Review Article

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Deprescribing Antidiabetic Agents to Prevent Hypoglycemia as an Adverse Drug Reaction in Elderly Patients: A Narrative Review

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ABSTRACT

Background: Older adults with diabetes experience high rates of drug-induced hypoglycemia, driven primarily by insulin and sulfonylurea therapies. However, clinical inertia and fear of rebound hyperglycemia frequently impede routine medication de-escalation in clinical practice. Objective: This review synthesizes current evidence regarding antidiabetic-induced hypoglycemia risk profiles and actionable implementation strategies for deprescribing in older adults. Methods: A literature search was conducted in PubMed and Google Scholar (2016–2026) for primary research evaluating antidiabetic hypoglycemia risk and the feasibility of deprescribing in geriatric populations. Four primary original research studies met the inclusion criteria for detailed synthesis. Results: Deprescribing high-risk antidiabetic agents significantly reduces severe hypoglycemia, particularly among vulnerable individuals with renal insufficiency, while safely maintaining stable glycemic control. Successful execution relies on interprofessional collaboration between primary care providers and pharmacists, utilizing strategies such as academic detailing, pre-visit planning, educational brochures, and direct clinical interventions. Conclusion: Embedding multidisciplinary deprescribing frameworks into primary care transitions diabetes management away from rigid glycemic targets toward safer, individualized, and patient-centered care.

Keywords: *Deprescribing, Antidiabetic, Adverse Drug Reaction, Elderly*

INTRODUCTION

The global burden of diabetes mellitus is expanding rapidly. Estimates from the International Diabetes Federation (2025), indicate that nearly 588.7 million adults aged 20–79 were living with the condition in 2024, with projections reaching 853 million by 2050. Indonesia reflects this severe trend, with approximately one in nine adults affected. Among older adults, diabetes poses distinct clinical challenges by accelerating muscle loss, functional decline, and comorbid conditions such as chronic kidney disease, hypertension, stroke, and coronary heart disease. Furthermore, this demographic experiences a greater prevalence of geriatric syndromes, including cognitive deficits, fall risks, frailty, and polypharmacy (American Diabetes Association, 2025).

Among the adverse drug reactions (ADRs) associated with diabetes management, drug-induced hypoglycemia is notably prevalent. Previous studies report that drug-induced hypoglycemia accounts for a relative frequency of 46.25% among drug-related problems, with 21.7% (n=139) of patients experiencing hypoglycemic incidents of varying severity (Al-Azayzih et al., 2024; Shariff et al., 2019). The likelihood of developing drug-induced hypoglycemia rises significantly among individuals who are at least 65 years old, have had diabetes for over a year, present with multiple comorbidities, or take more than one antidiabetic medication (Shariff et al., 2019). Insulin therapy carries the strongest association with hypoglycemic events compared to other agents (Al-Azayzih et al., 2024). Furthermore, comparative risk rankings for serious hypoglycemia identify glyburide as posing the highest risk, followed by glimepiride, glipizide, repaglinide, nateglinide, rosiglitazone, pioglitazone, and metformin, with overall risk escalating alongside higher daily dosages (Leonard et al., 2018).

To mitigate these risks, medication deprescribing serves as a vital clinical approach. Deprescribing is defined as a structured clinical practice, it involves systematically lowering doses or discontinuing pharmacotherapy when potential risks outweigh therapeutic benefits. Its primary objective is to manage polypharmacy, lessen treatment burden, and enhance patient outcomes as well as overall quality of life. While not a novel concept, deprescribing has been successfully applied to minimize polypharmacy in geriatric care and to taper glucose-lowering therapy when clinically warranted, such as following bariatric surgery in type 2 diabetes patients (Bradley et al., 2023).

Despite its clear theoretical benefits, implementing antidiabetic deprescribing in routine clinical practice encounters significant hurdles. A major obstacle is clinical inertia among healthcare providers, alongside widespread apprehension regarding potential rebound hyperglycemia. Furthermore, the lack of concise, practical guidelines that are easily interpreted and applied by multidisciplinary healthcare teams continues to limit the widespread adoption of deprescribing protocols. Therefore, a comprehensive review synthesizing evidence on antidiabetic-induced hypoglycemia risk profile and actionable deprescribing strategies is needed to improve patient safety.

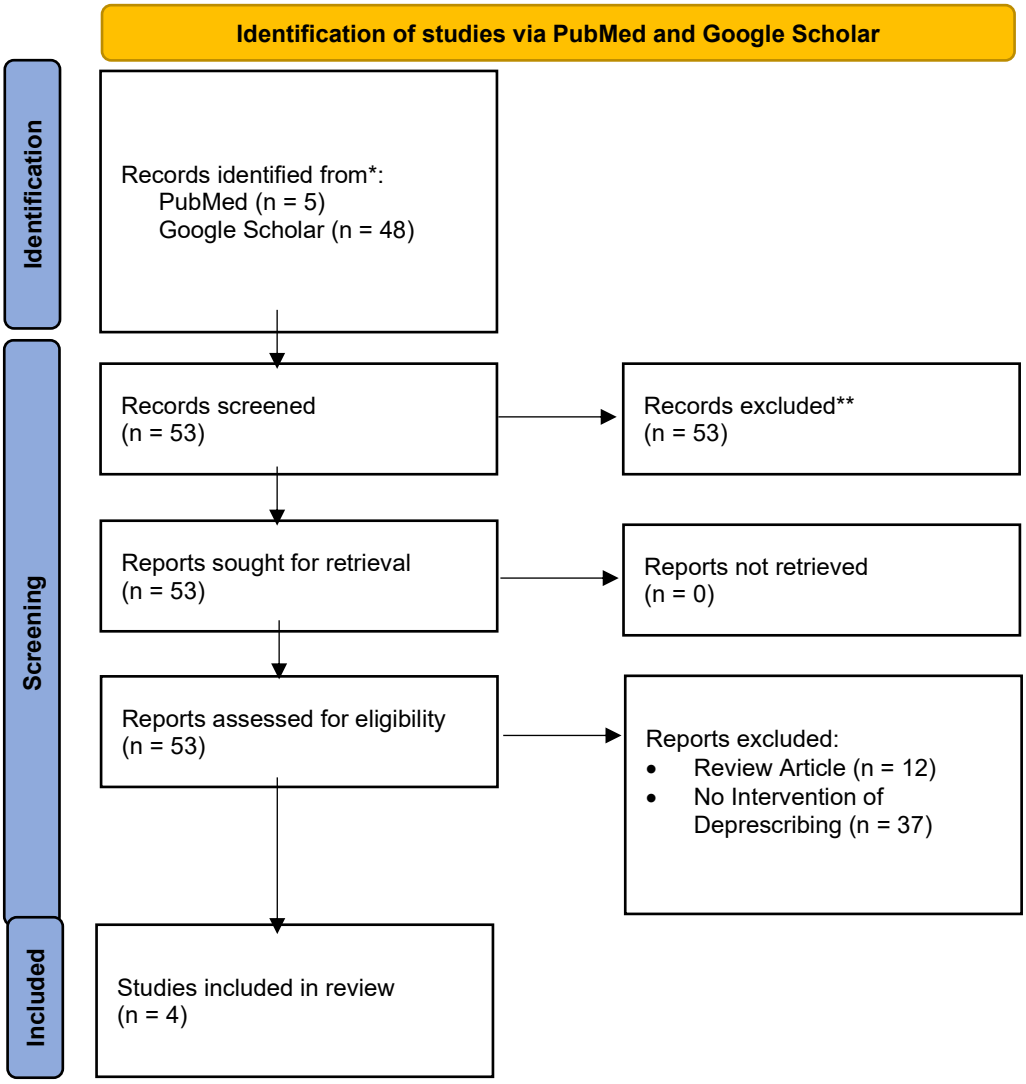
METHODS

A literature search was performed in PubMed and Google Scholar for relevant studies published in English over the last decade (2016 – 2026). Keywords incorporated into the search string were: (“Hypoglycemia” OR “Drug-Induced Hypoglycemia”) AND (“Adverse Drug Reaction” OR “ADR”) AND (“Deprescribing” OR “Medication Reconciliation”) AND (“Older Adults” OR “Geriatrics”). Inclusion criteria comprised original research articles (e.g. randomized controlled trials, cohort studies, observational studies) focusing on antidiabetic-induced hypoglycemia risk and deprescribing feasibility. Narrative reviews, systematic reviews, meta-analyses, conference abstracts, and editorials were excluded to ensure data synthesis was derived directly from primary clinical evidence. After screening titles, abstracts, and full-text articles for relevance to the review objective and eligibility criteria, studies that were non-original research, unrelated to antidiabetic deprescribing, or did not evaluate hypoglycemia outcomes in older adults were excluded. Ultimately, four original research articles met the inclusion criteria and were included in the narrative synthesis.

RESULTS AND DISCUSSION

Based on the predefined inclusion and exclusion criteria, a total of four primary original research studies were included in this synthesis Figure 1. These studies evaluated the risk of antidiabetic-induced hypoglycemia and the implementation of deprescribing strategies among older adults. A comprehensive summary of the study design, participant characteristics, primary outcomes, and clinical implications of the included studies is presented in Table 1.

Figure 1. Identification of studies via PubMed and Google Scholar



Tabel 1. Synthesis of Primary Included Studies on Antidiabetic Deprescribing and Hypoglycemia Risk

Article	Study Population & Setting	Main Finding	Deprescribing & Clinical Strategy
Grant et al., 2025	450 eligible patients aged ≥65 years with type 2 diabetes managed across primary care clinics at Kaiser Permanente Northern California.	1) At 6 months, diabetes medication deprescribing rates were significantly higher in the Academic Detailing (AD) plus patient previsit activation arm compared with the AD-only arm. 2) No statistically significant difference in severe self-reported hypoglycemia was observed between arms at 6 months.	Comparative effectiveness RCT evaluating academic detailing with or without patient-oriented previsit activation to promote shared decision-making.
Busque et al., 2025	89 candidate patients in a managed care setting aged ≥80 years with tightly controlled glycemia (HbA1c ≤6.5%) and recent sulfonylurea use (within 120 days).	1) Sulfonylurea therapy was successfully discontinued in 41% (n = 37) of eligible candidates following pharmacist intervention. 2) Post-intervention HbA1c levels remained safely within recommended clinical target ranges.	Clinical pharmacist-led intervention designed to systematically discontinue sulfonylureas and reduce severe hypoglycemia risk in vulnerable octogenarians.

Article	Study Population & Setting	Main Finding	Deprescribing & Clinical Strategy
Jones et al., 2024	1) 5,071 older adults (2,539 intervention vs. 2,532 historical controls) across 3 US Veterans Affairs medical centers. 2) Subgroup at high hypoglycemia risk included diabetic patients with HbA1c <7%, age ≥65, renal insufficiency, or cognitive impairment on insulin/sulfonylureas.	1) Overall deprescribing rate was significantly higher in the intervention cohort (29.5% vs. 25.8%) 2) In the hypoglycemia-risk cohort, deprescribing reached 27.3% in the intervention group vs. 25.1% in controls.	Patient-directed educational brochure mailed 2–3 weeks prior to scheduled primary care visits to empower shared clinical decision-making.
Starke et al., 2025	Target trial emulation of 171,318 older adults (>65 years) on metformin add-on therapy from German routine claims data.	1) DPP4i initiation demonstrated a strong protective effect against severe hypoglycemia in new users 2) Marked risk reduction for severe hypoglycemia was observed in patients with severe renal insufficiency	Target trial emulation evaluating population-level harm reduction by substituting high-risk sulfonylureas with glucose-dependent DPP4 inhibitors as metformin add-on therapy.

Promoting antidiabetic deprescribing among geriatric patients requires structured clinical strategies that combine clinical education and patient activation. Grant et al. demonstrated that coupling primary care physician academic detailing (AD) with patient pre-visit activation significantly elevated diabetes medication deprescribing rates compared to AD alone (15.8% vs 9.0% at 6 months, p=0.01). Multidisciplinary involvement, particularly pharmacist-led interventions, demonstrated high efficacy in medication de-escalation. Specifically, Busque et al. a 41% discontinuation rate of sulfonylureas based on clinical pharmacist-led intervention among the elderly with tightly controlled glycemia (HbA1c ≤6.5%), with average HbA1c levels safely remaining within target ranges post-intervention. Similarly, Jones et al. observed that patient-directed educational brochures delivered prior to clinical appointments enhanced overall deprescribing likelihood (OR = 1.17).

The clinical imperative for deprescribing or transitioning high-risk antidiabetic agents is rooted in drug-specific pharmacodynamics and age-related physiological changes. Sulfonylureas stimulate glucose-independent insulin secretion, substantially elevating hypoglycemia risk in older adults, and are associated with a substantially higher risk of hospitalization (Ling et al., 2021). Furthermore, in terms of mechanism, sulfonylureas exert both their therapeutic and adverse effects by inhibiting various potassium channels, either directly or indirectly through Epac2A activation. Suppression of these potassium channels induces cell membrane depolarization, which prompts the opening of voltage-dependent calcium channels. The subsequent influx of calcium triggers insulin release, lowering blood glucose levels but simultaneously driving the risk of adverse events such as hypoglycemia (Li & Yun, 2025).

In a large target trial emulation, Starke et al. demonstrated that replacing sulfonylureas with glucose-dependent DPP inhibitors yielded a 49% risk reduction in severe hypoglycemia among new users and a 69% reduction among patients with severe renal insufficiency. Crucially, across all trials, medication de-escalation did not increase severe hypoglycemic events or lead to adverse glycemic deterioration. In type 2 diabetes mellitus, blunted secretion of glucagon-like peptide-1 (GLP-1) impairs the physiological incretin effect, the augmented insulin response typically triggered by oral glucose compared to intravenous glucose. Dipeptidyl peptidase-4 (DPP-4) inhibitors counteract this deficit by blocking the enzymatic breakdown of incretin hormones, specifically GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). By suppressing serum DPP-4 activity by over 80%, these agents effectively double active GLP-1 levels, significantly improving postprandial glucose control and lowering glycated hemoglobin levels. Crucially, because GLP-1 stimulates pancreatic beta-cell insulin release strictly in a glucose-dependent manner, DPP-4 inhibitors lower blood glucose without increasing the risk of hypoglycemia (Florentin et al., 2022).

Antidiabetic medication de-escalation is most urgently needed among vulnerable populations where the harms of intensive therapy outweigh the benefits. Decreased kidney function slows drug clearance, causing sulfonylureas to accumulate in the body. Starke et al. demonstrated that switching from sulfonylureas to DPP-4 inhibitors provided the greatest protective benefit against severe hypoglycemia in patients with severe renal insufficiency. Moreover, Strict glycemic control in older adults offers minimal long-term benefit while drastically increasing immediate hypoglycemia risk. Busque et al. (HbA1c $\leq$ 6.5%) and Jones et al., (HbA1c $\leq$ 7.0%) specifically used these tight targets to identify ideal candidates for drug de-escalation. In addition, older patients or those with memory decline (Grant et al., 2025; Jones et al., 2024) are particularly vulnerable to mealtime irregularity, accidental dosing errors, and impaired recognition of warning symptoms (hypoglycemia unawareness). Furthermore, age-related blunting of autonomic responses, compounded by cognitive and mobility impairments, severely compromises an older adult's ability to detect and manage falling blood glucose, drastically escalating the risk of severe hypoglycemia (Hope et al., 2018).

A key strength of the synthesized evidence lies in the complementary diversity of study methodologies, ranging from pragmatic randomized controlled trials and pharmacist-led interventions to large-scale target trial emulations using real-world data. This multi-methodological framework provides both high internal validity regarding implementation tactics and extensive population-level generalizability across different healthcare systems. However, several limitations warrant consideration. First, observational claims data based on Starke et al. remain vulnerable to unmeasured residual confounding and lack granular clinical detail, such as exact self-monitored blood glucose logs or mild hypoglycemic events. Second, trials evaluating patient-reported outcomes from Grant et al. are susceptible to recall bias. Finally, because several interventions were evaluated within large, integrated health delivery networks, the implementation success of these strategies may differ when translated to fragmented or fee-for-service primary care settings.

Deprescribing in older adults with diabetes is primarily driven by financial burden, patient preferences, and the need to prevent adverse events such as hypoglycemia caused by sulfonylureas and insulin (Bradley et al., 2023). Implementing structured deprescribing in clinical practice is both safe and feasible, enhancing medication adherence and overall patient satisfaction without compromising glycemic control (Mehnaz et al., 2025). To operationalize this approach, clinicians can apply practical frameworks like the A–G mnemonic, evaluating Age, Behavioral/cognitive decline, Comorbidities, Duration of diabetes, End-of-life considerations, Frailty/falls/functional decline, and Glycemic goals to prioritize patient safety and quality of life when pharmacotherapy no longer offers a net clinical benefit (Samajdar & Joshi, 2025). Ultimately, adopting systematic de-escalation tools empowers clinicians to transition from aggressive glucose-lowering strategies toward a tailored approach that prioritizes patient safety, functional independence, and overall quality of life.

CONCLUSION

Deprescribing high-risk diabetes medications in older adults effectively mitigates severe hypoglycemia, particularly among vulnerable individuals with renal insufficiency, while safely maintaining stable glycemic control. Successful implementation relies on interprofessional collaboration between primary care providers and pharmacists, using targeted strategies such as academic detailing, pre-visit planning, educational materials, and direct clinical interventions. Ultimately, embedding these multidisciplinary approaches into routine practice enables a tailored care model that prioritizes patient safety, functional well-being, and individualized needs over rigid glycemic targets.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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