

RISK OF DIABETIC KETOACIDOSIS AND HYPERGLYCEMIC HYPEROSMOLAR STATE ASSOCIATED WITH THE USE OF ANTIPSYCHOTIC DRUGS

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ABSTRACT

Antipsychotic drugs (APDs) are classified into two classes: typical or first-generation antipsychotics (FGAs), and atypical or second-generation antipsychotics (SGAs). The mechanisms of actions by which these two classes mediate their effects overlap, but with some notable differences. Atypical antipsychotics have been associated with the metabolic syndrome (MetS) defined as increase weight, increased diabetes and glucose abnormalities, and dyslipidemia.

In recent years, accrued evidence has shown that atypical APDs are associated with adverse diabetic complications, namely diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS). APDs, both typical and atypical, are critical for the treatment mental disorders such as schizophrenia and bipolar disorder. In addition, they are used off-label to treat other neurological and behavioural conditions such as obsessive-compulsive disorders, Tourette's syndrome, anxiety, and agitation. Therefore, it is crucial to have a better understanding the association between DKA or HHS and these important medicines.

This thesis comprises five studies that examine the relationship between adverse events of DKA or HHS and treatment with APDs that were approved for use by the United States Food and Drugs Administration (US FDA). Chapters 2 and 3 are two systematic reviews that summarize findings from 125 case reports and 13 observational studies, respectively. Findings summarized in Chapter 2 support an association between atypical APD use and DKA or HHS. Chapter 3 summarizes findings from five analytical and eight descriptive observational studies, which suggest a possible association between atypical APDs and DKA. Chapter 4 explores safety signals associated with atypical APDs and adverse DKA events using the US FDA Adverse Events

Reporting System (FAERS). Results from this analysis corroborate the conclusions drawn from Chapters 2 and 3. Chapters 5 and 6 present analyses of electronic health records (EHRs), comprising real-world data in the Cerner Health Facts® (Health Facts) database collected between 2000 and 2016. An analysis of the temporal patterns of APD use is presented in Chapter 5, both atypical and typical APDs as a class and for individual drugs. While atypical APD use increased in the US overtime, an overall decrease was observed for typical antipsychotics. The results of a nested-case control study examining the association between DKA and APDs by class and by individual drugs are presented in Chapter 6. Findings do not support an association between antipsychotic drugs and DKA. However, subgroup analyses by age group and level of comorbidity provide additional evidence of potential associations for certain higher risk populations, particularly the elderly and those suffering with multiple comorbidities.

The findings presented in the five chapters support a possible association between DKA adverse events and atypical APD use. While there is insufficient evidence to present conclusions for HHS, future research is warranted to better understand the association between these drugs and diabetic complications.

Dedicated to my late father, Mr. Fayad Haddad,

For his patience and his belief in me, and

for encouraging me to pursue my education

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LIST OF ABBREVIATIONS

AACE	American Association of Clinical Endocrinology
ADA	American Diabetes Association
ADHD	Attention deficit hyperactivity disorder
ADE	Adverse drug events
AE	Adverse events
APD	Antipsychotic drug
APA	American Psychiatric Association
BG	Blood Glucose
CDC	Centre for Disease Control
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CMI	Comorbidity Index
CNODES	Canadian Network for Observational Drug Effect Studies
CPRD	Clinical Practice Research Database
CR	Case report
CS	Case series
D2	Dopamine 2
D3	Dopamine 3
DSEN	Canada Drug Safety
DM	Diabetes mellitus
DMO	4-N'-desmethyl-olanzapine
DKA	Diabetic ketoacidosis
ECFV	Extracellular Fluid Volume
ECPRD	English Clinical Practice Research Datalink
EHR	Electronic Health Records
EMA	European Medicines Agency
EuDKA	Euglycemic Diabetic ketoacidosis
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FGA	First-generation antipsychotic
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
HGP	Hepatic Glucose Production
HHS	Hyperglycemic hyperosmolar state
HNF-1 α	Hepatocyte nuclear factor-1 α
HR	Hazard Ratio
5-HT	5-hydroxytryptamine
5-HT2A	5-hydroxytryptamine 2A receptors
ICD	International Classification of Disease
ISPAD	International Society for Pediatric and Adolescent Diabetes
LADA	Latent Autoimmune Diabetes in Adulthood
MedDRA	Medical Dictionary for Regulatory Activities

MetS	Metabolic Syndrome
MDD	Major Depressive Disorder
M3	Muscarinic 3
NAASO	North American Association of the Study of Obesity
NAFLD	Non-alcoholic fatty liver disease
NCC	Nested case-control
NHANES	National Health and Nutrition Examination Survey
OHAT	Office of Health Assessment and Translation
OR	Odds ratio
RR	Relative Risk
RCT	Randomized Control Trial
SGA	Second-generation antipsychotic
SGLT-2	Sodium Glucose Co-Transporter 2
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
US	United States
USDSS	United States Diabetes Surveillance System

CHAPTER 1

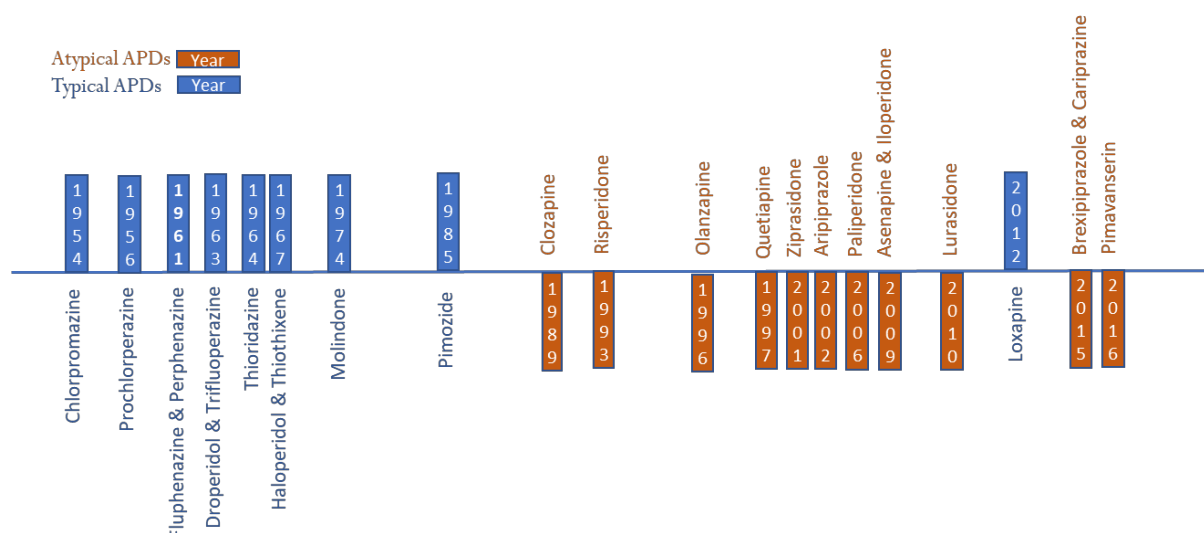
INTRODUCTION

1.1 Antipsychotic Drugs

Antipsychotic drugs (APDs) have been clinically used to treat disabling neurological conditions for more than seventy years. The first typical APD, chlorpromazine, was discovered in France in the early 1950's (Anton-Stephens, 1954) and introduced on the United States (US) market in 1954 under the trade name Thorazine (Shorter, 1997; Crilly, 2007). This discovery was followed by the emergence of many other APDs. Clozapine was synthesized in 1958, but was only approved by the US Food and Drug Administration (FDA) in 1989 to treat treatment-resistant schizophrenia (Crilly, 2007). Although clinicians recognized the unique efficacy of clozapine, precaution and regular monitoring are required due to safety concerns, and its use has remained limited (de Bartolomeis et al. 2022). Other atypical antipsychotics were also discovered during this time (Figure 1.1). Atypical antipsychotics, also known as second-generation antipsychotics, or SGAs - as opposed to their first-generation predecessors, or FGAs - has revolutionized the treatment of neurological disorders.

The mechanisms of action of APDs are complex and multifaceted. What is known is that all APDs act on post-synaptic dopamine 2 (D2) receptors, as antagonists or partial agonists, with a direct positive effect on symptoms (Grunder et al. 2003; Quintana & Beaulieu, 2019). These drugs generally have a wide range of receptor targets (Table 1.1).

Figure 1.1. Timeline of Approval of Atypical (n = 13) and Typical Antipsychotic Drugs (n = 12) by the United States Food and Drugs Administration, 1954-2016^{1,2,3}.



¹Approval dates may differ between countries. Antipsychotic drugs approved by the Food and Drug Administration and the year of approval are shown.

²Sources: U.S. Food and Drug Administration, n.d.; U.S. Food and Drug Administration, 2022.

³Indication of use of antipsychotic drugs may be updated to include other diagnoses overtime.

Table 1.1. Receptor Affinities for Selected Atypical and Typical Antipsychotic Drugs¹.

Antipsychotic Drug	Receptor					
	D2 dopamine	5HT _{2c} serotonin	5HT _{1a} serotonin	M ₃ muscarinic	α ₂ adrenergic	H ₁ histamine
Atypical Antipsychotic Drugs						
Aripiprazole	++++ [†]	+++	++++	–	++	+
Clozapine	+++	+++	++	+++	++	+++
Olanzapine	+	+++	+	+++	+	+++
Quetiapine	+	+	+	+	+++	++
Risperidone	+++	++++	++	–	++++	++
Ziprasidone	+++	++++	++++	–	++	+
Typical Antipsychotic Drugs						
Chlorpromazine	++++	++++	+	++++	+	++++
Haloperidol	++++	++	–	+	+	+/-

++++, very high; +++, high; ++, moderate; +, low; –, negligible; [†], Partial agonist.

¹Adapted from Casey et al. 2001; Holt et al. 2019.

Typical APDs such as haloperidol have strong antagonistic features for D2 receptors, but they are known to cause acute movement disorders such as dystonic reactions and akathisia, non-acute parkinsonism, and tardive syndromes (Burkhard, 2014; Caroff & Campbell, 2016; Friedman, 2019; Friedman, 2020). Atypical APDs have an affinity for other receptors such as serotonin or 5-hydroxytryptamine (5-HT) 2A receptors (5-HT_{2A}). Newer atypical drugs such as aripiprazole, brexpiprazole and cariprazine act as partial agonists of dopamine receptors, D₂ and D₃, and are known to have a “stabilizer” effect. Their features allow them to act as functional antagonists within the mesolimbic system where a hyperdopaminergic state may contribute to positive symptoms, and as functional agonists in the mesocortical pathway, where extracellular dopamine levels are low to mitigate negative and cognitive symptoms (Lieberman 2004; Mailman & Murphy, 2010; Stahl, 2010). It is important to note that the overall properties of typical and atypical APDs overlap and both classes of drugs have beneficial uses. For example, chlorpromazine has an affinity for 5-HT_{2A} receptors and amisulpiride, another typical APD, does not induce alarming motor movement disorders (Leucht et al. 2002; Trichard et al. 1998). Since their discovery, however, atypical APDs are more commonly used than their predecessors due to their versatility in receptor binding, reduced motor side effects, and notable benefits in the treatment severe mental illnesses (Metzler, 2000).

1.2 Consensus Statement on Antipsychotic Drugs and Diabetes

Accrued clinical and epidemiological evidence has shown APDs are associated with metabolic syndrome (MetS), defined by the presence of metabolic abnormalities including weight gain and diabetes, along with acute decompensation such as diabetic ketoacidosis (DKA),

dyslipidemia, and elevated blood pressure (Carli et al. 2021). These clinical conditions are considered risk factors for the development of cardiovascular disease.

A consensus conference convened by the American Diabetes Association (ADA), the American Psychiatric Association (APA), the American Association of Clinical Endocrinology (AACE) and the North American Association of the Study of Obesity (NAASO) was held in 2003 to discuss the relationship between atypical antipsychotics and the development diabetes (ADA, 2003). Experts from the US FDA and representatives from pharmaceutical companies discussed the types of research needed to better elucidate the association between APDs and MetS, the prevalence of obesity, pre-diabetes, and type 2 diabetes mellitus (T2DM) in those using atypical APDs, and the importance of monitoring patients in light of these serious risks. At the time, the panel recommended baseline screening methods, which are still relevant today, to precede the use of any APD, or as soon as clinically feasible (Table 2). Since that time, evidence linking DKA (Guenette et al. 2013; Vuk et al. 2017) and hyperglycemic hyperosmolar state (HHS) with APD use has accrued; however, there are no fulsome reviews on the association between APDs and HHS.

1.3 Large Administrative Databases

Large administrative databases have been increasingly used in epidemiological research. These “big data” repositories are advantageous due to their accessibility, possibility to link multiple data sources to mitigate data gaps, cost-efficiency, and longitudinal representation of large populations (Ulrich et al. 2022). They have been used in different types of research that include analysis of trends overtime, safety and effectiveness studies, disease monitoring and complex predictive modeling to improve patient outcomes (Mahmud et al. 2022). These attributes

Table 1.2. Monitoring Protocol for Patients Using Atypical Antipsychotic Drugs¹.

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	5 years
Personal/family history	✓					✓	
Weight (BMI)	✓	✓	✓	✓	✓		
Waist circumference	✓					✓	
Blood pressure	✓			✓		✓	
Fasting plasma glucose	✓			✓		✓	
Fasting lipid profile	✓			✓			✓

Abbreviations: BMI, Body Mass Index.

¹Adapted from ADA (2003).

make the use of these data sources highly beneficial for research; however, they pose many challenges that need to be taken into consideration at the initial planning phases of research projects. Generally, the reasons for data collection and the methods used to do so are driven by operational needs such as recording vital events, and provision and monitoring services (Hand, 2018; Shaw et al. 2022), rather than research. Nevertheless, they are data rich and allow the evaluation of health outcomes across different healthcare providers and settings, as well as analysis of healthcare utilization over time. These databases include electronic health records (EHR), insurance claims data and other administrative sources of data.

1.3.1 Cerner Corporation's Health Facts® Database

The Cerner Corporations' Health Facts® (Health Facts) database is a de-identified, longitudinal database that contains EHR data from more than 600 healthcare facilities and 70 million patients in the United States (US). It comprises patient information generated by healthcare encounters and submitted by healthcare facilities in real-time. Health Facts includes clinical

and administrative information on patient demographics, diagnoses, procedures, medications, lab results and vital signs. In support of research and analysis in the healthcare industry, it has been used to identify patients with specific diseases and to estimate prevalence of drug use in a given population (Crispo et al. 2015; Farhat et al. 2019) and the identification of risk factors and predictors of health outcomes (Crispo et al. 2016; Farhat et al. 2020; Taher et al. 2021; 2022).

1.3.2 The United States Food and Drugs Administration Adverse Event Reporting System Database

The US FDA Adverse Event Reporting System (FAERS) is a database that collects information on adverse events, medication errors and product quality issues to support the FDA's post-marketing safety surveillance program. It contains over 15 million adverse events received from manufacturers, consumers (patients, family members, lawyers), and healthcare professionals (physicians, pharmacist, nurses) (US FDA, 2018). The system aims to identify safety concerns for pharmaceutical and therapeutic biologic products after they have been approved for use by the FDA, and to guide evidence-based regulatory decision-making and public health interventions (US FDA, 2018; Khaleel et al. 2022; Sakaeda et al. 2013). FAERS has been previously used to analyze the relationship between pharmaceutical products and adverse events (Gravel et al. 2023; Taher et al. 2021; 2022).

Health Facts has been previously used to study the association between intervention and hyperglycemia (Bath et al. 2020; Tarbunou et al. 2019; Vogel et al. 2017). A recent analysis by Pawar and colleagues (2022) conducted used a retrospective study design in Health Facts to evaluate the incidence of thiamine supplementation in patients with alcohol use disorder and DKA in the US. FAERS has been previously utilized to evaluate adverse events of diabetic

complications such as DKA (He et al. 2023) and interventions such as APDs (Kimura et al. 2015; Subeesh et al. 2019).

1.4 Objectives of the Thesis

Current evidence supports the need for additional retrospective and prospective analytical epidemiological studies as well as mechanistic studies (e.g., animal models, cellular models) to enhance our understanding on the risk of APD use and hyperglycemic emergencies, namely DKA and HHS. Furthermore, a focused approach to elucidate the mechanisms of actions for select first- and second-generation APDs on receptor affinities would provide insight on how they potentially mediate this relationship. Although randomized controlled trials (RCTs) deliver the highest level of evidence while limiting confounding and biases, the serious nature of DKA and HHS discourages the study of these two conditions as the main endpoint in clinical trials. To my knowledge, the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) open label RCT trial study is the only experimental study that evaluated the association between APD use and DKA as a secondary endpoint and findings indicated no significant association (Strom et al. 2011).

The primary objective of this thesis was to examine the association between the use of APDs and diabetic complications, namely DKA and HHS. To achieve this, I completed five original studies to address the following five objectives.

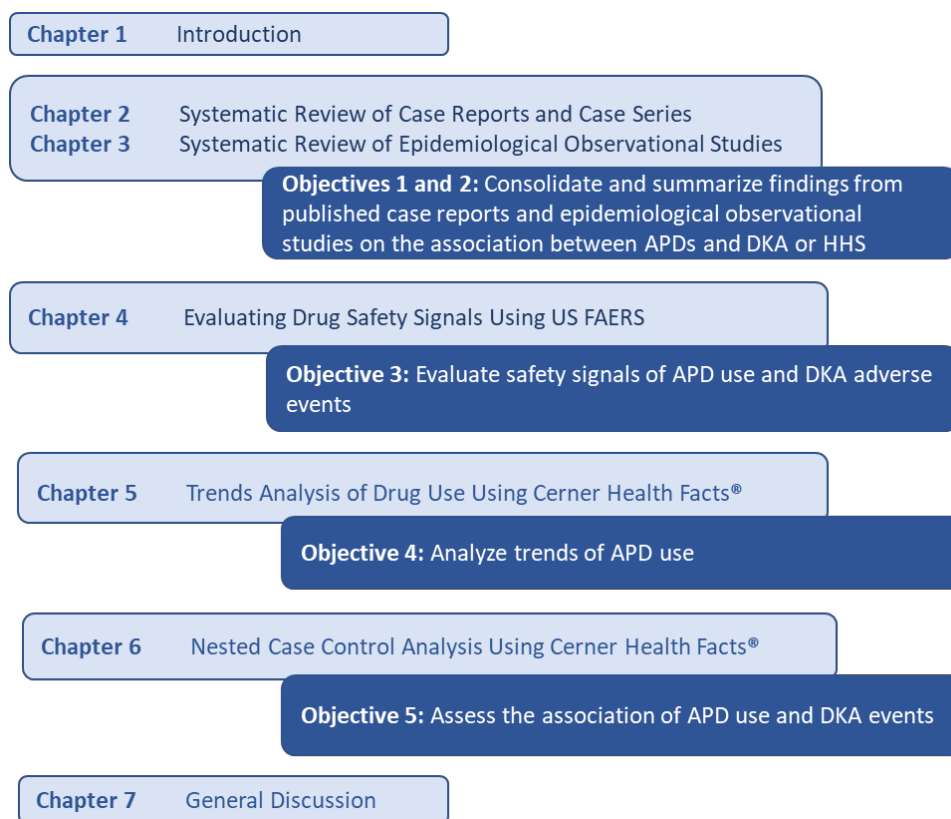
1. To conduct a systematic review of published case reports and case series examining the potential risks of DKA and HHS associated with typical and atypical APDs.
2. To conduct a systematic review of observational studies - analytical and descriptive - to evaluate the potential risks of DKA and HHS associated with typical and atypical APDs.

3. To identify safety signals of adverse drug events, specifically DKA, with the use of typical or atypical APDs using FAERS.
4. To investigate the prevalence of atypical and typical APD use as a class of drug or as individual drugs in the United States using the Cerner Health Facts database.
5. To assess the risks of adverse DKA events associated with the use of atypical and typical APDs as a class or individually among patients diagnosed with diabetes using in a nested case-control study design in the Cerner Health Facts database.

1.5 Organization of the Thesis

This thesis is composed of five original studies, presented in manuscript format in Chapters 2 to 6 (Figure 1.2). Chapters 2 and 3 are systematic reviews that evaluate findings from case reports/case series and from epidemiological observational studies that reported a potential association between APD exposure and DKA and HHS. These two chapters are designed to meet Objectives 1 and 2. Chapter 4 evaluates spontaneous reporting of DKA events due to APD use and the focus of this chapter is to achieve objective 3. Chapters 5 and 6 utilize data EHR derived from HF. Chapter 5 presents a study describing the trends in APD use in the US inpatient setting from 2000-2016 and accomplishes Objective 4. Chapter 6 presents a case-control analysis to assess the risks of APD use and DKA events in a diabetic cohort of inpatients and this fulfills Objective 5. Each chapter is accompanied with supplemental material that provides additional relevant information. The general discussion of the thesis (Chapter 7) summarizes the main findings from each chapter and discusses main epidemiological concepts in relation to each objective.

Figure 1.2. Organization of the Thesis.



Abbreviations: APD, Antipsychotic drugs; DKA, Diabetic ketoacidosis; HHS, hyperglycemic, hyperosmolar state; US FAERS, United States Food and Drugs Administration Adverse Events Reporting System.

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CHAPTER 2

PREFACE

This chapter presents the first manuscript that addresses Objective 1 of the thesis. The objective was to conduct a systematic review of case reports and case series to evaluate the potential association between exposure to antipsychotic drug use and two diabetic complications, specifically diabetic ketoacidosis and hyperglycemic hyperosmolar state. Information was abstracted on exposure, diagnosis, patient or family history of diabetes, qualitative assessment and quantitative data on relevant biomarkers, and treatment used to resolve these two potentially fatal conditions.

The search strategy was completed with the help two librarians from the University of Ottawa's Health Sciences library, Ms. Karine Fournier and Dr. Lindsay Sekora. Search themes and terms were based *on prior* knowledge in the literature. The same research strategy was used for Chapters 2 and 3 (Systematic Review of Observational Studies).

Contribution Statement

For this systematic review, I developed the initial study protocol and the search strategy with guidance of my thesis supervisor (DK), and Dr. NF. I synthesized and interpreted the findings, performed descriptive analysis, and drafted the manuscript. NH and NF screened references for inclusion in the systematic review, abstracted key data elements from the references that met the inclusion criteria and performed the critical appraisal for the case reports. JG provided expert advice on the diabetic complications. Members of my thesis advisory committee (YC, DM, MM CG) contributed to the development of the study protocol and provided feedback during our meetings. The manuscript received a critical review from DK and NF.

Antipsychotic Drugs and the Risk of Diabetic Complications:

A Systematic Review of Clinical Evidence

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ABSTRACT

Background: In recent years, epidemiological and clinical evidence has suggested an association between the use of second (SGAs), but not first (FGAs), generation antipsychotics and hyperglycemic complications, notably diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS).

Objective: To conduct a systematic review of evidence established in case reports (CRs) on adverse drug reactions, specifically DKA and HHS, associated with the use of FGAs and SGAs.

Methods: Pertinent bibliographic databases (MEDLINE, EMBASE and PsycINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL)) were searched using index phrases and keywords up until October 20, 2022. Eligible CRs had to have discussed exposure to at least one US FDA approved antipsychotic drug (APD) and assessed DKA or HHS.

Results: A total of 125 CRs were included in the systematic review (DKA, n = 100; HHS, n = 24; both conditions, n = 1). Patients in the 30- to 39-year-old age group accounted for the highest

number of emergencies (n = 41, 33%): these occurred mostly in males (n = 88, 71%). The most common mental health diagnosis was schizophrenia (n = 64, 50%), followed by bipolar disorder (n = 20, 16%). Olanzapine was associated with the highest number of DKA cases (n = 41, 41%), followed by clozapine (n = 21, 21%). Average blood glucose for DKA and HHS patients at presentation were 800 mg/dl and 1,194 mg/dl, respectively. Average hemoglobin A1c levels were 12.7% and 12.1%, respectively, for these two conditions. Of the 12 reported fatalities, treatment with olanzapine was noted in four DKA cases and in one HHS case. A critical appraisal of CRs recommends clinicians continue to monitor metabolic risk factors, as well as provide diabetes education about prevention of acute diabetic complications.

Conclusion: This analysis provides additional evidence of an association between use of atypical APDs and DKA or HHS.

Keywords: Antipsychotic drugs, diabetic ketoacidosis, hyperglycemic hyperosmolar state, case reports

2.1 INTRODUCTION

2.1.1 Antipsychotic Drugs

Antipsychotic drugs (APDs) are classified into two classes, first-generation antipsychotics (FGAs) also known as typical APDs, and second-generation antipsychotics (SGAs), or atypical APDs, based on their mechanisms of action. Atypical APDs offer advantages over their predecessors and overall cause less extrapyramidal health effects, such as dystonia, dyskinesia, akathisia, and parkinsonism, although these symptoms may overlap in some agents within the two classes (Aringhieri et al. 2018; Carli et al. 2021). Atypical APDs are now more commonly prescribed to treat serious mental illnesses including schizophrenia, bipolar disorder, and other psychotic

disorders (Carli et al. 2021). While they can improve outcomes in treatment compliant patients (Kasper & Resinger, 2003; Skarsfeldt et al. 1996, Stip et al. 1996), this class of drugs may result in the development of metabolic syndrome (MetS), which is defined by weight gain, dyslipidemia, fasting hyperglycemia and increased blood pressure, thus leading to reduced life expectancy and poor adherence to treatment in those suffering from schizophrenia and other psychotic disorders (Carli et al. 2021).

2.1.2 Hyperglycemic Complications

Evidence of an increased risk of hyperglycemic complications, notably diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS), due to treatment with atypical APDs has accrued in recent years. To date, this association has not been widely reported with typical antipsychotics. DKA and HHS share a number of common risk factors, including newly diagnosed Type 1 diabetes mellitus (T1DM) or Type 2 diabetes mellitus (T2DM), inconsistent insulin treatment, inadequate insulin therapy in hospital settings, infections (such as skin and urinary track infections), acute coronary/vascular event, trauma, and treatment with glucocorticoids, beta-blockers, thiazide diuretics, certain atypical APDs (Ananth et al. 2004; Buse et al. 2003; Caro et al. 2002; Fayman et al. 2017; Gianfrancesco et al. 2003), as well as some chemotherapeutic agents (Ben Salem et al. 2011; Evans, 2019; Gerich et al. 1971; Fayman et al. 2017; Goguen & Gilbert, 2018). Both conditions are characterized by insulinopaenia and severe hyperglycaemia. New DM diagnosis (present in 17.2%–23.8% of cases), infection (14.0%–16.0%), poor treatment compliance (41.0%–59.6%), other causes (9.7%–18.0%), and unidentified causes (3.0%–4.2%) are some of the triggering factors for DKA in the US (Umpierrez et al. 2016). Patients with a history of DM are more likely to report HHS. Its

primary triggering factors include infection (30–60%), forgetting to take insulin or another antidiabetic medicine, and co-morbidities such myocardial infraction (Fayman et al. 2017; Umpierrez et al. 2016).

Some 30% of patients with DKA have features of both DKA and HHS (Gosmanov et al. 2021; Hassan et al. 2022). Clinically, DKA is characterized by hyperglycaemia, hyperketonemia, and metabolic acidosis, and can be classified from mild to severe with plasma glucose levels of more than 250 mg/dl. HHS is characterized by plasma glucose higher than 600 mg/dl and serum osmolarity over 320 mmol/kg (Kitabchi et al. 2006; 2009). The latter condition, which is less common, occurs without ketoacidosis and ketonaemia (Stoner, 2017). Table 2.1 summarizes the diagnostic criteria for these two relatively rare conditions.

2.1.3 Hospitalization Rates for Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

Despite well defined diagnostic criteria and treatment regimens, DKA and HHS are significant contributors to morbidity and mortality in diabetes patients (Kibatchi et al. 2009). The Centre for Disease Control's United States Diabetes Surveillance System (CDC USDSS) analyzed DKA hospitalization rates between 2000 to 2014. The incidence of DKA declined slightly between 2000 and 2009, and then increased, accounting for 140,000 and 169,000 hospitalizations in 2009 and 2014, respectively (CDC, 2014, Benoit et al. 2018). This trend was also observed in other countries such as England (Zhong et al. 2018) and Finland (Thomas, 2020).

While all age groups experienced an increase in DKA hospitalization rates of $\geq 6.0\%$ annually, the increase was more pronounced among those less than 45 years of age. In contrast, in-hospital case fatalities declined across all age groups in both males and females during the same period (Benoit et al. 2018). HHS is a less common event than DKA, with admissions comprising fewer

than 1% of all diabetic-related illnesses leading to hospitalization (Fishbein and Palumbo, 1995; Kitabchi *et al.* 2001; Pasquel and Umpierrez, 2014).

2.1.4 Epidemiology of Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

DKA is more frequently seen in T1DM patients but is also observed in about a third of all T2DM cases (Fayman *et al.* 2017; Wang *et al.* 2008). According to an analysis from the Prospective Diabetes Registry in Germany, where DKA admission rate was 4.8 (95% CI, 4.5-5.1) per 100 patient-years, risk factors for DKA include high levels of HbA1c, having diabetes for an extended period, being an adolescent, and being a female (Fayman *et al.* 2017; Karges *et al.* 2015).

According to the T1D Exchange Clinic Network, young adults between the ages of 18 and 25 years have the highest incidence of DKA (5%, defined as an incident within the previous three months) (Fayman *et al.* 2017; Goguen & Gilbert, 2018; Miller *et al.* 2015).

The incidence of DKA in patients with T2DM ranges from 0.32 to 2.0 per 1,000 patient-years (Wang *et al.* 2008), and from 4.6 to 8.0 per 1,000 patient-years in those with T1DM (Kitabchi *et al.* 2006). Ketosis-prone diabetes, which will not be covered in this review, is a disease that affects people who have DKA but do not meet the criteria for T1DM. Older persons with T2DM are more likely to experience HHS (Pasquel & Umpierrez, 2014), but children and younger adults have also been found to experience this condition (Goguen & Gilbert, 2018; Rosenbloom, 2010).

2.1.5 Pathophysiology of Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

DKA and HHS, two distinct conditions share some common pathways leading to pathogenesis and clinical diagnosis (Canarie *et al.* 2007; Hassan *et al.* 2022; Wachtel 1990), but with some differences. Both complications are characterized by insulin deficiency (absolute insulin

deficiency in the case of DKA and relative insulin deficiency in the case of HHS), hyperglycemia, urinary losses of water and electrolytes (sodium, potassium, chloride) and severe extracellular fluid volume (ECVF) depletion. ECFV depletion and hyperosmolarity are characteristics of HHS, whereas ketoacidosis is a hallmark of DKA (Goguen & Gilbert, 2018). Both conditions are also characterized by the presence of high levels of counter-regulated hormones (Alberti 1975; Hassan et al. 2022) such as cortisol, catecholamines, glucagon and growth hormones.

In people with T1DM and insulin insufficiency, hyperglycemia reduces ECFV and leads to urinary losses of water and electrolytes such salt, potassium, and chloride. As cell depletion occurs, ketoacidosis, a symptom of DKA, will develop when potassium is expelled from cells in the body due to high glucagon levels and insulin shortage. High levels of catecholamine that suppress insulin release can also develop in T2DM patients, resulting in HHS, which is characterised by ECFV depletion and hyperosmolarity (Hassan et al. 2022; Kitabchi et al. 2009).

2.1.6 Pathogenesis of Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

The pathogenesis of DKA and HHS are summarized as follows. Islet cells in the pancreas cannot produce insulin, leading to insulin deficiency (1), which results in the liver producing more glucose to feed the body and therefore increased gluconeogenesis in the bloodstream (2). In addition, as an alternative source of energy, the body breaks down fat leading to ketone bodies accumulating in the bloodstream (3). Ketone bodies and glucose pass through to the urine while being filtered in the kidney (4). The combination of hyperglycemia and high ketone levels cause decreased glomerular filtration rate. As such, considerable water is lost which leads to dehydration and can worsen the ketoacidosis (5). The development of HHS is less acute than DKA and progresses slowly over a period of days or weeks. There is sufficient

insulin in patients with HHS, which suppresses lipolysis and the production of ketone bodies; however, the amounts of insulin are not insufficient to prevent a more pronounced hyperglycemia and dehydration and more extreme mental health status than DKA (Ghimire & Dhamoon, 2023). As with DKA, steps 1-4 do occur with HHS, but this leads to hyperosmolality with minimal or no ketogenesis (Figure 2.1).

2.1.7 Management of Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

The management of DKA or HHS events requires laboratory evaluation, administration of insulin (or transition to subcutaneous insulin) to resolve hyperglycemia, correction of electrolyte imbalance to restore normal ECFV and tissue perfusion, resolution of ketoacidosis (in the case of DKA) and treatment of coexistent illnesses (Goguen & Gilbert, 2018).

Treatment of DKA And HHS in adults is generally based on the following summarized protocol (Goguen & Gilbert, 2018; Hassan et al. 2022):

1. Treatment with insulin to lower serum glucose levels rapidly.
 - a. Insulin will also inhibit glucagon secretion, lipolysis and ketogenesis.
 - b. In case of DKA, simultaneous resolution of ketoacidosis with the addition of 5% dextrose.
2. Subsequent subcutaneous administration of rapid-acting insulin analogs to replace regular insulin.
 - a. Avoidance of the use of rapid-acting insulin analogs in hypertensive patients, severe DKA and HHS cases.
3. Full resolution of DKA or HHS will require serum glucose level ≤ 250 mg/dL.
4. Full resolution of DKA requires serum bicarbonate ≥ 18 mEq/L, a blood PHD of > 7.30 , and a normal anion gap.
5. Full resolution of HHS requires serum osmolality < 310 mOsm/kg.
6. Continued surveillance of biomarkers is essential to prevent recurrence.

2.1.8 Treatment with Antipsychotic Drugs and Diabetic Adverse Events

In recent years, case reports (CRs) have supported the potential association between the use of SGAs and DKA (Guenette et al. 2013; Vuk et al. 2017), while less information is available on HHS. There have also been a handful of observational studies, both analytical and descriptive, that support this association.

This systematic review will summarize available CRs with epidemiological and clinical evidence for both DKA and HHS. The specific objective is to provide an in-depth review of these adverse events due APD use, both typical and atypical, and synthesize currently available evidence on the etiology of these two conditions.

2.2 METHODS

2.2.1 Search Strategy and Databases

The search strategy for this review was developed in consultation with a librarian from the University of Ottawa's Health Sciences Library. A search of the four pertinent bibliographic databases (MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO) was conducted to identify potentially relevant studies using the relevant subject headings and keywords detailed in Supplementary Material I. The database searches identified records published up until October 20, 2020.

2.2.2 Data Screening and Abstraction

Duplicate publications were identified using Endnote (Clarivate Analytics, 2018. Version X9. Available from <https://endnote.com>). Screening of unique records was performed using a two-stage process: Level 1 (title and abstract) screening followed by Level 2 (full-text screening).

Screening forms were created in Distiller SR (Evidence Partners, 2018) (Supplementary Material II). Relevant quantitative and qualitative data from all CRs included in the review were abstracted into an Excel spreadsheet, including demographic characteristics (gender, age, ethnicity), clinical information (diagnosis, treatment, history of DM, comorbidities, co-mediations, and prognosis), and quantitative and qualitative data on relevant biomarkers such as levels of glucose or HbA1c, body weight change, presence or absence of ketones, and osmolality). Two reviewers (NH and NF) independently carried out Level 1 and Level 2 screening in duplicate. In case of conflicts, resolution was reached by consensus. Data extraction was completed by one of the two reviewers (NH), with duplicate data abstraction conducted on 10% of the included studies as a quality control measure (NF). Observational studies that were eligible for analysis were included in a separate review (Chapter 3) and were therefore excluded from the present review.

2.2.3 Eligibility Criteria

2.2.3.1 Exposure Assessment

Included CRs were classified on the basis of exposure being evaluated as monotherapy with any APD or concomitant use of APDs. FDA-approved FGAs considered included: Haloperidol (marketed as Haldol), Loxapine (Loxitane), Molindone (Moban), Thiothixene (Navane), Pimozide (Orap), Trifluoperazine (Stelazine), Chlorpromazine (Thorazine), Fluphenazine, Perphenazine, "Perphenazine amitriptyline", Prochlorperazine, Thioridazine, and Droperidol (Inapsine). SGAs or atypical APDs included: Aripiprazole (Abilify), Asenapine Maleate (Saphris), Clozapine (Clozaril), Iloperidone (Fanapt), Lurasidone (Latuda), Olanzapine (Zyprexa),

Olanzapine/Fluoxetine (Symbyax), Paliperidone (Invega), Quetiapine (Seroquel), Risperidone (Risperdal), Ziprasidone (Geodon), Capiprazine (Vryalar), and Pimavanserin (Nuplazid).

2.2.3.2 Outcomes of Interest

The objective was to assess the risk of antipsychotic usage with respect to the following outcomes: DKA, HHS, or DKA and HHS as co-conditions.

2.2.3.3 Study Design

Both CRs and case-series (CS) were included in the present review, with observational studies included in a companion review (Haddad et al. 2023).

2.2.3.4 Inclusion Criteria

Included CRs or CSs mentioned use of at least one FDA-approved APD type and the evaluation of at least one of the outcomes of interest (DKA, HHS or DKA/HHS). Abstracts in both English and French were evaluated without restriction on geographic location. Conference abstracts that presented a comprehensive case report from which data can be extracted were considered for inclusion. This review covered patients of various ages who had taken antipsychotic medications (typical and atypical): there were no limitations on the indication of use of APDs or the age of the cases.

CRs were only included if the article clearly indicates the diagnosis of DKA or HHS: reports, describing information only on biomarkers (e.g., levels of glucose, HbA1C) without clinical diagnosis of one (or both) of these two conditions were excluded.

2.2.3.5 Exclusion Criteria

CRs were excluded if the outcome of interest was not DKA or HHS, if the APD was never approved or no longer approved for use, or if APDs were not the exposure of interest suspected

of causing the complication. Systematic reviews, literature reviews, editorials, and commentaries, as well as meta-analysis were excluded. As previously mentioned, eligible observational studies are detailed in a separate review (Chapter 3).

2.2.4 Biomarkers

Information on specific biomarkers such as glucose levels, HBA1C levels, presence of ketones, and osmolality levels was extracted when available. Blood glucose (BG) levels in mg/dl were abstracted, and serum or plasma glucose levels were converted to BG (otherwise, if it was not specified, it was presumed that quantitative data are for BG). Data permitting, average levels of BG, and HbA1c were calculated for three distinct periods: 1) prior to complication; 2) at presentation of the complication; and 3) after resolution of the complication. The final test results served as the foundation for all analysis, and we assumed the last clinical result provides a more accurate indication of patient follow-up.

2.2.5 Critical Appraisal

The Joanna Briggs Critical Appraisal tool was used to evaluate the quality of information in each CR against eight criteria (Supplementary Material III). CRs were evaluated for completion on patient demographics, medical history, clinical conditions at presentation, diagnostic tests and the results, interventions or treatment post-intervention of the medical condition, identification of adverse or unanticipated events, and lessons learned (Gagnier et al. 2013; Moola et al. 2020). Critical appraisal for all CRs was performed by one reviewer (NH) and a 10% sample of the included studies by a second reviewer (NF).

2.3 RESULTS

2.3.1 Selection of Studies

A total of 2,086 potentially relevant reports and studies were identified by our database searches. Of these, 125 CRs were included in the systematic review following full text review. Figure 2.2 shows an overview of the selection of studies included in the systematic review.

2.3.2 Demographic Characteristics

A total of 124 (CRs) summarized information on patients admitted to a hospital with a diagnosis of DKA or HHS and that were treated with an APD known to be marketed in the United States. Demographic characteristics (age, sex, and race), diagnosis, treatment with APDs, history of diabetes, test results for relevant metabolic markers and treatment and recovery for each DKA or HHS patient are shown in Tables 2.2 and 2.3, respectively, with further details found in Supplementary Material Tables S2.1 and S2.2.

Among these CRs, 71% ($n = 88$) were attributed to males and 27% ($n = 34$) were attributed to females (Table 2.4). Of the 124 CRs, African Americans and Caucasians accounted for 19% ($n = 23$) and 19% ($n = 24$) of CRs, respectively. The highest proportion of complications attributed to an APD occurred in the 18–49-year age group: the 30–39-year-old age group accounted for 33% ($n = 41$) of all CRs, followed by the 40 – 49 year age group at 27% ($n = 33$) and the 18 – 29 year age group at 23% ($n = 28$). DKA was notably more common than HHS, accounting for 81% ($n = 100$) of all CRs while HHS accounted for 19% ($n = 24$) of CRs. One CR described both conditions occurring simultaneously in a 28-year-old Caucasian obese male (Body Mass Index (BMI) of 33.2 Kg/m²) with strong family history of T2DM and a high sugar diet (Hui Fang et al. 2018) and was

not included in the analysis (following discontinuation of risperidone, as well as lifestyle and diet changes, the patient fully recovered).

As mentioned previously, single use of antipsychotic medicine was assumed unless polypharmacy was clearly stated at the time of presentation. The use of a single APD accounted for majority of CRs at 73% (n = 91), while the concurrent use of multiple (in most cases, two) APDs accounted for 27% (n = 34) of CRs. APDs were prescribed to treat schizophrenia in 52% (n = 64) of reported cases, followed by bipolar disorder (16%, n = 20) and depressive disorders (10%, n = 12). Patients with two or more diagnoses accounted for 14% (n = 17) of reported CRs. These include a combination of those listed in Table 2.4, in addition to other conditions such as: borderline personality disorder, attention deficit hyperactivity disorder (ADHD), anxiety, mood disturbance, and other. SGAs were the primary suspect drugs thought to result in the occurrence of DKA or HHS. Specifically, olanzapine was listed as the primary suspect drug in 38% (n = 47) of all CRs included in the analysis, followed by clozapine (18%, n = 22), quetiapine (15%, n = 19), and risperidone, (11%, n = 13).

Discontinuation of the APD suspected of causing the diabetic complication occurred in 70% (n = 87) of patients as a preventative measure. For some patients, treatment continued with a newly prescribed APD, resulting in switching of APDs in 33% of patients (n = 41). The most common co-morbidities reported were acute renal failure, acute pancreatitis, hypertension, hyperlipidemia, and depression, cited in 29% (n = 36) of CRs. Overall, 15% (n = 18) of patients had a history of or were active alcohol and/or substance users at the time of the complication (Table 2.4).

2.3.3 Specific Outcomes

2.3.3.1 Diabetic Ketoacidosis

Since DKA accounted for most CRs (n = 100, 81%), patient demographics, mental health diagnosis, APD treatment and comorbidities align with overall patient characteristics in Table 2.4. The 30-to-39-year-old age group accounted for the highest count and proportion of patients with DKA (32%, n = 32), with most of those being male (72%, n = 72). African Americans and Caucasians accounted for 20% (n = 20) and 19% (n = 19) of CRs, respectively. Schizophrenia was reported as being the main reason of APD use at 59% (n = 59), followed by bipolar disorder at 14% (n = 14). Olanzapine was the primary APD suspected to cause a DKA occurrence in 41% (n = 41) of CRs. Single APD use accounted for 73% (n = 73) of cases, discontinuation of the suspected agent occurred in 71% of the cases (n = 71), while switching to another APD occurred in 37% (n = 37) of the cases. Twenty eight percent of CRs (n = 28) noted concurrent co-morbidities at the time of admission, and 22% (n = 22) of affected individuals had a history or were active alcohol/substance and/or tobacco users.

2.3.3.2 Hyperglycemic Hyperosmolar State

HHS accounted for 19% of the overall count (n = 24). As with DKA, the 30–39-year-old age group accounted for most cases (38%, n = 9) and were male (67%, n = 16). Most CRs did not specify a race. Patients had diagnoses of schizophrenia, bipolar disorder, and depressive disorders, but also other diagnoses as well. HHS occurrence was linked to treatment with olanzapine and quetiapine in 29% (n = 7) of CRs each (Table 2.4).

2.3.4 History of Diabetes

CRs included information on patient and family history of diabetes, and on relevant biomarkers, including levels of serum, plasma, and BG; HbA1c concentration, presence/absence of ketones, and serum osmolality. While the level of detail varied among CRs, data was sufficient to support quantitative analysis on biomarkers such as BG and HbA1C levels in three distinct periods: 1) prior to presentation with the condition 2) at presentation with DKA or HHS, and 3) after treatment of either condition, or subsequent follow up with the latest test result being included. Of the 124 CRs, approximately a quarter were reported to have a history of family diabetes (n = 30, 24%), irrelevant of the patient's history, 7% (n = 8) of CRs had a known patient history of DM, while 59% (n = 73) did not have any known family or patient history of DM (Table 2.5). Overall, 41% (n = 51) of patients were diagnosed with T1DM, T2DM or new-onset DM prior to or after DKA or HHS. As discussed below, these results provide important insights on temporal changes in these key biomarkers.

2.3.5 Relevant Biomarkers

2.3.5.1 Glucose

Over a third of CRs reporting qualitative information on serum glucose levels were “normalized” or “controlled” after treatment and resolution of the complication (37%, n = 45). For this review, plasma and serum glucose were converted to BG levels to ensure consistency when averages were calculated, when possible. In CRs where DKA was the outcome, the average glucose level prior to presentation was 107.9 mg/dl (n = 27). This average increased markedly to 800 mg/dL (n = 96) at presentation or shortly after admission. Following treatment of DKA, average BG levels were 143.5 mg/dl. In CRs where the patient suffered from HHS with

reported use of an APD, the levels of BG were 100, 1,194 and 125 mg/dl before presentation, at presentation and after resolution of HHS, respectively. It is important to note that BG levels at presentation were available for most DKA cases (n = 96) and all HHS cases (n = 24) (Table 2.5).

2.3.5.2 Hemoglobin A1c (HbA1C)

HbA1C levels reflect average blood sugar levels over the past two to three months. For patients presenting with DKA, HbA1C levels were 6.3% (n = 5), 12.7% (n = 44) and 6.4% (n = 21) before presentation, at presentation or shortly thereafter, and after resolution of the case, respectively. Similarly, HbA1C levels in patients presenting with HHS were 5.8% (n = 6), 12.1% (n = 12) and 6.0% (n=4) during these same periods (Table 2.5). These results should be interpreted with caution due to the low number of CRs reporting on this biomarker. However, the averages provide an indication of temporal changes in HbA1C over these three periods (Table 2.5).

2.3.5.3 Presence of Ketones

The presence of serum and urine ketones is an indicator of DKA and was confirmed in 77% (n = 77) of DKA cases; while no CR confirmed the absence of ketones, 23% (n = 23) of DKA CRs did not specify the presence or absence of this biomarker. Some CRs indicated categorized the presence of ketones as mild, moderate, or severe, and others cited ketones as being simply positive or present. The occurrence of HHS may be accompanied with trace levels of ketones, as reflected in the qualitative description on some of the CRs: nine HHS CRs had reported the presence of ketones, while nine CR noted the absence of ketones (Table 2.5).

2.3.6 Treatment with Insulin

Insulin was administered to 88% of patients (n = 109) to treat DKA or HHS (Supplemental Tables S2.1 and S2.2). Overall, less than a quarter of all cases recovered fully (n = 28, 23%) (Table 2.5), and insulin and/or antihyperglycemic medications were discontinued within few months of the complication episode. Partial recovery – defined as the patient required treatment with insulin or an antidiabetic due to a prior or new diagnosis of T1DM, T2DM, other types of DM, or the patient's diabetic condition was controlled solely by diet – was noted in 61% of CRs (n = 75). Death was reported for twelve CRs (10%) (Tables 2.5 and 2.6).

2.3.7 Olanzapine and Clozapine, and Diabetic Ketoacidosis

Olanzapine and clozapine are SGAs suspected of causing the highest proportion of DKA cases at 41% and 21%, respectively (Table 2.7). Schizophrenia accounted for the highest proportion of mental health diagnosis for olanzapine at 57% (n = 22) and clozapine at 81% (n = 17) of CRs. The time to complication from initiation of antipsychotic treatment, when reported, varied by APD, with an average of 11.2 months and 6.2 months for olanzapine and clozapine, respectively. Treatment with quetiapine, risperidone and aripiprazole contributed to DKA within 1 day to 24 months of initiation of therapy. The suspect APD was discontinued in 71% of DKA CR attributed to olanzapine treatment (n = 29) and 62% of DKA CRs attributed to clozapine treatment (n = 13). In case olanzapine, antipsychotic treatment was switched to another APD after DKA in 37% (n = 15) of cases; in the case of clozapine, the switching occurred in 48% (n = 10) after the complication. In most patients, recovery was considered partial; Almost fifty-nine percent (n = 24) of patients receiving olanzapine and 67% (n = 14) of patients who were treated

with clozapine were required to manage their existing DM condition or new-onset DM with oral hypoglycemics or diet management alone.

2.3.8 Critical Appraisal of Case Reports

Using the Joanna Briggs Institute critical appraisal tools, a critical evaluation was conducted for all CRs (n = 125) using eight distinct criteria to assess the amount of information reported on demographic details, medical history, clinical condition at presentation, methods and results for diagnosis, the intervention, post-intervention information, adverse treatment reactions, and lessons learned. Five case studies (4%) satisfied all eight requirements. Most reports described the clinical condition (86%, n = 108) and diagnostic methods and results (89%, n = 111), while 38% (n = 47) of CRs provided details on the intervention used to resolve the complication. Only 11% (n = 14) of cases experienced an adverse event such as hypoglycemia after receiving treatment for DKA or HHS. A majority of CRs (70%, n = 87) suggested a path forward for lessons learned, including routine monitoring of relevant biomarkers for patients who have been prescribed APDs (Figure 2.3, Supplemental Material Table S2.3).

2.4 DISCUSSION

This article provides a comprehensive overview of the risk of DKA or HHS attributed to treatment with an antipsychotic medication. Our findings indicate that the development of antipsychotic-induced DKA appears to be primarily reported with the use of olanzapine and clozapine as a single medication or in combination with other APDs within the initial 12 months of therapy. Jin et al. (2004) conducted a systematic review on the use of atypical APDs and

glucose dysregulation and noted the same observation about the two APDs, but within six months of initiation of therapy.

Our findings indicate that DKA and HHS events occurred in a predominantly male population, and in the 30–39-year age group. These risk factors, as well as being of non-Caucasian ethnicity, have also been discussed by others, specifically for DKA events (English & Williams, 2004; Kitabchi et al. 2009; Vuk et al. 2017). On the other hand, our findings support that Caucasian race/ethnicity is also a risk factor for developing this condition. This is corroborated by a recent population-based cross-section study in Croatia who estimated the incidence of DKA in a well-defined predominantly Caucasian population. The adjusted incidence rate of overall was 17.0 (95% CI: 14.9-19.4) and it was higher over 2-fold higher in males than in females (24.8 vs 10.9) and was mainly associated with T2DM (Kruljac et al. 2017). It is important to note we cannot preclude biases that may affect the publication of case reports including racial biases (Mallinger et al. 2006; Ventura et al. 2022) and differential patterns of prescription of antipsychotic medicine in certain populations (Aggarwal et al. 2021; Maestri et al. 2021). We acknowledge that prescription practice may differ between countries, health care settings and can shift due to market influence.

Findings indicated most patients who developed DKA had been diagnosed with schizophrenia and were being treated with olanzapine, an atypical APD. People suffering from this neurological condition have an elevated risk for diabetes (Suvisaari et al. 2016; Ward & Druss, 2015). One observational study showed that the incidence of DM presenting as DKA (new-onset DM) in schizophrenia patients is 10-fold higher than in the general population (Hendersen

et al. 2007). It is also well-established that metabolic syndrome conditions in patients treated with APDs are due to insulin resistance and weight gain (Bak et al. 2014; Henderson et al. 2006). It has been shown insulin resistance can inhibit the response to treatment with an APD and may be an indicator of schizophrenia, independent of demographic elements (sex, age and gender), lifestyle and clinical factors in first-episode antipsychotic naïve patients (Tomasik et al. 2019). A recent systematic review and meta-analysis of atypical APDs trials in healthy volunteers demonstrated that these medications could lead to a decrease in insulin resistance and an increase in weight gain directly, independent of the psychiatric condition. Insulin resistance is not dependent on weight gain, and both factors were determined to be associated with duration of drug use (Burghardt et al. 2018).

Another recent systematic review evaluated the association between use of antidepressant and antipsychotic drugs and weight gain in cohort studies (Alonso-Pedrero et al. 2019). Evaluation of results from 27 cohort studies that included children and adult subjects showed that atypical antipsychotics (quetiapine, olanzapine, clozapine, risperidone and aripiprazole) and typical antipsychotics (haloperidol and trifluoperazine) increased body weight $\geq 7\%$ from baseline, a clinically significant result. Patients treated with antidepressants demonstrated a 5% weight gain. Furthermore, antipsychotic switching can be associated with weight gain or loss, usually with the gain exceeding the loss (Campforts et al. 2023). Antipsychotic-naïve patients were more susceptible to gain weight (Bak et al. 2014; Campforts et al. 2023; Tek et al. 2016). In our current analysis, it was difficult to establish an accurate timeline for weight changes relative to APD since some patients had an elevated BMI prior to the occurrence of the complication, or

their BMI was unknown, but it is safe to assume that most patients were not antipsychotic-naïve, considering their diagnosis with different neurological conditions.

There is evidence that both olanzapine and clozapine are associated with prominent weight gain (Allison et al. 1999; Alvarez Jimenez et al. 2008; Bak et al., 2014; 2021; Correll et al. 2011; Huhn et al. 2019; Leucht et al. 2013; Parsons et al. 2009; Pillinger et al. 2020; Rummel-Kluge et al. 2010). Both drugs may also increase the risk of DKA (Koller et al. 2001; 2002). Campforts et al. (2023) suggested that a weight increase or decrease of 7% or more can provide a better understanding of body weight changes associated with treatment with APDs in lieu of evaluating weight as a continuous variable. In the present review, most cases presenting with DKA were attributed to treatment with olanzapine, followed by clozapine, while most HHS cases were either attributed treatment with olanzapine or quetiapine. A recent comparative review and meta-analysis conducted by Yu et al. (2019) compared individual SGAs - aripiprazole, ziprasidone and risperidone - to olanzapine in Chinese patients with schizophrenia: olanzapine was found to be more likely to induce insulin resistance in these patients. In addition to a significant higher insulin resistance index, patients treated with olanzapine had a significantly higher fasting blood glucose and fasting insulin levels than patients treated with the other SGAs.

In the CRs included in this review, the occurrence of DKA or HHS preceded the diagnosis of a diabetic condition in most reports. There could be several reasons for this. First, in the absence of an absolute or relative insulin deficiency for the patient, diabetic biomarkers were not assessed. Second, the potential for an increased risk of a hyperglycemic emergency due to

treatment with an APD was not of concern at the time of treatment, and therefore glucose levels were not evaluated further. This is supported by the average glucose level of 107.9 mg/dl prior to presentation with a diabetic complication in the CRs that provided this glycemic information. Third, patient compliance to clinical follow up may have been limited, and therefore, there may have been reduced availability of diagnostic tests and corresponding results.

The diabetogenic properties of antipsychotic drugs are not fully understood. As such, the mechanisms of action by which olanzapine and clozapine may cause a hyperglycemic crisis remains unclear, but it is possible they involve different factors, and it is hypothesized that APDs can exert a strong antagonism of multiple receptors and subsequent increased insulin resistance through inhibition of pancreatic insulin secretion. Vuk et al. (2017) even suggested that in patients maybe suffering from insulin resistance prior to antipsychotic treatment, there is the added factor of multi-receptor antagonists' antipsychotics that would produce a state of artificial insulinopenia which presents as DKA. This is supported by the resolution of DKA and HHS based on discontinuation of the agent, dietary changes, or administration of a hypoglycemic drug once insulin is withdrawn (Ai et al. 1999; Coli et al. 1999; Koval et al. 1999). It is clear from our analysis and as reported by others (Guenette et al. 2013) that antipsychotic induced DKA can occur after initiation of treatment, in the presence or absence of weight gain. There could be several explanations for new-onset DKA. First, patients may have a pre-existing T1DM condition that will result in the development of DKA. Second, the development of T2DM will result in a higher BMI and insulin resistance overtime. And third, sudden and severe new

onset of DKA can imitate acute antipsychotic insulin resistance, unrelated to BMI increase (Vuk et al. 2017).

2.4.1 Strengths

Our systematic review offers a thorough analysis of CRs where DKA or HHS were the outcome of interest and was attributed to the use of at least one APD. This review included data that support earlier conclusions about DKA, and to our understanding, is the first fulsome analysis of CRs on HHS. Additionally, where data was available, we assessed pertinent biomarkers at three different times for each CR: prior to presentation with the complication, during presentation, and after resolution of the hyperglycemic crisis. These evaluations supported known facts regarding changes in glucose and HbA1C values in patients hospitalized with these hyperglycemic emergencies. To shed light on diagnostic methods and the aetiology of both conditions, we critically appraised each CR against eight specific criteria developed by the Joanna Briggs Institute. This evaluation provided insight into the diagnostic criteria as well as the management of DKA and HHS.

2.4.2 Limitations

Each CR is written uniquely and with a varied level of information. It was challenging to create a precise timeline of events, including historical information regarding each case, even though we exercised due diligence in extracting all pertinent information. We recognize there are data gaps in the information presented on patient history, quantitative data, and condition management. There are also limitations in interpreting HHS data, considering the small number of CRs and the lack of previous reviews on this issue. Nonetheless, CRs offer valuable

information on the etiology of DKA and HHS, and they may be used to suggest future research questions; however, conclusions drawn from these publications should be interpreted with caution.

2.5 CONCLUSION

This review provides additional evidence of an association between APDs and two hyperglycemic complications, namely DKA and HHS. More research is needed to shed light on the mechanisms of action of these drugs and ensure effective and safe use in patients who are susceptible to developing conditions associated with metabolic syndrome. Even though we acknowledge that this evaluation may be somewhat subjective, this information offers important clinical insight into the etiology of these conditions in relation to APD use and will encourage a preventative approach to address hyperglycemic emergencies.

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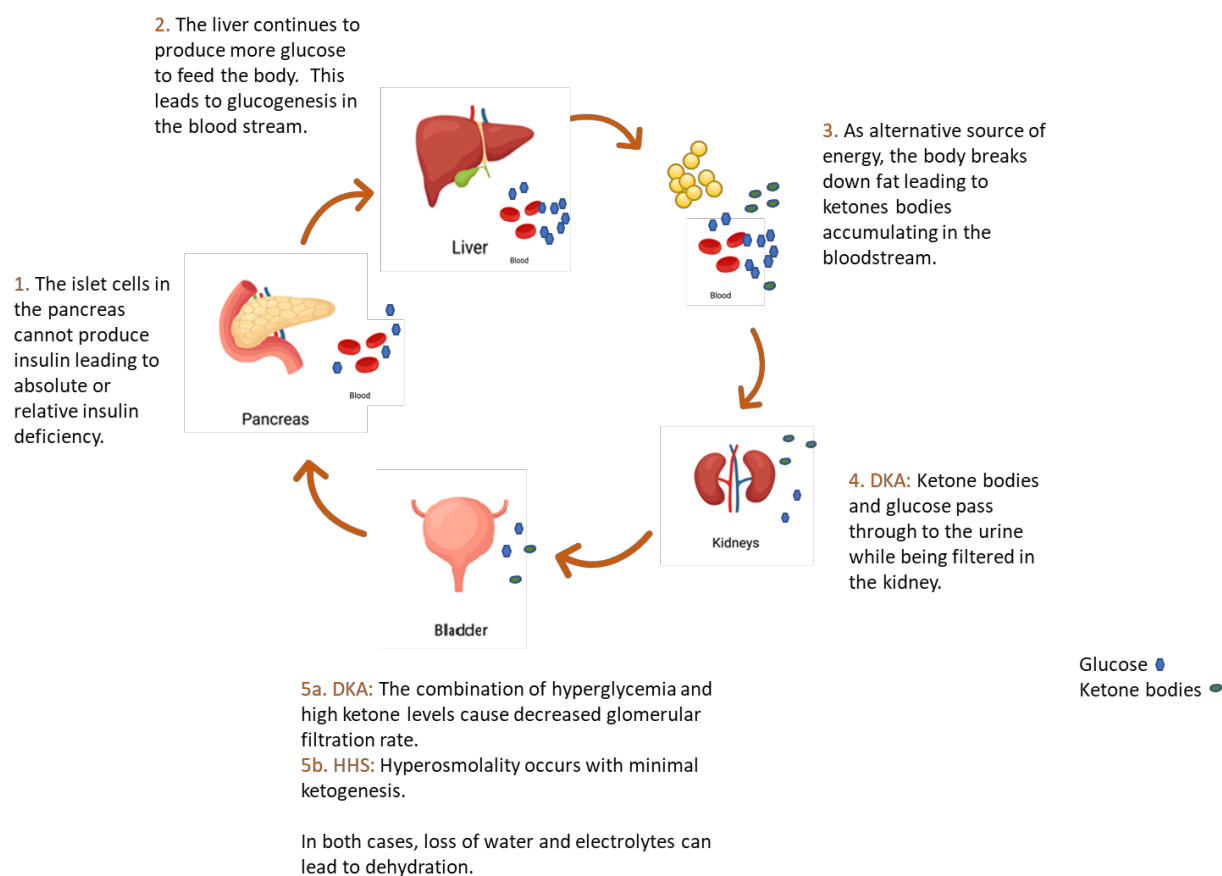
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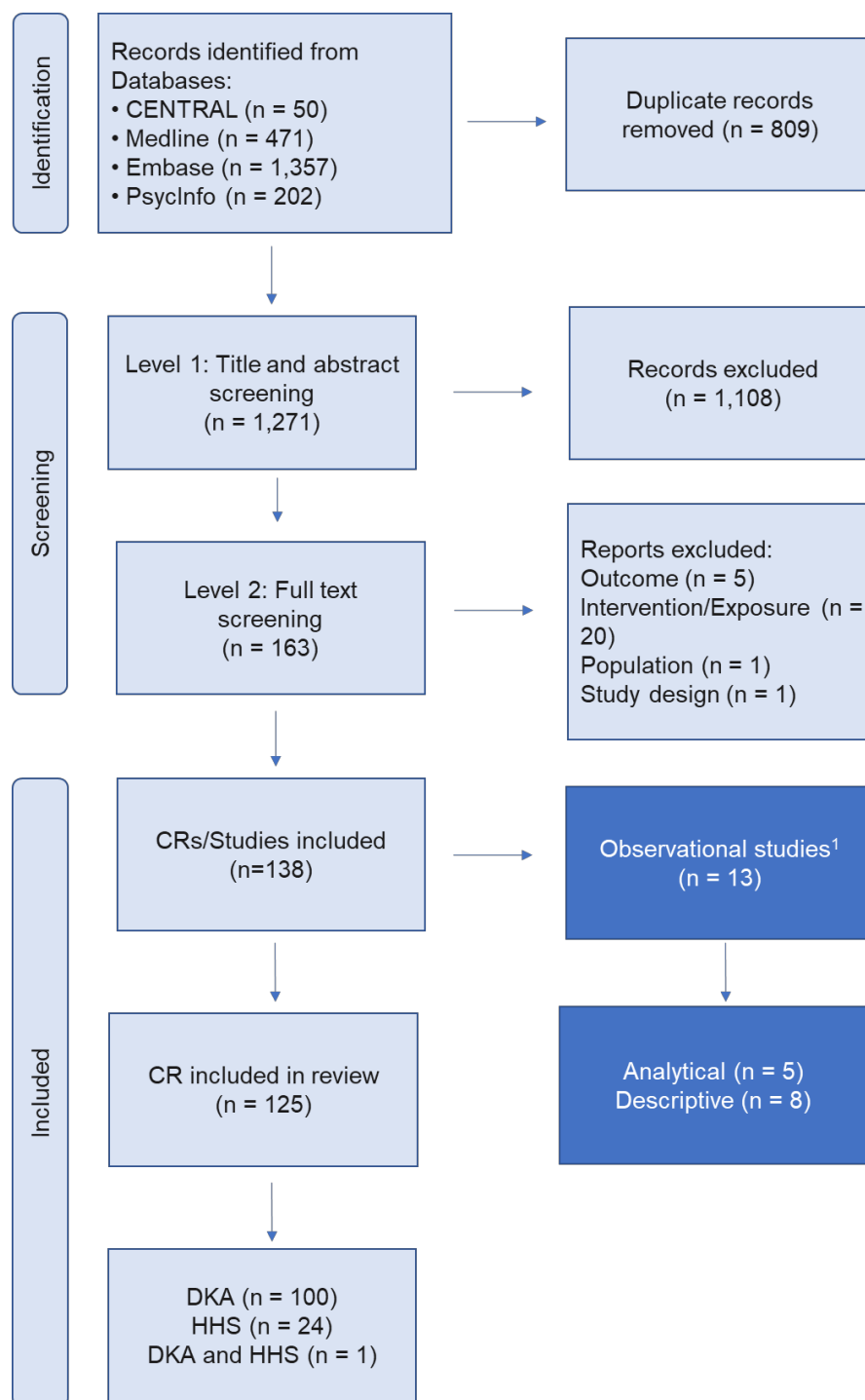
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FIGURES

Figure 2.1. Pathogenesis of Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State¹

Abbreviations: DKA, Diabetic ketoacidosis; HHS, Hyperglycemic hyperosmolar state

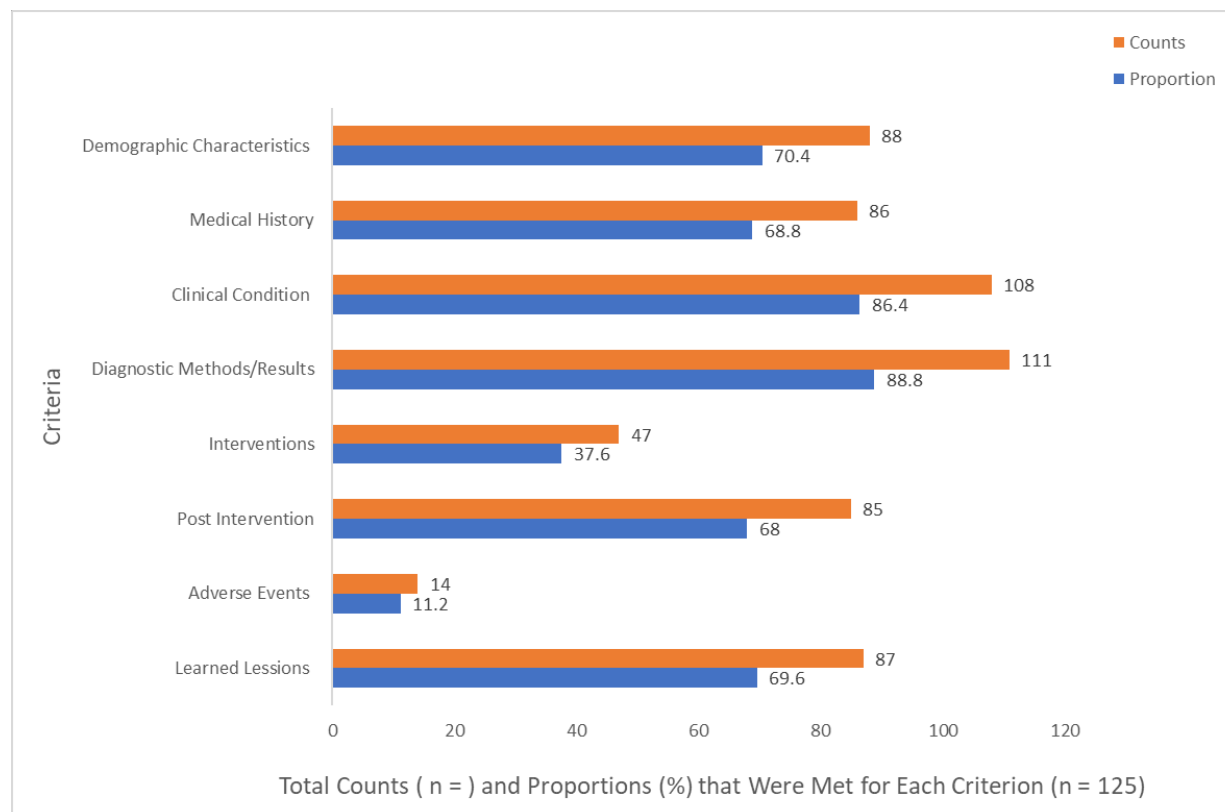
¹Adapted from the Nipro-Group Corporation. Available at: <https://www.nipro-group.com/en/inspire/diabetic-ketoacidosis-dka-why-should-it-matter-me>

Figure 2.2. Flow Chart for the Selection of Case Reports Included in the Systematic Review¹

Abbreviations: CR, Case Report; CENTRAL, Cochrane Central Register of Controlled Trials; DKA, Diabetic ketoacidosis; HHS, Hyperglycemic hyperosmolar state.

¹A separate review for observational studies is presented in Chapter 3 of the thesis.

Figure 2.3. Overall Results for the Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2}.



¹The Joanna Briggs Tool for Critical Appraisal was used as a quality assessment tool for each case report.

²Cases were fatalities occurred could not be assessed for every criterion. **TABLES**

Table 2.1. Diagnostic Criteria for Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State in the United States¹.

Diagnostic Criteria	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose, mg/dl (mmol/L)	>250 (13.9)	>250 (13.9)	>250 (13.9)	>600 (>33.3)
The presence of ketones in the Urine or blood, mmol/l	Positive	Positive	Positive	Small traces
Confirmation of acidosis - Serum bicarbonate mmol/l	15 - 18	10 - < 15	< 10	>20 mmol/L
Confirmation of acidosis - pH	7.25 - 7.30	7.00 - < 7.24	< 7.00	>7.30
Confirmation of acidosis- Anion gap	>10	>12	>12	<12
Mental health changes	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

Abbreviations: DKA, Diabetic Ketoacidosis; HHS, Hyperglycemic hyperosmolar state.

¹Adapted from Kitabchi et al. (2006; 2009)

Table 2.2. Summary of the Characteristics of Patients Diagnosed with Diabetic Ketoacidosis Associated with Antipsychotic Drug Use (n = 100)¹⁻⁶.

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
1	Agrawal <i>et al.</i> (2016)	45,M, African American	BD	Olanz. (NS)	MT	3 months	Y	D	No patient history	N	800	NS	Y	Y
2	Ai <i>et al.</i> (1998)	30,M, Afro-Caribbean	S	Cloz. (300)	MT	5 months	Y	NS	No patient/family history	After	439.2	11	Y	Y
3	Akunjee <i>et al.</i> (2018)	36,NS, African American	S	Olanz. (NS)	PP (Risp.)	NS	Y olanz.	I	Patient History	N	NS	13.7	NS	Y
4	Al-Amri (2009)	27,F, Arab	BD	Olanz. (10)	MT	2.5	Y	I (33.3)	No history	After	695.7	NS	Y	Y
5	Alex <i>et al.</i> (2018)	38,M, Indian	SD, BD	Cloz. (250)	MT	3 months	Y	SM	Family history	After	378	14	Y	Y
6	Ananth <i>et al.</i> (2004)	46,M, NS	BD	Risp. (3)	MT	2 years	Y	NS	No family history	NS	1201	NS	NS	Y
7	Aruna <i>et al.</i> (1995)	26,M, NS	BD	Chlorp. (1000)	PP (Halop.)	1 month	Y	NS	Family history	N	NS	4.2	Y	Y
8	Avella <i>et al.</i> (2004) (Case 1)	37,F, African American	S, BD, BPD	Olanz. (15)	MT	3 years	N/A	NS (OB)	No patient history	N	839	NS	Y	N/A

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
9	Avella et al. (2004) (Case 2)	27,M, NS	BD	Olanz. (7.5)	MT	2.5 years	N/A	NS (OB)	No patient history	N	640	14.3	Y	N/A
10	Avella et al. (2004) (Case 3)	34,M, NS	S	Olanz. (7.5)	MT	4-5 months	N/A	NS	No patient history	N	833	14.7	Y	N/a
11	Avram (2001)	33,M, Caucasian	S	Cloz. (100)	MT	8 months	Y	D (32.5/OW)	No patient/family history	N	544.3	14	Y	Y
12	Buch et al. (2003)	42,M, Caucasian	S	Olanz. (15)	MT	3 months	Y	D	No patient/family history	N	642.6	NS	Y	Y
13	Cardinale et al. (2019)	46,F, NS	DP	Arip. (NS)	MT	24	NS	NS	NS	NS	720	NS	NS	Y
14	Chellamuthu et al. (2010)	42,M, South Asian	S	Risp. (NS)	MT	NS	Y	SM	No patient/family history	After	1679.4	13.8	NS	Y
15	Cho & Lindenmeyer (2009)	45,F, Black	S	Cloz. (NS)	PP (Halop.)	16 months	Y cloz.	NS	No patient history	NS	400	NS	Y	NS
16	Church et al. (2005)	34,F, African American	S	Arip. (30)	PP (Olanz.)	4 days	Y	NS	Patient history	Before	502.4	NS	Y	Y

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
17	Colli et al. (1999)	31,M, Caucasian	SD, BD	Cloz. (200)	MT	3 months	Y for 3 days	I (29/OW)	No patient/family history	N	756	NS	Y	Y
18	Courvoisie et al. (2004)	7,M, Caucasian	BD	Olanz. (2.5)	MT	9 months	Y	I (OW)	Family history	NS	260	NS	Y	Y
19	Croarkin et al. (2000) ²	42,M, Caucasian	MDD, PS	Risp. (4)	MT	6 months	Y	NS (31)	No patient/family history	NS	565	11.4	Y	Y
20	Crown et al. (2007)	NS,NS, African Canadian	DP, ANX	Olanz. (10)	MT	18 months	Y	SM	No patient/family history	After	701.2	14.9	Y	Y
21	Dahri et al. (2002)	22,M, Caucasian	S	Olanz./ Risp. (10/8)	PP	1 year	Y both	NS (40/OW)	Family history	N	432	NS	Y	Y
22	Das et al. (2018)	40,F, NS	BD	Quet. (400)	MT	10 months	Y	NS (40.9/OB)	No patient/family history	After	443	9.2	Y	Y
23	de Boer & Gaete (1992)	44,M, NS	S	Chlorp. (800)	PP (Zuclop.)	3 weeks	Y	NS (OW)	No patient history	N/A	1126.8	NS	NS	NS
24	Dhamija et al. (2008)	12,M, Caucasian	MD	Arip. (NS)	MT	6 months	Y	I	No patient history	NS	478	NS	NS	Y

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
25	Dibben et al. (2005) (Case 1)	51,F, Caucasian	S	Quet. (400)	MT	2 years	Y	S (31/OB)	No patient/family history	NS	954	7.2	Y	Y
26	Dibben et al. (2005) (Case2)	33,M, Asian	S	Risp. (1.8)	MT	8 months	Y prior to DKA occurrence	S (28/OW)	No patient history	After	1189.8	13.4	Y	Y
27	Fullbright & Breedlove (2006)	42,M, African American	S	Olanz. (40)	MT	7 months	Y	D (33/OB)	No patient history	NS	1386	NS	Y	Y
28	Gatta et al. (1999) ⁴	31,M, Caucasian	O	Olanz. (10)	PP (Traditional APDs, NS)	3 months	Y	D (40)	No patient/family history	N	648	14.7	Y	Y
29	Goldstein et al. (1999) (Case 1)	42,F, Caucasian	S	Olanz. (10)	MT	6	Y	I (36)	Family history	N	1107.8	11.6	Y	Y
30	Goldstein et al. (1999) ⁴ (Case 2)	40,F, Caucasian	S	Olanz. (10)	MT	17 months	Y	I (27.2/OB)	No patient/family history	N	1008.7	NS	Y	Y
31	Greenfield et al. (2002)	38,M,NS	S	Thior. (NS)	MT	NS	Y	NS	Patient history	After	887.4	13.6	Y	Y
32	Hepburn & Brzozowska (2016) ³	44,M, NS	S	Cloz. (NS)	MT	13 years	Y, during hospitalization Reduced dose (150 mg/day)	SM	Patient & family history	After	419.4	14.6	Y	Y

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
33	Horber et al. (2018)	52,F, NS	S	Risp. (NS)	MT	Many years	NS	NS	No patient/family history	N	1687	12.2	Y	Y
34	Howes & Rifkin (2004)	41,F, NS	S	Olanz. (20)	MT	3 months	N	I (29.3)	Family history	N	1075.3	NS	Y	Y
35	Itoh et al. (2019)	66,M, NS	DP	Quet. (25)	MT	3 months	Y	I	Family history	N	1709	13.1	Y	Y
36	Iwaku et al. (2017)	32,M, NS	S	Olanz. (5)	PP (Quet.)	5 months	Y	D (16.9)	No family/patient history	N	490	15.5	Y	Y
37	Jalota et al. (2015)	21,M, Asian	S	Quet. (NS)	MT	1 year	Y	I (OB)	Family history	After	378	13.3	Y	Y
38	Johnson et al. (2002)	49,M, Caucasian	S	Olanz. (20)	MT	11 months	N	I (37.8/OB)	No patient/family history	N	368	NS	Y	Y
39	Kahn & Bourgeois (2007) (Abstract)	29,M, African American	S	Olanz. (30)	MT	NS	Y	NS	Family history	After	1652	15.2	Y	Y
40	Kasmi (2013)	29,M, Arab	NS	Cloz. (NS)	MT	NS	Y	NS (OB)	No patient/family history	After	NS	NS	NS	NS

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
41	Kibbey et al. (2010)	29,M, Asian	S	Arip. (40)	MT	12	N, Half dose	I (40/OB)	No family history	N/A	781.2	15.9	Y	Y
42	Kinoshita et al. (2014)	29,M, Asian	DP	Olanz. (2.5)	MT	3 months	Y	NS	No patient / family history	N	771	9.6	Y	Y
43	Kostakoglu et al. (1996)	42,M, NS	S	Cloz. (350)	MT	4 weeks	Y	NS (OB)	Family history	N	338.7	NS	Y	Y
44	Koval et al. (1994)	34,F, African American	S	Cloz. (250)	MT	6 weeks	Y	NS	family history	After	1064.3	NS	Y	Y
45	Kyriazis et al. (2006)	33,M, Caucasian	PS	Olanz. (20)	MT	4 months	Y	NS (37)	family history	N	478	NS	Y	Y
46	Lafayette et al. (2003)	22,F, Hispanic/Italian	S	Cloz. (150)	PP (Risp.)	9 weeks	Y	D (33/OB)	Family history	N	445.2	12.2	Y	Y
47	Laghate & Gupta (2004)	31,M,NS	BD	Chlorp./ Halop. (200 /10) (I)	PP	NS	Y, both	NS	Family history	N	580	NS	Y	Y
48	Lindmeyer et al. (1999)	50,M, African American	S, ASPD	Olanz. (30)	PP (Fluph.)	6	Y	D	No history	N	1200	NS	NS	Y

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
49	Lu & Yan (2009)	27,M, NS	S	Risp. (NS)	MT	2 months	Y	NS	No patient history	N	1127.8	13.7	Y	Y
50	Mcfarlane & Fisher (2006)	33,M, NS	S	Olanz. (10)	PP (Quet.)	two years	y	D	No patient/family history	N	1422	NS	Y	Y
51	Madsen (2014)	27,M, NS	S	Quet. (400)	MT	1 year	N/A	N	No family history	N	504	NS	NS	N/A
52	Makhzoumi et al. (2008)	44,M, African American	S	Arip. (30)	PP (Fluph.)	0.6	Y	D (41.1/OB)	No patient/family history	After	813	14.9	Y	Y
53	Maksimovic et al. (2006)	29,M, Caucasian	S	NS (NS)	PP (Risp./Prom)	NS	N	NS	no history	N	540	12.9	Y	Y
54	Marlowe et al. (2007)	45,M, NS	BD	Quet. (800)	MT	6 months	Y	S (27.6)	No patient history	After	1492	NS	Y	Y
55	Maule et al. (1999)	50,F, Caucasian	S	Cloz. (400)	MT	30 days	N Red. dose (100-150mg)	NS	family history	N	1000	NS	Y	Y
56	Miller et al. (2008)	56,M, African American	BD	Loxap. (100)	PP (Zipras.)	3 months	N	D (37/OB)	No patient/family history	NS	722	NS	Y	Y

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
57	Mithat et al. (2005)	37,M,NS	S	Risp. (4)	MT	6 months	Y	I (32.7)	No family/patient history	N	562.6	NS	Y	Y
58	Mohan (1999)	30,M,Black	S	Cloz. (325)	MT	3 months	Y	NS	No patient/family history	After	342	NS	NS	NS
59	Muench & Carrey (2001)	38,M,Caucasian	BD	Olanz. (20)	MT	12 months	N	I (31)	Family history: unsure	Before	765	13.4	Y	Y
60	Nahas et al. (2010) (Abstract)	45,F,NS	S	Olanz. (NS)	MT	3 years	Y	NS	Family history	N	621.7	10.3	Y	Y
61	Niazi et al. (2007)	28,M,Arab	S	Olanz. (NS)	MT	18 months	Y	NS (37.7/OB)	No patient/family history	N	709.2	NS	Y	Y
62	Nicolai (2001)	33,M,Indian	S	Cloz. (450)	MT	5 years	Y	NS	NS	N	1479.1	NS	Y	Y
63	Patel et al. (2011) (Abstract)	32,M,NS	DP	Arip. (NS)	MT	3	Y	NS	NS	After	1116	NS	NS	Y
64	Pathmanathan (2013) (Abstract)	53,M,NS	S	Quet. (600)	MT	NS	N Red. dose	NS	Patient history	Before	452	14.2	Y	Y

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
65	Peterson & Bird (1996)	46,M, African American	S	Cloz. (500)	MT	5 weeks	Y	SM	Family history	N	662.6	NS	Y	Y
66	Pierides (1997)	50,M,NS	S	Cloz. (300)	MT	10 days	Y	NS	NS	N	367.8	NS	NS	Y
67	Pillai et al. (2006)	45,M,NS	S	Cloz. (NS)	PP (Risp.)	3 months	N/A	D	Family history	N	416	8.9	Y	Y
68	Popli et al. (1997)	32,M,Black	S	Cloz. (425)	MT	8 weeks	Y Briefly	I (OW)	Family history	After	808.7	NS	Y	Y
69	Ragucci & Wells (2001)	46,F, African American	BD, DP	Olanz. (15)	MT	14 months	Y	SM (39)	Family history	After	957	TBD	Y	Y
70	Rahat et al. (2005)	28,M, NS	S	Olanz. (10)	MT	1 year	N	NS	NS	N	550	NS	Y	N
71	Rashid et al. (2009)	30,F, Asian	S	Quet. (200)	PP (Zipras.)	7 months	Y All APDs	SM (OB)	No patient/family history	NS	1081	NS	Y	NS
72	Ratnakaran (2015)	68,M, NS	DP	Quet. (25)	MT	One day	Y	NS (23)	Family history	After	363	NS	Y	Y

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event 1	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
73	Reddymasu et al. (2006)	33,M, African American	S	Arip. (NS)	MT	18 months	Y	I (41)	No patient/family history	N/A	1769	NS	NS	Y
74	Sa et al. (2013)	29,M, NS	PRD, Hyp, PS	Olanz. (10)	MT	32 months	Y	I (31.7)	No patient or family history	After	1216	13.8	Y	Y
75	Sato et al. (2008)	46,F, Asian	S	Risp. (3)	MT	4 months	NS	SM (21.9)	Family history	N	926	12.2	Y	Y
76	Seaburg et al. (2001)	27,M, African American	S	Olanz. (10)	MT	29 months	N	D (27)	No patient history	After	1240	NS	Y	Y
77	Selva & Scott (2001)	16,F, Hispanic	MDD, AVH	Olanz. (15)	PP (Risp.)	6	Y	I (OW)	Family history	N	581.7	17.7	Y	Y
78	Singh et al. (2013)	35,M, NS	S	Olanz. (10)	PP (Halop.)	13 days	Y	NS	No patient/family history	N	625	NS	Y	Y
79	Sirois (2008)	41,F, Black	DP	Quet. (400)	PP (Risp.)	37 days	NS	NS (37.2)	No patient / family history	NS	1472.4	NS	NS	Y
80	Smith et al. (1999)	40,M,Afro-Caribbean	S	Cloz. (NS)	MT	16 days	NS	NS	No patient / family history	N	990	NS	Y	Y

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event 1	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
81	Straker et al. (2002)	44,F, African American	S	Olanz. (20)	PP (Halop.)	1 month	Y olanz.	I	No patient/family history	After	500	5.9	NS	Y
82	Strassnig et al. (2013) (Case 1)	25,F, Canadian Aboriginal	S	Cloz. (NS)	MT	6 months	Y	I	NS	After	660.6	NS	NS	Y
83	Takashashi et al. (2005)	72,M, Asian	DP	Quet. (50)	PP (Tiapride)	11 days	NS	NS	No patient/family history	After	973	NS	Y	Y
84	Taslipinar et al. (2008) ⁵	26,M, NS	S	Risp. (6)	MT	5 months	Y (31)	NS	No family history	N	338	11.2	Y	Y
85	Tavakoli & Arguisola (2003)	35,M, Caucasian	BD	Olanz. (5)	MT	18 months	Y	I (OW)	Family history	NS	NS	NS	NS	NS
86	Torrey et al. (2003)	45,M, NS	BD	Olanz. (30)	PP (Risp.)	1 month	N/A	NS	No patient history	N	N/A	NS	N/A	N/A
87	Tsuchiyama et al. (2004)	28,M, Asian	S	Olanz. (10)	MT	1 month	Y (28.7)	D	Family history	N	1080	13.7	Y	Y
88	Tugwell et al. (2020)	28,F, African	PM, PS	Olanz. (40)	MT	4	Y	I	Patient & family history	N	896.4	15.8	Y	Y

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event ₁	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
89	Varma et al. (2007)	35,F, NS	BD	Olanz. (10)	MT	6 weeks	Y	NS (28.4)	No patient history	N	1647	13.2	Y	Y
90	Vincent et al. (2017)	39,M, NS	BD, SZA	Risp. (3)	MT	1 year	Y	NS	No patient history	N	457	15.3	Y	Y
91	Vuk et al. (2017)	33,M, Caucasian	S	Cloz. (200)	PP (Halop.)	3 weeks	Y Halop. briefly	I	No patient/family history	After	914.4	8.5	Y	Y
92	Waldman & Yaren (2002)	33,M, Aboriginal	S	Olanz. (30)	MT	3 months	Y Reinstated and disc. again	I	No patient history	After	675	NS	Y	Y
93	Watkins et al. (2011)	55,M, African American	D	Arip. (10)	MT	6	Y	I	No patient history	N	714	13.5	Y	Y
94	Whicher et al. (2019)	28,M, NS	S	Olanz. (10)	PP (Arip.)	3	NS	NS	NS	Y	432	NS	Y	Y
95	Wilson et al. (2002) (Case 1)	48,M, African American	PS	Olanz. (30)	MT	40 weeks	N	I (26.5)	No patient/family history	N	361	NS	NS	Y
96	Wilson et al. (2002) (Case 2)	38,F, African American	S	Olanz. (15)	MT	8 weeks	NS	I (34.7)	No patient/family history	N	578	NS	NS	Y

Patient No	Citation	Age, Sex, Race	Diag.	Primary APD	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after DKA event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Ketones +	Trt w. Insulin
97	Wilson et al. (2002) (Case 3)	64,M, Caucasian	S	Quet. (40)	MT	8 weeks	NS	I (30.2)	Family history, unclear patient history	N	NS	NS	NS	NS
98	Wilson et al. (2002) (Case 4)	26,F, African American	S	Risp. (3)	PP (Cloz.)	7 weeks	Y Risp.	I (40.1/OB)	No patient/family history	N	437	NS	NS	Y
99	Wilson et al. (2002) (Case 5)	33,M, African American	S	Cloz. (550)	PP (Olanz.)	4 weeks	N	I (36.8)	No patient /family history	N	317	NS	NS	Y
100	Wong et al. (2007)	22,M, Asian	S, DPD	Olanz. (10)	MT	39 months	Y	I (28.5)	No personal/family history	N	721.8	11.9	Y	Y

Abbreviations: BG., Blood Glucose; Compl., complication; Diag., diagnosis; Disc., discontinued; Qual, Qualitative; Hist., history; HbA1C., hemoglobin A1c; +, positive; Trt w., treatment with;

ANX, Anxiety; ASPD, Antisocial personality disorder; AVH, Auditory and Visual hallucinations; BD, Bipolar disorder; BPD, Borderline personality disorder; DP, Depression; DPD, Dissocial personality disorder; Hyp, hypochondriasis; MD, Mood disturbances; MDD, Major depressive disorder; PM, Postpartum mania; PRD, personality disorder; PS, Psychosis; S, Schizophrenia; SD, Schizophrenia disorder; SZA, Schizoaffective disorder.

OB, Obesity; OW, Overweight;

Arip., Aripiprazole; Chlorp., Chlorpromazine; Cloz., Clozapine; Halop, Haloperidol; Olanz., Olanzapine; Loxap, Loxapine; Prom, Promazine; Quet., Quetiapine; Risp, Risperidone; Thior., Thioridazine; Zipra., Ziprasidone; Zuclo., Zuclopenthixol.

D, Decrease; I, Increase; M, Male; N, No; F, Female; SM, Same; MT, Monotherapy; NS, Not specified; PP, Polypharmacy; Y, Yes.

¹Any antidiabetic drugs excluding insulin.

²The case report detailed few months from the administration of the APD to time to complication, therefore a mid-point of 6 months was assumed.

³For this CR, it took 13 years to complication. As this is a significant outlier relative to other CRs of patients treated with the same drug, the time to complication was not included in subsequent analysis for this CR.

⁴Other includes treatment refractory disorder, drug induced conditions.

⁵Added after cross reference with Vuk et al. (2017).

⁶Hui Fang et al. (2018) described a co-occurrence with diabetic ketoacidosis and hyperglycemic hyperosmolar state and was not included in the Tables.

Table 2.3. Summary of the Characteristics of Patients Diagnosed with Hyperglycemic Hyperosmolar State Associated with Antipsychotic Drug Use (n = 24)^{1,2}.

Patient No	Citation	Age, Sex , Race	Diag.	Primary APDS Dose (mg/day)	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after HHS event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Osm. Levels	Trt w. Insulin
1	Ahuja et al. (2010)	35,F, Caucasian	BD	Olanz. (10)	MT	5 weeks	Y	SM	No patient/family history	N	1,647	13.2	373 mOsm/kg	Y
2	Balzan & Cacciottolo (1992)	50,M, Caucasian	DP, PS	Halop. (20)	PP (Triflu.)	5 days	NS	NS	No patient history	N	810	NS	368 mOsm/kg	Y
3	Campanella et al. (2009)	48,M, NS	S, MDD	Aripip. (30)	MT	NS	Y	NS	No patient history	N	2,474	NS	NS	Y
4	Cerimele (2008)	39,M, NS	S, PS of EP	Risp. (4)	MT	36 months	Y	I (OB)	No patient history	N	1,025	14.6	378 mOsm/kg	Y
5	Chen et al. (2003)	33,M, East Asian	BD	Olanz. (5)	PP (Halop.)	5 days	Y	NS	No patient/family history	Y	975	13.6	324 mmol/kg	Y
6	Chen et al. (2011)	39, M,NS	BD	Quet. (100)	PP (Arip., Sulp.)	5 months	Y, Quet.	D	Family history	Y, NS	713	13.6	1084 mmol/kg	Y
7	Endoh et al. (2012)	36,M, Asian	NA	Olanz. (7.5)	MT	6 weeks	Y	NS (30.7)	Family History	Y	1,605	12.3	426 mOsm/kg	Y
8	Franco et al. (2012) (Abstract)	66,F, Hispanic	ALZ	Quet. (100)	MT	NS	Y	NS	NS	N	832	NS	428 mOsm/L	Y

Patient No	Citation	Age, Sex , Race	Diag.	Primary APDS Dose (mg/day)	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after HHS event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Osm. Levels	Trt w. Insulin
9	Franco et al. (2015)	50,M, Caucasian	BD	Quet. (NS)	MT	6 months	Y	NS (OB)	Patient history	NS	533	10.4	NS	Y
10	Kaino et al. (2017)	27,F, NS	PD	Olanz. (20)	MT	4 months	Y	NS	No patient history	Y	762	NS	430 mOsm/L	Y
11	Kaya et al. (2014)	67,M, NS	DEM, DP, PS	Quet. (200)	MT	25 days	Y	NS	Patient history	Y	693	12	400 mOsm/kg	Y
12	Khan et al. (2011)	36,M, NS	MDD	Quet. (400)	MT	NS	N/A	NS (OB)	NS	NS	2,198	NS	376 mOsmol/Kg	Y
13	Letourneau et al. (2011)	26,M, Caucasian	S	Zipras. (160)	MT	10 weeks	Y	I (38)	Family history	Y, Met	1,224	13.5	NS	Y
14	Maust et al. (2015)	19,M, African American	S	Perph. (8)	MT	1 week	Y	NS (27)	No family history	Y	995	9.7	328 mOsm/Kg	Y
15	McCall et al. (2004)	35,F, African American	BD	Olanz. (10)	MT	3 months	Y	NS (OB)	Family history	N	1,896	NS	399 mOsm/kg	Y
16	Meatherall et al. (2002)	31,M, NS	S	Olanz. (20)	MT	0.7 month	N/A	I (28)	No patient/family history	N	284	12.3	N/A	N/A

Patient No	Citation	Age, Sex , Race	Diag.	Primary APDS Dose (mg/day)	Type of Therapy	Time to compl.	APD Disc.	Overall Weight Changes (BMI/Qual.)	Hist. DM	Antidiabetic before / after HHS event ¹	BG at Pres. (mg/dl)	HbA1C at pres. (%)	Osm. Levels	Trt w. Insulin
17	Milano et al. (2016)	41,F, NS	BD	NS (NS)	PP (Quet., Luras.)	NS	N/A	NS	No patient history	N	1,403	NS	371 mmol/kg	Y
18	Raza S. (2007)	37,F, NS	PS	Quet. (NS)	MT	1 week	Y	NS	No patient/family history	NS	2,034	NS	NS	Y
19	Rock et al. (2009)	25,M, NS	S & M.S.	Halop. (NS)	MT	NS	NS	SM	Patient history	Y	880	NS	380 mOsm/kg	Y
20	Roefero & Mukherjee (2001)	51,M, Caucasian	PTSD, BD	Olanz. (25)	MT	7.5 months	Y	SM (OB)	No patient/family history	N	1,388	13.3	405 mOsm/L	Y
21	Short & Nolan (1994)	61,F, NS	S	Cloz. (250)	PP (Triflu., Chlorp.)	0.5	U	NS (OW)	NS	Y	1,542	NS	NS	N
22	Takanobu et al. (2015)	47,M, NS	S	Risp. (6)	PP (Levom, Chlorp.)	NS	NS	NS	Patient history No family history	Y	401	7	402 mOsm/L	Y
23	Tollefson et al. (1983)	49,F, NS	BD	Loxa. (150)	MT	9 days	Y	NS	No patient/family history	N	942	NS	314 mOsm/L	Y
24	Yeung & Lee. (2015) (Abstract)	45,M, African American	NS	Quet. (400)	MT	NS	NS	NS	NS	N	1,400	NS	NS	Y

Abbreviations: BG., Blood Glucose; Compl., complication; Diag., diagnosis; Disc., discontinued; Qual, Qualitative; Hist., history; HbA1C, Hemoglobin A1c; Osm, Osmolality; Trt w., Treatment with.

ALZ, Alzheimer; BD, bipolar disorder; DP, Depression; DEM, dementia; EP, epilepsy; MDD, major depressive disorder; M.S., Munchausen syndrome; NA, Narcolpesy; PS, psychosis; PTSD, Post traumatic stress disorder; S, Schizophrenia.

OB, Obesity; OW, Overweight.

Arip., Aripiprazole; Chlorp, Chlorpromazine; Halop, Haloperidol; Levom, Levomeprazine; Lura, Lurasidone; Olanz., Olanzapine; Quet., Quetiapine; Perph, Perphenazine; Risp., Risperidone; Sulp, Sulpiride; Trifu, Trifluoperazine; Zipra, Ziprasidone.

D, Decrease; I, Increase; M, Male; N, No; F, Female; SA, Same; MT, monotherapy; N, no; NS, Not specified; PP, Polypharmacy; U, Unsure; Y, yes.

¹Any antidiabetic drugs excluding insulin.

²Hui Fang et al. (2018) described a co-occurrence with diabetic ketoacidosis and hyperglycemic hyperosmolar state and was not included in the Tables.

Table 2.4. Descriptive Statistics on Demographic Characteristics, Diagnosis, Antipsychotic Drug Use, Comorbidities and Other Issues in Patients Diagnosed with Diabetic Ketoacidosis (n = 100) or Hyperglycemic Hyperosmolar State (n = 24) Case Reports¹⁻⁷.

	DKA	HHS	Overall (n = 124)
	Counts (%)		
Biological Sex			
Male	72 (72)	16 (67)	88 (71)
Female	26 (26)	8 (33)	34 (27)
NS	2 (2)	---	2 (2)
Age, y			
<18	3 (3)	0 (0)	3 (2)
18-29	24 (24)	4 (17)	28 (23)
30-39	32 (32)	9 (38)	41(33)
40-49	28 (28)	5 (21)	33 (27)
50-59	8 (8)	3 (13)	11 (9)
60-69	3 (3)	3 (13)	6 (5)
>69	1 (1)	---	1 (0.8)
NS	1 (1)	---	---
	Avg.±SD (37.3±11.2)	Avg.±SD (41.4±12.6)	
Race ¹			
African American	20 (20)	3 (13)	23 (19)
Caucasian	19 (19)	5 (21)	24 (19)
Asian	10 (10)	2 (8)	12 (10)
Other	18 (18)	1 (4)	19 (15)
NS	33 (33)	13 (54)	46 (37)
Mental Health Diagnoses			
Schizophrenia	59 (59)	5 (21)	64 (52)
Bipolar Disorder	14 (14)	6 (25)	20 (16)
Depressive disorders (including severe depression)	8 (8)	4 (17)	12(10)
Psychosis Disorders	2 (2)	1 (4)	3 (2)
Other Diagnoses ²	2 (2)	4 (16)	6 (5)
Two or more diagnoses ³	14 (14)	3 (13)	17 (14)
NS	1 (1)	1 (4)	2 (2)
Primary Antipsychotic Causing Complication			
Atypical Antipsychotics			
Olanzapine	41 (41)	7 (29)	47 (38)
Clozapine	21 (21)	1 (4)	22 (18)
Quetiapine	12 (12)	7 (29)	19 (15)
Risperidone	11 (11)	2 (8)	13(11)
Aripiprazole	8 (8)	1 (4)	2 (2)
Typical Antipsychotics	4 (4)	1 (4)	5 (4)
Combination of two APDs ⁴	2 (2)	---	2 (1)
NS	1 (1)	1 (4)	2 (1)
Type of Therapy			
Monotherapy	73 (73)	18 (75)	91 (73)
Polypharmacy	28 (28)	6 (25)	34 (27)

Table 2.4. Descriptive Statistics on Demographic Characteristics, Diagnosis, Antipsychotic Drug Use, Comorbidities and Other Issues in Diabetic Ketoacidosis (n = 100) or Hyperglycemic Hyperosmolar State (n = 24) Case Reports¹⁻⁷ (cont.).

	DKA	HHS	Total (n = 124)
	Counts (%)		
AAP Discontinued			
Yes	71(71)	16 (68)	87(70)
No	12 (12)	---	12(10)
NS/N/A or Unsure	15 (15)	8 (21)	23(19)
Antipsychotic Switching			
After DKA/HHS	37 (37)	4 (17)	41(33)
N	29 (29)	8 (33)	37(30)
Other (NS, U, Before DKA/HHS or N/A)	33(33)	12 (50)	46(37)
Comorbidities			
Yes	28(28)	8 (33)	36(29)
None	26 (26)	5 (21)	31(25)
NS	46 (46)	11 (46)	57(46)
Other issues			
Substance/Alcohol Abuse	14 (14)	4 (17)	18(15)
Tobacco Use	6 (6)	---	6(5)
Tobacco Use & Alcohol Abuse/ Tobacco Use and Substance Abuse	2 (2)	---	2(2)
None	35(35)	12(50)	47(38)
NS/N/A	43 (43)	8 (33)	51(41)

Abbreviations: APD, antipsychotic; Avg, Average; NS, not specified; DKA, diabetic ketoacidosis; HHS, Hyperglycemic Hyperosmolar State

¹Proportions are based on total DKA reports (100) or HHS reports (24) or overall (124)

²Other race includes Aboriginal, African, African Canadian, Afro-Caribbean, Arab, Black, Hispanic, Indian, Mixed Race.

³Other diagnoses includes Schizophrenia-like psychosis of epilepsy, Alzheimer's dementia, treatment refractory disorder, thioridazine induced cutaneous leukocytoclastic vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA), panic disorder, mood disorders.

⁴Two or more diagnoses may include a combination of those listed in the table in addition to borderline personality disorder, ADHD, oppositional defiant disorder, anxiety, epilepsy, mental retardation, mood disturbance, narcolepsy, obsessive-compulsive disorder, childhood attention deficit and hyperactivity disorder, antisocial or dissociation personality disorder, Munchausen syndrome, post-traumatic stress, hypochondriasis, auditory and visual hallucinations, postpartum mania

⁵Combination of two antipsychotics causing diabetic complication: One case was attributed to atypical APDs: treatment with clozapine and risperidone; one case was attributed to typical APDs: treatment with chlorpromazine and haloperidol.

⁶Other antipsychotic switching includes fatal cases, one case where switching occurred before DKA, cases it is unclear if switching occurred.

⁷For case reports, APD monotherapy was assumed unless polypharmacy treatment with more than one APD at the time of presentation was clearly stated in the report.

Table 2.5. Descriptive Statistics on History of Diabetes and Relevant Biomarkers for Diabetic Ketoacidosis (n = 100) and Hyperglycemic Hyperosmolar State (n = 24) in Case Reports¹⁻⁴.

	Counts (%)	
	DKA	HHS
History of Diabetes, as detailed in the report		
Known Family history	26 (26)	4 (17)
Known patient history	4 (4)	4 (17)
Patient and family history	2 (2)	0 (17)
No known family /patient history	61(61)	12(50)
NS	7 (7)	4 (17)
Diagnosed with DM		
Prior to complication ¹	7 (7)	5(21)
After complication	32(32)	7(29)
Total diagnosis with DM (prior and after complication)	39 (39)	12(50)
Case Reports with Reported Blood Glucose level in mg/dl		
Before complication	27 (27)	9 (38)
Avg. BG±SD	107.9±18.5	100±18.2
At presentation	96 (96)	24 (100)
Avg. BG±SD	800±386	1,194±574.2
After resolution	36 (36)	7 (29)
Avg. BG±SD	143.5±61.6	124.9±29
HbA1C test		
Before complication	5 (5)	6 (25)
Avg. HbA1C±SD	6.3±4.3	5.8±0.8
At presentation	44 (44)	12 (50)
Avg. HbA1C±SD	12.7±2.7	12.1±2.1
After resolution	21 (21)	4 (17)
Avg. HbA1C±SD	6.4±1.3	6.0±0.5
Presence of Blood or Urine Ketones		
Ketone positive	77 (77)	9 (38)
Ketone negative	0 (0)	9 (38)
NS / NA	23 (23)	6 (25)
Weight		
Overweight/Obese ³	46 (46)	10 (42)
Weight ↑	31 (31)	3 (13)
Weight ↓	14 (14)	1 (4)
No change	11 (11)	3 (13)
NS	44 (44)	17 (71)
Type of Recovery⁴		
Full	24 (24)	4 (17)
Partial	61 (61)	14 (58)
Fatal	8 (8)	4 (17)
NS ³	7 (7)	1 (4)

Abbreviations and symbols: Avg, Average; BG, blood glucose; SD, Standard deviation; ↑, increase; ↓, decrease.

¹Patient diagnosed with a type of DM prior to complication, this coincided with the number of patients who had history of DM prior.

²Counts and average of glucose levels do not include quantitative assessment such as descriptions of glucose levels (normal, ↑, ↓)

Plasma and serum glucose levels, when indicated were converted to BG levels.

³Based on qualitative assessment in the CR, or the BMI when available.

⁴Full recovery: The patient would not require antidiabetic or insulin therapy long term, and treatment to manage any diabetes condition would be reduced and eventually stopped fully in the months after the resolution of DKA or HHS. Partial recovery: patient was on antidiabetics to treat any diabetes condition prior to, or after the occurrence of DKA or HHS. In addition, this includes patients (n = 2), where DM was managed solely based on diet.

Table 2.6. List of Case Reports where Fatalities Occurred (n = 12).

Citation	Primary APD/Outcome
Avella et al. (2004) Fatal Olanzapine-Induced Hyperglycemic Ketoacidosis (Case 1)	Olanzapine/DKA
Avella et al. (2004). Fatal Olanzapine-Induced Hyperglycemic Ketoacidosis (Case 2)	Olanzapine/DKA
Avella et al. (2004). Fatal Olanzapine-Induced Hyperglycemic Ketoacidosis (Case 3)	Olanzapine/DKA
de Boer and Gaete (1992) Neuroleptic malignant syndrome and diabetic ketoacidosis.	Chlorpromazine/DKA
Khan et al. (2011) Quetiapine Induced Fatal Neuroleptic Malignant Syndrome (NMS) and Hyperosmolar Hyperglycemic Nonketotic Coma (HHNC)	Quetiapine/HHS
Lu & Yan (2009) Risperidone-associated newly diagnosed diabetes and fatal diabetes ketoacidosis in a young schizophrenic patient.	Risperidone/DKA
Madsen (2014) Fatal hypertriglyceridemia, acute pancreatitis and diabetic ketoacidosis possibly induced by quetiapine	Quetiapine/DKA
Meatherall et al. (2002) Fatality from Olanzapine induced hyperglycemia	Olanzapine/HHS
Milano et al. (2016) An uncommon complication of hyperosmolar hyperglycemic state: bilateral above knee amputations	NS/HHS
Pillai et al. (2006) Diabetic ketoacidosis associated with atypical antipsychotic drug, clozapine treatment: Report of a case and review of literature	Clozapine/DKA
Rock et al. (2009) Haloperidol-induced Neuroleptic syndrome complicated by hyperosmolar hyperglycemic states.	Haloperidol/HHS
Torrey et al. (2003) Fatal olanzapine-induced acidosis	Olanzapine/DKA

Table 2.7. Descriptive Statistics for Olanzapine or Clozapine-Induced Diabetic Ketoacidosis Case Reports¹⁻⁴.

Characteristics	DKA	
	Olanzapine (n = 41)	Clozapine (n = 21)
Gender (n,%)¹		
Female	12 (29)	5 (24)
Male	27 (66)	16 (77)
Unknown	2 (4.9)	---
Age (years; mean±SD)	34.5±9.1	36.4 ± 8.0
Race ^c (n,%)¹		
Caucasian	9 (22)	4 (19)
Afr. American	11 (27)	3 (14)
Other ²	10 (24)	10 (48)
Unknown	11 (27)	4 (19)
Diagnosis (n,%)¹		
Schizophrenia	22 (57)	17 (81)
Bipolar Disorder	8 (20)	1 (5)
Other ³	11 (27)	2 (10)
NS	---	1 (5)
Average time to complication (in months)	11.2	6.2
Dose (mg/day); mean±SD]⁴	15.5 ± 9.8	300±130
APD discontinued (n,%)¹	29 (71)	13 (62)
Switching after DKA or HHS (n, %)¹	15 (37)	10(48)
Recovery		
Full	12 (29)	4 (19)
Partial	24 (59)	14 (67)
Death	4 (10)	1 (5)
NS	1 (2)	2 (10)

Abbreviations: SD, Standard deviation.

¹Proportions are based on the total count for each SGA.

²Other race includes Aboriginal, African Canadian, Arab, Asian, Hispanic, and mixed race.

³Other diagnosis includes psychosis, depression, other mood disorders, and other diagnosis.

⁴Mean dose is based on the highest dose received prior to complication if the dosage was titrated.

SUPPLEMENTAL MATERIAL S2

The following supplemental material provides the search strategy using four bibliographic databases (Supplemental Material I), Distiller SR form for Level 1 screening (Supplemental Material II), the Joanna Briggs Criteria for Assessment of Case Reports (Supplemental Material III). Supplemental Material IV presents additional detailed information for each case report (CR) is presented in (Tables S2.1 and S2.2) and critical appraisal for each CR (Table S2.3).

Supplemental Material I: Search Strategies.

MEDLINE

- 1 Aripiprazole/
(abilify or Aripiprazole or asenapine maleate or saphris or clozaril or clozapine or iloperidone or fanapt or lurasidone or latuda or olanzapine* or zyprexa or symbyax or paliperidone or invega or quetiapine or seroquel or risperidone or risperdal or ziprasidone or geodon or cariprazine or Vraylar or Pimavanserin or Nuplazid).ti,ab,kw.
- 2
- 3 clozapine/
- 4 Lurasidone Hydrochloride/
- 5 Paliperidone Palmitate/
- 6 Quetiapine Fumarate/
- 7 Risperidone/
- 8 Pimavanserin/
- 9 cariprazine/
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- 11 diabetes complications/ or diabetic coma/ or hyperglycemic hyperosmolar nonketotic coma/ or diabetic ketoacidosis/
- 12 (diabet* adj3 complication*).ti,ab,kw.
- 13 hyperglycemi*.ti,ab,kw.
- 14 (diabet* adj3 ketoacidosis).ti,ab,kw.
- 15 (diabet* adj3 (coma* or hyperglycemi*)).ti,ab,kw.
- 16 11 or 12 or 13 or 14 or 15
- 17 10 and 16
- 18 HALOPERIDOL/
(Haloperidol or Haldol or Loxapine or Loxitane or Molindone or Moban or Thiothixene or Navane or Primozide or Orap or Trifluoperazine or Stelazine or Chlorpromazine or Thorazine or Fluphenazine or Perphenazine or "Perphenazine amitriptyline" or Prochlorperazine or Thioridazine or Droperidol or Inapsine).ti,ab,kw.
- 19
- 20 CHLORPROMAZINE/
- 21 FLUPHENAZINE/
- 22 Loxapine/
- 23 PERPHENAZINE/
- 24 Prochlorperazine/
- 25 PROCHLORPERAZINE/
- 26 THIORIDAZINE/

- 27 TRIFLUOPERAZINE/
- 28 THIOTHIXENE/
- 29 Thioridazine/
- 30 Droperidol/
- 31 LOXAPINE/
- 32 MOLINDONE/
- 33 PIMOZIDE/
- 34 Fluphenazine/
- 35 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
or 31 or 32 or 33 or 34
- 36 16 and 35
- 37 17 or 36
- 38 10 or 35
- 39 16 and 38
- 40 limit 39 to yr="2019 -Current"

CENTRAL

- 1 Aripiprazole/
- (abilify or Aripiprazole or asenapine maleate or saphris or clozaril or
clozapine or iloperidone or fanapt or lurasidone or latuda or olanzapine*
- 2 or zyprexa or symbyax or paliperidone or invega or quetiapine or
seroquel or risperidone or risperdal or ziprasidone or geodon or
cariprazine or Vraylar or Pimavanserin or Nuplazid).ti,ab,kw.
- 3 clozapine/
- 4 Lurasidone Hydrochloride/
- 5 Paliperidone Palmitate/
- 6 Quetiapine Fumarate/
- 7 Risperidone/
- 8 Pimavanserin/
- 9 cariprazine/
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- diabetes complications/ or diabetic coma/ or hyperglycemic
- 11 hyperosmolar nonketotic coma/ or diabetic ketoacidosis/
- 12 (diabet* adj3 complication*).ti,ab,kw.
- 13 hyperglycemi*.ti,ab,kw.
- 14 (diabet* adj3 ketoacidosis).ti,ab,kw.
- 15 (diabet* adj3 (coma* or hyperglycemi*)).ti,ab,kw.
- 16 11 or 12 or 13 or 14 or 15
- 17 10 and 16
- 18 HALOPERIDOL/
- (Haloperidol or Haldol or Loxapine or Loxitane or Molindone or Moban
or Thiothixene or Navane or Primozide or Orap or Trifluoperazine or
- 19 Stelazine or Chlorpromazine or Thorazine or Fluphenazine or
Perphenazine or "Perphenazine amitriptyline" or Prochlorperazine or
Thioridazine or Droperidol or Inapsine).ti,ab,kw.
- 20 CHLORPROMAZINE/

- 21 FLUPHENAZINE/
- 22 Loxapine/
- 23 PERPHENAZINE/
- 24 Prochlorperazine/
- 25 PROCHLORPERAZINE/
- 26 THIORIDAZINE/
- 27 TRIFLUOPERAZINE/
- 28 THIOTHIXENE/
- 29 Thioridazine/
- 30 Droperidol/
- 31 LOXAPINE/
- 32 MOLINDONE/
- 33 PIMOZIDE/
- 34 Fluphenazine/
- 35 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
or 31 or 32 or 33 or 34
- 36 16 and 35
- 37 17 or 36
- 38 10 or 35
- 39 16 and 38
- 40 limit 39 to yr="2019 -Current"

EMBASE

- 1 Aripiprazole/
(abilify or Aripiprazole or asenapine maleate or saphris or clozaril or
clozapine or iloperidone or fanapt or lurasidone or latuda or olanzapine*
2 or zyprexa or symbyax or paliperidone or invega or quetiapine or
seroquel or risperidone or risperdal or ziprasidone or geodon or
cariprazine or Vraylar or Pimavanserin or Nuplazid).ti,ab,kw.
- 3 clozapine/
- 4 Lurasidone Hydrochloride/
- 5 Paliperidone Palmitate/
- 6 Quetiapine Fumarate/
- 7 Risperidone/
- 8 Pimavanserin/
- 9 cariprazine/
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
diabetes complications/ or diabetic coma/ or hyperglycemic
11 hyperosmolar nonketotic coma/ or diabetic ketoacidosis/
12 (diabet* adj3 complication*).ti,ab,kw.
- 13 hyperglycemi*.ti,ab,kw.
- 14 (diabet* adj3 ketoacidosis).ti,ab,kw.
- 15 (diabet* adj3 (coma* or hyperglycemi*)).ti,ab,kw.
- 16 11 or 12 or 13 or 14 or 15

- 17 10 and 16
- 18 HALOPERIDOL/
(Haloperidol or Haldol or Loxapine or Loxitane or Molindone or Moban or Thiothixene or Navane or Primozide or Orap or Trifluoperazine or
- 19 Stelazine or Chlorpromazine or Thorazine or Fluphenazine or Perphenazine or "Perphenazine amitriptyline" or Prochlorperazine or Thioridazine or Droperidol or Inapsine).ti,ab,kw.
- 20 CHLORPROMAZINE/
- 21 FLUPHENAZINE/
- 22 Loxapine/
- 23 PERPHENAZINE/
- 24 Prochlorperazine/
- 25 PROCHLORPERAZINE/
- 26 THIORIDAZINE/
- 27 TRIFLUOPERAZINE/
- 28 THIOTHIXENE/
- 29 Thioridazine/
- 30 Droperidol/
- 31 LOXAPINE/
- 32 MOLINDONE/
- 33 PIMOZIDE/
- 34 Fluphenazine/
- 35 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
- 36 16 and 35
- 37 17 or 36
- 38 10 or 35
- 39 16 and 38
- 40 limit 39 to yr="2019 -Current"

PsycINFO

- 1 Aripiprazole/
(abilify or Aripiprazole or asenapine maleate or saphris or clozaril or clozapine or iloperidone or fanapt or lurasidone or latuda or olanzapine* or zyprexa or symbyax or paliperidone or invega or quetiapine or seroquel or risperidone or risperdal or ziprasidone or geodon or cariprazine or Vraylar or Pimavanserin or Nuplazid).ti,ab,kw.
- 3 clozapine/
- 4 Lurasidone Hydrochloride/
- 5 Paliperidone Palmitate/
- 6 Quetiapine Fumarate/
- 7 Risperidone/
- 8 Pimavanserin/
- 9 cariprazine/
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

- 11 diabetes complications/ or diabetic coma/ or hyperglycemic
hyperosmolar nonketotic coma/ or diabetic ketoacidosis/
- 12 (diabet* adj3 complication*).ti,ab,kw.
- 13 hyperglycemi*.ti,ab,kw.
- 14 (diabet* adj3 ketoacidosis).ti,ab,kw.
- 15 (diabet* adj3 (coma* or hyperglycemi*)).ti,ab,kw.
- 16 11 or 12 or 13 or 14 or 15
- 17 10 and 16
- 18 HALOPERIDOL/
(Haloperidol or Haldol or Loxapine or Loxitane or Molindone or Moban
or Thiothixene or Navane or Primozide or Orap or Trifluoperazine or
- 19 Stelazine or Chlorpromazine or Thorazine or Fluphenazine or
Perphenazine or "Perphenazine amitriptyline" or Prochlorperazine or
Thioridazine or Droperidol or Inapsine).ti,ab,kw.
- 20 CHLORPROMAZINE/
- 21 FLUPHENAZINE/
- 22 Loxapine/
- 23 PERPHENAZINE/
- 24 Prochlorperazine/
- 25 PROCHLORPERAZINE/
- 26 THIORIDAZINE/
- 27 TRIFLUOPERAZINE/
- 28 THIOTHIXENE/
- 29 Thioridazine/
- 30 Droperidol/
- 31 LOXAPINE/
- 32 MOLINDONE/
- 33 PIMOZIDE/
- 34 Fluphenazine/
- 35 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
or 31 or 32 or 33 or 34
- 36 16 and 35
- 37 17 or 36
- 38 10 or 35
- 39 16 and 38
- 40 limit 39 to yr="2019 -Current"

Supplementary Material II: Level 1 Title and Abstract Screening.

1. Should this study be included in Stage 2 screening?

- ☐ Yes
- ☐ Unsure
- ☐ No

2. Reason for exclusion:

- ☐ Population
- ☐ Interventions(s)/Exposure(s)
- ☐ Comparison
- ☐ Outcome(s)
- ☐ Study Design

Supplemental Material III: Critical Appraisal Checklist and Explanations for Case Reports.

The Joanna Briggs Institute

Introduction

The Joanna Briggs Institute (JBI) is an international, membership-based research and development organization within the Faculty of Health Sciences at the University of Adelaide. The Institute specializes in promoting and supporting evidence-based healthcare by providing access to resources for professionals in nursing, midwifery, medicine, and allied health. With over 80 collaborating centres and entities, servicing over 90 countries, the Institute is a recognized global leader in evidence-based healthcare.

JBI Systematic Reviews

The core of evidence synthesis is the systematic review of literature of a particular intervention, condition or issue. The systematic review is essentially an analysis of the available literature (that is, evidence) and a judgment of the effectiveness or otherwise of a practice, involving a series of complex steps. The JBI takes a particular view on what counts as evidence and the methods utilized to synthesize those different types of evidence. In line with this broader view of evidence, the Institute has developed theories, methodologies and rigorous processes for the critical appraisal and synthesis of these diverse forms of evidence in order to aid in clinical decision-making in health care. There now exists JBI guidance for conducting reviews of effectiveness research, qualitative research, prevalence/incidence, etiology/risk, economic evaluations, text/opinion, diagnostic test accuracy, mixed-methods, umbrella reviews and scoping reviews. Further information regarding JBI systematic reviews can be found in the JBI Reviewer's Manual on our website.

JBI Critical Appraisal Tools

All systematic reviews incorporate a process of critique or appraisal of the research evidence. The purpose of this appraisal is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. All papers selected for inclusion in the systematic review (that is – those that meet the inclusion criteria described in the protocol) need to be subjected to rigorous appraisal by two critical appraisers. The results of this appraisal can then be used to inform synthesis and interpretation of the results of the study. JBI Critical appraisal tools have been developed by the JBI and collaborators and approved by the JBI Scientific Committee following extensive peer review. Although designed for use in systematic reviews, JBI critical appraisal tools can also be used when creating Critically Appraised Topics (CAT), in journal clubs and as an educational tool.

JBI Critical Appraisal Checklist for Case Reports

Reviewer _____

Date _____

Author _____

Year _____

Record Number _____

	Yes	No	Unclear	Not applicable
1. Were patient's demographic characteristics clearly described?	☐	☐	☐	☐
2. Was the patient's history clearly described and presented as a timeline?	☐	☐	☐	☐
3. Was the current clinical condition of the patient on presentation clearly described?	☐	☐	☐	☐
4. Were diagnostic tests or assessment methods and the results clearly described?	☐	☐	☐	☐
5. Was the intervention(s) or treatment procedure(s) clearly described?	☐	☐	☐	☐
6. Was the post-intervention clinical condition clearly described?	☐	☐	☐	☐
7. Were adverse events (harms) or unanticipated events identified and described?	☐	☐	☐	☐
			☐	☐
8. Does the case report provide takeaway lessons?	☐	☐		

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Explanation of case reports critical appraisal

Moola, S., Munn, Z., Tufanaru, C., Aromataris, E., Sears, K., Sfetcu, R., Currie, M., Qureshi, R., Mattis, P., Lisy K., & Mu, P.-F. (2017). Chapter 7: Systematic reviews of etiology and risk. In E. Aromataris & Z. Munn (Eds.), Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute. Retrieved from <https://reviewersmanual.joannabriggs.org/>

Case Reports Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. Were patient's demographic characteristics clearly described?

Does the case report clearly describe patient's age, sex, race, medical history, diagnosis, prognosis, previous treatments, past and current diagnostic test results, and medications? The setting and context may also be described.

2. Was the patient's history clearly described and presented as a timeline?

A good case report will clearly describe the history of the patient, their medical, family and psychosocial history including relevant genetic information, as well as relevant past interventions and their outcomes. (CARE Checklist 2013)

3. Was the current clinical condition of the patient on presentation clearly described?

The current clinical condition of the patient should be described in detail including the uniqueness of the condition/disease, symptoms, frequency, and severity. The case report should also be able to present whether differential diagnoses was considered.

4. Were diagnostic tests or methods and the results clearly described?

A reader of the case report should be provided sufficient information to understand how the patient was assessed. It is important that all appropriate tests are ordered to confirm a diagnosis and therefore the case report should provide a clear description of various diagnostic tests used (whether a gold standard or alternative diagnostic tests). Photographs or illustrations of diagnostic procedures, radiographs, or treatment procedures are usually presented when appropriate to convey a clear message to readers.

5. Was the intervention(s) or treatment procedure(s) clearly described?

It is important to clearly describe treatment or intervention procedures as other clinicians will be reading the paper and therefore may enable clear understanding of the treatment protocol. The report should describe the treatment/intervention protocol in detail; for e.g. in pharmacological management of dental anxiety - the type of drug, route of administration, drug dosage and frequency, and any side effects.

6. Was the post-intervention clinical condition clearly described?

A good case report should clearly describe the clinical condition post-intervention in terms of the presence or lack thereof symptoms. The outcomes of management/treatment when presented as images or figures would help in conveying the information to the reader/clinician.

7. Were adverse events (harms) or unanticipated events identified and described?

With any treatment/intervention/drug, there are bound to be some adverse events and in some cases, they may be severe. It is important that adverse events are clearly documented and described, particularly when a new or unique condition is being treated or when a new drug or treatment is used. In addition, unanticipated events, if any that may yield new or useful information should be identified and clearly described.

8. Does the case report provide takeaway lessons?

Case reports should summarize key lessons learned from a case in terms of the background of the condition/disease and clinical practice guidance for clinicians when presented with similar cases.

References:

Gagnier, J. J., Kienle, G., Altman, D. G., Moher, D., Sox, H., Riley, D., & CARE Group (2013). The CARE guidelines: consensus-based clinical case reporting guideline development. *Headache*, 53(10), 1541–1547. <https://doi.org/10.1111/head.12246>

Supplemental Material IV – Detailed tables and critical appraisal for each case report.

Table S2.1. Summary of Characteristics of Patients Diagnosed with Diabetic Ketoacidosis Associated with Antipsychotic Drug Use (n = 100)^{1,2}.

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	BG (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	Glucose (Quant., mg/dl) •Prior to/on initiation of trt. - •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
1	Agrawal et al. (2016)	•Polyuria, polydipsia, weight loss	Y (Risp.)	N New onset DKA	NS NS Norm.	NS 800 NS	NS NS NS	•Insulin and fluid resuscitation (70 units, twice daily 10 units 3 times a day)	N, off insulin within 6 months	Y	Full	NS	NS	NS
2	Ai et al. (1998)	•Severe vomiting	Y (Olanz.)	NS, on antidiabetic to manage/ Y, T2DM	NS NS Norm.	NS 439.2 NS	NS 11 NS	•Sliding scale insulin, IV rehydration, + potassium supplements (NS)	Y, Hypoglycaemic agent	Y	Partial	•Mild Asthma •Hidradenitis suppurativa	•Minocycline	N
3	Akunjee et al. (2018)	•Fatigue, polyuria, polydipsia, confusion	N	NS / NS	NS Imp. Imp.	NS NS NS	NS 13.7 5.8	•IV insulin, dialysis and mechanical ventilation. •Discharged on glargine insulin (NS)	N	Y	Full	NS	N	NS
4	Al-Amri (2009)	•Progressive somnolence, polyuria, polydipsia	Y (Halop.)	N / New onset DM	Normal NS Norm.	NS 695.7 NS	NS NS NS	•Insulin, Metformin and intravenous fluids (NS)	Y, insulin	Y	Partial	NS	•Clonazepam valproate	NS
5	Alex et al. (2018)	•Vomiting, headache, fever	Y (Aripip.)	N / Y, T2DM	NS NS NS	111.9 378 69.7	NS 14 NS	•Insulin and IV potassium infusions (NS)	Y, Insulin, metformin	Y	Partial (diet mgt.)	NS	NS	NS

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	BG (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	Glucose (Quant., mg/dl) •Prior to/on initiation of trt. - •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
6	Ananth et al. (2004)	•Seizure, coma, somnolence, high fever	N	N / N	NS NS Norm.	NS 1,201 NS	NS NS NS	•Insulin (NS)	N	Y	Full	NS	•Lithium carbonate	NS
7	Aruna et al. (1995)	•Thirst, dryness of mouth, weight loss, fatigue	N	N / Y, T1DM	Urine NS NS ?	NS NS 119	NS 4.2 NS	•Fluids, soluble insulin (20 units/day, then stopped due to hypogl.)	N	Y	Full	N	NS	NS
8	Avella et al. (2004) (Case 1)	•Tutti-frutti odor, •Olanzapine in the liver	N/A	N / N/A	NS NS NS N/A	NS 839 N/A	NS NS N/A	N/A	N/A	N/A	Fatal	•Bronchitis •Herniated lumbar disc •Right lateral strabismus	•Albuterol •Clonazepam •Inderal •Neurontin •Celebrex •Topirimate	•Tobacco use
9	Avella et al. (2004) (Case 2)	N/A	N/A	N / N/A	NS NS N/A	NS 640 N/A	NS 14.3 N/A	N/A	N/A	N/A	Fatal	NS	•Fluoxetine	•Tobacco use
10	Avella et al. (2004) (Case 3)	N/A	N/A	N / N/A	NS NS N/A	NS 833 N/A	NS 14.7 N/A	N/A	N/A	N/A	Fatal	N	N	NS

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	BG (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	Glucose (Quant., mg/dl) •Prior to/on initiation of trt. - •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
11	Avram (2001)	•Nausea, vomiting, dehydration, abdominal pain	N	N / U	NS Present NS	NS 544.3 83	NS 14 NS	•IV insulin and hydration, electrolyte replacement (40 U morning; 25 units evening)	N	Y	Full	N	•Sertraline •Ranitidine •Trihexyphenidyl	NS
12	Buch et al. (2003)	•Nausea, vomiting, polyuria, polydipsia, weight loss	Y (Flupe.)	N / N	NS NS Normal.	NS 642.6 NS	NS NS NS	•Insulin and IV fluids (6 U/H)	N	Y	Full	N	•NS	NS
13	Cardinale et al. (2019)	•Acute respiratory failure	NS,N/A	NS/ NS	NS NS NS	NS 720 NS	NS NS NS	•Lipid lowering rosuvastatin, insulin therapy, continuous renal replacement therapy	NS	U	NS	NS	•NS	N
14	Chellamuthu et al. (2010)	Reduced conscious level, Diarrhoea, vomiting	Y (Halop.)	N / T2DM	NS NS NS	NS 1,679.4 NS	NS 13.8 7.2	•Fluid replacement and insulin	Y,Insulin, metformin	Y	Partial	NS	•NS	NS
15	Cho & Lindenmeyer (2009)	•Epigastric pain, emesis, dizziness, lethargy.	Y (Arip, discon; Molindone; Halop. Continued)	N / New onset?	NS Normal NS NS	NS 400 NS	NS NS NS	NS	NS	Y	Partial	•Obesity, •asthma •dyslipidemia	•Valproic acid •Nortriptyline •Albuterol inhaler •Ibuprofen	•Substance abuse •Cocaine •Alcoholism

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	BG (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	Glucose (Quant., mg/dl) •Prior to/on initiation of trt. - •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
16	Church et al. (2005)	•Nausea, vomiting, malaise	N	Y, T2DM	NS NS NS	NS, 502.4, 310.5	NS NS NS	•IV insulin, fluids (NPH: 70/30 insulin 36 U morning; 20 U evening)	Y	Y	Partial	NS	•Diazepam	NS
17	Colli et al. (1999)	•Obtundation, dehydration	N	N / N	Evidence NS NS	NS 756 92.9	NS NS 5.9	•IV insulin, fluids. (40 U)	N	Y	Partial, (diet mgt)	NS	•N	N
18	Courvoisie et al. (2004)	•Polyuria, polydipsia, nocturia, decreased appetite, lethargy, abdominal pain	N	N / New onset DM	NS U(+) NS	NS 260 170	NS NS 5.9	•Insulin (6 units NPH and 2 units regular morning, 3 units NPH, and 4 units regular evening)	N	Y	Partial	•Attention Deficit hyperactivity disorder •Oppositional defiant disorder	•Valproic acid, •Guanfacine •Amphetamine	N
19	Croarkin et al. (2000)	•Polyuria, polydipsia, daily emesis, abdominal pain. Delirious, reduced consciousness, disorientation	Y (Quet.)	N / Insulin dependent T1DM	NS, U(+) NS	NS 565 NS	NS 11.4 NS	•IV insulin, hydration and electrolyte management (NS)	Y, insulin	NS	Partial	•HIV	•Fluoxetine •Trazodone	N
21	Crown et al. (2007)	•Polyuria, polydipsia	N	N / New onset T2DM	Normal Elevated NS	NS 701.2 180	NS 14.9 NS	•IV insulin, fluids (30/70 28 units, morning; 12 units evening)	Y, Metformin	N	Partial	•Hypertension	•Paroxetine •Clonazepam •Atenolol	N

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
22	Dahri et al. (2002)	•Polyuria, polydipsia, nocturia, epigastric pain	Y (NS)	N / New-onset DM	NS NS NS	NS 432 NS	NS NS NS	•Insulin (NS)	Y, Insulin	U	Partial	NS	•Clonazepam •Benztropine	NS
23	Das et al. (2018)	•Excessive tiredness, afebrile, normal vitals. Glasgow Coma Scale of 15	Y (Amisul.)	N / New-onset DM	NS NS NS	NS 443 90	NS 9.2 NS	•Insulin, fluid, saline	Y, Metformin	NS	Partial	NS	•Valproate	NS
24	de Boer & Gaete (1992)	•Stiffness, high fever, difficulty rousing, comatose	N	N / New onset DM	NS NS Normal.	138.6 1,126.8 NS	NS NS N/A	•NS •IV Dantrolene sodium, 100 mg (NS)	N/A	N/A	Fatal	NS	NS	•Tobacco use
24	Dhamija et al. (2008)	•Polyuria, polydipsia, irritability, changes to behavior and decreased school performance	NS	N / N	NS NS Normal	NS 478 NS	NS NS NS	•IV insulin, fluids	NS	NS	Full	•Intractable epilepsy •Mental retardation •Mood disturbance	NS	NS
25	Dibben et al. (2005) (Case 1)	•Confusion, comatose, eventual paralysis	NS	N / Diabetes insipidus	NS NS NS	109.8 954 126	NS 7.2 5.5	•IV insulin, ventilatory support (15-20 U/H)	N	Y	Partial (diet mgt, non compliant)	•Hypothyroidism •Hyperlipidemia •Hypertension	•Lithium •Thyroxine •Simvastatin •Aspirin •Atenolol	N

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
26	Dibben et al. (2005) (Case2)	•Drowsiness, polyuria	NS	N / New onset DM	U(-) NS NS	NS 1,189.8 108	NS 13.4 6.2	•Insulin (Mixtard, 30 10U + 14U)	Y, Metformin	Y	Partial (non compliant use of antidiabetic drugs)	NS	NS	NS
27	Fullbright & Breedlove (2006)	•Lethargy, slurred speech, unsteady gait, weakness	Y (Zipras.)	N / None	NS NS NS	100 1,386 99	NS NS 3.6	•IV Insulin, fluids •Day 3: Subc. insulin (NS)	N	Y	Full	•Past medical sleep apnea •Hyperlipidemia •Gastroesophageal reflux disease •Hypertension	•Divalproex	N
28	Gatta et al. (1999)	•Asthenia, Polyuria, dehydration	N	N / None	NS NS Low	NS 648 NS	NS 14.7 Normal	•IV Insulin, fluids (Three insulin injections, 64 U: 3 regular injections and 1 of NPH insulin Stopped after 15 days)	N	Y	Partial (diet mgt)	N	N	N
29	Goldstein et al. (1999) (Case 1)	•Polydipsia, polyuria, dizziness, decreased appetite, diffused abdominal pain, malaise.	Y (Quet.)	N / NS	Normal U(4+) Normal	NS 1107.8 NS	NS 11.6 NS	•IV insulin, fluids (NPH insulin 30 U q A.M. and 10 U q P.M., and regular insulin 10 U q A.M.)	Y	Y	Partial	N	•Valproic Acid	N

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
30	Goldstein et al. (1999) (Case 2)	•Flu symptoms, malaise, anorexia, nausea, abdominal discomfort somnolence, minimally arousable	Y (Risp.)	N / NS	Normal NS Normal.	NS 1,008.7 NS	NS NS NS	•IV insulin + hydration (NPH, 15 U sc bid, cefotetan (500 mg bid)	N	NS	Full	NS	•Cold elixir	N
31	Greenfield et al. (2002)	•Gastrointestinal bleeding, pleomorphic vasculitis eruption	Y (Risp.)	Y, T2DM	NS NS Controlled	NS 887.4 NS	NS 13.6 NS	•Insulin, hydration (NS)	Y, Metformin	Y	Partial	N	N	N
32	Hepburn & Brzozowska (2016)	•Abdominal pain, vomiting, polyuria, polydipsia	Y (Amisul., briefly; Cloz. reinstated.)	Y, T2DM	NS NS Controlled	NS 419.4, NS	12 14.6 7.6	•IV insulin, hydration, electrolyte repl., deep venous thrombosis prophylaxis	Y Insulin, saxagliptin, metformin	Y	Partial	•Hypertriglyceridemia	N	N
33	Horber et al. (2018)	•Abdominal pain, nausea, vomiting, severely altered mental status, restlessness, somnolence	N	N / T1DM	NS U(+) NS	NS 1,687 331	NS 12.2 NS	•IV insulin, fluids, sodium bicarbonate (NS)	Y, Insulin	NS	Partial	N	•Benzodiazepines	N
34	Howes & Rifkin (2004)	•Thirst, polydipsia Glasgow Coma Scale: 6	N	N / NS	NS NS Normal.	99 1,075.3 NS	NS NS NS	•Insulin (32 units twice daily)	Y	Y	Partial	N	•Sodium Valproate	N

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
35	Itoh et al. (2019)	•Thirst, polyuria, drowsiness. No acetone breath. Mild pain in the left lower quadrant.	Y	N / T2DM	NS NS NS	83 1,709 285	6.3 ,13.1 5	•IV insulin, saline	Y, for 18 days	Y	Partial	•Internal hemorrhoids	•Paroxetine •Mianserin •Tiapride •Suvorexant •Ramelteon	N
36	Iwaku et al. (2017)	•Polyuria, polydipsia, oral dryness, general fatigue, loss of appetite, nausea.	Before DKA (Quet.)	N / New-onset T1DM	Normal U(4+) Normal	NS 490 NS	NS 15.5 7	•IV insulin •40 months after discharge: <0.5 U/Kg/day	Y, Insulin	Y	Partial	NS	NS	NS
37	Jalota et al. (2015)	•Abdominal pain, vomiting, polydipsia and polyuria.	Y (Amisul.)	N / ketone prone T2DM	NS NS NS	99 378 138.6	NS 13.3 NS	•IV Insulin, fluid resuscitation •Subc. Insulin (NS)	Y, Metformin, oral hypoglycemics	Y	Partial	N	N	•Tobacco use •History alcohol abuse
38	Johnson et al. (2002)	•Nausea, vomiting, polyuria, polydipsia,	N	N / None	U(normal) U(4+) NS	89 368 164	NS NS 6.5	•Insulin, fluids (After discharge: 78 U)	N	Y	Full	NS	NS	NS
39	Kahn & Bourgeois (2007) (Abstract)	•Decreased consciousness, minimal response, distress. Dried blood in/around the mouth, mild tenderness to palpation in the epigastrium, brown heme-positive stool in the rectum. Glasgow Coma Scale score was 10.	Y (Arip.)	N / N	NS U(Large) Normal.	110.4 1,652 NS	NS 15.2 NS	•Insulin, fluids, intubation for airway protection (NS)	N	N	Full	NS	•Alprazolam (not prescribed, from a friend)	•Cocaine abuse

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
40	Kasmi (2013)	•Nausea, vomiting, breathing issues, incontinence Glasgow Coma Scale Score: 5	NS	N / NS	Normal Elevated NS	NS NS NS	NS NS NS	•Glycemic agents (NS)	NS	NS	NS	NS	NS	•Drug overdose •alcoholism
41	Kibbey et al. (2010)	•Lethargy, dry cough, polyuria, polydipsia, disorientation, volume depletion, afebrile, tachypneic, weight loss.	N/A	N / NS	NS NS NS	NS 781.2 145.8	NS 15.9 NS	•IV insulin, fluids (At discharge: 330 U/day)	Y, Insulin	NS	Partial	N	N	N
42	Kinoshita et al. (2014)	•Nausea, vomiting, thirst	NS	N / NS	Normal NS NS	NS 771 100	5.3 9.6 6	•Insulin, hydration (37-44 units insulin injections, 4 X / day Day 27: Insulin Glulisine and Insulin Glargine)	Y	Y	Partial	N	•Duloxetine	•History of tobacco use
43	Kostakoglu et al. (1996)	•Sweating, anorexia, blurred vision, diplopia and a state of stupor	Y (Fluph)	N / NS	NS 4+ NS	105.2 338.7 93	NS NS NS	•IV insulin and hydration •Day 4: regular insulin injections - 40 units of isophane, 20 units of regular insulin (morning); 20 units of isphone, 10 U of regular insulin (evening).	N	Y	Partial (diet mgt)	NS	NS	NS

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
44	Koval et al. (1994)	•Comatose	Y (Halop.)	N / N	Normal U(+) NS	NS 1,064.3 104.3	NS NS NS	•IV insulin and hydration, ventilation support (At discharge: 13 U morning)	N	Y	Full	N	•Lithium carbonate, 1200 mg/day Benztropine, 2 mg/day	N
45	Kyriazis et al. (2006)	•Intense epigastric pain, food vomiting, tachypnea	Y (Risp.)	N / NS	Normal NS Low	NS 478 NS	NS NS Normal	•IV insulin, fluids (Subc : 30-20 U for 5 days)	N	Y	Partial (diet mgt)	N	N	N
46	Lafayette et al. (2003)	•Lethargy, menstrual spotting, cramping, breast tenderness, nausea and vomiting. Hyperventilation, shortness of breath, chest discomfort	N	N / NS	Normal NS NS	126 445.2 110	NS 12.2 NS	•IV insulin (Subc. 38 units of isophane insulin b.i.d. + 20 units of regular insulin b.i.d)	N	Y	Partial (diet mgt)	N	•Lorazepam •Risperidone •Benztropine •Multivitamin /calcium supplements	•Substance dependence
47	Laghate & Gupta (2004)	•Vomiting, abdominal pain and heavy breathing	N	N / NS	NS U(+) Norm.	NS 580 NS	NS NS NS	•IV insulin, fluids, ceftazidime, metronidazole, potassium chloride, and calcium gluconate (NS)	N	Y	Full	NS	•Sodium Valproate	NS
48	Lindmeyer et al. (1999)	•Drowsiness, lethargy, unresponsiveness to verbal commands.	N	N / NS	NS NS Norml.	NS 1,200 NS	N NS NS	IV insulin, 5% dextrose fluid	N	NS	Full	N	•Divalproex sodium	•Substance dependence

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49	Lu & Yan (2009)	•Fever	N/A	N / NS	NS NS Normal.	NS 1,127.8 NS	NS 13.7 N/A	•IV Insulin, fluids (NS)	N/A	N/A	Fatal	NS	NS	NS
50	Mcfarlane & Fisher (2006)	•Dyspnea, drowsiness, confusion, polyuria, polydipsia, confusion and agitation	N	N / NS	NS NS NS	NS 1,422 NS	NS NS 5.4	•IV insulin, fluids (biphasic insulin regimen: NS)	Y, Insulin	Y	Partial	NS	•Folic Acid	•History of drug abuse •history of alcohol abuse
51	Madsen (2014)	•Thirst, vomiting, abdominal pain	N/A	N / N/A	Normal NS U(4/4)	NS 504 N/A	NS NS NS	NS	N/A	Fatal	None	N	None	N
52	Makhzoumi et al. (2008)	•Urinary incontinence, somnolence, drowsiness, difficulty arousing, lethargy, difficulty moving upper extremities, refusing nutrition by the mouth	Y, (Halop. as needed; Fluph. reinstated)	N / NS	NS NS NS	109.6 813 215	NS 14.9 NS	•IV insulin, fluids. (Subc. NS)	Y	Y	Partial	•Hyperlipidemia	•Valproic acid •Benztropine, •Atorvastatin	N

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
53	Maksimovic et al. (2006)	•Malaise, abdominal pain, nausea, vomiting, polydipsia, polyuria	N	N / NS	NS U(+) Norm.	NS 540 NS	NS 12.9 NS	•IV insulin, fluids	Y	N	Partial	N	N	•Tobacco use
54	Marlowe et al. (2007)	•Somnolence Arousable	NS	N / N	Normal NS NS	99 1,492 90	NS NS 7	•IV insulin, fluids (NS)	N	Y	Full	NS	•Valproic acid	NS
55	Maule et al. (1999)	•Vomiting, obtusion dehydration, comatose	N	N / N/A	NS U(4+) NS	NS 1,000 108	NS NS NS	•Insulin and fluids (Subc: 32 U)	Y, Insulin but withdrawn due to hypoglycemia	NS	Partial (diet mgt)	N	•Valproic acid	N
56	Miller et al. (2008)	•Vomiting, lethargy, fatigue, thirst, increased urination	N	N / New onset DM	NS NS NS	92 722 NS	NS NS 7.5	•Insulin (NPH insulin: 35 U, twice a day)	Y, Insulin	NS	Partial	•Hypertension •Gastroesophageal reflux disease •Diverticulosis	•Aspirin •Lactulose •Lamotrigine •Loratadine •Loxapine •Nifedipine •Omeprazole •Ziprasidone	•Tobacco use

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
57	Mithat et al. (2005)	•NS	NS	N / N	Normal NS NS	NS 562.6 88.7	NS NS NS	•IV insulin, fluids, potassium (1.15 u/kg as IV bolus + 0.1 units.kg-1.h-1 IV insulin infusion)	N	Y	Full	N	•Valproate •Lithium	N
58	Mohan (1999)	•Sore throat, lethargy, slurred speech, thirst	Y (Risp. discontin., Typical APDs)	N / Y	NS NS Normal.	NS 342 NS	NS NS NS	NS	Y, Glibenclamide	Y	Partial	NS	NS	NS
59	Muench & Carrey (2001)	•Polyuria, polydipsia, nausea, vomiting, dizziness	NS	New onset T2DM prior	NS high NS	97 765 200	NS 13.4 NS	•IV insulin, fluids •Subc. insulin (80 U-morning; 35 U-evening) •half dose after 2 months	Y, Insulin	Y	Partial (previous diag. of T2DM)	•History of Hepatitis A	•Venlafaxine •Valproic acid •Atorvastatin •Propranolol	•Tobacco use, •History of substance abuse (meth.)
60	Nahas et al. (2010) (Abstract)	•Polyuria, polydipsia, blurred vision, nausea, emesis	Y (Arip.)	N / NS	NS NS NS	NS 621.7 NS	NS 10.3 NS	•IV insulin, fluids, saline (NS)	Y, Insulin	NS	Partial	NS	NS	NS
61	Niazi et al. (2007)	•Stupor, confusion, dehydration, polyuria and polydipsia, drowsiness, arousable	Y (Risp.)	N / NS	NS U(3+) Normal.	NS 709.2 NS	NS NS NS	•Insulin, IV fluids, potassium supplements (NS)	N	Y	Full	Hypertriglyceridemia	NS	N

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
62	Nicolai (2001)	•Unconsciousness	Y (Halop.)	NS / NS	NS NS Normal.	NS 1,479.1 NS	NS NS NS	•Insulin, fluid and potassium supplementation (NS)	N	NS	Full	None	•Valproate	N
63	Patel et al. (2011) (Abstract)	•NS	NS	N / NS	NS NS Normal.	NS 1116 NS	6.5 NS NS	•IV insulin, (60 U/day)	Y, insulin and metformin	NS	Partial	NS	NS	NS
64	Pathmanathan (2013) (Abstract)	•Nausea, vomiting, polyuria, polydipsia	N/A	T2DM prior	Controlled NS High	NS 452 NS	7.4 14.2 NS	•IV insulin, fluids (48 U)	Y, insulin	NS	Partial, (previous diag. of T2DM)	•Hypertension	•Metformin	NS
65	Peterson & Bird (1996)	•Stupor	NS	N / T2DM	Normal Urine(+) Normal.	NS 662.6 NS	NS NS NS	•IV insulin and rehydration (NS)	Y	Y	Partial	•Hypertension	•Lithium carbonate •Bethanechol •Verapamil	•History of substance use •History of alcohol use
66	Pierides (1997)	•Lethargy, thirst, chest pain, dyspnoea	NS	N / NS	Normal NS Improved	NS 367.8 NS	NS NS NS	•Subc. insulin (NS)	NS	NS	U	NS	N	NS

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67	Pillai et al. (2006)	•Thirst, exhaustion, frequent urination, drowsiness, unresponsiveness, unrecordable blood pressure, emancipation, unconsciousness	N/A	N / NS	Normal U(+) NS	NS 416 200	NS 8.9 N/A	•IV insulin, fluids, ventilation, antibiotics, PCV. (NS)	N/A	N/A	Fatal	N	N	N
68	Popli et al. (1997)	•Hypotension, obtusion, dehydration	N/A	N / NS	NS NS NS	NS 808.7 143	NS NS NS	•Insulin and IV fluids (NS)	Y, Glyburide	Y	Partial	NS	•Ephedrine	•History of substance abuse
69	Ragucci & Wells (2001)	•Abdominal pain, dizziness, polyuria, dyspnea	Y (Risp.)	N / NS	NS U(+) Normal.	83 957 NS	NS TBD 5.8	•IV insulin, fluids 33/17 units (morning) and 16/9 units (evening)	Y. Metformin. Insulin slowly discontinued.	Y	Partial	Hypertension	•Valproic acid •Carbamazepine •Hydrochlorothiazide/triamterene •Conjugated estrogens	NS
70	Rahat et al. (2005)	•Polyuria, polydipsia, unconsciousness, agitation, dehydration, hyperpyrexia, stiffness	N	NS / NS	NS NS NS	NS 550 NS	NS NS NS	•Life support management, physostigmine and centrally acting cholinergic	N/A	NS	Full	Depression	N	NS

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
71	Rashid et al. (2009)	•Abdominal pain, polyuria, polydipsia, vomiting.	Y (Halop.)	N / NS	NS NS NS	NS 1,081 NS	NS NS NS	NS	NS	Y	NS	PCOS	NS	N
72	Ratnakaran (2015)	•Drowsiness, slurred speech, disorientation, decreased response to questions, increased psychomotor activity. Afebrile. No signs of dehydration, no odor in breath.	N	N / NS	NS U(+) NS	NS 363 155	NS NS NS	•IV insulin and saline (subcutaneous: 6 U (morning/pm); 4 U (evening))	Y, Glibenclamide, metformin.	NS	Partial	N	•Escitalopram •Clonazepam	N
73	Reddymasu et al. (2006)	•Fatigue, dyspepsia, epigastric pain	Y (Halop.)	N / New onset DM	NS NS NS	NS 1,769 NS	NS NS NS	•IV insulin, fluids (NS)	Y, Insulin	Y	Partial	NS	NS	N
74	Sa et al. (2013)	•Hyperthermia, nausea, vomiting, mental deterioration	NS	N / NS	Normal NS NS	NS 1,216 200	NS 13.8 6.2	•IV insulin, fluids • ≥ 4 L/day	N	Y	Partial (lifestyle changes)	N	•Valproic acid •Clonazepam •Lorazepam	N

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
75	Sato et al. (2008)	•Loss of consciousness	U, (++) Levomep)	N / New onset T1DM	NS NS Improved	88 926 NS	NS 12.2 NS	•Insulin, IV fluid (NS)	Y	Y	Partial	•Acute Polyendocrine Syndrome	NS	NS
76	Seaburg et al. (2001)	•Agitation, incontinence, polydipsia, polyphagia, nausea, vomiting	N, (++) halop)	N / New onset	NS NS NS	NS 1,240 122	NS NS 7.5	•Insulin and rehydration (Subcutaneous 70/30 insulin 40 U (morning) and 20 U (evening)	Y, Pioglitazone, metformin	Y	Partial	•Seizure disorder developmental •disability	•Valproic Acid	N
77	Selva & Scott (2001)	•Lethargy, vomiting, inability to walk	N	N / T2DM	NS Significant Increasing	NS 581.7 NS	NS 17.7 10.5	•IV insulin (0.05 U/kg/ hour)	NS	Y	Partial	•DiGeore syndrome	•Venlafaxine	NS
78	Singh et al. (2013)	•Nausea, vomiting and abdominal pain	Y NS	N / N	NS NS NS	89 625 250	NS NS NS	•IV insulin and fluid (NPH evening; and three premeal regular insulin, NS)	N	Y	Full	NS	NS	NS
79	Sirois (2008)	•Glasgow Scale 5/15	NS	N / NS	Normal NS Normalized	90 1,472.4 NS	NS NS NS	•Insulin (NS)	Y, Insulin	NS	Partial	NS	•Venlafaxine	NS
80	Smith et al. (1999)	•Excessive sedation, nocturnal incontinence, postural hypertension, confusion, smell of ketones.	NS	N / NS	NS NS Resolved	NS 990 NS	NS NS NS	•Insulin (Insulin mixtard, 30 units twice daily)	Y, Insulin	Y	Partial	NS	NS	NS

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
81	Straker et al. (2002)	•Gastrointestinal distress, deterioration of mental status, hypotension	Y (Zipras.)	N / NS	NS NS NS	155 500 150	NS 5.9 NS	•IV Insulin drip (NPH insulin, NS)	N	NS	Partial (diet mgt)	•Hepatitis C •Seizure disorder	•Phenytoin	•Substance abuse •Alcohol dependence
82	Strassnig et al. (2013) (Case 1)	•NS	Y Typical APD)	N / Transient T2DM	NS NS NS	NS 660.6 73.8	NS NS NS	•Insulin injections, oral hypoglycemics (NS)	N	Y	Full	NS	NS	NS
83	Takashashi et al. (2005)	•Somnolent, difficulty with speech	NS, (++)Halop)	N / N	NS NS Controlled	132 973 NS	NS NS NS	•IV insulin and fluids (Subc. insulin injection, 34-20 i.u./d for two weeks)	N	Y	Full	NS	N	•History of alcohol abuse
84	Taslipinar et al. (2008) ¹	•Confusion, lethargy	Y (Zipras)	N / N	NS NS Normal.	NS 338 NS	NS 11.2 NS	•IV insulin and hydration (Intermittent subcutaneous insulin, NS)	N	Y	Full	NS	NS	NS
85	Tavakoli & Arguisola (2003)	NS	NS	N / T1DM	NS NS NS	94 NS NS	NS NS NS	NS	Y, insulin	Y	Partial	NS	•Valproic acid •Venlafaxine	•History of Substance Abuse •History alcohol abuse

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
86	Torrey et al. (2003)	NS	N/A	N / N/A	Normal (PM) N/A N/A	NS N/A N/A	NS NS N/A	N/A	N/A	N/A	Fatal	N	•Lithium •Fluoxetine •Bupropion	•History of alcohol abuse •History of substance abuse
87	Tsuchiyama et al. (2004)	•Thirst, malaise, mild confusion	N	N / N	NS NS Improved	NS 1080 NS	NS 13.7 NS	•Insulin (100 U/day)	N	Y	Full	NS	NS	NS
88	Tugwell et al. (2020)	•Weakness, drowsiness, volume depletion	N/A	Y, gest. DM / ketone prone T2DM	NS NS Normal.	127.8 896.4 NS	NS 15.8 5.8	•Insulin (NS)	Y, Metformin, empagliflozin	Y	Partial	•Gestational diabetes	•Clonazepam •Valproic acid	N
89	Varma et al. (2007)	•General malaise, drowsiness, difficulty rousing, tachycardic, hypotensive, dehydration. Glasgow score of 3	Y (Risp)	N / N/A	NS U(+) NS	NS 1647 189.2	NS 13.2 NS	•IV insulin, fluid, electrolyte resuscitation •Broad spectrum antibiotics (NS)	Y	NS	Partial	N	NS	N
90	Vincent et al. (2017)	•Vomiting, nausea, fatigue, weakness, abdominal pain, dehydration	Y (Cloz)	N / NS	NS NS Reduced	NS 457 NS	NS 15.3 NS	•Insulin, fluids (NS)	NS	NS	Unsure	NS	NS	NS

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
91	Vuk et al. (2017)	•High blood pressure, tachycardia, disorientation, vomiting, somnolence, hypotension, tachycardia, tachypnea acetone smell	Y (Amilsul.)	N / NS	NS NS Normal.	115.2 914.4 NS	NS 8.5 NS	•Standard therapy (Long acting insulin, 10 IU)	Y	Y	Partial	NS	•Bisoprolol	NS
92	Waldman & Yaren (2002)	•Paleness, dyspnea	Y (Quet., then Cloz.)	N / NS	NS NS Fluct.	117 675 NS	NS NS NS	•Insulin (NS)	Y, Glyburide	Y	Partial	NS	N	NS
93	Watkins et al. (2011)	•Altered mental status, nausea, vomiting, abdominal pain, slurred speech	NS	N / New onset DM	NS NS NS	132 714 153	NS 13.5 NS	•IV insulin, saline (5 units/ twice per day)	Y, Insulin	NS	Partial	•Hyperlipidemia	•Sertraline	N
94	Whicher et al. (2019)	•Vomiting, abdominal Pain, dehydration	N/A	NS / T2DM	NS NS NS	NS 432 NS	NS NS NS	•Insulin	Y, Metformin	Y	Partial	NS	•NS	N
95	Wilson et al. (2002) (Case 1)	•Thirst, urination, confusion	N	N / NS	NS NS Controlled	NS 361 NS	NS NS NS	•Low-dose insulin (5 U/day)	NS	Y	Unsure	NS	•NS	NS

Patient No	Citation	Clinical Signs and symp.	APD switch after DKA	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol.	Trt. for DKA (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up?	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs)	Other known issues
96	Wilson et al. (2002) (Case 2)	•Thirst, urination, confusion	NS	N / NS	NS NS Controlled	NS 578 NS	NS NS NS	•IV fluid and insulin (NS)	N	Y	Partial (diet mgt)	•Mental retardation	•Lithium •Valproic Acid	•History of alcohol abuse
97	Wilson et al. (2002) (Case 3)	•Unresponsiveness	NS	N / NS	NS NS NS	120 NS NS	NS NS NS	•NS	NS	Lost to follow up	Lost to follow up	•Chronic obstructive pulmonary disease •Prostate cancer	•Propranolol	NS
98	Wilson et al. (2002) (Case 4)	•Thirst, obtundation	N (Cloz. Continued)	N / NS	NS NS NS	NS 437 NS	NS NS NS	•Insulin therapy (Insulin 70/30 units/ day)	N	Y	Partial (diet mgt)	NS	•Mesoridazine •Clonazepam •Lithium •Venlafaxine	•History of substance abuse
99	Wilson et al. (2002) (Case 5)	•Disorientation	N	N / NS	NS NS NS	NS 317 NS	NS NS NS	•Insulin (NS)	Y, Insulin	Y	Partial	NS	N	NS
100	Wong et al. (2007)	•General and chest discomfort, fatigue, vomiting, nausea, dehydration, breath smelled like ketones.	Y (Halop)	N / NS	Normal U(+) NS	NS 721.8 75.6	NS 11.9 5.7	•IV insulin, fluids, and electrolytes (29 U morning; 16 units evening)	Y	Y	Partial (diet mgt)	NS	•Sodium valproate	NS

Abbreviations: BG., Blood Glucose; Compl., complication; HbA1c, hemoglobin A1c; Qual., Qualitative; Quant., quantitative; Co-morb, comorbidities; +, positive; - negative; ++, added APD to trt; recov., recovery; resol., resolution; symp., symptoms; Trt. treatment;

Arip., Aripiprazole; Chlorp., Chlorpromazine; Cloz., Clozapine; Halop, Haloperidol; Olanz., Olanzapine; Loxap, Loxapine; Prom, Promazine; Quet., Quetiapine; Risp, Risperidone; Thior., Thioridazine; Zipra, Ziprasidone; Zuclo., Zuclopenthixol.

N, No; Y, yes; NS, Not specified.

¹Added after cross reference with Vuk et al. (2017).

²Hui Fang et al. (2018) described a co-occurrence with diabetic ketoacidosis and hyperglycemic hyperosmolar state and was not included in the Tables.

Table S2.2. Summary of the Characteristics of Patients Diagnosed with Hyperglycemic Hyperosmolar State Associated with Antipsychotic Drug Use (n = 24)¹.

Patient No	Citation	Clinical Signs and symp.	APD switch after HHS	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for HHS (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
1	Ahuja et al. (2010)	•Polyuria, polydipsia, malaise, drowsiness, •Vomiting, unresponsive	Y (Risp).	N/ T2DM	NS U(Present) Normal	99 1,647 NS	NS 13.2 NS	•Insulin, ventilatory support and fluids (NS)	Y, Insulin	Y	Partial	NS	N	N
2	Balzan & Cacciottolo (1992)	Dehydration, muscle rigidity, Parkinsonian tremor, unresponsiveness, Comatose	NS	N/ Y	NS, U(heavy) Normal	NS 810 NS	NS NS NS	•IV insulin, fluids (40 U / Day)	Y, Insulin	N	Partial	N	•Tricyclic antidepressants	N
3	Campanella et al. (2009)	•Cough, lethargy, confusion, waning consciousness. •Mild tongue fasciculations, fine resting tremors. •Gross purposeful movements with all 4 extremities, slurred speech, etc.	Y (other APDs, NS)	N/ N	NS Present Normal	NS 2,473.9 NS	NS NS NS	•IV insulin, saline, antibiotics, oxygen, ventilation support, etc. (Subc: 10 U)	N	Y	Full	•Chronic alcoholism with multiple episodes of withdrawal	•Cogentin •Depakoate ER •Diphenhydramine hydrochloride	•Alcoholism
4	Cerimele (2008)	•General Malaise, vomiting, polyuria, polydipsia	N	N/ T2DM	NS NS NS	NS 1,025.2 NS	NS 14.6 NS	•Insulin, fluids, electrolyte management (NS)	Y	NS	Partial	N	•Carbamazepine, •Hydrochlorothiazide •Ranitidine •Atenolol •Paroxetine	N

Patient No	Citation	Clinical Signs and symp.	APD switch after HHS	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol.1	Trt. for HHS (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs)2	Other known issues
5	Chen et al. (2003)	•Malaise, polyuria, polydipsia	N	N/ NS	Normal U(+) NS	NS 974.8 NS	NS 13.6 NS	•IV insulin, rehydration (10 U, 3 times/ day)	Y, Metformin Glibenclamide	Y	Partial	N	•Valproic acid •Lithium	N
6	Chen et al. (2011)	•Thirst, fatigue, poor appetite, depressed mood	N	N/ New Onset	NS NS Normal.	67 713.04 NS	NS 13.6 6.5	•IV insulin, volume resuscitation (NS)	Y, Glucose lowering agents	Y	Partial	NS	•Valproic acid •citalopram	NS
7	Endoh et al. (2012)	•Decreased consciousness Glasgow Coma Scale score: 10	NS	N/ N	NS U(4+) NS	NS 1,605 100	NS 12.3 5.4	•IV insulin and saline •Subc. 70/30 (8 U/d)	N	Y	Full	•Depression	•Bromazepam •Vamoxapine •Lithium •Mianserin •Methylphenidate •Paroxetine hydrochloride	N
8	Franco et al. (2012) (poster abstract)	•Weak, change in appetite, changes in mental status, episodes of unresponsiveness, twitching of left arm	N	NS/ NS	NS NS Normal.	NS 832.2 NS	NS NS NS	•Insulin (NS)	NS	NS	Partial	•Hypertension •Osteoporosis	•Simvastatin 2 •Memantine •Donepezil •Diltiazem •Alendronate	N

Patient No	Citation	Clinical Signs and symp.	APD switch after HHS	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for HHS (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
9	Franco et al. (2015)	•Fatigue, polyuria, polydipsia	Y (Zipras.)	T2DM prior	NS NS NS	NS 533 173.9	NS 10.4 NS	•IV insulin (NS)	Y, Insulin	Y	Partial	•Hyperlipidemia •Irritable bowel syndrome •Generalised anxiety disorder	NS	N
10	Kaino et al. (2017) ²	•Thirst, disturbed consciousness with fever, hyperglycemia, hyperosmolarity and elevated creatine phosphokinase. Glasgow Coma Scale: 11	NS	N/ NS	Normal, U(positive) Normal	94 762 NS	4.9 NS NS	•IV insulin, rehydration, ventilator support. •Oral therapy with vildagliptine (NS)	NS	NS	U	NS	NS	NS
11	Kaya et al. (2014)	•Decreased oral intake, confusion, somnolence, tachycardia, dryness, reduced turgor Glasgow coma scale: 14	NS	T2DM prior	Normal NS NS	NS 693 137	7.2 12 NS	•IV insulin, hydration (NS)	Y, Metformin, gliclazide	NS	Partial	NS	•Oral antidiabetics	NS
12	Khan et al. (2011)	•Tremor, agitation, coma	N/A	NS/ N/A	NS NS NS	NS 2,198 NS	NS NS NS	•IV fluids, insulin, K, phosphate replacement (NS)	N/A	N/A	Fatal	•Childhood attention deficit and hyperactivity disorder	NS	NS

Patient No	Citation	Clinical Signs and symp.	APD switch after HHS	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for HHS (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
13	Letourneau et al. (2011)	•Vomiting, dizziness, diminished level of consciousness, polyuria, polydipsia	Y (Halop.)	N T2DM	NS NS NS	118.8 1,224 102.6	5.9 13.5 5.9	•IV insulin hydration, (10U, tapered over 72 hours)	Y, Metformin	Y	Partial	NS	NS	N
14	Maust et al. (2015)	•Fatigue, dizziness, increased urinary frequency	NS	Y (on antidiabetic)	NS NS NS	NS 995 NS	5.6 9.7 6.1	•Insulin, rehydration (NS)	Y, Sitagliptin, metformin	Y	Partial	NS	•Metformin	N
15	McCall et al. (2004)	•Unresponsiveness, polyuria, polydipsia, blurred vision, headache, nausea, vomiting	N	N,NS	NS NS NS	NS 1,896 106	NS NS NS	•IV insulin, fluids, antibiotics (NPH insulin 29 U SQ qam and 17 U SQ qpm, and regular insulin 5 U SQ at each meal and use insulin sliding scale as needed.)	Y, Insulin	Y	Partial	•Seizure disorder •hypertension	•Benztropine •Valproic acid	•History of substance abuse

Patient No	Citation	Clinical Signs and symp.	APD switch after HHS	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for HHS (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
16	Meatherall et al. (2002)	•Loss of appetite, abdominal discomfort, polydipsia, polyuria	N/A	N/ NS	NS N/A NS	130 284 NS	NS 12.3 N/A	•N/A	N/A	N	Fatal	NS	N	•History of alcohol and substance abuse
17	Milano et al. (2016)	•Polydipsia, polyuria, malaise, vomiting, diarrhea. Altered and agitated state, febrile, tachycardic, normotensive, Kussmaul respirations.	N	N/ NS	NS NS NS	NS 1,403 NS	NS NS NS	•IV insulin, fluids (NS)	NS	Y	Fatal	N	NS	NS
18	Raza (2007)	•Dehydration, abdominal pain, vomiting and drowsiness. Glasgow coma scale: 10	NS	N/ NS	NS U(lots) Normal	93.6 2,034 NS	NS NS NS	•IV insulin, saline, potassium replacement, prophylactic anticoagulant (NS)	NS	NS	Partial (transferred to diabetic ward)	N	NS	N
19	Rock et al. (2009)	•Hyperthermia, decreased level of consciousness. •Comatose on admission	N/A	T2DM prior	NS NS NS	NS 880 NS	NS NS N/A	•IV insulin, saline (NS)	N/A	N/A	Fatal	NS	•Metformin •biperiden	NS

Patient No	Citation	Clinical Signs and symp.	APD switch after HHS	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. - •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for HHS (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
20	Roefero & Mukherjee (2001)	Hallucinations, polydipsia, polyuria	N	N/ N	Normal U(4) NS	108 1,387.8 105	5 13.3 NS	•IV Insulin, fluids (NPHS: 15 U morning; 10 U evening)	No	Y	Full	•Posttraumatic stress disorder •Ethanol abuse •Hypertension •Coronary artery disease •Esophageal strictures	•Gabapentin •Isosorbide dinitrate •Venlafaxine •Lansoprazole	N
21	Short & Nolan (1994)	•Thirst, disorientation, fluctuating consciousness level, •Drowsiness, urinary incontinence, incoherence in speech	NS	N/ NS	Normal NS Normal	NS 1,542.17 NS	NS NS NS	•Actrapid insulin, IV saline, heparin (NS)	Y, Gibencalamide	NI	Partial	•Mild Hypertension	N	N

Patient No	Citation	Clinical Signs and symp.	APD switch after HHS	DM Diag. before/ after Compl.	Glucose (Qual.): •Prior to/on initiation of trt. •After APD trt. •After resol.	BG (Quant., mg/dl) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	HbA1c (%) •Prior to/on initiation of trt. •After APD trt. •After resol. ¹	Trt. for HHS (Last recorded insulin dosage)	Trt. with insulin or antidiabetic required after resol.	Was patient followed up	Recov. after resol.	Co-morb.	Concomitant Meds (other than APDs) ²	Other known issues
22	Takanobu et al. (2015)	•Obtundation, lethargy, afebrile, muscle pain, rigidity, restlessness, monology, high fever, stupor	NS	Y/ Mild DM prior	NS NS Normal	102.6 401 NS	5.9 7 NS	•IV Insulin, fluids (subcutaneous insulin, NS)	N	Y	Partial (diet mgt.)	NS	•Promethazine •Phenobarbital •Flunitrazepam •Nitrazepam •Biperiden •Mianserin •Antiucclerative	NS
23	Tollefson et al. (1983)	•Polyuria, polydipsia. transient coma, delirium	N	N/ N	Normal NS NS	87 942 150	NS NS NS	•IV insulin (NS)	N	Y	Full	NS	•Lithium	NS
24	Yeung & Lee (2015) (Abtract)	•Fever and increased heart rate	NS	NS/ NS	NS NS NS	NS 1,400 NS	NS NS NS	•IV Insulin, fluids (NS)	Y	NS	Partial	NS	•Methadone •Trazodone	•Substance abuse

Abr: BG., Blood Glucose; Compl., Complication; HbA1c, Hemogolgin A1c; Qual., Qualitative; Quant., Quantitative; Co-morb, Comorbidities; +, Positive; - Negative; ++, Added APD to trt; recov., recovery; resol., resolution; symp., symptoms; Trt., treatment;
Arip., Aripiprazole; Chlorp., Chlorpromazine; Cloz., Clozapine; Halop, Haloperidol; Olanz., Olanzapine; Loxap, Loxapine; Prom, Promazine; Quet., Quetiapine; Risp, Risperidone; Thior., Thioridazine; Zipra, Ziprasidone; Zuclo., Zuclopenthixol.
N, No; N, no; NS, not specified; Y, yes.
¹Hui Fang et al. (2018) described a co-occurrence with diabetic ketoacidosis and hyperglycemic hyperosmolar state and was not included in the Tables.

Table S2.3. Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2}.

Citation	Criteria								Overall Assessment
	(1) Were the patient's demographic characteristics clearly described?	(2) Was the patient's history clearly described and presented as a timeline?	(3) Was the current clinical condition of the patient on presentation clearly described?	(4) Were diagnostic tests or assessment methods and the results clearly described?	(5) Was the intervention(s) or treatment procedure(s) clearly described?	(6) Was the post-intervention clinical condition clearly described?	(7) Were adverse events (harms) or unanticipated events identified and described?	(8) Does case report provide takeaway lessons?	Does it meet all 8 criteria
Agrawal et al. (2016)	Y	N	Y	Y	Y	Y	N	Y	N
Ahuja et al. (2010)	Y	Y	Y	Y	N	Y	N	Y	N
Ai et al (1998)	Y	N	Y	Y	N	Y	N	Y	N
Akunkee et al. (2018)	N	N	N	N	N	Y	N	Y	N
Al-Amri (2009)	Y	Y	Y	Y	Y	Y	N	Y	N
Alex et al. (2018)	Y	Y	Y	Y	N	Y	N	Y	N
Ananth et al. (2004).	Y	Y	Y	Y	N	Y	N	N	N
Aruna et al. (1995)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Avella et al. (2004)	Y	Y	N/A	N/A	N/A	N/A	N/A	N	N
Avella et al. (2004)	Y	N	N/A	N/A	N/A	N/A	N/A	N	N
Avella et al. (2004)	Y	N	N/A	N/A	N/A	N/A	N/A	N	N
Avram (2004).	Y	Y	Y	Y	Y	Y	N	Y	N

Table S2.3. Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2} (cont.).

Citation	Criteria								Overall Assessment
	(1) Were the patient's demographic characteristics clearly described?	(2) Was the patient's history clearly described and presented as a timeline?	(3) Was the current clinical condition of the patient on presentation clearly described?	(4) Were diagnostic tests or assessment methods and the results clearly described?	(5) Was the intervention(s) or treatment procedure(s) clearly described?	(6) Was the post-intervention clinical condition clearly described?	(7) Were adverse events (harms) or unanticipated events identified and described?	(8) Does case report provide takeaway lessons?	Does it meet all 8 criteria
Balzan & Cacciottolo (1992)	Y	Y	Y	Y	Y	Y	N	Y	N
Buch et al. (2003)	Y	Y	Y	Y	Y	Y	N	Y	N
Campanella et al. (2009)	Y	N	Y	Y	Y	Y	N	N	N
Cardinale et al. (2019)	Y	N	N	Y	Y	N	N	N	N
Cerimele (2008)	Y	Y	Y	Y	N	N	N	Y	N
Chellamuthu et al. (2010)	Y	N	Y	Y	Y	Y	N	N	N
Chen et al. (2003)	Y	Y	Y	Y	N	Y	N	Y	N
Chen et al. (2011)	Y	Y	Y	Y	N	Y	N	Y	N
Cho & Lindenmeyer (2009)	Y	Y	Y	N	N	Y	N	Y	N
Church et al. (2005)	Y	N	Y	Y	Y	Y	N	Y	N
Colli et al. (1999)	Y	Y	Y	Y	Y	Y	N	Y	N
Courvoisie et al. (2004)	Y	Y	Y	Y	Y	Y	Y	Y	Y

Table S2.3. Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2} (cont.).

Citation	Criteria								Overall Assessment
	(1) Were the patient's demographic characteristics clearly described?	(2) Was the patient's history clearly described and presented as a timeline?	(3) Was the current clinical condition of the patient on presentation clearly described?	(4) Were diagnostic tests or assessment methods and the results clearly described?	(5) Was the intervention(s) or treatment procedure(s) clearly described	(6) Was the post-intervention clinical condition clearly described?	(7) Were adverse events (harms) or unanticipated events identified and described?	(8) Does case report provide takeaway lessons?	Does it meet all 8 criteria
Croarkin et al. (2000)	Y	N	Y	Y	N	N	N	N	N
Crown et al. (2007)	N	Y	Y	Y	Y	Y	N	Y	N
Dahri et al. (2002)	Y	Y	Y	Y	N	N	N	Y	N
Das et al. (2018)	N	Y	Y	Y	Y	N	N	Y	N
de Boer & Gaete (1992)	N	Y	Y	Y	N	N	N/A	N	N
Dhamija et al. (2008)	Y	N	N	Y	N	N	N	Y	N
Dibben et al. (2005) (Case 1)	Y	Y	Y	Y	Y	Y	N	Y	N
Dibben et al. (2005) (Case2)	Y	Y	Y	Y	N	Y	N	Y	N
Endoh et al. (2012)	Y	Y	Y	Y	Y	Y	N	Y	N

Table S2.3. Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2} (cont.).

Citation	Criteria								Overall Assessment
	(1) Were the patient's demographic characteristics clearly described?	(2) Was the patient's history clearly described and presented as a timeline?	(3) Was the current clinical condition of the patient on presentation clearly described?	(4) Were diagnostic tests or assessment methods and the results clearly described?	(5) Was the intervention(s) or treatment procedure(s) clearly described	(6) Was the post-intervention clinical condition clearly described?	(7) Were adverse events (harms) or unanticipated events identified and described?	(8) Does case report provide takeaway lessons?	Does it meet all 8 criteria
Fang et al. (2018)	Y	Y	Y	Y	Y	Y	N	N	N
Franco et al. (2012) (Abstract)	Y	N	Y	N	N	N	N	Y	N
Franco et al. (2015)	Y	N	Y	Y	N	Y	N	Y	N
Fullbright & Breedlove (2006)	Y	Y	Y	Y	N	Y	N	Y	N
Gatta et al. (1999)	Y	Y	Y	Y	N	Y	N	Y	N
Goldstein et al. (1999) (Case 1)	Y	Y	Y	Y	N	Y	N	Y	N
Goldstein et al. (1999) (Case 2)	Y	Y	Y	Y	N	Y	N	Y	N
Greenfield et al. (2002)	N	N	N	Y	N	N	N	N	N
Hepburn & Brzozowska (2016)	Y	Y	Y	Y	Y	Y	N	Y	N

Table S2.3. Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2} (cont.).

Citation	Criteria								Overall Assessment
	(1) Were the patient's demographic characteristics clearly described?	(2) Was the patient's history clearly described and presented as a timeline?	(3) Was the current clinical condition of the patient on presentation clearly described?	(4) Were diagnostic tests or assessment methods and the results clearly described?	(5) Was the intervention(s) or treatment procedure(s) clearly described?	(6) Was the post-intervention clinical condition clearly described?	(7) Were adverse events (harms) or unanticipated events identified and described?	(8) Does case report provide takeaway lessons?	Does it meet all 8 criteria
Horber et al. (2018)	N	Y	Y	Y	N	Y	N	Y	N
Howes & Rifkin (2004)	N	Y	Y	Y	N	Y	N	Y	N
Itoh et al. (2019)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Iwaku et al. (2017)	N	Y	Y	Y	Y	Y	N	N	N
Jalota et al. 2015)	N	Y	Y	Y	N	N	Y	Y	N
Johnson et al. (2002)	Y	Y	Y	Y	N	Y	N	N	N
Kahn & Bourgeois (2007) (Abstract)	Y	Y	Y	Y	N	Y	N	Y	N
Kaino et al. (2017)	Y	Y	Y	Y	N	Y	N	N	N
Kasmi (2013)	N	N	N	N	N	N	N	N	N

Table S2.3. Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2} (cont.).

Citation	Criteria								Overall Assessment
	(1) Were the patient's demographic characteristics clearly described?	(2) Was the patient's history clearly described and presented as a timeline?	(3) Was the current clinical condition of the patient on presentation clearly described?	(4) Were diagnostic tests or assessment methods and the results clearly described?	(5) Was the intervention(s) or treatment procedure(s) clearly described	(6) Was the post-intervention clinical condition clearly described?	(7) Were adverse events (harms) or unanticipated events identified and described?	(8) Does case report provide takeaway lessons?	Does it meet all 8 criteria
Kaya et al. (2014)	Y	Y	Y	Y	N	N	N	Y	N
Khan et al. (2011)	N	N	Y	Y	N	N/A	N/A	Y	N
Kibbey et al. (2010)	Y	Y	Y	Y	N	Y	N	Y	N
Kinoshita et al. (2014)	Y	Y	Y	Y	Y	Y	N	Y	N
Kostakoglu et al. (1996)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Koval et al. (1994)	Y	N	Y	Y	Y	Y	Y	N	N
Kyriazis et al. (2006)	Y	Y	Y	Y	Y	Y	N	Y	N
Lafayette et al. (2003)	Y	N	Y	Y	Y	Y	N	Y	N
Laghate & Gupta (2004)	N	N	Y	Y	N	Y	N	Y	N
Letourneau et al. (2011)	Y	Y	Y	Y	Y	Y	N	Y	N
Lindmeyer et al. (1999)	Y	Y	Y	Y	Y	Y	N	Y	N
Lu & Yan (2009)	N	N	N	Y	N	N/A	N/A	Y	N

Table S2.3. Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2} (cont.).

Citation	Criteria								Overall Assessment
	(1) Were the patient's demographic characteristics clearly described?	(2) Was the patient's history clearly described and presented as a timeline?	(3) Was the current clinical condition of the patient on presentation clearly described?	(4) Were diagnostic tests or assessment methods and the results clearly described?	(5) Was the intervention(s) or treatment procedure(s) clearly described	(6) Was the post-intervention clinical condition clearly described?	(7) Were adverse events (harms) or unanticipated events identified and described?	(8) Does case report provide takeaway lessons?	Does it meet all 8 criteria
Mcfarlane & Fisher (2006)	Y	Y	Y	Y	N	Y	N	N	N
Madsen (2014)	Y	Y	Y	N	N/A	N/A	Y	E	N
Makhzoumi et al. (2008)	Y	Y	Y	Y	N	Y	N	Y	N
Maksimovic et al. (2006)	Y	N	Y	Y	N	Y	N/A	N	N
Marlowe et al. (2007)	N	N	N	Y	N	Y	N	Y	N
Maule et al. (1999)	Y	Y	Y	Y	N	Y	Y	Y	N
Maust et al. (2015)	Y	N	Y	Y	N	Y	N	Y	N
McCall et al. (2004)	N	N	Y	Y	Y	Y	N	Y	N
Meatherall et al. (2002)	Y	Y	Y	Y	N/A	N/A	N/A	N	N
Milano et al. (2016)	N	N	Y	Y	N	N	N	Y	N
Miller et al. (2008)	Y	N	Y	Y	N	N	N	Y	N
Mithat et al. (2005)	N	Y	N	Y	Y	Y	N	N	N

Table S2.3. Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2} (cont.).

Citation	Criteria								Overall Assessment
	(1) Were the patient's demographic characteristics clearly described?	(2) Was the patient's history clearly described and presented as a timeline?	(3) Was the current clinical condition of the patient on presentation clearly described?	(4) Were diagnostic tests or assessment methods and the results clearly described?	(5) Was the intervention(s) or treatment procedure(s) clearly described?	(6) Was the post-intervention clinical condition clearly described?	(7) Were adverse events (harms) or unanticipated events identified and described?	(8) Does case report provide takeaway lessons?	Does it meet all 8 criteria
Mohan (1999)	Y	Y	Y	Y	N	Y	N	N	N
Muench & Carrey (2001)	Y	N	Y	Y	Y	Y	N	Y	N
Nahas et al. (2010) (Abstract)	N	Y	Y	N	N	N	N	Y	N
Niazi et al. (2007)	Y	Y	Y	Y	N	Y	Y	Y	N
Nicolai (2001)	Y	Y	Y	Y	N	Y	N	N	N
Patel et al. (2011) (Abstract)	N	N	N	Y	Y	N	N	Y	N
Pathmanathan (2013) (Abstract)	N	N	Y	Y	Y	Y	N	Y	N
Peterson & Bird (1996)	Y	Y	Y	Y	N	Y	N	N	N
Pierides (997)	Y	Y	Y	Y	N	N	N	N	N

Table S2.3. Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2} (cont.).

Citation	Criteria								Overall Assessment
	(1) Were the patient's demographic characteristics clearly described?	(2) Was the patient's history clearly described and presented as a timeline?	(3) Was the current clinical condition of the patient on presentation clearly described?	(4) Were diagnostic tests or assessment methods and the results clearly described?	(5) Was the intervention(s) or treatment procedure(s) clearly described?	(6) Was the post-intervention clinical condition clearly described?	(7) Were adverse events (harms) or unanticipated events identified and described?	(8) Does case report provide takeaway lessons?	Does it meet all 8 criteria
Pillai et al. (2006)	N	Y	Y	Y	N	Y	N	Y	N
Popli et al. (1997)	Y	N	Y	Y	N	Y	N	Y	N
Ragucci & Wells (2001)	Y	Y	Y	Y	Y	Y	N	Y	N
Rahat et al. (2005)	Y	N	Y	Y	N	N	N	N	N
Rashid et al. (2009)	Y	Y	Y	Y	N	N	N	Y	N
Ratnakaran (2015)	N	Y	Y	Y	Y	Y	N	Y	N
Raza S. (2007)	N	N	Y	Y	N	Y	N	Y	N
Reddymasu et al. (2006)	N	Y	Y	Y	N	N	N	Y	N
Rock et al. (2009)	N	N	Y	Y	N	N/A	N/A	Y	N
Roefero & Mukherjee (2001)	Y	Y	Y	Y	Y	Y	N	Y	N
Sa et al. (2013)	Y	Y	Y	Y	N	Y	N	Y	N
Sato et al. (2008)	N	Y	Y	Y	N	Y	N	N	N

Table S2.3. Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2} (cont.).

Citation	Criteria								Overall Assessment
	(1) Were the patient's demographic characteristics clearly described?	(2) Was the patient's history clearly described and presented as a timeline?	(3) Was the current clinical condition of the patient on presentation clearly described?	(4) Were diagnostic tests or assessment methods and the results clearly described?	(5) Was the intervention(s) or treatment procedure(s) clearly described?	(6) Was the post-intervention clinical condition clearly described?	(7) Were adverse events (harms) or unanticipated events identified and described?	(8) Does case report provide takeaway lessons?	Does it meet all 8 criteria
Seaburg et al. (2001)	Y	Y	Y	Y	Y	Y	Y	Y	N
Selva & Scott (2001)	Y	Y	Y	Y	Y	N	N	Y	Y
Short & Nolan (1994)	Y	Y	Y	Y	Y	Y	N	N	N
Singh et al. (2013)	N	Y	Y	Y	N	Y	Y	N	N
Sirois (2008)	Y	Y	Y	Y	N	N	N	N	N
Smith et al. (1999)	N	Y	Y	Y	N	N	N	Y	N
Strassnig et al. (2013) (Case 1)	N	Y	N	Y	N	Y	N	Y	N
Straker et al. (2002)	Y	Y	Y	Y	N	N	Y	Y	N
Takashashi et al. (2005)	Y	Y	Y	Y	Y	Y	N	Y	N
Takanobu et al. (2015)	N	Y	Y	Y	N	Y	N	Y	N
Tavakoli & Arguisola (2003)	Y	Y	N	N	N	N	N	Y	N

Table S2.3. Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2} (cont.).

Citation	Criteria								Overall Assessment
	(1) Were the patient's demographic characteristics clearly described?	(2) Was the patient's history clearly described and presented as a timeline?	(3) Was the current clinical condition of the patient on presentation clearly described?	(4) Were diagnostic tests or assessment methods and the results clearly described?	(5) Was the intervention(s) or treatment procedure(s) clearly described	(6) Was the post-intervention clinical condition clearly described?	(7) Were adverse events (harms) or unanticipated events identified and described?	(8) Does case report provide takeaway lessons?	Does it meet all 8 criteria
Tollefson et al. (1983)	Y	Y	Y	Y	N	Y	N	N	N
Torrey et al. (2003)	Y	Y	N	N	N	N/A	N/A	Y	N
Taslipinar et al. (2008)	N	Y	Y	Y	N	Y	N	Y	N
Tsuchiyama et al. (2004)	Y	Y	Y	Y	Y	Y	N	Y	N
Tugwell et al. (2020)	Y	N	Y	Y	Y	Y	Y	Y	N
Varma et al. (2007)	N	U	Y	Y	N	N	N	Y	N
Vincent et al. (2017)	N	Y	Y	Y	N	Y	N	Y	N
Vuk et al. (2017)	Y	Y	Y	Y	N	Y	N	N	N
Waldman & Yaren (2002)	Y	Y	Y	Y	N	Y	N	Y	N
Watkins et al. (2011)	Y	Y	Y	Y	Y	Y	N	Y	N
Whicher et al. (2019)	Y	N	Y	N	Y	Y	Y	Y	N
Wilson et al. (2002) (Case 1)	Y	N	Y	Y	Y	N	N	N	N

Table S2.3. Critical Appraisal of Case Reports (n = 125) Against Eight Criteria Detailed in the Joanna Briggs Tool^{1,2} (cont.).

Citation	Criteria								Overall Assessment
	(1) Were the patient's demographic characteristics clearly described?	(2) Was the patient's history clearly described and presented as a timeline?	(3) Was the current clinical condition of the patient on presentation clearly described?	(4) Were diagnostic tests or assessment methods and the results clearly described?	(5) Was the intervention(s) or treatment procedure(s) clearly described	(6) Was the post-intervention clinical condition clearly described?	(7) Were adverse events (harms) or unanticipated events identified and described?	(8) Does case report provide takeaway lessons?	Does it meet all 8 criteria
Wilson et al. (2002) (Case 2)	Y	N	Y	Y	Y	N	N	N	N
Wilson et al. (2002) (Case 3)	N	Y	N	N	N	N	N	N	N
Wilson et al. (2002) (Case 4)	N	Y	Y	N	Y	N	N	N	N
Wilson et al. (2002) (Case 5)	N	Y	N	Y	N	Y	N	N	N
Wong et al. (2007)	Y	Y	Y	Y	Y	Y	N	Y	N
Yeung & Lee. (2015) (Abstract)	N	N	Y	Y	N	N	N	N	N

¹The Joanna Briggs Tool for Critical Appraisal was used as a quality assessment tool for each case report.

²Cases were fatalities occurred could not be assessed for every criterion.

CHAPTER 3

PREFACE

This chapter comprises the second manuscript that addresses Objective 2. A systematic review of observational studies was conducted to evaluate the potential association between exposure to antipsychotic drug use and two diabetic complications, specifically diabetic ketoacidosis and hyperglycemic hyperosmolar state. Information was abstracted on database sources, patient population, study design, methods, exposure and outcomes, along with data on demographic variables, effect estimates and relevant covariates, when available. Strengths, limitations, and conclusions were also noted.

The search strategy was completed with the help of two librarians from the University of Ottawa's Health Sciences library, Ms. Karine Fournier and Dr. Lindsay Sekora. Content expertise was based *on prior* knowledge in the literature. The same research strategy was used for Chapters 2 (Systematic Review on Case Reports and Case Series) and 3.

Contribution Statement

For this systematic review, I developed the initial study protocol and the search strategy with guidance of my thesis supervisor (DK) and NF. I synthesized the findings, drew conclusions, and drafted the manuscript. NH and NF screened references for inclusion in the systematic review, abstracted key data elements from the references that met the inclusion criteria and performed quality assessment for the included observational studies. JG provided expert advice on the diabetic complications. Members of my thesis advisory committee (YC, DM, MM, CG) contributed to the development of the study protocol and provided feedback during our meetings. The manuscript received a critical review from DK and NF.

Chapter 3: Antipsychotic Drugs and the Risk of Diabetic Complications:

A systematic Review of Observational Studies

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ABSTRACT

Background: In recent years, case reports and case series have suggested an association between the use of second (SGAs), but not first-generation antipsychotics (FGAs), also known as atypical and typical APDs, respectively, and hyperglycemic complications, notably diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS). Although this evidence is informative, there is a need for more observational studies to strengthen this body of knowledge.

Objective: To conduct a systematic review of evidence established in observational studies on adverse drug events, specifically DKA and HHS, associated with the use of FGAs and SGAs.

Methods: Pertinent bibliographic databases (MEDLINE, EMBASE and PsycINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL)) were searched using appropriate

index phrases and keywords through to October 20, 2020. Exposure included at least one United States Food and Drugs Administration (US FDA) approved antipsychotic drug (APD); outcomes were limited to DKA and HHS.

Results: A total of 13 observational studies were included in this review, including five analytical and eight descriptive studies, varying in scope and describing different case definitions, study populations, exposure, and outcomes. The observational studies support existing evidence of an association between atypical APDs and DKA, mainly. As a class, typical APDs were associated with an increased risk of DKA, when compared to non-antipsychotic drug use. Although some studies evaluated this association in relation to HHS, there is insufficient information to draw conclusions for this outcome at this time.

Conclusion: This analysis provides additional evidence of an association between use of atypical APDs and DKA. Additional analytical studies using administrative health databases are needed to clarify this association.

Keywords: Antipsychotic drugs, diabetic ketoacidosis, hyperglycemic hyperosmolar state, analytical studies, descriptive studies.

3.1 INTRODUCTION

The prevalence of diabetes in individuals who are administered antipsychotic drugs (APDs) to treat mental illness is about 10%, 2-3-fold higher than the general population (Holt, 2019; Holt et al. 2015; Vancampfort et al. 2013). Although APDs are indicated primarily to treat schizophrenia and bipolar disorder, these medicines are also used off label to treat other conditions such as depression, anxiety, Tourette's syndrome, personality disorders and obsessive-compulsive disorders (Chokhawala & Stevens, 2023; Holt et al. 2019). The underlying

mechanisms of action of APDs are not fully understood, but accrued evidence suggests they play a role in the etiology of diabetes and hyperglycemic emergencies (Holt, 2019). All antipsychotics have antagonistic effects on dopamine D2 receptors in the mesolimbic and mesocortical pathways of the brain, with variable effects on muscarinic, histamine and adrenergic receptors. First-generation antipsychotics or FGAs, also known as typical antipsychotics, cause extrapyramidal movement disorders and hyperprolactinemia disorders due their antagonistic properties acting on dopamine receptors in the nigrostriatal and tuberoinfundibular systems, respectively (Amato et al. 2018; Holt, 2019). This history paved the way for the development of second-generation antipsychotics (SGAs), also known as atypical APDs, to minimize extrapyramidal effects. SGAs have a lower affinity for D2 receptors overall, and are also antagonist of 5HT2 serotonin receptors, and some, such lurasidone and aripiprazole, are strong 5HT1a agonists (Amato, 2015). The latter has unique pharmacological properties and manifests partial D2 agonism (Tuplin et al. 2017).

In this article, we are interested in whether antipsychotic medications cause or contribute to the development of hyperglycemic complications. A meta-analysis comparing drug-naïve subjects presenting with a first episode of schizophrenia to control subjects found that metabolic health problems are present at the time of initiation of the mental health condition, and patients are at an increased risk of developing diabetes mellitus (DM) (Pillinger et al. 2017). In recent years, evidence has accrued correlating the use of atypical APDs with adverse health outcomes including increased weight gain and development of diabetes and dyslipidemia. This evidence prompted experts in the United States to publish a consensus statement on the risk of these and other health effects in patients who are treated with atypical APDs (ADA, 2004).

Diabetes is a multifactorial disease involving genetic, lifestyle and other risk factors. As such, it is difficult to determine with certainty if an APD caused diabetes or hyperglycemic complications. Investigation of this association is made more challenging due to low patient compliance with treatment: it is estimated that less than 50% of schizophrenia patients are fully adherent to APD treatment (Garcia et al. 2015). To address this issue, new approaches were introduced to enhance compliance to the prescribed treatment plan such as utilizing new routes of administration including short-acting intramuscular clozapine preparation, transdermal asenapine, modification of existing compounds, and oral long-acting medication formulation (Taub et al. 2021).

Absolute insulin deficiency due to the loss of pancreatic β cells characterizes Type 1 diabetes mellitus (T1DM), also known as autoimmune diabetes, a chronic disease with elevated blood sugar levels (Katsarou et al. 2017). Type 2 diabetes mellitus (T2DM) is characterized by abnormal β cell activity, resulting in relative insulin deficiency marked by decreased insulin secretion (Guillausseau et al. 2008). Both conditions reduce peripheral glucose uptake and increase hepatic glucose production (ADA, 2022; DeFronzo et al. 2015; Shulman, 2014). DKA and HHS are two potentially fatal hyperglycemic complications of DM that involve elevated blood glucose levels due to insulin deficiency and require intensive insulin therapy (Fayman et al. 2017). Patients with T1DM are more likely to experience DKA, which is more prevalent than HHS. However, DKA cases reported in T1DM patients account for at least one-third of all cases (Wang et al. 2008).

Recent systematic reviews of case reports and case series support accumulating evidence of an association between atypical APDs and DKA (Guenette et al. 2013; Haddad et al. 2023; Vuk et

al. 2017) and HHS (Haddad et al. 2023). The objective of this review is to evaluate and synthesize information from observational studies to shed light on the associations between antipsychotic medications and hyperglycemic emergencies, specifically DKA and HHS.

3.2 METHODS

3.2.1 Research Strategy and Databases

The following bibliographic databases were searched to identify observational studies of interest: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO through to October 20, 2020 (Figure 3.1). A secondary search consisting of hand-searching of reference lists and citation tracking was conducted to complement the primary search strategy. The search strategy, detailed in Supplementary Material I, was reviewed by a research librarian from the University of Ottawa's Health Sciences Library.

3.2.2 Data Screening and Abstraction

EndNote (Clarivate Analytics, 2018. Version X9. Available from <https://endnote.com>) was used to remove duplicate records identified from the database search. This was followed by two levels of screening by two independent reviewers to determine study eligibility. Phase 1 involved screening of titles and abstracts (Supplemental Material II). Phase 2 involved full text screening of all records retained from Phase 1. Screening was performed using Distiller SR (Evidence Partners, 2018). Pertinent data was abstracted from each eligible study using Excel. Subsequently, observational studies were categorized as analytical or descriptive. Analytical studies included the presentation of effect estimates (relative risk, odds ratios) using cohort nested case-control study designs. Descriptive studies focused mainly on data retrieved from

hospital death certificates, bibliographical databases, the FDA MedWatch Program and included descriptive analysis or simple regression models.

The following information was abstracted from studies that met the inclusion criteria:

type/names of databases, patient population, study design, methods (overall sample size and study period, description of the statistical analysis, inclusion and exclusion criteria), information on exposure (class of APDs, individual APDs, treatment information such as duration, dose, and form; notes on exposure ascertainment); information on outcomes of interest and outcome ascertainment; results on demographic variables (age, sex and ethnicity of study participants), adjusted/unadjusted effect estimates, or raw data (counts, exposed/nonexposed, events/nonevents), relevant covariates; and conclusions including strengths and limitations.

Analytical studies analyzed administrative databases and presented adjusted or unadjusted risk estimates. Descriptive studies used pharmacovigilance and bibliographical databases to draw their conclusions.

Data abstraction was completed by one of the two reviewers (NH), with duplicate data abstraction conducted on a 10% random sample of the studies as a quality control measure (NF).

3.2.3 Eligibility Criteria

3.2.3.1 Inclusion Criteria

Observational studies were considered if they evaluated at least one of the two outcomes of interest, DKA or HHS, and evaluated at least one FDA-approved APD type as an exposure (Table 3.1). Studies in which hyperglycemic conditions, including DKA and HHS were pooled, were

included. Both English and French abstracts were considered. There were no restrictions on location, indication of APD use, or patient age.

3.2.3.2 Exclusion criteria

Studies were excluded if the outcomes examined were not DKA or HHS, if the APD was never approved or was discontinued from use in the US, or if APDs were not suspected to be responsible for one of the outcomes. Meta-analysis, editorials, comments, literature reviews, and systematic reviews were not included. Case reports that were eligible for analysis were included in a second review (Chapter 2) and were, therefore, excluded from the present review.

3.2.4 Quality Assessment

The quality of each included observational study was assessed using the Office of Health Assessment and Translation (OHAT) risk of bias rating tool, which is applicable to diverse study designs. It comprises seven domains: selection bias, confounding bias, attrition/exclusion bias, detection biases for exposure and for outcome characterization, reporting bias, and other possible biases (National Toxicology Program (NTP), 2015). A three-tiered approach was used to determine the overall study quality according to the Handbook for Conducting a Literature-Based Health Assessment (NTP, 2019). Tier 1 qualifies as “definitely” or “probably” low risk for bias; Tier 3 qualifies as “definitely” or “probably” high risk of bias. Tier 2 included studies that could not be classified as low or high risk of bias. Evaluation of the risk of bias was done by one of the two reviewers (NH) with the second reviewer (NF) verifying a 10% sample of the studies evaluated.

3.3 RESULTS

3.3.1 Scope of Included Studies

The criteria for inclusion were met by 13 observational studies, five analytical and eight descriptive. The studies varied in scope with respect to the case definition, study population, exposure to APDs, reported outcomes, effect estimates, or descriptive analysis of the results.

3.3.2 Analytical Studies

Three of the analytical studies chose patients with schizophrenia as their study subjects (Henderson et al. 2007; Leslie & Rosenheck, 2004, Polcwiartek et al. 2017). Ramazwamy et al. (2007) and Lipscombe et al. (2014) selected patients who had received an APD. All analytical studies focused their analysis on atypical APD mainly, except for Leslie and Rosenheck (2004), and Lipscombe and colleagues (2014), who also analyzed typical APDs as a class.

Henderson et al. (2007) provided descriptive results for DKA and HHS but refocused their analysis on the incidence of new-onset diabetes mellitus presenting as DKA events and compared it to those with known DM status presenting as DKA for various atypical APDs, possibly because there were few ($n = 4$) HHS cases (Table 3.2). Three studies provided effect estimates for the association between antipsychotic medications and DKA using hazard ratios, attributable risks, or crude rates (Leslie & Rosenheck, 2004; Lipscombe et al. 2014; Ramazwamy et al. 2007). In the sole nested case control study that satisfied inclusion requirements, Polcwiartek et al. (2017) evaluated the odds ratio for this association. One study presented a pooled analysis of hyperglycemia (Lipscombe et al. 2014), and, although valuable, the interpretation of the reported association between APDs and DKA or HHS was challenging to decipher.

3.3.3 Summary of Effect Estimates from Analytical Studies

The incidence of new DM presenting as DKA in a population of inpatients and outpatients diagnosed with schizophrenia in Boston, Massachusetts between 1995 and 2001 was 2.2% and 0.8% for clozapine and olanzapine, respectively, followed by risperidone at 0.2%. The authors also found a significant difference between clozapine and risperidone in the incidence of diabetes presenting as DKA ($p < 0.0001$) (Henderson et al. 2007). During the seven-year follow up, the authors did not find any significant differences in age, glucose levels at the time of DKA occurrence, or hemoglobin A1c (HbA1c) levels between patients with new-onset DM presenting as DKA when compared to those with known DM. The overall incidence of DKA in patients suffering from schizophrenia and related disorders was 1.67% of all DKA cases in the hospital.

Using the Department of Veteran Affairs administrative health records database, Leslie and Rosenheck (2004) studied an older, predominantly male, outpatient diabetes-naïve population, diagnosed with schizophrenia and who developed diabetes (7.3%) or who were hospitalized for DKA (0.2%). The authors used Cox proportional hazard models to model the time to DM diagnosis and time to DKA hospitalization. Hazard ratios (HR) for diabetes were highest with the use of clozapine (HR: 1.57, 95% CI (1.31–1.89) and olanzapine (HR: 1.15, 95% CI=1.07–1.24), followed by treatment with quetiapine (HR: 1.20, 95% CI (0.99–1.44) and risperidone (HR: 1.01, 95% CI: 0.93–1.10), but were not significantly different from typical APDs, and the attributable risks of DM associated with atypical APD use were small in the range of 0.05% for risperidone to 2.03% for clozapine. HR for DKA hospitalization were larger than the DM model and were significant for clozapine at 3.75 (95%CI: 1.39–10.09) and olanzapine at 1.77 (95% CI: 1.05–2.98).

However, attributable risks were relatively small and ranged for 0.004% for risperidone to 0.071% for clozapine.

Polcwiartek et al. (2017) also evaluated this association in patients with schizophrenia who did not have diabetes and estimated odds ratios for atypical APDs as a class due to the low number of individual drugs. The odds ratio for the association between atypical APD exposure and DKA within three months prior to the event was 2.60 (95% CI: 1.06, 6.38) in the crude model. After adjusting for low or moderate/high Charlson comorbidity score within 1 year prior to the event, the odds ratio was 2.58 (95% CI: 1.04, 6.40); odds ratios were 2.65 (95%CI: 1.06, 6.59) and 4.06 (95% CI: 1.48, 11.11) after adjusting for diabetogenic and psychotropic co-medications within 3 months prior to the event, respectively. The authors concluded most APDs, including typical agents, are at risk of developing DKA but the findings were not shown for individual drugs due to the limited number of cases.

In a retrospective cohort of patients receiving an atypical APD (Ramazwamy et al. 2007), the unadjusted risk of developing of DKA was 1.8 times greater with olanzapine treatment when compared to risperidone ($p = 0.0096$); this relative risk (RR) was reduced to 1.62 after adjustment for relevant covariates, but remained statistically significant ($p = 0.033$). The unadjusted risk of DKA for olanzapine was 10.7 per 10,000 patients, and 6.0 per 10,000 patients for risperidone. The risk estimates for quetiapine and clozapine should be interpreted with caution due to the low number of events (Table 3.2).

Lipscombe et al. (2014) pooled hyperglycemia, DKA, and HHS into one aggregate outcome and assessed this association in the APD-naïve patient group in two sub-populations comprised patients with or without diabetes. Risperidone and olanzapine had crude incidence rates of

9.45 per 1,000 persons (95%CI: 6.32-12.59) and 9.62 per 1,000 (95%CI: 4.90-14.33), respectively, in patients with diabetes aged between 18 to 65 years of age. The crude event rates for risperidone and olanzapine in patients without diabetes were 0.36 (95%CI: 0.22-0.50) and 0.51 (95% CI: 0.30-0.73), respectively. After adjusting for relevant covariates, the hazard ratio for an olanzapine-related hyperglycemic event was 1.15 (95%CI: 0.71-1.86) overall, and 1.19 (95%CI: 0.52–2.72) in those with pre-existing DM and there was no significant increase of hyperglycemic events between new users of risperidone and olanzapine. In patients aged 66 years of age or more, incidence rate in diabetics for risperidone and olanzapine were 7.07 per 1,000 persons (95%CI: 6.00–8.14) and 6.74 per 1,000 persons (95%CI: 4.90–8.57), respectively. The rates were much lower in non-diabetics at 0.85 per 1,000 persons (95% CI: 0.67–1.02) for risperidone and 0.78 per 1,000 persons (95% CI: 0.49–1.08) for olanzapine. The research group also completed a secondary nested case-control analysis for cases who experienced a hyperglycemic event matched to controls who did not. While the authors did not present quantitative results in their paper, they noted that there were no statistical differences in outcomes between the current use of olanzapine, other atypical, or typical antipsychotic medicines compared to current exposure to risperidone. Due to the lack of information, this secondary analysis was not included in the tables (Table 3.2; Supplemental Table S3.1).

3.3.4 Descriptive Studies

The inclusion criteria were satisfied by a total of eight descriptive studies as described below. Ely and colleagues (2013) examined Medical Examiner Records in New York City. For this analysis, death certificates and toxicology data from former psychiatric patients treated with atypical APDs were analyzed for electrolytes and glucose, including urine and blood tests,

medical history, and toxicology results, which provided information on drug use and metabolic markers. Jin et al. (2002) used bibliographic databases and compared patient characteristics for those who developed new-onset DM only and those who developed DKA after initiation of atypical APD treatment. A prospective cohort of young patients in Germany and Austria suffering with T1DM treated with typical and atypical APDs was conducted by Galler et al. (2015) and compared those who were administered antipsychotic medicines to those who did not receive it. Koller and colleagues (2001; 2002; 2003; 2004) used the FDA MedWatch Drug Surveillance Program, Medline and selected abstracts from meetings to present descriptive statistics for hyperglycemia and associated exacerbations with an emphasis on acidosis, ketosis, mainly, but without a consistent distinction between these conditions and DKA in all the results that were presented. The authors also noted the occurrence of HHS, but only provided sufficient details for two of the HHS cases, suspected to be induced by olanzapine (Koller et al. 2002). Another study examined the efficacy of olanzapine and haloperidol in schizophrenia patients at the Tanzawa Hospital in Japan and reported no DKA events (Suzuki et al. 2013). This study was not included in the descriptive tables or the risk of bias quality control assessment.

3.3.5 Summary of Descriptive Statistics

Descriptive observational studies included in this review provide additional evidence of a potential association between atypical APD use and hyperglycemic complications, mainly DKA (Table 3.3; Supplemental Material, Table S3.2). Ely et al. (2013) used New York's City Medical Examiner Records for psychiatric patients treated with the most used APDs United States, namely: quetiapine, olanzapine, risperidone, ziprasidone, and clozapine. Death occurred in ten patients with schizophrenia: three decedents had a combined diagnosis of schizophrenia and

bipolar disorder; one patient was diagnosed with bipolar disorder and another with major depression. The authors concluded APD use was the primary cause of death in 16 of the decedent cases, while the immediate cause of death in all cases was DKA. The detection of blood ketones for 17 decedents supported their conclusions.

A prospective analysis of a German/Austrian diabetes survey of young patients who were 25 years of age or older and diagnosed with T1DM indicated 0.48% of participants were treated with APDs, with risperidone being the most prescribed atypical APD ($n = 122$, 42%), followed by quetiapine ($n = 19$, 7%). Pipamperone was the most prescribed typical APD at 10% ($n = 29$), followed by promethazine, prochlorperazine and haloperidol at 6% each ($n = 18$, 17 and 16, respectively). Poisson regression analysis for classes of drugs showed that the risk of DKA in patients undergoing with atypical APD treatment compared to patients who were not who were not receiving these drugs was 0.12 vs. 0.05 ($p < 0.001$) per patient-year of observation; the risk of DKA for patients receiving typical APD treatment was 0.13 vs 0.05 ($p < 0.001$) per patient-year (Galler et al. 2013).

A series of analysis of the FDA MedWatch Drug Surveillance Program by Koller and colleagues evaluated the association between four different atypical APDs and hyperglycemia, including acidosis, ketosis, DKA and HHS. As mentioned previously, the authors did not consistently distinguish between these states of diabetic complications or did not provide sufficient information on DKA or HHS cases. Based on their findings, they suggested a potential association between certain atypical APDs - namely clozapine, risperidone, olanzapine, and quetiapine - and hyperglycemia (Koller et al. 2001; 2002; 2003; 2004) (Table 3.3; Supplemental Material, Table S3.2).

3.3.6 Study Quality and Risk of Bias

All studies included in this review were subject to an assessment of study quality and risk of bias using the OHAT tool, except for the analysis by Suzuki and colleagues (2013). Their analysis did not find any association between serious adverse DKA events between the olanzapine and haloperidol-treated elderly patients with agitated schizophrenia.

Three analytical studies (Lipscombe et al. 2014; Polcwiartek et al. 2017; Ramaswamy et al. 2007) had “definitely or probably” low risk of bias for key the three key criteria (confounding bias and detection biases for exposure and outcome). Two analytical studies (Henderson et al. 2007; Leslie & Rosenheck, 2014) and two descriptive studies (Galler et al. 2015; Jin et al. 2002) were classified in Tier 2 because they did not meet the criteria for the first or second tier. Five descriptive studies were classified as Tier 3 with “probably or definitely” high risk of bias (Ely et al. 2013; Koller et al. 2001;2002;2003;2004) (Supplemental Material Table S3.3).

3.4 DISCUSSION

The present review provides an overview of observational studies that evaluated the potential association between treatment with APDs and serious complications of diabetes, specifically DKA and HHS. Henderson et al. (2007) reported an incidence of new-onset DM presenting as DKA that was 10 times higher than in the general population in patients with schizophrenia treated primarily with clozapine, olanzapine, and risperidone (14.9 vs 1.4 cases per 10,000 patient years, $p < 0.00001$). Elevated levels of HbA1c indicate that DM may have been undiagnosed prior to DKA events observed in this study. These findings are corroborated by Lipscombe et al. (2014), who found that while the risks remain low, those with pre-existing diabetes remain at greater risk of developing diabetic emergencies after initiation of APD

treatment. Using a nationwide German-Austrian diabetes survey, Galler et al. (2015) concluded the rate of acute DKA in young patients was higher in those treated with APDs when compared to patients who did not receive these medications.

While these findings supplement and support those from our case report/case series review (Chapter 2; Haddad et al. 2023), many published observational analyses on the incidence of DKA and HHS are do not consider indication of use of antipsychotic medications. In a multicentre initiative of prospective diabetes patients involving 437 centres in Germany, Austria, Switzerland, and Luxembourg, Tittel and colleagues (2020) evaluated the occurrence of DKA and HHS in patients with pre-existing diabetes. Findings indicated that being diagnosed with T1DM and being of younger age were strong indicators for diabetic emergencies associated with DKA and HHS, although both conditions also occurred in those diagnosed with T2DM. Patients who experienced DKA and HHS had worse metabolic control, and both conditions were linked to heavy drinking and comorbidities such as dementia, stroke, chronic kidney disease and depression. Recent retrospective analysis of a diabetic cohort based in Ethiopia corroborates that the incidence of hyperglycemic emergencies is higher in those diagnosed with diabetes (Abate et al. 2023). Although diabetic duration is a strong predictor of developing complications, conclusions are varied (Getie et al. 2021; Mansour et al. 2016). It would be worth investigating this predictor in future observational studies.

Leslie et al. (2004) concluded that despite the small risk, the severity of the event justifies a closer examination of the attributable risk for clozapine and risperidone monotherapy in diabetes-naïve older male populations with schizophrenia. Ramaswamy et al. (2007) estimated that the attributable risk of DKA was 1.62 times higher with olanzapine monotherapy compared

to risperidone monotherapy, irrespective of DM diagnosis ($p = 0.033$). A descriptive analysis of a diabetes-naïve outpatient population established an association between clozapine and DKA early in the course of treatment; notably, the administration of antidiabetic medications was negatively correlated with DKA ($p < 0.0001$) (Nihalani et al. 2007). Koller and colleagues evaluated spontaneous reporting of hyperglycemic adverse events, including DKA and HHS, and the use of clozapine (Koller et al. 2001) and olanzapine (Koller et al. 2002) in the US FDA MedWatch Surveillance Program. These descriptive studies are very informative and provide additional weight to existing evidence of an association between APDs and DKA and HHS. However, for the purpose of this review, these findings cannot be interpreted unequivocally, as the authors do not always differentiate between distinct states of hyperglycemia, including acidosis, ketosis and DKA when presenting their results.

A recent evaluation of case reports indicated that clozapine and olanzapine treatments may be associated with DKA (Haddad et al. 2023). A review by Cohen et al. (2012) compared one-year incidence rates and mortality rates due to DKA adverse events involving use of clozapine. The incidence of DKA was 1.2 - 3.1%, with a case fatality rate of 20 - 31%. The high risk of mortality renders DKA one of the riskiest side effects, even with low dose and early course of treatment with clozapine (Nihalani et al. 2007).

In addition to synthesized evidence from case reports, evaluation of rare but life-threatening conditions such as DKA and HHS using prospective or retrospective cohorts is necessary. Randomized controlled trials (RCTs) cannot support hypothesis testing for every conceivable research question, particularly those involving life-threatening conditions. To our knowledge,

The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) open label RCT trial study led by Strom and colleagues (2011) is the only RCT that evaluated the association between APD use and DKA as a secondary endpoint. Two treatment groups – ziprasidone or olanzapine – were compared in schizophrenia patients enrolled from eighteen different countries.

Hospitalization rates for DKA in both treatment groups were low, consistent with the reported medical history of T1DM in both groups at baseline also being low (<3%). In a primary intent-to-treat analysis, there were no differences between the two treatment groups with respect to DKA (Relative risk (RR): 1.00, 95% CI: 0.29-3.45). A secondary analysis of person-time on assigned treatment provided similar results (RR: 1.11, 95% CI: 0.32 – 3.85). It is recommended that these results be interpreted with caution since they are underpowered due to the small sample size in each treatment group.

Most studies included in this review cautioned against establishing a causal link between APD use and DKA or HHS, since strong and justifiable assumptions are needed to infer causality from observational studies (Andrade, 2014). Although adjusting for measured and known confounders is possible, a significant effect estimate does not imply that a drug is responsible for the outcome being examined. Therefore, when assessing the relationship between drug exposures and life-threatening conditions, it is important to evaluate the weight of evidence for causality to properly interpret the observed associations between antipsychotic use and DKA or HHS. This is especially important when the underlying biological mechanisms of actions linking exposure and outcome are not fully understood.

Antipsychotic medication users are at elevated risk of developing hyperglycemia due to several risk factors, including genetic and lifestyle health determinants (Holt, 2019). In a second scenario proposed by the author, antipsychotics may have a causal effect and raise the risk of this metabolic disorder through their direct impact on body weight, insulin resistance and impaired insulin secretion. Holt (2019) suggests these two possibilities are not mutually exclusive. These scenarios can be extrapolated to serious diabetic complications such as DKA and HHS. Consideration also needs to be given to off-label use of APDs and non-adherence to treatment. APDs are first-line treatments for severe mental illnesses such as schizophrenia, yet off-label prescribing to treat other conditions such as mood disorders, anxiety disorders and insomnia are widespread practices across all age categories (Carton et al. 2015). As mentioned earlier, the seriousness of the mental health conditions for which these medications are prescribed can lead to reduced compliance with clinical treatment regimens (Garcia et al. 2015). These factors, as well as dose-dependance and biological plausibility, introduce additional layers of complexity in distinguishing between association and causality. Although we adapted the scenarios presented by Holt (2019) to provide a high-level overview of the potential association and inference of causality of APD drug use and hyperglycemic emergencies (Figure 3.2), we are fully cognizant more research is necessary to understand the etiology of DKA and HHS.

3.4.1 Strengths

To our knowledge, this is the first comprehensive review of descriptive and analytical observational research that seeks to clarify the relationship between APD medication use and hyperglycemic complications, namely DKA and HHS. As was evident in our review on case

reports (Haddad et al. 2023), there is a need for additional observational studies to provide robust effect estimates for this newly emerging and complex association.

3.4.2 Limitations

The varied scope and methodology of the independent studies included in this review made it challenging to conduct a meta-analysis to quantitatively summarize overall findings. To this date, there are a limited number of observational studies that evaluated APD exposure and its association with diabetic emergencies. This may be due to various reasons: (1) off-label use of APDs adds another layer of complexity to the interpretation of effect estimates, particularly since information on indication of use is not always available; (2) non-compliance to treatment can have a strong effect on the true differences between groups, biasing results toward the null since statistical power is reduced; and (3) gaps in data availability and collection, particularly the lack of relevant biomarkers, can have a strong impact on data quality. These limitations make it difficult to draw firm conclusions on the strength of evidence for a causal relationship between APDs and DKA and HHS.

3.5 CONCLUSION

Observational studies provide further evidence that support an association between atypical antipsychotic drug use and DKA. Studies also suggest that as a class, typical antipsychotic drugs are associated with a higher risk of DKA. Future research should aim to use prospective and retrospective analytical studies to examine this association in depth. At this point in time, there is insufficient evidence to draw conclusions regarding HHS. Nonetheless, although HHS is less common than DKA, it is important to evaluate this outcome in relation to antipsychotic use. As

the mechanisms leading to these complications are multifactorial and complex, preventative measures would allow for an early recognition of symptoms and treatment.

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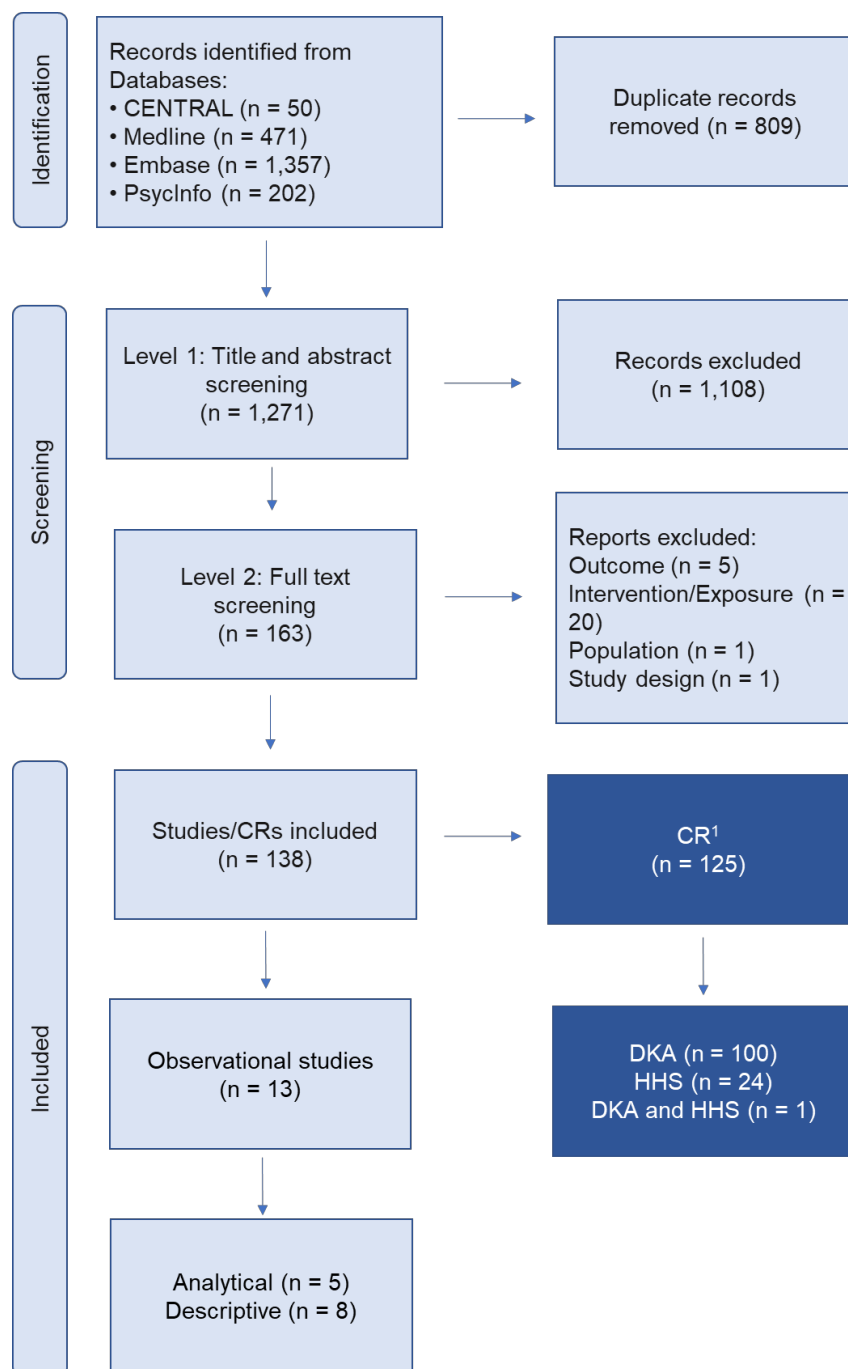
<https://doi.org/10.1002/wps.20069>

Vuk, A., Kuzman, M. R., Baretic, M., & Osvatic, M. M. (2017). Diabetic ketoacidosis associated with antipsychotic drugs: case reports and a review of literature. *Psychiatria Danubina*, 29(2), 121–135. <https://doi.org/10.24869/psyd.2017.121>

Wang, Z. H., Kihl-Selstam, E., & Eriksson, J. W. (2008). Ketoacidosis occurs in both Type 1 and Type 2 diabetes--a population-based study from Northern Sweden. *Diabetic medicine : a journal of the British Diabetic Association*, 25(7), 867–870. <https://doi.org/10.1111/j.1464-5491.2008.02461.x>

FIGURES

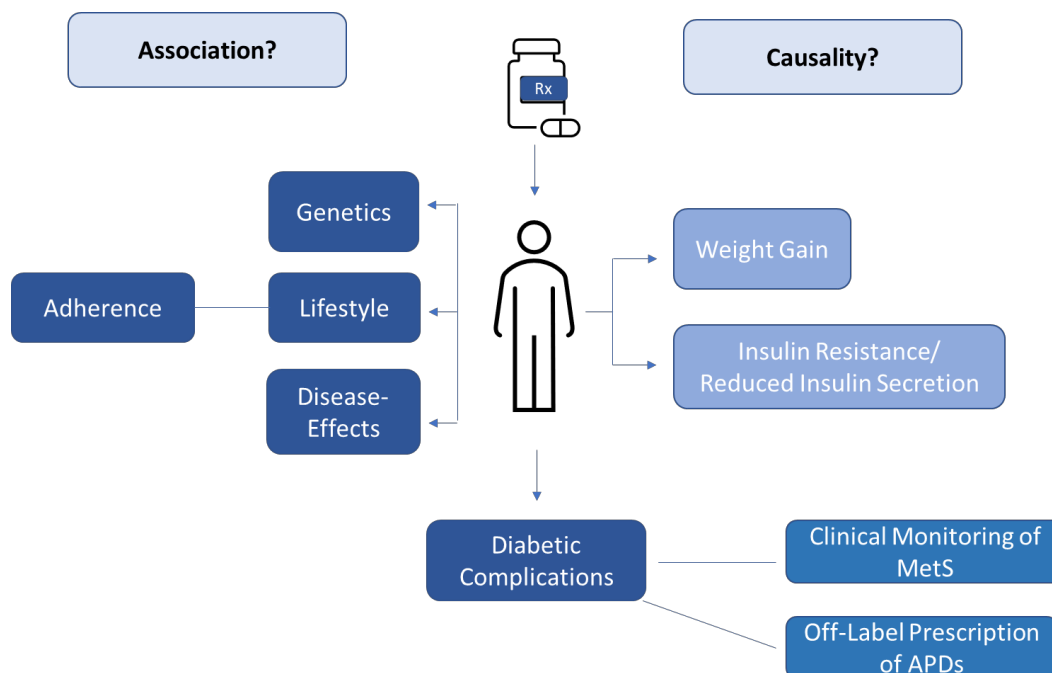
Figure 3.1. Flow Chart for the Selection of Observational Studies Included in the Systematic Review¹.



Abbreviations: ADP, Antipsychotic Drug; CR, Case report; DKA, Diabetic ketoacidosis; HHS, Hyperglycemic hyperosmolar state.

¹A separate review of case reports is presented in Chapter 2 of the thesis.

Figure 3.2. Possible Scenarios Explaining the Association Between Antipsychotic Drugs and Diabetic Complications: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State¹.



Abbreviations: APD, Antipsychotic Drug; MetS, Metabolic Syndrome.

¹Adapted from Holt (2019).

Association and causality are not necessarily mutually exclusive. An individual is prescribed an APD to treat a mental illness. Genetic risk factors, lifestyle elements such as: nutrition and exercise habits, substance abuse, adherence to APD use, and disease effects such as schizophrenia and comorbidities may predispose the patient to develop complications of diabetes. Biological and clinical issues that are outside the control of the patient may be on the causal pathway: it is also well established that APDs such as clozapine and olanzapine increase weight gain, insulin resistance and cause impaired insulin secretion. The off-label prescription of APDs is an added complexity. External factors such as the lack of clinical monitoring may also contribute to the development of diabetic complications.

TABLES

Table 3.1. List of Atypical (n = 13) and Typical (n = 12) Antipsychotic Drugs Included in the Search Strategy.

Atypical APDs Name of drug (market name)	Typical APDs Name of drug (market name)
Aripiprazole (Abilify)	Haloperidol (Haldol)
Asenapine Maleate (Saphris)	Loxapine (Loxitane)
Clozapine (Clozaril)	Molindone (Moban)
Iloperidone (Fanapt)	Thiothixene (Navane)
Lurasidone (Latuda)	Pimozide (Orap)
Olanzapine (Zyprexa)	Trifluoperazine (Stelazine)
Olanzapine/Fluoxetine (Symbyax)	Chlorpromazine (Thorazine)
Paliperidone (Invega)	Fluphenazine
Quetiapine (Seroquel)	Perphenazine or Perphenazine amitriptyline
Risperidone (Risperdal)	Prochlorperazine
Ziprasidone (Geodon)	Thioridazine
Capiprazine (Vryalar)	Droperidol (Inapsine)
Pimavanserin (Nuplazid)	

¹Source: FDA, 2022

Table 3.2. Characteristics of Analytical Observational Studies¹.

1 st Author (publication year) & location	Databases	Patient population	Study Design Study Period Sample Size	Exposure/ Outcome	Raw Effect Estimates or descriptive counts/proportions	Adjusted Effect Estimates
Henderson et al. (2007) Boston Massachusetts, United States of America	•Inpatients and outpatients at the Massachusetts General Hospital •Research Patient Data Registry (RPDR), an electronic database linking administrative and clinical laboratory data	•Patients with schizophrenic disorders treated with atypical antipsychotic agents.	•Retrospective Cohort •January 1, 1995 to December 31, 2001. •819,308 inpatients and outpatients and who attended the Massachusetts General Hospital.	Exposure: Atypical APDs: •Olanzapine: 10-30mg/day •Clozapine: 175-550mg/day •Quetiapine: 175-500 mg/day •Risperidone: 2 mg/day Outcome: •DKA in new-onset or existing DM •HHS in new-onset or existing DM	DKA in known DM •Mean BG: 690±158 mg/dL •Mean HbA1c: 11.2%±3.6 •No differences between patients with new-onset DM presenting as DKA and patients with known DM presenting as DKA for age, glucose levels at presentation, or hbA1c levels New-onset DM presenting as DKA Incidence for each drug over a 7-year period. •clozapine (n=226, 2.2%); •olanzapine (n=776, 0.8%); •risperidone (n=585, 0.2%); •No incidence for quetiapine (n=479) or ziprasidone (n=57). •Significant difference in incidence of DM presenting as DKA between clozapine and risperidone (p<.00001) •The inclusion of HHS cases would increase the incidence of olanzapine to 1.0% Follow up period (up to 6 years) •8/11: discontinued insulin •3/11: DM resolved upon switching of APD drug •1/11 switched from olanzapine to risperidone and no antidiabetics •1/11: DM resolved after switching from olanzapine to risperidone •1/11 Recurrent of DKA and death from heparin-induced thrombocytopenia •1/2 HHS case: DM resolved after switching from olanzapine to aripiprazole.	N/A

1 st Author (publication year) & location	Databases	Patient population	Study Design Study Period Sample Size	Exposure/ Outcome	Raw Effect Estimates or descriptive counts/proportions	Adjusted Effect Estimates
Leslie & Rosenheck (2004) United States of America	•Administrative Data from the Department of Veterans Affairs	•Patients with schizophrenia for whom a stable regimen of antipsychotic monotherapy was prescribed	NR •June 1999 to September 2001 •73,946	Exposure: Atypical APDs: ▪Clozapine, ▪Risperidone ▪Olanzapine ▪Quetiapine •Typical APDs as a class Outcome: DKA	•88 patients (0.2%)	Hazard ratios (n=88). <i>Only significant results were presented.</i> •Clozapine: HR=3.75 (CI: 1.39–10.09) •Olanzapine: HR=1.77 (CI: 1.05–2.98) Attributable risks: <i>Presented for only two atypical APDs as a range:</i> •Risperidone, 0.004% •Clozapine, 0.071%

1 st Author (publication year) & location	Databases	Patient population	Study Design Study Period Sample Size	Exposure/ Outcome	Raw Effect Estimates or descriptive counts/proportions	Adjusted Effect Estimates
Lipscombe et al. (2014) Canada, United Kingdom ¹	•Administrative health data from 7 Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia) •Administrative data from the UK United Kingdom General Practice Research Database (GPRD, renamed Clinical Practice Research Datalink or CPRD)	•Patients newly dispensed an antipsychotic medication.	•Multicentre retrospective cohort •April 1, 1998- March 31, 2010 •Canada: Total source population of approximately 34 million. •UK: 12 million residents •725,489 patients newly exposed to antipsychotic medication	Exposure: •Atypical antipsychotics: Risperidone (Reference), olanzapine •Other atypical antipsychotics including: Clozapine, Quetiapine, Ziprasidone, Paliperidone, Aripiprazole •Typical antipsychotics including: Chlormezanone, Chlorpromazine, chlorprothixene, Flupenthixol, Fluphenazine, Fluspirilene, Haloperidol Levomepromazine/Metho trimeprazine, Loxapine, Mesoridazine, Perphenazine, Pimozide, Pipotiazine, Tetrabenazine, Thiopropazate, Thioproperazine, Thiproperazine, Thioridazine, Thiothixene, Trifluoperazine, Zuclopenthixol. Outcome: •DKA •HHS	All hyperglycemia events pooled together: crude event rate (per 1000 person years, 95% CI) By Age group 18-65 years Diabetes (n=16,793) •Risperidone 9,45 (6.32-12.59) •Olanzapine 9.62 (4.90-14.33) •Other Atypical 11.71 (9.01-14.41) •Typical 14.20 (10.23-18.18) •Overall 11.49 (9.78-13.21) No diabetes (n=307,724) •Risperidone 0.36 (0.22-0.50) •Olanzapine 0.51 (0.30-0.73) •Other Atypical 0.30 (0.20-0.41) •Typical 0.46, (0.30-0.63) •Overall 0.39 (0.31-0.46) By Age group 66+ years Diabetes (n=75,970) •Risperidone 7.07 (6.00-8.14) •Olanzapine 6.74 (4.90-8.57) •Other Atypical 4.98 (3.76-6.20) •Typical 7.35 (5.95-8.76) •Overall 6.64 (5.98-7.30) No diabetes (n=325,007) •Risperidone 0.85 (0.67-1.02) •Olanzapine 0.78 (0.49-1.08) •Other Atypical 0.67 (0.45-0.90) •Typical 1.03, (0.79-1.27) •Overall 0.85 (0.74-0.97)	•Fixed-effect-meta-analyses: Age 18-65 years Overall HR (95%CI) •Risperidone 1.00 – •Olanzapine 1.15 (95%CI: 0.71–1.86) •Other Atypical 0.94 (95%CI: 0.64–1.38) •Typical 0.95 (95%CI: 0.61–1.54) Diabetes HR 95% CI •Risperidone 1.00 – •Olanzapine 1.19 (95%CI: 0.52–2.72) •Other Atypical 0.89 (95%CI: 0.45–1.68) •Typical 1.09 (95%CI: 0.61–1.95) Age 66+ years Overall HR 95%CI •Risperidone 1.00 – •Olanzapine 1.13 (95%CI: 0.87–1.48) •Other atypical 0.69 (95%CI: 0.53–0.90) •Typical 1.03 (95%CI: 0.73–1.45) Diabetes HR (95%CI) •Risperidone 1.00 – •Olanzapine 1.12 (95%CI: 0.80–1.56) •Other Atypical 0.68 (95%CI: 0.49–0.95) •Typical 0.62 (95%CI: 0.41–0.95)

1 st Author (publication year) & location	Databases	Patient population	Study Design Study Period Sample Size	Exposure/ Outcome	Raw Effect Estimates or descriptive counts/proportions	Adjusted Effect Estimates
Polcwiartek et al. (2017) Denmark	Nationwide healthcare registers: •The Danish Civil Registration System from 1968 - data on birth date, sex and migrations •The Danish Psychiatric Central Research Register from 1969 -data on psychiatric admissions and diagnoses •The Danish National Patient Register from 1977 - data on admissions and diagnoses for physical conditions •The Danish National Prescription Register from 1995 - data on prescription-based medications •The Danish Register of Causes of Death from 1970 - data on mortality.	•Diabetes-naïve schizophrenia population	•Retrospective nested case-control •1 January 1995 to 31 December 2014 •29,955	Exposure: Exposure within 3 months prior to event •FGA (low-potency, mild-potency and high-potency) •SGAs: Amisulpride, aripiprazole, asenapine, clozapine, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone •Data on antipsychotic polypharmacy (i.e. exposure to more than one antipsychotic) were reported, and antipsychotic dose was calculated as the amount of Defined Daily Dose. No specific dose was provided. Outcome: DKA •Secondary outcomes: •Long-term outcomes such as DKA readmissions	•Cases (n = 28) •(controls (n = 137) Crude: •Association between antipsychotic exposure within 3 months prior to event and DKA OR: 2.60 (95%CI: 1.06, 6.38) For cases: •APD exposure (within 3 months prior to event) •Any antipsychotic (n = 20, 71.4%) DDD of antipsychotics: Median 6.1 [1.0–31.1] •Antipsychotic polypharmacy (n = 2, 7.1%) FGAs •Low-potency (n = 3, 10.7%) •Mid-potency (n = 2, 7.1%) •High-potency (n = 1, 3.6%) SGAs •Amisulpride (n = 1, 3.6%) •Clozapine (n = 4, 14.3%) •Olanzapine (n = 3, 10.7%) •Quetiapine (n = 4, 14.3%) •Risperidone (n = 4, 14.3%) For controls: •APD exposure (within 3 months prior to event) •Any antipsychotic (n = 67, 48.9%) •DDD of antipsychotics [Median: 5.3 [0.3–28.0] •Antipsychotic polypharmacy (n = 28, 20.4%) FGAs •Low-potency (n = 16, 11.7%) •Mid-potency (n = 15, 10.9%) •High-potency (n = 5, 3.6%) SGAs Aripiprazole (n = 3, 2.2%)/•Clozapine (n = 7, 5.1%) •Olanzapine (n = 31, 22.6%)/•Paliperidone (n = 2, 1.5%) •Quetiapine (n = 8, 5.8%)/•Risperidone (n = 13, 9.5%)/•Sertindole (n = 1, 0.7%)/•Ziprasidone (n = 1, 0.7%)	•Due to limited number of cases, ORs for individual antipsychotics were not estimated. Model 1: •Association between antipsychotic exposure within 3 months prior to event and DKA OR: 2.58 (95% CI: 1.04, 6.40) Model 2: •Association between antipsychotic exposure within 3 months prior to event and DKA OR: 2.65 (95% CI:1.06, 6.59) Model 3 •Crude: Association between antipsychotic exposure within 3 months prior to event and DKA OR: 4.06 ((95% CI: 1.48, 11.11)

1 st Author (publication year) & location	Databases	Patient population	Study Design Study Period Sample Size	Exposure/ Outcome	Raw Effect Estimates	Adjusted Effect Estimates
Ramaswamy et al. (2007) California, United States of America	•California Medicaid data	•Patients receiving an atypical APD	•Retrospective cohort •July 1997 to September 2000 •141,286	Exposure: Atypical APDs: •Clozapine, olanzapine, quetiapine, risperidone Outcome: •DKA	Attributable cases of DKA and the unadjusted risk per 10,000 patients •Cases of DKA in the risperidone group (n = 31; 6.04 per 10,000 patients); •Cases of DKA in the olanzapine group (n = 55; 10.72 per 10,000 patients); •Cases of DKA in the quetiapine group (n = 4; 5.64 per 10,000); •Cases of DKA in the clozapine group (n = 1; 12.25 per 10,000). •The number of cases for the clozapine and quetiapine cohorts are small and do not provide a reliable estimation. •Unadjusted risk of DKA was 1.8 (p=0.0096) times higher with olanzapine than risperidone.	•Adjusted risk of DKA was 1.62 (p=0.033) times higher with olanzapine monotherapy than risperidone.

Abbreviations: APD, Antipsychotic Drug; DKA, Diabetic ketoacidosis; DM, Diabetes Mellitus; HHS, Hyperglycemic Hyperosmolar State; CR, Case Report; DM, Diabetes mellitus; X², chi-square.

Symbols: <, less than.

¹Lipscombe et al. (2014) performed a secondary analysis using a nested-case-control for pooled hyperglycemic events. Findings indicated there was no significant statistical differences in outcomes between current use of olanzapine and other APDs when compared to current use of risperidone. The study power was limited, and the results were not presented in detail. Therefore, it is not included in the Tables.

Table 3.2. Characteristics of Descriptive Observational Studies^{1,2}

1 st Author (publication year) & location	Databases	Patient population	Study Design Study Period Sample Size	Exposure/ Outcome	Description of Main Results
Ely et al. (2013) New York City, New York, United States of America	•New York City Medical Examiner Records	•Psychiatric patients treated with atypical APDs.	•Retrospective cohort •January 2005 to December 2009 •20	Exposure: •Quetiapine (n=7) •Olanzapine (n=6) •Risperidone (n=3) •Ziprasidone (n=1) •Clozapine (n=1) Outcome: •DKA	Deaths with evidence of psychiatric therapy or history: •Schizophrenia (n = 10) •Schizophrenia/bipolar disorder (n=3) •Bipolar disorder (n =2) •Major depression (n = 2) Metabolic markers: •Average BMI: 33 (range: 24-60) •Glucose mean (mg/dL): 1,095 (range: 417-4,256) •Blood ketones: n = 17
Galler et al. (2015) Germany, Austria	•Nationwide German/Austrian Diabetes Survey	•Patients with T1DM ≤ 25 years of age	•Prospective cohort •N/A •60,162	Exposure: •Atypical and typical APDs (by class) Outcome: •Rate of episodes of DKA (rate per 1 patient-year)	Rates of episode of DKA (per 1 patient-year): Overall characteristics of subjects •Without APD: 0.06 •With APD: 0.16 •Poisson Model: p < 0.0001 Regression analysis adjusted for age, sex and DM duration and with the diabetes centre. Atypical: •Without APD: 0.05 •With APD: 0.12 •Poisson Model: p < 0.001 Typical •Without APD: 0.05 •With APD: 0.13 •Poisson Model: p < 0.001

1 st Author (publication year) & location	Databases	Patient population	Study Design Study Period Sample Size	Exposure/ Outcome	Description of Main Results
Jin et al. (2002) (All)	•Medline, PsycINFO	•Cases of new-onset DM or DKA following initiation of atypical APD treatment	•Retrospective cohort •1980-2001 •45	Exposure: •Atypical APDs ▪Clozapine ▪Olanzapine ▪Quetiapine ▪Risperidone Outcome: DKA	•19 cases of DKA •APDs for DM and DKA (not stratified) ▪Clozapine n=20, 44% ▪Olanzapine n=19, 42% ▪Risperidone n=3, 7% ▪Quetiapine n=3, 7% •42% of patients presented with DKA as their first manifestation of DM: Blood glucose > 500 mg/dl •Characteristics of DKA cases (X ² or t-test comparing to those who had DM. (p value if significant) ▪Gender (Female): 26.3 (p=0.029) ▪Overweight at baseline: 58.3% (p=0.002) ▪Age: 37 (p=0.010) ▪Weight gain: 36.4% ▪Family history of DM: 38.9% ▪Blood glucose: 750 mg/dl (p=0.024)

1 st Author (publication year) & location	Databases	Patient population	Study Design Study Period Sample Size	Exposure/ Outcome	Description of Main Results
Koller et al. (2001) ¹ (US and International Sources)	•FDA MedWatch Drug Surveillance Program. •Other Sources: ▪Published cases identified in MEDLINE. ▪Selected abstracts from national endocrinology and diabetes meetings. ▪IMS health National Prescription Audit Plus and the IMS National Disease and Therapeutic Index for drug utilization data.	•Clozapine-treated patients.	•Retrospective, pharmacovigilance survey of spontaneously reported adverse events. Study Period: •FDA MedWatch Drug Surveillance System: January 1990-February 2001. •Medline: January 1985 to February 2001. •384.	Exposure: •Atypical: Clozapine Outcome: •DKA, HHS	•Severity of disease ranged from mild glucose intolerance to DKA or HHS. •51 cases, primarily with new onset DM, blood glucose levels were ≥ 700 mg/dL. •26 of these where for acidosis or ketosis. •63% of cases occurred within 3 months of initiation of clozapine therapy. •DKA was identified in one euglycemic hospitalized patient, aged 54, post- mortem.
Koller et al. (2002) ¹ (US and International Sources)	•FDA MedWatch Drug Surveillance Program •Other Sources: ▪Published cases identified in MEDLINE. ▪Selected abstracts from national psychiatry meetings. ▪IMS health National Prescription Audit Plus and the IMS National Disease and Therapeutic Index for drug utilization data.	•Olanzapine-treated patients	•Retrospective, pharmacovigilance survey of spontaneously reported adverse events Study Period: •FDA MedWatch Drug Surveillance System: January 1994-May 2001 •MEDLINE: through May 2001.	Exposure: •Atypical APD: Olanzapine Outcome: •DKA, HHS	•Severity of disease ranged from mild glucose intolerance to DKA or HHS. •2 cases of HHS •Glucose: 1,676 mg/dl and 800 mg/dl •8 months prior: the first patient had a fasting glucose of 131 mg/dl and a hemoglobin A1c of 6.4%. The second patient developed hyperglycemia again with rechallenge. •1 patient developed DKA after reinstitution of olanzapine.

1 st Author (publication year) & location	Databases	Patient population	Study Design Study Period Sample Size	Exposure/ Outcome	Description of Main Results
Koller EA et al. (2003) ¹ (US and International Sources)	•FDA MedWatch Drug Surveillance Program •Other Sources: ▪Published cases identified in MEDLINE. ▪Selected abstracts from national psychiatry meetings. ▪IMS health National Prescription Audit Plus and the IMS National Disease and Therapeutic Index for drug utilization data.	•Risperidone-treated patients	Retrospective, pharmacovigilance survey of spontaneously reported adverse events. Study Period: February 1993-February 2002 •FDA MedWatch Drug Surveillance System: •MEDLINE: through February 2002.	•Exposure: Atypical: Risperidone Outcome: •DKA, HHS	•Severity of disease ranged from mild glucose intolerance to DKA or HHS. •Newly diagnosed DM was defined based on glucose levels and DKA or ketosis and physician institution of an antidiabetic drug. •≥ 500-699 mg/dl in patients with new-onset DM with exacerbation (n = 5) (not only DKA or HHS) •1 patient with exacerbation of DM was receiving combination therapy •≥ 700-999 mg/dl in patient with new-onset DM with exacerbation (n = 1).
Koller & Webber (2004) ¹ (US and International Sources)	•FDA MedWatch Drug Surveillance Program •Other Sources: ▪Published cases identified in MEDLINE. ▪Selected abstracts from national psychiatry meetings. ▪IMS health National Prescription Audit Plus and the IMS National Disease and Therapeutic Index for drug utilization data.	•Quetiapine-treated patients	Retrospective, pharmacovigilance survey of spontaneously reported adverse events Study Period: •FDA MedWatch Drug Surveillance System and •MEDLINE: January 1997-July 2002	Exposure: •Atypical: Quetiapine Outcome: •DKA, HHS	•Severity of disease ranged from mild glucose intolerance to DKA or HHS. •Newly diagnosed DM was defined based on glucose levels and DKA or ketosis and physician institution of an antidiabetic drug. •21 cases of DKA or ketosis. •occurred in patient with pre-existing DM after rechallenging with quetiapine (n =1) •Glucose levels ≥ 500 mg/dl (n = 19). •1 recurrence: glucose level 1,570 mg/dl and ketosis) within 2 weeks of rechallenge. Following extension of study period through November 2003: •4 new ketoacidosis cases, 1 acidosis. •A new-onset DM presenting as HHS resulted in death (n = 1) •One patient developed DKA while on risperidone after quetiapine discontinuation. •One patient experienced DKA when rechallenged with quetiapine.

Abbreviations: APD, Antipsychotic Drug; CR, Case Report; DM, Diabetes Mellitus; χ^2 , chi-square.

Symbols: $\geq$, greater than or equal to; $\leq$, less than or equal to.

¹Koller et al. (2001; 2002; 2003; 2004) analysed different hyperglycemic complications, including DKA and/or HHS. The authors did not always differentiate between all the hyperglycemic complications and demographic information is also presented for acidosis and ketosis.

²The analysis by Suzuki et al. (2013) concluded there was no serious adverse DKA events occurred between the two groups administered: intramuscular olanzapine and intramuscular haloperidol. Therefore, it is not included in this Table.

SUPPLEMENTAL MATERIAL S3

The following supplemental material provides the search strategy using four bibliographic databases (Supplemental Material I), the Distiller SR form for level 1 screening (Supplemental Material II). Supplemental Material III contains additional detailed information for each observational study are presented (Tables S3.1 and S3.2) and the quality assessment and risk of bias ratings for included studies (Table S3.3).

Supplemental Material I: Search Strategies

MEDLINE

- 1 Aripiprazole/
(abilify or Aripiprazole or asenapine maleate or saphris or clozaril or clozapine or iloperidone or fanapt or lurasidone or latuda or olanzapine* or zyprexa or symbyax or paliperidone or invega or quetiapine or seroquel or risperidone or risperdal or ziprasidone or geodon or cariprazine or Vraylar or Pimavanserin or Nuplazid).ti,ab,kw.
- 2
- 3 clozapine/
- 4 Lurasidone Hydrochloride/
- 5 Paliperidone Palmitate/
- 6 Quetiapine Fumarate/
- 7 Risperidone/
- 8 Pimavanserin/
- 9 cariprazine/
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- 11 diabetes complications/ or diabetic coma/ or hyperglycemic hyperosmolar nonketotic coma/ or diabetic ketoacidosis/
- 12 (diabet* adj3 complication*).ti,ab,kw.
- 13 hyperglycemi*.ti,ab,kw.
- 14 (diabet* adj3 ketoacidosis).ti,ab,kw.
- 15 (diabet* adj3 (coma* or hyperglycemi*)).ti,ab,kw.
- 16 11 or 12 or 13 or 14 or 15
- 17 10 and 16
- 18 HALOPERIDOL/
(Haloperidol or Haldol or Loxapine or Loxitane or Molindone or Moban or Thiothixene or Navane or Primozide or Orap or Trifluoperazine or Stelazine or Chlorpromazine or Thorazine or Fluphenazine or Perphenazine or "Perphenazine amitriptyline" or Prochlorperazine or Thioridazine or Droperidol or Inapsine).ti,ab,kw.
- 19
- 20 CHLORPROMAZINE/
- 21 FLUPHENAZINE/
- 22 Loxapine/
- 23 PERPHENAZINE/
- 24 Prochlorperazine/
- 25 PROCHLORPERAZINE/
- 26 THIORIDAZINE/

- 27 TRIFLUOPERAZINE/
- 28 THIOTHIXENE/
- 29 Thioridazine/
- 30 Droperidol/
- 31 LOXAPINE/
- 32 MOLINDONE/
- 33 PIMOZIDE/
- 34 Fluphenazine/
- 35 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
or 31 or 32 or 33 or 34
- 36 16 and 35
- 37 17 or 36
- 38 10 or 35
- 39 16 and 38
- 40 limit 39 to yr="2019 -Current"

CENTRAL

- 1 Aripiprazole/
- (abilify or Aripiprazole or asenapine maleate or saphris or clozaril or
clozapine or iloperidone or fanapt or lurasidone or latuda or olanzapine*
or zyprexa or symbyax or paliperidone or invega or quetiapine or
seroquel or risperidone or risperdal or ziprasidone or geodon or
cariprazine or Vraylar or Pimavanserin or Nuplazid).ti,ab,kw.
- 3 clozapine/
- 4 Lurasidone Hydrochloride/
- 5 Paliperidone Palmitate/
- 6 Quetiapine Fumarate/
- 7 Risperidone/
- 8 Pimavanserin/
- 9 cariprazine/
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- 11 diabetes complications/ or diabetic coma/ or hyperglycemic
hyperosmolar nonketotic coma/ or diabetic ketoacidosis/
- 12 (diabet* adj3 complication*).ti,ab,kw.
- 13 hyperglycemi*.ti,ab,kw.
- 14 (diabet* adj3 ketoacidosis).ti,ab,kw.
- 15 (diabet* adj3 (coma* or hyperglycemi*)).ti,ab,kw.
- 16 11 or 12 or 13 or 14 or 15
- 17 10 and 16
- 18 HALOPERIDOL/
- (Haloperidol or Haldol or Loxapine or Loxitane or Molindone or Moban
or Thiothixene or Navane or Primozide or Orap or Trifluoperazine or
Stelazine or Chlorpromazine or Thorazine or Fluphenazine or
Perphenazine or "Perphenazine amitriptyline" or Prochlorperazine or
Thioridazine or Droperidol or Inapsine).ti,ab,kw.
- 20 CHLORPROMAZINE/
- 21 FLUPHENAZINE/

- 22 Loxapine/
- 23 PERPHENAZINE/
- 24 Prochlorperazine/
- 25 PROCHLORPERAZINE/
- 26 THIORIDAZINE/
- 27 TRIFLUOPERAZINE/
- 28 THIOTHIXENE/
- 29 Thioridazine/
- 30 Droperidol/
- 31 LOXAPINE/
- 32 MOLINDONE/
- 33 PIMOZIDE/
- 34 Fluphenazine/
- 35 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
or 31 or 32 or 33 or 34
- 36 16 and 35
- 37 17 or 36
- 38 10 or 35
- 39 16 and 38
- 40 limit 39 to yr="2019 -Current"

EMBASE

- 1 Aripiprazole/
(abilify or Aripiprazole or asenapine maleate or saphris or clozaril or
clozapine or iloperidone or fanapt or lurasidone or latuda or olanzapine*
or zyprexa or symbyax or paliperidone or invega or quetiapine or
seroquel or risperidone or risperdal or ziprasidone or geodon or
cariprazine or Vraylar or Pimavanserin or Nuplazid).ti,ab,kw.
- 3 clozapine/
- 4 Lurasidone Hydrochloride/
- 5 Paliperidone Palmitate/
- 6 Quetiapine Fumarate/
- 7 Risperidone/
- 8 Pimavanserin/
- 9 cariprazine/
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
diabetes complications/ or diabetic coma/ or hyperglycemic
hyperosmolar nonketotic coma/ or diabetic ketoacidosis/
(diabet* adj3 complication*).ti,ab,kw.
- 11 hyperglycemi*.ti,ab,kw.
- 12 (diabet* adj3 ketoacidosis).ti,ab,kw.
- 13 (diabet* adj3 (coma* or hyperglycemi*)).ti,ab,kw.
- 14 11 or 12 or 13 or 14 or 15
- 15 10 and 16

- 18 HALOPERIDOL/
(Haloperidol or Haldol or Loxapine or Loxitane or Molindone or Moban or Thiothixene or Navane or Primozide or Orap or Trifluoperazine or
- 19 Stelazine or Chlorpromazine or Thorazine or Fluphenazine or Perphenazine or "Perphenazine amitriptyline" or Prochlorperazine or Thioridazine or Droperidol or Inapsine).ti,ab,kw.
- 20 CHLORPROMAZINE/
- 21 FLUPHENAZINE/
- 22 Loxapine/
- 23 PERPHENAZINE/
- 24 Prochlorperazine/
- 25 PROCHLORPERAZINE/
- 26 THIORIDAZINE/
- 27 TRIFLUOPERAZINE/
- 28 THIOTHIXENE/
- 29 Thioridazine/
- 30 Droperidol/
- 31 LOXAPINE/
- 32 MOLINDONE/
- 33 PIMOZIDE/
- 34 Fluphenazine/
- 35 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
or 31 or 32 or 33 or 34
- 36 16 and 35
- 37 17 or 36
- 38 10 or 35
- 39 16 and 38
- 40 limit 39 to yr="2019 -Current"

PsycINFO

- 1 Aripiprazole/
(abilify or Aripiprazole or asenapine maleate or saphris or clozaril or
- 2 clozapine or iloperidone or fanapt or lurasidone or latuda or olanzapine*
or zyprexa or symbyax or paliperidone or invega or quetiapine or
- 3 seroquel or risperidone or risperdal or ziprasidone or geodon or
- 4 cariprazine or Vraylar or Pimavanserin or Nuplazid).ti,ab,kw.
- 5 clozapine/
- 6 Lurasidone Hydrochloride/
- 7 Paliperidone Palmitate/
- 8 Quetiapine Fumarate/
- 9 Risperidone/
- 10 Pimavanserin/
- 11 cariprazine/
- 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- 13 diabetes complications/ or diabetic coma/ or hyperglycemic
- 14 hyperosmolar nonketotic coma/ or diabetic ketoacidosis/

- 12 (diabet* adj3 complication*).ti,ab,kw.
- 13 hyperglycemi*.ti,ab,kw.
- 14 (diabet* adj3 ketoacidosis).ti,ab,kw.
- 15 (diabet* adj3 (coma* or hyperglycemi*)).ti,ab,kw.
- 16 11 or 12 or 13 or 14 or 15
- 17 10 and 16
- 18 HALOPERIDOL/
(Haloperidol or Haldol or Loxapine or Loxitane or Molindone or Moban
or Thiothixene or Navane or Primozide or Orap or Trifluoperazine or
- 19 Stelazine or Chlorpromazine or Thorazine or Fluphenazine or
Perphenazine or "Perphenazine amitriptyline" or Prochlorperazine or
Thioridazine or Droperidol or Inapsine).ti,ab,kw.
- 20 CHLORPROMAZINE/
- 21 FLUPHENAZINE/
- 22 Loxapine/
- 23 PERPHENAZINE/
- 24 Prochlorperazine/
- 25 PROCHLORPERAZINE/
- 26 THIORIDAZINE/
- 27 TRIFLUOPERAZINE/
- 28 THIOTHIXENE/
- 29 Thioridazine/
- 30 Droperidol/
- 31 LOXAPINE/
- 32 MOLINDONE/
- 33 PIMOZIDE/
- 34 Fluphenazine/
18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
or 31 or 32 or 33 or 34
- 35 16 and 35
- 36 17 or 36
- 37 10 or 35
- 38 16 and 38
- 39 limit 39 to yr="2019 -Current"

Supplementary Material II: Level 1-Title and Abstract Screening

1. Should this study be included in Stage 2 screening?

- ☐ Yes
- ☐ Unsure
- ☐ No

2. Reason for exclusion:

- ☐ Population
- ☐ Interventions(s)/Exposure(s)
- ☐ Comparison
- ☐ Outcome(s)
- ☐ Study Design

Supplemental Material III-Detailed Tables and, Quality Assessment and Risk of Bias

Table S3.1. Characteristics of Analytical Observational Studies¹.

1 st author (publication year) & location	Inclusion/ Exclusion Criteria	Brief Description of Statistical Methods	Age of Study Participants	Sex of Study Participants	Ethnicity of Study Participants	Strengths /Limitations
Henderson et al. (2007) Boston Massachusetts, United States of America	• Inclusion: Patients diagnosed with schizophrenic disorders (ICD-9 295.0-295.3), DKA and HHS (250.1-250.3) and record of the following atypical antipsychotic agents: clozapine, olanzapine, risperidone, quetiapine and ziprasidone. • Exclusion Patients who were not diagnosed with schizophrenic disorders and those treated with atypical APDs in the study.	• Total person years of observation time calculated as follows: adding up the time each person was followed in the database between January 1, 1995, and December 31, 2001. • For patients suffering from schizophrenia or schizoaffective disorder, the time each person received an atypical APD was added. • The total number of patients receiving treatment with each atypical APD and duration of treatment during the 7-year study period was tabulated. • Event occurrence: For patients who had an event, DKA or HHS, only the time preceding the event was added / year of observation. • Total number of events (DKA or HHS) was divided by total observation time. • The time to event per year was calculated, and the number of events was tallied. • Incidence per 10,000 patients patient years was calculated. • Comparison between diabetes and DKA in the general population: ▪ Used the 1.4/10,000 patient years of diabetes presenting as DKA in the general population for equality testing. ▪ Incidence in the general hospital population with the incidence in patients with schizophrenia using χ^2 test. ▪ The comparisons between diabetes presenting as DKA and DKA in known DM patients were performed using the 2-tailed Student t test. Statistical significance was evaluated with p values < .05.	New-onset DM: DKA (n = 11): mean $\pm$ SD: 42 $\pm$ 12 years (range: 26-64) New-onset DKA in patients with DM (n = 8): mean $\pm$ SD: 44 $\pm$ 12 years (range: 23-64) HHS: • Case 1, age= 55 • Case 2, age = 29	For the entire sample: • Male (n = 401,461, 49%) • Female (n = 417,847, 51%) For those diagnosed with schizophrenia or schizoaffective disorder (n = 4,850): • Male (n = 2,619, 54%) • Female (n = 2,231, 46%) For those with new onset diabetes mellitus presenting with DKA: • Male (n = 5, 45%) • Female (n = 6, 55%)	Schizophrenia or schizoaffective disorder diagnoses: • White, n = 3584 (74%) • Black, n = 631 (13%) • Hispanic, n = 326 (7%) • Asian, n = 69 (1%) New onset DM presenting as DKA (n = 11) • White, n = 8 (73%) • Black, n = 2 (18%) • Hispanic, n = 1 (9%) Known DM presenting as DKA (n = 8) • White, n = 5 (63%) • Black, n = 2 (25%) • Hispanic, n = 1 (12%)	Strengths: • Findings mirror non-psychiatric general population studies Limitations: • Potentially, some patients received treatment for DKA at other institutions and these were not recorded in the medical records or results, leading to an underestimation of the occurrence of DKA. • Potentially, some patients were treated with an APD that was not recorded in inpatient/outpatient records. • Prior use of APDs was not controlled for the analysis.

1 st & 2 nd authors (publication year) & location	Inclusion/ Exclusion Criteria	Brief Description of Statistical Methods	Age of Study Participants	Sex of Study Participants	Ethnicity of Study Participants	Strengths /Limitations
Leslie & Rosenheck (2004) United States of America	Inclusion: •Patients receiving APD monotherapy. •Patients without a DM diagnosis. Exclusion: •Patients treated with ziprasidone or aripiprazole since these two APDs were recently approved at the time of the study. •Patients with an outpatient claims for DM or < two medical primary care visits in the previous 6 months.	•Cox proportional hazards models to model the time to DKA hospitalization. •Independent variables: Atypical APDs, end date, age, gender, race, income, comorbid mental health diagnoses, levels of service use during the stable period, degree of VA service-connected disability. •Attributable risk of DKA associated with each atypical APD defined as: estimated proportion of patients taking each drug who would not have received a diagnosis of DKA if they had not been taking a conventional antipsychotic)	NR	NR	NR	Strengths: •The results offer insight into the risk DKA in an older, predominantly male population with schizophrenia from whom APD monotherapy is prescribed. Limitations: •Findings may not be generalizable to other populations or health care systems. •Possible unidentified cases of DKA outside the Department of Veterinary Affairs •Data was not available to identify medication taken prior to the study period. Medications prescribed before/after the drugs identified for the study may have influenced the risk of DKA.

1 st author (publication year) & location	Inclusion/ Exclusion Criteria	Brief Description of Statistical Methods	Age of Study Participants	Sex of Study Participants	Ethnicity of Study Participants	Strengths /Limitations
Lipscombe et al. (2014) Canada, United Kingdom ¹	Inclusion: •Patients ≥ 18 years and newly treated with an APD. Exclusion: •Patient < 18 years of age on the cohort entry • 66 years of age in the provinces where drug benefit coverage started at age 65 (Nova Scotia, Ontario and Alberta) • Patient had fewer than 365 days of enrollment in their health plan • Patient resided in a nursing home • Patient received more than one antipsychotic medication • Patient hospitalized with the primary study outcome within 30 days preceding cohort entry • Patient hospitalized for greater than 30 consecutive days in the year preceding cohort entry • Patient received renal dialysis n the year preceding cohort entry • Patient received palliative care in the year preceding cohort entry	• One primary and two secondary pair-wise comparisons of the risk of a hyperglycemic emergency • Reference group: Risperidone / • Primary comparator: Olanzapine • Secondary comparators: Other typical and atypical antipsychotics • Propensity score with inverse probability of treatment weighting (IPTW) to estimate marginal treatment effects. • Propensity score represented the predicted probability treatment of the comparator antipsychotic (versus risperidone) based upon a set of baseline patient characteristics that we believed could influence the risk of hyperglycemic emergency. • Regression on age, sex, and the following pre-specified covariates: calendar year of cohort entry; history of diabetes, schizophrenia, and dementia, neighbourhood income quintile, Romano Comorbidity Index; number of hospitalizations, outpatient family physician consultations and outpatient psychiatric consultations in the year preceding cohort entry; and concurrent exposure to selected drugs that are markers of disease or could influence glucose control. • The CPRD team added smoking status, alcohol consumption, and body mass index. • Cox proportional hazards regression model to regress the hazard of the adverse event on treatment status. • Estimation of the cause-specific hazard: subjects were censored on the occurrence of death. • Treatment effects were estimated separately for patients aged 18–65 years and 66 years and older, as well as within each age group for the subset of patients with pre-existing diabetes. • All analyses were carried out independently at each study site-each site remaining blinded to results from other sites until the finding were pooled. • Meta-analyses were performed independently by a team member not involved in the site-level analyses (RP) using fixed-effect models with inverse variance weighting. • The magnitude of between-site heterogeneity was estimated using I2 statistic.	• > 18 years - 65 years • > 66 years (55%)	• Male aged 18 years - 65 years (47.5%) • Female aged 18 years - 65 years (52.5%) • Male aged > 66 years (39.4%) • Female > 66 years (60.6%)	NR	Strengths: • Analysis limited to new users of APDs among patients who were likely to be receiving the medication for similar indications. • Adjusted for treatment characteristics at baseline. Limitations: • The potential for residual confounding

1 st author (publication year) & location	Inclusion/ Exclusion Criteria	Brief Description of Statistical Methods	Age of Study Participants	Sex of Study Participants	Ethnicity of Study Participants	Strengths /Limitations
Polcwiartek et al. (2017) Denmark	Inclusion: •Patients diagnosed schizophrenia (ICD-10: F20.x) in the Danish Psychiatric Central Research Register. •Cases were defined as having an incident onset of DKA event identified using ICD-10 discharge diagnoses: E1x.1, E10.0B, E11.0E or E12.0C. •Individuals who were alive and not migrated. Exclusion: Cases and controls: •Diagnosis from emergency room visits due to low validity. •All cases and controls with a prior history of pancreatitis, pancreatic cancer or polycystic ovary syndrome were excluded as these conditions may involve different mechanisms for developing diabetes and potentially DKA.	•Differences between cases of post-DKA T1DM vs T1DM, and cases of post-DKA T2DM vs T2DM were examined •Continuous variables: non-parametric Mann-Whitney U test •Categorical variables: Fisher's exact or the X² test •Controls were selected using a risk-set sampling strategy (up to 5 randomly selected controls), alive and not migrated prior to event. Controls were assigned an index date identical to that of the corresponding case. •Conditional logistic regression: to examine the association between antipsychotic exposure and DKA •Crude and adjusted ORs (95% CIs) with no antipsychotic exposure as a reference. •Adjustments for confounders: 1. Charlson Comorbidity Index (CCI): disregarded diagnoses included in the CCI < 1 year prior to event. Low, CCIH score 1, moderate/High scores, CCI score ≥ 2. 2. Diabetogenic co-medication exposure (within 3 months prior to event): thiazides, beta blockers, oral contraceptives, glucocorticoids, calcineurin inhibitors 3. psychotropic co-medication exposure (within 3 months prior to event): antiepileptics, anticholinergics, lithium, benzodiazepines, antidepressants. Co-medication exposure: categorical variable only including integer numbers (e.g., two co-medications yielded twice the listed OR estimate). • Data management and analysis were performed using Stata, version 14.1 and R software, version 3.3.2 • All analysis were two-sided, p values < 0.05 were considered statistically significant.	•Mostly adults > 18 years - DKA cases (n = 28) •Age at first antipsychotic exposure in years: 32.4 (26.6-37.1) •Age at schizophrenia onset in years: 32.3 (27.1 and 37.6) •Age at DKA onset/index date in years: 37.7 (30.7-44.6) Control cases (n = 137) •Age at first antipsychotic exposure in years: 30.8 (26.2-35.8) •Age at schizophrenia onset in years: 32.5 (27.7 and 37.6) •Age at DKA onset/index date in years: 36.8 (29.5-44.2)	•Cases: ▪21 males (75%) ▪7 females (25%) Controls ▪102 males (74.5%) ▪35 females (25.5%)	NR	Strengths: NR Limitations: •Observational design: findings represent associations and not causal inferences. •Unmeasured/Unknown confounders due to unavailability of information may have biased the results: family history of diabetes, ethnicity, unhealthy lifestyle, BMI, severity of schizophrenia, medication adherence, and changes in prescription patterns. •Confounding by indication could underestimate the risks of DKA associated with high metabolic APDs, as physicians may less likely be to prescribe them to someone with known risk factors. •Unable to distinguish from other similar metabolic emergencies, including HHS and lactic acidosis using blood samples. •Carry over effects due to cumulative exposure although only the influence of antipsychotic exposure within 3 months prior to event was carried. •Use of non-exposure population as reference, knowing that this heterogeneous population may affect our findings as it differs in physical health status and access to healthcare.

1 st Author (publication year) & location	Inclusion/ Exclusion Criteria	Brief Description of Statistical Methods	Age of Study Participants	Sex of Study Participants	Ethnicity of Study Participants	Strengths / Limitations
Ramaswamy et al. (2007) California, United States of America	Inclusions: • Patients receiving an atypical APD • Initial antipsychotic prescription: first prescription for an antipsychotic agent after a 6-month period during which there were no claims for antipsychotic medications. Exclusions: • Cases where polypharmacy of APD were used for treatment	• Logistic regression: RR of DKA • Controlling for potential confounding factors. • Interactions were tested between the group variable and selected predictors (i.e., Those variables where significant differences between risperidone and olanzapine were observed). • Logistic regression model: while restricting the sample based on exposure category. • The goodness-of-fit statistic was assessed using the Hosmer and Lameshow test. • Multicollinearity was assessed through evaluation of variance inflation factors. • All statistical tests were two-tailed. • Analyses were conducted using SAS/STAT software, Version 8.	• Olanzapine: Mean age ± SD: 45.5 ± 14.2 • Risperidone: Mean age ± SD: 55.0 ± 21.5	Olanzapine (n = 55) • Male (n = 23, 41.8%) • Female (n = 32, 58.2%) Risperidone (n = 31) • Male (n = 9, 29.0%) • Female (n = 22, 71.0%) Data on the patients' sex were not available in a few cases.	Olanzapine • White 22 (40.0%) • African American 18 (32.7%) • Other 4 (7.3%) • Missing data 11 (20.0%) Risperidone • White 16 (51.6%) • African American 6 (19.4%) • Other 2 (6.5%) • Missing data 7 (22.6%)	Strengths: • Findings consistent with published case reports, and some studies that suggest a possible elevated risk of diabetes with olanzapine vs. Risperidone. Note: this has not always been a consistent finding. • Duration of exposure: important predictor of diabetic ketoacidosis risk. Limitations: • Retrospective nature of study and limited number of variables available restricts any inference of causality. Olanzapine treatment: significant risk factor even after adjusting for other confounders. • Small sample sizes, retrospective designs, and variance in reporting of demographic variables limit the types of analysis. • Limit to the generalizability of findings. • Claims screening using specified codes may introduce source of bias • No assessment was made of the impact of dose variation.

Abbreviations: APD, Antipsychotic Drug; DKA, Diabetic ketoacidosis; DM, Diabetes Mellitus; HHS, Hyperglycemic Hyperosmolar State; CR, Case Report; DM, Diabetes Mellitus; X², chi-square.

Symbols: <, less than.

¹Lipscombe et al. (2014) performed a secondary analysis using a nested-case-control for pooled hyperglycemic events. Findings indicated there was no significant statistical differences in outcomes between current use of olanzapine and other APDs when compared to current use of risperidone. The study power was limited, and the results were not presented in detail. Therefore, it is not included in the Tables.

Table S3.2. Characteristics of Descriptive Observational Studies^{1,2}

1 st Author (publication year) & location	Inclusion/ Exclusion Criteria	Brief Description of Statistical Methods	Age of Study Participants	Sex of Study Participants	Ethnicity of Study Participants	Strengths /Limitations
Ely et al. (2013) New York City, New York, United States of America	Inclusion •Decedents treated with SGA (n = 17) Exclusion •Decedents where treatment of SGAs prior to death could not be determined (n = 3)	•Deaths certificates and toxicology data were searched for instances of DKA and hyperglycemia. •Retrospectively analysed the medical examiner records which included the autopsy, toxicology, police, and medical examiner investigators' reports. •Post-mortem blood was collected and toxicologic analysis was completed on all decedents. •Samples were routinely screened for opiates, barbiturates, amphetamines, benzoylecgonine and benzodiazepines by enzyme or radioimmunoassay. •Urine and blood were analyzed by gas chromatography for basic drugs including olanzapine, quetiapine, and clozapine or by a reference laboratory for risperidone and ziprasidone. •Vitreous fluid collected at time of autopsy was analysed for glucose.	Average age: 48 (range: 32- 57)	•15 males •2 Females	•2 White •4 Hispanic •11 Black	Strengths: •First large series describing death due to DKA in patients receiving atypical APDs. Limitations: •Accurate post-mortem intervals were not known in most decedents, as most were found dead at home for an unclear duration. •Correlations between specific antipsychotic medication dosages and the magnitude of the hyperglycemia were not made, as they would have limited interpretive value given the variable post-mortem fall in the vitreous glucose concentrations. •Two of the decedents were moderately decomposed but had enough urine for glucose quantification. •Specific antipsychotic dosage information at the time of death was extracted in approximately half of the deaths. In the remaining decedents, prescribed medication did not have specific dosage instructions. •Detailed chronic medication history for evaluation was not always available.

1 st Author (publication year) & location	Inclusion/ Exclusion Criteria	Brief Description of Statistical Methods	Age of Study Participants	Sex of Study Participants	Ethnicity of Study Participants	Strengths /Limitations
Galler et al. (2015) Germany, Austria	Inclusion: • Patients with T1DM ≤ 25 years of age with a diabetes duration of more than 6 months.	• Clinical characteristics and laboratory parameters were assessed. • Frequency of episodes of DKA (pH < 7.30) defined according to the ISPAD. Exposure: • Duration of APD use was assessed. Analysis: • Hierarchical random effects regression models (linear, logistic, or Poisson): diabetes center as a random effect and adjusting for age, sex, and diabetes duration. • Prevalence and frequencies of complications: presented as either proportions or event rates per 1 patient-year.	Median age for patients with T1DM •Without APD: 15.5 (95%CI: 11.8, 17.6) •With APD: 17.0 (95%CI: 14.2, 18.3)	Male/Female ratio for patients with T1DM •Without APD: 52%/38% •With APD: 60%/40%	NR	Strengths: • First analysis that examines metabolic and glycemic control in youth with T1DM treated with typical and atypical APDs. Limitations: • Small sample: schizophrenia and disorders requiring APDs are rare among the general population and youth with T1DM. • Limited study power • Insufficient information about the underlying diagnoses and possible associations with metabolic and glycemic control for which the APD was prescribed. • Cross sectional research design: descriptive and not able to demonstrate causal effects.
Jin et al. (2002) (All)	Inclusion: •Patients with new-onset DM associated with the use of atypical APDs. Exclusion: •Patients with a history of glucose intolerance or diagnosis of DM before starting the atypical APD. •Patients wit-controlled DM who had an exacerbated condition after the use of the atypical APD.	•Data was collected for: age, gender, ethnicity, family history of DM, baseline weight, weight gain, type of atypical APD and duration of exposure, number and type of adjunctive medications, blood glucose at time of diagnosis, presence of DKA. •Descriptive analysis to examine distribution of demographic characteristics. •Data Analysis: ▪ X² for categorical variables. ▪ Student's t-test for continuous variables.	•Mean age for DKA cases: 37 years	•Female: 26.3%	•African American 52.6%	Strengths: •Unique and preliminary data: the risks of new-onset DM in patients using atypical APDs •Path forward for future research: the roles of ethnicity, obesity and atypical APDs. Limitations: •Small sample sizes and inconsistent reporting of demographic variables (e.g., weight gain). •Reporting bias •Not representative of the general population of schizophrenia. •Retrospective nature of CRs: no adequate comparison group (control) for estimation of risk. •Cannot assess causality

1 st Author (publication year) & location	Inclusion/ Exclusion Criteria	Brief Description of Statistical Methods	Age of Study Participants	Sex of Study Participants	Ethnicity of Study Participants	Strengths /Limitations
Koller & Schneider (2001) (US and International Sources)	Exclusion: •Patients without definitive documentation were classified separately.	•Database searches •Assessment: Documentation of diabetes, severity of hyperglycemia, new onset of hyperglycemia, demographic features, time to onset of hyperglycemia, and effect of drug discontinuation. •Newly diagnosed DM: Fasting glucose level of ≥ 126 mg/d; random glucose level ≥ 200 mg/dl; or elevated glycosylated hemoglobin A1c (HbA1c) glycohemoglobin values; and/or presence of metabolic acidosis or ketosis; and/or physician institution of an antidiabetic drug. •Descriptive report based primarily on summary statistics due to missing data on demographics and clinical information. •Descriptive statistics: correlation coefficients. X^2 tests, and unpaired t tests (all two-tailed) to assess the relationship between certain variables or groups; p values ≤ 0.05 were considered significant. •Exposure: estimated by multiplying the number of prescriptions by the duration of a prescription. •Reporting rates: determined from the US reports and estimates of patient exposure.	Mean age: 36 $\pm$ 10 (range 22-57)	•Male: Female - 2:5	NR	Strengths: •The FDA MedWatch system can provide signals of adverse events associated with marketed drugs. Limitations: •lack of control populations, incomplete case descriptions, and substantial under-reporting •underreporting is a characteristic of systems such as MedWatch

1 st Author (publication year) & location	Inclusion/ Exclusion Criteria	Brief Description of Statistical Methods	Age of Study Participants	Sex of Study Participants	Ethnicity of Study Participants	Strengths /Limitations
Koller et al. (2002) Olanzapine- Associated Diabetes Mellitus (US and International Sources)	Exclusion: •Patients without definitive documentation were classified separately.	•Database searches •Assessment: Documentation of diabetes, severity of hyperglycemia, new diagnosis of hyperglycemia, demographic features, time to onset of hyperglycemia, and effect of drug discontinuation. •Newly diagnosed DM: Fasting glucose level of ≥ 126 mg/d; random glucose level of 200 mg/dl; or elevated glycohemoglobin values; and/or presence of metabolic acidosis or ketosis; and/or physician institution of an antidiabetic drug. •Descriptive report based primarily on summary statistics due to missing data on demographics and clinical information. •Descriptive statistics: correlation coefficients. X^2 tests, and unpaired t tests (all two-tailed) to assess the relationship between certain variables or groups; p values ≤ 0.05 were considered significant. •Exposure: estimated by multiplying the number of prescriptions by the duration of a prescription. •Reporting rates: determined from the US reports and estimates of patient exposure.	N/A	For patients who died: 8 M and 7 females. Otherwise, NS	Without specifying DKA or HHS: •n = 50 - high glucose levels (≥ 700 mg/dl): •African American, n = 21 •Caucasian, n = 27 Ethnic background was provided for 15 fatalities: •Caucasian, n = 6 •African-American, n = 1 •Asian, n = 1 •Unknown, n = 7	Strengths: •MedWatch system can provide signals for adverse events, including those that cannot be identified during relatively short efficacy trials. Limitations: •Spontaneous adverse event reporting can lead to underreporting. •Distortions of reporting may occur overtime as prescribers become aware of a particular adverse event from experience, literature, and/or changes to product labels. •Control populations were absent and case descriptions may be incomplete. •Insufficient information on risk factors for DM such as family history, body weight information. •Indirect comparisons of age distribution of the cases with population patterns derived from another study can be biased by several factors: cannot make causality inference or determine incidence. •Detection bias, pre-existent risk factors, prior drug therapy, or concomitant drugs may have contributed to hyperglycemia.

1 st Author (publication year) & location	Inclusion/ Exclusion Criteria	Brief Description of Statistical Methods	Age of Study Participants	Sex of Study Participants	Ethnicity of Study Participants	Strengths /Limitations
Koller et al. (2003) Risperidone- Associated Diabetes Mellitus: A pharmacovigilance study (US and International Sources)	Exclusion: •Patients whose acidosis was not related to or did not occur in the setting of hyperglycemia. •Patients without definitive documentation were classified separately.	•Database searches •Monotherapy: Treatment with risperidone or haloperidol •Combination Therapy: Risperidone and haloperidol. •Control: Haloperidol-associated hyperglycemia •Assessment: Documentation of diabetes, severity of hyperglycemia, new diagnosis of hyperglycemia, demographic features, time to onset of hyperglycemia, and effect of drug discontinuation. •Newly diagnosed DM: Fasting glucose level of ≥ 126 mg/d; random glucose level of 200 mg/dl; or elevated glycohemoglobin values; and/or presence of ketoacidosis or ketosis; and/or physician institution of an antidiabetic drug. •Descriptive summary statistics: missing data on demographics and clinical information. •Descriptive statistics: correlation coefficients. X^2 tests, and unpaired t tests (all two-tailed) to assess the relationship between certain variables or groups; p values ≤ 0.05 were considered significant. •Exposure: estimated by multiplying the number of prescriptions by the duration of a prescription. •Reporting rates: determined from the US reports and estimates of patient exposure.	NR	NR	NR	Strengths: •Voluntary pharmacovigilance systems can signal adverse events that are not identified in the relatively short clinical trials with small and select populations used for registration of drugs. Limitations: •Limited by a lack of contemporaneous randomized control populations, incompleteness case descriptions, and substantial underreporting.

1 st Author (publication year) & location	Inclusion/ Exclusion Criteria	Brief Description of Statistical Methods	Age of Study Participants	Sex of Study Participants	Ethnicity of Study Participants	Strengths /Limitations
Koller et al. (2004) A survey of reports of Quetiapine- Associated Hyperglycemia and DM (US and International Sources)	Exclusion: •Patients whose acidosis was not related to or did not occur in the setting of hyperglycemia. •Patients without definitive documentation were classified separately.	•Database searches. •Assessment: Documentation of diabetes including severity of hyperglycemia, new diagnosis of hyperglycemia, demographic features, time to onset of hyperglycemia, and effect of drug discontinuation. •Newly diagnosed DM: Fasting glucose level of ≥ 126 mg/d; random glucose level ≥ 200 mg/dl; or elevated glycohemoglobin values; and/or presence of ketoacidosis or ketosis; and/or physician institution of an antidiabetic drug. •Descriptive report based primarily on summary statistics due to missing data on demographics and clinical information. •Descriptive statistics: correlation coefficients. X^2 tests, and unpaired t tests (all two-tailed) to assess the relationship between certain variables or groups; p values ≤ 0.05 were considered significant. •Exposure: estimated by multiplying the number of prescriptions by the duration of a prescription. •Reporting rates: determined from the US reports and estimates of patient exposure.	For all hyperglycemic events: •n = 42 (data NS for n = 4) •Mean $\pm$ SD: 35.3 $\pm$ 16.2 years (range: 5–76 years) •Nine < 19 years.	For all hyperglycemic events: •Male: Female ratio: 1.9 (n = 43) in all hyperglycemia subgroups.	For all hyperglycemic events: n = 19 African American, n = 13 white, n = 6. Asian, n = 3	Strengths: •The FDA MedWatch system can provide signals of adverse events associated with marketed drugs. Limitations: •Lack of control populations, incomplete case descriptions, and substantial under-reporting •underreporting is a characteristic of systems such as MedWatch.

Abbreviations: BMI, Body mass index; CR, Case report; DCCT, Diabetes Control and Complications Trial; DKA, Diabetic ketoacidosis; DM, Diabetes Mellitus; HHS, Hyperglycemic hyperosmolar state; ISPAD, International Society for Pediatric and Adolescent Diabetes; SDS, Standard Deviation Score; X^2 , chi-square.

Symbols: $\geq$, greater than or equal to; $\leq$, less than or equal to.

¹Koller et al. (2001; 2002; 2003; 2004) analysed different hyperglycemic complications, including DKA and/or HHS. The authors did not always differentiate between all the hyperglycemic complications and demographic information is also presented for acidosis and ketosis.

² The analysis by Suzuki et al. (2013) concluded there was no serious adverse DKA events occurred between the two groups administered: intramuscular olanzapine and intramuscular haloperidol. Therefore, it is not included in this Table.

Table S3.3. Risk of Bias Criteria, Ratings and Tier Classification for Analytical Studies (n = 5) and Descriptive Studies (n = 7)¹⁻³

Citation	Risk of Bias Domains and Ratings							
	Key Criteria			Other Risk of Bias criteria				
	Confounding Bias	Detection Bias 1 (Exposure Characterization)	Detection Bias 1 (Outcome Characterization)	Selection Bias (Comparison Groups)	Attrition/ Exclusion Bias	Selective Reporting bias	Other Biases	Tier
Analytical Studies								
Henderson et al. (2007)	--	++	++	++	NR	++	-	Tier 2
Leslie & Rosenheck (2004)	--	-	NR	+	++	++	-	Tier 2
Lipscombe et al. (2014)	++	++	++	++	++	++	++	Tier 1
Polcwiartek et al. (2017)	++	++	++	++	++	++	++	Tier 1
Ramaswamy et al. (2007)	++	++	++	++	++	++	++	Tier 1
Descriptive Studies								
Ely et al. (2013)	--	++	++	-	++	++	++	Tier 3
Galler et al. (2015)	++	-	+	++	NR	++	++	Tier 2
Jin et al. (2002)	--	NR	-	--	NR	-	++	Tier 2
Koller et al. (2001) (Clozapine)	--	NR	-	--	NR	-	++	Tier 3
Koller et al. (2002) (Olanzapine)	--	NR	-	--	NR	-	++	Tier 3
Koller EA et al. (2003) (Risperidone)	--	NR	-	--	++	-	++	Tier 3
Koller & Webber (2004) (Quetiapine)	--	NR	-	--	++	-	++	Tier 3

¹Adapted from Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Office of Health Assessment and Translation (OHAT), Division of the National Toxicology Program, National Institute of Environmental Health Sciences, March 4, 2019.

²Risk of Bias definitions for the criteria: ++ Definitely low risk of bias; + Probably low risk of bias; --Definitely high risk of bias; - probably high risk of bias.

³Tiers are defined as follows: Tier 1: “definitely low” or “probably low” risk of bias for key items and “definitely low” or “probably low” risk of bias for most other applicable criteria. Tier 2: Study cannot be classified in Tier 1 or Tier 2. Tier 3” “definitely high” or “probably high” risk of bias for key items and “definitely high” or “probably high” risk of bias for most other applicable criteria.

CHAPTER 4

PREFACE

This chapter is the third manuscript of this thesis and addresses Objective 3. It evaluates safety signals of antipsychotic drug use and diabetic ketoacidosis using data from the US Food and Drugs Administration Adverse Event Reporting System. Second-generation antipsychotics and first-generation antipsychotics, also known as atypical or typical antipsychotics, respectively, were included in the analysis. Findings on safety signals diabetic ketoacidosis associated with individual medications as primary suspect drugs and secondary suspect drugs are presented. Comparators included all other drugs and psychotropic medications.

Contributions

For this study, I formulated the study design with the guidance of my supervisor (DK), and with input from CG and AA. I designed and implemented this study; I interpreted the findings and wrote the manuscript. CG, AA and DT contributed to the methodological aspect of the analysis. AA also contributed to a critical review of the manuscript. NF provided constructive feedback on the manuscript. My supervisor and members of my thesis advisory committee (YC, DM, MM, CG), provided suggestions and input on study design, statistical analysis, and interpretation of the findings. All co-authors contributed to the critical review of the manuscript.

Antipsychotic Drugs and the Risk of Diabetic Ketoacidosis:

Analysis of Data from the US FDA Adverse Reporting System

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ABSTRACT

Background: Antipsychotic drugs are used to treat a wide variety of neurological conditions. In recent years, accrued evidence has raised concern about the possible association of atypical antipsychotic drugs with diabetic ketoacidosis (DKA).

Objective: We aimed to explore safety signals for adverse drug events (ADEs), specifically DKA, associated with the use of typical or atypical antipsychotic drugs (APDs) utilizing data from the US Food and Drugs Administration Adverse Event Reporting System (FAERS).

Methods: We analyzed DKA reports where APDs were reported as primary and secondary suspect drugs and were compared to two reference groups: one that included all other drugs and another restricted to psychotropic drugs. These comparisons were based on twenty-year span of spontaneously reported data. Two signal detection techniques, the proportional reporting ratio (PRR) and the empirical Bayes geometric mean (EBGM), were used to search for a possible DKA signal in relation to use of APDs.

Results: Between 2000 and 2022, most DKA ADE originated from the United States (45.4%), were submitted by health care professionals (74.1%), and led to serious hospitalization in approximately three quarters of the cases (74.3%). As primary suspect drugs, quetiapine and olanzapine, two atypical APDs, were identified with potential drug safety signals when compared to other psychotropic drugs: with PRRs of 12.8 (95%CI: 11.9,13.8) and 12.4 (95%CI: 11.5,13.5), respectively. The corresponding EBGM values for these two atypical antipsychotics were 7.5 (90%CI: 7.2,7.9) and 8.8 (90%CI: 8.3,9.3). Comparable results were obtained when considering primary and secondary suspect drugs, with olanzapine showing the strongest PRR and EBGM signals: 12.6 (95%CI: 11.7,13.6) and 9.0 (90%CI: 8.6,9.5), respectively. Even after the exclusion of all ADE reports submitted by lawyers, the results consistently demonstrated strong signals associated with atypical APDs. This held true both when the analysis included primary suspect drugs only or expanded to consider both primary and secondary suspect drugs.

Conclusion: This analysis provides evidence of a safety signal between atypical APDs and DKA.

Keywords: Atypical antipsychotic drugs, diabetic ketoacidosis, FDA Adverse Event Reporting System (FAERS), SGLT-2 inhibitors.

4.1 INTRODUCTION

Antipsychotic drugs (APDs) are mainly grouped into two classes, typical - known as first-generation antipsychotics (FGAs) - and atypical or second-generation antipsychotics (SGAs). Although APDs are primarily indicated for the treatment of schizophrenia and bipolar disorder, they are frequently prescribed off-label for other conditions, including depression, anxiety, Tourette's syndrome, personality disorders, and obsessive-compulsive disorder (Chokhawala & Stevens, 2022; Holt, 2019).

Typical APDs are dopamine receptor antagonists and are known to cause extrapyramidal side effects and other complications such as: sedation, epileptogenic effects, abnormal heart conditions, as well as neuroleptic malignant syndrome. Atypical APDs are serotonin-dopamine antagonists; while they demonstrate fewer extrapyramidal side effects, rendering them potentially more useful clinically, accrued evidence indicates they may be associated with an increased risk of weight gain and development of metabolic syndrome (Chokhawala & Stevens, 2022).

Diabetic ketoacidosis (DKA) is the most common acute hyperglycaemic emergency in people with diabetes. A confirmed diagnosis for DKA requires three criteria: 1) elevated blood glucose levels or a family history of diabetes, 2) presence of urinary or blood ketones, and 3) a high anion gap metabolic acidosis. Early diagnosis, management and treatment of this condition ensures a solid prognosis for a condition that can otherwise be fatal (Dhatariya et al. 2020). Recent years have witnessed accrued reports of an association between atypical APDs and DKA (Guenette et al. 2013; Vuk et al. 2017). Risk factors associated with metabolic health concerns include personal and family history of diabetes mellitus, dyslipidemia, weight gain, and increased fasting plasma glucose. For these reasons, the US Food and Drug Administration (FDA), which has approved twelve atypical APDs as of 2016, issued safety warnings pertaining to their use. The FDA recommended ongoing monitoring of personal and family history of diabetes mellitus, dyslipidemia, weight, fasting plasma glucose and fasting lipid profile, among other health concerns, for all patients who are prescribed these drugs (Chokhawala & Stevens, 2022); such warnings may subsequently lead to the discontinuation of the triggering agent if warranted.

The FDA employs a variety of post-marketing surveillance methods to ensure drug safety, one of which is the FDA Adverse Event Reporting System (FAERS) (Hoffman et al. 2014; Khaleel et al. 2022; Szarfman et al. 2004; Weaver et al. 2008). This system, as a form of passive surveillance, is an inexpensive and publicly accessible tool designed for post-marketing monitoring, aimed at detecting new, rare, and severe adverse drug reactions (Alomar et al. 2020, Nour et al. 2019; Waller, 2006; Weaver et al. 2008; WHO, 2006; Khaleel et al. 2022), as well as medication errors involving human drugs and therapeutic biological (Rodriguez et al. 2021; Sakaeda et al. 2013). Currently, the FDA receives over one million spontaneous reports on adverse-event and medication errors of drug or biological product use annually, making it one of the largest pharmacovigilance databases in the world (Khaleel et al. 2022). It has been used previously to analyse adverse drug reports (ADRs) in relation to antipsychotic drugs in children and adults for other outcomes (He et al. 2022; Kato et al. 2015; Kimura et al. 2015).

The objective of this analysis is to assess the potential safety signals of APDs and DKA through utilizing available data from the FAERS and employing disproportionality analysis methods.

4.2 METHODS

4.2.1 Data Source

FAERS is a publicly available database initially launched in 1969, designed to support the FDA's post-marketing safety surveillance program for pharmaceutical products and therapeutic biologic drugs (Khaleel et al. 2022; Sakaeda et al. 2013). The database collects information on ADE submitted by pharmaceutical companies, healthcare professionals (such as physicians, pharmacists, and nurses), as well as consumers and lawyers (FDA, 2018; 2021).

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology (Brown et al. 1999; FDA, 2018; Sakaeda et al. 2013). The FAERS database consists of seven different data tables: 1) patient demographics; 2) therapeutic drug information; 3) adverse events; 4) outcomes of the event; 5) report sources; 6) drug therapy duration; and 7) indication for use/diagnosis. In the DRUG table, drugs fall under one of the following categories: primary suspect, secondary suspect, concomitant, or interacting. The designation of 'primary suspect' is determined by the submitter of a given ADE report, and reflects their judgement on which drug, if the subject was taking more than one, was likely responsible for the observed adverse event (Hoffman et al. 2014). The database generates raw datasets on a quarterly basis and is publicly accessible on the FDA website (FDA, 2018).

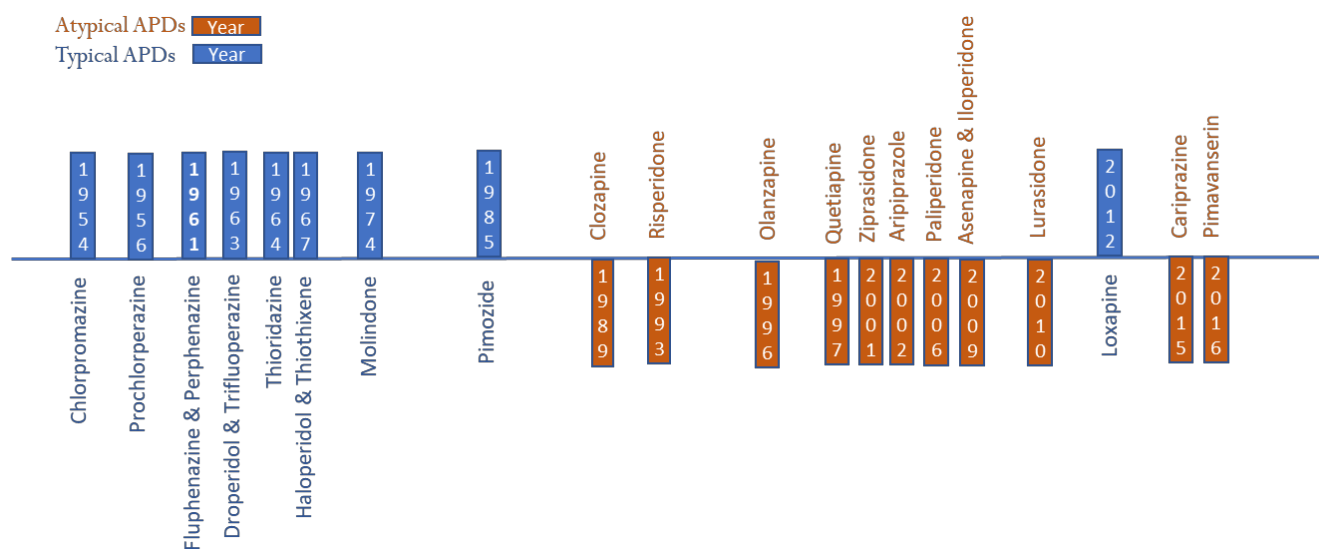
4.2.2 Data Cleaning

To ensure the integrity of our analysis, we implemented multiple stages of data processing. These steps involved cleaning the data, conducting spell checks, and standardizing drug names to ensure consistency. Additionally, we carried out deduplication of case reports to eliminate any duplicate entries. Furthermore, we conducted additional checks to identify reports that listed more than one antipsychotic as primary and secondary suspect drugs within the same report. We also identified reports that included both APDs and our comparator drugs of interest (psychotropic drugs).

4.2.3 Data Analysis

We extracted all ADE reports for antipsychotic drugs between first quarter of 2000 and quarter four of 2022 (Table 4.1, Figure 4.1), inclusive.

Figure 4.1. Timeline for Approval of Atypical (n= 12) and Typical Antipsychotic Drugs (n=12), by the United States Food and Drugs Administration, 1954-2016^{1,2,3}.



¹Sources: U.S. Food and Drug Administration, n.d.; U.S. Food and Drug Administration, 2022.

²Brexipiprazole, an atypical antipsychotic drug, was not included in this analysis.

³Indication of use of antipsychotic drugs may be updated to include other diagnoses overtime.

Table 4.1. Antipsychotic Drugs Included in the Signal Detection Analysis for Diabetic Ketoacidosis¹

Atypical Antipsychotic Drugs	Typical Antipsychotic Drugs
Aripiprazole	Chlorpromazine
Asenapine	Droperidol
Cariprazine	Fluphenazine
Clozapine	Haloperidol
Iloperidone	Loxapine
Lurasidone	Molindone
Olanzapine	Perphenazine
Paliperidone	Pimozide
Pimavanserin	Prochlorperazine
Quetiapine	Thioridazine
Risperidone	Thiothixene
Ziprasidone	Trifluoperazine

¹Source: FDA, 2022

To limit the risk of bias that may impact disproportionate reporting estimates, we evaluated the risk of DKA associated with individual APDs during the period that they were approved for use in the United States, since the majority of the reports originated from there (45.4%). A series of analyses were conducted as outlined in Table 4.2. We structured our study primarily around two comparator groups: one that encompassed all other drugs, and a more specific subset group composed only of psychotropic drugs (Table 4.3).

Our analysis plan was designed with the aim of reducing some of the inherent limitations to spontaneous reporting systems. For instance, to reduce the potential dilution of the drug safety signal for DKA due to antidiabetic drugs, the analysis was refined by retaining reports of psychotropic drugs only as the comparator group. The category of psychotropic drugs includes classes such as hypnotics, psychostimulants, anticonvulsants, antianxiety and bipolar disorder medications. As these substances impact brain activities linked to mental processes and behavior, they form a suitable comparator population for ADE reports (Table 4.3). To further enhance the reliability of our results, we also conducted different analyses utilizing Sodium glucose co-transporter 2 (SGLT-2) inhibitors as positive controls (Table S4.1).

The first two analyses (1a and 1b) were limited to primary suspect drugs only, and then re-analyzed (2a and 2b) to include primary and secondary suspect drugs as a sensitivity analysis.

As mentioned earlier, ADEs in FAERS are coded using the MedDRA terminology at the preferred term level (PT). For the purpose of this analysis, we focused on the PT: “diabetic ketoacidosis”.

Table 4.2. Analysis Plan for Drug Use and Diabetic Ketoacidosis Adverse Drug Events.

Analysis	Comparison
1a.	Individual APDs vs. all other drugs (primary suspect drugs only) [presented in Supplemental Material].
1b.	Individual APDs vs. psychotropic drugs (primary suspect drugs only).
2a.	Individual APDs vs. all other drugs (primary and secondary suspect drugs) [presented in Supplemental Material].
2b.	Individual antipsychotics drugs vs. psychotropic drugs (primary and secondary suspect drugs).
3a.	Sensitivity Analysis: Individual atypical APDs vs. psychotropic drugs, excluding submissions from lawyers (primary suspect drugs only).
3b.	Sensitivity Analysis: Individual atypical APDs vs. psychotropic drugs, excluding submissions from lawyers (primary and secondary suspect drugs only).
4a.	SGLT2 (positive control) vs. all other drugs, excluding antipsychotics (as primary suspects only) [presented in Supplemental Material].
4b.	SGLT2 (positive control) vs. psychotropic drugs, excluding antipsychotics, (primary suspect drugs only) [presented in Supplemental Material].

Abbreviations: APDs, Antipsychotic Drugs; SGLT-2, Sodium glucose co-transporters 2 inhibitors.

Table 4.3. List of Psychotropic drugs Used as a Comparator Drugs.

Psychotropic Drugs	Names of Drugs
Antidepressants	Amitriptyline, amoxapine, atomoxetine, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, selegiline, sertraline, tranylcypromine, trazodone, trimipramine, venlafaxine, vilazodone, vortioxetine
Psychostimulants	Dexmethylphenidate, dextroamphetamine, lisdexamphetamine methylphenidate
Hypnotics	Diphenhydramine, doxepin, eszopiclone, ramelteon, suvorexant, temazepam, triazolam, zaleplon, zolpidem
Anti-Anxiety	Alprazolam, atenolol, buspirone, chlordiazepoxide, clomipramine, clonazepam, clonidine, diazepam, gabapentin, guanfacine, lorazepam, oxazepam, prazepam, pregabalin, propranolol
Bipolar Disorder	Carbamazepine, divalproex, lamotrigine, lithium, oxcarbazepine, valproic acid

4.2.4. Statistical Methods

Data mining algorithms have been developed and enhanced to allow for a quantitative detection of signals within large databases. These signals are identified from the statistical association between a drug and adverse event reporting (Farrell et al. 2019). These computational methods function by comparing the relative reporting ratios of a particular event of interest against all other adverse events for the same drug, with reference to the reporting ratios for the same adverse event observed for all drugs within the database. The value for data mining methods lies in its capacity to analyze large databases for early detection of safety signals of newly marketed drugs; for the continued monitoring of safety issues for old drugs; and, for signal detection for nonserious adverse events (Fukazawa et al. 2018).

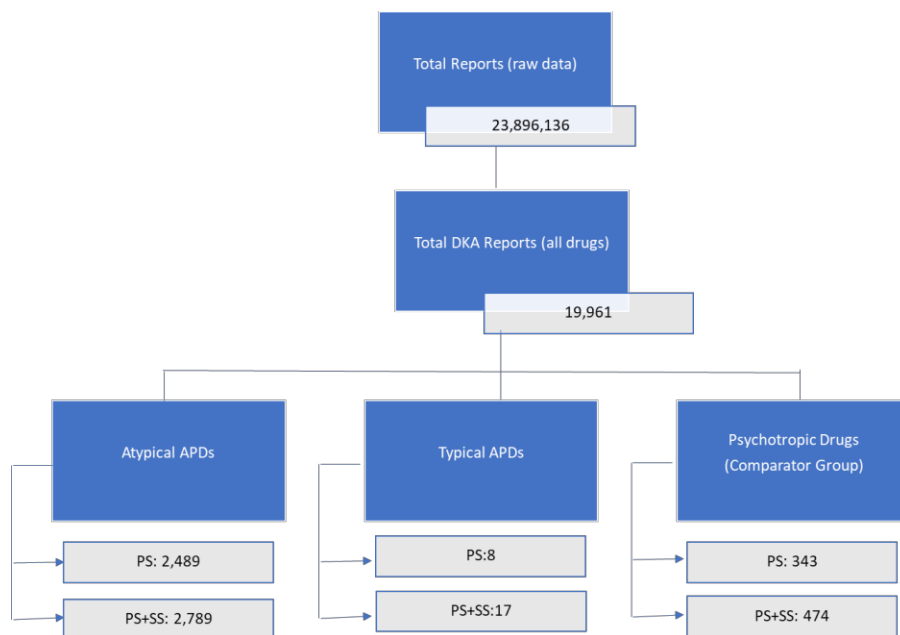
In the process of computing estimates for disproportionate reporting between APDs and DKA, we employed the proportional reporting ratio (PRR) and multi-item gamma Poisson shrinker (MGPS) algorithms, the latter yielding Empirical Bayesian Geometric Mean (EBGM) scores. These two methods demonstrate distinct performance characteristics in terms of sensitivity and specificity (Almenoff et al. 2006). The PRR method is known for its tendency to generate high false positive signals. To mitigate this, especially in cases of small or rare adverse event counts, the MGPS approach is employed. This method effectively 'shrinks' these estimates, thus reducing the risk of false positives signals associated with PRR method. For PRR, a signal of disproportionality is typically considered established when a lower bound (LB) of 1 or higher is achieved along with at least three reported cases. In the case of EBGM, the most commonly accepted criteria for a safety signal involve a threshold value of 2 for the lower limit of the 90% credibility interval around the EBGM (Deshpande, 2010).

4.3 RESULTS

4.3.1 Overview of Data from the Food and Drugs Administration Adverse Events Reporting System.

During the period spanning from the first quarter of 2000 to the last quarter of 2022, the FAERS database received a total of 23,896,136 spontaneous reports. Of these, 19,961 were reports of DKA. Atypical APDs, when considered as primary suspect drugs, accounted for 2,489 reports, constituting 12.5% of the DKA ADEs. Comparatively, other psychotropic drugs and typical APDs comprised smaller proportions of the DKA ADEs, with 1.7% (n = 343) and 0.04% (n = 8), respectively (Figure 4.2).

Figure 4.2. Flowchart for Diabetic Ketoacidosis Adverse Drug Events in the US Food and Drugs Adverse Events Reporting System, 2000-2022¹.



Abbreviations: DKA, Diabetic ketoacidosis; PS, primary suspect drugs; SS, secondary suspect drugs.

4.3.2 Description of Diabetic Ketoacidosis Adverse Events Reports

4.3.2.1. Reports by Country

Our analysis shows DKA reports were submitted predominantly from within the United States (45.4%, n = 9,055), followed by United Kingdom (n = 1,974, 9.9%) and Canada (n = 951, 4.8%) (Tables 4.4 and Supplementary Material, Table S4.2).

Table 4.4. Summary Counts and Proportions of Diabetic Ketoacidosis Adverse Drug Events by Country of Submission^{1,2}

Country	Counts (n = 19,661)	Proportion (%)
United States	9,055	45.4
United Kingdom	1,974	9.9
Canada	951	4.8
Japan	812	4.1
Australia	706	3.5
Germany	393	2.0
Spain	294	1.5
Israel	269	1.3
France	258	1.3
China	178	0.9

¹Data is shown for the ten countries which submitted the highest number of reports, by descending order.

²All other countries reporting at least one diabetic ketoacidosis event are shown in Supplemental Material (Table S4.2).

4.3.2.2. Demographic Characteristics

DKA adverse events between years 2000 and 2022 were slightly higher in females (48.4% n = 9,665) than males (43%, n = 8,582), while the sex was unknown in 8.6% (n=1,714) of the total reports. The highest proportion of reported ADRs were submitted by healthcare professionals at 74.1% (n = 14,794), followed by consumers at 22.3% (n = 4,460). Almost three quarters of DKA adverse events (74.3%, n = 14,839) led to hospitalization, while 14.2% (n = 2,828) were

considered life threatening and death was reported in 6.1% of the reports (n = 1,209) (Table 4.5).

Overall, reports on individuals between the ages of 31 to 70 years accounted for slightly over half of the ADRs at 53.7%. Those who were less than 31 years of age and over the age of 71 accounted for 11.5% and 8.8%, respectively, of all reports. Age was missing in slightly over a quarter of all cases at 26.1%. The 51- to 60-year-old age group accounted for the highest proportion of DKA ADRs at 17%, followed closely by those aged between 41 to 50 years at 14.7%. The 61-70 and 31-40 year age groups accounted for 12.8% and 9.2% of all reports, respectively.

4.3.2.3. Indications for Use

When analyzing information about the suspect drug, the indications for use of the reported drugs revealed the following findings. Among hyperglycemic conditions, type 2 diabetes mellitus (T2DM) accounted for the highest proportion (25.3 %, n = 5,057). Unspecified diabetes mellitus and type 1 diabetes mellitus (T1DM) accounted for comparable proportions of reports at 13.9% (n = 2,769) and 11.9% (n = 2,376). A breakdown of indication of use for neurological conditions showed that depression accounted for the highest proportion at 3.5% (n = 703), while both schizophrenia and bipolar disorder accounted for slightly smaller proportions at 3.0% (n = 608) and 2.1% (n = 426), respectively. Hypertension accounted for 3.4% (n = 671) (Table 4.6, Supplemental Material Table S4.3).

Table 4.5. Characteristics of all Diabetic Ketoacidosis Adverse Drug Reports in the US Food and Drugs Adverse Events Reporting System, 2000Q1 to 2022Q4^{1,2}

Demographics	Counts (n =)	Proportion (%) ¹
Gender		
Male	8,582	43
Female	9,665	48.4
Not Specified	1,714	8.6
Source of Report		
Health Care Professionals	14,794	74.1
Consumers	4,460	22.3
Not Specified	707	3.5
Types of Report and Outcome²		
Serious		
Hospitalized	14,839	74.3
Other Outcomes	10,393	52.1
Life Threatening	2,828	14.2
Died	1,209	6.1
Disabled	336	1.7
Required Intervention	160	0.8
Congenital Anomaly	7	0
Non-Serious	82	0.4
Age (years)		
0-10	164	0.8
11-20	904	4.5
21-30	1,220	6.1
31-40	1,837	9.2
41-50	2,933	14.7
51-60	3,386	17
61-70	2,554	12.8
71-80	1,352	6.8
80-90	384	1.9
90+	27	0.1
Missing	5,200	26.1

¹Proportions are based on the total count for DKA ADE (n = 19,961).

²A report may have multiple types of outcomes.

Table 4.6. Indication of Use for Drugs Reporting Diabetic Ketoacidosis Adverse Drug Events^{1,2,3}

Indication of Use	Counts (n =)	Proportion (%) ¹
Type 2 Diabetes Mellitus	5,057	25.3
Diabetes Mellitus	2,769	13.9
Type 1 Diabetes Mellitus	2,376	11.9
Depression	703	3.5
Hypertension	671	3.4
Schizophrenia	608	3
Bipolar Disorder	426	2.1
Anxiety	331	1.7
Pain	263	1.3
Sleep Disorder	188	0.9

¹Proportions are based on the total count for DKA ADE (n = 19,961).

²A report may have multiple indication of use.

³ Data is shown for the top ten indication of use. Other indications of use are shown in Supplemental Material (Table S4.3).

4.3.3 Antipsychotic Use and Diabetic Ketoacidosis

4.3.3.1 Antipsychotics (Atypical and Typical) vs Psychotropic Drugs - Primary Suspect Drugs Only.

DKA ADRs were reported with atypical and typical antipsychotic drugs between 2000 and 2022.

As seen in Table 4.7, as primary suspect drugs, quetiapine and olanzapine were shown to be associated with the highest number of reports and safety signals: [quetiapine: (n = 1,216, PRR=12.8 (95%CI: 11.9,13.8) and EBGM=7.5 (90%CI: 7.2,7.9); olanzapine: (n = 877; PRR=12.4 (95%CI: 11.5,13.5) and EBGM=8.8 (90%CI: 8.3,9.3)]. Both atypical antipsychotics, lurasidone and ziprasidone and three typical antipsychotic drugs: chlorpromazine, thioridazine and haloperidol were shown to generate signals with less than 10 reported ADRs each (Table S4.4). Comparable results were obtained when atypical antipsychotic drugs were compared to all

other drugs, with olanzapine and quetiapine being associated with the highest and second highest safety signals, respectively (Table S4.5).

Table 4.7. Comparison of Diabetic Ketoacidosis Signals with Atypical Antipsychotic Drugs vs Reference Psychotropic Drugs, as Primary Suspect Drugs Only, 2000-2022^{1,2}.

	Counts (n =)	PRR (LB, UB)	EBGM (LB, UB)
Atypical Antipsychotic Drugs			
Quetiapine	1,216	12.8 (11.9,13.8)	7.5 (7.2,7.9)
Olanzapine	877	12.4 (11.5,13.5)	8.8 (8.3,9.3)
Aripiprazole	117	1.1 (0.9,1.3)	1.1 (0.9,1.2)
Clozapine	144	1 (0.9,1.2)	1 (0.9,1.2)
Risperidone	96	0.7 (0.6,0.9)	0.7 (0.6,0.9)
Paliperidone	23	0.6 (0.4,0.8)	0.6 (0.4,0.8)

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio.

¹Data shown by descending order based on PRR signal strength.

²Antipsychotic Drugs with less than 10 Adverse Events are shown in Supplemental Material (Table S4.4).

4.3.3.2 Antipsychotics (Atypical and Typical) vs Psychotropic Drugs - Primary and Secondary Suspect Drugs Only.

ADEs for primary and secondary suspect atypical APDs were compared to those for psychotropic drugs. Olanzapine accounted for the second highest number of reports (n = 1,018) and generated the strongest safety signal [PRR= 12.6 (95%CI: 11.7,13.6); EBGM= 9.0 (90%CI: 8.6,9.5)]. Comparable to the analysis where APDs were primary suspect drugs, quetiapine continued to account for the highest number of reports (n = 1,243) but generated the second highest safety signal [PRR= 10.6 (95%CI: 9.9,11.4); EBGM= 7.0 (90%CI: 6.6,7.3)]. Aripiprazole, clozapine, risperidone, and paliperidone did not generate strong signals (Table 4.8). The same analysis with lurasidone and typical APDs generated counts less than 10 reports for each drug individually (Table S4.6). Comparable results were observed when compared to all other drugs (Supplementary Material, Table S4.7).

Table 4.8. Comparison of Diabetic Ketoacidosis Signals with Atypical Antipsychotic Drugs vs Reference Psychotropic Drugs, as Primary and Secondary Suspect Drugs, 2000-2022^{1,2}.

	Counts (n =)	PRR (LB, UB)	EBGM (LB, UB)
Atypical Antipsychotic Drugs			
Olanzapine	1,018	12.6 (11.7,13.6)	9.0 (8.6,9.5)
Quetiapine	1,243	10.6 (9.9,11.4)	7.0 (6.6,7.3)
Clozapine	190	1.5 (1.3,1.7)	1.5 (1.3,1.6)
Aripiprazole	139	1.3 (1.1,1.5)	1.3 (1.1,1.5)
Risperidone	151	1.1 (1,1.3)	1.1 (1,1.3)
Paliperidone	28	0.6 (0.4,0.9)	0.6 (0.4,0.8)
Ziprasidone	11	0.5 (0.3,0.9)	0.5 (0.4,0.10)
Typical Antipsychotic Drugs			
Haloperidol	12	0.4 (0.3,0.8)	0.4 (0.4,0.11)

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio.

¹Data shown by descending order based on PRR signal strength.

²Antipsychotic Drugs with less than 10 Adverse Events are shown in Supplemental Material.

4.3.3.3. Sensitivity Analysis: Reports of Diabetic Ketoacidosis with Atypical Antipsychotic Drugs vs Psychotropic Drugs, as Primary or as Primary and Secondary Suspect Drugs, Excluding Submissions from lawyers.

As a sensitivity analysis, we conducted analysis with atypical APDs as primary or secondary suspect drugs compared to the reference psychotropic drugs, excluding litigation adverse reports submitted by lawyers (Tables 4.9 and 4.10). In both analyses, olanzapine accounted for the highest counts of DKA ADRs and disproportionality signals, followed by quetiapine. As primary suspect drugs, a total of 535 DKA ADRs were reported for olanzapine, generating a PRR of 16.9 (95%CI: 15.2,18.8) and EBGM of 10.6 (90%CI: 9.9,11.4). In the case of primary and secondary suspect drugs, a total of 603 DKA ADRs were associated with this agent, resulting in a PRR of 15.0 (95%CI: 13.6,16.6) and an EBGM of 10.2 (90%CI: 9.5,10.9). APDs that generated counts less than 10 ADRs for each drug individually are shown in Supplemental Material (Tables S4.8 and S4.9).

Table 4.9. Comparison of Diabetic Ketoacidosis Signals with Atypical Antipsychotic Drugs vs Reference Psychotropic Drugs, as Primary Suspect Drugs, Excluding Submissions from Lawyers¹.

	Counts (n =)	PRR (LB, UB)	EBGM (LB, UB)
Atypical Antipsychotic Drugs			
Olanzapine	535	16.9 (15.2,18.8)	10.6 (9.9,11.4)
Quetiapine	252	4.6 (4,5.3)	3.9 (3.5,4.4)
Aripiprazole	115	2.2 (1.8,2.7)	2.1 (1.8,2.4)
Clozapine	134	1.9 (1.6,2.2)	1.8 (1.5,2)
Risperidone	91	1.3 (1.1,1.6)	1.3 (1.1,1.5)
Paliperidone	22	1.1 (0.7,1.7)	1.1 (0.8,1.6)

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio.

¹Data shown by descending order based on PRR signal strength.

²Antipsychotic Drugs with less than 10 Adverse Events are shown in Supplemental Material (Table S4.8).

4.3.3.4 Secondary Analysis: Sodium Glucose Co-Transporter 2 Inhibitors vs. Psychotropic drugs or All Other Drugs - Primary Suspect Drugs Only.

To confirm the utility of FAERS as a reliable source of data for detecting safety signals, we conducted signal detection analyses using SGLT-2 as positive control using psychotropic drugs or all other drugs as primary suspects only as the comparator groups. In brief, canagliflozin, empagliflozin and empagliflozin/metformin mixtures generated high counts and significant PRR and EBGM signals, with results differing only slightly between the two reference groups (Tables S4.10, S4.11).

Table 4.10. Comparison of Diabetic Ketoacidosis Signals with Atypical Antipsychotic Drugs vs Reference Psychotropic Drugs, as Primary and Secondary Suspect Drugs Excluding Submissions from Lawyers^{1,2}.

	Counts (n =)	PRR (LB, UB)	EBGM (LB, UB)
Atypical Antipsychotic Drugs			
Olanzapine	603	15 (13.6,16.6)	10.2 (9.5,10.9)
Quetiapine	277	3.8 (3.3,4.3)	3.4 (3,3.7)
Clozapine	175	2.6 (2.2,3)	2.4 (2.1,2.7)
Aripiprazole	130	2.3 (1.9,2.8)	2.2 (1.9,2.6)
Risperidone	107	1.5 (1.2,1.8)	1.5 (1.2,1.7)
Paliperidone	27	1.1 (0.7,1.6)	1.1 (0.8,1.5)
Ziprasidone	11	0.9 (0.5,1.6)	0.9 (0.6,1.4)
Typical Antipsychotic Drugs			
Haloperidol	12	0.8 (0.4,1.4)	0.8 (0.5,1.2)

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio.

¹Data shown by descending order based on PRR signal strength.

²Antipsychotic Drugs with less than 10 Adverse Events are shown in Supplemental Material (Table S4.9).

4.4 DISCUSSION

The present study analyzed the safety signals of APDs and DKA based on data collected between 2000 and 2022. Our results support accrued evidence of atypical APDs as potential risk factors for this hyperglycemic complication. Almost all reports were serious with many resulting in hospitalization, life-threatening prognoses, or even mortality. Approximately 50% of DKA ADRs were reported in females. The highest proportion of DKA ADRs were submitted by health care professionals (74.1%) and from within the United States (45.4%). Quetiapine and olanzapine, two atypical antipsychotics, accounted for the highest counts and disproportionality signals as a primary suspect drug when compared to psychotropic drugs. Quetiapine was the most prescribed atypical antipsychotic drug in the United States as between 2000 and 2016, based on the analysis of Cerner Corporation's Health Facts, followed by risperidone and olanzapine (Haddad et al. 2023). Furthermore, there has been accumulating

evidence of case reports supporting an association between the use of atypical APDs and DKA, mainly olanzapine and clozapine, although most case reports were attributed to male cases (Haddad et al. 2023).

A previous analysis of the FAERS database focussing on the relationship between APDs and hyperglycemic events between January 2004 to March 2013 showed that quetiapine resulted in a total of 12,471 case reports (28.8%), followed by olanzapine (37.9%), risperidone (27.0%), aripiprazole (23.7%) and clozapine (14.3%). This corroborates our results, where the highest counts were attributed to quetiapine and olanzapine. Typical APDs such as haloperidol, prochlorperazine and chlorpromazine accounted for 31.5%, 19.8%, and 35.7% of ADRS, respectively. The authors reported 1,090 DKA events associated with the use of APDs, with a very high reporting odds ratio of 40 (Kato et al. 2015). The reporting ratio increased with co-administration of multiple APDs (polypharmacy), an indication of an increase in signal strength. To further explore the robustness of our results, we conducted a sensitivity analysis that excluded submissions from lawyers. Our results corroborate previous studies where litigation-associated reports submitted by lawyers in FAERS did not have an impact on safety signals (Rogers et al. 2019). Litigation can, however, impact disproportionate reporting for outcomes such as renal failure, chronic kidney, kidney injury and tardive dyskinesia (Munoz & Dal Plan, 2019).

A study by Neha et al. (2021) concluded that overreporting due to notoriety bias is limited in FAERS. This bias, which is inherent when analysing this type of data (Bégaud & Dangoumau 2000), is defined as a selection bias in which a case has a greater chance of being reported if the subject is exposed to the studied factor known to cause, thought to cause, or likely to cause the

adverse event of interest. Their analysis focused on 31 drugs – excluding APDs -that had safety alert/label change notifications by FDA between 2009 and 2013. The impact of notoriety bias due to safety alerts was examined by evaluating the signal strength using the reporting odds ratio (ROR) and PRR two years before and after the safety alert. Although the authors observed increased reporting for eleven drugs following the issuance of the safety alert or label change by the FDA, while the reporting for twenty drugs remained unchanged or decreased.

Furthermore, an analysis using the Wilcoxon signed rank test indicated a lack of statistically significant difference with respect to the number of reports before and after the safety alert ($p = 0.330$, $Z = -0.974$). Although the FDA issued several warnings related to the use of antipsychotic drugs (FDA, 2016), it is difficult to evaluate the impact, if any, of notoriety bias on our analysis. This would be worth exploring in the future.

Recent case reports have provided evidence of a potential association between SGLT-2 and euglycemic DKA (defined as blood glucose < 250 mg/dL and presence of severe metabolic DKA), which occurs in both T1DM and T2DM patients (FDA, 2015; Palmer & Claig, 2021; Peters et al. 2015). Bleau et al. (2017) used FAERS to evaluate the relationship between SGLT-2 and DKA. Their analysis found that the risk of developing acidosis with SGLT-2 inhibitors was high in T1DM and T2DM patients, with 71% having euglycemic ketoacidosis. Therefore, to further validate our results, SGLT-2 served as a positive control for DKA signal detection in comparison to all other drugs or psychotropic drugs. Specifically, canagliflozin, empagliflozin and empagliflozin/metformin mixtures generated high PRRs and EBGs (Supplementary Material, Tables S4.10 and S4.11).

4.4.1 Strengths

Our analysis provides a comprehensive analysis of DKA reports with the use of APDs as primary and secondary suspect drugs. To mitigate the risk of bias that may impact disproportionate reporting estimates, we evaluated the risk of DKA associated with individual APDs during the period that they were approved for use in the United States. This approach, which adjusts for the calendar time of drug market authorization over the two-decade span of our analysis, underscores a key strength of our study in mitigating temporal bias. We can conclude with confidence based on the historical reporting data (Supplementary Material, Table S4.12) that our analysis was not subject to a “Weber Effect”, in which ADRs peaks at the end of the second year following market authorization (Hoffman et al. 2014). To enhance the robustness of our results, we utilized two different comparator groups: the first group consisted of all drugs, while the second group was specifically limited to psychotropic drugs. Other psychotropic medications, known for their effect on brain activities related to mental processes and behavior, were selected as a suitable comparator group, as they are not known to be associated with an increased risk of DKA. This refined approach was used to reduce noise and improve our disproportionality analyses.

4.4.2 Limitations

Analysing data from FAERS poses certain challenges and limitations (Alatawi et al. 2020; Hazell & Shakir, 2006; Poluzzi et al. 2010). First, due to unstructured entry of drug names, reporters may use generic or trade names with different naming structures from all over the world and sometime these have typographical errors (Khaleel et al. 2022). Second, although we did standardize drug names and performed multiple data cleaning steps, the FAERS data analyzed

here is not perfect. Nonetheless, we expect any remaining data inaccuracies or biases to be small enough so as not to undermine the main conclusions of our comprehensive series of analyses.

5.0 CONCLUSION

Our study identified potential safety signal associating for DKA in association with APDs, specifically with quetiapine and olanzapine. These two drugs displayed the highest volume of reports and showed significant disproportionality signals. Despite potential limitations intrinsic to self-reporting databases and although we cannot be certain of a causal relationship between the drugs and the adverse events included in the present suite of analyses, our results support the mounting body of evidence of a relationship between atypical APDs and DKA. Our findings underscore the need of conducting further investigations to corroborate these observations.

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SUPPLEMENTAL MATERIAL S4

The following supplemental information is included as supporting material to the manuscript. These include:

- **Supplemental Material I:** A list of sodium glucose co-transporter-2 inhibitors (SGLT-2) used as positive controls (Table S.4.1)
- **Supplemental Material II:** Country of origin of diabetic ketoacidosis adverse drug events (DKA, ADE) (Table S4.2) and indication of use associated with DKA ADE (Table S4.3)
- **Supplemental Material III:**
 - Additional Data for 2020-2022 where DKA ADE where less than ten:
 - Atypical and typical antipsychotic drugs (APDs) associated with reports on DKA ADEs compared to reference psychotropic drugs, or all other drugs as primary or as primary and secondary suspect drugs (Tables S4.4 to S4.7).
 - Sensitivity analysis excluding reports submitted from lawyers as primary, or primary and secondary suspect drugs (Tables S4.8 and S4.9).
 - Positive Control-All counts: Data Tables on reports of DKA signals using SGLT-2 compared to psychotropic substances and all other drugs as primary suspect drugs (S.4.10 and S4.11).
- **Supplemental Material IV:** Information on historical counts of DKA events by atypical APD use and year (Table S.4.12) and total counts of DKA ADE (Table S.4.13), 2000-2022.
- **Supplemental Material V:** Information on the period 2000-2020.
 - Atypical or typical APDs associated with reports on ketonuria (Tables S4.14 and S4.15) or hyperglycemic hyperosmolar State ADEs (Tables S4.16 and S4.17) compared to all other drugs as primary suspect drugs only, or primary and secondary suspect drugs.
- **Supplemental Material VI:** Information on the period 2000-2016.
 - Atypical APDs or SGLT-2s and DKA ADEs compared to all other drugs as primary suspect drugs only (Tables S.4.18 and S.4.19).
- **Supplemental Material VII:** Heat Map showing DKA ADE in relation to atypical APD use, 2000-2020.

Supplemental Material I

Table S4.1. List of Sodium Glucose Co-Transporter 2 Inhibitors, as Single Drugs or Mixtures, Used as a Positive Control for Signal Detection of Diabetic Ketoacidosis.

SGLT-2 Inhibitors and Mixtures	Canagliflozin, canagliflozin/metformin hydrochloride, dapagliflozin, dapagliflozin/metformin, empagliflozin, empagliflozin/linagliptin, empagliflozin/metformin, ertugliflozin
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Abbreviation: SGLT-2, Sodium Glucose Co-Transporter-2 Inhibitors.

Supplemental Material II

Table S4.2. Country of Origin of Adverse Drug Events for Diabetic Ketoacidosis^{1,2}.

Country where Event occurred	Count (n =) Proportion (%)	Country where Event occurred	Count (n =) Proportion (%)	Country where Event occurred	Count (n =) Proportion (%)
United States, US	9,055 (45.4)	Belgium, BE	28 (0.1)	Zimbabwe, ZW	4 (0)
United Kingdom, GB	1,974 (9.9)	Pakistan, PK	27 (0.1)	Bahrain, BH	3 (0)
Canada, CA	951 (4.8)	Poland, PL	27 (0.1)	Estonia, EE	3 (0)
Japan, JP	812 (4.1)	Finland, FI	26 (0.1)	Haiti, HT	3 (0)
Australia, AU	706 (3.5)	Argentina, AR	24 (0.1)	Indonesia, ID	3 (0)
Germany, DE	393 (2)	Czech Republic, CZ	22 (0.1)	Iceland, IS	3 (0)
Spain, ES	294 (1.5)	Croatia, HR	21 (0.1)	Jamaica, JM	3 (0)
Israel, IS	269 (1.3)	Bulgaria, BG	19 (0.1)	Kenya, KE	3 (0)
France, FR	258 (1.3)	Chile, CL	14 (0.1)	Puerto Rico, PR	3 (0)
China, CN	178 (0.9)	Hong Kong, HK	14 (0.1)	Trinidad and Tobago, TT	3 (0)
Brazil, BR	168 (0.8)	Romania, RO	14 (0.1)	Uganda, UG	3 (0)
Italy, IT	147 (0.7)	Hungary, HU	12 (0.1)	Belarus, BY	2 (0)
Denmark, DK	130 (0.7)	Jordan, JO	1 (0.1)	Gibraltar, GI	2 (0)
Ireland, IE	128 (0.6)	Slovakia, SK	10 (0.1)	Honduras, HN	2 (0)
Portugal, PT	128 (0.6)	Ethiopia, ET	9 (0)	Malawi, MW	2 (0)
Greece	103 (0.5)	Luxembourg, LU	9 (0)	Afghanistan, AF	1 (0)
India, IN	102 (0.5)	Peru, PE	9 (0)	Aruba, AW	1 (0)
Netherlands, NL	91 (0.5)	Serbia, RS	9 (0)	Barbados, BB	1 (0)
Norway, NO	85 (0.4)	Iran, IR	7 (0)	Bangladesh, BD	1 (0)
Sweden, SE	84 (0.4)	Kazakhstan, KZ	7 (0)	Burkina Faso, BF	1 (0)
Switzerland, CH	80 (0.4)	Vietnam, VN	7 (0)	Brunei Darussalam, BN	1 (0)
Turkey, TR	78 (0.4)	Cuba, CU	6 (0)	Bouvet Island, BV	1 (0)
South Africa, ZA	78 (0.4)	Kuwait, KW	6 (0)	Botswana, BW	1 (0)
Austria, AT	77 (0.4)	Lebanon, LB	6 (0)	Serbia and Montenegro, CS	1 (0)
Taiwan, TW	70 (0.4)	Nepal, NP	6 (0)	Algeria, DZ	1 (0)
Saudi Arabia, SA	64 (0.3)	Oman, OM	6 (0)	Guatemala, GT	1 (0)
South Korea, KR	55 (0.3)	Qatar, QA	6 (0)	North Korea, KP	1 (0)
Singapore, SG	52 (0.3)	Slovenia, SI	6 (0)	Macao, MO	1 (0)
New Zealand, NZ	51 (0.3)	Cyprus, CY	5 (0)	Malta, MA	1 (0)
Mexico, MX	49 (0.2)	Palestine, State of, PS	5 (0)	Mauritius, MU	1 (0)
Egypt, EG	47 (0.2)	Ukraine, UA	5 (0)	Réunion, RE	1 (0)
Philippines, PH	40 (0.2)	Venezuela, VE	5 (0)	El Salvador, SV	1 (0)
Russia, RU	40 (0.2)	Costa Rica, CR	4 (0)	Uruguay, UY	1 (0)
Colombia, CO	39 (0.2)	Ecuador, EC	4 (0)		
Malaysia, MY	35 (0.2)	Iraq, IQ	4 (0)		
Thailand, TH	33 (0.2)	Latvia, LV	4 (0)		
United Arab Emirates, AE	29 (0.1)	Morocco, MA	4 (0)		

¹Data is shown by descending order of counts for submissions.²A total of 2,520 reports (12.3%) did not specify the reporting country.

Table S4.3. Indications of Use for Drugs Associated with Diabetic Ketoacidosis Adverse Events^{1,2,3}.

Indication of use	Count (n =) Proportion (%) ¹	Indication of use	Count (n =) Proportion (%) ²
Type 2 Diabetes Mellitus	5,057 (37)	Ill-Defined Disorder	83 (0.4)
Diabetes Mellitus	2,769 (25.3)	Breast Cancer	80 (0.4)
Type 1 Diabetes Mellitus	2,376 (13.9)	Non-Small Cell Lung Cancer	80 (0.4)
Depression	703 (11.9)	Diabetes Mellitus Inadequate Control	78 (0.4)
Hypertension	671 (3.5)	Renal Transplant	75 (0.4)
Schizophrenia	608 (3.4)	Blood Glucose Increased	73 (0.4)
Bipolar Disorder	426 (3)	Immunosuppressant Drug Therapy	72 (0.4)
Anxiety	331 (2.1)	Schizoaffective Disorder	70 (0.4)
Pain	263 (1.7)	Constipation	69 (0.4)
Sleep Disorder	188 (1.3)	Latent Autoimmune Diabetes In Adults	66 (0.3)
Prophylaxis	182 (0.9)	Peritoneal Dialysis	66 (0.3)
Diabetes Mellitus Management	175 (0.9)	Neuropathy Peripheral	63 (0.3)
Insomnia	170 (0.9)	Plasma Cell Myeloma	63 (0.3)
Hypothyroidism	164 (0.9)	Cardiac Disorder	58 (0.3)
Gastroesophageal Reflux Disease	152 (0.8)	Renal Cell Carcinoma	57 (0.3)
Multiple Sclerosis	150 (0.8)	Thrombosis Prophylaxis	56 (0.3)
Malignant Melanoma	147 (0.8)	Diabetic Ketoacidosis	55 (0.3)
Rheumatoid Arthritis	146 (0.7)	Insulin-Requiring Type 2 Diabetes Mellitus	54 (0.3)
Hypercholesterolaemia	133 (0.7)	Back Pain	53 (0.3)
Hyperlipidaemia	127 (0.7)	Asthma	52 (0.3)
Blood Cholesterol Increased	118 (0.6)	Mental Disorder	52 (0.3)
Psychotic Disorder	116 (0.6)	Breast Cancer Metastatic	51 (0.3)
Dyslipidaemia	107 (0.6)	Metastatic Renal Cell Carcinoma	51 (0.3)
Hepatitis C	107 (0.5)	Neuralgia	47 (0.3)
Blood Pressure Measurement	102 (0.5)	Immunosuppression	46 (0.2)
Blood Cholesterol	93 (0.5)	Seizure	45 (0.2)
Hyperglycaemia	92 (0.5)	Acute Lymphocytic Leukaemia	43 (0.2)
Metastatic Malignant Melanoma	91 (0.5)	Blood Glucose Abnormal	43 (0.2)
Nausea	86 (0.5)	Dyspepsia	43 (0.2)
HIV Infection	83 (0.4)	Epilepsy	43 (0.2)

¹Data is shown by descending order of counts for indication of use.

²Proportions are based on total count for DKA ADE (n=19,961).

³Counts less than 20 are not shown.

Table S4.3. Indications of Use for Drugs Associated Diabetic Ketoacidosis Adverse Events^{1,2,3}
(cont.)

Indication of use	Count (n =) Proportion (%) ²	Indication of use	Count (n =) Proportion (%) ²
Psoriasis	43 (0.2)	Diarrhoea	29 (0.1)
Thyroid Disorder	42 (0.2)	Lung Neoplasm Malignant	29 (0.1)
Affective Disorder	41 (0.2)	Prophylaxis Of Nausea And Vomiting	29 (0.1)
Diabetic Neuropathy	41 (0.2)	Chronic Obstructive Pulmonary Disease	28 (0.1)
Bipolar I Disorder	40 (0.2)	Glycosylated Haemoglobin Increased	27 (0.1)
Cardiac Failure	40 (0.2)	Pulmonary Arterial Hypertension	27 (0.1)
Atrial Fibrillation	39 (0.2)	Anxiety Disorder	26 (0.1)
Colon Cancer	39 (0.2)	Gout	26 (0.1)
Muscle Spasms	39 (0.2)	Vitamin D Deficiency	26 (0.1)
Attention Deficit Hyperactivity Disorder	38 (0.2)	Hodgkin's Disease	25 (0.1)
Crohn's Disease	38 (0.2)	Pulmonary Embolism	25 (0.1)
Urinary Tract Infection	38 (0.2)	Arthralgia	24 (0.1)
Covid-19	37 (0.2)	Hypertriglyceridemia	24 (0.1)
Post-Traumatic Stress Disorder	37 (0.2)	Psoriatic Arthropathy	24 (0.1)
Headache	36 (0.2)	Cardiovascular Event Prophylaxis	23 (0.1)
Prophylaxis Against Transplant Rejection	36 (0.2)	Endocrine Ophthalmopathy	23 (0.1)
Prostate Cancer	36 (0.2)	Gastric Cancer	23 (0.1)
Weight Decreased	36 (0.2)	Hypoglycaemia	23 (0.1)
Arthritis	35 (0.2)	Renal Disorder	23 (0.1)
Anaemia	34 (0.2)	Chronic Hepatitis C	22 (0.1)
Lung Adenocarcinoma	34 (0.2)	Gestational Diabetes	22 (0.1)
Premedication	33 (0.2)	Pneumonia	22 (0.1)
Agitation	32 (0.2)	Hypersensitivity	21 (0.1)
Anticoagulant Therapy	32 (0.2)	Major Depression	21 (0.1)
Contraception	31 (0.2)	Prophylaxis Against Graft Versus Host Disease	21 (0.1)
Infection	31 (0.2)	Bladder Cancer	20 (0.1)
Mania	31 (0.2)	Blood Cholesterol Abnormal	20 (0.1)
Osteoporosis	31 (0.2)	Hallucination, Auditory	20 (0.1)
Coronary Artery Disease	30 (0.2)	Migraine	20 (0.1)
Vomiting	30 (0.2)		

¹Data is shown by descending order of counts for indication of use.

²Proportions are based on total count for DKA ADE (n=19,961).

³Counts less than 20 are not shown.

Supplemental Material III

Table S4.4. Comparison of Diabetic Ketoacidosis Signals with Typical and Atypical Antipsychotic Drugs vs. Reference Psychotropic Drugs, as Primary Suspect Drugs Only, 2000-2022^{1,2,3}.

	Count (n =)	PRR (LB, UB)	EBGM (LB, UB)
Atypical Antipsychotic Drugs			
Lurasidone	7	0.7 (0.3,1.4)	0.7 (0.4,1.2)
Ziprasidone	9	0.5 (0.2,0.9)	0.5 (0.3,0.8)
Typical Antipsychotic Drugs			
Chlorpromazine	2	N/A	N/A
Thioridazine	1	N/A	N/A
Haloperidol	5	0.3 (0.1,0.8)	0.3 (0.2,0.6)

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio; N/A, Not applicable.

¹Data shown by descending order based on PRR signal strength.

²Only counts where adverse events were less than ten then shown.

³Due to a small sample size (N<3), following standard procedures in pharmacovigilance and signal detection, no analysis is undertaken for such instances as no signals can be generated.

Table S4.5. Comparison of Diabetic Ketoacidosis Signals with Atypical and Typical Antipsychotic Drugs vs. Other Drugs, as Primary Suspect Drugs Only, 2000-2022^{1,2}.

	Count (n =)	PRR (LB, UB)	EBGM (LB, UB)
Atypical Antipsychotic Drugs			
Olanzapine	877	13.2 (12.4,14.2)	12.7 (12,13.4)
Quetiapine	1,216	11.8 (11.1,12.5)	11.1 (10.6,11.7)
Aripiprazole	117	1.6 (1.3,1.9)	1.6 (1.4,1.8)
Clozapine	144	1.5 (1.3,1.8)	1.5 (1.3,1.8)
Risperidone	96	1.1 (0.9,1.3)	1.1 (0.9,1.3)
Paliperidone	23	N/A	N/A
Ziprasidone	9	0.7 (0.4,1.3)	0.7 (0.4,1.2)
Lurasidone	7	0.5 (0.2,1)	0.5 (0.3,0.8)
Typical Antipsychotic Drugs			
Chlorpromazine	2	N/A	N/A
Thioridazine	1	N/A	N/A
Haloperidol	5	0.5 (0.2,1.2)	0.5 (0.2,1)

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio; N/A, Not applicable.

¹Data shown by descending order based on PRR signal strength.

²Due to a small sample size (N<3), following standard procedures in pharmacovigilance and signal detection, no analysis is undertaken for such instances as no signals can be generated.

Table S4.6. Comparison of Diabetic Ketoacidosis Signals with Atypical and Typical Antipsychotic Drugs vs. Psychotropic Drugs, as Primary and Secondary Suspect Drugs, 2000-2022^{1,2,3}.

	Count (n =)	PRR (LB, UB)	EBGM (LB, UB)
Atypical Antipsychotic Drugs			
Lurasidone	8	0.8 (0.4,1.6)	0.8 (0.5,1.4)
Typical Antipsychotic Drugs			
Chlorpromazine	2	N/A	N/A
Pimozide	1	N/A	N/A
Fluphenazine	1	N/A	N/A
Thioridazine	1	N/A	N/A
Droperidol	1	N/A	N/A

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio; N/A, Not applicable.

¹Data shown by descending order based on PRR signal strength.

²Reports where counts were less than ten are shown.

³Due to a small sample size (N<3), following standard procedures in pharmacovigilance and signal detection, no analysis is undertaken for such instances as no signals can be generated.

Table S4.7. Comparison of Diabetic Ketoacidosis Signals with Atypical and Typical Antipsychotic Drugs vs. all Other Drugs, as Primary and Secondary Suspect Drugs, 2000-2022^{1,2}.

	Count (n =)	PRR (LB, UB)	EBGM (LB, UB)
Atypical Antipsychotic Drugs			
Olanzapine	1,018	12.1 (11.4,12.9)	11.7 (11.1,12.3)
Quetiapine	1,243	9.5 (9,10.1)	9.2 (8.7,9.6)
Clozapine	190	2 (1.7,2.3)	2 (1.7,2.2)
Aripiprazole	139	1.7 (1.4,2)	1.7 (1.5,1.9)
Risperidone	151	1.5 (1.3,1.8)	1.5 (1.3,1.7)
Paliperidone	28	0.7 (0.5,1.1)	0.7 (0.5,1)
Ziprasidone	11	0.6 (0.4,1.2)	0.6 (0.4,1)
Lurasidone	8	0.5 (0.3,1.1)	0.5 (0.3,0.9)
Typical Antipsychotic Drugs			
Chlorpromazine	2	N/A	N/A
Pimozide	1	N/A	N/A
Fluphenazine	1	N/A	N/A
Thioridazine	1	N/A	N/A
Droperidol	1	N/A	N/A
Haloperidol	12	0.6 (0.3,1)	0.6 (0.4,0.9)

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio; N/A, Not applicable.

¹Data shown by descending order based on PRR signal strength.

²Due to a small sample size (N<3), following standard procedures in pharmacovigilance and signal detection, no analysis is undertaken for such instances as no signals can be generated.

Table S4.8. Comparison of Diabetic Ketoacidosis Signals with Atypical and Typical Antipsychotic Drugs vs. Psychotropic Drugs, as Primary Suspect Drugs Only, Excluding Submissions from Lawyers, 2000-2022^{1,2,3}.

	Count (n =)	PRR (LB, UB)	EBGM (LB, UB)
Atypical Antipsychotic Drugs			
Ziprasidone	9	0.9 (0.5,1.8)	0.9 (0.6,1.6)
Lurasidone	7	0.8 (0.4,1.8)	0.8 (0.5,1.5)
Typical Antipsychotic Drugs			
Chlorpromazine	1	N/A	N/A
Thioridazine	1	N/A	N/A
Haloperidol	5	0.6 (0.3,1.5)	0.6 (0.3,1.2)

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio; N/A, Not applicable.

¹Data shown by descending order based on PRR signal strength.

²Reports where counts were less than ten are shown.

³Due to a small sample size (N<3), following standard procedures in pharmacovigilance and signal detection, no analysis is undertaken for such instances as no signals can be generated.

Table S4.9. Comparison of Diabetic Ketoacidosis Signals with Atypical and Typical Antipsychotic Drugs vs. Psychotropic Drugs, as Primary and Secondary Suspect Drugs, Excluding Submissions from Lawyers, 2000-2022^{1,2,3}.

	Count (n =)	PRR (LB, UB)	EBGM (LB, UB)
Atypical Antipsychotic Drugs			
Lurasidone	8	1 (0.5,2)	1 (0.6,1.7)
Typical Antipsychotic Drugs			
Pimozide	1	N/A	N/A
Fluphenazine	1	N/A	N/A
Thioridazine	1	N/A	N/A
Droperidol	1	N/A	N/A
Chlorpromazine	1	N/A	N/A

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio; N/A, Not applicable.

¹Data shown by descending order based on PRR signal strength.

²Reports where counts were less than ten are shown.

³Due to a small sample size (N<3), following standard procedures in pharmacovigilance and signal detection, no analysis is undertaken for such instances as no signals can be generated.

Table S4.10. Comparison of Diabetic Ketoacidosis Signals with Sodium Glucose Co-Transporter 2 Inhibitors Alone or in Mixtures vs. Psychotropic Drugs, as Primary suspect Drugs Only, 2000-2022^{1,2}.

SGLT2 Alone and Mixtures	Count (n =)	PRR (LB, UB)	EBGM (LB, UB)
Dapagliflozin	1,392	39.5(37.4,41.7)	34.7(33.2,36.3)
Empagliflozin	2,795	36(34.5,37.6)	27.3(26.4,28.1)
Canagliflozin	3,151	35.3(33.9,36.7)	25.6(24.9,26.4)
Empagliflozin\metformin	259	31.7(28.1,35.7)	31(28.0,34.3)
Empagliflozin\linagliptin	130	23.4(19.7,27.6)	23.1(20.0,26.7)
Canagliflozin\metformin	100	18.9(15.6,22.9)	18.7(15.9,22.1)
Dapagliflozin\metformin	133	16.8(14.2,19.8)	16.6(14.4,19.1)
Ertugliflozin	20	9.1(5.9,14.0)	9.1(6.3,13.0)

Abbreviations: LB, Lower bound; UB, Upper Bound; SGLT-2, Sodium Glucose Co-Transporter-2 Inhibitors; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio.

¹Data shown by descending order based on PRR signal strength.

Table S4.11. Comparison of Diabetic Ketoacidosis Signals with Sodium Glucose Co-Transporter 2 Inhibitors Alone or in Mixtures vs. All Other Drugs, as Primary Suspect Drugs Only, 2000-2022¹.

SGLT2 Alone and Mixtures	Count (n =)	PRR (LB, UB)	EBGM (LB, UB)
Dapagliflozin	1,392	212.3 (201.4,223.7)	197.3 (188.8,206.2)
Empagliflozin	2,795	180.5 (173.6,187.7)	155 (150.3,159.9)
Empagliflozin\metformin	259	178.5 (158.6,200.9)	176.2 (159.1,195.1)
Canagliflozin	3,151	173.2 (166.9,179.8)	145.7 (141.5,150.0)
Empagliflozin\linagliptin	130	132.2 (111.7,156.4)	131.3 (113.7,151.6)
Canagliflozin\metformin	100	107.1 (88.3,129.8)	106.5 (90.5,125.5)
Dapagliflozin \metformin	133	94.9 (80.2,112.1)	94.2 (81.7,108.6)
Ertugliflozin	20	51.6 (33.5,79.7)	51.6 (36.0,73.8)

Abbreviations: LB, Lower bound; UB, Upper Bound; SGLT-2, Sodium Glucose Co-Transporter-2 Inhibitors; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio.

¹Data shown by descending order based on PRR signal strength.

Supplemental Material IV

Table S4.12. Historical Counts of Diabetic Ketoacidosis Adverse Event Reports Associated with Atypical Antipsychotic Drugs, 1993-2022.

Atypical APD	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Aripiprazole	0	0	0	0	0	0	0	0	0	0	0	3	12	9	69	12	33	21	17	8	5	11	10	23	35	14	21	17	18	17
Clozapine	3	3	0	0	2	8	6	4	18	18	21	3	4	8	39	5	9	7	7	1	13	6	8	4	9	17	12	2	21	26
Lurasidone	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	3	4	1	0	2	1	9
Olanzapine	0	0	0	0	7	15	14	16	34	22	43	44	81	125	403	25	94	54	123	18	7	11	49	12	24	15	24	23	45	63
Paliperidone	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	3	1	2	0	7	2	7	4	5	3	2	1	5	1
Quetiapine	0	0	0	0	0	1	1	6	7	14	8	9	16	19	914	102	323	234	163	22	22	24	26	13	19	26	41	15	24	14
Risperidone	0	1	0	0	0	2	3	7	6	12	5	9	22	26	130	17	74	57	32	8	2	16	17	4	9	12	7	1	8	6
Ziprasidone	0	0	0	0	0	0	0	0	0	1	0	0	0	2	11	0	1	2	0	1	1	0	0	2	1	0	2	1	0	0
Total	3	4	0	0	9	26	24	33	65	67	77	69	135	189	1,566	162	537	376	344	58	58	71	118	65	106	88	109	62	122	136

Abbreviation: APD, Antipsychotic Drug

Table S4.13. Total Counts of Diabetic Ketoacidosis Adverse Drug Events Associated with Atypical Antipsychotics, 1993-2022.

Atypical APD	Total Count (n =)
Quetiapine	2,063
Olanzapine	1,391
Risperidone	493
Aripiprazole	355
Clozapine	284
Paliperidone	45
Ziprasidone	25
Lurasidone	23
Total	4,679

¹Data presented by descending order.

Supplemental Material V

Table S4.14. Comparison of Ketonuria Signals with Atypical or Typical Antipsychotic Drugs vs. All Other Drugs as Primary Suspect Drugs Only, 2000-2020^{1,2}.

Antipsychotic Drugs	Count (n =)	PRR (LB, UP)	EBGM (LB, UP)
Fluphenazine	3	145.6 (46.5,456.4)	143 (62.8, 325.5)
Prochlorperazine	3	120.4 (38.4,377.4)	118.3 (52,269.2)
Olanzapine	82	27.4 (20.2,37.2)	14.2 (11.9,17)
Haloperidol	1	N/A	N/A
Clozapine	16	2.3 (1.4,3.8)	2.2 (1.5,3.2)
Paliperidone	1	N/A	N/A
Quetiapine	5	0.6 (0.3,1.6)	0.7 (0.3,1.3)
Aripiprazole	1	N/A	N/A
Risperidone	1	N/A	N/A

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio; N/A, Not applicable.

¹Data shown by descending order based on PRR signal strength.

²Due to a small sample size (N<3), following standard procedures in pharmacovigilance and signal detection, no analysis is undertaken for such instances as no signals can be generated.

Table. S4.15 Comparison of Ketonuria Signals with Atypical or Typical Antipsychotic Drugs vs. All Other Drugs as Primary Suspect and Secondary Suspect Drugs, 2000-2020^{1,2}.

Antipsychotic Drugs	Count (n =)	PRR (LB, UB)	EBGM(LB, UB)
Fluphenazine	4	46.74 (17.4,125.54)	46 (22,96)
Prochlorperazine	3	24.61 (7.88,76.83)	24.3 (10.7,55.4)
Olanzapine	87	17.16 (13.22,22.28)	11.5 (9.6,13.7)
Thioridazine e	1	N/A	N/A
Chlorpromazine	1	N/A	N/A
Clozapine	17	1.94 (1.18,3.17)	1.9 (1.3,2.8)
Haloperidol	2	N/A	N/A
Risperidone	7	0.67 (0.32,1.42)	0.7 (0.4,1.2)
Paliperidone	1	N/A	N/A
Quetiapine	5	0.51 (0.21,1.24)	0.5 (0.3,1)
Aripiprazole	2	N/A	N/A

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio; N/A, Not applicable.

¹Data shown by descending order based on PRR signal strength.

²Due to a small sample size (N<3), following standard procedures in pharmacovigilance and signal detection, no analysis is undertaken for such instances as no signals can be generated.

Table S.4.16 Comparison of Hyperglycemic Hyperosmolar State Signals with Atypical or Typical Antipsychotic Drugs vs All Other Drugs as Primary Suspect Drugs Only, 2000-2020^{1,2}.

Antipsychotic Drugs	Count (n =)	PRR (LB, UP)	EBGM (LB, UB)
Olanzapine	89	26.5 (19.8,35.5)	14 (11.7,16.6)
Haloperidol	1	N/A	N/A
Risperidone	13	N/A	1.5 (1,2.3)
Pimavanserin	1	N/A	N/A
Clozapine	4	0.5 (0.2,1.3)	0.5 (0.2,1)

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio; N/A, Not applicable.

¹Data shown by descending order based on PRR signal strength.

²Due to a small sample size (N<3), following standard procedures in pharmacovigilance and signal detection, no analysis is undertaken for such instances as no signals can be generated.

Table S4.17 Comparison of Hyperglycemic Hyperosmolar State Signals with Atypical or Typical Antipsychotic Drugs vs. All Other Drugs as Primary and Secondary Suspect Drugs, 2000-2020^{1,2}.

Antipsychotic Drugs	Count (n =)	PRR (LB, UP)	EBGM (LB, UP)
Olanzapine	92	21.8 (16.7,28.5)	13.3 (11.2,15.8)
Chlorpromazine	4	16.9 (6.3,45.4)	16.6 (8,34.7)
Quetiapine	41	5.5 (3.9,7.8)	4.7 (3.7,6.1)
Ziprasidone	1	N/A	N/A
Haloperidol	2	N/A	N/A
Risperidone	14	N/A	N/A
Pimavanserin	1	N/A	N/A
Aripiprazole	4	0.6 (0.2,1.5)	0.6 (0.3,1.2)
Clozapine	4	0.5 (0.2,1.3)	0.5 (0.2,1)

Abbreviations: LB, Lower bound; UB, Upper Bound; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio; N/A, Not applicable.

¹Data shown by descending order based on PRR signal strength.

²Due to a small sample size (N<3), following standard procedures in pharmacovigilance and signal detection, no analysis is undertaken for such instances as no signals can be generated.

Supplemental Material VI

The following supplemental material provides information on the relationship between atypical antipsychotic drugs (APDs) (Table S.4.19) or sodium glucose co-transporter-2 inhibitors (SGLT-2) used as a positive control (Table S.4.20) and diabetic ketoacidosis adverse drug events (DKA ADE) for the period of 2000 to 2016. This is the same study period for the analysis of trends in antipsychotic drug use (Chapter 5), and the nested-case-control study (Chapter 6) on the association between antipsychotic drugs and diabetic ketoacidosis conducted using Cerner Health Facts®.

Table S4.18. Comparison of Diabetic Ketoacidosis Signals with Atypical Antipsychotic Drugs vs. All Other Drugs as Primary Suspect Drugs Only, 2000-2016¹.

Atypical Antipsychotic Drugs	Count (n =)	PRR	EBGM
Quetiapine	1,172	15.5 (14.3,16.8)	8.4 (8.0,8.8)
Olanzapine	769	11.9 (10.9,13.0)	8.5 (8.0,9.0)
Clozapine	104	1.0 (0.8,1.2)	1.0 (0.8,1.1)
Aripiprazole	52	0.9 (0.7,1.1)	0.9 (0.7,1.1)
Risperidone	81	0.7 (0.6,0.9)	0.7 (0.6,0.9)
Paliperidone	12	0.7 (0.4,1.2)	0.7 (0.4,1.0)
Lurasidone	3	0.7 (0.2,2.3)	0.7 (0.3,1.7)
Ziprasidone	4	0.2 (0.1, 0.5)	0.2 (1.0,0.4)

Abbreviations: LB, Lower bound; UB, Upper Bound; SGLT-2, Sodium Glucose Co-Transporter-2 Inhibitors; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio.

¹Data shown by descending order based on PRR signal strength.

Table S4.19 Comparison of Diabetic Ketoacidosis Signals with Sodium Glucose Co-Transporter-2 Inhibitors Alone or in Mixtures vs. All Other Drugs as Primary Suspect Drugs Only, 2000-2016¹.

SGLT-2 or Mixtures	Count (n =)	PRR (LB, UB)	EBGM (LB, UB)
Canagliflozin	1,411	106.4 (98.5, 115)	45.6 (43.6, 47.6)
Dapagliflozin	588	120.3 (110.2, 131.1)	94.2 (88.1, 100.8)
Empagliflozin	248	51.7 (45.5, 56.5)	41.5 (37.1, 45.8)
Canagliflozin\metformin	54	44.5 (34.2, 57.8)	30.5 (23.7, 37.3)
Empagliflozin\linagliptin	38	41.3 (30.2, 56.6)	26.2 (19.3, 33.2)
Dapagliflozin propanediol\metformin	33	39.5 (28.2, 55.3)	24.3 (17.4, 31.2)
Empagliflozin\metformin	6	48.6 (22.3, 105.8)	10.3 (3.7, 17.0)

Abbreviations: LB, Lower bound; UB, Upper Bound; SGLT-2, Sodium Glucose Co-Transporter-2 Inhibitors; EBGM, Empirical Bayes Geometric Mean; PRR, Proportional reporting ratio.

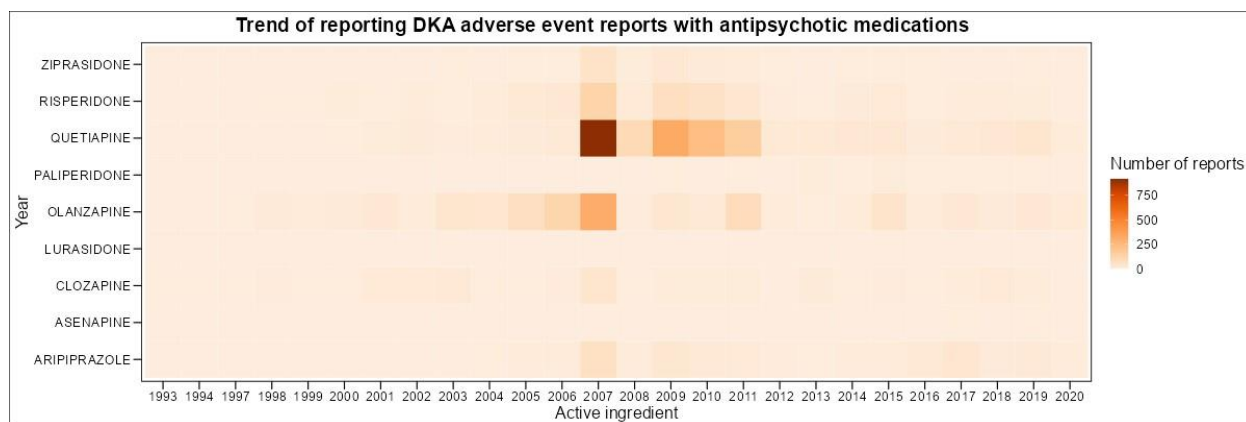
¹Data shown by descending order based on PRR signal strength.

Supplemental Material VII

A heat map displaying aggregate counts of DKA ADEs in relation to atypical APD use is shown for the period 2000-2020.

As shown in the heatmap, quetiapine is the most reported antipsychotic drug associated with diabetic ketoacidosis adverse events, followed by olanzapine.

Figure S4.1. Heat Map for Data Visualization that Displays Aggregated Counts of Diabetic Ketoacidosis Adverse Drug Events in Relation to Atypical Antipsychotic Drug Use, 2000-2020.



CHAPTER 5

PREFACE

This chapter is the fourth manuscript of this thesis that addresses Objective 4. The prevalence of antipsychotic drug use was assessed using the electronic health records in the Cerner Health Facts® database. To understand the patterns of use of these medicines, first-generation antipsychotics, also known as typical antipsychotics, and second-generation antipsychotics, known as atypical antipsychotic drugs, were assessed as a class of drugs or individually in a population of adult inpatients between 2000 and 2016 in the United States.

Contributions

For this analysis, I formulated the study design with the guidance of my supervisor (DK). I performed the analysis and wrote the manuscript. Members from my thesis advisory committee (YC, DM, FM and CG) provided advice on statistical analysis and interpretation of the findings during our meetings. NF and JG provided constructive guidance on the methodological aspect of this analysis. AA provided a critical review of the methodology. DK and NF critically reviewed this manuscript.

Ethics Approval

Ethics approval for this study was received from the Ottawa Health Science Network Research Ethics Board at the Ottawa Hospital, Ottawa, Canada (Appendix A).

Trends in Antipsychotic Drug Use in the United States, 2000-2016

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ABSTRACT

Objective: To evaluate long-term trends in the prevalence of use of atypical and typical antipsychotic drugs (APDs), as classes of drugs and as individual drugs, in the United States (US).

Methods: The Cerner Corporations' Health Facts® database for the period January 1, 2000 and December 31, 2016 was used to analyze the prevalence of APD use for all adult inpatients aged 18 years of age or older who were prescribed at least one antipsychotic agent. Prevalence of APD use was standardized by age, sex, race and census region.

Results: Typical and atypical antipsychotic prescribing patterns in the U.S. differed over the period 2000 to 2016. While the use of atypical APDs increased overall, the use of typical antipsychotic medicine decreased, but remained more prevalent. Overall, haloperidol and prochlorperazine, were two most prescribed antipsychotic medicines throughout the study period. From 2000 to 2011, prochlorperazine and haloperidol were the first and second most prescribed typical APDs, respectively; haloperidol became the most prescribed antipsychotic of this class as of 2012. Quetiapine was the most prescribed atypical antipsychotic medicine,

followed by risperidone and olanzapine until 2014. Olanzapine was the second most prescribed atypical APD as of 2014.

Conclusion: There was a notable decline in the use of atypical antipsychotics medicine between 2005 and 2008, which may be a direct impact of the Food and Drugs Administration warnings and the American Diabetes Association consensus position, but only for a short time. Usage patterns observed in this study supports existing evidence of off-label use of antipsychotic drugs in the United States.

5.1 INTRODUCTION

Antipsychotic drugs (APDs) can be classified as typical or first-generation antipsychotics (FGAs) and atypical or second-generation antipsychotics (SGAs). The discovery of clozapine in the 1950's, the prototype of atypical APDs, led to the expansion and subsequent use of this class of drugs (Meltzer, 2013). However, clozapine was only approved to treat treatment-resistant schizophrenia by the United States Food and Drugs Administration (US FDA) in 1989 (Crilly, 2007). APDs are indicated to treat psychotic disorders, mainly schizophrenia and bipolar disorder (Kane & Correll, 2010; Maher et al., 2011; Meltzer, 2013). They are also used off-label to treat a wide range of neurological and behavioural conditions, including resistant-depression, obsessive-compulsive disorder, autism spectrum disorder, sleep disorders and agitation (Meltzer, 2013). The FDA approved quetiapine to treat schizophrenia and bipolar disorder, and haloperidol to treat schizophrenia, Tourette syndrome and certain behavioral disorders and hyperactivity in children (Rahman & Marwaha, 2021).

There are important differences between these two classes of antipsychotic agents. At clinically effective doses, atypical antipsychotics cause less undesirable extrapyramidal effects

such as dystonia, tardive dyskinesia and neuroleptic malignant syndrome than do typical antipsychotics (Meltzer, 2013). This clinical property makes them a more attractive treatment option than their predecessors. Secondly, the two classes may differ in their mechanisms of action. Typical APDs act mainly as antagonists on dopamine 2 (D2) receptors, while atypical APDs are also antagonists to serotonergic neurotransmitters such as 5-HT_{2A} and have other non-D2 receptor-mediated actions (Kapur & Remington, 2001; Marcus et al. 2010; Meltzer et al. 1989; 2013).

Over the last two decades, it has become evident that APDs, although effective, may cause serious adverse events. Because of this, the US FDA issued a black box warning in 2005 to convey concerns that the use of atypical APDs can cause mortality in elderly patients suffering from dementia. A second black box warning including typical antipsychotics was subsequently issued in 2008. Other drug safety communications ensued, targeting specifically the increased risk of skin reactions or new impulse control problems associated with APDs (FDA, 2005; 2008; 2016; Table 5.1).

In recent years, several studies measured the prevalence of use of APDs in patient populations suffering from major depressive disorder (MDD), Parkinson's disease, and anxiety disorders among those treated in different care settings. (Bower et al. 2018; Herzig et al. 2016; Rhee et al. 2018). Despite safety concerns regarding APD use in older adults and an initial awareness of the risks associated with atypical APDs in those suffering with dementia (Dorsey et al. 2010, Rubino et al. 2020), these agents continue to be used to treat dementia, schizophrenia, and other psychotic disorders in older adults living long-term care settings (Olsson et al. 2015). Furthermore, controlled trials established benefits of atypical APDs to treat insomnia,

obsessive-compulsive disorder, anxiety and other conditions (Maglione et al. 2011; Treméau et al. 2006). However, longitudinal studies are complicated by the characteristics of the condition under treatment and side effects of these medications prompting irregular use by the patient.

There is also increasing evidence that APDs are associated with neurological and metabolic side effects (Lieberman, 2004; Sohler, 2016). In particular, atypical APDs have been associated with obesity, diabetes and dyslipidemia (ADA, 2004; Solmi et al. 2017), and may increase the risk of cardiovascular disease. This led the American Diabetes Association (ADA) to publish consensus positions on the risk of atypical APDs for obesity and diabetes and promoting regular monitoring of the metabolic syndrome (ADA, 2004).

The objective of this study is to establish long-term trends in the prevalence of use APDs by class, and by individual typical or atypical antipsychotics in the U.S. We hypothesized that as the prevalence of use of atypical APDs increased over the years, the use of typical APDs would decrease. We also sought to examine the possible effects of FDA warnings about APDs on prescription patterns in the US population.

5.2 METHODS

This study was approved by the Health Sciences and Science Research Ethics Board at the University of Ottawa, Ottawa, ON, Canada (Reference # H-11-20-5598).

5.2.1 Data Source

Study data was derived from Cerner Corporations' Health Facts® database for the period January 1, 2000 and December 31, 2016. This database captures and stores de-identified, longitudinal electronic health records (EHRs) and includes information on patient demographics,

encounters, diagnoses, prescriptions, procedures, laboratory tests, location of services/patients, hospitals, and billing. Health Facts contains data from over 65 million patients with over 84 million acute admissions, emergency, and ambulatory visits and more than 151 million orders for nearly 4,500 drugs by name and brand. It was previously used in the analysis of trends in medication use in inpatients, including concomitant use of clopidogrel and proton pump inhibitors (Farhat et al. 2019) and antiparkinsonian drugs (Crispo et al. 2015).

5.2.2 Study Population

All encounters with patients 18 years of age or older hospitalized between January 1, 2000 and December 31, 2016 were identified in each quarter for each calendar year in the database. All inpatients meeting these criteria comprised the study cohort.

To ensure that only patients with available pharmacy data in Health Facts were included in the study, eligible encounters had to have at least one recorded medication order. We restricted the analysis to individuals with complete demographic information (age, sex, and race) to allow for direct standardization (Crispo et al. 2015). Demographic data considered including patient age (patient age was stratified into categories: 18-64 years, 65-84 years and ≥ 85 years), sex (male or female), race (Caucasian, African American, Hispanic, or other). Care setting characteristics included census region (Northeast, South, Midwest, or West), urban or rural setting, and teaching status of the health care facility. Since each quarter year was analyzed cross-sectionally, patients with multiple eligible encounters could be included in multiple quarters, but not in the same quarter.

5.2.3 Exposure Assessment

The quarterly and annual prevalence of APD use among adult inpatients who were prescribed at least one antipsychotic drug was standardized by age, sex, race, and census region. APDs approved by the FDA were classified into two classes (Table 5.2).

All drug orders that were dispensed were considered valid and assumed to have been used by the patient. Considering the nature of the conditions for which APDs are prescribed, we assumed they were administered to the patient by hospital health care professionals and as prescribed. The number of inpatients with an antipsychotic drug prescription was calculated quarterly and annually by drug class and for individual drugs from January 1, 2000 to December 31, 2016. Annual data are reported in the main manuscript, with quarterly information presented in Supplemental Material.

5.2.4 Statistical Analysis

The prevalence of antipsychotic use was analyzed cross-sectionally by year and quarter.

Prevalence of use was defined as the ratio of the number of unique patients that received at least one antipsychotic drug during a hospital encounter to the total number of unique patients that met the inclusion criteria during same period. Data from the 2010 American Community Survey (USA Census Bureau) was used to calculate standardized (age, sex, race and census region) annual prevalence of antipsychotic drug use to examine prescribing trends overtime. To better understand patterns of antipsychotic use by class, we stratified our analysis into typical and atypical APDs. All statistical analysis were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Quarterly prevalence for APD use are shown in Supplemental Material (Tables S5.4-S5.6).

5.3 RESULTS

5.3.1 Demographics, Geographic Distribution and Care Setting Characteristics

A total of 5,539,077 adult inpatients with 8,551,028 distinct encounters that met the inclusion criteria were identified. The mean age of subjects was 51.3 years (SD = 19.6) with the majority of inpatients aged between 18 to 64 years (64.8%). Females accounted for 59.8% of inpatients, while males accounted for 40.2%. Of patients with known race, 75.4% were reported as Caucasian, 15.1% as African American and 2.0% as Hispanic, with 7.5% included as other races. The southern and northeast census regions had the highest proportions of patients, accounting for approximately the third of the population at 33.6% and 31.5% each, while the Midwest and western regions of the United States were represented by 18.4% and 16.6% of adult inpatients, respectively. Most patients were admitted to an urban hospital (80.3%) and 67.8% or healthcare organizations were a teaching facility (Table 5.3).

5.3.2 Prevalence of Use of Antipsychotic Drugs by Class

The use of typical antipsychotics decreased during the study period while the use of atypical antipsychotics increased between 2000 and 2016 (Figure 5.1, Supplemental Material Table S5.1). These trends support our hypothesis that as atypical APDs became widely used in recent years, the use of their predecessors decreased overall.

In 2000, the prevalence of use of atypical antipsychotics was 2.6% and fluctuated throughout the study period, increasing to 6.6 in 2016, representing a percent change of 153.6%. An evident increase in this class of agents was observed as of 2004, with slight fluctuations until the end of the study period. A noticeable decrease was observed between 2005 and 2008, which coincides with the FDA's warnings pertaining to their use. Although the use of typical

antipsychotics decreased from 13.1% in 2000 to 8.8% in 2016 (a 32.8% decrease), it is evident from this trend, these drugs continue to be widely used in the US. Decrease in typical APD was observed between 2005 and 2008 and after 2013, but this change was most noticeable between 2001 and 2002.

5.3.3 Prevalence of Use of Typical Antipsychotic Drugs

The annual use of individual typical APDs in the United States between 2000 and 2016 are shown in Figure 5.2 (Supplementary Material Table S5.2). Prochlorperazine and haloperidol represented the first and second most prescribed typical antipsychotic medications until 2011, following which haloperidol became the most prescribed drug of this class.

Although the prevalence of use antipsychotics fluctuated over the study period, overall decrease was observed for most antipsychotics, except for haloperidol. There was a notable decrease in prevalence of use for chlorpromazine (decreasing from 0.5% in 2000 to 0.37% in 2016), droperidol (3.25% in 2000 and 0.33% in 2016) and prochlorperazine (7.08% in 2000 and 3.61% in 2016) across the study period, and a consistent decrease for all three drugs since 2012. In contrast, the use of haloperidol (2.85% in 2000 and 4.69% 2016) increased overall, while the use of fluphenazine (0.11% in 2000 and 0.09% in 2016) remained relatively stable but decreased overall. The prevalence of use of loxapine, perphenazine, thioridazine, thiothixene, and trifluoperazine decreased consistently.

5.3.4 Prevalence of Use of Atypical Antipsychotic Drugs

As shown in Figure 5.3 (Supplementary Material Table S5.3), the prevalence of use of atypical APDs increased overall for individual drugs over the study period, with slight fluctuations.

Quetiapine was the most prescribed drug (increasing from 0.50% in 2000 and 2.94 in 2016); this

was followed by olanzapine (1.13% in 2000 and 1.77% in 2016) and risperidone (1.18% in 2000 and 1.33% in 2016). Risperidone was consistently more commonly used than olanzapine between 2005 and 2013, and olanzapine became the second most prevalent atypical APD as of 2014. The prevalence of use of clozapine remained stable during the study period (0.12% in 2000 and 0.11% in 2016). Other drugs were not available in 2000, but their use increased following market authorization: ziprasidone prevalence increased from 0.12% in 2001 to 0.63% in 2016 and aripiprazole increased from 0.17% in 2003 to 0.91% in 2016.

The patterns of use of atypical APDs as a class demonstrated a notable decrease between 2005 and 2008. Individually, there is a marked decrease in the use of olanzapine, and risperidone beginning in 2005, as well as for quetiapine and ziprasidone beginning in 2006, which coincides with the timing of FDA's black box warnings and the ADA consensus position on atypical APDs. The use of aripiprazole, a newer drug, increased between 2003 and 2009, and has subsequently continued to be used consistently (Figure 5.3, Supplementary Material Table S5.3).

5.4 DISCUSSION

The present study examined trends in use of APD in the US from 2000 to 2016. Atypical APD use increased over the study period, while the use of typical APDs decreased during the same time. Quetiapine was the most prescribed atypical antipsychotic medicine, followed by risperidone and olanzapine. From 2000 to 2011, prochlorperazine and haloperidol were the first and second most prescribed typical antipsychotic agents, respectively; haloperidol became the most prescribed typical ADP as of 2012. Overall, haloperidol remained the most prescribed antipsychotic agent through the study period, followed by prochlorperazine.

A recent study by Su et al. (2020) compared trends in antipsychotic medication use in Asia and the US. Findings from a 5% random sample from the United States Medicare Database showed that quetiapine had the highest incidence (new user) and prevalence rates in the United States (incidence rate (IR): 8.1 – 9.5 per 1,000 patient-years, and prevalence rate (PR): 18.0–18.4 per 1000 subject, 2007 - 2011) in those aged 65 years of age or older. In patients who were younger than 65 years of age, quetiapine continued to have the highest incidence and prevalence rate followed by risperidone (IR: 14.2-18.2 per 1,000 patient-years; PR: 55.7-56.0 per 1,000 subjects, 2007-2011). Weber et al. (2015) examined data from 30 adult psychiatric inpatients who received an APD at The Ohio State University Wexner Medical Center. Quetiapine was the most prescribed atypical APD in inpatients suffering from anxiety disorders in 2013 (56.7%), followed by aripiprazole at 16.7%. Olanzapine and risperidone were both prescribed at a prevalence of 13.3%. In this study, the only typical antipsychotic prescribed to inpatients was haloperidol with a prevalence of 10%. Findings on outpatient settings are further described below.

Herzig *et al.* (2016) evaluated patterns of ADPs use in adult inpatients admitted to an urban academic medical centre in Boston, Massachusetts between August 2012 and August 2013 for conditions, other than primary psychiatric disorders including delirium, anxiety and agitation. Nine percent of total adult admissions (n = 1,537) were prescribed APDs, with 83% receiving atypical antipsychotics and 32% receiving typical antipsychotics. Fifteen percent of patients were exposed to both drug classes. Interestingly, 55% of inpatients taking APDs were started on this medication postadmission. Subgroup analysis by indication of use found that 53% and 12% of initiations of treatment were prescribed for delirium and probable delirium,

respectively. In this analysis, quetiapine and olanzapine were the most prevalent atypical APDs at 3.3% each and haloperidol was the most commonly used typical APD at 2.4%, consistent with our findings that these drugs were among the most commonly used, although the prevalence of use in Health Facts differed. While we did not conduct similar subgroup analyses on reasons for indications, these findings suggest that ADPs continue to be prescribed off-label to treat other conditions such as delirium. Haloperidol and atypical APDs are commonly used to treat this condition, especially in those experience severe conditions (Collet et al. 2018). However, the benefits of using these haloperidol and atypical APDs such as olanzapine, risperidone and quetiapine to treat delirium are not always evident (Nikooie et al. 2020).

A more recent study analyzed the prescription patterns of APDs in adult inpatients admitted to a large community teaching hospital in Georgia between 2016 and 2017 (Phan et al. 2019). Haloperidol was the most used antipsychotic, which corroborates our findings: the authors suggested this could be due to the possible administration of this drug by different routes, and potentially more evidence-based indications for this antipsychotic. Ziprasidone, olanzapine, quetiapine and risperidone were the most frequently used atypical APDs after haloperidol. In our analysis, the prevalence of use of ziprasidone was higher in 2016 as compared to 2000 but decreased consistently as of 2005. Variations in prescribing patterns could be due to different hospital prescribing practices in the US as previously suggested (Herzig et al. 2016). This is also supported by additional evidence of unexplained variation in antipsychotic prescribing rates in nursing homes (Chen et al. 2010; Cioltan et al. 2017).

Although we did not analyze the use of APDs by age, recent literature supports the safety profile of quetiapine prescribed to the elderly, generally suffering from higher rates of

dementia and Parkinson's disease (Kales et al. 2011; 2012). Haloperidol, one of the most studied and frequently used ADPs, continues to be widely used worldwide. It is also effective in treating delirium due to fewer anticholinergic effects (Markowitz & Narasimhan, 2008), which may partly explain its consistent use in the United States. In another study, Kim et al. (2018) analyzed patterns of antipsychotic use in older adult inpatients (65 years or older) using data from the Premier Healthcare Database, which contains information from over 700 hospitals accounting for 20% of all hospitalizations in the US. The authors suggested that antipsychotic medications were often prescribed off-label for postoperative delirium. While the use of haloperidol and risperidone declined between 2004 and 2014, the use of quetiapine tripled over this same period.

Other studies focused on the prevalence of antipsychotic use in outpatient settings. While this is not within the scope of our analysis, differences in usage patterns may be attributed to how different care settings operate. Dennis and colleagues (2020) reported that prevalence of combined antipsychotic use (atypical and typical) in US adults was 1.6% (n= 320) over a five year period from 2013 to 2018 using pooled data from the National Health and Nutrition Examination Survey (NHANES) of non-institutionalized residents. This is consistent with an estimated prevalence of 1.73% in a previous outpatient setting analysis (Olfson et al. 2012). Aripiprazole and quetiapine accounted for 40.8% and 32.3% of prescriptions, followed by risperidone at 13.2%, while haloperidol and prochlorperazine were prescribed to 1.1% and 7.0% of outpatients, respectively, in an academic psychiatric setting in 2013 (Weber et al. 2015). Rhee et al. (2018) examined rates of APDs prescribing between 2006 and 2015 in adults with MDD in office-based outpatient settings. APD prescriptions initially increased between 2006

and 2009 (18.5% to 24.9%) and then decreased to 18.9% in 2015 and outpatient visits of patients aged 75 years of older declined significantly over the 10 year study period, reflecting FDA concerns about adverse events of antipsychotics in the elderly. Quetiapine, aripiprazole, risperidone were the most prescribed atypical APDs at 36%, 27.7% and 22% throughout the study period. Haloperidol was prescribed to a significantly lesser extent, but remained the most commonly prescribed typical antipsychotic medicine. Bower et al. (2018) measured the prevalence of patients with Parkinson Diseases taking antipsychotics in Olmsted County, Minnesota; of the 296 patients examined on January 1, 2006, the overall prevalence of antipsychotic use was 9.8%, with quetiapine being the most prevalent APD used on that day.

5.4.1 Strengths

This study evaluates the prevalence of APD use in a large inpatient cohort derived from multiple treatment centres spanning a 16-year period representing all four-census regions of the US population. To our knowledge, this is the largest study exploring trends in APDs use by class and by individual drugs. Results are standardized for age, sex, race and census region to reflect the demographics of the US population. Our analysis is consistent with findings from previous studies that were more limited in scope and population size.

5.4.2 Limitations

Our study is subject to several limitations. First, the study was restricted to inpatients who were prescribed at least one antipsychotic drug. As such, we could not draw direct comparisons between inpatient and outpatient settings. Second, we did not consider the concomitant use of other medications – other psychotropic drugs– which could influence the prescription of antipsychotics at the individual patient level. Lastly, there is a lack of

understanding of antipsychotic prescription practices within US hospitals, which could have been influenced by clinical preference, drug pricing and availability.

5.5 CONCLUSION

As expected, typical and atypical antipsychotic prescribing patterns in the United States differed over the period 2000 to 2016. There was a notable decline in the use of atypical antipsychotics between 2005 and 2007, which may be a direct impact of FDA warnings and the ADA consensus position, but only for a short time. Usage patterns observed in this study supports existing evidence of off-label use of antipsychotic drugs in the United States.

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TABLES

Table 5.1. List of Black Box Warnings and Safety Communications Issued by the Food and Drugs Administration Related to Antipsychotic Drugs¹.

Year	Type of Warning	Antipsychotic Medicine	Description
2005	Black Box Warning	Atypical: •Aripiprazole •Olanzapine •Olanzapine fluoxetine •Quetiapine •Risperidone •Clozapine •Ziprasidone	•Increased mortality in the elderly
2008	Black Box Warning	All APDs: •Typical and atypical	•Increased mortality in elderly patients with dementia-related psychosis
2011	Drug Safety Communication	All APDs: •Typical and atypical	•Drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns
2011	Drug Safety Communication	Atypical: •Asenapine maleate	•Serious allergic reactions
2014	Drug Safety Communication	Atypical: •Ziprasidone	•Associated with rare but potentially fatal skin reactions
2015	Drug Safety Communication	Atypical: •Clozapine	•FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines
2016	Drug Safety Communication	Atypical: •Aripiprazole	•New impulse-control problems to gamble, binge eat, shop, and have sex
2016	Drug Safety Communication	Atypical: •Olanzapine	•Rare but serious skin reactions

Abbreviation: APD, Antipsychotic drug.

¹Source: (FDA, 2005;2008; 2016).

Table 5.2. List of and Year of Approval of Atypical (n = 13) and Typical (n = 12) Antipsychotic Drugs approved by the Food and Drugs Administration in the United States¹.

Atypical APDs (Year of Approval)	Typical APDs (Year of Approval)
Aripiprazole (2002)	Chlorpromazine (1954)
Asenapine (2009)	Droperidol (1963)
Brexipiprazole (2015)	Fluphenazine (1961)
Capiprazine (2015)	Haloperidol (1976)
Clozapine (1989)	Loxapine (2012)
Iloperidone (2009)	Molindone (1974)
Lurasidone (2010)	Perphenazine (1961)
Olanzapine (1996)	Pimozide (1985)
Paliperidone (2006)	Prochlorperazine (1956)
Pimavanserin (2016)	Thioridazine (1964)
Quetiapine (1997)	Thiothixene (1967)
Risperidone (1993)	Trifluoperazine (1963)
Ziprasidone (2001)	

¹(FDA, 2022)

Table 5.3. Characteristics of Adults Inpatients Included in the Study (n = 5,539,077)¹

Characteristic	Unique Patients (Counts n =)	Proportion (%)
Sex		
Female	3,311,071	59.8
Male	2,228,006	40.2
Age (years)		
18 to 64	3,589,269	64.8
65 to 84	1,553,011	28.0
≥ 85	396,797	7.2
Race		
African American	835,291	15.1
Caucasian	4,177,620	75.4
Hispanic	111,769	2.0
Other	414,397	7.5
Census Region		
Midwest	1,018,853	18.4
Northeast	1,741,829	31.5
South	1,859,425	33.6
West	918,970	16.6
Hospital Status		
Rural	1,089,222	19.7
Urban	4,449,855	80.3
Teaching Status		
Teaching	3,244,633	67.8
Non-Teaching	1,538,575	32.2
Missing	755,869	13.6

¹Other Race includes Asian, biracial, Pacific Islander, Middle Eastern and Native American

FIGURES

Figure 5.1. Standardized Annual Prevalence of Use of Antipsychotic Drugs by Class in Adult Inpatients, 2000-2016, United States.

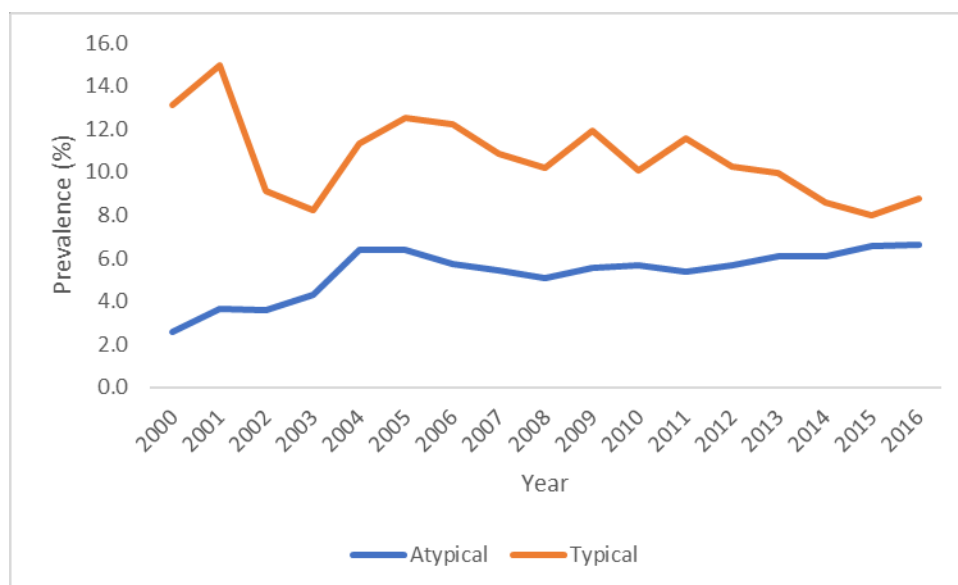
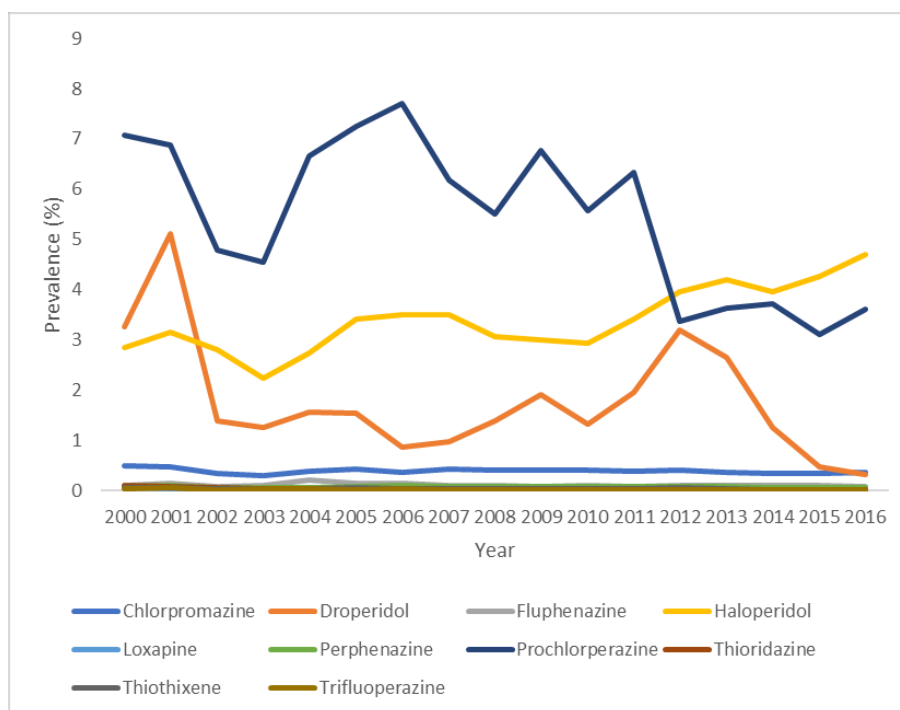
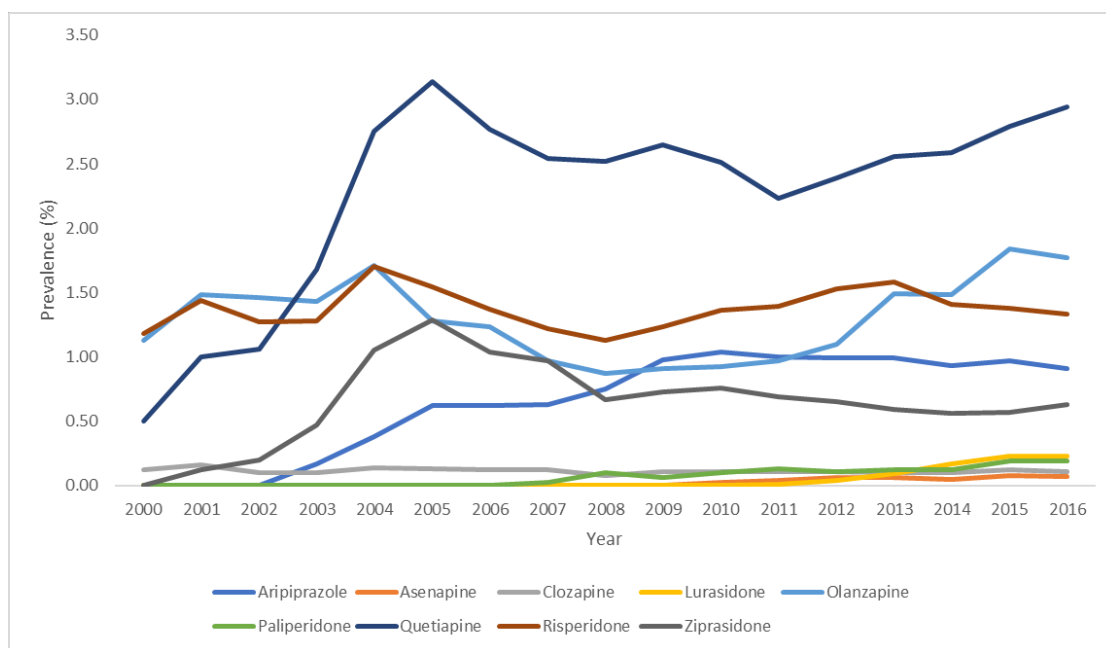


Figure 5.2. Standardized Annual Prevalence of Use of Individual Typical Antipsychotic Drugs in Adult Inpatients, 2000-2016, United States¹.



¹Molindone and pimozide did not have any prevalence of use and are not included.

Figure 5.3. Standardized Annual Prevalence of Use of Individual Atypical Antipsychotic Drugs in Adult Inpatients, 2000-2016, United States¹.



¹Brexipiprazole, caripiprazine and pimavanserine did not have any prevalence of use and are not included.

SUPPLEMENTAL MATERIAL S5

The objective of the Supplemental Material is to provide a more fulsome overview of the annual and quarterly prevalence of use of antipsychotic drugs (APDs) by class and Individual drugs in adult inpatients (≥ 18 years of age). This includes:

- Standardized annual prevalence of use of APDs by class (Table S5.1.).
- Standardized prevalence of use of atypical and typical APDs (Tables S5.2. and S5.3.)
- Standardized quarterly prevalence of use of APDs by class (Table S5.4.)
- Standardized quarterly prevalence of use of atypical and typical APDs (Tables S5.5. and S5.6).

Table S5.1. Annual Prevalence of Use of Atypical and Typical Antipsychotic Drugs by Class, 2000-2016, United States.

Year	Atypical Antipsychotic Drugs	Typical Antipsychotic Drugs
2000	2.6	13.1
2001	3.7	15.0
2002	3.6	9.1
2003	4.3	8.2
2004	6.4	11.4
2005	6.4	12.5
2006	5.7	12.3
2007	5.4	10.9
2008	5.1	10.2
2009	5.5	11.9
2010	5.7	10.1
2011	5.4	11.6
2012	5.7	10.3
2013	6.1	10.0
2014	6.1	8.6
2015	6.6	8.0
2016	6.6	8.8

Table S5.2. Standardized Annual Prevalence of Use of individual Typical Antipsychotic Drugs in Adult Inpatients, 2000-2016, United States.

Year	Chlorpromazine	Droperidol	Fluphenazine	Haloperidol	Loxapine	Molindone	Perphenazine	Pimozide	Prochlorperazine	Thioridazine	Thiothixene	Trifluoperazine
2000	0.5	3.27	0.11	2.85	0.06	0	0.08	0.01	7.08	0.11	0.05	0.03
2001	0.47	5.11	0.15	3.16	0.03	0	0.1	0	6.87	0.09	0.06	0.05
2002	0.34	1.39	0.09	2.8	0.03	0	0.06	0	4.78	0.05	0.03	0.02
2003	0.3	1.25	0.11	2.23	0.03	0	0.06	0	4.55	0.03	0.04	0.03
2004	0.39	1.57	0.22	2.74	0.02	0.01	0.05	0	6.65	0.04	0.03	0.03
2005	0.43	1.54	0.15	3.42	0.08	0.01	0.07	0	7.25	0.03	0.05	0.02
2006	0.37	0.87	0.14	3.51	0.02	0	0.1	0	7.7	0.02	0.03	0.03
2007	0.42	0.98	0.1	3.5	0.01	0	0.07	0	6.18	0.02	0.04	0.02
2008	0.4	1.39	0.1	3.06	0.02	0	0.08	0	5.5	0.02	0.03	0.02
2009	0.4	1.92	0.09	3	0.02	0	0.08	0	6.77	0.01	0.03	0.02
2010	0.41	1.33	0.1	2.93	0.02	0	0.07	0	5.57	0.01	0.04	0.01
2011	0.39	1.95	0.09	3.41	0.02	0	0.09	0	6.33	0.01	0.04	0.02
2012	0.4	3.2	0.1	3.95	0.02	0	0.08	0	3.38	0.01	0.05	0.01
2013	0.37	2.66	0.1	4.2	0.04	0	0.07	0	3.64	0.01	0.04	0.02
2014	0.35	1.26	0.11	3.95	0.03	0	0.05	0	3.72	0.01	0.02	0.02
2015	0.34	0.48	0.11	4.26	0.03	0	0.05	0	3.11	0.01	0.02	0.01
2016	0.37	0.33	0.09	4.69	0.02	0	0.05	0	3.61	0.01	0.01	0.01

Table S5.3. Standardized Annual Prevalence of Use of individual Atypical Antipsychotic Drugs in Adult Inpatients, 2000-2016, United States.

Year	Aripiprazole	Asenapine	Brexipiprazole	Caripiprazine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Pimavanserin	Quetiapine	Risperidone	Ziprasidone
2000	0	0	0	0	0.12	0	0	1.13	0	0	0.5	1.18	0
2001	0	0	0	0	0.16	0	0	1.48	0	0	1	1.44	0.12
2002	0	0	0	0	0.1	0	0	1.46	0	0	1.06	1.27	0.2
2003	0.17	0	0	0	0.1	0	0	1.43	0	0	1.68	1.28	0.47
2004	0.38	0	0	0	0.14	0	0	1.71	0	0	2.75	1.7	1.05
2005	0.62	0	0	0	0.13	0	0	1.28	0	0	3.14	1.54	1.29
2006	0.62	0	0	0	0.12	0	0	1.23	0	0	2.77	1.37	1.04
2007	0.63	0	0	0	0.12	0	0	0.97	0.02	0	2.54	1.22	0.97
2008	0.75	0	0	0	0.08	0	0	0.87	0.1	0	2.52	1.13	0.67
2009	0.98	0	0	0	0.11	0	0	0.91	0.06	0	2.65	1.23	0.73
2010	1.04	0.02	0	0	0.11	0	0	0.92	0.1	0	2.51	1.36	0.76
2011	1	0.04	0	0	0.11	0	0.01	0.97	0.13	0	2.23	1.39	0.69
2012	0.99	0.06	0	0	0.11	0.01	0.04	1.1	0.11	0	2.39	1.53	0.65
2013	0.99	0.06	0	0	0.1	0	0.09	1.49	0.12	0	2.56	1.58	0.59
2014	0.93	0.05	0	0	0.1	0.01	0.17	1.48	0.12	0	2.59	1.41	0.56
2015	0.97	0.08	0	0	0.12	0	0.23	1.84	0.19	0	2.79	1.38	0.57
2016	0.91	0.07	0	0	0.11	0	0.23	1.77	0.19	0	2.94	1.33	0.63

Table S5.4. Standardized Quarterly Prevalence of Use of Atypical and Typical Antipsychotic Drugs by Class in Adult Inpatients, 2000-2016, United States.

Quarter	Atypical Antipsychotic Drugs	Typical Antipsychotic Drugs
2000-Q1	2.25	11.27
2000-Q2	2.63	13.42
2000-Q3	2.52	13.27
2000-Q4	2.77	13.26
2001-Q1	3.51	14.23
2001-Q2	3.78	14.51
2001-Q3	3.55	16.34
2001-Q4	3.74	15
2002-Q1	3.74	12.08
2002-Q2	3.65	8.66
2002-Q3	3.53	7.73
2002-Q4	3.47	8.09
2003-Q1	3.61	7.96
2003-Q2	4.12	8.2
2003-Q3	5.02	8.43
2003-Q4	5.01	8.48
2004-Q1	5.77	9.26
2004-Q2	5.91	9.02
2004-Q3	5.98	11.53
2004-Q4	7.36	13.98
2005-Q1	7.35	12.12
2005-Q2	6.38	12.2
2005-Q3	6.06	12.78
2005-Q4	6.02	12.95
2006-Q1	5.97	12.07
2006-Q2	5.74	12.93
2006-Q3	5.61	12.35
2006-Q4	5.66	11.76
2007-Q1	5.27	10.92
2007-Q2	5.59	10.34
2007-Q3	5.15	10.33
2007-Q4	5.61	11.69
2008-Q1	5.41	10.12
2008-Q2	5.24	10.67
2008-Q3	4.99	10.27
2008-Q4	4.81	9.82

Table S5.4. Standardized Quarterly Prevalence of Use of Atypical and Typical Antipsychotic Drugs by Class in Adult Inpatients, 2000-2016, United States (cont.).

Quarter	Atypical Antipsychotic Drugs	Typical Antipsychotic Drugs
2009-Q1	5.41	11.29
2009-Q2	5.68	12.52
2009-Q3	5.62	12.48
2009-Q4	5.41	11.33
2010-Q1	5.87	10.27
2010-Q2	5.7	10.37
2010-Q3	5.78	9.68
2010-Q4	5.43	9.83
2011-Q1	5.32	11.56
2011-Q2	5.32	11.94
2011-Q3	5.7	11.83
2011-Q4	5.18	11.11
2012-Q1	5.52	11.09
2012-Q2	5.43	10.16
2012-Q3	5.88	9.51
2012-Q4	5.84	10.27
2013-Q1	5.95	9.91
2013-Q2	6.2	10.5
2013-Q3	6.23	10.27
2013-Q4	5.91	9.22
2014-Q1	6.05	8.79
2014-Q2	6.06	8.32
2014-Q3	6.11	8.61
2014-Q4	6.15	8.76
2015-Q1	6.61	8.4
2015-Q2	6.46	7.81
2015-Q3	6.82	8
2015-Q4	6.45	7.92
2016-Q1	6.67	8.04
2016-Q2	6.76	8.76
2016-Q3	6.66	8.61
2016-Q4	6.41	9.64

Table S5.5. Standardized Quarterly Prevalence of Use of Individual Typical Antipsychotic Drugs in Adult Inpatients, 2000-2016, United States.

Quarter	Chlorpromazine	Droperidol	Fluphenazine	Haloperidol	Loxapine	Molindone	Perphenazine	Pimozide	Prochlorperazine	Thioridazine	Thiothixene	Trifluoperazine
2000-Q1	0.64	2.05	0.07	3.2	0	0	0.05	0	5.93	0.06	0.03	0.06
2000-Q2	0.51	3.42	0.13	3.21	0.09	0	0.11	0.01	6.83	0.19	0.06	0.02
2000-Q3	0.46	3.01	0.12	2.65	0.07	0.01	0.07	0.01	7.79	0.11	0.07	0.02
2000-Q4	0.49	3.76	0.09	2.6	0.03	0	0.07	0	7.03	0.06	0.04	0.04
2001-Q1	0.53	4.11	0.21	3.14	0.02	0.01	0.11	0	6.94	0.12	0.06	0.04
2001-Q2	0.42	4.77	0.17	3.06	0.02	0	0.12	0	6.89	0.09	0.06	0.07
2001-Q3	0.51	5.91	0.1	3.41	0.04	0	0.08	0	7.42	0.07	0.05	0.05
2001-Q4	0.43	5.98	0.08	3.07	0.02	0	0.09	0	6.19	0.07	0.05	0.04
2002-Q1	0.47	3.49	0.1	3.13	0.04	0	0.05	0	5.53	0.07	0.04	0.03
2002-Q2	0.38	0.58	0.08	2.88	0.02	0	0.06	0	4.92	0.03	0.05	0.03
2002-Q3	0.24	0.77	0.1	2.54	0.04	0	0.05	0	4.28	0.04	0.02	0.02
2002-Q4	0.3	0.7	0.09	2.69	0.02	0	0.09	0	4.46	0.03	0.01	0.01
2003-Q1	0.32	0.96	0.11	2.63	0.01	0	0.03	0	4.24	0.02	0.04	0.02
2003-Q2	0.31	1.34	0.09	2.15	0.04	0	0.07	0	4.52	0.04	0.05	0.03
2003-Q3	0.3	1.54	0.16	1.9	0.04	0	0.09	0	4.68	0.05	0.05	0.06
2003-Q4	0.27	1.36	0.08	1.95	0.05	0.02	0.07	0	5.01	0.03	0.03	0.01
2004-Q1	0.39	0.97	0.29	2.46	0	0	0.08	0	5.33	0.05	0.02	0.03
2004-Q2	0.39	0.2	0.17	2.65	0.02	0	0.06	0.01	5.72	0.03	0.03	0.04
2004-Q3	0.34	1.33	0.25	2.45	0.02	0	0.05	0	7.52	0.02	0.02	0.01
2004-Q4	0.41	2.97	0.19	3.16	0.04	0.02	0.04	0	7.43	0.06	0.05	0.04
2005-Q1	0.39	1.59	0.19	3.27	0.05	0.01	0.08	0	6.93	0.01	0.03	0.04
2005-Q2	0.45	1.49	0.21	3.27	0.19	0	0.07	0	6.89	0.03	0.07	0.02
2005-Q3	0.45	1.69	0.09	3.4	0.05	0	0.06	0	7.45	0.05	0.05	0.01
2005-Q4	0.42	1.39	0.11	3.71	0.02	0.01	0.06	0	7.71	0.04	0.06	0.03
2006-Q1	0.41	1.48	0.15	3.46	0.02	0	0.1	0.01	6.83	0.01	0.03	0.03
2006-Q2	0.36	0.87	0.13	3.65	0.03	0	0.08	0	8.32	0.01	0.03	0.02
2006-Q3	0.34	0.66	0.13	3.54	0.01	0	0.09	0	8.05	0.03	0.03	0.03
2006-Q4	0.37	0.63	0.14	3.42	0.02	0	0.12	0.01	7.53	0.02	0.02	0.03

Table S5.5. Standardized Quarterly Prevalence of Use of Individual Typical Antipsychotic Drugs in Adult Inpatients, 2000-2016, United States (cont.).

Quarter	Chlorpromazine	Droperidol	Fluphenazine	Haloperidol	Loxapine	Molindone	Perphenazine	Pimozide	Prochlorperazine	Thioridazine	Thiothixene	Trifluoperazine
2007-Q1	0.42	0.64	0.09	3.07	0.01	0.01	0.06	0	7.01	0.02	0.03	0.01
2007-Q2	0.38	0.73	0.09	3.51	0.02	0	0.08	0	5.97	0.02	0.04	0.02
2007-Q3	0.4	0.91	0.11	3.67	0	0	0.07	0	5.57	0.03	0.03	0.02
2007-Q4	0.45	1.51	0.11	3.64	0.02	0	0.05	0	6.3	0.03	0.07	0.02
2008-Q1	0.42	1.4	0.13	3.31	0.02	0	0.09	0	5.14	0.02	0.04	0.02
2008-Q2	0.44	1.34	0.11	3.42	0.02	0	0.07	0	5.62	0.02	0.04	0.02
2008-Q3	0.36	1.43	0.08	3.01	0.01	0	0.08	0	5.61	0.02	0.03	0.02
2008-Q4	0.38	1.37	0.08	2.62	0.02	0	0.08	0	5.58	0.02	0.02	0.02
2009-Q1	0.43	1.69	0.08	2.96	0.01	0	0.08	0	6.37	0.02	0.04	0.02
2009-Q2	0.42	2.04	0.09	3.03	0.03	0	0.06	0	7.24	0.01	0.04	0.03
2009-Q3	0.36	2.12	0.09	3.12	0.02	0	0.09	0	7.04	0.01	0.02	0.01
2009-Q4	0.41	1.84	0.09	2.87	0.01	0	0.07	0	6.43	0.01	0.03	0.02
2010-Q1	0.44	1.44	0.1	2.99	0.02	0	0.07	0	5.6	0.01	0.06	0.01
2010-Q2	0.44	1.52	0.1	3.14	0.03	0	0.06	0	5.47	0.01	0.03	0.01
2010-Q3	0.36	1.14	0.09	2.86	0	0	0.08	0	5.46	0.02	0.04	0.01
2010-Q4	0.38	1.18	0.1	2.67	0.01	0	0.07	0	5.78	0.01	0.04	0.02
2011-Q1	0.45	1.52	0.07	2.96	0.03	0	0.06	0	6.9	0.01	0.03	0.01
2011-Q2	0.37	1.52	0.08	3.37	0.02	0	0.09	0	6.94	0.01	0.03	0.02
2011-Q3	0.41	1.81	0.11	3.78	0.02	0	0.11	0	6.3	0.02	0.06	0.02
2011-Q4	0.35	2.84	0.09	3.47	0.02	0	0.09	0	5.3	0.01	0.05	0.02
2012-Q1	0.36	3.12	0.1	3.7	0.02	0	0.09	0	4.65	0.02	0.04	0.02
2012-Q2	0.41	2.85	0.1	4.1	0.02	0	0.08	0	3.24	0.01	0.05	0.01
2012-Q3	0.4	3.04	0.09	3.86	0.02	0	0.09	0	2.86	0.01	0.05	0.01
2012-Q4	0.42	3.74	0.1	4.12	0.03	0	0.09	0	2.78	0	0.06	0.02
2013-Q1	0.4	3.27	0.1	4.16	0.03	0	0.1	0	2.77	0.01	0.04	0.02
2013-Q2	0.38	2.94	0.11	4.61	0.03	0	0.08	0	3.64	0.02	0.04	0.02
2013-Q3	0.4	2.56	0.09	4.31	0.05	0	0.07	0	3.97	0.01	0.03	0.02
2013-Q4	0.3	2.04	0.09	3.8	0.03	0	0.05	0	3.98	0.01	0.04	0.01

Table S5.5. Standardized Quarterly Prevalence of Use of Individual Typical Antipsychotic Drugs in Adult Inpatients, 2000-2016, United States (cont.).

Quarter	Chlorpromazine	Droperidol	Fluphenazine	Haloperidol	Loxapine	Molindone	Perphenazine	Pimozide	Prochlorperazine	Thioridazine	Thiothixene	Trifluoperazine
2014-Q1	0.33	1.57	0.14	3.95	0.03	0	0.05	0	3.67	0.01	0.02	0.03
2014-Q2	0.32	1.4	0.11	3.89	0.02	0	0.05	0	3.48	0.01	0.01	0.01
2014-Q3	0.37	1.33	0.09	3.95	0.02	0	0.05	0	3.75	0.01	0.02	0.01
2014-Q4	0.38	0.76	0.11	4	0.03	0	0.04	0	3.96	0.01	0.02	0.01
2015-Q1	0.38	0.55	0.12	4.24	0.04	0	0.05	0	3.46	0.01	0.02	0.01
2015-Q2	0.35	0.53	0.1	4.28	0.03	0	0.05	0	2.8	0.01	0.02	0.01
2015-Q3	0.3	0.46	0.12	4.2	0.04	0	0.05	0	3.14	0.01	0.02	0.01
2015-Q4	0.34	0.36	0.11	4.33	0.02	0	0.06	0	3.01	0.01	0.02	0.01
2016-Q1	0.38	0.37	0.11	4.61	0.01	0	0.06	0	2.85	0.01	0.01	0.01
2016-Q2	0.36	0.34	0.11	4.85	0.02	0	0.05	0	3.42	0.01	0.01	0
2016-Q3	0.4	0.29	0.08	4.54	0.03	0	0.05	0	3.56	0.01	0.01	0.01
2016-Q4	0.35	0.33	0.07	4.77	0.02	0	0.04	0	4.51	0.01	0.01	0.01

Table S5.6. Standardized Quarterly Prevalence of Use of Individual Atypical Antipsychotic Drugs in Adult Inpatients, 2000-2016, United States.

Quarter	Aripiprazole	Asenapine	Brexipiprazole	Caripiprazine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Pimavanserin	Quetiapine	Risperidone	Ziprasidone
2000-Q1	0	0	0	0	0.02	0	0	0.9	0	0	0.37	1.18	0
2000-Q2	0	0	0	0	0.18	0	0	1.13	0	0	0.43	1.28	0
2000-Q3	0	0	0	0	0.11	0	0	1.13	0	0	0.42	1.14	0
2000-Q4	0	0	0	0	0.09	0	0	1.2	0	0	0.67	1.13	0
2001-Q1	0	0	0	0	0.16	0	0	1.44	0	0	1	1.43	0.01
2001-Q2	0	0	0	0	0.19	0	0	1.57	0	0	1.01	1.48	0.11
2001-Q3	0	0	0	0	0.19	0	0	1.3	0	0	0.92	1.46	0.19
2001-Q4	0	0	0	0	0.08	0	0	1.58	0	0	1.07	1.37	0.19
2002-Q1	0	0	0	0	0.1	0	0	1.63	0	0	1	1.33	0.15
2002-Q2	0	0	0	0	0.07	0	0	1.47	0	0	1.02	1.38	0.2
2002-Q3	0	0	0	0	0.07	0	0	1.32	0	0	1.12	1.25	0.22
2002-Q4	0	0	0	0	0.16	0	0	1.43	0	0	1.07	1.14	0.23
2003-Q1	0.04	0	0	0	0.1	0	0	1.21	0	0	1.3	1.21	0.26
2003-Q2	0.16	0	0	0	0.1	0	0	1.31	0	0	1.72	1.24	0.38
2003-Q3	0.29	0	0	0	0.11	0	0	1.57	0	0	2.08	1.44	0.76
2003-Q4	0.29	0	0	0	0.12	0	0	1.88	0	0	1.93	1.3	0.68
2004-Q1	0.25	0	0	0	0.16	0	0	2	0	0	2.18	1.49	0.73
2004-Q2	0.27	0	0	0	0.13	0	0	1.85	0	0	2.57	1.61	0.85
2004-Q3	0.31	0	0	0	0.13	0	0	1.54	0	0	2.66	1.68	0.91
2004-Q4	0.58	0	0	0	0.13	0	0	1.57	0	0	3.29	1.88	1.48
2005-Q1	0.61	0	0	0	0.1	0	0	1.65	0	0	3.38	1.81	1.41
2005-Q2	0.57	0	0	0	0.16	0	0	1.31	0	0	3.19	1.49	1.26
2005-Q3	0.56	0	0	0	0.12	0	0	1.13	0	0	3.02	1.46	1.26
2005-Q4	0.75	0	0	0	0.12	0	0	1.05	0	0	3.02	1.42	1.26

Table S5.6. Standardized Quarterly Prevalence of Use of Individual Atypical Antipsychotic Drugs in Adult Inpatients, 2000-2016, United States (cont.).

Quarter	Aripiprazole	Asenapine	Brexipiprazole	Caripiprazine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Pimavanserin	Quetiapine	Risperidone	Ziprasidone
2006-Q1	0.66	0	0	0	0.13	0	0	1.16	0	0	3.1	1.36	1.1
2006-Q2	0.61	0	0	0	0.1	0	0	1.02	0	0	2.98	1.43	1.07
2006-Q3	0.62	0	0	0	0.1	0	0	1.28	0	0	2.61	1.37	1.01
2006-Q4	0.6	0	0	0	0.14	0	0	1.41	0	0	2.51	1.33	1.01
2007-Q1	0.5	0	0	0	0.14	0	0	1.05	0	0	2.53	1.17	0.95
2007-Q2	0.62	0	0	0	0.12	0	0	1.06	0	0	2.72	1.17	1.09
2007-Q3	0.6	0	0	0	0.1	0	0	0.88	0.02	0	2.35	1.19	0.9
2007-Q4	0.76	0	0	0	0.12	0	0	0.93	0.04	0	2.54	1.31	0.94
2008-Q1	0.69	0	0	0	0.07	0	0	0.97	0.1	0	2.68	1.29	0.72
2008-Q2	0.77	0	0	0	0.09	0	0	0.94	0.11	0	2.61	1.13	0.72
2008-Q3	0.74	0	0	0	0.1	0	0	0.8	0.1	0	2.49	1.1	0.62
2008-Q4	0.8	0	0	0	0.06	0	0	0.81	0.08	0	2.33	1.04	0.62
2009-Q1	0.95	0	0	0	0.11	0	0	0.77	0.08	0	2.63	1.25	0.75
2009-Q2	1	0	0	0	0.11	0	0	0.93	0.07	0	2.74	1.29	0.75
2009-Q3	0.96	0	0	0	0.12	0	0	0.96	0.04	0	2.69	1.23	0.7
2009-Q4	0.99	0	0	0	0.11	0	0	0.95	0.05	0	2.55	1.15	0.71
2010-Q1	1.06	0.02	0	0	0.11	0	0	0.95	0.09	0	2.6	1.34	0.82
2010-Q2	1.06	0.03	0	0	0.11	0	0	0.88	0.09	0	2.56	1.35	0.76
2010-Q3	1.04	0.02	0	0	0.11	0.01	0	0.91	0.11	0	2.52	1.45	0.71
2010-Q4	1	0.01	0	0	0.12	0.01	0	0.93	0.13	0	2.31	1.29	0.76
2011-Q1	0.99	0.02	0	0	0.1	0	0	0.93	0.11	0	2.35	1.2	0.71
2011-Q2	1.06	0.04	0	0	0.1	0	0	0.92	0.12	0	2.22	1.26	0.69
2011-Q3	1.05	0.07	0	0	0.14	0	0.01	1.01	0.15	0	2.29	1.58	0.73
2011-Q4	0.9	0.04	0	0	0.09	0	0.02	1.01	0.14	0	2.1	1.47	0.62

Table S5.6. Standardized Quarterly Prevalence of Use of Individual Atypical Antipsychotic Drugs in Adult Inpatients, 2000-2016, US (cont.).

Quarter	Aripiprazole	Asenapine	Brexipiprazole	Caripiprazine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Pimavanserin	Quetiapine	Risperidone	Ziprasidone
2012-Q1	0.97	0.03	0	0	0.1	0.01	0.01	0.98	0.11	0	2.29	1.64	0.64
2012-Q2	0.99	0.06	0	0	0.13	0.01	0.03	1	0.14	0	2.19	1.43	0.67
2012-Q3	1.01	0.07	0	0	0.11	0	0.06	1.2	0.09	0	2.51	1.58	0.6
2012-Q4	0.99	0.08	0	0	0.12	0.01	0.05	1.2	0.11	0	2.55	1.49	0.67
2013-Q1	0.99	0.04	0	0	0.12	0	0.06	1.45	0.13	0	2.46	1.58	0.6
2013-Q2	1.04	0.07	0	0	0.1	0	0.07	1.43	0.13	0	2.57	1.67	0.62
2013-Q3	1.01	0.06	0	0	0.09	0	0.1	1.66	0.13	0	2.59	1.57	0.58
2013-Q4	0.93	0.06	0	0	0.09	0	0.1	1.42	0.11	0	2.58	1.51	0.56
2014-Q1	0.89	0.02	0	0	0.1	0.01	0.12	1.45	0.13	0	2.56	1.52	0.55
2014-Q2	0.91	0.04	0	0	0.09	0.01	0.17	1.48	0.09	0	2.58	1.45	0.56
2014-Q3	0.94	0.06	0	0	0.1	0.01	0.19	1.44	0.12	0	2.65	1.32	0.56
2014-Q4	0.97	0.07	0	0	0.09	0	0.2	1.55	0.13	0	2.57	1.37	0.57
2015-Q1	0.97	0.05	0	0	0.12	0	0.21	1.76	0.17	0	2.81	1.44	0.53
2015-Q2	1.01	0.09	0	0	0.13	0	0.22	1.76	0.18	0	2.69	1.38	0.54
2015-Q3	0.98	0.08	0	0	0.11	0	0.26	2.05	0.21	0	2.82	1.36	0.6
2015-Q4	0.91	0.1	0	0	0.1	0	0.22	1.81	0.18	0	2.86	1.35	0.59
2016-Q1	0.93	0.05	0	0	0.12	0	0.22	1.8	0.16	0	2.94	1.38	0.58
2016-Q2	0.93	0.07	0	0	0.1	0	0.24	1.92	0.22	0	2.87	1.36	0.65
2016-Q3	0.89	0.07	0	0	0.12	0	0.23	1.78	0.2	0	2.96	1.33	0.7
2016-Q4	0.88	0.06	0	0	0.11	0	0.25	1.59	0.17	0	2.97	1.24	0.59

CHAPTER 6

PREFACE

This chapter is the fifth manuscript of this thesis and addresses Objective 5. A nested-case control study design was used to examine the association between antipsychotic drugs and diabetic ketoacidosis using the Cerner Health Facts® database between 2000 and 2016.

Exposure to second-generation or first-generation antipsychotic agents, also known as atypical or typical antipsychotics, was evaluated by class or drugs or individual drugs in both cases and controls.

Contributions

For this study, I formulated the study design with the guidance of my supervisor (DK) and FM. I designed the analysis, performed the statistical analysis, interpretation of the findings, and wrote the manuscript. DP contributed to the methodological and statistical aspects of the analysis. JG, NF and AA contributed to methodological aspects of the analysis. JG (University of Toronto) provided expert advice on covariates. My supervisor, and members of my thesis advisory committee (YC, DM, MM, CG) provided suggestions and input on study design, statistical analysis, and interpretation of the findings during our meetings. The manuscript received a critical review from DK.

Ethics Approval

Ethics approval for this study was received from the Ottawa Health Science Network Research Ethics Board at the Ottawa Hospital, Ottawa, Canada (Appendix A).

Risk of First Occurrence of Diabetic ketoacidosis in Diabetic Patients Administered

Antipsychotic Drugs: A Nested Case-Control Analysis

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ABSTRACT

Objective: To investigate associations between exposure to typical and atypical antipsychotic drugs (APDs) and the risk of diabetic ketoacidosis (DKA) in an adult diabetic population.

Methods: We conducted a nested case-control study design using electronic health records abstracted from the Health Facts® database from 2000-2016. Eligible cases included inpatients 18 years of age or older who had a first occurrence of DKA. Each case was matched to five randomly selected controls using incidence density sampling by sex and age. We used conditional logistic regression to calculate the risk of DKA following use of typical and atypical APDs, both by class and by individual drugs, with adjustment for relevant covariates.

Results: A total of 35,102 DKA cases and 175,510 controls were included in our study. Analysis on the entire study population did not reveal an increased risk of DKA associated with APD use. However, subgroup analysis by age and comorbidity status indicated a potential association

between typical APD use and DKA risk. Haloperidol was associated with an increased risk of DKA in patients who are older than 40 years with a moderate to higher level of comorbidities. Prochlorperazine was associated with an increased risk of DKA in the younger and healthier population. Atypical APDs as a class were associated with an increased risk of DKA in the healthy elderly. Exposure to ziprasidone, an atypical APD, was associated with an increased risk of this complication in the elderly who experienced a moderate level of comorbidities.

Conclusion: Our study identified a slightly elevated risk of DKA associated with the use of antipsychotic medicines in specific population subgroups. Further studies are needed to clarify these associations using other data sources.

Keywords: Nested Case-Control, diabetic ketoacidosis, antipsychotic drugs.

6.1 INTRODUCTION

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are characterized by severe hyperglycemia and insulinopenia and represent two of the most serious, potentially life-threatening diabetic complications in patients with poorly controlled diabetes (Fayfman et al. 2017). DKA occurs mainly in young patients with type 1 diabetes mellitus (T1DM) and can occur in patients with type 2 diabetes mellitus (T2DM), while HHS is an emergency condition seen in adults and elderly patients with T2DM (Fayfman et al. 2017). Survival is dependent on early recognition of symptoms and effective treatment with insulin therapy to reduce blood glucose (BG) levels, the administration of electrolyte replacement and intravenous rehydration, and the understanding and mitigation of possible precipitating events (Fayfman et al. 2017; Goguen & Gilbert, 2018). Ketonemia is a hallmark of DKA, while hyperosmolarity is a key characteristic of HHS; both conditions can co-occur in about 30% of patients (Gosmanov et al. 2021; Hassan et

al. 2022). Although there are overlapping features for both conditions, including common precipitating factors leading to the development of either condition, this paper will focus on the association between antipsychotic drugs (APDs) and DKA, which is notably more common than HHS.

An increasing trend in DKA hospital admissions in the United States has been observed in recent years. This complication accounted for more than 140,000 hospitalizations in 2009 (Benoit et al. 2018), 168,000 hospitalizations in 2014 (Benoit et al. 2018; CDC, 2014) and 220,340 hospital admissions in 2017 (Ramphul & Joynauth, 2020; Gosmanov et al. 2021). DKA hospitalization in 2014 was more common among those 45 years old or younger with a rate of 44.3 per 1,000 and was the lowest in the elderly population aged 65 years or older with a rate of less than 2.0 per 1,000 as shown using data from the Agency of Healthcare Research and Quality's National Inpatient Sample (Benoit et al. 2018). Ramphul and Joynauth (2020) reported a consistent and increasing trend in the DKA hospitalization rate from 2003 to 2017. In 2017, the occurrence of DKA in the US was the highest amongst those 45 years of age or younger: 176 cases per 10,000 hospital admissions among those under 18 years of age, and 137 cases per 10,000 in individuals 18 to 44 years of age. The rates for those aged 45 to 64, 65 to 84, and 85+ years were 68.4, 18.7 and 5.9 per 10,000 hospital admissions, respectively.

Precipitating factors in the development of DKA are varied and, while some are preventable, others are less evident. These include the omission of insulin or an insufficient dosing regimen of this hormone, as well as infection, myocardial infarction, cerebrovascular accidents, pulmonary embolism, pancreatitis, alcohol and illicit drug use (Gosmanov et al. 2021; Kitabchi et al. 2009). Different classes of drugs can also induce DKA events, including corticosteroids,

thiazide diuretics and sympathomimetic agents, stimulants that act directly on adrenergic receptors or in an indirect manner by increasing the levels of catecholamines, thus mimicking the effects of endogenous agonists of the sympathetic nervous system.

Second-generation antipsychotic drugs (SGAs), also known as atypical antipsychotic drugs (APDs), are also suspected to increase the risk of diabetes (Ananth et al. 2004; Buse et al. 2003; Caro et al. 2002; Gianfrancesco et al. 2003) and DKA (Ananth et al. 2004; Gosmanov et al. 2021; Kitabshi et al. 2006). Comprehensive reviews of case reports have corroborated a possible association between atypical APDs and DKA (Guenette et al. 2013; Haddad et al. 2023; Vuk et al. 2017). Several observational studies also suggest an association between use of atypical APDs and DKA (Henderson et al. 2007; Leslie & Rosenheck, 2004; Ramaswamy et al. 2007) or both atypical and typical APDs and DKA (Galler et al. 2015; Polcwiartek et al. 2017). Henderson and colleagues (2007) reported that the incidence of new-onset diabetes presenting as DKA in patients experiencing schizophrenia or schizoaffective disorders was more than 10-fold higher than what was reported in the general population (14.9 vs 1.4 per 10,000 patient years); the incidence of DKA among individuals with these conditions was also higher than that in the general hospital population (2.0 per 10,000 patient years). The incidence of DKA varies across different atypical APDs in new-onset DM presenting as DKA, with clozapine demonstrating the highest prevalence of use at 2.2%, followed by olanzapine (0.8%) and risperidone at (0.2%). There was no reported use of quetiapine and ziprasidone in those who experienced a DKA event. Leslie and Rosenheck (2004) concluded that hazard ratios (HR) associated with treatment with atypical APDs in the DKA model were larger than just the diabetes mellitus model, but the attributable risks were small ranging from 0.004% for

risperidone to 0.071% for clozapine. Clozapine and olanzapine treatment were associated with a higher DKA risk (HR: 3.75; 95CI: 1.39-10.09) and (HR: 1.77; 95%CI: 1.05-2.98). Ramaswamy and colleagues (2007) evaluated the risk of DKA in patients receiving olanzapine or risperidone in a population of new APD users and found that the risk of DKA was greater for patients exposed to olanzapine, after adjusting for relevant confounding factors. Galler and colleagues (2015) used a prospective cohort of young patients with T1DM to compare the risk of DKA in those receiving APDs (by class, typical or atypical) and those who were not receiving APDs. The risk of DKA was significantly higher in subjects receiving APDs. Polcwiartek et al. (2017) used a nested case control study design to evaluate the association between exposure to APDs and DKA, T1DM and T2DM. Exposure to APDs was associated with an increased risk of DKA (OR:2.60; 95%CI: 1.06-6.38) and T2DM (OR:1.64; 95%CI: 1.48-1.83) in a diabetes-naïve population of individuals with schizophrenia.

The objective of this study is to investigate associations between exposure to typical and atypical APDs, both as a class and for individual drugs, and the risk of DKA in an adult inpatient diabetic population using a large U.S. electronic medical records database.

6.2 METHODS

6.2.1 Data Source

Data from the Cerner Corporation's Health Facts® Data Warehouse (Health Facts), Kansas City, Missouri, US was used for this analysis. Health Facts is an electronic health records (EHR) database that contains information for over 65 million de-identified unique patients and close to 450 million encounters from 1 January 2000 to 31 December 2016. Approximately, 500 US healthcare facilities representative of all US census regions contributed time-stamped

information on admissions, discharges, diagnoses, demographics, drug prescriptions, insurance status and health-care settings. This analysis focused on inpatient encounters since prescription data for outpatient settings is less complete in Health Facts.

The study protocol was approved by the Office of Research Ethics and Integrity of the University of Ottawa (H-11-20-5598).

6.2.2 Cohort Selection

We identified an initial retrospective cohort comprising a dynamic diabetic population of adult inpatients (≥ 18 years of age) between 1 January 2000 to 31 December 2016. All diabetic inpatients (1,720,085 unique patients and 4,706,671 encounters for an average of 2.7 encounters per patient) were eligible for cohort entry without restricting to a specific type of diabetes. Patients with diabetes were identified based on the *International Classification of Diseases, Ninth Revision* (ICD-9) and *Tenth Revision* (ICD-10) codes for primary or secondary diagnosis (ICD-9:250.x; 249.3; ICD-10E08.x; E09.x; E11.x; E13.x and V12.21), excluding DKA cases and HHS cases (Supplemental Material II), or those who received an antidiabetic medication approved for use by the Food and Drugs Administration (FDA) (Gourgari et al. 2017) (Supplemental Material II) based on the date of hospital discharge. We assumed the patient remained a diabetic once they entered the cohort until their last encounter. We used antidiabetic medication as a proxy for diabetes since this algorithmic approach can be used when ICD9/10 codes are not available, as previously done by others (Eastwood et al. 2016; Mathur et al. 2017).

Patients with a history of pancreatitis, pancreatic cancer, and other associated conditions, neuroleptic malignant syndrome, rhabdomyolysis and acute kidney failure ($n = 70,439$) were

excluded from the analysis (Supplemental Material IV) as these conditions may predispose to DKA based on *a priori* knowledge (Haddad et al. 2023; Polcwiartek et al. 2017) or and in consultation with an expert (Dr. J. Goguen, personal communications).

Women who received antidiabetic medication to treat polycystic ovary syndrome (PCOS) or gestational diabetes were excluded from the analysis as these conditions may be treated off-label with certain antidiabetic medications (n = 2,685). Tobacco use was assessed as ever/never use (Supplemental Material III).

6.2.3 Identification of Cases and Controls

The parent diabetic cohort was used to select subjects for this analysis. Cases were identified as the first occurrence of DKA based on ICD-9 or ICD-10 codes (ICD-9 codes: 250.1; 250.12; 250.13; 249.1; 249.11; ICD-10 codes: E08.10; E08.11; E09.10; E09.11; E10.10; E10.11; E13.11; Supplemental Material I and II). The index date (discharge date) for the case represents the first encounter when a patient was admitted with a DKA event. Controls were selected using incidence density risk set sampling. To ensure consistency in the control matching process, only patients with complete information were used. For each case, controls were matched based on sex (male/female) or similar age (± 5 years), with the encounters closest to the case index date being chosen for matching purposes. Up to 5 controls were randomly selected for each case. Under our control selection algorithm, a case can serve as a control prior to becoming a case.

6.2.4 Medication Exposure

Exposure to APDs was assessed using the hospital pharmacy orders available in Health Facts. Patient records were searched to determine if medication was dispensed to cases and controls. Patients were classified as exposed or unexposed to APDs if they received at least one APD

(ever/never use). Inpatient medication exposure was grouped by class of APD (typical or atypical); individual APDs were also examined based on their prevalence of use in Health Facts (Haddad et al. 2023) (Table 6.1).

We also assessed the use (ever/never) of psychotropic or diabetogenic drugs (Supplemental Material) as previously described (Polcwiartek et al. 2017) and in consultation with an expert (Dr. J. Goguen, personal communications).

Table 6.1. Antipsychotic Drugs Considered in the Case-Control Study.

Antipsychotic Drugs Exposure by Class	
Atypical	Asenapine, aripiprazole, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, cariprazine, pimavanserin, brexpiprazole
Typical	Chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, molindone, perphenazine, prochlorperazine, thioridazine, trifluoperazine, pimozide, thiothixene
Antipsychotic Drugs Exposure by Individual Drugs	
Atypical	Olanzapine, quetiapine, risperidone, ziprasidone and aripiprazole
Typical	Haloperidol, prochlorperazine, droperidol

6.2.5 Comorbidities

Electronic hospital admission records for each patient were assessed for the presence (ever/never) of 26 comorbidities (congestive heart failure, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension (complicated and uncomplicated), paralysis, other neurological disorders, hypothyroidism, liver disease, renal failure, peptic ulcer disease (including bleeding), HIV/AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, anemia (blood loss and deficiency), alcohol abuse, drug abuse, psychosis and depression based on the Elixhauser comorbidity measures (ECM) (Quan et al. 2005). We

combined complicated and uncomplicated hypertension, as well as anemia due to blood loss or deficiency. We excluded diabetic comorbidities since the parent cohort from which cases and controls were selected was comprised of patients who experienced this condition. A comorbidity index (CMI) defined as the sum of all detected comorbidities for a given patient was then calculated. The CMI was stratified into three categories based on comorbidity score (CMI 0-1, 2-4 or 5+) for analysis purposes.

6.2.6 Age-Group Analysis

To better understand of the effect estimates by age on the association between APDs and DKA, we conducted the same analyses described above (by class of APD or by individual drugs) with age stratified into three age groups (18-39, 40-64 and 65+).

6.2.7 Descriptive Analyses

Demographic characteristics of cases and controls were compared for the following variables: sex (male/female); age (18-30, 31-40, 41-50, 51-60, 61-70, 71-80, and 81+), race (Caucasian, African American, Asian, Hispanic, or Other), and health insurance (insured, non-insured, missing/unknown). Other descriptive statistics included exposure to atypical or typical APDs (ever/never use) and covariates, diabetogenic and psychotropic drugs (ever/never), as well as tobacco use (ever/never). The means and standard deviations for continuous/polychotomous variables (age and CMI) were reported. For categorical variables, we reported the frequencies and percentages for cases and controls and made comparisons using the Chi-squared test.

6.2.8 Statistical Methods and Regression Analysis

We used conditional logistic regression to estimate the base odds ratio (OR) and corresponding 95% confidence interval (CI) of the risk of DKA event for APD users compared to nonusers.

Adjusted odds ratios (aORs) taking into account major confounding or modifying factors based on *a priori* knowledge or expert advice were also estimated.

Three logistic regression models were fitted. The base model included age and sex as matching variables and use of APDs (ever/never) as the independent variable, as well as the sum of the comorbidity index. Second, we fitted a minimally adjusted model including race and tobacco use as well as all the variables in the base model. Third, we fitted a maximally adjusted model that adding use of psychotropic or diabetogenic medications. We assessed the fitted models for multicollinearity and found no evidence of strong correlations among the predictor variables in the models. We repeated the same series for regression models using exposure to individual antipsychotics as predictors of DKA. The choice of individual drugs was determined based in a previous analysis on the prevalence of use of APDs. Antipsychotic medicine with a prevalence of use of more than 1% at one point in time were included (Haddad et al. 2023). All statistical analyses were completed using SAS software, version 9.4 (SAS Institute, version 9.4).

6.3 RESULTS

6.3.1 Parent Cohort and Identification of Cases

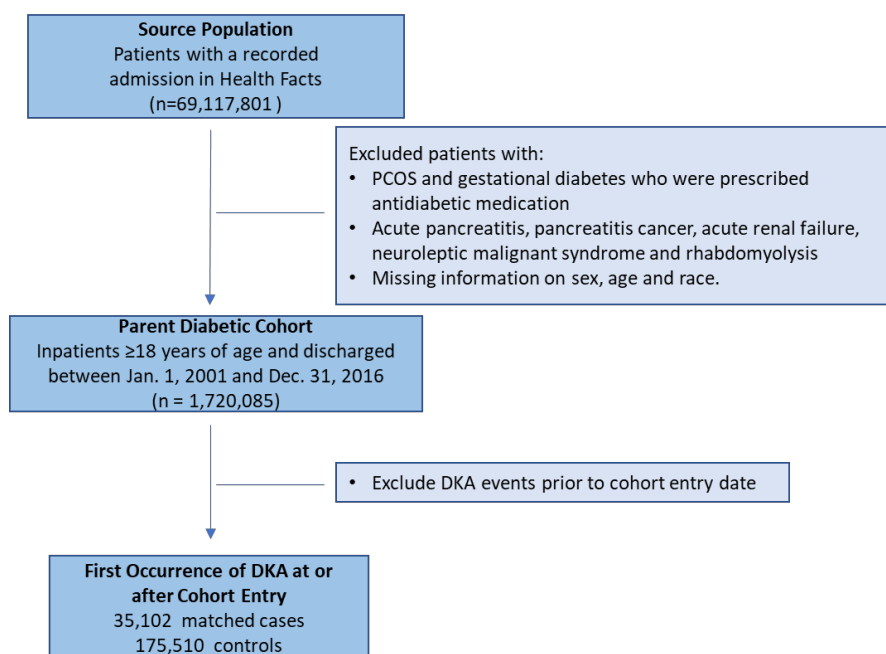
In our analysis, we identified a dynamic cohort of adult diabetic inpatients (n = 1,720,085, 4,706,671 encounters) with a mean age of 63.5 years. Females accounted for slightly over half of the patients in the cohort (50.4%), and most patients were Caucasian (69.4%), followed by African American (17.0%) (Table 6.2).

Table 6.2. Characteristics of the Parent Diabetic Cohort (1,720,085 Unique Patients).

Characteristic	Mean ($\pm$) or Count (%)
Age (years)	63.5 $\pm$ 15.8
Comorbidity Index	2.6 $\pm$ 2.0
Sex	
Male	851,386 (49.5)
Female	866,446 (50.4)
Other	2,252 (0.1)
Race	
Caucasian	1,194,293 (69.4)
African American	291,768 (17.0)
Hispanic	34,144 (2.0)
Asian	28,235 (1.6)
Other	171,645 (10)
Health Insurance	
Insured	948,622 (55.2)
Uninsured	65,986 (3.8)
Unknown/Missing	705,477 (41.0)

From this parent cohort, we identified 36,801 patients who experienced a first occurrence of DKA based on discharge date. Each DKA case which occurred at or after cohort entry was included in the analysis ($n = 35,102$), and matched on age and sex to five randomly selected controls for a total of 175,510 controls (Figure 6.1).

Figure 6.1. Selection of Study Cohort and Diabetic Ketoacidosis Cases from Health Facts®.



Abbreviations: DKA, Diabetic ketoacidosis; PCOS, Polycystic ovary syndrome

Table 6.3 summarizes demographic and clinical characteristics of cases and controls. There were approximately equal numbers of male ($n = 18,202$; 51.9%) and female ($n = 16,900$, 48.2%) cases, with controls displaying a breakdown by sex. Over half of the DKA cases were Caucasian ($n = 21,545$, 61.4%), while a little less than a third were reported to be African American ($n = 8,558$, 24.4%). The largest number of DKA cases was seen in the youngest age group of 18 to 30 years ($n = 7,495$; 21.4%), with slightly smaller numbers in the 51 to 60 age group ($n = 6,995$; 19.9%) and the 41 to 50 age group (6,804; 19.4%). More than half of DKA cases occurred in those aged 18-50 (56.5%). Based on the comorbidity score, patients who experienced a DKA event were less healthy than controls; a little over half had 2 to 4 comorbidities ($n = 18,110$;

51.6%), while those having 5 or more comorbidities accounted for 9.6% of cases (n = 3,369). Cases had a higher proportion of tobacco use (27.1%) than controls (19.2%). The prevalence of use of diabetogenic drugs was slightly lower among cases (28.7%) than controls (33.4%), as was the prevalence of use of psychotropic drugs among cases (46.7%) when compared to controls (51.5%). The differences between cases and controls were statistically significant for race, number of comorbidities, tobacco use, and exposure to diabetogenic or psychotropic drugs ($p < .0001$). Cases and controls used atypical or typical APDs at different frequencies. Overall, those experiencing a DKA event used these agents at a lesser frequency than controls either by class of APD or by individual drug. Atypical APD use in cases was 4.9% compared to 6.3% for controls; and cases and 7.8% of cases used a typical APD compared to 8.9% of controls. Similar observations were made for haloperidol where the extent of exposure to this drug was comparable between cases (3.7%) and controls (3.8%).

6.3.2 Regression Analysis

6.3.2.1 Entire Study Population

We performed conditional regression analysis on the matched DKA cases and controls using three different models to estimate the base odds ratio (OR^0), minimally adjusted odds ratio (aOR^1) and maximally adjusted odds ratio (aOR^2). A primary analysis of the entire study population showed that atypical [OR^0 : 0.66 (95%CI: 0.64-0.69); aOR^1 : 0.66 (95%CI: 0.63-0.68); aOR^2 : 0.79 (95%CI: 0.76-0.83)] or typical APDs [OR^0 : 0.71: (95%CI 0.69-0.73); aOR^1 : 0.71 (95%CI: 0.69-0.73); aOR^2 : 0.86 (95%CI: 0.83-0.89)] as a class were not associated with an increased risk of DKA. Fitting these same models for individual atypical or typical APDs did not identify an increased risk of DKA associated with the use of any of these medications (Table 6.4). Although

risk estimates at both the class and individual medication level did not show an increased risk of DKA, all odds ratios were significantly less than one.

6.3.2.2 Stratification by Comorbidity Index Level

We stratified the study population into three groups based on comorbidity status (CMI Score: 0-1, 2-4 and 5+). Neither atypical or typical APDs as a class showed an increased risk of DKA risk after adjusting for exposure and relevant covariates in the base, minimally adjusted or maximally adjusted models (Table 6.5). However, both classes showed a slight non-significant increase in DKA risk in patients with 5 or more comorbidities [atypical APDs [OR⁰: 1.10 (95%CI: 0.88-1.38); aOR¹: 1.10 (95%CI: 0.87-1.37); aOR²: 1.11 (95%CI: 0.88-1.39)]; typical APDs [OR⁰: 1.09(0.90-1.31); aOR¹: 1.09(95%CI: 0.90-1.32); aOR²: 1.11 (95%CI: 0.91-1.35)]. The observed increase in risk for atypical APDs may be attributed to quetiapine, olanzapine and ziprasidone, as shown in Table 6.5, and to haloperidol for typical APDs. Haloperidol is the only single drug that generated a significant risk of DKA among those with 5 or more comorbidities [(OR⁰: 1.39 (95%CI: 1.10-1.74); aOR¹: 1.40 (95%CI: 1.11-1.76); aOR²:1.43 (95%CI: 1.13-1.81)].

6.3.3.3 Age Group Stratification for the Maximally Adjusted Model

Stratification of the study population by age showed marginally significant adjusted ORs for prochlorperazine [aOR²:1.10 (95%CI: 1.02-1.20)] for the youngest age group, 18 to 39 years of age. The risk of DKA associated with use of haloperidol was significantly increased among those 65 years of age or older [aOR²: 1.28 (95%CI: 1.17-1.40)]. There was no evidence that quetiapine, risperidone, olanzapine and aripiprazole increased the risk of DKA in those aged 65 years of age or older (Table 6.6).

Table 6.3. Characteristics of Cases and Controls^{1,2,3}.

Characteristics	No (%) of Patients		p-value
	Cases	Controls	
Total No of participants	35,102	175,510	
Gender¹			0.9988
Male	18,202 (51.9)	90,907 (51.8)	
Female	16,900 (48.2)	84,403 (48.1)	
Race²			<0.0001
Caucasian	21,545 (61.4)	109,757 (62.5)	
African American	8,558 (24.4)	41,755(23.8)	
Asian	366 (1.0)	2,057 (1.2)	
Hispanic	847 (2.4)	5,004 (2.9)	
Other/Unknown	3,786 (10.8)	1,6937 (9.7)	
Age Group¹			>0.999
18-30	7,495 (21.4)	37,475 (21.4)	
31-40	5,519 (15.7)	27,595 (15.7)	
41-50	6,804 (19.4)	34020 (19.4)	
51-60	6,995 (19.9)	34,724 (19.8)	
61-70	4,676 (13.3)	23,380 (13.2)	
71-80	2,409 (6.9)	12,045 (6.8)	
81+	1,204 (3.4)	6,020 (3.43)	
Health Insurance³			<0.0001
Insured	22,307 (63.6)	74,104 (42.2)	
Uninsured	4,197 (12.0)	9,139 (5.2)	
Unknown/Missing	8,598 (24.5)	92,267 (52.6)	
Comorbidity Score			<0.0001
0 - 1	13,623 (38.8)	100,982 (57.5)	
2-4	18,110 (51.6)	64,157 (36.6)	
5+	3,369 (9.6)	10,371 (5.91)	
Covariates			
Tobacco Use	9,523 (27.1)	33,613 (19.2)	<0.0001
Diabetogenic Drugs	10,061 (28.7)	58,636 (33.4)	<0.0001
Psychotropic Drugs	16,307 (46.7)	90,352 (51.5)	<0.0001
Antipsychotic Drugs			
Class of APDs			
Atypical Class	1,707 (4.9)	11,038 (6.3)	<.0001
Typical Class	2738 (7.8)	15677 (8.9)	<.0001
Individual Atypical APDs			
Quetiapine	774 (2.2)	4,837 (2.8)	<.0001
Risperidone	381 (1.1)	2,622 (1.5)	<.0001
Olanzapine	251 (0.7)	2,068 (1.2)	<.0001
Ziprasidone	168 (0.5)	1,272 (0.7)	<.0001
Aripiprazole	270 (0.8)	1,753 (1.0)	<.0001
Individual Typical APDs			
Haloperidol	1,289 (3.7)	6,720 (3.8)	0.1612
Prochlorperazine	1,276 (3.6)	7,060 (4.0)	0.0007
Droperidol	105 (0.3)	1,563 (0.9)	<.0001

¹Variables were matched on age and sex.
²Other race includes biracial, pacific islander, native American and Middle Eastern.
³Variable not included in the regression model.

Table 6.4. Base and Adjusted Odds Ratios for Diabetic Ketoacidosis Risk with Antipsychotic Drugs by Class and Individually for the Entire Population.

Exposure	Base Model OR ⁰ (95%CI)	Minimally Adjusted Model OR ¹ (95%CI)	Maximally Adjusted Model OR ² (95%CI)
Atypical APDs	0.66 (0.64-0.69)	0.66 (0.63-0.68)	0.79 (0.76-0.83)
Typical APDs	0.71 (0.69-0.73)	0.71 (0.69-0.73)	0.86 (0.83-0.89)
Individual Atypical APDs			
Quetiapine	0.64 (0.61-0.68)	0.64 (0.60-0.68)	0.76 (0.72-0.81)
Risperidone	0.63 (0.59-0.68)	0.63 (0.59-0.68)	0.75 (0.69-0.81)
Olanzapine	0.50 (0.46-0.55)	0.50 (0.46-0.54)	0.58 (0.54-0.64)
Ziprasidone	0.59 (0.53-0.65)	0.58 (0.53-0.65)	0.70 (0.63-0.78)
Aripiprazole	0.64 (0.59-0.70)	0.64 (0.59-0.70)	0.78 (0.71-0.85)
Individual Typical APDs			
Haloperidol	0.76 (0.73-0.80)	0.76 (0.73-0.79)	0.91 (0.87-0.95)
Prochlorperazine	0.76 (0.74-0.79)	0.76 (0.73-0.79)	0.92 (0.88-0.96)
Droperidol	0.51 (0.46-0.56)	0.51 (0.46-0.56)	0.61 (0.55-0.67)

Abbreviations: APD, Antipsychotic Drug; OR, Odds ratio; CI, Confidence Interval.

6.3.3.4 Joint Effects of Age and Comorbidity Index Level for the Maximally Adjusted Model

Based on the results obtained following the stratification by age or by CMI score, we further stratified the study population by age and comorbidity. For CMI level 0-1, atypical APDs showed a slightly increased and significant risk of DKA as a class [aOR²: 1.32 (95%CI: 1.01-1.70)] for those aged 65 years or older. This appeared to be attributable to all atypical APDs except for ziprasidone (Table 6.7). Haloperidol and prochlorperazine were associated with an increased risk of DKA in the oldest [65+ years of age, aOR²: 1.59 (95%CI: 1.22-2.07)] and the youngest age group [18-39 years of age, aOR²: 1.18 (95%CI: 1.07-1.30)]. Exposure to ziprasidone generated a marginally significant OR in the oldest age group in those with 2 to 4 comorbidities [aOR²: 1.56 (95%CI: 1.03-2.36)]. Haloperidol was associated with a significant risk

of DKA for those over 40 years of age: [aOR²: 1.10 (95%CI: 1.01-1.21) for those aged 40-64; aOR²: 1.26 (95%CI: 1.10-1.42) for those 65+].

The two classes of APDs – atypical and typical – showed a non-significant increased risk of DKA in those aged 40-64 years and those 65+ years of in those with 5+ comorbidities: for atypical APDs [aOR²: 1.33 (95%CI: 0.94-1.87)] in those aged 65+ years, and for typical APDs, [aOR²: 1.10 (95%CI: 0.83-1.47)] in those ages 40-64 years and [aOR²: 1.13 (95%CI: 0.86-1.50)] among those 65+ years of age (Table 6.7). For atypical APDs, quetiapine, olanzapine, risperidone and ziprasidone appeared to contribute to this increased risk. While the risk of DKA associated with typical APDs was mainly driven by haloperidol, which generated a significant increase in risk in both age groups [aOR²:1.43 (95%CI: 1.01-2.04)]; in those aged 40-64 years and [aOR²: 1.46 (95%CI: 1.05-2.23)] among those 65+ years of age and to a lesser extent droperidol, which showed a non-significant risk in these same age groups. Prochlorperazine was associated with a four-fold increase in risk in those aged 18-39 years of age [aOR:4.45 (95%CI: 0.51-39.18)], although this estimate was highly uncertain and not significant.

Table 6.5. Base and Adjusted Odds Ratios for Diabetic Ketoacidosis Risk with Antipsychotic Drugs by Class or Individual Drugs Stratified by Level of Comorbidity.

Population and Medication	Base Model OR ⁰ (95%CI)	Minimally Adjusted Model aOR ¹ (95%CI)	Maximally Adjusted Model aOR ² (95%CI)
Comorbidity level			
<i>CMI: 0-1</i>			
Atypical APDs	0.45 (0.42-0.49)	0.44 (0.40-0.47)	0.62 (0.57-0.68)
Typical APDs	0.59 (0.56-0.62)	0.58 (0.55-0.61)	0.83 (0.79-0.89)
<i>CMI: 2-4</i>			
Atypical APDs	0.72 (0.68-0.77)	0.74 (0.70-0.79)	0.85 (0.80-0.90)
Typical APDs	0.76 (0.72-0.80)	0.77 (0.73-0.81)	0.89 (0.84-0.93)
<i>CMI: 5+</i>			
Atypical APDs	1.10 (0.88-1.38)	1.10 (0.87-1.37)	1.11 (0.88-1.39)
Typical APDs	1.09 (0.90-1.31)	1.09 (0.90-1.32)	1.11 (0.91-1.35)
Comorbidity level			
<i>CMI: 0-1</i>			
Individual Atypical APDs			
Quetiapine	0.43 (0.38-0.48)	0.41 (0.37-0.46)	0.57 (0.51-0.65)
Risperidone	0.47 (0.41-0.55)	0.46 (0.40-0.53)	0.64 (0.55-0.75)
Olanzapine	0.33 (0.28-0.39)	0.32 (0.27-0.38)	0.44 (0.37-0.53)
Ziprasidone	0.37 (0.30-0.45)	0.36 (0.29-0.45)	0.52 (0.42-0.65)
Aripiprazole	0.46 (0.39-0.55)	0.5 (0.38-0.53)	0.66 (0.55-0.78)
Individual Typical APDs			
Haloperidol	0.50 (0.46-0.54)	0.49 (0.45-0.53)	0.68 (0.63-0.75)
Prochlorperazine	0.79 (0.74-0.85)	0.77 (0.72-0.83)	1.11 (1.03-1.19)
Droperidol	0.39 (0.33-0.47)	0.39 (0.32-0.47)	0.53 (0.44-0.66)
<i>CMI: 2-4</i>			
Individual Atypical APDs			
Quetiapine	0.69 (0.64-0.75)	0.71 (0.65- 0.77)	0.81 (0.74-0.88)
Risperidone	0.65 (0.58-0.73)	0.66 (0.59-0.74)	0.76 (0.68-0.85)
Olanzapine	0.58 (0.51-0.66)	0.60 (0.52-0.68)	0.68 (0.59-0.77)
Ziprasidone	0.76 (0.65-0.89)	0.78 (0.66-0.91)	0.87 (0.74-1.02)
Aripiprazole	0.66 (0.58-0.75)	0.68 (0.60-0.78)	0.79 (0.68-0.90)
Individual Typical APDs			
Haloperidol	0.88 (0.83-0.94)	0.90 (0.84-0.95)	1.03 (0.96-1.10)
Prochlorperazine	0.73 (0.68-0.77)	0.73 (0.69-0.78)	0.84 (0.78-0.90)
Droperidol	0.61 (0.53-0.71)	0.61 (0.53-0.71)	0.71 (0.61-0.82)
<i>CMI: 5+</i>			
Individual Atypical APDs			
Quetiapine	1.20 (0.91-1.63)	1.22 (0.91-1.64)	1.23 (0.92-1.65)
Risperidone	0.90 (0.59-1.37)	0.89 (0.59-1.36)	0.90 (0.59-1.38)
Olanzapine	1.07 (0.68-1.69)	1.06 (0.67-1.68)	1.08 (0.68-1.71)
Ziprasidone	1.14 (0.58-2.26)	1.12 (0.56-2.22)	1.12 (0.57-2.23)
Aripiprazole	0.88 (0.51-1.51)	0.88 (0.51-1.52)	0.90 (0.52-1.54)
Individual Typical APDs			
Haloperidol	1.39 (1.10-1.74)	1.40 (1.11-1.76)	1.43 (1.13-1.81)
Prochlorperazine	0.83 (0.62-1.11)	0.82 (0.61-1.10)	0.82 (0.61-1.10)
Droperidol	0.81 (0.45-1.47)	0.83 (0.46-1.51)	0.84 (0.46-1.53)

Abbreviations: APD, Antipsychotic Drug; CMI, Comorbidity Index; OR, Odds ratio; CI, Confidence Interval.

Table 6.6. Maximally Adjusted Odds Ratios for Diabetic Ketoacidosis Risk with Antipsychotic Drugs by Class and Individual Drugs Stratified by Age Group.

Exposure	Age (years)		
	18 to 39	40 to 64	65+
Atypical APDs	0.59 (0.54-0.63)	0.85 (0.80-0.90)	1.09 (1.00-1.20)
Typical APDs	0.77 (0.73-0.82)	0.89 (0.85-0.93)	0.95 (0.88-1.02)
Individual Atypical APDs			
Quetiapine	0.59 (0.53-0.66)	0.80 (0.74-0.87)	1.03 (0.91-1.2)
Risperidone	0.49 (0.42-0.57)	0.81 (0.73-0.90)	1.1 (0.95-1.30)
Olanzapine	0.36 (0.30-0.43)	0.64 (0.57-0.73)	1.08 (0.90-1.30)
Ziprasidone	0.50 (0.42-0.64)	0.83 (0.72-0.95)	1.20 (0.90-1.61)
Aripiprazole	0.66 (0.57-0.78)	0.85 (0.75-0.96)	0.98 (0.73-1.33)
Individual Typical APDs			
Haloperidol	0.57 (0.52-0.62)	1.00 (0.94-1.06)	1.28 (1.17-1.40)
Prochlorperazine	1.10 (1.02-1.20)	0.92 (0.86-0.97)	0.68 (0.61-0.76)
Droperidol	0.70 (0.59-0.83)	0.58 (0.51-0.63)	0.61 (0.48-0.77)

Abbreviations: APD, Antipsychotic Drug; OR, Odds ratio; CI, Confidence Interval.

Table 6.7. Maximally Adjusted Odds Ratios for Diabetic Ketoacidosis Risk with Antipsychotic Drug Use by Class and Individually Stratified by Age Group for Different Levels of Comorbidity.

Exposure	Age (years)		
	18 to 39	40 to 64	≥65
Comorbidity Level: CMI: 0-1			
Atypical Antipsychotics	0.48 (0.42-0.54)	0.70 (0.62-0.80)	1.32 (1.01-1.70)
Typical Antipsychotics	0.77 (0.71-0.84)	0.89 (0.81-0.98)	1.03 (0.84-1.26)
Individual Atypical APDs			
Quetiapine	0.49 (0.42-0.59)	0.57 (0.47-0.69)	1.23 (0.87-1.76)
Risperidone	0.40 (0.31-0.51)	0.84 (0.68-1.04)	1.43 (0.92-2.23)
Olanzapine	0.28 (0.21-0.37)	0.50 (0.37-0.66)	1.57 (1.00-2.45)
Ziprasidone	0.36 (0.26-0.50)	0.80 (0.59-1.11)	0.63 (0.24-1.83)
Aripiprazole	0.50 (0.39-0.65)	0.80 (0.62-1.04)	1.62 (0.76-3.47)
Individual Typical APDs			
Haloperidol	0.48 (0.43-0.55)	0.84 (0.73-0.97)	1.59 (1.22-2.07)
Prochlorperazine	1.18 (1.07-1.30)	1.10 (0.97-1.23)	0.79 (0.59-1.05)
Droperidol	0.67 (0.52-0.87)	0.44 (0.33-0.59)	0.40 (0.20-0.79)
Comorbidity Level: CMI: 2-4			
Atypical Antipsychotics	0.60 (0.52-0.69)	0.90 (0.83-0.98)	1.06 (0.92-1.22)
Typical Antipsychotics	0.78 (0.70-0.87)	0.92 (0.86-0.98)	0.92 (0.83-1.03)
Individual Atypical APDs			
Quetiapine	0.56 (0.46-0.67)	0.87 (0.77-0.97)	1.00 (0.82-1.23)
Risperidone	0.5 (0.38-0.64)	0.77 (0.66-0.90)	1.14 (0.9-1.44)
Olanzapine	0.42 (0.32-0.56)	0.74 (0.62-0.88)	1.0 (0.75-1.30)
Ziprasidone	0.57 (0.42-0.78)	0.97 (0.79-1.20)	1.56 (1.03-2.36)
Aripiprazole	0.72 (0.55-0.94)	0.82 (0.69-0.97)	0.79 (0.51-1.24)
Individual Typical APDs			
Haloperidol	0.66 (0.56-0.77)	1.10 (1.01-1.21)	1.26 (1.10-1.42)
Prochlorperazine	1.07 (0.93-1.23)	0.86 (0.78-0.94)	0.62 (0.53-0.72)
Droperidol	0.75 (0.53-1.05)	0.71 (0.59-0.87)	0.67 (0.48-0.95)
Comorbidity Level: CMI: 5+			
Atypical Antipsychotics	3.24 (0.47-4.12)	0.92 (0.66-1.27)	1.33 (0.94-1.87)
Typical Antipsychotics	1.22 (0.25-5.88)	1.10 (0.83-1.47)	1.13 (0.86-1.50)
Individual Atypical APDs			
Quetiapine	1.84 (0.27-2.51)	1.06 (0.71-1.57)	1.49 (0.93-1.39)
Risperidone	<0.001 (<0.001->999.999)	0.57 (0.30-1.07)	1.48 (0.81-1.71)
Olanzapine	1.29 (0.07-21.89)	1.27 (0.65-2.46)	1.00 (0.50-1.99)
Ziprasidone	0.65 (0.03-15.1)	0.70 (0.27-1.82)	2.15 (0.69-1.73)
Aripiprazole	>999.999 (<<0.001- >999.999)	0.95 (0.48-1.86)	0.67 (0.24-1.83)
Individual Typical APDs			
Haloperidol	1.15 (0.16-8.53)	1.43 (1.01-2.04)	1.46 (1.05-2.23)
Prochlorperazine	4.45 (0.51-39.18)	0.81 (0.54-1.21)	0.79 (0.51-1.23)
Droperidol	0.57 (0.02-13.44)	0.64 (0.28-1.45)	1.29 (0.49-3.42)

Abbreviations: APD, Antipsychotic Drug; CMI, Comorbidity Index; OR, Odds ratio; CI, Confidence Interval.

6.4 DISCUSSION

This analysis investigated the associations between exposure to APDs and the risk of DKA in a dynamic population of adult diabetic inpatients spanning 16 years of data. Our results are based on a large, nested case-control study comprised of 35,102 DKA cases matched on age and sex to 175,510 controls. Overall, findings do not support an association between the risk of DKA and atypical or typical APDs as a class or as individual drugs. Notably, an increased risk of DKA was observed in subgroup analyses stratified by comorbidity levels or by age groups. As a class, atypical APDs were associated with an increased risk of DKA in healthy seniors (65+ years of age with less than 2 comorbidities). Ziprasidone, an atypical APD showed an association in seniors who were moderately healthy (2 to 4 comorbidities). Haloperidol, a typical APD, was associated with an increased risk of DKA in patients older than 40 years with a moderate to higher level of comorbidities. Stratification by age group showed that use of prochlorperazine was associated with an increased risk of DKA in the healthiest subjects 18 to 39 years of age. Haloperidol and prochlorperazine are the two most prevalent APDs, although the overall prevalence of use of typical APDs as a class decreased overtime in the 16 year study period ending in 2016 (Haddad et al. 2023). While we analyzed race as an independent predictor, results were varied and inconsistent. Overall, those aged less than 50 years accounted for over half of the cases, which has also been reported by others (Benoit et al. 2018; Ramphul & Joynauth, 2020).

Systematic reviews on case reports have supported an association between atypical APDs and DKA (Guenette et al. 2013; Haddad et al. 2023; Vuk et al. 2017). A recent analysis of adverse drug reaction reports in the U.S. FDA Adverse Event Reporting System (FAERS) database,

showed that olanzapine and quetiapine generated potential significant safety signals for adverse DKA events (Haddad et al. 2023). To date, only a handful of observational studies have investigated the association between use of APDs and DKA. These studies vary widely in scope, case definition, study population, exposure ascertainment, and outcome of interest (Haddad et al. 2023).

Our findings did not support an association between olanzapine and an increased risk of DKA, as has been previously reported (Ramsaway et al. 2007; Leslie & Rosenheck, 2004). In a retrospective analysis of inpatients and outpatients in a Boston hospital, Henderson and colleagues (2007) reported one patient who experienced new-onset DM presenting as DKA while receiving treatment with haloperidol decanoate, olanzapine and chlorpromazine; in another case, the discontinuation of olanzapine and switching to risperidone reversed DKA, and in one case re-institution of olanzapine due to psychiatric decompensation led to a recurrent case of DKA and subsequent death from heparin-induced thrombocytopenia. In the absence of additional observational studies that are more closely aligned methodologically, it is important to note that this evidence gap renders it challenging to reach firm conclusions based on real-world evidence.

Current research also indicates that antipsychotic medicines vary in terms of their effect on metabolic dysregulation, including glucose concentrations and other risk factors that may be involved in the development of DKA. Pillinger et al. (2020) conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) that recruited schizophrenia patients. They aimed to evaluate APD-induced changes to clinical markers including body weight, BMI, cholesterol and glucose concentrations, as well their relationship to age, sex, ethnicity, baseline

weight and baseline metabolic parameters. The authors noted differences in how APDs expressed metabolic side-effects. Olanzapine and clozapine, considered the two most efficacious drugs, exhibited the strongest effect on metabolic dysregulation, including increased glucose concentration, weight gain and BMI alteration, whereas aripiprazole and ziprasidone were two of the more benign atypical APDs. Haloperidol had the least effect on weight gain, the weakest association with BMI, and there was no evidence of changes in glucose concentrations –quetiapine, risperidone and aripiprazole also did not have a notable impact on glucose levels. Interestingly, aripiprazole had a positive effect on High density lipoprotein (HDL) cholesterol (good cholesterol) and it was observed to increase. The study also found that increased baseline bodyweight as well as being male and of non-white ethnicity were strong predictors of APD-induced metabolic dysregulation. Results suggest that there is overlap between risk factors for metabolic disease in the general population and people with APD-induced metabolic disease (Pillinger et al. 2020). This adds another layer of complexity to understanding the multifactorial mechanisms in the way APDs exert their effects. Preclinical studies have shown that glucose dysregulation and insulin resistance are more reliably observed than weight gain and hypertension, and that the effect on glucose dysregulation varies between different APDs. Factors such as drug-specific events, diet and treatment regimens complicate comparisons among pre-clinical studies (Boyda et al. 2010).

Laboratory markers were not examined in the present study because they were not available throughout the 16 year study period. However, there is evidence that antipsychotic-induced weight gain is inversely related to baseline BMI, which may reflect prior APD exposure or regression to the mean (Manu et al. 2015). An increase in BMI of 1 kg/m² results in an 8.4%

increase in the risk of developing diabetes (Cooper et al. 2016). A study investigating the relationship between BMI and heart failure in the Framingham Heart Study reported an increase in the risk of heart failure of 5% in men and 7% in women for each increment of 1 kg/m² BMI. When compared with subjects with a normal BMI, obese subjects had a two-fold increase in the risk of heart failure (Kenchiah et al. 2002). Our results suggested APDs are associated with an increased risk of DKA in those over 40 years of age with multiple comorbidities. Given the increased risk for comorbidities such as cardiovascular disease associated with metabolic dysregulation, it is important for clinicians to evaluate all relevant risk factors when prescribing antipsychotics, particularly in patients with important risk factors such as being non-white, being male, and having high BMI, in addition to considering the overall efficacy and tolerability of the antipsychotic (Huhn et al. 2019). An analysis of the National Health and Nutrition Examination Survey (NHANES) found that APD users reported a higher prevalence of comorbid chronic diseases and took on average 2.3 prescription medication when compared to patients who were not taking APDs (Dennis et al. 2020).

In an open label prospective study involving patients with schizophrenia or psychotic disorders, treatment with ziprasidone reduced the rate of occurrence of MetS and associated risk factors including waist circumference, blood pressure, fasting triglycerides, HDL cholesterol or fasting plasma glucose (Chue et al. 2014). These findings were corroborated by Zhan and Dai (2012), who enrolled subjects with a first episode of schizophrenia and examined the efficacy and metabolic effects of paliperidone, aripiprazole and ziprasidone. The authors found that the group receiving aripiprazole had a higher risk of increased fasting blood glucose and elevated HbA1c, while ziprasidone demonstrated no significant changes in glucose metabolism. This

may explain, in part, the protective effects that we observed for exposure to ziprasidone and the risk of DKA in our analysis. It is possible to extrapolate these findings to the present analysis, as glucose dysregulation is a risk factor for diabetic emergencies, even though APDs may invoke different mechanisms to exert their therapeutic mechanisms of action.

Bernardo et al. (2021) abstracted information from 40 studies to assess the risk of occurrence of metabolic disorders in adult inpatients treated with atypical APDs as a class or individually that reported the occurrence of diabetes, DKA, HHS, and other metabolic risk factors such as weight gain, obesity, dyslipidemia and hypertension and MetS. Two of the studies included in their analysis evaluated the potential risk of APD-induced DKA or HHS (Leslie & Rosenheck, 2004; Lipscombe et al. 2014). The first study by Leslie et al. (2004) was conducted in a diabetic naïve schizophrenic veteran population and concluded there is increased risk of DKA with clozapine (HR 3.75, 95% CI) and olanzapine (HR 1.77, 95% CI 1.05–2.98), whereas the attributable risk was small ranging from 0.004% for risperidone and to 0.0071% for clozapine, respectively. Lipscombe and colleagues pooled all hyperglycemic emergencies together, but their findings indicated the risk of DKA is low after initiation of APDs. Recent analyses used the National Health Insurance Research Database of Taiwan (NHIRD) to evaluate the risk of hyperglycemic emergencies episodes, specifically DKA or HHS, in association with APD use in diabetic patients experiencing schizophrenia (Chen et al. 2020) or bipolar disorder (Tsai et al. 2020). The authors evaluated the duration of APD prescription on the risk of hyperglycemic emergencies risk. In the schizophrenia cohort, findings indicated that prolonged use of APD was associated with a lower risk of hyperglycemic emergencies, suggesting a protective effect (Chen et al. 2020). Subgroup analysis stratified by duration of exposure generated similar

results for both crude and adjusted hazard ratios in the bipolar disorder cohort (Tsai et al. 2020). Although the authors did not specify which class of APD they analyzed, we cannot rule out the possibility that protracted exposure to APDs may have led to the protective effects that we observed in our analysis.

In our analysis, we observed a change in direction of the OR estimates (an increase) between the minimally adjusted model to the maximally adjusted model, with the latter including further adjustment for psychotropic and diabetogenic drugs. While the ORs did not generate significant effect estimates, we cannot exclude the possibility that these medications are confounding the association between APDs and DKA. Future analyses excluding patients who were prescribed these medications may possibly help elucidate their impact as confounders or effect modifiers on this association.

Sample size and exposure prevalence are two important determinants of an association between exposure and outcome when exposure in the general population is limited. It is possible that the discrepancies observed with our findings are a consequence of the large sample size used in our study. Austin and colleagues (2002) used a simulation analysis to examine the effect of sample size and exposure prevalence on bias in the estimated OR. A small sample size and a low prevalence of exposure with small to moderate effect sizes can generate biased estimates of an association between drug and diseased status. The bias becomes negligible as sample size increases (specifically, when $n \geq 2000$), even with low prevalence of drug exposure. Low prevalence of exposure is not optimal in this type of study design, and we observed very small or moderate effect sizes. However, we consider the large size of our sample size, as well as the exposed number of controls in the entire population

matched by age and sex to reduce this bias in our analysis. Furthermore, our analysis showed that ziprasidone -the least prevalent APD in those experiencing DKA - was associated in an increased risk in the elderly who had 2 to 4 comorbidities.

6.4.1 Strengths

We analysed a large dynamic cohort of cases and controls matched on age and sex using incidence density sampling and spanning 16 years of data. To the best of our knowledge, this is the largest assessment of antipsychotic associated DKA using a rich real-world EHR database comprising information from over 500 health centers and covering all US census areas. To accomplish this, we used an algorithmic approach to ascertain the diabetic status in the parent cohort and identified inpatients using ICD-9/10 codes coupled with the use of antidiabetic medication. We assumed first occurrence of DKA is the most accurate diagnosis since it is possible the history of the patient is recorded in subsequent encounters, and it is possible that other hyperglycemic complications were coded as DKA in the US. We used incidence density risk set sampling to match cases to controls as this method has been demonstrated to yield consistent risk estimates in nested case-control analyses (Lubin et al. 1984; Robins et al. 1986). This method was also used in previous nested case-control analyses using Heath Facts (Farhat et al. 2020; Taher et al. 2021). Our data permitted an analysis of classes of antipsychotic medicines (typical and atypical), as well as individual drugs measured as ever/never drug use. The large sample permitted us to stratify by age-group and by CMI levels. Based on *a priori* knowledge and expert advice, we adjusted for major known confounders and effect modifiers, including 26 comorbidities, tobacco use, and concurrent medication exposure to ensure a methodologically robust analysis.

6.4.2 Limitations

Our analysis has several limitations that are worth noting. First, we cannot discount the possibility of misclassification of exposure or outcome. We did not have access to information on patients' adherence to the prescribed antipsychotic treatment regimen, or possible switching and discontinuation of medicines. Furthermore, as this is an inpatient setting, we expect the medication management system would ensure compliance because all medications are mainly delivered by hospital staff; nonetheless, it is possible that individuals who only used an APD for a short time only or who have stopped using it are classified as never users, resulting in misclassification of exposure. In the United States, APDs are prescribed in 1.7% of adult of outpatient visits, and increasingly from non psychiatrist physicians (Olfson et al. 2012). An analysis of NHANES between 2012 and 2018 indicated that the prevalence of APD use among non-hospitalized adults in in the United States was 1.6% (Dennis et al. 2020). These factors, along with data gaps on outpatient drug utilization, limit a comprehensive examination of the impact of polypharmacy. However, with the available data, it was estimated that combination APD use (polypharmacy) occurred in less than 2% of the study population. Furthermore, limited information on frequency, duration or dosage of drug use limits the ability to precisely determine the extent of the drug's effect on DKA risk. Access to pre-existing medical records and assessing biomarkers for exposure (metabolites assessment), when available, could help reduce misclassification of exposure in future studies. To mitigate non-differential misclassification of disease status (unrelated to exposure), we isolated first-occurrence of DKA cases. However, we cannot entirely eliminate this source of misclassification error, which can lead to an underestimation of the strength of the association (Gilbert et al. 2014). Validating

the diagnosis using specific biomarkers such as glucose levels and the presence of ketones or osmolality will help differentiate between hyperglycemic diagnosis (such as HHS) with greater confidence. Considering the urgent care requirement to treat DKA, and the need for regular medical monitoring to detect the potential risk, the possibility for differential misclassification of the outcome is considered low (e.g., those exposed to an APD may seek medical attention and this could lead to a more frequent underdiagnosis of DKA in those not exposed to APDs). We also acknowledge the possibility of residual and unmeasured confounding, since we were not able to adjust for other confounding factors such as lifestyle, BMI, physical activity levels, family history of diabetes, or severity of disease. In addition, we cannot completely rule out the possibility of confounding by indication and we did not evaluate the impact of psychiatric diagnoses on the association between APD use and DKA. Further research can address this issue by matching on indication or restricting the study to those who were not diagnosed with indications for APD use (e.g. schizophrenia).

6.5 CONCLUSION

DKA is a serious diabetic complication that can be fatal if not treated effectively. Findings from the present study indicated that although APDs may exert their effects through different mechanisms of action, results do not support an overall increased risk of DKA and APD use in diabetics. Subgroup analysis by comorbidity level or age group demonstrated possible associations between APD use and DKA risks, particularly in elderly patients with have multiple comorbidities. Regular clinical monitoring of glucose dysregulation in this population is therefore crucial. Additional retrospective and prospective studies based on real-world observation data are needed to provide a better understanding of these associations. Pre-

clinical studies to better understand the mechanisms of actions of antipsychotic medicines will shed light on how they exert their actions and may lead in some cases to hyperglycemic emergencies such as DKA.

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SUPPLEMENTAL MATERIAL S6

The objective of this supplemental material is to provide additional information in support of the information presented in the case control analysis. This includes:

- **Supplemental Material I:** Counts of first occurrence of diabetic ketoacidosis (DKA) by year, 2000-2016 (Table S6.1)
- **Supplemental Material II:** *International Classification of Diseases, Ninth Revision* (ICD-9) and *Tenth Revision* (ICD-10) codes for primary or secondary diagnoses to identify: patients with diabetes in the parent diabetic cohort, and the list of antidiabetic drugs used as a proxy to identify diabetic patients. ICD-9/10 used to identify primary and secondary diagnoses of DKA cases, as well as patients diagnosed with hyperglycemic hyperosmolar State (HHS) (Tables S6.2-S6.5).
- **Supplemental Material III:** List of diabetogenic drugs and psychotropic substances used as covariates in the logistic regression model (Tables S6.6 and S6.7) and ICD-9/10 codes to identify tobacco use (Table S6.8).
- **Supplemental Material IV:** ICD-9/10 codes to identify conditions that were excluded from the analysis (Table S6.9).

Supplemental Material I - Counts of first occurrences of occurrence of diabetic ketoacidosis by Year.

Table S6.1. Counts of First Occurrence of Diabetic Ketoacidosis Events by Year, 2000-2016¹.

Year	First Occurrence of Diabetic Ketoacidosis Count (n =) ¹
2000	124
2001	245
2002	221
2003	115
2004	87
2005	184
2006	369
2007	592
2008	813
2009	1,188
2010	1,623
2011	2,529
2012	3,624
2013	5,204
2014	5,511
2015	5,998
2016	6,675
	35,102¹

¹Total number of cases included in the analysis

Supplemental Material II - Identification of the Parent Diabetic Cohort Based on International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) or Antidiabetic Medication.

Table S6.2. Diagnosis Codes to Identify the Parent Diabetic Population¹

Type	Diagnosis Code
ICD9	249.3; 250.x
ICD10	E08.x; E09.x; E10.x; E11.0; E13.x; V12.21

¹ICD9/10 codes used to identify DKA and HHS were removed from the parent cohort.

Table S6.3. List of Antidiabetic Medication Approved by the Food and Drugs Administration, Used as a Proxy to Identify Patients with Diabetes.

Class	Names of the Drug
Alpha-glucosidase inhibitor	Miglitol, acarbose
Amylin analogs	Pramlintide acetate
ATP-dependent K ⁺ channel binders	Nateglinide
Biguanide and sulfonylurea combination	Glyburide and metformin hydrochloride, glipizide/metformin HCl
Biguanides	Metformin hydrochloride, extended release
Bile acid sequestrant indicated	Colesevelam hydrochloride
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Alogliptin benzoate, sitagliptin and simvastatin, linagliptin, saxagliptin, sitagliptin phosphate
Dopamine receptor agonist	Bromocriptine mesylate
DPP-4 inhibitor and biguanide combination	Sitagliptin and metformin HCl extended-release, linagliptin plus metformin hydrochloride, sitagliptin/metformin HCl, linagliptin and metformin hydrochloride, alogliptin and metformin hydrochloride
Glucagon-like peptide-1 (GLP-1) receptor agonists	Dulaglutide, abirglutide, exenatide extended-release, liraglutide, Exenatide, lixisenatide, liraglutide injection
Meglitinide and biguanide combination	Repaglinide/metformin hydrochloride
Insulin	Insulin types
Sodium-glucose co-transporter-2 (SGLT2) inhibitors	Empagliflozin, dapagliflozin, canagliflozin
Sulfonylureas	Glipizide, glyburide, glimepiride, chlorpropamide, tolbutamide, tolazamide
Thiazolidinedione, biguanide or sulfonylurea combinations	Pioglitazone hydrochloride and metformin hydrochloride, rosiglitazone maleate and metformin HCl, pioglitazone and metformin hydrochloride, extended release, pioglitazone hydrochloride and glimepiride, glimepiride/rosiglitazone, rosiglitazone, pioglitazone

Source: Gourgari et al. 2017

Table 6.4. Diagnosis Codes to Identify Cases of Diabetic Ketoacidosis.

ICD9/10	Diagnosis Code	Description
ICD9	250.1	Diabetes with ketoacidosis
ICD9	250.12	Diabetes mellitus with ketoacidosis, type II or unspecified type, uncontrolled
ICD9	250.13	Diabetes mellitus with ketoacidosis, Type I [juvenile Type], uncontrolled
ICD9	249.1	Secondary diabetes mellitus with ketoacidosis
ICD9	249.11	Secondary diabetes mellitus with ketoacidosis, uncontrolled
ICD10-CM	E08.10	Diabetes mellitus due to underlying condition with ketoacidosis without coma
ICD10-CM	E08.11	Diabetes mellitus due to underlying condition with ketoacidosis with coma
ICD10-CM	E09.10	Drug or chemical induced diabetes mellitus with ketoacidosis without coma
ICD10-CM	E09.11	Drug or chemical induced diabetes mellitus with ketoacidosis with coma
ICD10-CM	E10.10	Type 1 diabetes mellitus with ketoacidosis without coma
ICD10-CM	E10.11	Type 1 diabetes mellitus with ketoacidosis with coma
ICD10-CM	E13.10	Other specified diabetes mellitus with ketoacidosis without coma
ICD10-CM	E13.11	Other specified diabetes mellitus with ketoacidosis with coma

Table 6.5. Diagnosis Codes to Identify Cases of Hyperglycemic Hyperosmolar State¹.

ICD9/10	Diagnosis Code	Description
ICD9	249.2	Secondary diabetes mellitus with hyperosmolarity
ICD9	250.2	Diabetes mellitus with hyperosmolarity
ICD9	249.21	Secondary diabetes mellitus with hyperosmolarity, uncontrolled
ICD9	249.2	Secondary diabetes mellitus with hyperosmolarity, not stated as uncontrolled, or unspecified
ICD9	250.22	Diabetes mellitus with hyperosmolarity, type II or unspecified type, uncontrolled
ICD9	250.23	Diabetes mellitus with hyperosmolarity, type I [juvenile Type], uncontrolled
ICD10-CM	E11.01	Type 2 diabetes mellitus with hyperosmolarity with coma

¹These cases were removed from the analysis due to the similarities and overlap with DKA.

SUPPLEMENTAL MATERIAL III - Lists of Diabetogenic and Psychotropic drugs Used as Covariates as Groups of Drugs in the Logistic Regression Model, *and International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) Codes Used to Identify Tobacco Use.*

Table S6.6. List of Diabetogenic Drugs.

Class	Drug Name
Corticosteroids	Betamethasone, cortisone,
Calcineurin inhibitors	Cyclosporine, pimecrolimus, tacrolimus
Statins	Atorvastatin, fluvastatin, lovastatin, pivalastatin, pravastatin, rosuvastatin , simvastatin

Table S6.7. List of Psychotropic Drugs.

Class	Drug Name
Antidepressants	Desipramine, amitriptyline, nortriptyline, clomipramine, trazodone, nefazodone, fluoxetine, bupropion, sertraline, paroxetine, venlafaxine, desvenlafaxine, fluvoxamine, mirtazapine, citalopram, escitalopram, duloxetine, vilazodone, atomoxetine, vortioxetine, levomilnacipran, phenelzine, tranylcypromine, selegiline, trimipramine, protriptyline, amoxapine.
Psychostimulants	Methylphenidate, dexamethylphenidate, dextroamphetamine, lisdexamphetamine
Bipolar Disorder Medications	Lithium
Benzodiazepine	Carbamazepine, oxcarbazepine,
Anticonvulsants	Valproic acid, divalproex, amotrigine
Anti-Anxiety Medication	Diazepam, chlordiazepoxide, clonazepam, lorazepam, alprazolam, buspirone, gabapentin, pregabalin, clonidine, guanfacine, clomipramine, prazepam, oxazepam.
Hypnotics	Temazepam, triazolam, zolpidem, zaleplon, eszopiclone, ramelteon, diphenhydramine, doxepin, suvorexant.

Table S6.8. *International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) Used to Identify Used to Identify Tobacco Use.*

Tobacco Use	
Type	Diagnosis Code
ICD9	305.1, V15.82, F17.293
ICD10	F17, F17.290, F17.293, Z72

¹*International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10).*

SUPPLEMENTAL MATERIAL IV - Identification of Conditions Excluded from the Analysis Based on International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10).

Table S.6.9 List of *International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) Codes for Other Excluded Conditions*¹.

Acute Pancreatitis and Other Pancreatic Conditions	
Type	Diagnosis Code
ICD9	157, 557, 557.1
ICD10	K85.x, K86.x

Acute Kidney Failure	
Type	Diagnosis Code
ICD9	584.5, 584.6, 584.7, 584.8, 584.9
ICD10	N170, N272, N172, N178, N179

¹ICD9/10 codes are different from those included in the Elixhauser Comorbidity Index.

Rhabdomyolysis	
Type	Diagnosis Code
ICD9	728.88
ICD10	M62.82

Malignant Neuroleptic Syndrome	
Type	Diagnosis Code
ICD9	333.92
ICD10	G21.0

¹International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10).

CHAPTER 7

7. GENERAL DISCUSSION

7.1 Overview of Chapters and Objectives

In the previous thesis chapters, I presented two systematic reviews (Chapters 2 and 3) and three analytical papers (Chapters 4 to 6) that examined the clinical and epidemiological evidence on the association between antipsychotic drugs (APDs) and diabetic complications, namely diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS), both of which are serious emerging health issues (Figure 7.1).

The systematic reviews evaluated published case reports (CRs) and case series (Chapter 2) and observational studies (Chapter 3) that contain relevant information on the use of both atypical or second-generation antipsychotics (SGAs) and typical or first-generation APDs (SGAs) and the occurrence of DKA or HHS events. Two previous systematic reviews of CRs evaluated the association between APDs and DKA (Guenette et al. 2013; Vuk et al. 2017): my systematic reviews are wider in scope and discuss both outcomes. In addition, Chapter 2 evaluates data on blood glucose (BG) levels and hemoglobin A1c (HbA1c), when such data was available.

I used the United States Food and Drugs Administration (US FDA) Adverse Event Reporting System (FAERS) database (Chapter 4) to analyze spontaneous reporting and drug safety signals of atypical APDs associated with DKA adverse drug reactions for the period 2000-2022; I also conducted a similar analysis restricted to the period 2000 to 2016 (presented in Supplemental Material) to coincide with the study periods for Chapters 5 and 6. Potential drug safety signals were identified for quetiapine and olanzapine as primary and as secondary suspect drugs,

compared to either psychotropic drugs, or to all other drugs. The use of two reference categories (psychotropic drugs and all drugs other than antipsychotics) demonstrated robustness of these safety signals.

The analysis of trends in prescribing practice (Chapter 5) examined the long-term trends of FDA-approved APD use overtime, both by class and by individual drugs, in the US using Cerner Health Facts® (Health Facts) between 2000 and 2016. Based on conclusions drawn from the systematic reviews and the FAERS analysis, I hypothesized that the prevalence of use of atypical APDs will increase overtime, and expected a concomitant decrease in the prevalence of use of their predecessors. Overall, haloperidol remained the most prescribed antipsychotic medicine in Health Facts. In the atypical APD class, findings show that quetiapine had the highest prevalence of use in the US between 2000-2016, followed by risperidone and olanzapine. While the observed trends show an overall decrease in the use of typical APDs, the use of prochlorperazine and haloperidol, remained prevalent throughout the study period: they were the first and second most prescribed typical APDs, respectively, with haloperidol becoming the most prescribed drug in this class as of 2012, while prochlorperazine decreased consistently as of 2011. To the best of my knowledge, this is the largest trends examining the prevalence of APD use by class (typical and atypical) and for twenty-five individual drugs irrespective of patient diagnosis.

Considering the evidence presented in Chapters 2 to 5, I decided to analyse the risk of first occurrence of DKA events with use of APDs as a class, followed by additional analyses of a selected number of the more commonly used individual APDs (Chapter 6). The decision to focus on DKA as an endpoint, to the exclusion of HHS, was because hyperglycemic

complications are generally coded as DKA events in healthcare settings in the US (Dr. J. Goguen, personal communication). Consequently, Chapter 6 presents the finding from a nested case-control (NCC) study designed to evaluate this association. Following a thorough and systematic evaluation of covariates based *a priori* knowledge, expert advice (Dr. J. Goguen, personal communication), and information available in Health Facts during the study period, multivariable logistic regression analyses were used to control for the effects of relevant covariates on the occurrence of DKA. Findings from the case-control analysis did not reveal an increased risk of DKA associated with APD use. However, subgroup analysis by age group and level of comorbidities indicated a potential association with APD drug use and DKA risk in the elderly and/or those who had multiple comorbidities except for prochlorperazine. Exposure to this antipsychotic medicine was associated with an increased risk of DKA in the younger and healthier population. Haloperidol was associated with an increased risk of DKA for all age groups in those who experienced multiple comorbidities. Atypical APDs as a class were associated with an increased risk of DKA in the healthy elderly, and ziprasidone was associated with an increased risk in the elderly who experienced a moderate level of comorbidities.

All objectives of the PhD thesis were accomplished as described above and the findings from Chapters 2, 3, and 4 provided accrued evidence of a potential, yet incompletely understood, association between APD use and diabetic complications, mainly DKA. The NCC (Chapter 6) provided evidence of a possible association in specific populations, yet additional analyses are needed to reach a strong conclusion. The first and second objectives are addressed in Chapters 2 and 3, with objectives 3 to 5 addressed in Chapters 4 to 6, respectively (Figure 7.1).

Figure 7.1. Relationship between the Research Objectives and the Individual Studies Presented in the Thesis.



Abbreviations: APD, Antipsychotic drugs; DKA, Diabetic ketoacidosis; HHS, hyperglycemic, hyperosmolar state; US FAERS, United States Food and Drugs Administration Adverse Events Reporting System

The general discussion presented in this concluding chapter will examine the following questions.

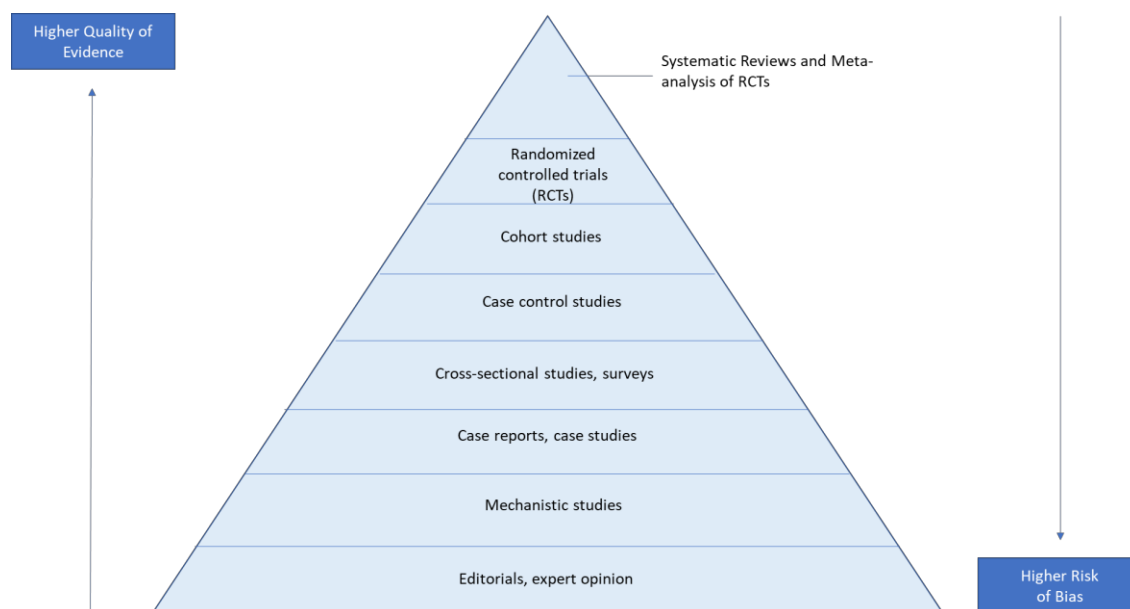
1. How can the findings from the different chapters be integrated into a solid evidence-based synthesis?
2. What are the advantages and disadvantages of analyzing CRs and EHRs?
3. Why was the nested case-control study design chosen to evaluate the risk of APD use and DKA?

4. How did the identification of diabetics, the ascertainment of exposure and outcome contribute to the robustness of the analysis?
5. How can analysis of polypharmacy and dosage be incorporated in future research?
6. What are some of the possible biological mechanisms of action of antipsychotic drug-induced DKA?
7. In conclusion, can we establish an association between the use of atypical APDs and hyperglycemic complications, namely DKA and HHS?
8. What recommendations can be made to enhance the safety of atypical and typical APDs with respect to avoiding hyperglycemic complications?

7.2 Integrated Evidence Synthesis

The evidence hierarchy pyramid shown in Figure 7.2 can be used to present the strengths and limitations of the evidence presented in this thesis.

CRs and Case series are designed to examine patient medical records for anecdotal evidence of an association between exposure and outcome. While a single CR cannot be used to infer causality, Chapter 2 includes a critical appraisal of a number of cases describing antipsychotic-induced DKA or HHS. I used the Joanna Briggs Institute (JBI) criteria to critically appraise the content of each report against the eight JBI criteria (Gagnier et al. 2013; Moola et al. 2020). As noted previously, each CR is written differently, and although this flexible approach provides a certain freedom that is lacking when publishing other types of epidemiological study designs, it

Figure 7.2. Hierarchy of Evidence Pyramid¹.

¹Adapted from Krewski et al (2022); Yetley et al. (2017).

is important for clinicians to adopt a more “standardized” approach when consolidating information into single CRs to describe the use of atypical APDs and DKA or HHS. This standardization will support aggregate case series analysis, which can provide stronger evidence than a single CR.

Using a second systematic review (Chapter 3), I evaluated information from five analytical and eight descriptive observational studies, which varied in scope pertaining to the case definition, study populations, exposure, and outcomes and overall study design. Based on the information provided, it was not possible to present an integrated quantitative characterization of this body of evidence. Nonetheless, this body evidence supports a possible association between atypical APD use and DKA (Henderson et al. 2007; Leslie & Rosenheck, 2004; Ramaswamy et al. 2007), and between atypical and typical APDs and DKA (Galler et al. 2015; Polcwiartek et al. 2017).

Diabetic patients in particular are more susceptible to develop this outcome when exposed to APDs as previously suggested (Abate et al. 2023; Lipscombe et al. 2014; Vuk et al. 2017). To further evaluate the quality of these studies, I used the Office of Health Assessment and Translation (OHAT) approach for systematic reviews and evidence integration to assess the risk of bias for each study. Analytical studies were classified in tier 1 (low risk of bias) or tier 2 (study did not meet criteria for low or high). Five descriptive studies were classified as tier 3 where the risk of bias was high (mainly due to the pooled presentation of hyperglycemia in the findings). This evidence indicates there is a need for more observational research, both retrospective and prospective, to ascertain the possible association between APDs and DKA or HHS.

Based on findings in the two systematic reviews, I decided to proceed with the three analytical studies as described above. The FAERS database, a post-marketing pharmacovigilance tool, was used to provide an assessment of how often DKA events have been co-reported with antipsychotic medicines as primary or secondary suspect drugs. Although I cannot establish with certainty that a DKA adverse event was due to the use of an atypical APD (in other words, it was not possible to infer causality), and I was not able to calculate effect estimates (increased incidence) of the adverse event in the US population, two important safety concerns were observed for two atypical APDs, quetiapine and olanzapine, and DKA adverse events.

Chapter 5 examines the trends in antipsychotic drug use by class and by individual drug in the US using the Health Facts database, irrespective of indication. This analysis showed that haloperidol and prochlorperazine are the two most prevalent antipsychotic drugs used in Health Facts, while quetiapine and olanzapine are amongst the top three prescribed atypical

APDs in the US. Overall, the use of atypical APDs increased in inpatient settings throughout the study period adding weight to the findings presented in the previous chapter.

Descriptive and analytical findings described in these four chapters paved the way forward for a NCC study design (Chapter 6), in which I compared DKA cases and controls with respect to their past exposure to APDs by class and by individual drug. Findings from the case-control analysis did not reveal an increased risk of DKA associated with APD use. However, subgroup analysis by age group and level of comorbidities indicated a potential association with the exposure to haloperidol and DKA risk in those who had multiple comorbidities. Prochlorperazine was associated with an increased risk of DKA those 18 to 39 years of age and relatively healthier population. Atypical APDs as a class were associated with an increased risk of DKA in the healthier elderly subjects, and ziprasidone, an atypical APD, was associated with an increased risk in the elderly who experienced a moderate level of comorbidities. Together, reviews of the relevant literature, pharmacovigilance analysis and real-world evidence from Health Facts provide three distinct evidence streams on which to evaluate strength of evidence for an association between APDs and DKA or HHS.

7.3 Strengths and Limitations of Case Reports

CRs have many valuable attributes as described by Nissen & Wynn (2014), although they are considered less rigorous methodologically than analytical epidemiological studies. I summarize some of their positive attributes and limitations below.

1. *Detecting new emerging issues to inform the medical community and sensitize readers:*

CRs can provide uncontrolled observations on symptoms and clinical findings, progress of the illness, the chosen interventions and potential complications associated with

treatment, prognosis, and information on the follow up period, if such information is available.

2. *Developing new hypothesis:* CRs are important in drug safety surveillance (Abou Chakra et al. 2010). Consistent communication between clinical and academic investigators may lead to insights on possible associations between intervention and outcome, and on generating novel hypotheses that can be tested using comparative studies (both observational and experimental). They are particularly important in the field of psychiatry, since many drugs used to treat severe mental illnesses were discovered by chance (Ban 2006). For example, chlorpromazine was discovered serendipitously in 1950 by the French pharmaceutical company Rhône-Poulenc. It was initially intended to be used in the fields of anaesthesiology, the antishock area, and in artificial hibernation technique, and not in the field of psychiatry. It was in the mid-1955's that the effective neuroleptic properties of this antipsychotic became evident (López-Muñoz et al. 2005).
3. *Ethical issues and rare conditions:* DKA and HHS are rare but life-threatening conditions. Experimental research with real-world patient populations may be limited due to ethical constraints, and may be subject to low study power due to the small numbers of participants enrolled in relevant studies. In this case, CR and case series are considered “natural experiments” that can be used to inform clinical practice. This can be complemented by non-experimental research on human subjects and pre-clinical studies in animals or *in vitro* for hypothesis testing to support or refute a possible association between APDs use and diabetic complications.

4. *Education and change in clinical practice:* CRs add value to medical learning at the clinical level: this is particularly relevant in the field of psychiatry where the treatment strategies for a patient must be clearly understood. Furthermore, CRs can contribute significantly to the enhancement of preventative measures or changes in clinical practice. Their accrued publication can prompt safety communications from the FDA (as seen for SGLT-2 inhibitors) or a consensus statement from the ADA (2004) regarding the use of atypical APDs and the metabolic syndrome (MetS), as well as recommendations for clinical monitoring of relevant biomarkers for hyperglycemic emergencies (Goguen & Gilbert 2016). Stronger measures may result in a discontinuation or change in the treatment regimen (e.g., switching to a different APD, or change in dosage of the APD suspected of causing the complication) (Chapter 2).

There are certain limitations to CRs that are worth noting.

1. *Population and Generalization:* CRs do not constitute a representative sample of a particular population and cannot generate quantitative epidemiological information since they do not have a denominator needed for the calculation of the incidence or prevalence rates of adverse events. Nonetheless, it is possible information presented in CRs is overinterpreted by the reader in terms of generalizability and causal inference. On the other hand, case series can analyse aggregate CRs and refute or support the existence of an association, prompting hypothesis testing through future experimental and non-experimental research and surveillance. As presented in Chapter 3, case series have been used to provide descriptive analysis of the association of atypical APDs and DKA (Jin et al. 2002).

2. *The retrospective nature of the CRs:* Information is consolidated after the occurrence of a DKA or HHS event. Patient medical histories often lack information on relevant biomarkers prior to the event, and as such CRs may be incomplete and do not provide a comprehensive full picture about the case.
3. *Biases:* Due to their retrospective nature, CRs are more susceptible to recall and information biases. Clinicians do not have all the necessary information that should or could have been obtained from the patients, families, or health care professionals. Information bias may also occur due to subjective interpretations by those reading the CR (Nissen and Wynn, 2014).

7.4 Methodological Aspects of the Analytical Studies

7.4.1 The Use of Administrative Health Databases in Epidemiology

In the Introduction to my thesis presented in Chapter 1, I referenced studies that used large administrative data for epidemiological research to study patterns of drug use over time, including estimation of quantitative indicators of the association between an intervention/drug exposure and outcome/disease. These data warehouses comprise data from hospitalization databases (e.g., diagnosis, procedures, admissions), physicians claim databases (physician visits, laboratory tests), registration systems (patient registration data) and prescription medication records and hospitalization charts (Van Walraven et al. 2012). However, their usefulness in comparative research is hindered by certain limitations. First, data recorded may not contain all the information required to answer a specific research question. Second, they require a ‘gold standard’ definition of the outcome/disease of interest for precise estimation of an association. Third, they require linkage of databases to mitigate the risk of bias due to missing data

elements and confounding, which may not always be feasible (Van Walraven et al. 2012; Waikar et al. 2006). These limitations are further addressed below.

7.4.2 Benefits and Disadvantages of Using Electronic Health Records.

The benefits for using EHRs for epidemiological research outweigh their disadvantages. Several advantages have been noted by Farmer and colleagues (2018). First, data is prospectively collected in real-time limiting the effect of recall bias; this is particularly relevant for diabetes, a chronic but changing disease, where the availability of near-real-time data is crucial. Generally, EHRs include detailed prescribing and dispensing information on medication use as well as information on comorbidities that may affect the outcome of interest. These rich sources of data can be obtained through appropriate linkages across datasets from different healthcare settings. The large sample size increases study power and findings are more representative of the source population and allow for more accurate generalizations (Bhaskaran et al. 2014; Brauer et al. 2016; Herrett et al. 2015; Schmidt et al. 2014).

Duan and colleagues (2020) compared FAERS and Health Facts to examine evidence of consistency of pharmacovigilance outcomes for acute mania patients. The authors evaluated safety outcomes for 12 first-line antiemetic drugs including haloperidol, aripiprazole, olanzapine, quetiapine, and risperidone in FAERS and compared these to data from Cerner Health Facts® after extracting encounters and medication order status. They used a data mining method to map *International Classification of Diseases* (ICD) codes used in Health Facts to Medical Dictionary for Regulatory Activities (MedDRA) used in FAERS to ensure comparison of evidence is based on the same terminology; they subsequently quantified consistency of evidence from the two data sources statistically. The authors concluded it is important have an

appropriate definition of adverse events under different contexts since this is a limitation when using multiple data sources for drug safety analyses. There is a need for more sophisticated analytical methods and modeling tools to complement these gaps for evidence synthesis, as well as evaluating clinical notes for additional information. Table 7.1 compares characteristics between the two databases.

Table 7.1. Comparison of the United States Food and Drugs Administration Adverse Event Reporting System and Health Facts¹.

Characteristics	FAERS	Health Facts
Diagnosis	Based on MedDRA terms.	Based on ICD9/10 Diagnosis codes recorded for all encounters. May or may not have a relation with the medication.
Cohort	Spontaneous Reporting System, voluntary based. Submissions from consumers, health care professionals, lawyers, and industry.	Data is retrieved from hospitals. Detailed information entered by hospital staff.
Evaluation of Adverse Events	Post-medication surveillance of AE that are reported	ICD9/10 codes may or may not have a relation to the medication.
Control Group	Only cases with AE are reported. No control group.	All encounter information was recorded. Control group.
Temporal Relationship	Post-medication reporting of AE and year of AE. No other time-related information.	Time stamps for encounters (admission and discharge dates)

Abbreviations: AE, Adverse events; FAERS, Food and Drugs Administration Adverse Event Reporting System; ICD, International Classifications of Disease; MedDRA, Medical Dictionary for Regulatory Activities.

¹Adapted from Duan et al. (2020).

7.5 Study Design

7.5.1 Nested Case-Control Study Design

For the final analysis presented in this thesis (Chapter 6), I chose a NCC study design. The modern view is that both experimental (e.g., randomized control trials, RCTs) and non-experimental studies (e.g., NCC and cohort studies) are both essential to evaluate the effect

estimates of drug treatment with respect to a condition in a specific population (Gamble et al. 2014). RCTs are the gold standard for the evaluation of clinical endpoints, but they have insufficient power due to a small sample size, a shorter length of follow up, and influences attributed to changes to patient behaviour and aspects of clinical care. Key populations, including ethnic minorities and patients with multi-morbidities may be underrepresented (Edwards et al. 2016; Hussain-Gambles et al. 2004; Zhang et al. 2013). NCCs generate comparable risk estimates to cohort study design (Breslow et al. 1983; Liddell et al. 1977; Lubin & Gail, 1984). They also allow the analysis of data for a subset of a larger cohort, thereby realizing efficiencies in of time and resources (Essebag et al. 2005; Etminam, 2004; Sedwick, 2014).

7.5.2 Ascertainment of Diabetic Status

Farmer and colleagues (2018) provided recommendations to reduce biases and confounding in diabetes epidemiology. The NCC analysis examines the association between exposure to APDs and DKA as an endpoint in a diabetic cohort (Chapter 6). Desirable attributes for this analysis include the following:

1. To confidently identify patients with diabetes.
2. To address time-varying exposure and if possible, limit to incident users of medication when examining treatment effects and compare treatments that would be used at similar stages of the disease.
3. To confidently identify the outcome and evaluate if combining prevalent and incident cases be relevant for the question of interest.
4. To address time-dependent confounding.

7.5.2.1 Identification of Subjects with Diabetes

For ascertainment of disease status, it is important to accurately identify and categorize the diabetic status of all subjects within the cohort from which cases and controls will be chosen. Diabetes is a chronic condition with a long latency period between disease onset and diagnosis. This is complicated by other challenges, such as the misclassification of DM type (e.g., type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), other forms of diabetes). To address this issue, I used a dynamic cohort of DM patients, including all diabetes types to reduce the chance of misclassification and biased estimation of the impact of diabetes on the outcome (i.e., DKA). Second, I used a combined approach to integrating diagnostic and medication information. The case definition for the NCC included a diabetic cohort of patients diagnosed based on ICD9/10 codes and/or those who were prescribed an FDA-approved antidiabetic medication: having been prescribed an antidiabetic medication can be used as a proxy for diabetes when ICD9/10 codes are unavailable. This approach was previously used to overcome these biases. Mathur and colleagues (2017) used an algorithm to classify patients based on the presence of T1DM or T2DM and they confirmed the diagnosis with supporting information such as prescriptions of antidiabetic medications, elevated blood glucose, and diabetes process of care measures. Eastwood et al. (2016) derived and tested algorithms for prevalent and incident diabetes using linked primary and secondary care data in the English Clinical Practice Research Datalink (ECPRD). This included assigning algorithms based on diabetes status and other supporting information such as diabetic medication, blood testing and diabetes process care of codes (e.g., foot screening).

7.5.2.2 Exposure Status

The exposure status of study participants to an antipsychotic medicine may change overtime due to change in the prescribed treatment plan or the patient's lack of adherence to treatment. In Health Facts, this assessment is complicated by possibly incomplete medical histories or drug utilization records for the patient. Restricting the analysis to the 'new-user' design as proposed by Strom (2022) may address this issue. However, limiting the analysis to the new-user design will also reduce sample size and the study power. Using the new-user design was not possible in my analysis due to lack of information on prior history of APD use, as well as possible switching and discontinuation of certain drugs. In addition, it is possible patients were prescribed APDs in outpatient settings and these are not fully captured in Health Facts. I addressed this by analysing exposure to APDs as ever or never use in an inpatient setting and I assumed these agents would be administered by health care professionals considering they are used to treat mental health diagnoses. To fully explore the association between APDs and DKA, I evaluated atypical and typical APDs as classes of drugs in addition to individual drug exposure. I assumed exposure would be affected by the same unmeasured confounders as the primary association of interest (atypical APDs).

7.5.2.3 Outcome Ascertainment

Patient care generally requires the involvement of different healthcare professionals, which can affect the measurement and accuracy of risk factors and outcomes. Furthermore, it is possible that the history of a DKA diagnosis was recorded at multiple encounters in Health Facts. To address this issue, I chose the first occurrence of a DKA event for each patient as the outcome of interest. As some patients were diagnosed with diabetes and/or DKA at the first encounter

(first time they were registered in Health Facts), I analyzed incident cases if they occurred on the same date or after the patient was determined to be diabetic. This approach is also consistent with the findings from Chapter 2 and 3 since DKA events occurred in those with no known history of DM, or in those experiencing a diabetic condition.

7.5.2.4 Unmeasured Confounding

To adjust for potential confounders, I examined a previous example of a NCC study on the association of APDs use and DKA (Polcwiartek et al. 2017). Furthermore, I confirmed this information in two different ways, through (1) systematic review of the literature on the association between certain covariates and DKA, and (2) by seeking expert clinical advice (Dr. J. Goguen, personal communications).

While I exercised due diligence in minimizing potential confounding, I was not able to adjust for covariates for which data was unavailable (e.g., trauma); incomplete information on time-dependent covariates (e.g., BMI) over the 16-year study period was also a limitation of my NCC study. These data gaps increase the risk of residual and unmeasured confounding. Similarly, EHRs do not generally include information on diet and physical activity, both of which could be relevant confounders when examining diabetes-related exposures and outcomes (Farmer et al. 2018).

7.6 Type of Therapy

The results presented in Chapter 2 categorized treatment into monotherapy or polypharmacy. This is different from how others have presented their findings. In two comprehensive reviews on DKA CRs in the literature (Guenette et al. 2013; Vuk et al. 2017), the authors categorized treatment into single drug use, combined drug use, or not reported. However, there were also

notable differences in how each review classified and reported APD polypharmacy. In my systematic review, I assumed the patient received monotherapy treatment with an APD, unless it was clearly stated the patient was using more than one APD at the time of the complication. As previously mentioned, temporality is not always clearly delineated in CRs, and data on APD polypharmacy may not always be available. However, most CRs included in the analysis discuss one suspected causative agent for the hyperglycemic complications. Furthermore, in the case of polypharmacy treatment, the resolution of DKA or HHS can occur after the discontinuation of the causative agent only, discontinuation of all APDs, or after a new reduced dosage was introduced as part of a new treatment plan. Based on their classification and the high number of 'non-reported', both Guenette et al. (2013) and Vuk et al. (2017) reported that half of all DKA cases occurred after the introduction of polypharmacy. Vuk et al. (2017) suggested that olanzapine or clozapine may be associated with an increased risk of DKA during combination treatment with more than one APD. Correl et al. (2007) compared newly admitted psychiatric inpatients who were receiving APD monotherapy (n = 294) or APD polypharmacy (n = 70). Their findings indicated that patients receiving a combination therapy of APDs - while it is not independently associated with the observed clinical symptoms - have higher rates of MetS and lipid markers of insulin resistance. Other risk factors may affect this association, including demographic and anthropometric measurements.

In the future, more robust non-experimental studies are needed to have a clearer understanding of the effects of monotherapy and polypharmacy APD use, since polypharmacy complicates the interpretation of the effect of single APD drug contribution on the risk of occurrence of DKA.

7.7 Antipsychotic Drug Dosage

A study by Ulcickas Yood et al. (2011) analyzed data from three US healthcare systems using diabetes-naïve adult patients who were not prescribed an APD within three months of the index date. Findings indicated the risk of developing diabetes among individuals who were exposed to olanzapine, risperidone or quetiapine increased with higher therapeutic doses. In the case of aripiprazole and ziprasidone, there was no apparent dose-dependent relationship, and these newer medications did not appear to increase the risk of diabetes. The authors recommended interpreting these results with caution due to the small sample size with aripiprazole and ziprasidone and the low precision of hazard ratio estimation. As noted in Chapter 3, Koller et al. (2001,2002,2003,2004) used spontaneous reports to study APD safety signals manifest as hyperglycemia, including DKA and HHS. The authors concluded the association between the atypical APDs clozapine, olanzapine, risperidone and quetiapine and hyperglycemia (including DKA and other hyperglycemic exacerbations) is not dose-dependent, and the risk is not diminished with extended therapy. However, these results need to also be interpreted with caution since spontaneous reports cannot infer causality, and the authors do not always differentiate between DKA and other hyperglycemic exacerbations when presenting their results. As detailed in Chapter 2, reduced dosages of APDs were administered after DKA or HHS for some cases to ensure the patient continued to be treated for mental illnesses or behavioral conditions. While this is informative, further analysis analyzing safe and effective doses of APDs would be beneficial. Since APD use was evaluated as ever/never, the potential impact of drug dosage has not been taken into account.

7.8 The Use of Sodium-Glucose Cotransporter 2 Inhibitors as a Positive Control

The FDA issued a drug safety communication on the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors - specifically canagliflozin, dapagliflozin and empagliflozin - that were developed to treat T2DM and approved for use between 2013 and 2017, and the increased the risk of DKA (FDA, 2015). The FDA communication was supported in part by an analysis of 20 atypical clinical cases of acidosis, captured between March 2013 and June 2014 in FAERS and these included cases of DKA, ketoacidosis and ketosis in patients who mostly had T2DM. BG levels, when available, were lower compared to typical cases of DKA (FDA, 2015). This was followed by recommendations from the European Medicines Agency (EMA) in 2016 to mitigate the risks of DKA by limiting the use of these drugs, and a warning by Health Canada after it concluded there is evidence that supports a link between the use of these hypoglycemic drugs and the risk of DKA in T2DM patients, although it was noted that DKA also occurred in T1DM patients (Health Canada, 2016). The benefits of treatment with SGLT-2 outweigh the risks, if used as authorized, and the FDA updated their guidelines recently recommending the interruption of treatment with SGLT2 inhibitors and monitoring ketoacidosis in patients scheduled for surgery or are hospitalized (FDA, 2020), followed by resumption of treatment with these agents once ketone values normalized and the patient's condition stabilised.

Goldenberg et al. (2016) reviewed 46 CRs of DKA. Twenty-four CRs had T2DM, 15 had T1DM, and others had pancreatic (Type 3c) diabetes or latent autoimmune diabetes in adulthood (LADA). Seventy percent of the CRs presented had euglycemic DKA (euDKA), an atypical form of DKA characterized by lower-than-anticipated glucose levels (plasma glucose levels < 14 mmol/L), which can possibly delay diagnosis and the timely treatment of this life-threatening

condition. Since then, additional case reports have added to the weight of evidence for an association between SGLT-2 inhibitors and the risk of DKA (Aung et al. 2019; Dorcely et al. 2021; Lee & Ahn, 2019).

These findings were corroborated recently by He et al. (2023). Using the FAERS database, they analyzed cases of SGLT-2-associated with both euDKA and DKA. These drugs were associated with significantly higher reporting of these rare outcomes. Sampani et al. (2020) reviewed existing epidemiological, pathophysiological, and treatment data from clinical trials to shed light on the risk of euDKA as a complication of SGLT2 inhibitors. While the rate of DKA in clinical trials was low, it could be underestimated due to the atypical presentation of this complication.

Considering this cumulative body of evidence, I used SGLT-2 as a positive control in the FAERS analysis (Chapter 4) for three reasons: 1) to ensure accuracy and reliability of the analysis by comparing the safety signals of SGLT-2s and atypical APDs; 2) to provide a standard comparison to determine whether observed adverse events (AE) associated with SGLT-2s are statistically significant when compared to the expected results; and 3) to identify the possibility of false positives by comparing the rates of AE associated with atypical APDs to the rate of AE associated with SGLT-2s. The results obtained using SGLT-2s as a positive control corroborate the findings of the analysis with atypical APDs, allowing me to draw evidence-based conclusions on the safety and effectiveness of atypical APDs from this analysis with greater confidence. I was not able to use SGLT-2 as a positive control for the NCC analysis, either as a class of drug or

individual drugs. These antidiabetic agents were FDA-approved only as of 2013 and their prevalence of use was low in the parent diabetic cohort (Chapter 6).

7.9 Plausible Biological Mechanisms of Antipsychotic Drug-induced Diabetic Ketoacidosis

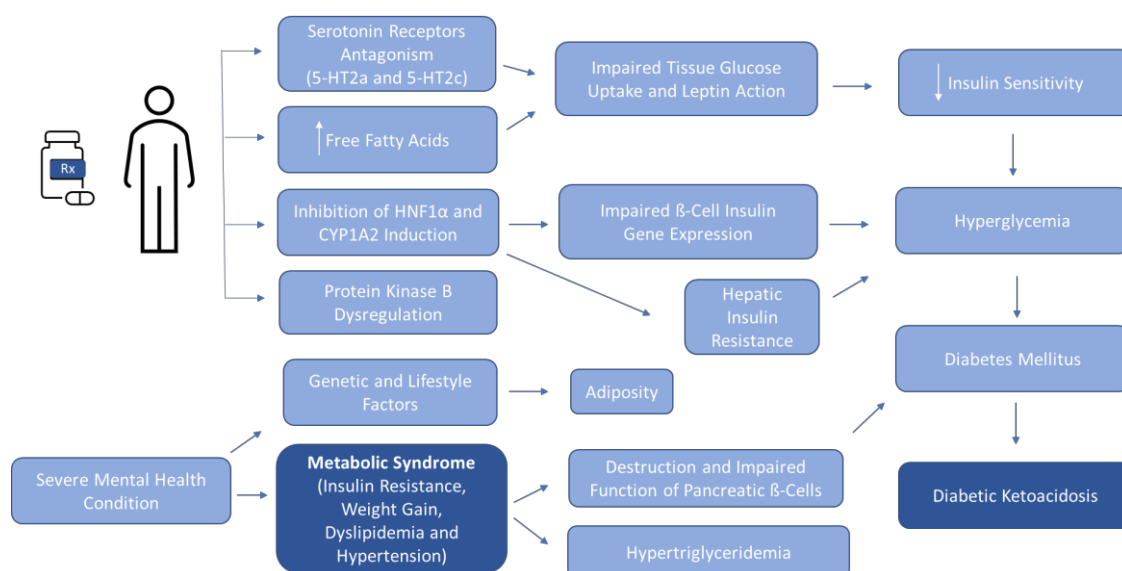
In the previous sections, I presented three different evidence streams to evaluate the potential association between APDs and diabetic complications, particularly DKA. The results obtained in the different chapters are informative, but there are some inconsistencies in the results from the different data sources. For example, the NCC shifted the focus to older patients who may also experience multiple comorbidities. This indicates the need for an integrated research approach to better understand this association. It is, therefore, important to explore biological pathways that may explain this association.

A cross-sectional survey of Canadian households found that atypical APDs are generally associated with metabolic syndrome (defined by fasting glucose ≥ 5.6 mmol/L, high blood pressure, obesity) (Hirsch et al. 2018). Moreover, RCTs have shown that atypical APDs are linked to serious metabolic side-effects such as weight gain, hypertension, dyslipidemia and T2DM (Chaplin & Taylor, 2004). These serious conditions have resulted in patients discontinuing treatment and experiencing serious long term health conditions (McEvoy et al. 2005).

The literature presents many plausible theories to explain the possible mechanisms of action of antipsychotic medicines and DM and diabetic emergencies, including DKA and HHS. However, to date, no single underlying mechanism has been identified. The modalities of antipsychotic-induced DKA and HHS are complex and multifactorial, encompassing the following factors:

drug-induced weight gain (e.g., use clozapine and olanzapine) resulting in abdominal adiposity; the development of MetS syndrome (defined by insulin resistance, central obesity, dyslipidemia and hypertension); antagonisms of serotonin receptors; and dyslipidemia mediated pancreatic β -cell damage (Buchholz et al. 2008). Similar pathways were proposed by Vuk et al. (2017) and Holt (2019). In Chapter 3, I presented a simplified scenario, adapted from Holt (2019) on the possible interplay between association and causality for APD-induced DKA or HHS. Below, I elaborate on what I presented in Chapter 3 and present a more fulsome discussion with a focus on cellular pathways (Figure 7.3).

Figure 7.3. Mechanisms of Action of Antipsychotic Drug Induced Diabetic Ketoacidosis^{1,2}.



¹Adapted from Buchholz et al. (2008); Holt (2019); Vuk et al. (2017).

²This is a simplified image intended to provide an overview of how different molecular and cellular pathways may lead to DKA. It is not intended to provide a detailed appreciation of all modulating factors and/or interactions.

7.9.1 Weight Gain

MetS is generally more prevalent in schizophrenia patients compared to the general population (Heiskanen et al. 2003). As noted in Chapter 2, most patients who had an occurrence of DKA were previously diagnosed with schizophrenia (59%), and 31% of these patients experienced weight gain, while 46% were described as overweight or obese. It is difficult to draw fulsome conclusions on weight gain or BMI since 44% of CRs did not report this information. Some of the observational studies presented in Chapter 3 examine this risk factor. Jin et al. (2002) found that 50% of cases with new-onset DM or DKA did not report significant weight gain at the time of presentation, potentially indicating a more direct APD-mediated effect on glucose metabolism or regulation independent of adiposity, a notion also suggested by others (Holt, 2019; Vuk et al. 2017).

Starrenburg & Bogers (2009) presented a simplified theory of how weight gain induced by atypical APDs can exacerbate insulin resistance. It is, however, important to note that there is a complex interplay between the different factors involved. First, weight gain is a common side effect of some -but not all- atypical APDs such as olanzapine and clozapine, and it is not experienced by all patients. Second, risk factors other than obesity, such as genetics, the age of the patient, and lifestyle (notably sedentary) are key factors that can contribute to insulin resistance. Third, while insulin resistance may lead to the development of a diabetic condition, other risk factors include genetics, inflammation, and β -cell dysfunction can also have a direct impact on this outcome.

7.9.2 Antipsychotic Drugs and the Nervous System

Most atypical APDs have a strong serotonin 5-hydroxytryptamine (5-HT_{2A}) receptor antagonistic properties, a characteristic feature that could indicate a more direct receptor-mediated effect of APDs on glucose tolerance, independent of weight gain.

Gilles et al. (2005) used a double-blind, placebo-controlled crossover study and healthy male subjects without relevant physical or mental disease to assess the hypothesis that antagonism of the serotonin (5-HT)-2 receptor impairs insulin sensitivity. Subjects were treated with ketanserin, a 5-HT₂ antagonist, and compared with subjects who received the placebo. Ketanserin was shown to impair insulin sensitivity ($p=0.047$), which may have been mediated by the suppression of 5-HT(2A) receptor mediated glucose uptake in skeletal muscle.

Two animal studies aimed to investigate weight gain-independent mechanisms of atypical APD induced changes in insulin secretion by deconstructing their binding profiles with representative antagonists in healthy rats. The first study by Hahn et al. (2011) found that direct inhibitory effects of muscarinic (M₃) and serotonergic (5HT₂) antagonism on insulin secretion is possibly related to the effects of antipsychotic agents on glucose dysregulation. The authors suggested that a prolonged dopamine 2 (D₂) blockade with antipsychotics may increase the likelihood the depletion of insulin stores and an eventual defect in pancreatic compensation (functional deterioration). A second study by the same group of researchers found that α_1 and 5HT_{2A} receptor antagonism may be involved in glucose dysregulation with atypical APD treatment, as treatment with prazosin (a selective α_1 antagonist) and MDL100907 (a selective 5HT_{2c} antagonist) resulted in significant decreases in both insulin and C-peptide secretion compared to their respective controls (Guenette et al. 2013). These studies suggest

atypical APDs can have direct effects on glucose homeostasis, independent of weight gain, and that different receptor binding profiles may contribute to these effects.

7.9.3 Antipsychotic Drugs and the Endocrine System

7.9.3.1 Leptin and Fatty Cells

Leptin, a hormone produced by fatty cells in the body, has a direct effect on central physiological functions including inhibitory control of appetite. Leptin resistance or reduced leptin secretion may play a role in the development of early onset morbid obesity. However, it has been suggested that even with increase in leptin levels, the use of atypical APDs has been shown to increase fat deposition, which may indicate this class of drugs can interfere with the effect of leptin in the hypothalamus by blocking 5-HT_{2c} receptors and contributing to an unfavorable metabolic profile (Nonogaki et al. 1998).

7.9.3.2 Olanzapine-A complex Mechanism of Action

Although some CRs (Chapter 2) and observational studies (Chapter 3) suggested olanzapine involvement in the occurrence of DKA, findings from the NCC analysis (Chapter 6) did not demonstrate an association between this antipsychotic and an increased risk of DKA. As such, it is important to briefly discuss its mechanism of action.

Olanzapine was shown to increase the risk of developing DM compared to typical APDs (Koro et al. 2002), and the first three months of olanzapine treatment are associated with increased risk of DM when compared to risperidone (Caro et al. 2002). Melkersson et al. (2000) analyzed data fourteen patients diagnosed with schizophrenia or related psychosis and treated with olanzapine. They observed a weight increase was observed in almost all the patients (12/14) and a little over half of participants reported a BMI above normal limits (8/14) during a median

treatment time of five months. Elevated glucose and insulin levels were observed in (3/14) (other patients were normoglycemic) and (10/14), respectively, while increased leptin and blood lipids were reported for eight participants. Eight participants had higher than normal levels of triglycerides and 11 participants had above normal cholesterol levels. The authors suggested that insulin secretion and hyperleptinemia may be contribute to mechanisms behind olanzapine-induced weight gain. Weight gain and other metabolic markers such as BG, triglycerides and cholesterol inversely correlated with serum concentrations of 4-N'-desmethyl-olanzapine (DMO), a metabolite of olanzapine, suggesting DMO may have a normalizing effect on the metabolic abnormalities as opposed to its parent drug (Melkersson et al. 2000).

An et al. (2022) explored the relationship between metabolic parameters and steady-state plasma concentrations of olanzapine and DMO in olanzapine-treated inpatients with schizophrenia. Plasma concentrations of olanzapine and DMO were measured, and fasting blood samples were taken to measure metabolic parameters including insulin, glucose, cholesterol, triglycerides, and C-reactive protein. Higher plasma olanzapine concentrations were associated with higher C-reactive protein and homocysteine levels, while lower plasma DMO concentrations were associated with higher glucose and triglyceride levels and insulin resistance, suggesting again that olanzapine and its metabolite DMO may have different effects on olanzapine-induced metabolic abnormalities. Tsuchiyama et al. (2004) summarized findings for a 28-year-old male presenting with DKA who has a family history of DM (Chapter 2). The metabolic profile post-olanzapine discontinuation showed plasma insulin response during oral glucose tolerance tests improved, and that this correlated with a decrease in free fatty acid

levels. Therefore, regular monitoring of various metabolic parameters and drug levels is recommended in olanzapine-treated patients with schizophrenia.

7.9.3.3 Liver Function and Hepatocyte Nuclear Factor-1 α

Insulin regulates liver metabolism through complex signaling pathways. Individuals who are insulin-resistant fail to suppress hepatic glucose production (HGP); however, there continues to be excessive lipid synthesis. As a consequence of this reduced hepatic function, hyperglycemia, hypertriglyceridemia and non-alcoholic fatty liver disease (NAFLD) may develop. It is possible that interplay between the intrahepatic and extrahepatic pathways modulates liver metabolism due to insulin-resistance, as well as lipid metabolism (Santoleri & Titchenell, 2018).

Hepatocyte nuclear factor-1 α (HNF-1 α) is a transcription factor which is highly expressed in the liver and is involved in glucose co-regulation (Buchholz et al. 2008). The inhibition of this transcription factor can contribute to impairments in pancreatic β -cell insulin gene expression and insulin secretory response to glucose (Wang et al. 1998). Subsequently, hyperglycemia can be induced by the direct inhibition of HNF-1 α or during induction of cytochrome P4501A2 (CYP1A2), a liver enzyme regulated *in vitro* by HNF-1 α that activates the transcriptional activity of the CYP1A2 gene (Chung & Bresnick, 1997). It is worth noting that olanzapine is metabolized by P450 isoenzymes 1A2 and 2D6 and can lead to death by acute intoxication as reported by Merrick et al. (2001).

7.9.4. Mechanisms of Antipsychotic-Induced Diabetic Ketoacidosis.

Elaborating on the pathways suggested by Buchholz and colleagues (2008), Vuk et al. (2017) posited three potential modalities to explain how APD-induced DKA can develop in patients with new onset T2DM, as their analysis found that 90% of CRs were classified as this type of

DM. The authors also suggested a sedentary lifestyle and negative symptoms characterized by a diminution or absence of normal behaviors related to motivation or interest including avolition (lack of motivation and inability to complete tasks), anhedonia (lack of interest in activities), asociality or reduced expression such as: blunted affect (reduced intensity in emotional response), alogia (impaired ability in thinking that affects speech) (Correll & Schooler, 2020) can play a role in weight gain and DM. The possible scenarios include: 1) DKA as a complication of pre-existing DM; 2) DKA may manifest as new onset of T2DM following an increase in BMI and insulin resistance caused by antipsychotic medicines; and 3) a sudden presentation of DKA associated with APD-induced insulin resistance, independent of weight gain. The authors also suggested that protein kinase B (AKT) - an enzyme that plays an important role in various cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription, and cell migration (Hajdúch et al. 2001; Lawlor et al. 2001) - is activated by olanzapine (Lu et al. 2004): this may explain, in part, the effect of olanzapine on cell proliferation and utilization of nutrients including glucose uptake. It is important to note that protein kinase signal is disrupted in those with schizophrenia (Emamian et al. 2004) or DM (Whiteman et al. 2002).

As mentioned in Chapter 2, DKA can develop in patients with insulin deficiency, elevated glucagon levels, elevated serum levels of glucose and free fatty acids due to lipolysis. According to Vuk et al. (2017), patients can develop a reversible toxic event, possibly induced by APDs, which can subsequently have an effect on the β -cells of the pancreas, independent of weight gain and/or insulin resistance. Other pathways include the blockade of 5-HT_{1A/2A/2C} serotonergic, histaminergic, muscarinic receptors and the activation of β -adrenergic receptors of pancreatic

cells (Houseknecht et al. 2007, Schwenkreis et al. 2004). In individuals with pre-existing insulin resistance, the addition of a multireceptor antagonist antipsychotic medicine may trigger a state of "artificial insulinopenia" that presents as DKA (Vuk et al. 2017).

7.9.5. CONCLUSION

The systematic review of CRs (Chapter 2) analyzed 125 CRs of patients with diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). To my knowledge this is the first in-depth analysis of CRs on the latter condition, which includes a synthesis of evidence presenting a descriptive assessment of pertinent biomarkers prior to, at and after presentation, providing additional ascertainment of the outcomes. Most emergencies (33.1%) occurred in the 30- to 39-year-old age group and were predominantly male (88%). Schizophrenia was the main diagnosis for half the cases (51.6%), followed by bipolar disorder (16.1%). The average blood glucose levels at presentation were 800 mg/dl for DKA and 1,194 mg/dl for HHS, with average hemoglobin A1c levels of 12.7% and 12.1%, respectively. In CRs where DKA was the primary outcome, olanzapine was associated with the highest count (41%), followed by clozapine (21%). The review identified 12 fatalities where olanzapine was the primary APD used in five of the cases. This critical appraisal of case reports emphasized the importance of educating APD users on the risks associated with these agents. This view aligns with the American Diabetes Association's (ADA) consensus on the importance of monitoring metabolic risk factors, as well as the importance of being cognizant of personal and family history of diabetes. Patient education coupled with clinical awareness by healthcare professionals and subsequent monitoring of the patient – regardless of diabetic status- could help mitigate the precipitating factors leading to DKA or HHS occurrence, and possible re-occurrence.

A second systematic review analyzed 13 observational studies, consisting of five analytical and eight descriptive studies, which varied in scope on the case definition, study populations, exposure, and outcomes. These studies provide further evidence of the association between atypical APDs and typical APDs as a class and DKA, while there is insufficient information to draw conclusions about the association between APDs and HHS.

Analytical studies make use of the rich data in the FAERS and the Health Facts databases EHRs databases. Using the FAERS database, two atypical antipsychotic drugs - quetiapine and olanzapine - were identified as potential drug safety signals for DKA, with higher PRRs and EBGM values compared to other psychotropic drugs. This was followed by a trends analysis using the Health Facts database comprised of EHRs spanning the period 2000 and 2016.

Findings from this analysis show the prevalence of use of atypical antipsychotic drugs increased overall during the study period, in contrast to the overall decrease of their predecessors.

Corroborating results from the FAERS analysis, quetiapine was the most prescribed atypical antipsychotic medicine, followed by risperidone and olanzapine. Prochlorperazine and haloperidol were the most prescribed typical APDs overall.

Based on the findings of the previous Chapters, a NCC evaluated the risk of DKA in association with the use of APDs as a class of drugs, or individually. Findings showed that the elderly and those who suffer from multiple comorbidities are at higher risk of developing DKA in those who received an APD. Atypical APDs, as a class, was associated with the development of DKA in a healthier elderly population.

These three distinct evidence streams provide valuable information that can direct future research on the association between antipsychotic medicines and diabetic complications.

Higher on the evidence hierarchy, systematic reviews and critical appraisals of CRs and the assessment of the risk of bias for observational studies add valuable information to the existing body of evidence on the etiology of DKA. The FAERS and NCC analyses, two rich sources of data, further added to this accumulating body of evidence. Nonetheless, differences in the results indicate a need for more well conducted large scale studies in diverse populations.

7.9.6. RECOMMENDATIONS

The evidence presented in the five chapters provide a path forward with the following recommendations.

1. As per the ADA consensus on atypical APD use and MetS (ADA 2004), psychiatrists, clinicians and healthcare workers involved in the treatment of patients who are receiving APDs should be mindful of the diabetogenic properties of atypical antipsychotic medicines and be conscious of the importance of regular monitoring of relevant biomarkers (glucose levels, hemoglobin levels, BMI), which can be indicative of more serious underlying health issues.
2. Considering the severity of mental illnesses and the impacts of negative symptoms on the patient's emotions and behavioral response (i.e., sedentary lifestyle, low adherence to treatment), implementation of new methods that facilitate adherence to treatments is essential to ensure patient safety and health.
3. The factors underlying APD-induced DKA or HHS are not fully understood. CRs are valuable in providing crucial information; however, they are not designed to generate or refute hypothesis that can be tested. There is a need for retrospective and prospective observational studies on key populations, such as those diagnosed with schizophrenia

who are diabetes-naïve, and using other data sources such as the Canada Drug Safety and Effectiveness Network-Canadian Network for Observational Drug Effect Studies (DSEN-CNODES) and the Clinical Practice Research Database (CPRD) in the United Kingdom to better elucidate the association between atypical APDs and both DKA and HHS.

4. Mechanistic research focusing on select APDs such as haloperidol and olanzapine to better understand the cellular pathways modulating the pharmacological effect of APDs is needed. In particular, mechanistic studies can help in:
 - a. understanding the molecular targets of these drugs is important to apply this knowledge to clinical safety;
 - b. developing safer and more effective drugs tailored to patient needs;
 - c. defining effective doses producing the desired therapeutic effects; and
 - d. discovering other indications for use, thus reducing off-label use of APDs.

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APPENDIX A

ETHICS APPROVAL

Ethics approval from the University of Ottawa's Office of Research Ethics and Integrity was issued for research protocol comprising two studies of this thesis (Chapters 5 and 6).

The following documents are included in this Appendix.

- Certificate of Ethics Approval Issued on June 30th, 2021.
- Certificate of Ethics Approval Renewed on June 30th, 2022.

CERTIFICAT D'APPROBATION ÉTHIQUE | CERTIFICATE OF ETHICS APPROVAL**Numéro du dossier / Ethics File Number**

H-11-20-5598

Titre du projet / Project Title

The association between atypical antipsychotic drugs and diabetic complications, namely diabetic ketoacidosis and hyperglycaemic hyperosmolar state.

Type de projet / Project Type

Thèse de doctorat / Doctoral thesis

Statut du projet / Project Status

Approuvé / Approved

Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)

30/06/2021

Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)

29/06/2022

Équipe de recherche / Research Team**Chercheur /
Researcher****Affiliation****Role**

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Chercheur Principal / Principal Investigator

Daniel KREWSKI

Département d'épidémiologie et santé publique / Department of Epidemiology and Public Health

Superviseur / Supervisor

Conditions spéciales ou commentaires / Special conditions or comments

Le Comité d'éthique de la recherche (CÉR) de l'Université d'Ottawa, opérant conformément à l'*Énoncé de politique des Trois conseils* (2014) et toutes autres lois et tous règlements applicables, a examiné et approuvé la demande d'éthique du projet de recherche ci-nommé.

L'approbation est valide pour la durée indiquée plus haut et est sujette aux conditions énumérées dans la section intitulée "Conditions Spéciales ou Commentaires". Le formulaire « Renouvellement ou Fermeture de Projet » doit être complété quatre semaines avant la date d'échéance indiquée ci-haut afin de demander un renouvellement de cette approbation éthique ou afin de fermer le dossier.

Toutes modifications apportées au projet doivent être approuvées par le CÉR avant leur mise en place, sauf si le participant doit être retiré en raison d'un danger immédiat ou s'il s'agit d'un changement ayant trait à des éléments administratifs ou logistiques du projet. Les chercheurs doivent aviser le CÉR dans les plus brefs délais de tout changement pouvant augmenter le niveau de risque aux participants ou pouvant affecter considérablement le déroulement du projet, rapporter tout événement imprévu ou indésirable et soumettre toute nouvelle information pouvant nuire à la conduite du projet ou à la sécurité des participants.

The University of Ottawa Research Ethics Board, which operates in accordance with the *Tri-Council Policy Statement* (2014) and other applicable laws and regulations, has examined and approved the ethics application for the above-named research project.

Ethics approval is valid for the period indicated above and is subject to the conditions listed in the section entitled "Special Conditions or Comments". The "Renewal/Project Closure" form must be completed four weeks before the above-referenced expiry date to request a renewal of this ethics approval or closure of the file.

Any changes made to the project must be approved by the REB before being implemented, except when necessary to remove participants from immediate endangerment or when the modification(s) only pertain to administrative or logistical components of the project. Investigators must also promptly alert the REB of any changes that increase the risk to participant(s), any changes that considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project or the safety of the participant(s).

Riana MARCOTTE

Responsable d'éthique en recherche / Protocol Officer

Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences de la santé et sciences / Health Sciences and Sciences Research Ethics Board**

CERTIFICAT D'APPROBATION ÉTHIQUE | CERTIFICATE OF ETHICS APPROVAL**Numéro du dossier / Ethics File Number**

H-11-20-5598

Titre du projet / Project Title

The association between atypical antipsychotic drugs and diabetic complications, namely diabetic ketoacidosis and hyperglycaemic hyperosmolar state.

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Researcher****Affiliation****Role**

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Département d'épidémiologie et santé publique / Department of Epidemiology and Public Health

Superviseur / Supervisor

Conditions spéciales ou commentaires / Special conditions or comments

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Safaa LAMHOUEB

Coordonnateur de l'éthique / Ethics Coordinator

Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences de la santé et sciences / Health Sciences and Sciences Research Ethics Board**