one and one-half years after commencing SEROQUEL, the patient was hospitalized (he could not hold a cup in his hand). On admission, the patient was almost "conscious", deep reflex was mildly increased, BP was 138/86, pulse 100 bpm, blood sugar 1348 mg/dl, and temperature was 37.9°C. Two days later, a brain computed tomography (CT) scan was normal, blood sugar level was 1280 mg/dl, and urinary sugar was 4+. Treatment included insulin and an infusion solution. The event resolved the following day. It was unknown if the patient was discharged on insulin. The reporting physician considered that the event was related to "PET bottle syndrome" (drinking large amounts of sweetened soft drink; other details are unknown). Medical history included obesity. Concomitant medications included haloperidol, biperiden, trihexyphenidyl, levomepromazine, and chlorpromazine/promethazine/phenobarbital combination (chlorpromazine is for which hyperglycemia and DM have been reported).

Comment: The reporting physician considered the event related to drinking large amounts of sweetened soft drink. This patient was also taking a concomitant medication for which hyperglycemia and DM have been reported.

2002AP02883: This report of possible "Diabetic ketoacidosis" described a 30-year-old female patient who was receiving SEROQUEL for the treatment of schizophrenic psychoses. The patient was concomitantly receiving haloperidol (30 mg/day gradually reduced to 5 mg/day), bromperidol (12 mg/day), biperiden (3 mg/day), triazolam (0.5 mg/day), flunitrazepam (1 mg/day), and distigmine bromide. The patient did not have a history of drinking or alcoholism, it is unknown whether her family had a history of DM, but the patient did not. SEROQUEL treatment (75 mg/day) was commenced in June 2001. This was titrated upwards to 200 mg while haloperidol was reduced from 30 mg to 5 mg. On 7 September 2002, one year and three months after commencing SEROQUEL treatment the patient developed symptoms of what was reported to be a common cold (diarrhea, retching, vomiting and

pyrexia) and her body temperature increased to 38-39 °C. On 8 September 2002, her fever resolved but gastrointestinal symptoms continued and anorexia occurred. On 9 September 2002 her diarrhea and vomiting continued and she received treatment with a drip infusion to prevent dehydration. During the evening her family recognized she was drinking a large amount of water and later that night the patient complained of difficulty breathing. On RE REDACT 2002, her difficultly breathing continued and she visited a local internist. Chest and abdominal X-ray results were normal; laboratory tests were not performed. The internist diagnosed the condition as psychiatric symptoms. She returned home after treatment with a drip infusion. During the evening her difficulty breathing increased. Her family recognized a sudden change in her condition and called an ambulance. At this time the patient possibly experienced a cardiac arrest. She underwent intubation, no vomit was recognized at the time and she died at approximately 1900. Her body weight had not markedly changed recently and she had a normal physique, due to this her blood sugar level had not been analyzed recently. Her eating habits were normal for a person of her age. The patient continued to receive SEROQUEL until the day of her death. An autopsy was performed, but the cause of death could not be determined. A detailed examination is being carried out histologically. The reporting physician considered that the diarrhea, pyrexia, retching, and vomiting were related to a common cold and commented that the patient was healthy. It was assumed, however, that the hyperglycemia, which may have occurred after DM, was triggered by the common cold. The physician considered that SEROQUEL caused the condition, since another patient developed hyperglycemia during SEROQUEL therapy. However, it is only a matter of speculation, since there was no objective data. Since excessive drinking and breathing difficulty occurred, the reporter also suspected that ketoacidosis possibly occurred and advanced to induce deterioration of her condition and death. It was considered that cardiac arrest possibly occurred due to hyperkalemia in such a condition.

Comment: The possibility that this case represented DKA was acknowledged by the reporting physician to be speculative because no laboratory blood tests (e.g. glucose, pH etc) were drawn. This patient had symptoms that were diagnosed as a common cold, but may have been gastroenteritis. In addition, the symptoms of nausea, vomiting, and diarrhea are also AE associated with distigmine, one of her concomitant medications. In summary, there was no objective data to support a diagnosis of diabetes or DKA, and possible alternative explanations for the events exist.

2001UW12078: This serious report of "Diabetic ketoacidosis" described a 57-year-old patient (sex unknown) who was receiving SEROQUEL (dose/duration unknown) for an unknown indication. The patient experienced DKA and died. Medical history was not provided. Concomitant medications included Risperdal (risperidone; for which DM has been reported), which was also considered a suspect medication. No further information was obtainable.

Comment: Diabetes mellitus has been reported with Risperdal use, which can initially present as DKA. Assessment of causality is difficult due to minimal information.

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2002UW08229: This serious report of "Diabetic ketoacidosis" described a 40-year-old female patient who was receiving SEROQUEL for the treatment of schizoaffective disorder and a depressed mood. The patient's SEROQUEL dose was gradually titrated to 300 mg/day over several months. Five months later the dose was increased to 200 mg 2x/day. The patient misunderstood the directions and took 200 mg/day from that time on. Approximately four months later the patient was found dead on the floor of her apartment. The police investigator's report stated that the patient's neighbor disclosed that the patient traded drugs, namely cocaine, crack, and marijuana, to let others drive her car, and that the patient was very depressed and hated herself, and spoke of wanting to commit suicide. Marijuana residue and seeds were found in her car. The autopsy report indicated that the cause of death was DKA, with a contributing factor of diabetic renal failure. The report also revealed that the patient had severe fatty liver metamorphosis, cholelithiasis, congestion of the viscera, and obesity. Lab values at autopsy from a vitreous specimen included Na 146 mmol/L, K 25.5 mmol/L, chloride 107 mmol/L, BUN 86.5 mg/dl, glucose 997 mg/dl, and creatinine 2.7 mg/dl. The patient's urine was positive for cocaine metabolites, and her heart blood was positive for cocaine, ethanol, acetone, and sertraline. Medical history included mental illness, smoker, obesity (weight 186 lb./height 66 inches), and cocaine, crack, and marijuana abuse. Concomitant medications included BuSpar (buspirone), Zoloft (sertraline), and Tequin (gatifloxacin).

Comment: The patient died from DKA with a contributing factor of diabetic renal failure. Diabetic renal failure suggests some degree of chronicity of diabetes that likely preceded SEROQUEL therapy. The patient also had a history of cocaine, crack, and marijuana abuse.

2002UW09406: This serious report of "Diabetic ketoacidosis" described a 36-year-old male patient who was prescribed SEROQUEL (400 mg/day) for the treatment of schizophrenia. One month after starting SEROQUEL the patient was hospitalized for DKA. Treatment included 10 units of insulin IV and then 10 units/hour IV. SEROQUEL was discontinued and it was not reported if SEROQUEL was restarted. Lab values on admission included: blood gas pH 7.26, glucose 1544 mg/dl, K^+ 6.1, BUN 64, creatinine 3.5, and urine positive for ketones. (Units listed whenever they were provided). The patient did recover from the event and was discharged from the hospital. Medical history included gastroesophageal reflux disease and no family history of diabetes. Concomitant medications included Prevacid (lansoprazole), ibuprofen, multivitamins, and Metamucil. No further information was provided.

Comment: Follow up information, particularly pre-hospitalization laboratory results for glucose, patient weight and height, has been requested.

2002GB01741: This serious report of "Ketoacidosis" described a 50-year-old male patient who had been receiving SEROQUEL (800 mg/day for a least three years) for the treatment of schizophrenia. During SEROQUEL therapy the patient developed ketoacidosis and was admitted to the hospital. SEROQUEL was discontinued. Medical history included psoriasis and a reported body mass index of "70". It also was reported that the patient had no family history of diabetes. Concomitant medications included Adalat (nifedipine; for which

hyperglycemia has been reported), Neotigason (acitretin), trazodone, and atorvastatin. At the time of the report the outcome was unknown.

Comment: Obesity was not reported but the patient had a reported BMI of "70". Obesity is a risk factor for type II diabetes. In addition, this report is confounded because the patient was taking a concomitant medication for which hyperglycemia has been reported.

2002GB01254: This serious report of "Diabetic ketoacidosis" described a male patient (age unknown) who was receiving SEROQUEL (300 mg/day) for the treatment of schizophrenia. One year and two months after starting SEROQUEL the patient was hospitalized with DKA. On admission, the glucose level was 46.6 (no units provided); the patient was dehydrated, and acidotic. The patient's HbA_{1C} was >12%. Type I or type II diabetes was suspected. The patient had become increasingly obese (BMI 48.7 kg/m2). Treatment included insulin, but at the time of the report, the event was ongoing. Concomitant medications included clozapine (for which hyperglycemia and ketoacidosis have been reported) and Zyprexa (olanzapine; for which diabetes and DKA have been reported).

Comment: This patient was obese (obesity is a risk factor for diabetes). In addition, the patient was taking concomitant medications for which diabetes or DKA have been reported. Thus, it is difficult to demonstrate a clear causal role for SEROQUEL.

2001UW14447: This serious report of "Diabetic ketoacidosis" described a 13-year-old male patient who was receiving SEROQUEL (300 mg/day) for the treatment of bipolar disorder to control his fear, aggression, and mood swings. Once on SEROQUEL, the patient developed a "cardiac situation" that started with an arrhythmia and progressed to ischemia. A stress test revealed ischemia and the patient was scheduled for cardiac catheterization. Approximately one month later, the patient was hospitalized for DKA and was discharged on insulin. The patient was in foster care and there was little information about family history, however, it was thought that there might be a family history of diabetes (several grandparents, mother). Medical history included morbid obesity. Concomitant medications included Depakote (valproate sodium; for which hyperglycemia has been reported). Additional information was requested.

Comment: This patient was obese (obesity is a risk factor for diabetes) and was taking a concomitant medication for which hyperglycemia has been reported. This patient may have had a positive family history for diabetes. Thus, it is difficult to demonstrate a clear causal role for SEROQUEL.

2001UW12263: This serious report of "Diabetic ketoacidosis" and "Hyperglycaemia NOS" described a 30-year-old male patient who was receiving SEROQUEL (300 mg/day) for an unknown indication. The patient experienced abdominal pain, polydipsia, and polyuria. Later that month DKA and hyperglycemia occurred. Treatment included glyburide and insulin. SEROQUEL therapy was continued. Medical history was not provided. Concomitant medications included olanzapine (for which DKA has been reported).

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Comment: This patient was taking a medication for which new onset DM and DKA have been reported. In addition, the report contained only minimal information making assessment difficult.

2001UW02143: This serious report of "Diabetic ketoacidosis" described a 48-year-old male patient who was receiving SEROQUEL (dose unknown) for a few months for treatment of an unspecified psychiatric disorder. The patient experienced DKA. The patient "was on a day of leave and returned lethargic" (report did not specify if the patient was in a long term care setting). The patient was seen in the emergency room and his blood glucose was found to be 630 mg/dl and ketones were found in his urine; the patient was admitted to the hospital. Treatment included insulin and intravenous fluids. Laboratory results revealed a low-normal C-peptide (no value given) and Anti-GAD results were pending. SEROQUEL was continued for a day or two before the patient was switched to haloperidol. At the time of this report the patient's blood sugar was reported to be 250 mg/dl on insulin 70/30 2x/day. The patient was discharged from the hospital 13 days after admission. Medical history included hyperlipidemia. Concomitant medications included Ativan (lorazepam) and an unspecified "statin" medication.

Comment: This report does not mention if the patient had pre-existing diabetes or not. Hyperlipidemia is a risk factor for diabetes. This report described a negative de-challenge (that is the hyperglycemia did not resolve after SEROQUEL was discontinued). The scant clinical detail makes it difficult to assess.

2000UW02905: This serious report of "Diabetic ketoacidosis" described an 18-year-old patient (sex unknown) who was receiving SEROQUEL (dose/duration/indication unknown). The patient was hospitalized with DKA, a blood sugar of 1200 (no units given), acute pancreatitis, and elevated lipids. Medical history was not provided. Concomitant medications included sertraline. Outcome of events is unknown. Additional information has been requested.

Comment: Because of the scant clinical detail, assessment is difficult.

2000UW01164: This serious report of "Ketoacidosis", "Diabetes mellitus NOS" and "Blood glucose increased" described a 43-year-old male patient who was receiving SEROQUEL (200 mg/day) for treatment of an unspecified mental illness. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 30 pounds. Fasting blood sugar showed glucose level over 700 (no units given). The patient developed ketoacidosis and was hospitalized where a diagnosis of new onset DM was made. SEROQUEL therapy continued. Medical history was not provided. Concomitant medications included venlafaxine. Outcome of the events is unknown. Additional information has been requested.

Comment: Because of the scant clinical detail, assessment is difficult.

1999AP05757: This serious report of "Ketoacidosis" and "Diabetes mellitus NOS" described a 25-year-old male patient who was receiving SEROQUEL (750 mg/day) for treatment of

psychosis. One year and nine months after starting SEROQUEL the patient was hospitalized due to the development of DM and ketoacidosis. It was also reported that he had experienced weight gain (amount and date of onset unknown). Treatment with insulin was initiated and the patient recovered with residual side effects, and SEROQUEL therapy was continued. Medical history was not provided. Concomitant medications included Priadel (lithium; for which hyperglycemia has been reported), Depixol (flupenthixol; for which a drug interaction with lithium resulting in a hyperglycemic reaction has been reported), and acamprosate.

Comment: This report is confounded with concomitant medications for which hyperglycemia has been reported. In addition, the weight gain could have triggered diabetes. Also, the scant clinical detail provided makes assessment difficult.

Coma (11)

Report Narratives

Reports of coma with previous history of diabetes (3)

2002AP04514: This report of "Nonketotic hyperglycaemic-hyperosmolar coma" described a 57-year-old female who was receiving SEROQUEL (75 mg/day) for the treatment of schizophrenia. After five months of SEROQUEL therapy the patient began taking prednisolone (20 mg/day; for which hyperglycemia, DM, DKA, and hyperosmolar coma have been reported). About one month later, the patient developed hyperglycemia (417-649; no units). SEROQUEL was discontinued and the patient began diet control. Nine days later the patient developed hyperosmolar non-ketotic diabetic coma. Chlorpromazine (for which hyperglycemia has been reported) and risperidone (for which DM has been reported) were discontinued and insulin was started. Prednisolone was decreased to 10 mg/day, then to 7.5 mg/day, and then discontinued. The patient recovered from the coma and the hyperglycemia resolved. Medical history included diabetes, ovarian cancer, and idiopathic thrombocytopenic purpura. Concomitant medications included levomepromazine, chlorpromazine, risperidone, and haloperidol.

Comment: This patient was taking multiple medications that are for which hyperglycemia, DM, DKA, and hyperosmolar coma have been reported.

2002AP01163: See Reports of DKA With Previous History of Diabetes in Appendix A above for narrative.

2002SE05071: This report of "Diabetic coma NOS" described a 51-year-old female patient who was initially treated with Zyprexa (5 mg/day) for the treatment of agitation. Four days later generalized tonic-clonic seizure occurred and Zyprexa was discontinued. The patient experienced agitation again six days later, so Zyprexa (5 mg/day) was restarted and a second seizure followed. The dose was increased to 10 mg/day, and phenytoin (300 mg/day) was started, as epileptic seizure was suspected. The agitation persisted. Eighteen days later, Zyprexa was discontinued and SEROQUEL was initiated. Four days after the first intake of SEROQUEL the patient experienced high fever, unconsciousness, urinary incontinence, and

elevated blood glucose level (700 mg/dl). Diabetic coma, urinary tract infection (UTI), and mild leucocytosis (urine) were diagnosed during the third day of the titration period with SEROQUEL. Initial body temperature was 40°C. Treatment included infusion of crystalline insulin and then 30 % mixtard insulin BID, and cyprofloxacine. (Glucose levels remained between 100 and 200 mg/dl.) The fever persisted for two days. (Conflicting information included that according to urine culture and antibiogram results, Amox and Clavulonate were started instead of Cyprofloxacine.) The fever resolved. SEROQUEL was discontinued and one week after the events started the patient recovered with sequelae. It was found that the dementia was increased. Concomitant medications included phenytoin (for which hyperglycemia has been reported), Rivastigmine (precaution for use in diabetic patients), Acarbose, Sertraline, Glucobay (acarbose) and Zyprexa (olanzapine: for which hyperglycemia, DM, and diabetic acidosis have been reported). Concurrent diseases included Alzheimer's type dementia, DM, and non-compliance with diet control during the last three months. "Decreased glucose absorption inhibitor" and high HbA_{1C} (11.02 %; no date provided) indicated poor control of blood glucose levels in this patient prior to receiving SEROQUEL.

Comment: An HbA_{1C} of 11.02 % indicated that the patient had poorly controlled diabetes prior to receiving SEROQUEL. The patient received olanzapine and phenytoin immediately prior to commencing SEROQUEL therapy, and experienced an UTI, elevated blood glucose (700 mg/dl) and coma three days after starting SEROQUEL. In addition to the non-dietary compliance, an acute UTI can contribute to a diabetic crisis.

Reports of coma with no previous history of diabetes reported (8)

2003AP01289: This report of "Nonketotic hyperglycaemic-hyperosmolar coma" described a male patient in his 70s who was receiving SEROQUEL for treatment of delirium. Medical history included rectal carcinoma, alcoholic liver disease, chronic pancreatitis, and schizophrenia. Concomitant medications included Ubretid (distigmine), Lopemin (loperamide; for which hyperglycemia has been reported), Biofermin (streptococcus faecalis/bacillus subtilis/lactobacillus), Miya-BM (clostridium butyricum), and polycarbophil. This patient had been diagnosed with rectal carcinoma and underwent an unspecified operation. After the surgery, the patient experienced delirium and was given SEROQUEL (25 mg). The dosage was increased to 50 mg the next day and 75 mg the following day, but then decreased to 50 mg on the fourth day of therapy. Eight days later the patient's blood sugar was 120 mg/dL (unspecified if FBS). Three days later SEROQUEL was discontinued for an unspecified reason. One week later, the patient became comatose and was transferred to another hospital. The patient's blood sugar was reported to be 500 mg/dL. Nonketotic acidosis was diagnosed, and thereafter the patient developed disseminated intravascular coagulation (DIC). On an unspecified date the patient was said to be recovering from the nonketotic acidosis but had sequelae after DIC.

Comment: This patient was taking a medication that is associated with hyperglycemia. Additionally, this patient had discontinued therapy with SEROQUEL one week prior to the event.

2002AP04136: This report of "Nonketotic hyperglycaemic-hyperosmolar coma" described a 74-year-old female patient who was receiving SEROQUEL (75 mg/day) for treatment of schizophrenia. Six months after starting SEROQUEL the patient developed a loss of appetite. Two days later her consciousness level decreased and trembling was observed. Her temperature was 37.8°C, oxygen saturation was 87%, and her heart rate was 120 bpm. She was not responsive when her name was called. Laboratory data showed fasting blood sugar 1100 mg/dl, sodium 157 mEq/L, potassium 5.1 mEq/L, chloride 114 mEq/L, urine sugar 4+, and negative urine ketone. Arterial blood gas analysis showed the following values: pH 7.37, base excess 1.5, pO_2 45.2, blood urea nitrogen 103.2 mg/dL, and creatinine 2.38 mg/dL. Left pneumonia was diagnosed according to chest x-ray and hyperosmolar (non-ketotic) coma was diagnosed according to laboratory data. Immediately a rapid infusion of 0.45% saline solution and antibiotic therapy were started. When an infusion of 2L was given, urination was observed. The patient's blood sugar was still 735 mg/dl and insulin 4 units/hour was started. All medications including SEROQUEL were discontinued. The next day, blood sugar was 82-280 mg/dL and the following values were noted: blood urea nitrogen 89.8 mg/dL, creatinine 1.67 mg/dL, sodium 157 mEq/L, potassium 4.7 mEq/L, and chloride 121 mEq/L. She was responsive to calling, and the infusion was continuing. Insulin was discontinued. The following day she could talk clearly, her temperature was 36.7°C, heart rate was 60 bpm, fasting blood sugar was 284 mg/dL, WBC 16,200/mm^3, and CRP 20.9. SEROQUEL was not restarted. Medical history included stage II breast cancer and concomitant diseases included mild renal function disorder, respiratory infection, and dehydration. Concomitant medications included Lasix (furosemide; for which hyperglycemia with dehydration has been reported), spironolactone, haloperidol, nemonapride, trihexyphenidyl, levomepromazine, magnesium oxide, and rilmazafone.

Comment: This patient developed an infection and also suffered from dehydration at the time of the event. The patient was also taking a medication for which hyperglycemia with dehydration has been reported.

2002GB02176: This serious report of "Diabetic coma NOS" and "Diabetes mellitus insulin-dependent" described a female patient in her fifties who had been receiving SEROQUEL (no more than 400 mg/day) for an unknown indication. The patient developed type I diabetes and was admitted to the intensive care unit in a diabetic coma. The patient had received a combination of Lithium (lithium; for which hyperglycemia has been reported) and SEROQUEL for two years with no ill effect. During hospitalization, the patient was found to be hypernatremic, for which the reporter suspected Lithium. The patient was reported to have no history or family history of diabetes. At the time of this report the patient's condition was improving. No treatment measures, other medical history, or concomitant medications were provided. Additional information was requested. Follow-up information indicated that the event of diabetic coma was the initial presentation for diabetes and that the patient had no known infection that might have precipitated the coma.

Comment: This report had minimal information and did not lend itself to analysis. Also, the development of true type I diabetes is most often due to an autoimmune or an inherited

disease. Furthermore, the report was confounded by a concomitant medication for which hyperglycemia has been reported.

2002UW05916: This serious report of "Nonketotic hyperglycaemic-hyperosmolar coma" and "Diabetes mellitus NOS" described a 12-year-old female patient who was receiving SEROQUEL while in a residential facility for nine months for treatment of behavior problems and aggression. One month prior to discharge, the dose of SEROQUEL was increased from 400 to 600 mg/day. Six days after discharge, the patient was hospitalized after experiencing a two-day history of mental status changes, polyuria, polydipsia, increased blood pressure, nausea, vomiting, abdominal pain, and sore throat. Blood glucose level was 1779 mg/dl. Abnormal lab tests included WBC = 18.3K, creatinine = 3.2 mg/dl, and BUN = 54 mg/dl. Plasma was negative for ketones. The patient was treated with potassium phosphate, cefotaxime, Versed (midazolam) for agitation, and Tylenol (acetaminophen). Despite the treatment, less than 12 hours later the patient became unconscious and died with a body temperature of 111°F. Cause of death was nonketotic hyperosmolar coma secondary to newly diagnosed DM. The patient also had an "unspecified" infectious process, which was felt to have precipitated the nonketotic hyperosmolar coma. An autopsy showed no evidence of infection, or any specific abnormalities other than the patient's height and weight. Medical history included mild mental retardation, seizure disorder, exceptionally tall and obese, and medical non-compliance (medical neglect). Concomitant medications included Celexa (citalopram), DDAVP (desmopressin), Ditropan (oxybutynin), and albuterol (for which hyperglycemia and DKA have been reported).

Comment: This patient had a history of obesity (risk factor for diabetes) and medical neglect, and presented with a sore throat and an elevated WBC (indicative of an infection), which can all contribute to the development of new onset diabetes presenting as NKHHC. In addition, this report is confounded by a concomitant medication for which hyperglycemia has been reported, and this also can contribute to such a presentation.

1999UW00969: This serious report of "Diabetes mellitus NOS" and "Nonketotic hyperosmolar coma" described a 28-year-old male patient who was receiving SEROQUEL (dose and duration unknown) for the treatment of schizophrenia. The patient presented to the emergency room with a temperature of 107°F, cardiac arrhythmias, focal twitching, increased tone, pupils were non-reactive, no reaction to noxious stimuli, bleeding from eyes and nose, liver enzymes twice normal (no values given), blood glucose 2240 (no units given), low potassium (no values given), CPK normal, and Lithium level was not elevated. There was no report of increase or decrease of body temperature before presentation. The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. Ativan (lorazepam), Dantrium (dantrolene), and anti-arrhythmics (unspecified) were started. 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 onset. He died on hospital day two. A tentative diagnosis of NMS was made with complete autopsy reports pending. Medical history included bipolar disease, hallucinations, and asthma. Concomitant medications included albuterol (for which hyperglycemia and DKA have been

reported), Eskalith (lithium; for which hyperglycemia has been reported), and Prilosec (omeprazole).

Follow-up information was received from the county coroner in the form of an autopsy final report and indicated the cause of death was complications of DM. The final findings were: 1) findings consistent with DM, 2) hepatomegaly with severe fatty metamorphosis, and 3) severe pulmonary congestion and hemorrhage. Comment from autopsy report: "This 28-year-old male died from multiple complications of a severe metabolic disorder of diabetic origin. He developed nonketotic hyperosmolar status which was followed by acidosis, hyperkalemia, hyperthermia, disseminated intravascular coagulation and cardiovascular instability." The autopsy report contained a clinical history as follows. "This patient was admitted to the hospital on the evening of 13 March 1999. He stayed in the hospital less than 12 hours and died on 14 March 1999. He was brought to the emergency room by ambulance, stuporous and with respiratory difficulty. He had a clinical history of mental disorder considered to be schizophrenia due to auditory hallucinations. His treatment included Depakote (divalproex) and Lithium (lithium), but the Depakote had been changed for SEROQUEL. He also had a history of asthma for which he used an albuterol inhaler. One week before the event the patient had flu-like symptoms and was seen by his primary doctor who prescribed Zithromax (azithromycin). However, he continued feeling poor, with progressive weakness until he collapsed in the bathroom. There was also a history of polydipsia, polyuria, and anorexia (10-15 lb. weight loss) for the three weeks prior to the event. On the day of admission the patient became confused. Upon admission the patient was febrile, dehydrated, and had labored respirations without evidence of bronchial obstruction. He developed hypoxemia and required intubation. Intravenous fluids were given, chest x-ray was unremarkable, and drug screen showed only acetaminophen. Laboratory evaluation revealed severe acidosis with a pH of 7.19, potassium of 3.3, sodium of 114 (no units given), and a blood glucose of 2,200 mg/dl. Insulin treatment was started with the presumption of DKA, however ketones were not significantly elevated. The serum osmolality was 377 (no units). Body temperature increased as high as 109 °F and he required physical means for cooling. The possibility of NMS was entertained and dantrolene was started. Potassium determination indicated hypokalemia of less than 2 mEq/l and he received potassium chloride. Further complications occurred, with widening of the QRS complex on the EKG and apparent disseminated intravascular coagulation, evidenced by multiple sources of bleeding (unspecified). He was transfused with eight units of packed cells. Amiodarone was given for his wide complex tachycardia, but he continued worsening and arrested with ventricular fibrillation. He was defibrillated and converted temporarily. After several shocks, a pacemaker was installed due to profound bradycardia. After he arrested again and required defibrillation, it was requested that no further shocks were given. The patient was pronounced dead at 0400. The most important clinical diagnoses were: 1) new onset DM with nonketotic hyperosmolar coma, 2) malignant neuroleptic syndrome with hyperthermia, 3) metabolic acidosis and severe hypokalemia, 4) disseminated intravascular coagulation, 5) respiratory failure, 6) wide complex tachyarrhythmia." Additional information from the autopsy report included the following. The patient's height and weight were reported as 69 inches and 200 pounds, respectively. Autopsy showed the lungs to be heavy and markedly congested with generalized acute pulmonary congestion and areas of alveolar hemorrhage; liver to be bulky and markedly

enlarged with the hepatic parenchyma showing fatty metamorphosis of microvesicular type involving approximately 90% of the hepatocytes and acute congestion with increased number of red cells in the sinusoid; spleen to be somewhat enlarged; and heart to have focal interstitial hemorrhage in sections from the right ventricle.

Comment: This report of previously undiagnosed diabetes that presented itself as a non-ketotic hyperosmolar coma is consistent with an infection (fever, flu-like symptoms) precipitating the non-ketotic hyperosmolar coma. It is not unusual for an initial presentation of diabetes to be non-ketotic hyperosmolar coma or DKA precipitated by infection or some other significant medical illness. The patient's concomitant medications include albuterol, a β-2 agonist. β-2 agonists are well known to cause hyperglycemia. There have even been reports of DKA in patients receiving albuterol. The concomitant medication in this report also included lithium, which has been reported to be associated with hyperglycemia. The DIC is probably related to sepsis, and the arrhythmias, including the terminal ventricular fibrillation, were probably related to the acidosis, with a possible contribution by the β-2 agonist.

2002AP02699: This report of "Blood pressure decreased", "Cyanosis NOS", "Consciousness disturbed", and "Blood glucose increased" described a 63-year-old female patient who was receiving SEROQUEL for schizophrenia and sleep disturbances, and experienced an elevated blood glucose level. The patient was hospitalized on 17 July 2002 due to autosynnoia and hypobulia and acute pneumonia developed. Four days later, delusional experience occurred for which haloperidol was administered intravenously. On the morning of 22 July 2002, the patient experienced generalized sweating, tremor, and rigidity. Creatine phosphokinase (CPK) was not increased and she was afebrile. Neuroleptic malignant syndrome (NMS) was suspected and dantrolene sodium was administered. The patient experienced a sudden onset of apnea that resolved later. These events were reported to have resolved. On 05 August 2002, the patient was hospitalized. The following afternoon, she commenced treatment with timiperone, biperiden and promethazine . At 20:30 hours she received estazolam, nitrazepam and SEROQUEL as sleeping pills. Three hours later, she experienced a decrease in blood pressure, cyanosis of her lip, and disturbed consciousness. The patient had facial pallor, cold extremities and was in a deep coma. Her blood pressure was 86/61 mmHg, body temperature 36.3 °C, pulse 142 bpm and respirations 21/minute. SEROQUEL and all other medications were discontinued on 06 August 2002. On 07 August 2002 at 00:50 hours, oxygen (6 L inhalation) was started. Treatment also included lactated Ringer's solution, xylitol solution, electrolytes and glucose solution, and L-aspartate potassium by continuous drip infusion. At 01:05 the patient's blood glucose was 360 mg/dl, at 09:10 it was 134 mg/dl. At 09:30, oxygen inhalation (4 L) and drip infusion continued. At 12:00 her blood glucose was 77 mg/dl. Her condition gradually improved and the events were reported to have resolved by 08 August 2002.

Comment: This 63-year-old patient with no reported history of diabetes had an isolated elevated blood glucose that normalized within a few hours, without any treatment reported that was directed specifically towards the elevated glucose. Since the patient was receiving a glucose infusion (and possibly two as Lactated Ringer's can contain glucose), the possibility is raised that the site where the blood was drawn for the glucose level may have been proximal

to the intravenous site of administration of the glucose-containing solution(s), thus yielding a falsely elevated blood glucose level. Conversely, if the blood glucose result was real; it could mean the patient was glucose intolerant and the medical stress of hypotension and coma caused hyperglycemia. In either case an alternative causal explanation other than SEROQUEL exists. Regarding the hypotension, cyanosis, and coma, two concomitant medications, timiperone and promethazine can cause hypotension; and hypotension can cause cyanosis. These two anti-psychotic medications and the sedatives estazolam and nitrazepam, cause CNS depression, and thus could be responsible for the coma.

2003UW02826: This report of "Coma" and "Blood glucose increased" described a 35-year-old male patient who was receiving SEROQUEL (1200 mg/day) for the treatment of paranoia. Medical history included schizophrenia, depression, hyperlipidemia, and alcohol, marijuana, cocaine and mushroom use in the past. Concomitant medications included Paxil (paroxetine) and haloperidol. After three months of therapy with SEROQUEL the patient escaped from the hospital. He was subsequently caught by the police and taken to jail. While in jail, the patient received no medications. The patient returned to the hospital 12 days later and resumed therapy with SEROQUEL and Paxil. The patient was given SEROQUEL (1200 mg) and Paxil (20 mg) that evening via a single dose (no titration). That same day the patient experienced acute delirium, unresponsiveness, decreased blood pressure (100 to132/40 to 60), increased pulse rate (105-150), pinpoint pupils, rambling with non-essential speech, and was non-ambulatory. An electrocardiogram (ECG) revealed sinus tachycardia and blood tests revealed decreased potassium (3.1 mmol/L) and increased glucose (203 mg/dL). A urine drug screen was negative. The patient was treated with sodium chloride, potassium infusion, oral potassium, and other medications (prn). The dose of SEROQUEL was decreased to 900 mg/day and the patient recovered the next day. Two days later the physician had increased the dose of SEROQUEL back to 1200 mg/day without any problems. The physician questioned a drug interaction with Paxil. No additional information is expected.

Comment: The patient's history of hyperlipidemia is a risk factor for the development of DM. Additionally, it is not clear that the patient's coma was related to the hyperglycemia. The patient's dose of SEROQUEL was reported to be 1200 mg/day, which exceeds the maximum dose recommended in the CDS. SEROQUEL is labeled for somnolence and coma with.

2002AP02947: This report of "Coma" and "Hyperglycaemia NOS" involves a 44-year-old female patient who was receiving SEROQUEL (100 mg/day) for the treatment of schizophrenic psychoses. It was reported that the patient did not have a history of obesity or diabetes mellitus. Concomitant medications included carbamazepine, tiapride, sofalcone, biperiden, and magnesium oxide. After 33 weeks and five days of SEROQUEL therapy the patient developed a fever (38°C). Three days later a physician saw the patient and diagnosed an aggravation of the patient's mental state. The patient was treated her with diazepam, haloperidol, and fluphenazine (all intramuscularly). Six days later, the patient visited the physician as she had not taken food or drink for six days; an infusion solution was administered to provide nutrition and hydration. Haloperidol was mixed into the solution. By the next day she weighed little more than 40 kg and was reported to have had an immeasurable blood pressure and a blood sugar level of 300 mg/dl. The patient was

hospitalized. The following day her condition was reported to have improved, however, laboratory tests revealed a creatinine of 5.1 mg/dl and a BUN of 114 mg/dl. During the early hours of the next morning her blood pressure and consciousness decreased again and she did not respond when called. Oxygen measured at fingertip was decreased to less than 80%, her body temperature was 37.4 °C, WBC was 13,300/mm^3, and she had no rigidity. The patient was considered to be suffering from dehydration, a decrease of urinary volume, disturbed consciousness, and the possibility of cerebral vascular disturbance and NMS were considered. She was transferred to another hospital. On arrival she was in a deep coma with an immeasurable blood pressure. A blood examination revealed hyperglycemia (blood sugar = 1057 mg/dl), acidosis, elevated CPK (2124 u/L), and hypernatremia. The next day hemodialysis with continuous hemofiltration was started. CPK was 15,215 u/L and blood sugar was 535 mg/dl. Disseminated intravascular coagulation (DIC) was noted. The following day, hyperglycemia, acidosis, hypernatremia, and dehydration resolved. The CPK peaked on at 78,690 u/L and dantrolene was started. On hospital day seven the DIC resolved. The following day her temperature was 38.7 °C and WBC was 14,400/mm^3. Two days later CPK was decreased to 2225 u/L and NMS was considered resolved. Continuous hemofiltration was stopped and the patient was transferred out of intensive care unit (ICU) the following day. An HbA_{1C} (date not reported) was reported to be 6.4%. A physician from the first hospital reviewed the patient's blood sugar levels and considered the hyperglycemia to be chronic, but not severe.

Comment: The labeled event, hyperglycemia (not diabetes) may have been was likely to be pre-existing. Based on the HbA_{1C} and the physician at the first hospital, it appears the patient had some chronicity to her hyperglycemia. The HbA_{1C} of 6.4% is slightly elevated. She may have had an infection (fever and increased WBC) that precipitated an acute increase in blood glucose. Infections are common precipitators of non-ketotic hyperosmolar coma or DKA in diabetes. IV haloperidol is a plausible explanation for the NMS. Other confounding factors include the dehydration, which may have caused or contributed to the increased CPK by rhabdomyolysis, as well as the possibility of infection as an explanation for the fever. Furthermore, the concomitant medications carbamazepine and tiapride have also been reported to cause NMS.

AUTO PAGE (AUTO NUMPAGES)

The European Agency for the Evaluation of Medicinal Products
Post-authorisation evaluation of medicines for human use

London, 13 June 2001
Doc. Ref: EMEA/CPMP/PhVWP/2216/01

Wording for the Summaries of Product Characteristics of Clozapine, Risperidone and Quetiapine with regard to Glucose Intolerance and Onset of Diabetes mellitus as agreed by the PhVWP in June 2001

Clozapine

Section 4.4. on Special warnings and precautions for use

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus may occur during treatment with clozapine (see also section 4.8). Severe hyperglycemia with ketoacidosis or coma has been reported in very rare cases, some of which have been fatal. Appropriate clinical monitoring is advisable, especially in diabetic patients and in patients with risk factors for the development of diabetes mellitus. Where follow-up data were available, discontinuation of clozapine resulted mostly in resolution of the glucose impairment, and reinstitution of clozapine has resulted in reoccurrence of glucose impairment.

Section 4.8 on Undesirable effects

In the table
under Common undesirable effects: Metabolic: Weight gain, impaired glucose tolerance, diabetes mellitus, hypertriglyceridemia.
under Very rare undesirable effects: Severe hyperglycemia, diabetic acidosis.

Risperidone and Quetiapine

Section 4.4. on Special warnings and precautions for use

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during quetiapine/risperidone treatment. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Section 4.8 on Undesirable effects

Hyperglycaemia or exacerbation of pre-existing diabetes mellitus has been reported in very rare cases (see also section 4.4 Special warnings and precautions for use).

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From: Jonsson, Marianne
Sent: Thursday, September 25, 2003 2:58 PM
To: Butler, George GC
Cc: Wingertz, Sue-Ellen; Trumble, Sharon M; Melville, Margaret G
Subject: Seroquel and glucose dysregulation

Importance: High

Attachments: Atypical antipsychotics - glucose intolerance.doc; SeroqGlucosePP.doc; Seroquel CDS text deviations glucose dysregulations.xls

Dear George,

Please find a table with countries that deviates from the CDS regarding glucose dysregulation. For you information, glucose dysregulation has been a recurrent item on the (hidden) agenda for the Pharmacovigilance Working Party (PhVWP) in Europe, since about year 2000. In June 2001, PhVWP sent out a letter (enclosed) to the marketing companies, expressing their "decision" on wording for the Summaries of Product characteristics regarding "glucose intolerance and onset of diabetes mellitus". This request did also include Clozapine and Risperidone.

Letter from PhVWP:

I have also enclosed the recently finalised Position paper on Glucose dysregulation:

BACKGROUND:
EUROPE:
As Seroquel is a MRP product, glucose wording has been imposition and implemented in the European text as a result of the request form PhVWP. AZ reluctantly agreed.
European countries outside MRP:
UK - MHRH imposed glucose wording in February 2003 and discussions are still ongoing.
Italy - glucose wording imposed by the authorities recently and discussions are still ongoing.
Switzerland - Nothing regarding glucose in their label.

US:
Discussions ongoing

JAPAN:
Glucose warnings including a boxed warning at the very front page of the label. We reluctantly agreed.

NEW ZEALAND:
Glucose text imposed about 1 year ago. We reluctantly agreed.

AUSTRALIA:
Authorities trying to impose glucose wording. Discussions ongoing.

THE INTERNATIONAL MARKETS:
Will have to follow the country of origin = UK.

MSDO markets:
Will normally follow the country of origin.

KOREA:
Is following Japan closely. We have recently sent the Position paper to Korea

Table with deviations:

I hope this is the explanation you would like to have and please do come back to me if you will need further information or if anything is unclear.

Kind regards,
Marianne

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Atypical ntipsychotics - gluc..

SeroqGlucosePP.do c (479 KB)

Seroquel CDS text deviations g...