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REVIEW

Atypical antipsychotics and diabetic ketoacidosis: a review

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Abstract
Rationale Atypical antipsychotics have been linked to weight gain and type 2 diabetes, but are also associated with diabetic ketoacidosis (DKA), which can occur more acutely and in the absence of weight gain.
Objectives Our aim was to review current case reports of DKA in the context of atypical antipsychotic treatment to better understand (a) the scope of the problem, (b) its relationship to different atypical agents, (c) risk factors, (d) long-term outcome, and (e) putative mechanisms of action.
Method Searches in PubMed/Medline, as well as the University of Toronto's Scholar Portal, were performed for all relevant articles/abstracts in English.
Results Sixty reports, yielding 69 cases, affirm that DKA is a rare but serious risk with almost all atypical antipsychotics; however, liability seems to vary between agents, at least partially mirroring risk of weight gain. Mean age of onset was 36.9 years (range 12–80), with 68 % of cases occurring in males, and 41 % in individuals of African American or African Caribbean descent. Over one third of cases present with either no weight gain or weight loss, and 61 % of these require ongoing treatment for glycemic control. Death occurred in 7.25 % of cases.
Conclusion While the underlying mechanisms are not well understood, antipsychotic-related DKA can occur soon after treatment onset and in the absence of weight gain. Although rare, clinicians must remain vigilant given its acute onset and potential lethality.

Keywords Schizophrenia · Diabetes · Side effects · Metabolic syndrome · Antipsychotics · Diabetic ketoacidosis

Introduction

Atypical antipsychotics, with clozapine as the prototype, now represent the treatment of choice in psychotic conditions such as schizophrenia (Hollingworth et al. 2010; Monshat et al. 2010; Shah et al. 2011). While their benefits have been challenged more recently (Geddes et al. 2000; Lieberman et al. 2005), early evidence of clinical superiority, in combination with reports of improved tolerability (Leucht et al. 2009a, b), led these newer agents to rapidly supplant their conventional counterparts in clinical use. Clozapine specifically garners a unique position in treatment algorithms, as it stands alone as the antipsychotic of choice in refractory schizophrenia (Moore et al. 2007; NICE 2009).

The newer antipsychotics are not without side effects, however, and it has been weight gain and related metabolic sequelae that have garnered the greatest attention and concern. The different atypical agents vary in their propensity to cause weight gain, with clozapine and olanzapine conferring the greatest risk (Allison et al. 1999a; Newcomer 2005). Similarly, awareness of the relative diabetogenic effect of the first four atypical antipsychotic compounds (clozapine, risperidone, olanzapine, and quetiapine) is credited to several landmark studies by Koller and colleagues, in which they analyzed data from the U.S. Food and Drug Association's

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(FDA) MedWatch surveillance program (Koller et al. 2001, 2003, 2004; Koller and Doraiswamy 2002). The liability for weight gain and related metabolic sequelae is now identified as a class effect and related warnings are now embedded in product monographs (Canadian Diabetes Association 2008). The risk and magnitude of weight gain associated with these drugs has, in turn, provided a strong rationale for the increased risk of type 2 diabetes, dyslipidemia, and metabolic syndrome also associated with the use of these medications (Newcomer 2005).

Reports of diabetic ketoacidosis (DKA), albeit uncommon (Leslie and Rosenheck 2004), argue against the position that glucose dysregulation associated with atypical antipsychotic use is related to weight gain alone. While excessive adiposity represents a significant risk factor for type 2 diabetes (Allison and Casey 2001), this is not the case with DKA, as it is most commonly linked to type 1 diabetes and/or physical illness (English and Williams 2004; Kitabchi et al. 2009; Trachtenbarg 2005). That it has been noted in conjunction with atypical antipsychotic use has important implications, both clinically and mechanistically. For example, DKA has been reported soon after the initiation of atypical antipsychotic treatment and in individuals who experience no significant changes in weight (Jin et al. 2002); these cases emphasize that weight gain cannot be used as the sole proxy for concerns regarding possible glucose abnormalities. The occurrence of DKA also raises questions from a mechanistic standpoint; it remains unclear whether these agents impact insulin and glucose metabolism via a single or two distinct mechanisms (i.e., one through antipsychotic-induced weight gain and one that is independent and more acute in nature).

Despite its high risk of mortality (English and Williams 2004), very little attention has been given to DKA in the context of atypical antipsychotic use. A previous review examining new onset diabetes associated with atypical antipsychotic use included 35 cases involving DKA; however, the time range spanned only 1966–2001 (Cohen 2004).

The present investigation represents an update specific to DKA with the aims of (a) providing a summary that could shed light on the current scope of the problem, (b) better understanding its presentation in the context of existing antipsychotic treatments, (c) examining the possible role of established risk factors (e.g., infection), (d) reviewing outcomes, and (e) commenting on mechanisms of action.

Materials and methods

This review focused on reports of DKA in association with the atypical antipsychotics available for use in North America at the time the review was initiated, namely aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. A Medline search was conducted via PubMed (http://www.ncbi.nlm.nih.gov/PubMed) using the following: "neuroleptic" or "antipsychotic" in combination with "ketoacidosis"; individual antipsychotic names (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) were also cross-referenced with "ketoacidosis." The same search terms were used in the University of Toronto's Scholar's Portal search engine in order to capture any missed reports (see Fig. 1). All relevant cases, where an abstract and/or text were available in English, until March of 2011 were analyzed.

Results

The search yielded 60 reports, with a total of 69 cases, and demographic details for each are detailed in Table 1.

Incidence/prevalence

This represents an important statistic for clinicians, although not one that is readily calculated by the present figure, as reports are not confined to a single region or country where estimates can be established based on data capturing antipsychotic use. Clearly, DKA is rare given the widespread use of antipsychotics; however, this is likely to be influenced by underreporting in the literature and to voluntary adverse event programs such as FDA's Medwatch. Calculations specific to schizophrenia over a 7-year interval indicate the following risk: 0.2 % (risperidone), 0.8 % (olanzapine), and 2.2 % (clozapine) (Henderson et al. 2007). That said, the incidence of diabetes presenting as DKA in schizophrenia has been calculated as 14.93 per 10,000 patient years, 10-fold higher than the calculated risk of 1.4 per 10,000 years in the general population (Henderson et al. 2007). In a 1-year follow-up of 56,849 patients with schizophrenia receiving antipsychotic monotherapy and without a history of diabetes, 0.2 % were hospitalized with DKA (Leslie and Rosenheck 2004). In individuals on atypical antipsychotics where diabetes is identified, the development of DKA is not uncommon; one study reported DKA developing in 5 of 11 such individuals (Wilson et al. 2003). This would suggest that liability for DKA may be increased in individuals with established type 2 diabetes although larger, prospective studies are required to establish this. Diagnosis was schizophrenia or schizoaffective disorder in approximately 70 % of the reported cases here.

Antipsychotic, dose, and duration

Notably, the greatest number of DKA cases has been reported with the two antipsychotics also associated with the highest liability for weight gain (i.e., clozapine, olanzapine) (see Table 2). It must be taken into consideration that we do not know the actual proportion of use of each antipsychotic; that

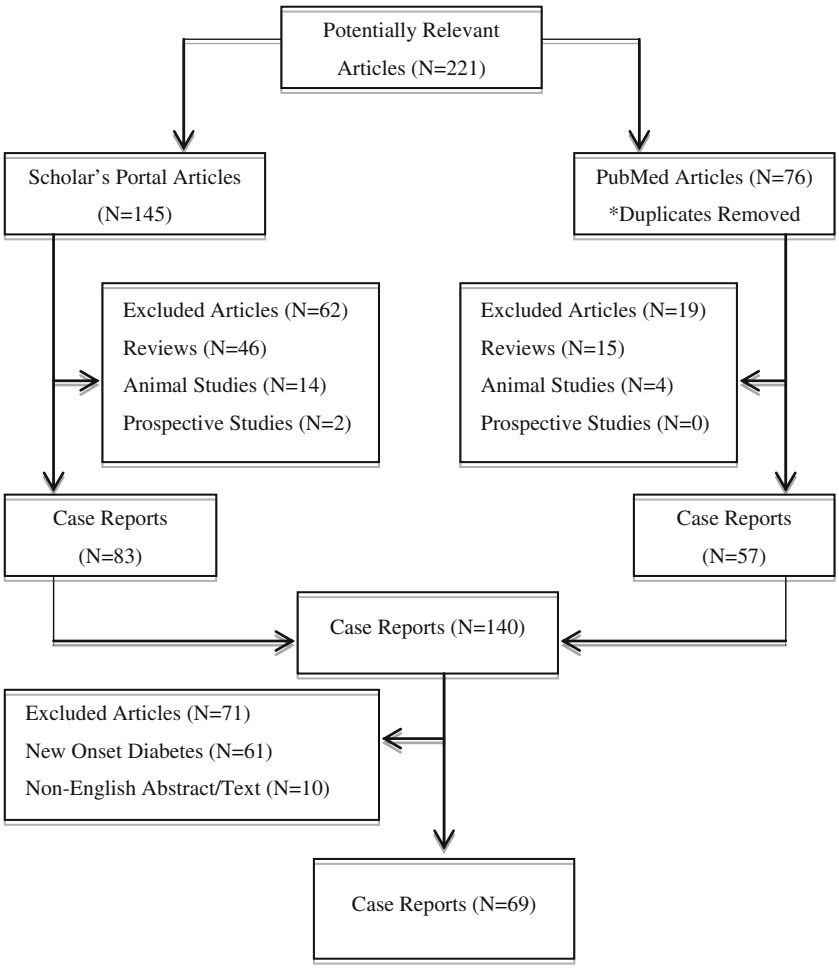

Fig. 1 Breakdown of literature search to capture cases of DKA with AAP treatment

said, it warrants comment that the number reported with clozapine is so high, despite evidence that it is used in a relatively small percent of patients (Agid et al. 2010; Conley and Kelly 2001; Kane 2011). Only one atypical agent, ziprasidone, had no associated reports of DKA, although there is one confirmed case involving severe hyperglycemia with this compound (Yang and McNeely 2002). Ziprasidone is an atypical antipsychotic that is considered more "weight neutral"; however, this is also true for aripiprazole (Baptista et al. 2008), although it has been linked to six cases of DKA. The mean dose for each of the antipsychotics did not exceed recommended therapeutic ranges, with the exception of aripiprazole in one case. The mean duration of antipsychotic treatment prior to DKA, where clearly established (N=65), was just over 9 months (range 4 days–4 years).

Age, gender, and ethno-cultural background

The calculated average age at time of DKA was 37.5 years (range 12–80), and the largest percentage of cases occurred in people aged 30–39 (Table 2). Approximately 70 % of cases were in the age range 30–49, while a further 20 % of cases occurred in individuals under the age of 29. The preponderance of cases were male (47/69, 68.1 %) (Table 2), and where reported (N=56), 41 % of individuals were of African American or African Caribbean descent, with a further 30 % occurring in Caucasians.

Other factors

In 39.0 % of cases where information was provided (16/41), antipsychotic use was associated with either no weight gain or weight loss. Despite infection being the most common precipitating cause for DKA, occurring in 30–50 % of cases (Umpierrez and Kitabchi 2003), it was identified in only two of the cases reported here.

Outcome

DKA is a serious medical emergency requiring immediate medical attention, which may include intravenous insulin therapy and various measures to restore electrolyte balance (Trachtenbarg 2005). Of note, effective treatment of acute DKA does not always equate with resolution of the underlying metabolic disturbance (see Table 3). A total of 50 cases provided follow-up in individuals where no personal

Table 1 Case reports (with demographic and clinical details) of DKA with AAP use

Report	Sex	Age	Ethnicity	Dx	AAP	Dose (mg)	Drug naive?	OV/OB?	Wt Change?	Hx HyGl?	FHx DM?	Tx time	PolyTx?	AP cont'd?	New AP?	DM Tx
Church et al. (2005)	F	34	AA	S	A	30	N	N/S	N/S	Y	N/S	4 days	Y	N	N	INS
Reddymasu et al. (2006)	M	33	AA	S	A	N/S	N/S	Y	INC	N	N	18 months	N/S	N	Y	INS
Dhamija and Verma (2008)	M	12	C	O	A	N/S	N/S	N/S	INC	N	N/S	6 months	Y	N	N	None
Makhzoumi et al. (2008)	M	44	AA	SD	A	15, 30	N	Y	DEC	N	N	17 days	Y	N	Y	INS, OHA
Babu et al. (2005)	F	15	N/S	BD	A	N/S	Y	N/S	N/S	N/S	N/S	4 months	Y	N	N	INS
Kibbey et al. (2010)	M	29	Filipino	S	A	40	N/S	N/S	INC	N/S	N	12 months	N	Y	N	INS
Wilson et al. (2003)	M	33	AA	SD	C	550	N	N/S	INC	N	N	1 month	Y	Y	N	INS
Lafayette et al. (2003)	F	22	Hispanic/Italian	S	C	150	N	Y	DEC	Y	Y	10 weeks	Y	N	N	Diet
Cho and Lindenmayer (2009)	F	45	AA	S	C	N/S	N	Y	N/S	N	N/S	2 months	Y	N	Y	N/S
Reis et al. (2007)	M	28	Hispanic	S	C	150	N/S	N	DEC	N/S	N	1 month	Y	N	N/S	Diet
Kristensen and Porksen (2003)	F	54	C	S	C	N/S	N/S	N/S	N/S	N/S	N/S	N/A	N/S	N/S	N/S	N/S
Koval et al. (1994)	F	34	AA	S	C	250	Y	N/S	N/S	N	Y	6 weeks	Y	N	Y	None
Kostakoglu et al. (1996)	M	42	N/S	O	C	350	N	Y	N/S	N	Y	4–5 weeks	N/S	N	Y	Diet
Peterson and Byrd (1996)	M	46	AA	S	C	500	N	N/S	N/S	N	Y	5 weeks	Y	N	N/S	INS
Pierides (1997)	M	50	N/S	S	C	300	N	N/S	N/S	N	N/S	6 days	N	N	N/S	N/S
Ai et al. (1998)	M	30	AC	S	C	300	N	N/S	N/S	N	N	5 months	Y	N	Y	OHA
Wirshing et al. (1998)	M	32	AA	SD	C	400	N/S	N	INC	N	N	18 months	N/S	Y	N	OHA
Colli et al. (1999)	M	31	C	SD	C	200	N	Y	INC	N	N	3 months	N	N	Y	None
Mohan et al. (1999)	M	30	AA	S	C	325	N	N/S	N/S	N	N	3 months	N/S	N	Y	OHA
Smith et al. (1999)	M	40	AC	S	C	N/S	N	Y	N/S	N	N	16 days	N/S	N/S	N/S	INS
Avram et al. (2001)	M	33	C	S	C	100	N	Y	INC/DEC	N	N	8 months	Y	N	N/S	None
Nicolai et al. (2001)	M	33	Indian	S	C	450	Y	N/S	N/S	N/S	N/S	4 years	Y	N	Y	None
Rigalleau et al. (2000)	M	38	C	S	C	N/S	N/S	Y	DEC	N/S	N	6 months	N/S	N	N/S	None
Maule et al. (1999)	F	50	C	N/S	C	400	N/S	N/S	N/S	N	N	1 month	N/S	Y	N	None
Wilson et al. (2003)	M	48	AA	O	OL	30	N	N/S	INC	N	N	10 months	N	Y	N	INS
Wilson et al. (2003)	F	38	AA	S	OL	15	N	N/S	INC	N	N	2 months	N	N/S	N	Diet
Torrey and Swalwell (2003)	M	45	AA	BD	OL	30	N	Y	N/S	N	N/S	1 month	Y	Death	Death	Death
Tavakoli and Arguisola (2003)	M	35	C	BD	OL	5	N	Y	INC	N	Y	18 months	Y	N	N/S	INS
Howes and Rifkin (2004)	F	41	N/S	SD	OL	20	N	Y	INC	N	Y	3.5 months	Y	Y	N	INS
Avella et al. (2004)	F	37	AA	BD	OL	15	N/S	N/S	N/S	N	N/S	3 years	Y	Death	Death	Death
Avella et al. (2004)	M	27	N/S	BD	OL	N/S	N/S	N/S	N/S	N	N/S	N/S	Y	Death	Death	Death
Avella et al. (2004)	M	34	N/S	S	OL	N/S	N/S	N/S	N/S	N	N/S	4–5 months	N	Death	Death	Death
Tsuchiyama et al. (2004)	M	28	Japanese	S	OL	10	N	Y	DEC	N/S	Y	1 month	N/S	N	N	None
Kyriazis et al. (2006)	M	33	C	O	OL	20	Y	Y	N/S	N	Y	4 months	N	N	Y	Diet
Kahn and Bourgeois (2007)	M	29	AA	S	OL	30	Y	N/S	N/S	N	Y	5 years	Y	N	Y	None
Varma et al. (2007)	F	34	N/S	BD	OL	10	Y	Y	N/S	N	N	6 weeks	N/S	N	Y	INS
Wong et al. (2007)	M	22	Chinese	S	OL	10	N	N	INC/DEC	N	N	39 months	Y	N	Y	INS
Niazy et al. (2009)	M	28	Kuwaiti	S	OL	N/S	N	N/S	N/S	N	N	18 months	N/S	N	Y	None

Table 1 (continued)

Report	Sex	Age	Ethnicity	Dx	AAP	Dose (mg)	Drug naive?	OV/OB?	Wt Change?	Hx HyGl?	FHx DM?	Tx time	PolyTx?	AP cont'd?	New AP?	DM Tx
Waldman and Yaren (2002)	M	33	Aboriginal	S	OL	30	N	N	INC	N	N/S	3 months	N	N	Y	OHA
Tsolaki et al. (2001)	F	80	Greek	O	OL	N/S	Y	N	N	N	N	10 months	Y	N	N	None
Saeverud and Gerlyng (2010)	M	42	N/S	N/S	OL	N/S	N/S	N/S	N/S	N/S	N/S	6 months	N/S	N	N/S	None
Fulbright and Breedlove (2006)	M	42	AA	S	OL	40	N	Y	DEC	N	N/S	40 days	Y	N	Y	None
Rigalleau et al. (2000)	M	41	C	O	OL	N/S	N/S	Y	DEC	N/S	N	3 months	N/S	N	N/S	None
Gatta et al. (1999)	M	31	C	S	OL	10	N	Y	DEC	N	N	3 months	Y	N	N	Diet
Goldstein et al. (1999)	F	42	C	SD	OL	10	N	N	INC	N	Y	6 months	N/S	N	Y	INS
Goldstein et al. (1999)	F	40	C	S	OL	10	N	Y	INC	N	N	17 months	Y	N	Y	None
Lindenmayer and Patel (1999)	M	50	AA	S	OL	30	N	Y	INC/DEC	N	N	8 months	Y	N	N/S	None
Muench and Carey (2001)	M	38	C	S	OL	20	N	Y	INC	Y	Y	12 months	Y	Y	N	INS
Ragucci and Wells (2001)	F	46	AA	BD	OL	15	N	Y	INC	N	Y	14 months	Y	N	Y	INS, OHA
Seaburg et al. (2001)	M	27	AA	S	OL	10	N	N/S	DEC	N	N/S	29 months	Y	Y	N	OHA
Selva and Scott (2001)	F	16	Hispanic	O	OL	10/15	N	N/S	INC	N	Y	6+ months	Y	N	N	None
Johnson et al. (2002)	M	49	C	S	OL	20	N	Y	INC	N	N	11 months	N/S	Y	N	None
Straker et al. (2002)	F	44	AA	S	OL	25	N	N/S	INC	N	N	7 weeks	Y	N	Y	Diet
Wilson et al. (2003)	M	64	C	S	Q	400	N	Y	INC	N/S	Y	2 months	N	N/S	N/S	N/S
Dibben et al. (2005)	F	51	C	S	Q	400	N	Y	N	N	N	2 years	Y	N	N	None
Macfarlane and Fisher (2006)	M	33	N/S	S	Q	600	N	N/S	DEC	N	N	4 weeks	Y	Y	N	INS
Marlowe et al. (2007)	M	45	N/S	S	Q	800	Y	Y	N	N/S	N/S	5 months	Y	N	N	None
Sirois (2008)	F	41	AA	O	Q	400	N	Y	N/S	N	N	37 days	Y	N/S	N/S	N/S
Rashid et al. (2009)	F	30	Bengali	S	Q	200	N	Y	N	N	N	2 months	Y	N	Y	None
Takahashi et al. (2005)	M	72	Asian	O	Q	50	Y	N	N/S	N	N	14 days	Y	N	Y	None
Wilson et al. (2003)	F	26	AA	SD	R	3	N	Y	INC	N	N	7 weeks	Y	N	N	Diet
Dibben et al. (2005)	M	33	Chinese	S	R	Depot	N/S	Y	N	N	N/S	8 months	N/S	N	N	None
Mithat et al. (2005)	M	37	N/S	BD	R	2–4	Y	Y	INC	N	N	6 months	Y	N	N	None
Hamanaka and Kamijo (2007)	M	32	Japanese	S	R	2–4	N/S	N/S	INC	N	Y	3 years	Y	Y	N	Diet
Sato et al. (2008)	F	46	Japanese	S	R	3	N	N	N	N	Y	4 months	N	N	Y	INS
Lu and Yan (2009)	M	27	N/S	S	R	N/S	N/S	N/S	N/S	N	N/S	2 months	N/S	Death	Death	Death
Chellamuth et al. (2010)	M	42	South East Asian	S	R	N/S	N/S	N/S	N/S	N	N	N/S	N/S	N	Y	INS
Croarkin et al. (2000)	M	42	C	O	R	4	N/S	N/S	N/S	N/S	N	N/S	Y	N	Y	INS
Ananth et al. (2004a)	M	46	N/S	BD	R	3	N/S	N/S	N/S	N/S	N	2 years	Y	N	N	None

Sex: *M* male, *F* female; ethnicity: *AA* African American, *AC* Afro-Caribbean, *C* Caucasian, *N/S* not specified; diagnosis (*Dx*): *BD* bipolar disorder, *S* schizophrenia, *SD* schizoaffective disorder, *O* other; atypical antipsychotic (*AAP*): *A* aripiprazole, *C* clozapine, *OL* olanzapine, *Q* quetiapine, *R* risperidone; drug naïve: *N* no, *Y* yes, *OV/OB* overweight or obese, *Wt change* change in weight while on antipsychotic, *Hx HyGl* history of hyperglycemia prior to taking antipsychotic, *Tx time* treatment time with antipsychotic before onset of DKA, *PolyTx* polypharmacy at time of DKA, *DM Tx* ongoing treatment (if any) for persistent diabetic symptoms, *INS* insulin, *OHA* oral hypoglycemic agent, *None* no treatment required

Table 2 Demographic data of DKA with AAP treatment, sorted by AAP

AAP	*N* (DKA)	*N* (schizophrenia)	M:F	Age (average, years)	Time to DKA (average, months)	Dose range (milligrams)	Age range (years)	*N* (all AAPs)	% (all AAPs)
Aripiprazole	6	3	4:2	27.8	6.8	15–40	Under 20	3	4.3
Clozapine	18	13	13:5	36.5	6.1	100–550	20–29	11	15.9
Olanzapine	29	15	19:10	37.8	11.8	5–40	30–39	25	36.2
Quetiapine	7	5	4:3	48.0	5.1	50–800	40–49	22	31.9
Risperidone	9	5	7:2	36.8	11.8	2–4	Over 50	8	11.6

history of glucose dysregulation was recorded prior to the onset of DKA (i.e., no history of diabetes). After acute treatment of DKA, 18 patients (36 %) had complete resolution of symptoms, no longer requiring treatment; seven (14 %) controlled their persistent diabetes with diet; and the remainder (approximately 50 %) relied on insulin, oral hypoglycemic agents, or both. Only nine of the subgroup (18 %) were continued on the antipsychotic administered in association with the DKA. Of these individuals, six (66.7 %) required ongoing pharmacological treatment, two (22.2 %) with an oral hyperglycemic agent, and four (44.4 %) with insulin therapy. Five deaths (7.25 % of all reported cases) underscore the life-threatening potential of DKA.

Discussion

The relationship between atypical antipsychotics, weight gain, and metabolic disturbances has received a great deal of focus in the last decade (Allison et al. 1999b; Allison and Casey 2001; Baptista et al. 2004, 2008; Henderson 2008; Newcomer 2005; Newcomer and Haupt 2006), understandable given that weight gain with a drug like olanzapine is as high as 30 kg over a 1-year period (Zipursky et al. 2005) and the prevalence of type 2 diabetes in schizophrenia is twofold greater than in the general population (Dixon et al. 2000; Zipursky et al. 2005). Although altering actual practice patterns (i.e., regular metabolic monitoring) has proven a challenge (Barnes et al. 2007; Haupt et al. 2009), it remains that numerous guidelines are in place to assist clinicians in monitoring patients on these medications (American Diabetes Association 2004; Canadian Diabetes Association 2008; Marder et al. 2004). Unfortunately, the presence of such guidelines has not necessarily translated to widespread implementation, as reflected in a large meta-analysis using pooled data from five countries to examine monitoring before (n=218,940 patients) and after (n=71,594) guideline implementation (Mitchell et al. 2012). Before guidelines, metabolic monitoring was suboptimal (i.e., one third of patients untested) for all parameters in the baseline phase (Mitchell et al. 2012), while a significant but modest change was noted in only one parameter, glucose testing. There were improvements in several other measures (e.g., weight, blood pressure, lipids), although these were not statistically significant, and monitoring remained suboptimal in all measures with the exception of weight.

In contrast, considerably less attention has been given to DKA, although this is not surprising; even assuming underreporting, the risk of DKA is quite rare (Leslie and Rosenheck 2004). However, its acuity and potential lethality argue for clinician awareness, as well as vigilance regarding its possible occurrence.

Clinical implications

For psychiatrists, what is paramount is the early identification of DKA to ensure appropriate treatment is initiated as quickly as possible. First and foremost in this process is recognizing that DKA can occur at any time following the onset of antipsychotic treatment and independent of weight gain. To

Table 3 Post-DKA treatment, for both diabetic and psychotic symptoms, sorted by AAP

Long-term antipsychotic treatment and glycemic status not reported in all cases. Values represent the number of cases where relevant data were provided

Outcome/drug	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone
DKA associated drug cont'd	1	3	5	1	1
OHA/insulin req'd long term	1/1	2/3	4/5	1/1	0/1
Drug discont'd w/o new compound	3	6	8	2	4
OHA/insulin req'd long term	2/3	1/5	1/8	0/2	0/4
Switch to new antipsychotic	2	7	11	2	3
OHA/insulin req'd long term	2/2	1/6	5/11	0/2	3/3
Fatalities	None	None	4	None	1

this point, in a review of 45 cases of new-onset diabetes and DKA following initiation of atypical antipsychotics, 42 % presented as DKA (Jin et al. 2002). Of the reported cases here with the necessary information, over one third recorded no weight gain or even weight loss prior to the occurrence of DKA. At the same time, weight gain over the course of treatment and the resulting metabolic consequences cannot be ignored as significant risk factors, reflected in the increased liability of DKA with an agent like olanzapine versus risperidone. For example, the adjusted risk of DKA for olanzapine, compared to risperidone, has been calculated to increase from 1.7 following >30 days of treatment to 3.5 after >180 days of treatment (Ramaswamy et al. 2007). Based on current case reports, it appears that all atypical antipsychotics are at risk of causing DKA, with the caveat that to date there have been no published cases involving ziprasidone, although there is a report of severe hyperglycemia (Yang and McNeely 2002). Albeit rare, clinicians should also be aware that DKA has also been reported with conventional antipsychotics and other psychotropic compounds such as lithium (de Boer and Gaete 1992; Kondziela et al. 1985; Laghate and Gupta 2004).

There has been one report assessing the risk factors of DKA versus type 2 diabetes in the context of atypical antipsychotic administration (Jin et al. 2002). A total of seven demographic variables were examined: gender, race, adjunctive medications, overweight at baseline, weight gain, family history of diabetes, age, and weeks on atypical antipsychotic. The DKA group was significantly different on three of these measures: higher proportion of females (26.3 vs. 3.8 %), lower proportion of overweight at baseline (58.3 vs. 100 %), and younger (37 vs. 43 years of age).

Although DKA is generally associated with type 1 diabetes, it can also occur in the type 2 form of the disease (English and Williams 2004; Kitabchi et al. 2009; Trachtenbarg 2005), which is more prevalent in African Americans (Watson 2008). In line with this, our data, and that of a previously published report (Jin et al. 2002), indicate that 40–50 % of reported DKA cases occur in this ethno-cultural group. A further study identified four of five individuals (80 %) with DKA related to atypical antipsychotics as African American (Wilson et al. 2003).

While DKA has been reported to occur twice as frequently in females in the general population (Krentz and Nattrass 2003), evidence related to atypical antipsychotics indicates that males constitute over two thirds of the sample; this too was noted in an earlier report (Jin et al. 2002). Along similar lines, infection is known as the most common cause of DKA in the general population (English and Williams 2004), but this has not been observed with DKA linked to atypical antipsychotics, both in the present sample and elsewhere (Jin et al. 2002).

As noted, evidence indicates that a number of individuals will initially present with DKA, and in the cases gathered here, five (7.25 %) were fatal, higher than the overall mortality rate of <5 % that has been reported in the general population (Umpierrez and Kitabchi 2003). For those who survive, DKA does not represent a temporary and time-limited medical emergency; in those cases gathered here with the information available, over 60 % continued treatment with an oral hyperglycemic agent and/or insulin, irrespective of their glycemic status before the onset of DKA.

Table 4 details the signs and symptoms of DKA. Depending on the context in which DKA develops, psychiatrists may or may not be directly involved in its treatment; however, the reader is referred to several reviews regarding current treatment recommendations (English and Williams 2004; Kitabchi et al. 2009; Trachtenbarg 2005).

Mechanisms of action

Much of the work to date has focused on the weight gain issue, premised on the notion that the metabolic side effects of atypical antipsychotics are secondary to this. There are notable differences in the propensity for weight gain among the atypical antipsychotics, with clozapine and olanzapine carrying the highest risk (Allison et al. 1999b; Newcomer 2005). The precise underlying mechanisms remain elusive; however, various factors including genetics, appetite, food choice, activity level, metabolism, and environmental factors (e.g., socioeconomic status) have been implicated (Ananth et al. 2004b; Baptista et al. 2008; Muller and

Table 4 Signs and symptoms of DKA (adapted with permission from Trachtenbarg 2005)

Laboratory	Mild	Moderate	Severe
Plasma glucose (mg/dL)	>250	>250	>250
Arterial pH	7.25–7.30	7.00–7.24	<7.00
Serum bicarbonate (mEq/L)	15–18	10–<15	<10
Urine ketones	Positive	Positive	Positive
Serum ketones	Positive	Positive	Positive
Beta-hydroxybutyrate	High	High	High
Effective serum osmolality (mOsm/kg)	Variable	Variable	Variable
Anion gap (mEq/L)	>10	>12	>12
Physical			
Polyuria			
Polydipsia			
Polyphagia			
Weakness			
Kussamul's respirations/fruity breath			
Nausea/vomiting ± coffee-ground emesis			
Body temperature normal/low			
Dehydration (e.g., dry mucous membranes, tachycardia, hypotension)			
Altered consciousness (e.g., alert to coma)			

Kennedy 2006). Evidence also points to changes in body composition (i.e., particularly visceral adiposity), versus absolute weight gain (Eder et al. 2001; Gilles et al. 2010; Haupt et al. 2007; Joseph et al. 2011). Atypical antipsychotics are characterized by heterogeneous receptor binding profiles, and considerable attention has been given to the role of specific receptors in the associated weight gain noted in association with their administration (Ananth et al. 2004a; Baptista et al. 2008; Kroeze et al. 2003; Meltzer 2007).

That a drug like aripiprazole, one of several antipsychotics thought to be more "weight neutral" (Baptista et al. 2008), has been linked to DKA, further fuels the argument that weight gain alone is not responsible for metabolic sequelae. A number of animal studies have confirmed the acute effects of a single dose of atypical antipsychotics on glucose and/or insulin metabolism (Assie et al. 2008; Boyda et al. 2010; Chintoh et al. 2009; Hahn et al. 2011; Houseknecht et al. 2007; Jassim et al. 2012; Murashita et al. 2007; Savoy et al. 2010; Smith et al. 2008, 2011; Tulipano et al. 2007). Although not entirely consistent, there is evidence that the atypicals with the highest liability for weight gain (i.e., olanzapine, clozapine) also appear to demonstrate the greatest acute effect (Assie et al. 2008; Boyda et al. 2010; Savoy et al. 2010; Smith et al. 2008). One human study, involving 3 days of olanzapine administration, reported elevated plasma glucose levels consistent with alterations in insulin sensitivity and/or pancreatic beta-cell secretion (Albaugh et al. 2011). Other human studies have addressed this same issue but employed dosing intervals in the range of 8–21 days (Hardy et al. 2007; Sacher et al. 2008; Sowell et al. 2002, 2003; Vidarsdottir et al. 2010a, b). The results, again not entirely consistent (Sowell et al. 2002, 2003), also suggest an acute effect; however, interpretation of these findings is compromised by weight gain (Sacher et al. 2008; Sowell et al. 2002, 2003; Vidarsdottir et al. 2010b). Furthermore, none of these studies examined changes in body composition. Of note, this work is being carried out in control subjects since schizophrenia itself has been linked to an increased risk of diabetes (Kohen 2004), thereby providing another possible confound in studies of this nature.

Work has also extended to the etiological factors underlying this acute effect. It is intuitively appealing that the mechanisms responsible for weight gain also account for the acute effects on glucose metabolism, and there is some support for this position from animal studies looking at multiple atypical antipsychotics (Assie et al. 2008; Boyda et al. 2010; Houseknecht et al. 2007; Savoy et al. 2010; Smith et al. 2011). Again, the fact that a drug like aripiprazole is associated with DKA suggests the story may not be so straightforward. There is evidence investigating the role of specific receptors in an acute model that would suggest the same. Both the H_1 and M_3 receptor binding affinity of atypical antipsychotics have been implicated in the diabetogenic potential of these drugs (Matsui-Sakata et al. 2005; Silvestre and Prous 2005). Olanzapine and clozapine have the highest binding affinity at these receptors (Roth et al. 2004), are strongly associated with glucose dysregulation in animal models (Chintoh et al. 2009), and have the highest clinical risk of diabetes (Leslie and Rosenheck 2004). Selective H_1 (histaminergic) blockade has not been found to affect insulin secretion acutely (Hahn et al. 2011), although it is thought to play a role in the weight gain associated with compounds like olanzapine and clozapine (Baptista et al. 2008; Kroeze et al. 2003; Meltzer 2007; Wirshing et al. 1999). In contrast, selective M_3 (muscarinic) blockade has been shown to decrease insulin secretion acutely (Hahn et al. 2011), in keeping with findings that this receptor subtype is highly expressed on pancreatic beta cells where it plays a central role in glucose-dependent acetylcholine modulation of insulin secretion (Gilon and Henquin 2001). These findings further illustrate the complexity of glucose metabolism in the context of atypical antipsychotic treatment. Finally, more recent work involving an acute animal model implicates a role for central mechanisms, with evidence that intracerebroventricular olanzapine administration activates hypothalamic AMPK and peripheral hepatic insulin resistance (Martins et al. 2010).

Limitations

In carrying out this review, we included only published reports and those in which at least an abstract was available in English. Any calculations regarding incidence and prevalence are likely to be compromised by underreporting; furthermore, the details provided by the authors varied considerably between reports, and the retrospective nature of the information leaves certain questions unanswered (e.g., prevalence of diabetes or pre-diabetes before DKA crisis). More than half of the reports involved individuals where there was polypharmacy, complicating the interpretation of a specific agent's contribution to the occurrence of DKA. Prospective trials are needed that capture first episode populations being started on antipsychotics, with monitoring at baseline and systematically over the course of treatment.

Final comment

The prescription of antipsychotics has expanded dramatically in the last decade, both in terms of indicated and off-label use (Alessi-Severini et al. 2012; Bulloch et al. 2012; Comer et al. 2011; Leslie and Rosenheck 2012; Pascual et al. 2010). With this much broader utilization, there is risk of complacency regarding adverse side effects that can occur with this class of drugs. Weight gain represents the driving force behind metabolic monitoring for individuals on atypical antipsychotics, but the risk of DKA reminds clinicians that

monitoring should be carried out at baseline and routinely throughout treatment. From a research perspective, it remains important to distinguish the acute effects of atypical antipsychotics on glucose metabolism from those on weight gain, at least until we better understand the underlying mechanisms that characterize each.

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