

DRUG-DRUG INTERACTIONS IN THE PHARMACOTHERAPY OF DIABETIC KETOACIDOSIS: A RETROSPECTIVE ANALYSIS FROM A TERTIARY CARE HOSPITAL IN PESHAWAR, PAKISTAN

Sadia Azeem^{*1}, Sarah Hussain², Waqas Haider Khan³, Kishmala Batool⁴

^{*1}Department of Pharmacy, Sarhad University of Science and Information Technology Peshawar, Pakistan

²Pharmacist (BS-17) Health & Population Department, Govt of the Punjab, Pakistan

³Mian Meer College of Pharmacy Jhang, Pakistan

⁴Department of pharmaceutical sciences, The Superior University, Lahore, Pakistan

^{*1}sadiaazeem87@gmail.com, ²sarahphrm@gmail.com, ³waqashaiderkhan14@gmail.com,

⁴kbatool21@hotmail.com

DOI: <https://doi.org/10.5281/zenodo.23038958>

Keywords

diabetic ketoacidosis; drug-drug interaction; medication safety; polypharmacy; clinical pharmacy; insulin therapy; tertiary care; Pakistan

Article History

Received: 30 January 2026

Accepted: 15 March 2026

Published: 31 March 2026

Copyright @Author

Corresponding Author: *

Sadia Azeem

Abstract

Background: Patients admitted with diabetic ketoacidosis (DKA) typically require complex, multi-drug regimens spanning insulin therapy, antibiotics, anticoagulants, and other supportive medications, creating meaningful potential for clinically significant drug-drug interactions (DDIs) that can compromise safety and complicate an already high-acuity presentation.

Objective: To identify and characterize the frequency, severity, and mechanisms of drug-drug interactions in the pharmacotherapy of hospitalized DKA patients at a tertiary care hospital in Peshawar, Pakistan.

Methods: A retrospective medical chart review of 20 DKA patients admitted to the Endocrinology Ward, Emergency Room, and Acute Medical Unit of Lady Reading Hospital, Peshawar. Complete prescribed medication lists were extracted for each patient and systematically screened for drug-drug interactions using the Drugs.com and Medscape interaction-checking databases, with severity classified as minor, moderate, or major.

Results: Across the 20-patient cohort, a total of 6 clinically relevant drug-drug interactions were identified: 2 (33.3%) classified as major and 4 (66.7%) as moderate. The major interactions were clonazepam-olanzapine (pharmacodynamic; increased risk/severity of adverse effects) and fluconazole-clopidogrel (pharmacokinetic; decreased clopidogrel metabolism/activation). The moderate interactions were moxifloxacin-insulin aspart (pharmacokinetic; increased insulin efficacy/hypoglycemia risk), aspirin-enoxaparin (pharmacodynamic; increased anticoagulant activity), doxylamine-tramadol (pharmacodynamic; additive CNS depression), and insulin glargine-dexamethasone (pharmacokinetic; increased hyperglycemia risk). By mechanism, 4 of 6 interactions (66.7%) were pharmacodynamic and 2 (33.3%) pharmacokinetic. No severe or contraindicated interactions were identified.

Conclusion: Clinically relevant drug-drug interactions, including two major-severity interactions, were identified in the pharmacotherapy of hospitalized DKA patients, most commonly involving psychotropic, anticoagulant, and glucose-modulating agent combinations. These findings support the routine use of



systematic interaction-checking tools and closer interdisciplinary communication between physicians, pharmacists, and nursing staff to detect and manage such interactions proactively in this high-acuity patient population.

1. INTRODUCTION

Diabetic ketoacidosis (DKA) is a medical emergency requiring urgent, multi-component treatment, including fluid resuscitation, insulin therapy, electrolyte replacement, and, frequently, treatment of a precipitating illness such as infection.[1] Because infection is the leading precipitant of DKA worldwide – accounting for an estimated 30–50% of cases – patients often require concurrent antimicrobial therapy alongside insulin and supportive medications, resulting in complex, multi-drug regimens delivered during a period of acute physiological instability.[2]

This combination of high medication burden and altered physiology (renal and hepatic perfusion changes, acid–base disturbance, fluctuating glycemic control) creates meaningful potential for clinically significant drug–drug interactions (DDIs), which can manifest as altered drug efficacy, increased toxicity, or destabilized glycemic control at a time when patients are already critically unwell.[1] Systematic identification of such interactions is therefore an important, though sometimes under-recognized, component of safe DKA pharmacotherapy.

This study retrospectively analyzes the complete prescribed medication regimens of 20 hospitalized DKA patients at a tertiary care hospital in Peshawar, Pakistan, to identify, classify, and characterize the clinically relevant drug–drug interactions present in real-world DKA pharmacotherapy, with the aim of informing pharmacist-led medication review priorities in this high-acuity population.

2. Materials and Methods

2.1 Study Design and Setting

A retrospective medical chart review was conducted in the Endocrinology Ward, Emergency Room, and Acute Medical Unit (AMU) of Lady Reading Hospital, Peshawar, Khyber Pakhtunkhwa, Pakistan, as part of a

structured clinical pharmacy clerkship conducted from July to September 2023.

2.2 Study Population

All patients admitted with a diagnosis of diabetic ketoacidosis during the data collection period were included; patients with a primary diagnosis other than DKA and pregnant women were excluded. A total of 20 patients met eligibility criteria and constituted the analytic sample.

2.3 Data Collection

For each patient, the complete list of prescribed medications – including both scheduled and as-needed agents, spanning insulin formulations, antimicrobials, analgesics, antiemetics, anticoagulants, gastrointestinal agents, and psychotropic medications – was extracted from the medical record using a structured proforma.

2.4 Drug–Drug Interaction Screening

Each patient's complete medication list was systematically screened for pairwise drug–drug interactions using the Drugs.com and Medscape.com interaction-checking databases. For each interaction identified, the interacting drug pair, interaction type (pharmacokinetic or pharmacodynamic), underlying mechanism, and severity classification (minor, moderate, or major, as assigned by the reference database) were recorded, with Stockley's Drug Interactions used as an additional reference source.

2.5 Data Analysis

Identified interactions were tabulated and summarized descriptively by severity classification and interaction mechanism (pharmacokinetic vs. pharmacodynamic).

2.6 Ethical Considerations

Data collection was conducted with the permission of the hospital administration as part of an approved clinical pharmacy clerkship. No

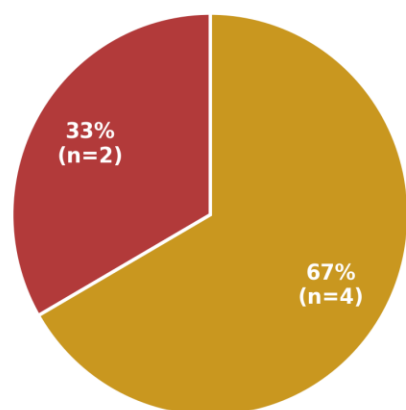
personally identifying information is presented in this manuscript; all case data were anonymized.

3. Results

Across the medication regimens of the 20-patient DKA cohort, screening identified a total of 6 clinically relevant drug-drug interactions. Of

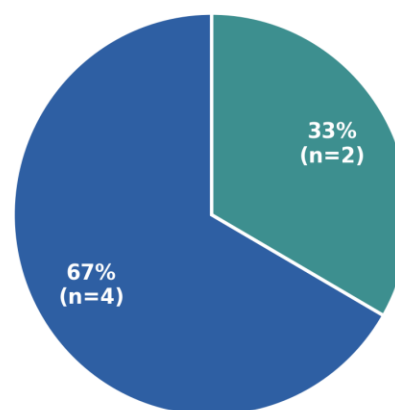
these, 2 (33.3%) were classified as major severity and 4 (66.7%) as moderate severity; no severe or contraindicated interactions were identified. By mechanism, 4 of the 6 interactions (66.7%) were pharmacodynamic in nature and 2 (33.3%) were pharmacokinetic (Table 1, Figure 1).

(a) Interaction severity (n = 6)



Major (n=2) Moderate (n=4)

(b) Interaction mechanism (n = 6)



Pharmacodynamic (n=4)
Pharmacokinetic (n=2)

Figure 1. (a) Severity distribution and (b) mechanism type of drug-drug interactions identified in DKA pharmacotherapy (n = 6 interactions).

3.1 Identified Drug-Drug Interactions

The two major-severity interactions involved clonazepam combined with olanzapine, in which the risk or severity of adverse effects (additive CNS/respiratory depression) may be increased, and fluconazole combined with clopidogrel, in which fluconazole's inhibition of CYP2C19-mediated metabolism can reduce the formation of clopidogrel's active metabolite, blunting its antiplatelet effect. The four moderate-severity interactions were: moxifloxacin with insulin

aspart, in which the hypoglycemic efficacy of insulin aspart can be increased; aspirin with enoxaparin, in which the anticoagulant activity of enoxaparin can be increased; doxylamine with tramadol, in which additive CNS depressant effects can occur; and insulin glargine with dexamethasone, in which corticosteroid-induced hyperglycemia can antagonize glycemic control and increase insulin requirements (Table 1, Figure 2).

Table 1. Drug-drug interactions identified in DKA pharmacotherapy (n = 6 interactions among 20 patients).

Drug pair	Interaction type	Mechanism / clinical effect	Severity
Clonazepam - Olanzapine	Pharmacodynamic	Increased risk/severity of adverse effects (additive CNS/respiratory depression)	Major
Fluconazole - Clopidogrel	Pharmacokinetic	Decreased metabolism/activation of clopidogrel (reduced antiplatelet effect)	Major
Moxifloxacin - Insulin aspart	Pharmacokinetic	Increased therapeutic (hypoglycemic) efficacy of insulin aspart	Moderate
Aspirin - Enoxaparin	Pharmacodynamic	Increased anticoagulant activity of enoxaparin	Moderate
Doxylamine - Tramadol	Pharmacodynamic	Increased CNS depressant activity of tramadol	Moderate
Insulin glargine - Dexamethasone	Pharmacokinetic	Increased risk/severity of hyperglycemia	Moderate

Reference source: *Drugs.com* and *Medscape.com* interaction checkers, cross-referenced against Stockley's Drug Interactions.

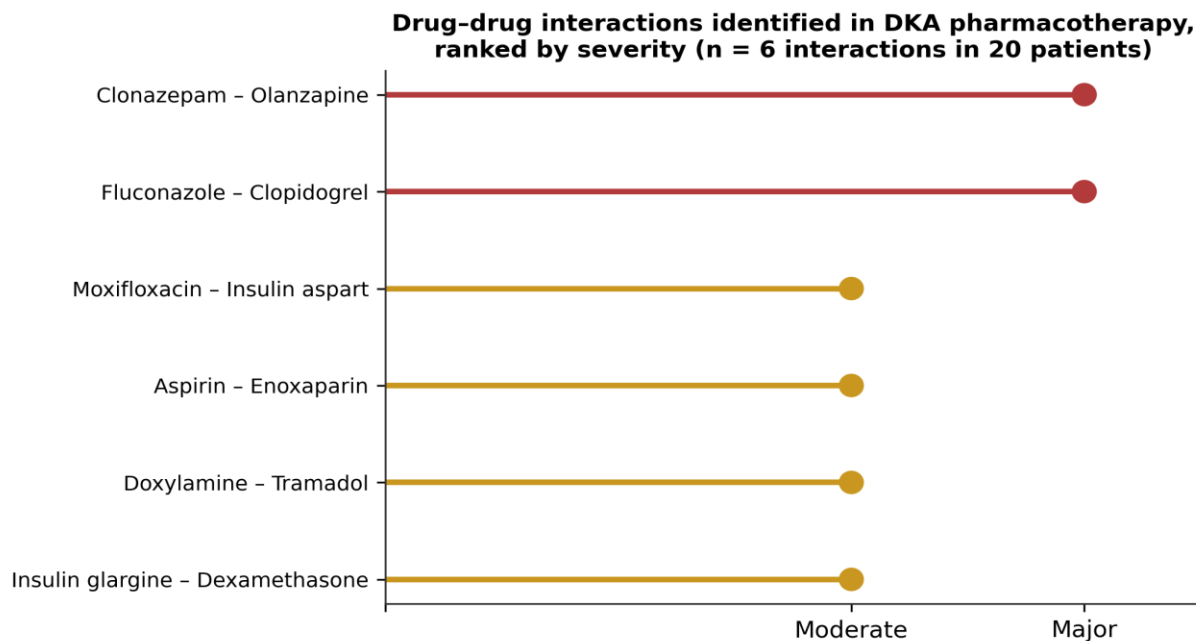


Figure 2. Drug-drug interactions identified in DKA pharmacotherapy, ranked by severity (n = 6 interactions among 20 patients).

3.2 Medication Context

These interactions arose against a backdrop of extensive polypharmacy typical of DKA management: insulin glargine (13 patients), biphasic insulin aspart (10), and human regular

insulin (9) were the most frequently prescribed antihyperglycemic agents, while broad-spectrum antibiotics (meropenem, ceftriaxone, cefotaxime, metronidazole, vancomycin), anticoagulants (enoxaparin, heparin, aspirin), proton-pump

inhibitors (omeprazole, esomeprazole), and psychotropic/sedative agents (clonazepam, doxylamine) were commonly co-prescribed for comorbid infection, thromboprophylaxis, gastrointestinal protection, and symptom control, respectively – the same medication classes implicated in the interactions identified above.

4. Discussion

This study identified 6 clinically relevant drug-drug interactions across the medication regimens of 20 hospitalized DKA patients – a rate of approximately 1 interaction per 3–4 patients – including two major-severity interactions. This finding underscores that even a relatively small, high-acuity cohort managed according to broadly standard DKA protocols can harbor clinically meaningful interaction risk once the full breadth of concurrently prescribed medications (insulin, antimicrobials, anticoagulants, gastrointestinal agents, and psychotropics) is systematically screened.

The two major interactions identified – clonazepam-olanzapine and fluconazole-clopidogrel – both carry direct clinical relevance in the DKA setting. Additive CNS and respiratory depression from combined benzodiazepine and antipsychotic use is a particular concern in patients who may already have altered consciousness from DKA itself, while reduced clopidogrel activation via fluconazole-mediated CYP2C19 inhibition could blunt antiplatelet protection in patients with concurrent cardiovascular risk – relevant given that coronary artery disease was documented as a comorbidity in this cohort. Both interactions illustrate why psychotropic and antifungal/antiplatelet co-prescribing deserves particular pharmacist attention in this population.

The four moderate interactions each carry plausible mechanistic relevance to DKA management specifically. Most notably, the interaction between insulin glargine and dexamethasone highlights a recurring clinical tension in DKA care: corticosteroids are sometimes required for comorbid conditions (e.g., COPD exacerbation, shock, or adrenal insufficiency) yet directly antagonize glycemic

control, the very parameter DKA management is working to correct – requiring closer glucose monitoring and insulin dose adjustment whenever corticosteroids are co-prescribed. Similarly, the aspirin-enoxaparin interaction reflects the additive bleeding risk relevant to patients receiving concurrent antiplatelet and anticoagulant therapy for thromboprophylaxis, while moxifloxacin-insulin aspart and doxylamine-tramadol reflect, respectively, altered glycemic response and additive sedation risk during antimicrobial and analgesic/antihistamine co-therapy.

Consistent with the source thesis's own observation, the primary driver of these interaction-related drug therapy problems appeared to be gaps in understanding and communication among healthcare providers rather than an absence of appropriate individual drug choices – pointing toward interdisciplinary medication review, rather than avoidance of any single agent, as the most actionable intervention. Systematic use of interaction-checking databases (such as those used in this study) at the point of prescribing, combined with routine pharmacist-led medication reconciliation, could plausibly intercept some or all of these interactions before they reach the patient.

4.1 Strengths and Limitations

This study benefits from a systematic, database-supported screening approach applied to complete medication lists for every patient in the cohort, allowing identification of interactions that might not be apparent through unaided clinical review alone. Limitations include the small sample size ($n = 20$), which limits the precision of interaction-frequency estimates and precludes statistical association testing; reliance on interaction databases (Drugs.com, Medscape) that classify theoretical or reported interaction potential rather than confirmed clinical harm in these specific patients (i.e., no adverse clinical events attributable to these interactions were independently confirmed in this review); and the retrospective design, which does not allow assessment of whether identified interactions were recognized or acted upon by the treating team at the time of prescribing.

5. Conclusion

Systematic interaction screening of DKA pharmacotherapy in this tertiary care cohort identified 6 clinically relevant drug-drug interactions, including two of major severity, most commonly involving psychotropic, antiplatelet/anticoagulant, and glucose-modulating agent combinations. These findings support routine, systematic drug-drug interaction screening and strengthened interdisciplinary communication between physicians, pharmacists, and nursing staff as practical, low-cost strategies to improve medication safety in DKA management.

5.1 Recommendations

- Incorporate routine, systematic drug-drug interaction screening (e.g., via Drugs.com, Medscape, or an integrated hospital pharmacy system) into standard DKA admission and prescribing workflows.
- Apply particular vigilance when corticosteroids, psychotropic agents, or antiplatelet/anticoagulant combinations are co-prescribed with insulin therapy in DKA patients, given the major and moderate interactions identified in these classes.
- Strengthen interdisciplinary communication between physicians, pharmacists, and nursing staff to ensure interaction alerts translate into timely clinical action.
- Pursue larger, multi-center studies with prospective monitoring to determine the clinical impact (e.g., hypoglycemia, bleeding, sedation events) of the interactions identified here.

6. Declarations

Consent for publication

Not applicable - no individual patient data or identifiable information are presented in this manuscript.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

7. References

- Eledrisi MS, Alshanti MS, Shah MF, Brolosy B, Jaha N. Overview of the diagnosis and management of diabetic ketoacidosis. *Am J Med Sci.* 2006;331(5):243-251.
- Umpierrez GE, Kitabchi AE. Diabetic ketoacidosis: risk factors and management strategies. *Treat Endocrinol.* 2003;2(2):95-108.
- Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care.* 2009;32(7):1335-1343.
- Savage MW, Dhatariya KK, Kilvert A, et al. Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. *Diabet Med.* 2011;28(5):508-515.
- Nyenwe EA, Kitabchi AE. The evolution of diabetic ketoacidosis: an update of its etiology, pathogenesis, and management. *Metabolism.* 2016;65(4):507-521.