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Treatment of Diabetic Ketoacidosis Associated With Antipsychotic Medication

Literature Review

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Abstract:

Background: The second-generation antipsychotics (SGAs) are associated with metabolic disturbances. Diabetic ketoacidosis (DKA) is a rare, but potentially fatal sign of acute glucose metabolism dysregulation, which may be associated with the use of SGAs. This study aims to review published reports of patients with schizophrenia and antipsychotic drug–associated DKA, focusing on the effective management of both conditions.

Methods: Using a predefined search strategy, we searched PubMed and EMBASE from their inception to July 2016. The search terms were related to "diabetic ketoacidosis" and "antipsychotic medication." Case reports, case series, and reviews of case series written in English language were included in the review.

Results: Sixty-five reports were analyzed. In most patients who developed antipsychotic-associated DKA, 1 or more suspected antipsychotic medications were discontinued. In 5 cases, a rechallenge test was trialed, and in only 1 case, it resulted in the elevation of blood glucose. The majority was subsequently treated with a different SGA in combination with insulin/oral hypoglycemic agents; although approximately a third of patients had a complete resolution of symptoms or could control diabetes with diet only at the point of discharge.

Conclusions: Patients taking antipsychotic medications should be regularly screened for insulin resistance and educated about potential complications of antipsychotic medications. This will allow clinicians to individualize treatment decisions and reduce iatrogenic contribution to morbidity and mortality. To achieve best treatment outcomes, antipsychotic-induced DKA should be treated jointly by psychiatry and endocrinology teams.

Key Words: antipsychotics, diabetes mellitus, diabetic ketoacidosis, schizophrenia, second-generation antipsychotics

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The second-generation antipsychotics (SGAs) are considered as the first line treatment for schizophrenia spectrum disorders. In addition to their effectiveness in treating psychotic symptoms, most SGAs are associated with significant weight gain and the development of glucose intolerance, thus causing diabetes mellitus, metabolic syndrome, and overall increased risk of cardiovascular morbidity and mortality.[1–3]

Diabetic ketoacidosis (DKA) is an acute complication of diabetes that mainly occurs in patients with type 1 diabetes, but it is not uncommon in patients with type 2 diabetes. This condition is a complex disordered metabolic state characterized by hyperglycemia, ketoacidosis, and ketonuria. With prompt treatment, DKA can be corrected without any complications developing. If left untreated, the condition can be life threatening. Diabetic ketoacidosis was once considered a hallmark feature that would differentiate individuals with diabetes mellitus type 1 from those with diabetes mellitus type 2, although reports of DKA occurring in patients with diabetes mellitus type 2 were described as well.[4] Epidemiologic studies have estimated that DKA-related hospitalizations have increased over the past 2 decades, reaching the rates of 32.4 per 1000 among people younger than 45 years, 3.3 among people aged 45 to 64 years, and 1.4 among people 65 years or older.[5]

Interestingly, in schizophrenia, DKA is often the first sign of antipsychotic (AP) drug–associated diabetes mellitus among patients. For example, Henderson et al[6] showed that the incidence of diabetes presenting as DKA in this population is more than 10-fold higher than that in the general population. Among those with preexisting diabetes mellitus, the rate is 30-fold higher.[7] Other risk factors include polypharmacy, olanzapine monotherapy, clozapine monotherapy, male sex, and middle age (45–60 years).[8] Antipsychotic-associated DKA has been associated with 13% mortality rate.[9,10]

The management of DKA (irrespective of whether it is part of diabetes mellitus type 1 or 2) consists of intravenous insulin therapy with concomitant glucose administration when plasma glucose levels fall below 300 mg/dL (16.7 mmol/L), sufficient volume and electrolyte replacement, and careful attention to identification and management of associated problems, such as acute pancreatitis and infection.[4] Despite all this, no recommendations exist for management of DKA in psychiatric patients. Given the long-term nature of psychiatric treatments, as well as high mortality rates of AP drug–associated DKA, this condition represents a compelling treatment challenge throughout the course of illness.

This study aims to review published reports of patients with schizophrenia and AP drug–associated DKA, focusing on the management of SGA-induced DKA.

METHODS

Using a predefined search strategy, we searched PubMed and EMBASE from their inception to July 2016. The search terms included "diabetic ketoacidosis," "antipsychotics," "atypical antipsychotics," "first

TABLE 1. Treatment Strategies Including AP Medication After AP-Associated DKA

AP Medication	
Initial SGA (n = 58)	**Switch After SGA-Induced DKA and Outcome**
Olanzapine (O) (n = 26)	7 continued (in 5 cases with insulin, in 1 insulin + OHT, in 1 without OHT) 19 discontinued: • 1 rechallenge, then again discontinued—switched to Q, then discontinued and switched to Cl (with insulin) • 11 switched to 5 R (3 cases with insulin, 2 cases with insulin + OHT) ▪ 2 Z (no HT) ▪ 1 Q (with insulin) ▪ 1 A (with OHT) ▪ 2 FGA (1 with insulin, 1 without OHT) • 2 with no APs (1 with insulin, 1 with OHT) • 5 N/R on AP therapy (without HT)
Clozapine (Cl) (n = 17)	2 continued (with OHT)—1 after rechallenge 15 discontinued: • 2 rechallenge then again discontinued—1 switched to FGA (with OHT) and 1 with no APs and HT • 9 switched to 5 FGA (2 cases with insulin, 1 with insulin + OHT, 2 cases without HT) ▪ 1 A then discontinued and switched to FGA (N/R HT) ▪ 2 R one then discontinued and switched to FGA (with OHT) ▪ 1 O (with OHT) • 4 N/R on AP therapy (2 with insulin, 2 without OHT)
Risperidone (R) (n = 6)	1 continued (with insulin) 5 discontinued: • 4 switched to 2 FGA (with insulin) ▪ 1 Q (with insulin) ▪ 1 Z (without HT) • 1 N/R on AP therapy/HT
Aripiprazole (A) (n = 6)	1 continued (with insulin) 5 discontinued: • 1 switched to FGA (with insulin) • 1 without APs (with insulin) • 3 N/R on AP therapy (1 case with insulin; 1 with insulin + OHT; 1 N/R on HT)
Quetiapine (Q) (n = 3)	3 discontinued: • 2 switched to 1 FGA (with OHT) ▪ 1 FGA + R (with OHT) • 1 N/R on later AP therapy (without HT)

HT indicates hypoglycemic therapy; N/R, no record; FGA, first-generation AP.

generation antipsychotics," "second generation antipsychotics," "clozapine," "olanzapine," "risperidone," "quetiapine," "ziprasidone," "aripiprazole," "paliperidone," "amisulpride," and "haloperidol." We also conducted hand searches of key journals and publications of experts in the field for potentially relevant articles. Articles reporting clinical cases of DKA associated with the use of AP agents were included. Only articles published in English language were included.

All potential studies were exported into reference management software. Next, duplicates were removed, and we conducted the initial screening of titles and abstracts for inclusion against the eligibility criteria. The full texts of articles meeting the criteria were obtained and reviewed. Data were extracted on patients characteristics (sociodemographic and clinical status) and psychiatric pharmacotherapy associated with DKA before and after the occurrence of DKA.

Using these key words, we selected 168 titles. After reading the article titles, we selected 140 abstracts in English-language articles from the period 1994 to 2015. Of these abstracts, we selected 83 case reports and reviews of case series and included them into the review. A total of 18 cases were excluded because of lack of provided information: in 11 cases, there was no record of AP therapy after DKA, and in 7 cases, patients were deceased. After applying the inclusion and exclusion criteria, 65 reports were included in this review. The final list included 44 case reports and 6 case series (Table 1, Fig. 1).

RESULTS

Sociodemographic and clinical characteristics of the patients are summarized in the Supplemental Digital Content 1, Supplementary Table (http://links.lww.com/JCP/A474).[10–59]

Antipsychotic Medication

Results of treatment options after AP drug–associated DKA are summarized in Figure 1. In the majority of reported cases (n = 58), DKA was associated with SGA monotherapy: olanzapine (n = 26), clozapine (n = 17), risperidone (n = 6), aripiprazole (n = 6), and quetiapine (n = 3). In most cases, the suspected SGA was withdrawn from treatment after detecting DKA. Subsequently, patients were put on different AP medications, as shown in Table 2.

In 5 cases, a rechallenge test was trialed. In 2 cases, clozapine was restarted 24 days and 2 months after the DKA, respectively. However, in both cases, clozapine was again discontinued because of elevation of serum glucose levels. In 1 case, clozapine was

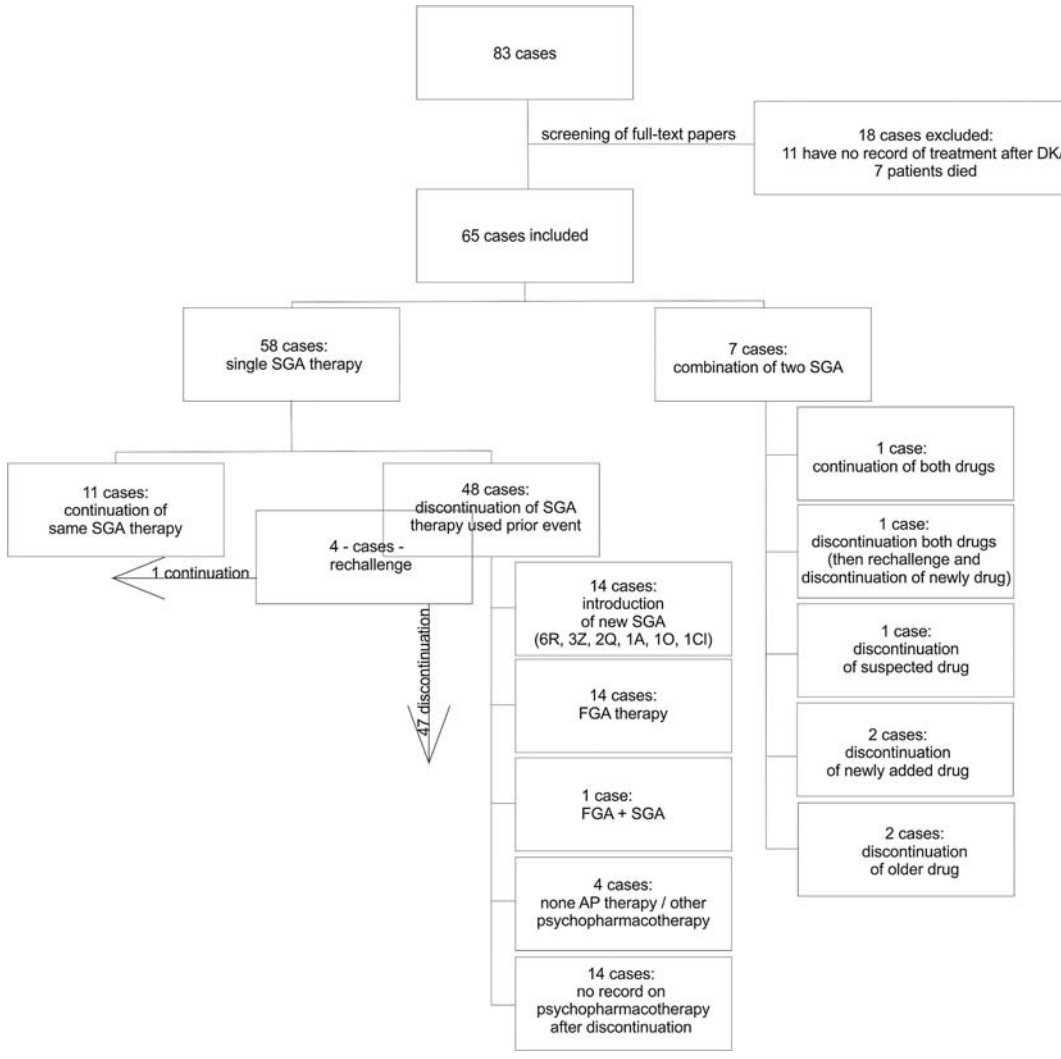

FIGURE 1. CONSORT (Consolidated Standards of Reporting Trials) diagram to report results of treatment options after AP-associated DKA. FGA indicates first-generation AP; R, risperidone; Z, ziprasidone; Q, quetiapine; A, aripiprazole; O, olanzapine; Cl, clozapine.

restarted and continued because of treatment resistance to other APs. Every subsequent discontinuation of clozapine due to the patient's noncompliance resulted in glucose level normalization, followed by the elevation of glucose levels after clozapine reintroduction. In 1 case, olanzapine was restarted after 1 month and discontinued after 3 days because of elevation of serum glucose levels. Blood glucose levels stabilized with oral hypoglycemic therapy (OHT). The patient was prescribed with clozapine, which again led to elevated glucose serum levels, regardless of the increased dose of OHT. One successful rechallenge was described in the patient treated with risperidone where DKA developed shortly after perospirone hydrochloride (a novel serotonin-dopamine antagonist) was added to risperidone. Risperidone was restarted in monotherapy 2 weeks after the DKA was detected, while insulin therapy was gradually replaced with diet.

In 7 cases, DKA was associated with polypharmacy, and authors reported the discontinuation of 1 or even both suspected agent (Fig. 1).

Antidiabetic Treatment

After the acute treatment of DKA, 19 patients completely recovered, and/or 10 patients were able to control diabetes mellitus with diet only. Among the patients who were discharged without antidiabetic treatment, in 1 case, hyperglycemia was reported after 6 months, but the circumstances in which this occurred were not reported. However, the majority of patients needed antidiabetic treatment with insulin (n = 30), oral hypoglycemic agent (n = 9), or both[4] at the time of hospital discharge regardless of the change in AP treatment. Among those who were discharged from the hospital with antidiabetic medication, the majority still needed antidiabetic treatment (n = 24) in the follow-up period; 5 patients had a complete resolution of diabetes mellitus, and the rest were lost in the follow-up (n = 14).

The hypoglycemic therapy after DKA is presented in Figure 2. In cases where APs were discontinued after DKA, the majority of patients were discharged without any antidiabetic medication. On the contrary, in cases where the same DKA-inducing AP was continued, most patients required insulin antidiabetic therapy at the time of discharge.

DISCUSSION

This literature review reveals that clinicians tend to use several strategies when treating patients with AP-associated DKA: (1) acute management includes discontinuation of the suspected

TABLE 2. Recommended Treatment Strategies for Patients at Risk of AP-Associated DKA

Psychiatrist: Preventive Measures

- Obtain personal and family history of diabetes.
- Monitor physical and laboratory measurements: BMI (baseline/monthly), abdominal girth (baseline/annually), blood pressure (baseline/3 mo/annually), fasting lipid profile (baseline/3 mo/annually).
- Monitor fasting plasma glucose (baseline/1 wk/3 mo/annually).
- Evaluate glycemia immediately if the patient experiences polyuria, weight loss, and thirst.
- Evaluate glycemia with 2-h oral glucose tolerance test with 75 g glucose in patients who (1) are overweight or obese, (2) have positive family history of diabetes, (3) personal history of gestational DM, (4) laboratory values of glucose intolerance in medical history.
- For patients with prediabetes, which according to American Diabetes Association criteria denotes (1) patients with impaired fasting glucose (fasting glucose ≥5.6 mmol/L) and/or (2) postprandial glucose intolerance (2-h plasma glucose ≥7.8 mmol/L) and/or (3) HBA_{1c} ≥5.7% (39 mmol/mol), monitoring should include glycated hemoglobin.
- Educate the patients and caregivers on symptoms and signs of diabetes.

Diabetologist: Acute Treatment of Patients With AP-Associated DKA

- Exclude the suspected agent in acute DKA.
- Follow the treatment protocol as in DM type 1: obtain metabolic stabilization with multiple daily injections scheme; ICA, IAA, and GAD antibodies should be obtained.
- Suspect AP-induced DKA/DM type 2.
- If antibodies are negative, discontinue the suspected SGA and gradually taper insulin (first the short-acting prandial one, then long-acting one); introduce metformin to reduce insulin resistance.

Multidisciplinary Approach: Post–Acute Treatment of Patients With AP-Associated DKA

- After discharge, these patients should be closely monitored by a diabetologist, to obtain slow reduction of insulin dose and possibly omission of insulin based on glycemic values (first reduce prandial and then basal insulin).
- Introduce metformin after the probable insulin discontinuation has been successfully achieved if there are no contraindications for metformin. The maximal dose of 2 g per day bid divided should be introduced until HbA_{1c} reaches less than 6%, then reduce the daily dose of metformin by half, and monitor HbA_{1c} in the next 3 to 6 mo. If HbA_{1c} is lower than 6%, metformin should be excluded from therapy.
- Revision of AP therapy should include switching to another SGA with lower propensity to DKA, unless it is already proven that the change in the basic AP will lead to significant deterioration of the patient's psychiatric status.

DM indicates diabetes mellitus; BMI, body mass index; ICA, islet cell antibodies; IAA, insulin autoantibodies; GAD, glutamic acid decarboxylase antibodies.

SGA agent and introduction of antidiabetic agents (insulin, OHT) and lifestyle changes (eg, diabetic diet); (2) post-DKA management includes switching to a different AP medication with lower propensity or reintroduction of the same AP medication. Most patients require continuous antidiabetic treatment. In several cases, both AP and antidiabetic treatment were discontinued.

The reintroduction of the same AP medication seems the least optimal because it is associated with a significant risk of relapse of diabetes mellitus or DKA. In the few cases where rechallenge was tried with the same therapeutic agent or the one from the similar pharmacological group (olanzapine, clozapine), glucose dysregulation was observed despite the use of insulin/or oral antidiabetic agent. Furthermore, in most cases, the maintenance of the same AP therapy required insulin therapy in multiple daily injection therapy. Apart from being very demanding on patients, there are numerous risks associated with such therapy (eg, hypoglycemia, ketoacidosis, chronic complications, etc), especially given the low compliance of patients with major psychiatric disorders.[60] Therefore, the decision to reintroduce the same AP together with insulin or oral antidiabetic should require a careful risk assessment taking into account the patient's psychiatric status, possibility to achieve remission with another AP, risk of new DKA, and the possibility to maintain normoglycemia. Given the periodic nature of schizophrenia and bipolar disorder, the option to discontinue both AP and antidiabetic treatment is not suggested either, as the risk of relapse of psychiatric symptoms is significant.[61]

Our results show that emergency treatment with insulin and fluid resuscitation led to complete recovery of AP-induced DKA in most cases.[62–66] However, this was found only when the suspected drug was discontinued. According to recently published reports, DKA does not seem to be a time-limited medical event. According to Guenette et al,[10] after acute treatment of DKA, 36% of patients had complete resolution of symptoms and required no treatment, 14% controlled diabetes mellitus with diet, and 50% relied on insulin, oral hypoglycemic agents, or both.[8] Similarly, we found that most reported patients needed continuation of antidiabetic therapy at the time of discharge. This might reflect a certain degree of β-cell failure, which possibly persists after the AP-associated DKA, although to the best of our knowledge no data were published on this topic.

Our findings indicate that patients with glucose intolerance needing AP treatment require interdisciplinary management provided by psychiatry and diabetology teams. In line with the

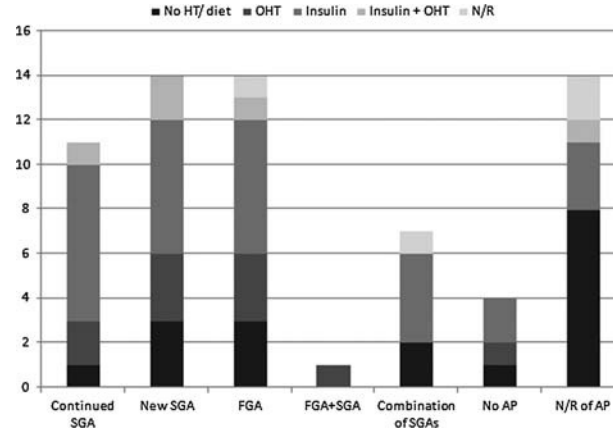

FIGURE 2. Hypoglycemic therapies after AP-induced DKA. HT indicates hypoglycemic therapy; ins, insulin; N/R, no record; AP, AP therapy; FGA, first-generation AP.

American Diabetes Association/American Psychiatric Association consensus conference (2016)[67] recommendations for metabolic monitoring of patients receiving atypical APs, psychiatrists should perform the following: obtain data on personal and family history of diabetes mellitus, screen at baseline and regularly monitor physical and laboratory indicators including waist circumference and glucose and lipids in blood, regularly assess adverse effects, and educate patients and their caregivers about AP-associated adverse effects. Diabetologists should diagnose and treat acute DKA following the treatment protocol (intravenous and later subcutaneous application of insulin) and make recommendations based on the type of diabetes. After DKA is diagnosed, the preferred treatment options include (1) exclusion of suspected agent in acute DKA; (2) application of the standard therapy for DKA; (2) given the morbidity and mortality associated with diabetes mellitus, as well as the need for long-term treatment, switching to another SGA with lower propensity to DKA, unless it is already proven that the change in the basic AP will lead to significant deterioration of the patient's psychiatric status; (3) slow reduction of insulin dose and possibly omission of insulin based on glycemic values (first reduce prandial and then basal insulin); (4) if there are no contraindications for metformin, the maximal dose of 2 g per day bid divided should be introduced until glycated hemoglobin (HbA_{1c}) reaches less than 6%. At that point, we recommend reducing the daily dose of metformin by half and monitoring HbA_{1c} in the next 3 to 6 months. If HbA_{1c} is lower than 6%, metformin should be excluded from therapy. Recommendations are summarized in Table 2.

CONCLUSIONS

The majority of the patients who developed AP-associated DKA were subsequently treated with a different SGA in combination with insulin/oral hypoglycemic. The field lacks prospective studies with longer follow-up of these patients. Therefore, the possible implications of these treatments over the longer course of illness remain unclear. Increased awareness of this problem among clinicians and patients is needed, as well as primary and secondary preventive actions such as systematic and periodic screening for insulin resistance and educating patients about potential complications of AP treatment. Patients with AP-induced DKA should be treated by psychiatry and diabetology teams and followed up to ensure somatic and mental health of these patients.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

REFERENCES

1. Daumit GL, Goff DC, Meyer JM, et al. Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. *Schizophr Res*. 2007;105:175–187.
2. De Hert M, Detraux J, van Winkel R, et al. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol*. 2011;8:114–126.
3. Hedenmalm K, Hägg S, Ståhl M, et al. Glucose intolerance with atypical antipsychotics. *Drug Saf*. 2002;25:1107–1116.
4. Newton CA, Raskin P. Diabetic ketoacidosis in type 1 and type 2 diabetes mellitus: clinical and biochemical differences. *Arch Intern Med*. 2004;164:1925–1931.
5. Centers for Disease Control, Division of Diabetes Translations. Diabetes Surveillance Report. Available at: https://www.cdc.gov/diabetes/statistics/dkafirst/fig4.htm. Accessed April 20, 2017.
6. Henderson DC, Cagliero E, Copeland PM, et al. Elevated hemoglobin A_{1c} as a possible indicator of diabetes mellitus and diabetic ketoacidosis in schizophrenia patients receiving atypical antipsychotics. *J Clin Psychiatry*. 2007;68:533–541.
7. Lipscombe LL, Austin PC, Alessi-Severini S, et al. Atypical antipsychotics and hyperglycemic emergencies: multicentre, retrospective cohort study of administrative data. *Schizophr Res*. 2014;154:54–60.
8. Vuk A, Kuzman MR, Baretic M, et al. Diabetic ketoacidosis associated with antipsychotic drugs: case reports and a review of literature. *Psychiatr Danub*. 2017;29:121–135.
9. Efstathiou SP, Tsiakou AG, Tsioulos DI, et al. A mortality prediction model in diabetic ketoacidosis. *Clin Endocrinol (Oxf)*. 2002;57:595–601.
10. Guenette M, Hahn M, Cohn T, et al. Atypical antipsychotics and diabetic ketoacidosis: a review. *Psychopharmacology (Berl)*. 2013;226:1–12.
11. Koval MS, Rames LJ, Christie S. Diabetic ketoacidosis associated with clozapine treatment. *Diabetes Care*. 1994;22:176–177.
12. Kostakoglu AE, Yazici KM, Erbas T, et al. Ketoacidosis as a side-effect of clozapine: a case report. *Acta Psychiatr Scand*. 1996;93:217–218.
13. Peterson GA, Byrd SL. Diabetic ketoacidosis from clozapine and lithium cotreatment. *Am J Psychiatry*. 1996;153:737–738.
14. Ai D, Roper TA, Riley JA. Diabetic ketoacidosis and clozapine. *Postgrad Med J*. 1998;74:493–494.
15. Pierides M. Clozapine monotherapy and ketoacidosis. *Br J Psychiatry*. 1997;171:90–91.
16. Popli AP, Konicki PE, Jurjus GJ. Clozapine and associated diabetes mellitus. *J Clin Psychiatry*. 1997;58:108–111.
17. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. *Biol Psychiatry*. 1998;44:778–783.
18. Colli A, Cocciolo M, Francobandiera F, et al. Diabetic ketoacidosis associated with clozapine treatment. *Diabetes Care*. 1999;22:176–177.
19. Gatta B, Rigalleau V, Gin H. Diabetic ketoacidosis with olanzapine treatment. *Diabetes Care*. 1999;22:1002–1003.
20. Goldstein LE, Sporn J, Brown S, et al. New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics*. 1999;40:438–443.
21. Mohan D, Gordon H, Hindley N, et al. Schizophrenia and diabetes mellitus. *Br J Psychiatry J*. 1999;174:180–181.
22. Smith H, Kenney-Herbert J, Knowles L. Clozapine-induced diabetic ketoacidosis. *Aust N Z J Psychiatry*. 1999;33:120–121.
23. Croarkin PE, Jacobs KM, Bain BK. Diabetic ketoacidosis associated with risperidone treatment? *Psychosomatics*. 2000;41:369–370.
24. Rigalleau V, Gatta B, Bonnaud S, et al. Diabetes as a result of atypical anti-psychotic drugs—a report of three cases. *Diabet Med*. 2000;17:484–486.
25. Avram AM, Patel V, Taylor HC, et al. Euglycemic clamp study in clozapine-induced diabetic ketoacidosis. *Ann Pharmacother*. 2001;35:1381–1387.
26. 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;14:278–282.
27. Nicolai J, Smith SJ, Keunen RW. Simultaneous side effects of both clozapine and valproate. *Intensive Care Med*. 2001;27:943.
28. Ragucci KR, Wells BJ. Olanzapine-induced diabetic ketoacidosis. *Ann Pharmacother*. 2001;35:1556–1558.
29. Selva KA, Scott SM. Diabetic ketoacidosis associated with olanzapine in an adolescent patient. *J Pediatr*. 2001;138:936–938.
30. Wirshing DA, Pierre JM, Eyeler J, et al. Risperidone-associated new-onset diabetes. *Biol Psychiatry*. 2001;50:148–149.
31. Johnson RP, Al-Taher MT, Madlock LE. Increasing insulin dose for olanzapine-related diabetes. *Am J Psychiatry*. 2002;159:150–151.
32. Waldman JC, Yaren S. Atypical antipsychotics and glycemia: a case report. *Can J Psychiatry*. 2002;47:686–687.

33. Wilson DR, D'Souza L, Sarkar N, et al. New-onset diabetes and ketoacidosis with atypical antipsychotics. *Schizophr Res*. 2003;59:1–6.
34. Tavakoli SA, Arguisola MS. Diabetic ketoacidosis in a patient treated with olanzapine, valproic acid, and venlafaxine. *South Med J*. 2003;96:729–730.
35. Tsuchiyama N, Ando H, Ota T, et al. Modulating effects of olanzapine on the development of diabetic ketoacidosis. *Diabet Med*. 2004;21:300–301.
36. Ananth J, Johnson KM, Levander EM, et al. Diabetic ketoacidosis, neuroleptic malignant syndrome, and myocardial infarction in a patient taking risperidone and lithium carbonate. *J Clin Psychiatry*. 2004;65:724.
37. Meyer JM, Leckband SG, Loh C, et al. Quetiapine-induced diabetes with metabolic acidosis. *Int Clin Psychopharmacol*. 2004;19:169–171.
38. Church CO, Stevens DL, Fugate SE. Diabetic ketoacidosis associated with aripiprazole. *Diabet Med*. 2005;22:1440–1443.
39. Dibben CR, Kalavalapalli SS, Linnington HE, et al. Diabetes associated with atypical antipsychotic treatment may be severe but reversible: case report. *Int J Psychiatry Med*. 2005;35:307–311.
40. Takahashi M, Ohishi S, Katsumi C, et al. Rapid onset of quetiapine-induced diabetic ketoacidosis in an elderly patient: a case report. *Pharmacopsychiatry*. 2005;38:183–184.
41. Macfarlane D, Fisher M. A combination of atypical antipsychotics and diabetic ketoacidosis. *Pract Diabetes Care*. 2006;23:205–206.
42. Reddymasu S, Bahta E, Levine S, et al. Elevated lipase and diabetic ketoacidosis associated with aripiprazole. *JOP*. 2006;7:303–305.
43. 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;60:192–194.
44. 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.
45. Kahn D, Bourgeois JA. Acute pancreatitis and diabetic ketoacidosis in a schizophrenic patient taking olanzapine. *J Clin Psychopharmacol*. 2007; 27:397–400.
46. Reis JS, Alvarenga T, Rosário PW, et al. Diabetes mellitus associated with atypical antipsychotic medications: case report and review of the literature [in English]. *Arq Bras Endocrinol Metabol*. 2007;51:488–493.
47. Sato Y, Yasui-Furukori N, Kaneko S, et al. New-onset diabetic ketoacidosis in a schizophrenic patient with multiple, autoimmune disease during treatment with risperidone. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:577–578.
48. Wong JO, Fu JC, Hung GB. Olanzapine-induced diabetic ketoacidosis in a Chinese man. *Hong Kong Med J*. 2007;13:73–74.
49. Dhamija R, Verma R. Diabetic ketoacidosis induced by aripiprazole in a 12-year-old boy. *Diabetes Care*. 2008;31:e50.
50. Taslipinar A, Yazici M, Kebapcilar L, et al. A case of diabetic ketoacidosis associated with risperidone treatment. *Turk J Endocrinol Metab*. 2008;12: 97–98.
51. Cho DY, Lindenmayer JP. Aripiprazole-induced agitation after clozapine discontinuation: a case report. *J Clin Psychiatry*. 2009;70:141–143.
52. Niazy M, Neyyarapally T, Baidas G. Severe diabetic ketoacidosis precipitated by an atypical antipsychotic drug. *Kuwait Med J*. 2009;41: 240–242.
53. Rashid J, Starer PJ, Javaid S. Pancreatitis and diabetic ketoacidosis with quetiapine use. *Psychiatry (Edgmont)*. 2009;6:34–37.
54. Kibbey KJ, Roberts AM, Nicholson GC. Diabetic ketoacidosis and elevated serum lipase in the setting of aripiprazole therapy. *Diabetes Care*. 2010;33:e96.
55. Watkins J, Ray S, Finch C. Aripiprazole-induced diabetic ketoacidosis: remaining vigilant. *Hosp Pharm*. 2011;46:432–435.
56. Sa YK, Yang H, Jung HK, et al. Olanzapine-induced diabetic ketoacidosis and neuroleptic malignant syndrome with rhabdomyolysis: a case report. *Endocrinol Metab*. 2013;28:70–75.
57. Tsolaki M, Symeonides G, Kazis A. Olanzapine induced diabetic ketoacidosis. *Psychiatriki*. 2001;13:222–227.
58. Fulbright A, Breedlove K. Complete resolution of olanzapine-induced diabetic ketoacidosis. *J Pharm Pract*. 2006;1:255–258.
59. Chellamuth P, Kong M, Gregory R. Ketosis-prone type 2 diabetes: an increasingly recognized entity. *Pract Diabetes*. 2010;27:18–19.
60. Lehner R, Dopke C, Cohen K, et al. Outpatient treatment adherence and serious mental illness: a review of interventions. *Am J Psychiatr Rehab [serial online]*. 2007;10:245–274.
61. Emsley R, Chiliza B, Asmal L, et al. The nature of relapse in schizophrenia. *BMC Psychiatry*. 2013;13:50.
62. Koller E, Malozowski S, Doraiswamy PM. Atypical antipsychotic drugs and hyperglycemia in adolescents. *JAMA*. 2001;286:2547–2548.
63. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. *Pharmacotherapy*. 2002;22:841–852.
64. Koller EA, Cross JT, Doraiswamy PM, et al. Risperidone-associated diabetes mellitus: a pharmacovigilance study. *Pharmacotherapy*. 2003;23: 735–744.
65. Liberty IF, Todder D, Umansky R, et al. Atypical antipsychotics and diabetes mellitus: an association. *Isr Med Assoc J*. 2004,6:276–279.
66. Jin H, Meyer JM, Jeste DV. Atypical antipsychotics and glucose dysregulation: a systematic review. *Schizophr Res*. 2004;71:195–212.
67. American Diabetes Association. Classification and diagnosis of diabetes. *Diabetes Care*. 2016;39:S13–S22.