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Glucose Intolerance with Atypical Antipsychotics

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Abstract

Background: Previous studies have suggested that the atypical antipsychotics clozapine and olanzapine may be associated with an increased risk of glucose intolerance and diabetes mellitus. Early studies have also suggested an association between use of conventional antipsychotics and the development of glucose intolerance.

Objective: To examine quantitatively the association between glucose intolerance including diabetes mellitus and the use of the atypical antipsychotics clozapine, olanzapine or risperidone, and to identify possible risk factors for the development of glucose intolerance during treatment with these drugs.

Methods: All reports suggestive of glucose intolerance for clozapine, olanzapine and risperidone were identified in the WHO database for adverse drug reactions. In the analyses of possible risk factors for glucose intolerance all other reports of adverse drug reactions for clozapine, olanzapine and risperidone were used as reference. Using the Bayesian Confidence Propagation Neural Network method, the strengths of the associations over time between glucose intolerance and the use of these drugs were analysed. For comparison, the strengths of the associations between glucose intolerance and the use of the conventional antipsychotics haloperidol and chlorpromazine were also analysed.

Results: Clozapine, olanzapine and risperidone were significantly associated with glucose intolerance. In contrast, chlorpromazine and haloperidol were not associated with glucose intolerance. For clozapine, olanzapine and risperidone grouped together, the following potential risk factors for glucose intolerance were identified: an underlying diabetic condition (odds ratio [OR] 10.22, 95% CI 8.20–12.73), an increase in weight (OR 2.36, 95% CI 1.76–3.17), male gender (OR 1.27, 95% CI 1.11–1.47), and concomitant use of valproic acid (OR 1.97, 95% CI 1.61–2.40), selective serotonin reuptake inhibitors (OR 1.63, 95% CI 1.33–1.99) or buspirone (OR 2.24, 95% CI 1.33–3.77).

Conclusion: Treatment with clozapine, olanzapine or risperidone appears to be associated with an increased risk of glucose intolerance.

Background

Compared with conventional antipsychotics, the new generation antipsychotic agents, often referred to as atypical antipsychotics, are characterised by a reduced liability to induce extrapyramidal symptoms.[1,2] Also other properties, such as an increased efficacy towards the negative symptoms of schizophrenia, lack of or small increases in prolactin levels, and effectiveness in some patients previously regarded as treatment-refractory, have been attributed to these second-generation antipsychotic drugs.[1,2]

It has been increasingly recognised that the atypical agents clozapine and olanzapine may cause glucose intolerance and hyperglycaemia.[3-8] Early studies have also suggested an association between conventional antipsychotics and altered glucose-insulin homeostasis.[9-12] Moreover, schizophrenia itself has been linked to an increased risk for developing hyperglycaemia or diabetes mellitus.[13-17] The possible mechanisms behind these effects are still largely unknown. Since it was shown that clozapine plasma concentrations were positively correlated to insulin levels in 13 clozapine-treated patients,[6] it may be anticipated that clozapine induces insulin resistance, which is associated with a compensatory increase in insulin secretion. Subjects who are unable to achieve this compensation develop diabetes mellitus. Antipsychotic agents, and particularly atypical antipsychotics such as clozapine and olanzapine, may also promote other metabolic effects such as excessive weight gain,[18,19] hypertriglyceridaemia,[20-23] and hyperleptinaemia.[24,25] All these effects may be part of a drug-induced metabolic syndrome.

Recently, it has been proposed that clozapine, and possibly also olanzapine, may be more likely to cause glucose intolerance compared with conventional antipsychotics.[5,20] No similar suspicion seems to have been put forward for risperidone, which has been suggested to be the drug of choice when an atypical agent is needed in a patient with diabetes mellitus.[26] Important risk factors for glucose intolerance in general are obesity, lack of physical activity, and a personal or family history of diabetes mellitus. Specific risk factors for glucose intolerance with atypical antipsychotics have not yet been characterised.

The aim of the present study was to identify the role of the atypical antipsychotics clozapine, olanzapine and risperidone in the development of glucose intolerance. Moreover, a further aim of the study was to identify possible risk factors for the development of glucose intolerance during treatment with these drugs.

Methods

The WHO Collaborating Centre for International Drug Monitoring receives summary clinical reports of individual adverse drug reactions from the national centres in 63 countries around the world. This information is stored in a large international database containing more than 2.5 million adverse drug reaction reports.

Reports were identified for clozapine, olanzapine and risperidone in the WHO database, which included the following diagnoses: glucose tolerance abnormal, hyperglycaemia, diabetes mellitus, diabetes mellitus aggravated, ketosis, diabetic coma and glycosuria. For convenience, all these diagnoses were designated glucose intolerance in this study. Duplicated reports were deleted from the database prior to the analysis. From each report, the following information can be obtained: country of origin, age and gender of the patient, suspected reactions, suspected as well as concomitant drug treatment, dosage, route of administration and duration of treatment of the suspected drug, date of onset of the adverse drug reaction, information on dechallenge and rechallenge, and outcome. Most reports, however, contain incomplete information.

Additional adverse drug reactions in the reported cases were also reviewed because the same adverse reaction can be coded in more than one way. For example, the adverse reaction term diabetes mellitus aggravated can be coded as hyperglycaemia and condition aggravated, and the term diabetic coma can be coded as coma and hyperglycaemia and acidosis. Moreover, additional adverse reaction diagnoses may indicate associated events,

such as increased serum lipid levels, increased or decreased weight, liver events, or pancreatitis.

To quantify the possible adverse effect of glucose intolerance, the strengths of the associations over time between glucose intolerance and the atypical antipsychotics clozapine, olanzapine and risperidone were analysed using the Bayesian Confidence Propagation Neural Network (BCPNN) technique on the data in the WHO database. The strengths of the associations between glucose intolerance and the conventional antipsychotics haloperidol and chlorpromazine were analysed for comparison. The BCPNN technique has been described in detail previously[27,28] and is now used routinely in signal detection analysis. In short, in the WHO database, all adverse reaction reports contain at least one drug and one adverse reaction. The BCPNN method is based on Bayes theorem and uses neural network architecture to search for unexpectedly strong dependencies between drugs and adverse reactions within the dataset. The dependencies are selected using a measure of disproportionality called the information component (IC). For each specific drug-adverse reaction combination an IC and its standard deviation (SD) can be calculated, and changes in its value can be examined over time. A drug-adverse reaction combination, which is reported more often than would be expected from the rest of the reports of the database, has a positive IC value. The IC value is based on the following information: the number of case reports with a particular drug, the number of case reports with a particular adverse reaction, the number of reports with the specific drug-adverse reaction combination, and the total number of reports. New data may cause the IC to either increase or decrease. When the IC value is calculated from large numbers, a new report is less likely to cause a fluctuation in the IC value. The SD for each IC provides a measure of the robustness of the value. An IC –2 SD value above zero demonstrates a significant positive quantitative association between the drug and the adverse reaction. The likelihood of a true association is higher when a significant quantitative association increases over time.

In the analyses of risk factors for glucose intolerance, χ^2-tests, Student's t-tests, Fisher's exact tests and Wilcoxon rank sum tests were used for statistical comparisons between groups. Statistical significance was defined as $p = 0.05$ or below.

Results

From its start in 1968 until December 2000, the WHO Collaborating Centre received 868 reports of glucose intolerance with clozapine (n = 480), olanzapine (n = 253), and risperidone (n = 138). The distribution of the reports over the searched reactions is presented in figure 1. In three cases, the patient received two atypical antipsychotics concomitantly. Therefore, the total number of reports is less than the sum of reports for the individual drugs.

The strengths of the associations over time between the atypical agents clozapine, olanzapine or risperidone and glucose intolerance are presented in figure 2. As the IC –2SD values were above zero for all the three compounds, they were significantly associated with glucose intolerance. For clozapine, first introduced in the early 1970s, the number of reports of glucose intolerance was very small until 1991 as reflected in the low and fluctuating IC values. For risperidone, introduced in 1993, and for olanzapine, introduced in 1996, reporting of glucose intolerance had already taken place in the first years after marketing as indicated by increasing and stabilising IC values. The strengths of the associations over time between chlorpromazine or haloperidol and glucose intolerance are presented in figure 3. In contrast to the atypical agents, chlorpromazine and haloperidol were not associated with glucose intolerance. The number of reports of glucose intolerance has remained small for both chlorpromazine and haloperidol, introduced in the early and late 1950s, respectively.

In 74% of the cases where the outcome after discontinuation of the drug was known (n = 114), the glucose intolerance had improved. A rechallenge with the drug was carried out in 24 cases (18 for clozapine, five for olanzapine, one for risperidone), and resulted in a reoccurrence of

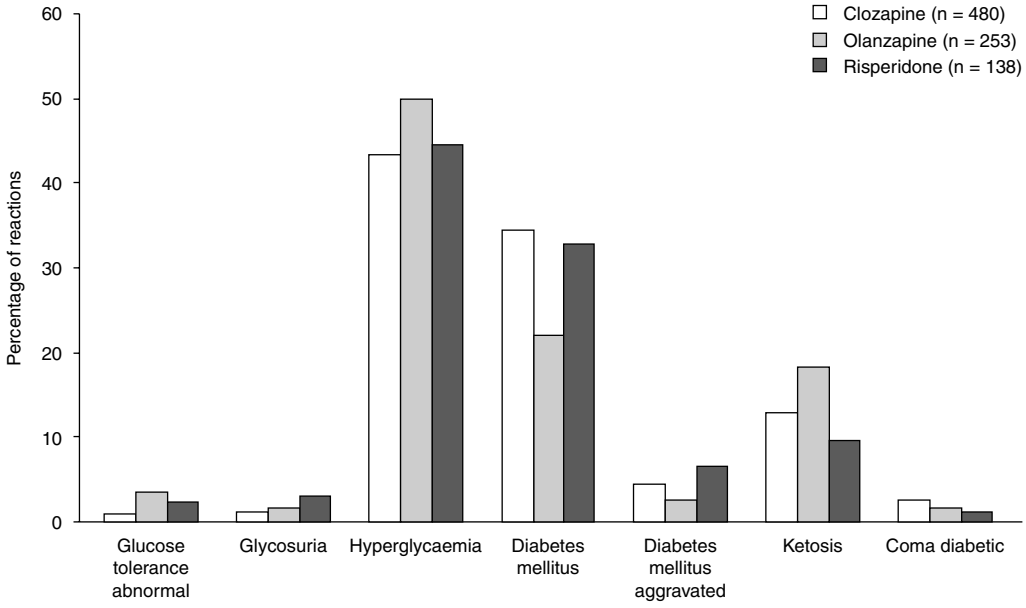

Fig. 1. Distribution of glucose intolerance reactions among atypical antipsychotics.

glucose intolerance in 17 cases (71%; 12 for clozapine, four for olanzapine, one for risperidone).

Of the reports of glucose intolerance with clozapine, olanzapine and risperidone, 505 (61.4%) concerned men and 318 (38.6%) concerned women. For all other adverse drug reactions with clozapine, olanzapine and risperidone, the corresponding proportions were 21 419 (55.5%) and 17 178 (44.5%), respectively. Using females as reference the odds ratio (OR) for males and glucose intolerance was 1.27 (95% CI 1.11–1.47). The mean ages of men and women with glucose intolerance were 40.0 and 42.5 years, respectively, and of those with other adverse reactions 39.1 and 43.9 years, respectively (difference not significant). Forty-nine cases (5.6%) of glucose intolerance reported an increase in

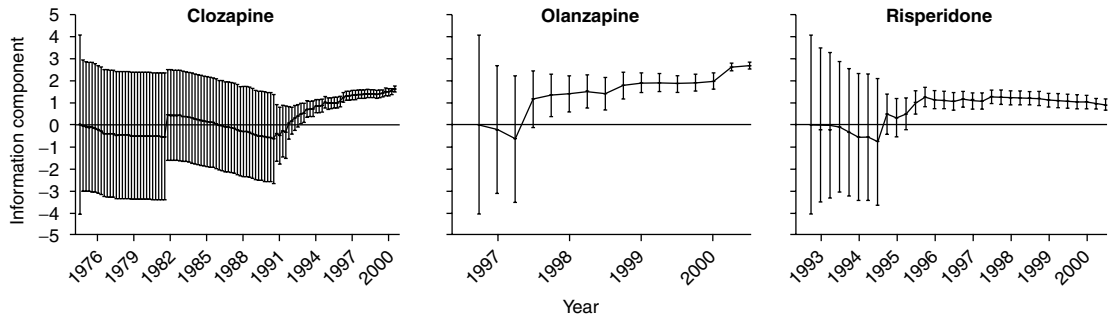

Fig. 2. The strengths of the associations over time between glucose intolerance and clozapine, olanzapine and risperidone. An information component (IC) value increasing with time, with an IC –2SD value above zero demonstrates a significant positive quantitative association between the drug and the adverse reaction.

weight (20 for clozapine, 24 for olanzapine, six for risperidone) compared with 1 022 (2.5%) of those with other adverse reactions (OR 2.36, 95% CI 1.76–3.17). Thirteen cases (1.5%) of glucose intolerance reported a decrease in weight (ten for clozapine, two for olanzapine, one for risperidone) compared with 176 (0.4%) of those with other adverse reactions (OR 3.55, 95% CI 2.02–6.27). Weight increase was twice as frequent with olanzapine compared with the other two agents.

The treatment durations until the onset of glucose intolerance were known in 47 cases. The median treatment duration was 13 (interquartile range 8–75) days for risperidone (n = 13), 52 (interquartile range 36–216) days for clozapine (n = 19) and 115 (interquartile range 50–181) days for olanzapine (n = 23). Most cases (87%; 41 of 47) occurred within the first year of treatment. The prescribed doses were known in 346 cases of glucose intolerance, and were not significantly different from those in cases with other adverse reactions (table I).

The use of concomitant drugs is presented in table II for clozapine, olanzapine and risperidone grouped together. The concomitant use of insulin or oral antidiabetic agents, which indicates the presence of an underlying diabetic condition, was associated with the highest OR for glucose intolerance (OR 10.22, 95% CI 8.20–12.73 for use of any antidiabetic drug). Use of valproic acid (OR 1.97, 95% CI 1.61–2.40), buspirone (OR 2.24, 95% CI 1.33–3.77), or selective serotonin reuptake inhibitors (OR 1.63, 95% CI 1.33–1.99) was also associated with significantly elevated ORs for glucose intolerance for all three agents combined, whereas the elevated ORs for β-blockers and thiazide diuretics did not reach statistical significance. Concomitant treatment with non-selective reuptake inhibitors, lithium, glucocorticoids, or conventional antipsychotics was not associated with an elevated OR for glucose intolerance for any of the three atypical agents studied. For the cytochrome P450 (CYP) 1A2 substrates clozapine and olanzapine, concomitant use of drugs known to inhibit this enzyme, such as fluvoxamine, cimetidine, and several fluoroquinolones, was not associated with an elevated OR for glucose intolerance

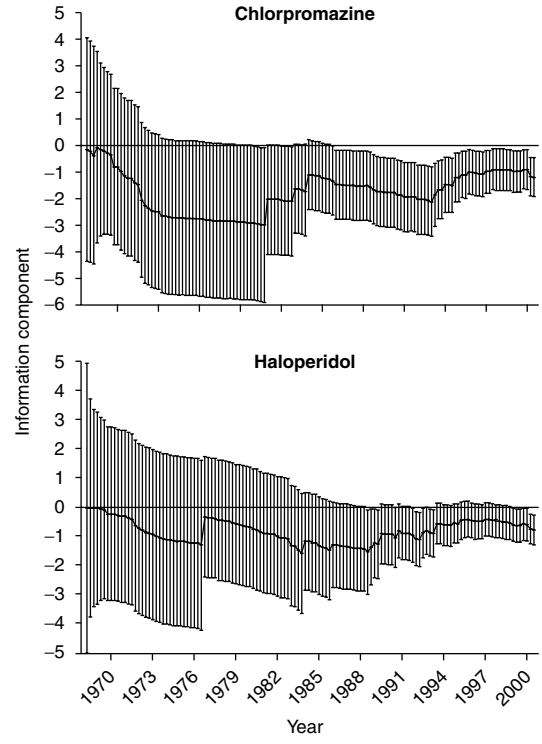

Fig. 3. The strengths of the associations over time between glucose intolerance and chlorpromazine and haloperidol. In contrast to the atypical agents, no associations were found.

(OR 0.51, 95% CI 0.16–1.60 for clozapine; OR 0.72, 95% CI 0.26–1.96 for olanzapine). Similarly, for the CYP2D6 substrate risperidone, concomitant use of drugs known to inhibit this enzyme, such as fluoxetine, paroxetine, and quinidine, was not associated with an elevated OR for glucose intolerance (OR 1.07, 95% CI 0.70–1.62).

All reports of glucose intolerance were scrutinised for the presence of pancreatitis, liver events, increased serum lipid levels, increased or decreased weight, aggravated pre-existing condition, acidosis or ketosis, coma and death. The distribution of these selected events is presented in figure 4. Within the reports of glucose intolerance for all atypical antipsychotics together, use of valproic acid was significantly associated with pancreatitis

Table I. Prescribed daily doses in adverse drug reaction reports of impaired glucose tolerance during treatment with clozapine, olanzapine and risperidone, compared with doses in cases of other adverse drug reactions

Suspected drug		Glucose intolerance	All other adverse drug reactions
Clozapine	No. of reports	252	17 079
	Mean dose ± SD (mg)	337 ± 182	353 ± 232
	Median dose, interquartile range	300, 200–450	300, 200–500
Olanzapine	No. of reports	30	1 977
	Mean dose ± SD (mg)	31 ± 89	19 ± 54
	Median dose, interquartile range	10, 10–15	10, 10–15
Risperidone	No. of reports	64	5 438
	Mean dose ± SD (mg)	7 ± 22	5 ± 12
	Median dose, interquartile range	4, 2–6	3, 2–6

SD = standard deviation.

(OR 2.44, 95% CI 1.22–4.86) and acidosis/ketosis (OR 2.17, 95% CI 1.40–3.37), selective serotonin reuptake inhibitors were significantly associated with coma (OR 2.40, 95% CI 1.25–4.61), buspirone was significantly associated with pancreatitis (OR 7.02, 95% CI 2.15– 2.98) and liver events (OR 4.83, 95% CI 1.31–17.76), and insulin, and oral antidiabetic agents were significantly associated with aggravated pre-existing condition (OR 13.50, 95% CI 7.48–24.35 for insulin; OR 2.32, 95% CI 1.04–5.20 for sulfonylureas; OR 4.31, 95% CI 1.30–14.30 for biguanides).

Discussion

In contrast to the conventional agents chlorpromazine and haloperidol all three atypical antipsychotics investigated in the study were associated with glucose intolerance. The results support the existence of a higher risk of glucose intolerance with atypical antipsychotics including risperidone as has already been suggested by others.[29]

A number of factors limit the generalisations that can be made from this material. Spontaneous reports of adverse drug reactions represent a suspicion that a drug caused the event, but the causal role is often not established. The reporting of adverse drug reactions may be influenced by several factors such as the extent of use of the drug, the year of introduction to the market, general knowledge of the effects and adverse effects of the drug, public attention to specific problems, and health professionals' attitudes to reporting of adverse drug reactions. It can generally be assumed that adverse drug reactions are both underreported and subject to biased reporting. Comparisons between individual drugs of the magnitudes of risk for an adverse drug reaction can therefore not be made. Despite these limitations, spontaneous adverse drug reaction reporting has become an established tool in drug monitoring.[30] The BCPNN method further increases the value of spontaneous reporting by facilitating early detection of adverse drug reactions and by providing a statistical measure of the likelihood and size of an association.[27]

Men were over-represented among reports of glucose intolerance in our study. This result is in agreement with a recent review of the published literature, which concluded that male gender might be a risk factor for glucose intolerance with atypical antipsychotics.[31] We did not find any relation between age and glucose intolerance, which was unexpected since glucose intolerance is known to be more common among the elderly. However, because we used all other adverse drug reactions to the studied drugs for comparison, our results do not exclude age as a possible risk factor for glucose intolerance. It is possible that the risk of developing an adverse drug reaction in general increases with increasing age.

An increase in weight was more common among reports of glucose intolerance compared with other adverse reactions. Because the risk of glucose intolerance is known to increase with increasing weight it might be assumed that the increased risk associated with the three atypical an-

Table II. Use of concomitant drugs in adverse drug reaction reports of impaired glucose tolerance during treatment with clozapine, olanzapine and risperidone

Concomitant drugs	Glucose intolerance (%) [n = 868]	All other adverse reactions (%) [n = 41 316]	Odds ratio (95% CI)
Any concomitant drug	61.1	53.9	1.34 (1.17–1.54)[a]
Insulin	6.5	0.5	14.93 (10.99–20.27)[b]
Sulfonylurea	4.8	0.8	6.53 (4.70–9.08)[b]
Biguanides	1.5	0.2	8.04 (4.45–14.52)[b]
SSRI[c]	12.9	8.3	1.63 (1.33–1.99)[d]
NSRI[e]	4.0	4.3	0.94 (0.67–1.33)
Valproic acid	13.4	7.3	1.97 (1.61–2.40)[f]
Buspirone	1.7	0.8	2.24 (1.33–3.77)[g]
Beta-blockers	3.6	2.5	1.43 (0.99–2.05)[h]
Thiazides	0.6	0.3	1.82 (0.74–4.46)
Lithium	7.0	6.6	1.07 (0.82–1.39)
Glucocorticoids	0.7	0.7	1.01 (0.45–2.26)
Antipsychotics[i]	11.6	12.9	0.89 (0.72–1.09)

a In the evaluation of the individual drugs, the OR was significantly elevated for risperidone (OR 1.76, 95% CI 1.21–2.56), but not for olanzapine (OR 1.31, 95% CI 0.99–1.73), or clozapine (OR 1.16, 95% CI 0.97–1.39).

b In the evaluation of the individual drugs, the ORs were significantly elevated for clozapine (OR 11.34, 95% CI 7.10–18.13 for insulin; OR 7.24, 95% CI 4.86–10.79 for sulfonylureas; OR 9.27, 95% CI 4.35–19.78 for biguanides), risperidone (OR 36.21, 95% CI 21.16–61.97 for insulin; OR 10.86, 95% CI 5.66–20.85 for sulfonylureas; OR 14.02, 95% CI 4.06–48.42 for biguanides), and olanzapine with the exception of biguanides (OR 9.96, 95% CI 5.18–19.17 for insulin; OR 3.67, 95% CI 1.64–8.20 for sulfonylureas; OR 3.03, 95% CI 0.69–13.25 for biguanides).

c The following drugs were included: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

d In the evaluation of the individual drugs, the OR was significantly elevated for clozapine (OR 1.98, 95% CI 1.45-2.70) and for olanzapine (OR 1.46, 95% CI 1.06-2.00), but not for risperidone (OR 0.99, 95% CI 0.59-1.65).

e The following drugs were included: amineptine, amitriptyline, clomipramine, desipramine, dibenzepine, dosulepine, doxepine, imipramine, lofepramine, maproteline, nortriptyline, opipramole, protriptyline, venlafaxine.

f In the evaluation of the individual drugs, the OR was significantly elevated for olanzapine (OR 2.79, 95% CI 2.06–3.79) and for risperidone (OR 2.38, 95% CI 1.47–3.85), but not for clozapine (OR 1.15, 95% CI 0.83–1.61).

g In the evaluation of the individual drugs, the OR was significantly elevated for olanzapine (OR 3.65, 95% CI 1.79–7.44), but not for clozapine (OR 1.39, 95% CI 0.51–3.77) or risperidone (OR 1.38, 95% CI 0.34–5.66).

h In the evaluation of the individual drugs, the OR was significantly elevated for olanzapine (OR 2.39, 95% CI 1.34–4.29), but not for clozapine (OR 0.98, 95% CI 0.56–1.72) or risperidone (OR 1.67, 95% CI 0.68–4.11).

i The following drug groups were included: phenothiazines, butyrophenones, thioxanthenes, and diphenylbutylpiperidines.

NSRI = non-selective reuptake inhibitors; **SSRI** = selective serotonin reuptake inhibitors.

tipsychotics is due to their effect on weight only. The average increase in weight associated with 10 weeks of treatment was 2.58kg for chlorpromazine, 1.08kg for haloperidol, 2.10kg for risperidone, 4.15kg for olanzapine and 4.45kg for clozapine in a meta-analysis.[32] These findings might support a relation between the average increase in weight and the risk of glucose intolerance. In a recent study,[29] however, even non-obese patients treated with clozapine and olanzapine exhibited abnormal glucose balance with decreased insulin sensitivity index. The decrease in weight seen more commonly among reports of glucose intolerance compared with other adverse reactions was considered to be secondary to the diabetic condition.

The prescribed doses in the cases of glucose intolerance did not differ significantly from those in all other adverse reactions. Furthermore, there was no overrepresentation among the cases of glucose intolerance of concomitant treatment with drugs known to inhibit the metabolism of clozapine and olanzapine via CYP1A2 or of risperidone via CYP2D6. These data may support the notion

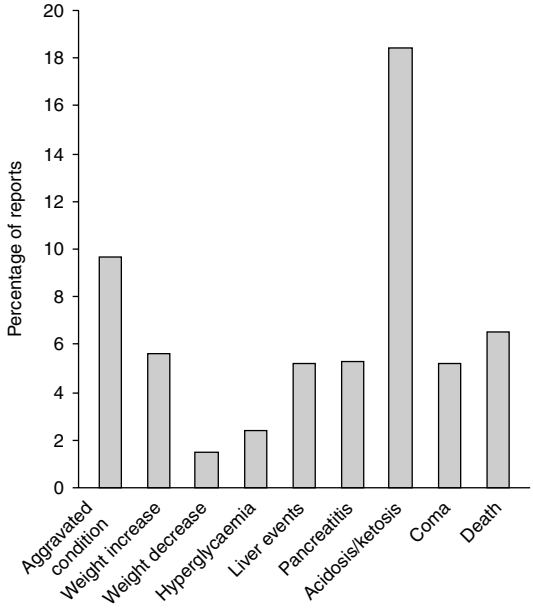

Fig. 4. Selected adverse reaction diagnoses in cases of glucose intolerance (n = 868). The aggravated condition includes the diagnoses diabetes mellitus aggravated and condition aggravated. Hyperlipidaemia includes the diagnoses hypercholesterolaemia and hypertriglyceridaemia. Liver events include the diagnoses increased liver enzymes or other liver parameters, abnormal liver function, fatty liver, and hepatomegaly. Pancreatitis includes the diagnoses increased serum amylase, lipase and pancreatitis.

that the dose is not an important risk factor for glucose intolerance. On the other hand, we compared with the doses used when all other adverse drug reactions, which mostly are dose-dependent, occurred. Therefore, it remains an open question whether the dose is a risk factor for glucose intolerance or not.

In most cases, where information regarding the treatment duration was available, glucose intolerance occurred within the first year of treatment. However, it should be taken into account that in the majority of the reports, the treatment duration was unknown. Therefore, the generalisability of the result is uncertain. Moreover, any association between a drug and an adverse drug reaction is more obvious, and thus more likely to be reported shortly after institution of treatment. Indeed, in a 5-year follow up study of patients treated with clozapine, patients continued to be diagnosed with diabetes mellitus throughout the study period.[20]

An underlying diabetic condition as reflected by concomitant use of insulin or oral antidiabetic agents was the strongest risk factor identified in the study. As expected, concomitant use of insulin or oral antidiabetic agents was found to associate significantly with aggravation of pre-existing diabetic disorder. Also, concomitant treatment with valproic acid, selective serotonin reuptake inhibitors or buspirone was found to be a significant risk factor for glucose intolerance. Interestingly, valproic acid is known to induce a metabolic syndrome with centripetal obesity, hyperinsulinaemia, lipid abnormalities and polycystic ovaries in women with epilepsy.[33]

The identification of selective serotonin reuptake inhibitors as significant risk factors for glucose intolerance with clozapine, olanzapine and risperidone was unexpected, since these drugs have been associated with a risk of hypoglycaemia in patients with diabetes.[34] However, one case report has been published, where paroxetine was associated with hyperglycaemia in a patient with no previous history of diabetes.[35] Studies in mice have shown inconsistent findings.[36,37] In one study,[36] fluoxetine and sertraline induced hypoglycaemia, but in another study,[37] fluoxetine and fluvoxamine induced hyperglycaemia. The discrepancy may at least in part be explained by differences in the experimental conditions, such as the timing of the blood sampling, as the hyperglycaemic effect was of short duration. The insulin levels were unchanged during hyperglycaemia, indicating suppression of insulin release. Patients who experience insulin resistance during treatment with, for example clozapine or olanzapine, may experience a decompensation with overt diabetes if the insulin secretion is inhibited. The findings in our study therefore support previous findings suggesting a relative inhibition of the insulin release by serotonin reuptake inhibitors.

Some further data exist to support an increased risk of glucose intolerance from concomitant treat-

ment with buspirone as found in the present study. In a published case report of severe hyperglycaemia with clozapine,[38] the event occurred soon after buspirone was added to the treatment. Buspirone is a serotonin 5-HT_{1A} receptor agonist. In a study in rats,[39] treatment with buspirone was associated with increased glucose levels with no change in the insulin secretion. A more selective 5-HT_{1A} receptor agonist 8-hydroxy-2(di-*n*-propylamino) tetralin (8-OH-DPAT), was associated with both increased glucose levels and decreased insulin secretion. The effects were abolished in the presence of a 5-HT_{1A} receptor antagonist, (–)-pindolol. Experimental data, therefore, indicate that buspirone may have similar effects on the glucose metabolism as the serotonin reuptake inhibitors.

In conclusion, we found that clozapine, olanzapine and risperidone were associated with glucose intolerance. We identified the following risk factors for glucose intolerance: an underlying diabetic condition, an increase in weight, male gender, and concomitant use of valproic acid, selective serotonin reuptake inhibitors, or buspirone. We suggest that patients treated with clozapine, olanzapine or risperidone should undergo regular monitoring of weight and blood glucose and plasma lipid levels, particularly in the presence of additional risk factors for diabetes mellitus. Although it cannot be excluded that the association seen in this study may due to the underlying condition treated rather than the drugs themselves, more frequent monitoring of blood glucose should be considered if valproic acid, a selective serotonin reuptake inhibitor or buspirone is instituted in a patient already taking clozapine, olanzapine or risperidone.

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