Psychiatria Danubina, 2017; Vol. 29, No. 2, pp 121–135 *Review*

DIABETIC KETOACIDOSIS ASSOCIATED WITH ANTIPSYCHOTIC DRUGS: CASE REPORTS AND A REVIEW OF LITERATURE

Antonia Vuk[1], Martina Rojnic Kuzman[2], Maja Baretic[3] & Martina Matovinovic Osvatic[3]

[1]*Psychiatric Hospital Sveti Ivan, Zagreb, Croatia*
[2]*Department of Psychiatry, University Hospital Centre Zagreb and the Zagreb School of Medicine, Zagreb, Croatia*
[3]*Department of Endocrinology, University Hospital Centre Zagreb, Zagreb, Croatia*

received: 12.7.2016; revised: 12.4.2017; accepted: 27.4.2017

SUMMARY

Background: *Second generation antipsychotics (SGAs) are associated with metabolic disturbances. Diabetic ketoacidosis (DKA) is a rare, but potentially fatal sign of acute glucose metabolism dysregulation linked to the use of SGAs.*

The aims of this article are to present patients with a history of psychotic disorders and of severe metabolic diabetic ketoacidosis, possibly associated with the use of antipsychotics, and to review the current literature on the topic of antipsychotic-induced DKA.

Method: *PubMed/Medline and EBSCO databases were searched using the keywords: diabetic ketoacidosis, antipsychotics, atypical antipsychotics, second generation antipsychotics, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, paliperidone, amisulpride and haloperidol. Case reports, case series and reviews of case series were included in the review.*

Results: *The majority of patients who developed DKA following treatment with antipsychotics were treated with olanzapine and clozapine in monotherapy or in combination with other antipsychotics. DKA mostly occurred in the first six months of antipsychotic treatment. Other risk factors included insulin resistance prior to antipsychotic treatment, male gender and middle age.*

Conclusion: *Clinicians should consider the risk of DKA when starting treatment with SGAs. Preventive measures for patients with psychotic disorders using antipsychotics should include regular assessment of risk factors and screening for diabetes before and after administering antipsychotics, especially in the first months of treatment. Whenever possible, polypharmacy should be avoided.*

Key words: *diabetic ketoacidosis – antipsychotics - atypical antipsychotics - risk factors*

* * * * *

INTRODUCTION

Second generation antipsychotics (SGAs) are considered the first line treatment for psychotic disorders, due to their effectiveness and lower propensity to produce extrapyramidal side effects (Correl et al. 2008, Leucht et al. 2009). Nevertheless, the majority of SGAs are associated with significant weight gain and the development of glucose intolerance, leading to diabetes and metabolic syndrome, and consequently, with increased risk of cardiovascular morbidity and mortality (Daumit et al. 2008, De Hert et al. 2011, Hedenmalm et al. 2002). According to Lipscombe et al. (2014) antipsychotic-induced hyperglycemic emergencies are rather uncommon (in the range of 1-2 events per 1000 person per years of exposure). However, antipsychotic-induced diabetic ketoacidosis DKA is associated with a high risk of mortality, approaching to 13% of cases (Efstathiou et al. 2002, Guenette et al. 2013).

Current reports suggest that antipsychotic-induced DKA is usually associated with the use of olanzapine and clozapine in monotherapy, and in combinations with other antipsychotics in the first 6 months of treatment (Jin et al. 2004). Identified risk factors include underlying type 1 diabetes, pre-diabetes, non-Caucasian ethnicity, acute physical illness, male gender and middle age (English & Williams 2004, Kitabchi et al. 2009). However, the underlying mechanisms of the antipsychotic-induced DKA are still unclear. In this paper, we present a patient without prior history of diabetes mellitus who developed SGA-induced DKA, and review the available literature on SGA-induced DKA. Our aim is to provide a description of risk factors and offer a possible explanation on the underlying mechanisms of DKA in persons treated with SGAs.

METHODS

We have searched the MEDLINE and EBSCO database using the following terms: diabetic ketoacidosis, antipsychotics, atypical antipsychotics, second generation antipsychotics, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, paliperidone, amisulpride and haloperidol. Haloperidol was included in the search for the analysis on the role of antipsychotic polypharmacy in DKA.

Using these key words, we selected 168 titles. After reading article titles, we selected 140 abstracts in English language, one in Norwegian and one in Portuguese, from the period 1994-2015, while the rest were discarded because they did not match the topic. After reading these abstracts, we selected 80 full papers (case reports, case series and case reviews) and included them into the review. Forty additional articles identified while reviewing bibliographies of the retrieved articles were also examined. The rest of the papers were excluded after reading the abstracts as the topic did not match our aims, or the papers could not be translated.

In total, we included 83 cases of diabetic ketoacidosis associated with the use of antipsychotic agents. We collected and examined articles in their entirety of 63 of these cases, while information on the rest of 17 cases was acquired from abstracts and case reviews. We described one additional case in total and two cases partially in the Table 1, and they were included in the analyses.

RESULTS

Clinical case

A 33-year-old Caucasian man was referred to our ward in the state of acute psychosis, which, according to the data from his mother, lasted for more than one year. He was diagnosed with schizophrenia according to the International Classification of Disorders, 10th revision).

The patient was physically healthy, with body mass index (BMI) in the range of normal weight. Before the introduction of antipsychotics, the standard laboratory tests (blood count, liver enzymes, urea, creatinine) and thyroid hormones were normal. Since fasting glucose level showed glucose intolerance (6.4 mmol/L), fasting insulin level was obtained (27.5 U/L). Calculated Homeostasis Model Assessment HOMA - 3.65 pointed to insulin resistance with steady state beta cell function 142%. (https://www.dtu.ox.ac.uk/homacalculator/download.php). He had no prior history of diabetes mellitus. Family history for diabetes mellitus was also negative.

At admission the patient was treated with olanzapine (20 mg/d) and subsequently with addition of low dose fluphenazine (5 mg/d) for 3 weeks, without any improvement of his psychiatric status. The pharmacotherapy was then modified. Olanzapine and fluphenazine were gradually discontinued, while clozapine (dose tapered to 200 mg/d) and later on haloperidol (15 mg/d) were introduced, which lead to a significant improvement in his psychiatric status in the next 3 weeks. He was also given bisoprolol, at a dose of 5 mg/d, for high blood pressure and tachycardia which developed soon after introducing clozapine. During that period he gained 3 kg but was still in the range of normal BMI. Suddenly, the patient developed disorientation and vomiting, followed by somnolence, hypotension, tachycardia, tachypnea and acetone smell of the breath in less than 24 hours. Laboratory test confirmed diabetic ketoacidosis with severe clinical presentation (blood glucose level of 50.8 mmol/L, urine ketone bodies +3 (10mmol/L). Increased glycated haemoglobin (HbA1C 8.5) indicated a previously undiagnosed glucose intolerance. Negative antibodies against glutamic acid decarboxylase (anti-GAD) and islet cell antibodies (ICA) excluded the diagnosis of autoimmune type I diabetes. He was transferred to Intensive care unit (ICU) and all antipsychotics were discontinued.

Following the standard therapy his metabolic state improved, and he was transferred to basal bolus insulin therapy (a combination of long acting insulin analogue and ultra-short acting insulin analogue before meals). The patient was dismissed from ICU and readmitted to psychiatric clinic where he continued insulin therapy and took part in diabetes and dietary education. In the next two weeks, the prandial insulin dosage was gradually reduced and metformin was introduced. However, in parallel with somatic improvement his psychiatric status worsened again, and he was again treated with haloperidol up to 10 mg and biperiden up to 6 mg daily, to counteract the haloperidol-induced extrapiramydal symptoms. Since his psychiatric status deteriorated further, with the development of paranoid delusions, and dissociative speech, amilsupride (800 mg) was introduced, which led to significant improvement. He was discharged at the 10th week of hospitalization, with a recommended daily dose of 10 mg of haloperidol, 800 mg of amisulpride, 6 mg of biperiden, 10 IU of long acting insulin and 2000 mg of metformin, and a diabetic diet. After one month out patients follow up, his glucose levels returned to normal levels. Insulin therapy was discontinued and metformin was tapered off to 500 mg. His psychiatric status improved further, and he continued his treatment with amisulpride 800 mg bid and haloperidol in lower dose (5 mg).

Case review

Sociodemographic and clinical characteristics of patients with antipsychotic-induced DKA

Sociodemographic and clinical characteristics of the patients are summarized in Table 1.

Overall, most patients were men (N=51, for 12 patients gender was not available), of different ethnical origin (Afro-American (N=25); Caucasian (N=20); Asian (N=9); Afro-Caribbean (N=1); Hispanic (N=1); Aborigine (N=1); non available (N=29). Age range of the patients was 12-80 years (N=79 patients) and mean age was 37.7 years (SD=11.4). The majority of patients had schizophrenia spectrum disorders (N=58) and bipolar disorder (N=7), other (N=11) or was not available (N=8).

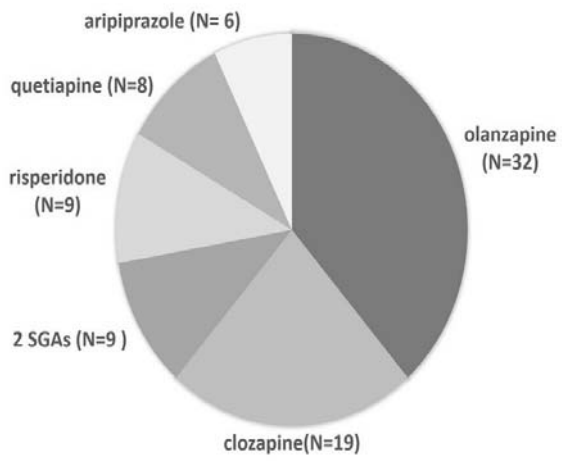

Figure 1. SGA applied in referred DKA cases

Table 1. Case reports of DKA with SGA use

No	Authors/ Reference	Patient age, gender, race	DG	Drug	Dose mg/d	CPZE	Polypharmacy	WG/WL (kg)	Over-weight	FH DM	PH DM	FBG	Symp	HbA1C %	BG mmol/L
1	Koval et al. 1994	34, female AfA	Sch	CL	250 (6w)	180.1	Y (lithium, benztropine)	N/R	Y	Y	N	normal	N/R	N/R	68
2	Kostakoglu et al. 1996	42, male	Psych D	CL	350 (4w)	252.2	N	N/R	Y	Y	N	6.72	few d	N/R	24.8
3	Peterson & Byrd 1996	46, male AfA	Sch	CL Lithium	500 (5w)	362.3	Y (lithium, bethanechol, verapamil)	N	N/R	Y	N	normal	N/R	N/R	42.33
4	Ai et al. 1997	30, male AfC	Sch	CL	300 (5m)	216.2	N	N/R	N/R	N	N	N/R	2-3d	11	N/R
5	Pierides 1997	50, male	Sch	CL	300 (10d)	216.2	Y (flupenthixol decanoate 80 mg)	N/R	N/R	N/R	N	normal	N/R	N/R	23.5
6	Popli et al. 1997	32, male AfA	Sch AbP	CL	425 (8w)	306.2	Y (ephedrine)	+3.6	Y	Y	N	normal	N/R	N/R	51.66
7	Wirshing et al. 1998	32, male AfA	SchA	CL	400 (18m)	288.2	N	+25.4	N	N	N	4.16-5.2	N/R	N/R	N/R
8	Wirshing et al. 1998	41, male AfA	SchA	CL	200 (5w)	144.1	N	N/R	Y	N	N	5-6.8	N/R	N/R	57.11
9	Colli et al. 1999	31, male W	SchA	CL	200 (3m)	144.1	N	+3	Y BMI 29	N	N	N/R	N/R	N/R	42
10	Gatta et al. 1999	31, male W	Sch	O	10 (3m)	188	Y (FGA)	-4	Y BMI 40	N	N	normal	N/R	14.7	36
11	Goldstein et al. 1999	42, female W	SchA	O	10 (6m)	188	Y (valproic acid)	+32	Y BMI 36	Y	N	normal	3w	11.6	70.77
12	Goldstein et al. 1999	40, female W	Sch	O	10 (18m)	188	N	+4.5/ -6.8	Y BMI 27.2	N	N	N/R	1w	N/R	64.44
13	Mohan et al. 1999	30, male AfA	Sch	CL	325 (3m)	234.2	N	N/R	N/R	N	N	N/R	N/R	N/R	19
14	Smith et al. 1999	40, male	N/R	CL	N/R	-	N	N/R	Y	N	N	normal	N/R	N/R	55
15	Croarkin et al. 2000	42, male W	Other	R	4 (several m)	333.3	Y (fluoxetine, trazodone)	N/R	N/R	N	N	N/R	3w	11.4	31.38
16	Rigalleau et al. 2000	41, male W	PsychD	O	N/R (3m)	-	N	-4	y	N	N	N/R	N/R	14.7	N/R
17	Avram 2001	33, male W	Sch	CL	100 (8m)	72.1	Y (sertraline, ranitidin, trihexyphenidil)	+13.9/-20.7	Y BMI 30.1	N	N	normal	3d	14	34.77
18	Muench & Carey 2001	38, male W	Sch	O	20 (12m)	376	Y (valproic acid, venlafaxine, propranolol, atorvastatine)	+15	Y BMI 31	N	Y 5d OHT	4.05-9.4	N/R	13.4	42.5

Table 1. Continues

No	Authors/ Reference	Patient age, gender, race	DG	Drug	Dose mg/d	CPZE	Polypharmacy	WG/WL (kg)	Over-weight	FH DM	PH DM	FBG	Symp	HbA1C %	BG mmol/L
19	Nicolai 2001	33, male As (Ind)	Sch	CL valproate	450 1000 (4y)	324.4 -	Y	N/R	N/R	N	N	N/R	5d	N/R	95.4
20	Ragucci 2001	46, female AfA	BAD	O	15 (14m)	282	Y (valproic acid, carbamaze-pine CR, hydrochlorthiazide/ triamteren, conj. estrogen)	N/R	Y BMI 39	Y	N	4.6	N/R	11.7	>55.55
21	Selva & Scott 2001	16, female AfA	Other	O R	15 (6m) N/R (6m)	282 -	Y (venlafaxine)	+13.6	Y	Y	N	N/R	N/R	17.7	37.16
22	Wirshing et al. 2001	52, AfA	Sch	R	8 (15m)	666.6	N	+7/-8	N/R	Y	N	4.8	3w	N/R	24.22
23	Johnson et al. 2002	49, male W	Sch	O	20 (11m)	376	N	+15.4	Y BMI 37.8	N	N	4.94	N/R	N/R	N/R
24	Waldman & Yaren 2002	33, male Ab	Sch	O	30 (3m)	564	N	+9	N	N/R	N	normal	N/R	N/R	37.5
25	Wilson et al. 2002	48, male AfA	PsychD	O	30 (10m)	564	N	N/R	N/R	N	N	N/R	N/R	N/R	20.5
26	Wilson et al. 2002	38, male AfA	Sch AbP	O	15 (2m)	282	N	N/R	N/R	N	N	N/R	N/R	N/R	32.11
27	Wilson et al. 2002	64, male W	Sch	Q	400 (2m)	227.9	N	N/R	N/R	Y	N	normal	N/R	N/R	N/R
28	Wilson et al. 2002	26, female AfA	Sch AbP	CL R	125 (5d) 3 (6w)	90 250	Y (lithium, clonazepam, venlafaxine)	N/R	N/R	N	Y 10d insulin	N/R	N/R	N/R	24.27
29	Wilson et al. 2002	33, AfA	SchA	O CL	10 (1m) 550 (6w)	188 396.3	Y	N/R	N/R	N	N	N/R	N/R	N/R	N/R
30	Tavakoli & Arguisola 2003	35, male W	BAD AbP	O	5 (18m)	94	Y (valproic acid venlafaxine)	+27.2	Y BMI 33.6	Y	N	normal	N/R	N/R	N/R
31	Torrey & Swallwell 2002	45, male AfA	BAD AbP	O R	30 (1m) 6	564 500	Y	N	N/R	N	N	normal	N/R	N/R	41.27
32	Tsuchiyama et al. 2003	28, male As	Sch	O	10 (1m)	188	N	+5	N/R	Y	N	N/R	N/R	13.7	60
33	Ananth et al. 2004	46	N/R	R	3 (2y)	250	Y (lithium)	N/R	NR	N	N	normal	N/R	N/R	66.72
34	Avella et al. 2004	37, AfA	BAD Sch PD	O	15	282	Y	N/R	N/R	N/R	N	N/R	N/R	N/R	N/R
35	Avella et al. 2004	27	BAD	O	N/R	-	Y (fluoxetine)	N/R	N/R	N	N	N/R	N/R	14.2	N/R

Table 1. Continues

No	Authors/ Reference	Patient age, gender, race	DG	Drug	Dose mg/d	CPZE	Polypharmacy	WG/WL (kg)	Over-weight	FH DM	PH DM	FBG	Symp	HbA1C %	BG mmol/L
36	Avella et al. 2004	34	Sch	O	N/R (4m)	-	N	N/R	N/R	N	N	N/R	N/R	14.7	N/R
37	Meyer et al. 2004	48, male W	Sch	Q	800 (4w)	455.8	Y (haloperidol)	+3.6/ -3.6	N/R	N/R	N	6.3	N/R	12.1	47.72
38	Church et al. 2005	34, female AfA	Sch	A O	30 (4d) 20 (several y)	376.4 376	Y (diazepam, metformin, rosiglitazone)	N/R	N/R	N/R	Y OHT	N/R	3d	N/R	32.1
39	Dibben et al. 2005	51, female W	Sch	Q	400 (2y)	227.9	Y (lithium, thyroxine, simvastatine, aspirin)	N	Y BMI 31	N	N	6.1	few days	7.2	53
40	Dibben et al. 2005	33, male As	Sch	R	25 mg/ 2w (8m)	-	N	N	Y BMI 28	N	N	8.6	N/R	N/R	66.1
41	Mithat et al. 2005	37, male	BAD	R	2-4 (6m)	166.7-333.33	Y (valproate, lithium)	+12	Y BMI 28.7	N	N	normal	N/R	N/R	35.94
42	Takashashi et al. 2005	72, male As	Other	Q	50 (14d)	28.5	Y (tiapride)	N/R	N BMI 21.3	N	N	7.3 after meal	4d	N/R	54.05
43	Mcfarlane & Fisher 2006	33	Sch	Q O	600 (4w) 10 (2y)	341.9 188	Y (folic acid)	-12	Y BMI 29	N	N	N/R	2W	N/R	79
44	Pillai et al. 2006	45, male	Sch	CL R	N/R (3m) N/R	- -	Y	-5	N/R	Y	N	normal	5d	8.9	23.11
45	Reddymasu et al. 2006	33, female AfA	Sch	A	N/R (18m)	-	N	+	Y BMI 41	N	N	N/R	N/R	N/R	98,27
46	Crown et al. 2007	male	N/R	O	10 (18m)	188	Y (paroxetine, atenolol, clonazepam, hydrochlortiazide)	N/R	Y BMI 31	N	N	normal	few d	14.9	44.8
47	Hamanaka & Kamijo 2007	32, male As	Sch	PH R	8 (9d) 4 (3y)	- 333.3	Y	+20	Y N/R 33.4	Y	N	N/R	4d	10.7	94.88
48	Kahn & Bourgeois 2007	29, male AfA	Sch AbP	O	30	564	Y (alprazolam)	N/R	N/R	Y	N	7.05 1d after in-troduction O	2d	15.2	91.77
49	Marlowe et al. 2007	45, male	Sch	Q	400 (5m)	227.9	Y (valproic acid)	N	Y BMI 27.6	N/R	N	normal	N/R	N/R	82.88
50	Reis et al. 2007	28	Sch	CL	150 (1m)	108.1	N	-15	N	N	N/R	N/R	2w	9.1	N/R
51	Sato et al. 2007	46, female As	Sch	R	3 (4m)	250	Y (levomepromazine)	N	N BMI 21.9	N	N	4.8 -7.6	N/R	12.2	51.44
52	Wong et al. 2007	22, male As	Sch, PD	O	10 (3y 3m)	188	Y (valproic acid)	+10/ -8	Y BMI 25.4	N	N	normal	3w	11.9	40.1

Table 1. Continues

No	Authors/ Reference	Patient age, gender, race	DG	Drug	Dose mg/d	CPZE	Polypharmacy	WG/WL (kg)	Over-weight	FH DM	PH DM	FBG	Symp	HbA1C %	BG mmol/L
53	Dhamija & Verma 2008	12, male W	Other	A	N/R (6m)	-	N	+	N/R	N	N	N/R	2m	N/R	26.55
54	Taslipinar et al. 2008	26, male	Sch	R	6 (5m)	500	N	N/R	Y BMI 31	N	N	N/R	N/R	11.2	18.77
55	Cho & Lindenmayer 2009	45, female AfA	Sch, AbP	CL	N/R (17m)	-	Y (haloperido, valproic acid, nortriptyline)	N/R	y	N/R	N	normal	N/R	N/R	22.22
56	Lu & Yan 2009	27, male As	Sch	R	N/R (2m)	-	N	N/R	N/R	N	N	N/R	N/R	13.7	72.05
57	Niazy et al. 2009	28, male	Sch	O	N/R (18m)	-	N	N/R	N/R	N/R	N/R	N/R	20d	N/R	N/R
58	Rashid et al. 2009	30, female	Sch	Q Z	200 (2m) 160 (9m)	114 255.5	Y	N	N/R	N/R	N	N/R	1d	N/R	60.05
59	Kibbey et al. 2010	30, male	Sch	A	20 (12m)	251	N	+20	Y BMI 40	N	N	N/R	4w	15.9	43.4
60	Saeverud & Gerlyng 2010	42, male	Other	O	7.5 (6m)	141	Y (escitaloprame, oxazepam, budesonide, terbutalin)	N/R	N/R	N/R	N	N/R	3d	N/R	38.8
61	Watkins et al. 2011	55, male AfA	Other	A	10 (6m)	125.5	Y (sertraline)	+16	N/R	N	N	7.33	1d	13.5	39.6
62	Sa et al. 2013	29, male	Other	O	30 (32m)	564	Y (valproic acid, clonazepam, lorazepam)	+34	Y BMI 31.7	N/R	N	normal	1w	13.8	67.55
63	Madsen 2014	27, male	Other	Q	400 (1y)	227.9	N	N/R	Y BMI 34	N	N	normal	2d	N/R	28
64	Case 1	33, male W	Sch	CL	200 (2 w)	144.1	Y (haloperidol, bisoprolol)	+3.6	N	N	N	6.4	2d	8.5	50.8
65	Case 2	27, male W	Sch	O	20 (several y)	376	N	-15	Y BMI 29.3	N	N	N/R	3d	12.6	21.4
66	Case 3	46, male W	Sch	O	10 (3y)	188	N	-3	Y BMI 33.1	Y	N	N/R	5d	16.7	34
67	Lyndenmayer & Patel 1999[2]	50, male AfA	Sch	O	30 (8m)	564	Y	+/-	N/R	N	N	N/R	N/R	N/R	N/R
68	Seaburg et al. 2001[2]	27, male AfA	Sch	O	10 (2y)	188	Y (valproic acid)	-13.6	N BMI 21.7	N	N	N/R	2W	N/R	68.88
69	Straker et al. 2002[2]	44, female AfA	Sch	O	25 (7w)	469.9	Y	N/R	N/R	N	N	N/R	N/R	N/R	N/R
70	Tsolaki et al. 2002[1,2]	80, female W (Greek)	Other	O	N/R (10m)	-	Y (paroxetine)	N	N	N	N	N/R	N/R	N/R	N/R

Table 1. Continues

No	Authors/ Reference	Patient age, gender, race	DG	Drug	Dose mg/d	CPZE	Polypharmacy	WG/WL (kg)	Over-weight	FH DM	PH DM	FBG	Symp	HbA1C %	BG mmol/L
71	Kristensen & Porksen 2003[2]	54, female W	Sch	CL	N/R	-	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
72	Lafayette 2003[2]	28, female His	Sch	CL	150 (10w)		Y (valproate)	-	N/R	Y	N/R	hyperglicemia	N/R	N/R	N/R
73	Howes & Rifkin 2004[2]	41, female	SchA	O	20 (3.5 m)	108.1	Y	-	N/R	Y	N	N/R	N/R	N/R	N/R
74	Babu et al. 2005[2]	15, female	BAD	A	N/R (4m)	-	Y	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
75	Fullbright & Breedlove 2006[1,2]	42, AfA	Sch	O	40 (40d)	751.9	Y	-	N/R	N/R	N	N/R	N/R	N/R	N/R
76	Kyriazis et al. 2006[2]	33, male W	Other	O	20 (4m)	376	N	+	N/R	Y	N	N/R	N/R	N/R	N/R
77	Varma et al. 2007[1,2]	35, female	BAD	O	10 (6w)	188	N/R	N/R	N/R	N	N	N/R	N/R	N/R	N/R
78	Makhzoumi et al. 2008[2]	44, male AfA	SchA	A	30 (17d)	376.4	Y	-	N/R	N	N	N/R	N/R	N/R	N/R
79	Sirosis 2008[2]	41, female AfA	Other	Q	400 (37d)	227.9	Y	N/R	N/R	N	N	N/R	N/R	N/R	N/R
80	Chellamuth et al. 2010[1,2]	42, male As	Sch	R	N/R (depot)	-	N/R	N/R	Y	N	N	N/R	1w	NR	N/R
81	Von Hayek 1999 [3]	N/R	N/R	O	N/R	-	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
82	Maule et al. 1999 [3]	N/R	N/R	CL	N/R	-	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
83	Sobel et al. 1999[3]	N/R	N/R	Q	N/R	-	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R

[1]abstract; [2]Guenette et al. 2013; [3]cases with SGA type information exclusively

Abbreviations: DG – diagnosis, W – white, AfA – Afro-American, AfC - Afro-Caribbean, His - hispanic, As - Asian, Ab – Aborigine, DG - diagnosis, Sch – Schizophrenia, SchA – Schizoaffective disorder, Psych D – psyhotic disorder, BAD – bipolar affective disorder, AbP - abuse of psychoactive substances, PD – personality disorder, O - olanzapine, Cl – Clozapine, R – risperidone, Q - quetiapine, Z – ziprasidone, A – Aripiprazole, PH - perospirone hydrochloride, CPZE – chlorpromazine dose equivalent, d – day, w - week, m – month, y – year, WG – weight gain (+), WL – weight loss (-), Y - yes, N - no, BMI – body mass index (kg/m2), FM DM – family history of diabetes melitus, PH DM – personal history of diabetes mellitus, FBG – fasting blood glucose prior starting SGA in mmol/L, Symp – symptoms of hyperglycemia/DKA, HbA1c - glycated haemoglobin in %, BG – blood glucose at admission/event, OHT- oral hypoglycemic therapy

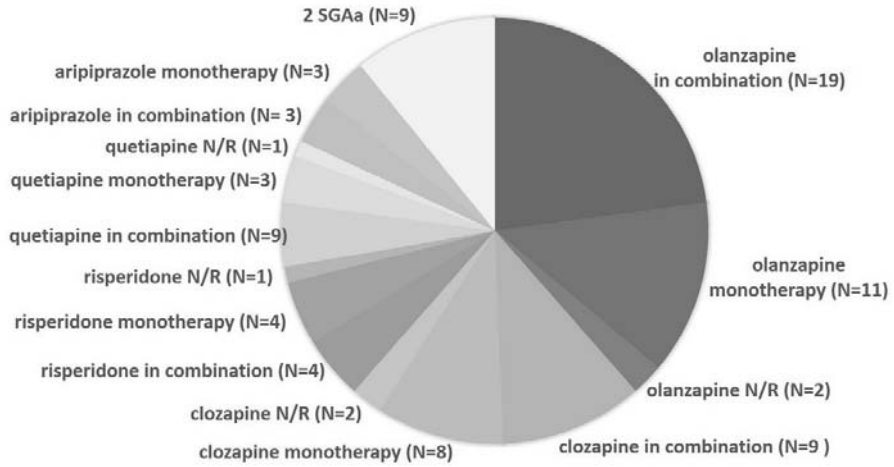

Figure 2. Mono- and polypharmacy distribution in referred DKA cases

In the majority of cases, DKA was associated polypharmacy (N=48), with 9 cases treated with 2 or more SGAs, 6 cases treated with a combination of a SGA and FGA, and for 8 cases the second antipsychotic was not specified. In 25 cases DKA was associated with SGA in monotherapy.

In the majority of cases where DKA was associated with a specific medication, the suspected agent was olanzapine (32 cases), followed by clozapine (19 cases), risperidone (9 cases), quetiapine (8 cases) and aripiprazole (6 cases) (Figure 1). We did not find any cases associating DKA with ziprasidone, paliperidone, haloperidol or amisulpride monotherapy. In 48 cases, DKA was associated with polypharmacy (Figure 2). The majority of cases involved the use of olanzapine as a single SGA drug (N=28) or a suspected agent in combination with another SGA (N=4). 18 cases involved the use of clozapine as a single SGA drug or a suspected agent in combination with another SGA.

Other most frequently reported concomitant drugs were first generation antipsychotics (FGA) (N=6), mood stabilizers (sodium valproate (N=11), lithium (N=6), clonazepam (N=3)), antidepressants (venlafaxine (N=4), fluoxetine (N=3), sertraline (N=2), paroxetine (N=2), escitalopram (N=1), bupropione (N=1), trazodone (N=1), notriptyline (N=1), benzodiazepines (N=5), β blockers (N=3), calcium channel blocker (N=1), statines (N=2), OHT (N=3), sympathomimetics (ephedrine – α and β adrenergic agonist) (N=1), parasympathomimetics (betanechol) (N=1), anticholinergics (benztropine, trihexyphenidyl) (N=2), histaminic antagonist (ranitidine) (N=1), corticosteroids (budesonide) (N=1), hormones (estrogen and tyroxine, N=2), and antidiuretics (hydrochlorothiazide) (N=2).

The reported daily doses (available for 65 cases) of each of the reported antipsychotics did not exceed the recommended therapeutic ranges. Duration of antipsychotic therapy prior the onset of DKA ranged from 4 days to 4 years (N=74). In about a half of the reported cases (N=45), DKA occurred within the 6 months after starting the introduction of the speculative drug.

Risk factors and clinical presentation of antipsychotic-induced DKA

In the majority of cases (N=72), DKA was the first clinical presentation of a newly diagnosed diabetes. Prodromes (such as polydipsia, polyuria and weakness) were reported only in 30 patients, and lasted from 1 day to 4 weeks.

Presenting glucose values were available for 55 patients and ranged from 18.77 mmol/L (338 mg/dL) to 98.27 mmol/L (1769 mg/dL). In 12 of these patients leukocytosis was noted. In three of them it was associated with pancreatitis and in one with uroinfection.

However, available data indicate previously unrecognized hyperglycemia (increased fasting blood glucose (FBG) (6.4-9.4 mmol/L) in eight of the cases, increased HbA1C (ranging from 7.2–17.7%) in 29 cases, confirmed diabetes in 4 patients (two cases 10 days prior event) and for 5 patients there were insufficient data for classification. Auto antibodies (N=13) were found negative in 11 patients and positive in 2 patients – indicating a newly diagnosed diabetes type 1.

Body weight prior to starting SGA therapy was available for 50 cases. 33 of those patients were overweight at the time of admission (underweight <18.5, normal weight 18.5-24.9, overweight 25-29.9, obesity >30 kg/m2) (Pasco et al. 2014). Weight change associated with SGA treatment was available for 45 cases. The majority of the patients experienced weight gain (N=25) ranging from 3 to 34 kg. Six of them also experienced a substantial weight loss prior DKA as a prodromal symptom of diabetes. Weight loss without prior weight gain was recorded in 12 patients – in 7 of these cases it was associated with DKA. In 8 patients, no weigh changes were noted during the antipsychotic treatment.

In 47 of the cases patients had negative family history of diabetes, while 18 patients had a positive family history for diabetes. In the remaining 18 cases data was not available.

DISCUSSION

Risk factors and clinical presentation of antipsychotic-induced DKA

The majority of the patients who developed DKA were diagnosed with schizophrenia. The hypothesis that schizophrenia spectrum disorders raise the risk of glucose intolerance is not a new one. Even in pre-antipsychotic era, higher incidence of diabetes mellitus among patients with schizophrenia then compared to the general population was reported (Thonnard-Neumann 1968). This seems to be the case for drug naïve first episode psychotic patients (Foley & Morley 2011), even among Croatian population (Medved et al. 2009). Recent genetic studies seem to support this hypothesis. Network and pathway-based systematic analysis for schizophrenia and diabetes mellitus type 2 provided the general pathway-based view of pathogenetic association between two diseases and reported a considerable overlap between the susceptibility genes for schizophrenia and diabetes mellitus type 2 (Liu et al. 2013).

The incidence of diabetes presenting as DKA in schizophrenia has been calculated as 10-fold higher than the calculated risk for the general population (Henderson et al. 2007). Risk factors for antipsychotic-induced glucose dysregulation include pre-existing diabetes, non-Caucasian ethnicity, first degree family history of DM and baseline obesity (Lipscombe et al. 2014, Wirshing et al. 2002, Jin et al. 2004). However, when comparing risk factors of DKA versus diabetes, the DKA group was significantly different and included a group of predominately younger males, with a lower proportion of overweight BMI at baseline (Jin et al. 2002).

Our results suggest similar risk factors for antipsychotic-induced DKA: average age younger than in general population of patients with diabetes type 2, gender imbalance with predominance of males, absence of autoimmune markers of diabetes, as well as the absence of significant weight gain. However, our results also suggest a period of insulin resistance or hyperglycemia preceding the development of DKA. It is unclear whether this indicates a susceptibility to diabetes inherent to patients with schizophrenia.

The role of antipsychotic medication in the development of DKA

There is little doubt that antipsychotics can increase the risk of diabetes among patients with psychotic disorders (Foley & Morley 2011), but also among patients with bipolar disorder (Olfson et al. 2006, Correl et al. 2008). Several reports suggested that SGAs have a significantly higher risk of diabetes and hyperglycemia compared to conventional antipsychotics (Smith et al. 2008, Yood et al. 2009), although SGAs differ significantly one from another in their propensity to induce diabetes (Smith et al. 2005, Meyer et al. 2008). The majority of case reviews and epidemiological studies suggest that the risk of diabetes is the highest for olanzapine and clozapine, followed by quetiapine (Jin et al. 2002, Ramaswamy et al. 2006), risperidone and amisulpride (Koller et al. 2001-2003, Foley & Morley 2011), while the risk for ziprasidone and aripiprazole is comparable to the risk of non-users of antipsychotics or users of conventional APs (Meyer et al. 2002, Lindenmayer et al. 2003). Likewise, according to our results, olanzapine and clozapine seem to have the highest potential for inducing DKA, either as monotherapy or in combination with other antipsychotics. Moreover, hyperglycaemia reoccurred in all patients with olanzapine and clozapine re-challenge (Koval et al. 1994, Popli et al. 1997, Colli et al. 1999, Waldman & Yaren 2002).

Although there were few cases where haloperidol contributed to the development of DKA in combinations with other SGAs, we found no cases of DKA associated with haloperidol, ziprasidone, paliperidone and amisulpride monotherapy. With the exception of haloperidol, this fact may reflect the lower number of cases / studies with those antipsychotics reported in the literature.

In more than half of the cases DKA appeared following the introduction of polypharmacy, suggesting that polypharmacy may be associated with a greater risk than either clozapine or olanzapine monotherapy. This is concordant with the findings that polypharmacy contributes to metabolic abnormalities in patients with schizophrenia (Correll et al. 2007). Possible explanations include pharmacodynamic factors (e.g. activation of more receptors) and pharmacokinetic factors (higher total daily dosages of combined antipsychotics or drug interactions at the liver level, both resulting in higher serum drug levels). This fact may be especially important in clinical practice, as, contrary to most guidelines, polypharmacy seem to be rather prevalent in the treatment of schizophrenia, reported - up to 40% in some regions and periods in history (Gallego et al. 2012). Polypharmacy seems to be conditioned by the severity of psychiatric symptoms (Katona et al. 2014). Nevertheless, clinicians should be aware of the possible seriousness of the metabolic side effects associated with its use.

Does antipsychotic-induced DKA occur in persons with susceptibility to diabetes mellitus?

In general, we suggest that antipsychotic-induced DKA can occur in persons susceptible to diabetes mellitus after the induction of diabetogenic agents such as antipsychotics. However, the nature of this interplay is unclear by a large. In clinical practice, the introduction of antipsychotics can lead to DKA as 1) a complication as preexisting diabetes type 1; 2) a presentation of a newly developed DM type 2, due to antipsychotic–induced increase of BMI and insulin resistance over time; 3) fulminant presentation of DKA imitating DM type associated with an acute antipsychotic-induced insulin resistance, unrelated to BMI increase.

	Haloperidol	Amisulpiride	Clozapine	Olanzapine	Risperidone	Quetiapine	Ziprasidone	Aripiprazole
D1	++	-	+	++	+	+	++	+
D2	+++	++++	+	++	+++	+	+++	++++
D3	++	+	+	++	++	+	++	+++
D4	++	-	++	++	++	-	+	+
5HT1A	-	-	+	-	+	+	++	+++
5HT1B	+	-	+	+	++	-	++	+
5HT1D	-	-	-	-	+	+++	+++	++
5HT1E	-	-	+	-	-	-	-	-
5HT2A	++	-	++	+++	++++	+	+++	+++
5HT2C	-	-	++	++	++	-	++	+
5HT6	-	-	++	+++	-	-	++	+
5HT7	+	++	++	+	+++	+	+++	++
α1A	++	-	+++	+	+++	++	++	++
α1B	+++	-	+++	+	++	++	+++	++
α2	+	-	+	++	++	+	++	+
H1	-	-	+++	+++	++	+++	+	++
M1	-	-	++	++	-	+	-	-
M2	-	-	++	++	-	-	-	-
M3	-	-	++	++	-	-	-	-
M4	-	-	++	+	-	+	-	-
DAT	-	-	++	+	-	-	-	-
NAT	-	-	+	+	-	-	++	-
5HTT	-	-	-	-	-	-	+	-

Receptor abbreviations: D1 - dopamine-1, D2 - dopamine-2 , D3 - dopamine-3, D4 - dopamine-4, 5HT1A - serotonin-1A, 5HT1B - serotonin-1B, 5HT1D - serotonin-1D, 5HT1E - serotonin-1E, 5HT2A - serotonin-2A, 5HT2C - serotonin-2C, 5HT6 - serotonin-6, 5HT7 - serotonin-7, α1A - α-adrenoreceptor-1A, α1B - α-adrenoreceptor-1B, α2 - α-adrenoreceptor-2, H1 -histamine-1, M1 - muscarinic-1, M2 - muscarinic-2, M3 - muscarinic-3, M4 - muscarinic-4, DAT - dopamine transporter, NAT - noradrenaline transporter, 5HTT - serotonin transporter protein

Figure 3. Relative receptor binding affinities of antipsychotics. Adapted from Roth et al. 2004, Nasrallah 2008, Hopkins 2009, Abbas et al. 2009

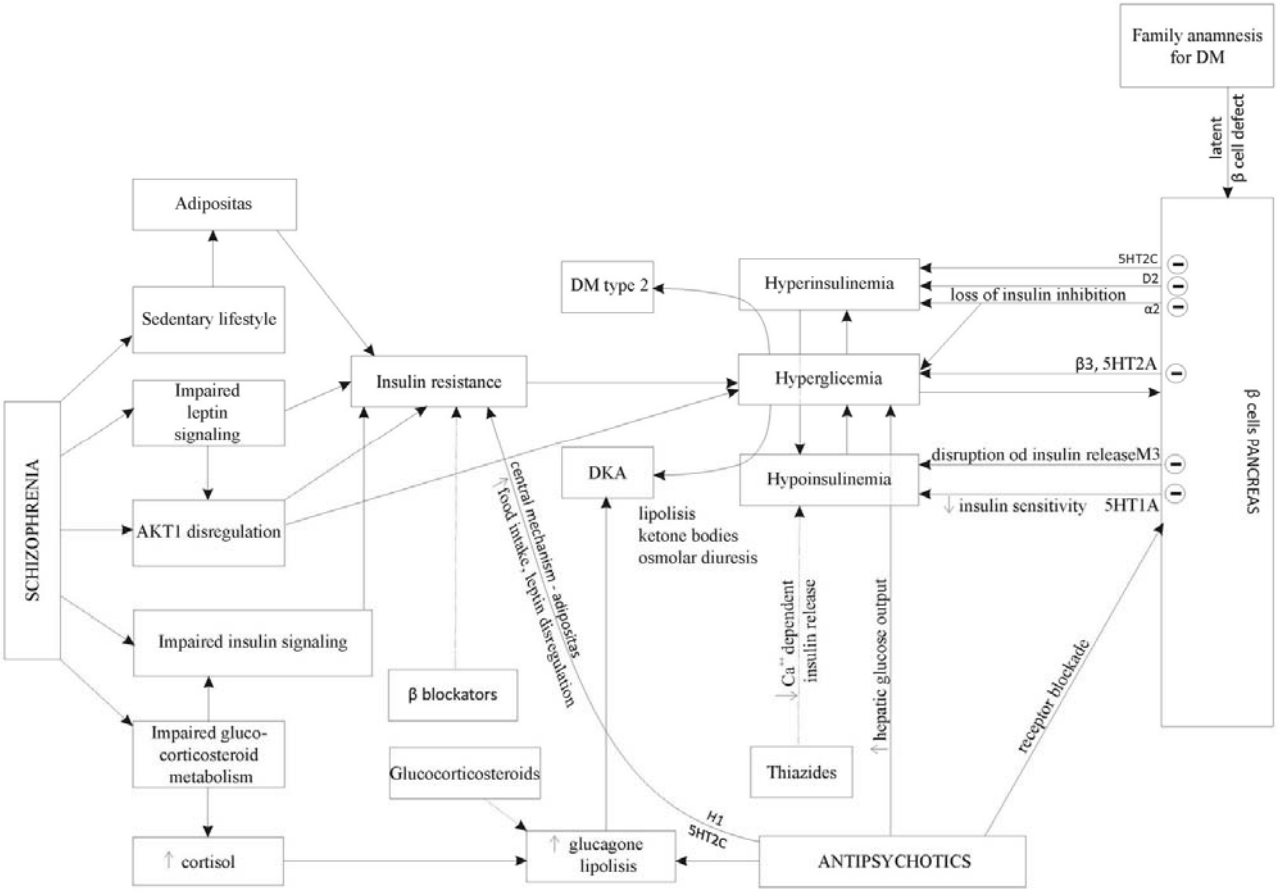

Figure 4. Suggested antipsychotic-induced DKA hypothetic mechanism (based on Buchholz et al. 2007, Houseknecht et al. 2007, Smith et al. 2008, Starrenburg & Bogers 2009, Hahn et al. 2011, Liu et al. 2013)

Although one would expect that persons with pre-existing diabetes type 1 are more prone to develop DKA, according to our analysis, up to 90% of reviewed cases were classified as newly diagnosed type 2 diabetes. However, this result may indicate that clinicians avoid the use of antipsychotics with higher propensity to gain weight (such as olanzapine) in persons with diabetes mellitus type 1.

Antipsychotic-induced DKA in new onset type 2 diabetes may result from a number of possible causes. The most common mechanism of antipsychotic-induced diabetes seem to follow the pathway of antipsychotic-induced increase of appetite and weight gain leading to abdominal adiposity and subsequent development of the insulin resistance and diabetes (Buchholz et al. 2007). The presence of negative symptoms and sedentary lifestyle of these patients may further contribute to or speed up the process of weight gain and the occurrence of diabetes. This mechanism of action is usually associated with the strong antagonism of serotonin 2C receptors (5HT2C) and histamine receptors (H1) in the hypothalamic regions, as exerted by olanzapine and clozapine (Hahn et al. 2011). Antipsychotic drugs exert many actions on the peripheral tissue as well, including adipose, muscular and pancreatic tissue and, in example, confer to insulin resistance through the increase of leptin or TNFα in the adipose tissue (Starrenburg & Bogers 2009). On the protein level, candidates include glucose transporters or postreceptor sites, such as the protein kinase B (also known as AKT1). AKT1 has important role in the regulation of metabolism, cell survival, motility, transcription and cell-cycle progression and its signaling is disrupted in many disorders, including diabetes as well as schizophrenia (Whiteman et al. 2002, Emamian et al. 2004, Liu et al. 2013). The activation of AKT1 could explain the association of clozapine and olanzapine with elevated levels of blood glucose, glycosylated haemoglobin and insulin leading to the development of type 2 diabetes mellitus, unfavorable effects on lipid profiles etc. (Dwyer et al. 2005, Girgis et al. 2008).

Alternatively, antipsychotic-induced DKA may follow another pathophysiological pathway. Indeed, significant weight gain was detected in only about a half of all reported cases. Even considering the fact that weight gain at the time of hospital admission may be misleading as some patients experienced weight loss as a sign of diabetes, changes in visceral adiposity more directly contribute to insulin resistance than absolute weight gain (Mitchell et al. 2011, Genuette et al. 2013). Secondly, DKA has been reported shortly after the initiation of antipsychotic treatment, and in individuals who experienced no significant changes in body weight (Jin et al. 2002). We suggest that antipsychotics exert an acute effect on pancreatic beta cell secretion, regardless of their propensity to induce weight gain (Smith et al. 2008, Albaught et al. 2011). In general, DKA occurs in severely insulinopenic patient with high levels of glucagon. Insulin deficiency (mostly due to autoimmune destruction of beta cell) shifts metabolism to triglycerides and amino acids instead of glucose. Serum levels of glycerol and free fatty acids (FFAs) rise because of uninhibited lipolysis. The excess of glucagon stimulates hepatic gluconeogenesis. Glucagon also stimulates mitochondrial conversion of FFAs into ketones. Insulin normally blocks ketogenesis by inhibiting the transport of FFA derivatives into the mitochondria. Thus, in patients without significant weight gain and/or insulin resistance, a reversible toxic event affecting only beta cells of pancreas secreting insulin, but not the α cells secreting glucagon may occur. Such "reversible" activation may be exerted by antipsychotics. In example, clozapine was found to hyperpolarize the rat pancreatic-cells membrane potential, resulting in a complete inhibition of electrical activity, unlike haloperidol (Best et al. 2005). Other possible mechanisms include the blockade of 5-HT1A/2A/2C serotonergic, histaminergic, muscarinic and activation of 2-adrenergic receptors of the pancreatic cells (Houseknecht et al. 2007, Schwenkreis et al. 2004).

Several reports confirmed the blockade of M3 receptors on pancreatic β-cells leads to impairment of glucose-dependent cholinergic-stimulated insulin secretion hence interfere with pancreatic attempt to redress peripheral insulin resistance (Starrenburg & Bogers 2009, Hahn et al. 2011). Postprandial – acute metabolic hyperinsulinemia and parallel aberrant increase of glucagon coincide with insulin resistance (Melkersson & Jansson 2004, Smith et al. 2008, Teff et al. 2013). Thus, we can speculate that cumulative additional activation of "risky" receptors on β pancreatic cells (histamine, muscarine, serotonin and adrenergic) may activate a common post receptor mechanism preventing only β cells of pancreas secretion of insulin and creating an artificial state of "insulinopenia". SGAs are a diverse group, encompassing drugs with different mechanisms of action, different pharmacodinamic profiles and different affinity to receptors (Roth et al. 2004, Nasrallah 2008, Hopkins 2009, Abbas et al. 2009), as summarized in Figure 3.

Concordant with this hypothesis, antipsychotics which exert a strong antagonism of multiple receptors (such as clozapine or olanzapine) employ multiple mechanisms leading to the inhibition of pancreatic insulin secretion. In persons with insulin resistance prior to antipsychotic treatment, addition of a multireceptor antagonists antipsychotic (or a combination of antipsychotics) would produce a state of "artificial insulinopenia" which presents as DKA. The hypothetic mechanism is presented in Figure 4.

CONCLUSION

Our findings suggest that new onset diabetes type 2 can occur early in the course of antipsychotic treatment, presenting with DKA. In the majority of cases, insulin resistance prior to antipsychotic treatment, diagnosis of schizophrenia, male gender, middle age, drug combi-

nations that included olanzapine and clozapine, and polypharmacy were found. DKA was preceded by often unrecognized clinical prodromes (such as polydipsia, polyuria and weakness) (about a third of cases) lasting from 1 day to 4 weeks before presenting as an emergency. However, high glycohemoglobin indicating glucose dysregulation preceded visible symptoms and accentuates the need for strict monitoring. Preventive measures for patients with schizophrenia taking antipsychotics include regular assessment of preexisting risk factors for diabetes before administering antipsychotics, regular screening for diabetes in the first months of antipsychotic treatment and avoidance of polypharmacy.

Limitations

This review has several limitations that need to be acknowledged. First, this review is based on case reports only, which limits our conclusions in the absence of research papers. Secondly, in the majority of cases, adverse drug reaction causality was based on timing and the pattern of illness, while re-challenge was performed only in few cases, and described elsewhere (Koval et al. 1994, Popli et al. 1997, Colli et al. 1999, Waldman & Yaren 2002), which may decrease the certainty that DKA was caused by the suspected medication (Edwards & Aronson 2000).

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Antonia Vuk: drafting the article, acquisition, analysis and interpretation of data, tabels and graphs design;

Martina Rojnic Kuzman: design of the study, drafting the final version of article and revising it critically for important intellectual content, analysis and interpretation of data;

Maja Baretic and Martina Matovinovic Osvatic: analysis and interpretation of data for the first draft and critical revision of the final version of the article.

References

1. *Ai D, Roper TA, Riley JA: Diabetic ketoacidosis and clozapine. Postgrad Med J 1998; 74:493–94.*
2. *Abbas AI, Hedlund PB, Huang XP, Tran TB, Meltzer HY, Roth BL: Amisulpride is a potent 5-HT7 antagonist: relevance for antidepressant actions in vivo. Psychopharmacology (Berl) 2009; 205:119-28.*
3. *Albaugh VL, Henry CR, Bello NT, Hajnal A, Lynch SL, Halle B et al.: Hormonal and metabolic effects of olanzapine and clozapine related to body weight in rodents. Obesity (Silver Spring) 2006; 14:36-51.*
4. *Ananth J, Johnson KM, Levander EM, Harry JL: Diabetic ketoacidosis, neuroleptic malignant syndrome, and myocardial infarction in a patient taking risperidone and lithium carbonate. J Clin Psychiatry 2004; 65:724.*
5. *Avella J, Wetli C, Wilson J, Katz M, Hahn T: Fatal olanzapine induced hyperglycemic ketoacidosis. Am J Forensic Med Pathol 2004; 25:172–75.*
6. *Avram AM, Patel V, Taylor HC, Kirwan JP, Kalhan S: Euglycemic clamp study in clozapine-induced diabetic ketoacidosis. Ann Pharmacother 2001; 35:1381–87.*
7. *Best L, Yates AP, Reynolds GP: Actions of antipsychotic drugs on pancreatic beta-cell function: contrasting effects of clozapine and haloperidol. J Psychopharmacol 2005; 19:597-601.*
8. *Buchholz S, Morrow AF, Coleman PL: Atypical antipsychotic-induced diabetes mellitus: an update on epidemiology and postulated mechanisms. Intern Med J 2008; 38:602-6.*
9. *Chellamuth P, Kong M, Gregory R: Ketosis-prone type 2 diabetes: an increasingly recognized entity. Pract Diabetes 2010, 27:18–9.*
10. *Cho DY & Lindenmayer JP: Aripiprazole-induced agitation after clozapine discontinuation: a case report. J Clin Psychiatry 2009; 70:141–3.*
11. *Church CO, Stevens DL, Fugate SE: Diabetic ketoacidosis associated with aripiprazole. Diabet Med 2005; 22:1440–3.*
12. *Colli A, Cocciolo M, Francobandiera F, Rogantin F, Cattalini N: Diabetic ketoacidosis associated with clozapine treatment. Diabetes Care 1999; 22:176–7.*
13. *Correll CU, Frederickson AM, Kane JM, Manu P: Does antipsychotic polypharmacy increase the risk for metabolic syndrome? Schizophr Res 2007; 89:91–100.*
14. *Correll CU, Frederickson AM, Kane JM, Manu P: Equally increased risk for metabolic syndrome in patients with bipolar disorder and schizophrenia treated with second-generation antipsychotics. Bipolar Disord 2008; 10:788-97.*
15. *Croarkin PE, Jacobs KM, Bain BK: Diabetic ketoacidosis associated with risperidone treatment? Psychosomatics 2000; 41:369–70.*
16. *Crown N, Feltham M, Bayliff CD: Olanzapine-Induced Diabetic Ketoacidosis Resulting in Prolongation of Hospital Stay: Clinical Outcome and Cost Issues. Can J Hosp Pharm 2007; 60:192-4.*
17. *Daumit GL, Goff DC, Meyer JM, Davis VG, Nasrallah HA, McEvoy JP et al.: Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. Schizophr Res 2007; 105:175–87.*
18. *De Hert M, Detraux J, Van Winkel R, Yu W, Correll CU: Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol 2011; 8:114–26.*
19. *Dhamija R & Verma R: Diabetic ketoacidosis induced by aripiprazole in a 12-year-old boy. Diabetes Care 2008; 31:50.*
20. *Dibben CR, Kalavalapalli SS, Linnington HE, Hynes FA, Dinneen SF, Adler AI et al.: Diabetes associated with atypical antipsychotic treatment may be severe but reversible: case report. Int J Psychiatry Med 2005; 35:307–11.*
21. *Dwyer DS, Donohoe D, Lu XH, Aamodt EJ: Mechanistic connections between glucose/lipid disturbances and weight gain induced by antipsychotic drugs. Int Rev Neurobiol 2005; 65:211–24.*
22. *Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356:1255-9.*

23. *Emamian ES, Hall D, Birnbaum MJ, Karayiorgou M, Gogos JA: Convergent evidence for impaired AKT1-GSK3beta signalling in schizophrenia. Nat Genet 2004; 36:131-7.*
24. *English P & Williams G: Hyperglycaemic crises and lactic acidosis in diabetes mellitus. Postgrad Med J 2004; 80:253–61.*
25. *Efstathiou SP, Tsiakou AG, Tsioulos DI, Zacharos ID, Mitromaras AG et al.: A mortality prediction model in diabetic ketoacidosis. Clin Endocrinol 2002; 57:595–601.*
26. *Foley DL & Morley KI: Systematic Review of Early Cardiometabolic Outcomes of the First Treated Episode of Psychosis. Arch Gen Psychiatry 2011; 68:609-16.*
27. *Fulbright A & Breedlove K: Complete resolution of olanzapineinduced diabetic ketoacidosis. J Pharm Pract 2006; 19:255–8.*
28. *Gallego JA, Bonetti J, Zhang J, Kane JM, CorrelL CU: Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res 2012; 138:18-28.*
29. *Gatta B, Rigalleau V, Gin H: Diabetic ketoacidosis with olanzapine treatment. Diabetes Care 1999; 22:1002–3.*
30. *Goldstein LE, Sporn J, Brown S, Kim H, Finkelstein J, Gaffey GK et al.: New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. Psychosomatics 1999; 40:438-443.*
31. *Girgis RR, Javitch JA, Lieberman JA: Antipsychotic drug mechanisms: links between therapeutic effects, metabolic side effects and the insulin signalling pathway. Mol Psychiatry 2008, 13:918–29.*
32. *Guenette M, Hahn M, Cohn T, Teo C, Remington G: Atypical antipsychotics and diabetic ketoacidosis: a review. Psychopharmacology 2013; 226:1-12.*
33. *Hahn M, Chintoh A, Giacca A, Xu L, Lam L, Mann S et al.: Atypical antipsychotics and effects of muscarinic, serotonergic, dopaminergic and histaminergic receptor binding on insulin secretion in vivo: an animal model. Schizophr Res 2011; 131:90–5.*
34. *Hamanaka S & Kamijo Y: New-onset diabetic ketoacidosis induced by the addition of perospirone hydrochloride in a patient treated with risperidone. Intern Med 2007; 46:199-200.*
35. *Hedenmalm K, Hagg S, Stahl M, Mortimer O, Spigset O: Glucose intolerance with atypical antipsychotics. Drug Saf 2002; 25:1107–16.*
36. *Houseknecht KL, Robertson AS, Zavadoski W, Gibbs EM, Johnson DE, Rollema H: Acute effects of atypical antipsychotics on whole-body insulin resistance in rats: implications for adverse metabolic effects. Neuropsychopharmacology 2007; 32:289–97.*
37. *Hopkins AL: Drug discovery: Predicting promiscuity. Nature 2009; 462:167-8.*
38. *Jin H, Meyer JM, Jeste DV: Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases. Ann Clin Psychiatry 2002; 14:59–64.*
39. *Jin H, Meyer JM, Jeste DV: A typical antipsychotics and glucose dysregulation: a systematic review. Schizophrenia Research 2004; 71:195–212.*
40. *Johnson RP, Al-Taher MT, Madlock LE, Guo M, Nasdahl CS: Increasing insulin dose for olanzapine-related diabetes. Am J Psychiatry 2002; 159:150–1.*
41. *Kahn D & Bourgeois JA: Acute pancreatitis and diabetic ketoacidosis in a schizophrenic patient taking olanzapine. J Clin Psychopharmacol 2007; 27:397–400.*
42. *Katona L, Czobor P, Bitter I: Real-world effectiveness of antipsychotic monotherapy vs. polypharmacy in schizophrenia: To switch or to combine? A nationwide study in Hungary. Schizophr Res 2012; 152:246-54.*
43. *Kibbey KJ, Roberts AM, Nicholson GC: Diabetic ketoacidosis and elevated serum lipase in the setting of aripiprazole therapy. Diabetes Care 2010; 33:96.*
44. *Kitabchi AE, Umpierrez GE, Murphy MB, Miles JM, Fisher JN: Hyperglycemic crises in diabetes. Diabetes Care 2009; 32:1335-43.*
45. *Koller EA & Doraiswamy PM: Olanzapine-associated diabetes mellitus. Pharmacotherapy 2002; 22:841–852.*
46. *Koller E, Malozowski S, Doraiswamy PM: Atypical antipsychotic drugs and hyperglycemia in adolescents. JAMA 2001; 286:2547–8.*
47. *Koller EA, Cross JT, Doraiswamy PM, Schneider BS: Risperidone-associated diabetes mellitus: a pharmacovigilance study. Pharmacotherapy 2003; 23:735–44.*
48. *Kostakoglu AE, Yazici KM, Erbas T, Guvener N: Ketoacidosis as a side-effect of clozapine: a case report. Acta Psychiatr Scand 1996; 93:217–8.*
49. *Koval MS, Rames LJ, Christie S: Diabetic ketoacidosis associated with clozapine treatment. Diabetes Care 1994; 22:176-7.*
50. *Lafayette JM, Pirl WF, Henderson DC: Low-dose clozapine and diabetic ketoacidosis. Psychosomatics 2003; 44:249–52.*
51. *Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM: Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009; 373:31–41.*
52. *Lipscombe LL, Austin PC, Alessi-Severini S, Blackburn DF, Blais L, Bresee L et al.: Atypical antipsychotics and hyperglycemic emergencies: multicentre, retrospective cohort study of administrative data. Schizophr Res 2014; 154:54-60.*
53. *Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman B, McEvoy JP et al.: Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. Am J Psychiatry 2003, 160:290–6.*
54. *Liu Y, Li Z, Zhang M, Deng Y, Yi Z, Shi T: Exploring the pathogenetic association between schizophrenia and type 2 diabetes mellitus diseases based on pathway analysis. BMC Med Genomics 2013; 6:17.*
55. *Lu CH & Yan YH: Risperidone-associated newly diagnosed diabetes and fatal diabetes ketoacidosis in a young schizophrenic patient. Diabetes Res Clin Pract 2009; 83:66–7.*
56. *Madsen KR: Fatal hypertriglyceridaemia, acute pancreatitis and diabetic ketoacidosis possibly induced by quetiapine. Br Med J Case Rep 2014. pii: bcr2013202039. DOI:10.1136/bcr-2013-202039*
57. *Macfarlane D & Fisher M: A combination of atypical antipsychotics and diabetic ketoacidosis. Pract Diabetes Care 2006; 23:205–6.*
58. *Marlowe KF, Howard D, Chung A: New onset diabetes with ketoacidosis attributed to quetiapine. South Med J 2007; 100:829–31.*
59. *Maule S, Giannella R, Lanzio M, Villari V: Diabetic ketoacidosis with clozapine treatment. Diabetes Nutr Metab 1999; 12:187-8.*

60. *Medved V, Rojnic Kuzman M, Jovanovic N, Grubisin J, Kuzman T: Metabolic syndrome in female patients with schizophrenia treated with second generation antipsychotics: a 3-month follow-up. J Psychopharmacol 2008; 23:915-22.*
61. *Melkersson K, Jansson E: The atypical antipsychotics quetiapine, risperidone and ziprasidone do not increase insulin release in vitro. Neuroendocrinol Lett 2005; 26:205-8.*
62. *Meyer PS, Bond GR, Tunis SL, McCoy ML: Comparison between the effects of atypical and traditional antipsychotics on work status for clients in a psychiatric rehabilitation program. J Clin Psychiatry 2002; 63:108-16.*
63. *Meyer JM, Davis VG, Goff DC, McEvoy JP, Nasrallah HA, Davis SM et al.: Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. Schizophr Res 2008; 101:273-86.*
64. *Meyer JM, Lekband SG, Loh CC, Moutier CY: Quetiapine-induced diabetes with metabolic acidosis. Int Clin Psychopharmacol 2004; 19:169 –71.*
65. *Mithat B, Alpaslan T, Bulent C, Cengiz T: Risperidone-associated transient diabetic ketoacidosis and diabetes mellitus type 1 in a patient treated with valproate and lithium. Pharmacopsychiatry 2005; 38:105–6.*
66. *Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M: Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders: a systematic review and meta-analysis. Schizophr Bull 2013; 39:306-18.*
67. *Mohan D, Gordon H, Hindley N, Barker A: Schizophrenia and diabetes mellitus. Br J Psychiatry J Ment Sci 1999, 174:180–1.*
68. *Muench J & Carey M: Diabetes mellitus associated with atypical antipsychotic medications: new case report and review of the literature. J Am Board Fam Pract 2001; 14:278–82.*
69. *Nasrallah HA: Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. Mol Psychiatr 2008; 13:27–35.*
70. *Niazy M, Neyyarapally T, Baidas G: Severe diabetic ketoacidosis precipitated by an atypical antipsychotic drug. Kuwait Med J 2009; 41:240–2.*
71. *Nicolai J, Smith SJ, Keunen RW: Simultaneous side effects of both clozapine and valproate. Intensive Care Med 2001; 27:943.*
72. *Olfson M, Marcus SC, Corey-Lisle P, Tuomari AV, Hines P, L'Italien GJ: Hyperlipidemia following treatment with antipsychotic medications. Am J Psychiatry 2006; 163:1821-25.*
73. *Peterson GA & Byrd SL: Diabetic ketoacidosis from clozapine and lithium cotreatment. Am J Psychiatry 1996; 153:737–8.*
74. *Pierides M: Clozapine monotherapy and ketoacidosis. Br J Psychiatry J Ment Sci 1997; 171:90–1.*
75. *Pillai L, Husainy SM, Ramchandani K: Diabetic ketoacidosis associated with atypical antipsychotic drug, clozapine treatment: Report of a case and review of literature. Indian J Crit Care Med 2006; 10:193–6.*
76. *Popli AP, Konicki PE, Jurjus GJ: Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997; 58:108-11.*
77. *Ragucci KR & Wells BJ: Olanzapine-induced diabetic ketoacidosis. Ann Pharmacother 2001; 35:1556–58.*
78. *Ramaswamy K, Masand PS, Nasrallah HA: Do certain atypical antipsychotics increase the risk of diabetes? A Critical review of 17 pharmacoepidemiologic studies. Ann Clin Psychiatry 2006; 18:183-94.*
79. *Rashid J, Starer PJ, Javaid S: Pancreatitis and diabetic ketoacidosis with quetiapine use. Psychiatry (Edgmont) 2009; 6:34–7.*
80. *Reddymasu S, Bahta E, Levine S, Manas K, Slay LE: Elevated lipase and diabetic ketoacidosis associated with aripiprazole. JOP 2006; 7:303–5.*
81. *Reis JS, Alvarenga T, Rosario PW, Menezes PA, Rocha RS, Purisch S: Diabetes mellitus associated with atypical antipsychotic medications: case report and review of the literature. Arq Bras Endocrinol Metabol 2007; 51:488–93.*
82. *Rigalleau V, Gatta B, Bonnaud S, Masson M, Bourgeois ML, Vergnot V et al.: Diabetes as a result of atypical antipsychotic drugs - a report of three cases. Diabet Med 2000; 17:484–6.*
83. *Roth BL, Sheffler DJ, Kroeze WK: Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. Nat Rev Drug Discov 2004; 3:353–359.*
84. *Sa YK, Yang H, Jung HK, Son JW, Lee SS, Kim SR et al.: Olanzapine induced diabetic ketoacidosis and neuroleptic malignant syndrome with rhabdomyolysis: A case report. Endocrinol Metab (Seoul) 2013; 28:70-5.*
85. *Saeverud HA & Gerlyng P: From prison with coma. Tidsskrift for den Norske legeforening 2010; 130:284–5.*
86. *Sato Y, Yasui-Furukori N, Kaneko S, Moriyama T: New-onset diabetic ketoacidosis in a schizophrenic patient with multiple, autoimmune disease during treatment with risperidone. Prog Neuro-Psychopharmacol Biol Psychiatry 2008; 32:577–8.*
87. *Schwenkreis P & Assion HJ: Atypical antipsychotics and diabetes mellitus. World J Biol Psychiatry 2004; 5:73-82.*
88. *Selva KA & Scott SM: Diabetic ketoacidosis associated with olanzapine in an adolescent patient. J Pediatr 2001; 138:936–8.*
89. *Smith GC, Chaussade C, Vickers M, Jensen J, Shepherd PR: Atypical antipsychotic drugs induce derangements in glucose homeostasis by acutely increasing glucagon secretion and hepatic glucose output in the rat. Diabetologia 2008; 51:2309–17.*
90. *Smith H, Kenney-Herbert J, Knowles L: Clozapine-induced diabetic ketoacidosis. Aust NZ J Psychiatry 1999; 33:120–121.*
91. *Smith RC, Lindenmayer JP, Bark N, Warner-Cohen J, Vaidhyanathaswamy S, Khandat A: Clozapine, risperidone, olanzapine, and conventional antipsychotic drug effects on glucose, lipids, and leptin in schizophrenia patients. Int J Neuropsychopharmacol 2005; 8:183-94.*
92. *Sobel M, Jaggers ED, Franz MA: New-onset diabetes mellitus associated with the initiation of quetiapine. J Clin Psychiatry 1999; 60:556–7.*
93. *Starrenburg FC & Bogers JP: How can antipsychotics cause diabetes mellitus? Insights based on receptor-binding profiles humoral factors and transporter proteins. Eur Psychiatry 2009; 24:164–170.*
94. *Subramaniam M, Chong S-A, Pek E: Diabetes mellitus and impaired glucose tolerance in patients with schizophrenia. Canadian Journal of Psychiatry 2003; 48:345-7.*
95. *Takahashi M, Ohishi S, Katsumi C, Moriya T, Miyaoka H: Rapid onset of quetiapine-induced diabetic ketoacidosis in an elderly patient: a case report. Pharmacopsychiatry 2005; 38:183–4.*

96. Taslipinar A, Yazici M, Kebapcilar L, Gök DE, Fiahin M, Yetkin S: A Case of Diabetic Ketoacidosis Associated with Risperidone Treatment. Turk Jem 2008; 12:97-8.
97. Tavakoli SA & Arguisola MS: Diabetic ketoacidosis in a patient treated with olanzapine, valproic acid, and venlafaxine. South Med J 2003; 96:729–30.
98. Teff KL, Rickels MR, Grudziak J, Fuller C, Nguyen H, Rickels K: Antipsychotic-Induced Insulin Resistance and Postprandial Hormonal Dysregulation Independent of Weight Gain or Psychiatric Disease. Diabetes 2013; 62:3232–40.
99. Thonnard-Neumann E: Phenothiazines and diabetes in hospitalized women. Am J Psychiatry 1968; 124:978-82.
100. Torrey EF & Swalwell CI: Fatal olanzapine-induced ketoacidosis. Am J Psychiatry 2003; 160:2241.
101. Tsolaki M, Symeonides G, Kazis A: Olanzapine induced diabetic ketoacidosis. Psychiatriki 2001; 13:222–7.
102. Tsuchiyama N, Ando H, Ota T, Sakurai M, Takamura T: Modulating effects of olanzapine on the development of diabetic ketoacidosis. Diabet Med 2004; 21:300–1.
103. Von Hayek D, Hüttl V, Reiss J, Schweiger HD, Füessl HS: Hyperglycemia and ketoacidosis associated with olanzapine. Nervenarzt 1999; 70:836-7.
104. Waldman JC & Yaren S: Atypical antipsychotics and glycemia: a case report. Can J Psychiatry 2002; 47:686–7.
105. Watkins J, Ray S, Finch C: Aripiprazole-Induced Diabetic Ketoacidosis: Remaining Vigilant. Hospital Pharmacy 2011; 46:432-35.
106. Whiteman EL, Cho H, Birnbaum MJ: Role of Akt/protein kinase B in metabolism. Trends Endocrinol Metab 2002; 13: 444-51.
107. Wilson DR, D'Souza L, Sarkar N, Newton M, Hammond C: New-onset diabetes and ketoacidosis with atypical antipsychotics. Schizophr Res 2003; 59:1–6.
108. Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC: Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998; 44:778–83.
109. Wirshing DA, Pierre JM, Eyeler J, Weinbach J, Wirshing WC: Risperidone-associated new-onset diabetes. Biol Psychiatry 2001; 50:148−9.
110. Yood M, Delorenze G, Quesenberry CP, Oliveria S, Tsai A, Willey V et al.: The incidence of diabetes in atypical antipsychotic users differs according to agent – results from a multisite epidemiologic study. Pharmacoepidemi Pharmacoepidemiol Drug Saf 2009; 18:791–99.

Correspondence:
Ass. Prof. Martina Rojnic Kuzman, MD, PhD
Department of Psychiatry, Zagreb University Hospital Centre
Kispaticeva 12, 10000 Zagreb, Croatia
E-mail: mrojnic@gmail.com