Advances in Clinical Pharmacology and Therapeutics

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Review

Polypharmacy in Type 2 Diabetes Mellitus and Related Conditions: A Double-Edged Sword: A Narrative Review

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Abstract

Type 2 diabetes mellitus (T2DM) is a multifaceted metabolic disease that is often associated with comorbidities like cardiovascular disease, hypertension, and dyslipidemia. Managing these coexisting conditions often requires the concurrent use of multiple medications, leading to polypharmacy. Polypharmacy is defined as the use of five or more drugs by the patient. While polypharmacy can be clinically appropriate, it also raises the risk of adverse drug events, therapeutic duplication, poor adherence, and increased healthcare burden. Polypharmacy affects 50-80% of patients with T2DM, especially in older adults. It is associated with increased risks of hypoglycemia, hospitalization, drug–drug interactions, and decreased adherence to antidiabetic therapies. The presence of polypharmacy may compromise glycemic control and is linked to higher rates of diabetes-related complications and mortality. On the other hand, appropriate polypharmacy, based on guideline-directed care, can improve cardiovascular and renal outcomes when carefully managed. Polypharmacy in T2DM represents a clinical challenge that requires a balance between comprehensive disease management and the minimization of iatrogenic harm. Individualized care, regular medication reviews, and deprescribing strategies are essential to optimize therapeutic outcomes in this high-risk population. This review seeks to examine the prevalence, underlying causes, clinical consequences, and management approaches of polypharmacy in individuals with T2DM, with a focus on its impact on glycemic control, treatment safety, and associated outcomes.

Keywords

Polypharmacy, Type 2 diabetes mellitus, Metabolic syndrome, MASLD, Deprescribing

Article History

Received: 5 July 2025 Revised: 22 August 2025

Accepted: 29 August 2025 Available Online: 3 September 2025

1. Introduction

Insulin resistance and relative insulin deficiency are hallmarks of type 2 diabetes mellitus (T2DM), a chronic metabolic disease that causes persistent hyperglycemia. T2DM is the most common type of diabetes, accounting for more than 90% of all cases globally. Its increasing incidence, especially in low- and middle-income nations, is a growing public health concern [1].

Obesity, inactivity, and unhealthy eating habits are just a few of the lifestyle, environmental, and genetic factors that interact intricately in the pathophysiology of T2DM. Chronic hyperglycemia in T2DM can result in a variety of microvascular and macrovascular complications if it is not properly controlled. These include diabetic nephropathy, retinopathy, and neuropathy on the microvascular level, as well as cardiovascular disease (CVD) such as coronary artery disease, stroke, and peripheral arterial disease on the macrovascular side [2,3].

In addition to these well-established complications, T2DM is frequently associated with other disorders, including hypertension, dyslipidemia, metabolic dysfunction-associated steatotic liver disease (MASLD), obstructive sleep apnea, and various forms of cancer. These comorbid conditions not only exacerbate the course of diabetes but also complicate its management, increasing the risk of morbidity and mortality [4-6].

Concurrent use of five or more medications is defined as polypharmacy. It is a growing concern in clinical practice, particularly among older adults and individuals with multiple chronic conditions. This phenomenon arises from the need to manage complex health issues but can lead to adverse outcomes if not carefully monitored [7].

The prevalence of polypharmacy varies widely, influenced by factors such as age, healthcare setting, and geographic location. For instance, studies have reported prevalence rates ranging from 4% among community-dwelling older adults to over 96% in hospitalized patients. In the United States, data from the National Health and Nutrition Examination Survey indicated that approximately 39% of adults aged 65 and older were taking five or more medications concurrently between 1999 and 2012 [7,8]. Another study revealed that polypharmacy was correlated with increased renal, cardiac and neurological risks in elderly patients with chronic conditions [9].

Polypharmacy is associated with several adverse outcomes, including increased risks of falls, frailty, cognitive decline, hospitalizations, and mortality. The complexity of managing multiple medications can also lead to medication non-adherence and drug-drug interactions, further complicating patient care [10,11]. Deprescribing involves a systematic process of identifying and discontinuing medications that may no longer be beneficial or might be causing harm, with the goal of optimizing patient outcomes [12-14]. In summary, while polypharmacy can be necessary for managing complex health conditions, it requires careful oversight to balance the benefits and risks associated with the use of multiple medications.

The objective of this review is to examine the prevalence, patterns, and clinical implications of polypharmacy among individuals with T2DM, with a specific focus on its association with common comorbid conditions such as hypertension, dyslipidemia, CVD, and chronic kidney disease (CKD). The review aims to evaluate the risks and benefits of polypharmacy in this population, explore its impact on treatment adherence, adverse drug reactions, and health outcomes, and highlight current strategies for optimizing medication management through de-prescribing and individualized care.

2. Polypharmacy and Diabetic Control in Patients with T2DM

T2DM is a chronic metabolic disorder characterized by insulin resistance and β-cell dysfunction, resulting in sustained hyperglycemia. The progressive nature of the disease and the frequent coexistence of comorbidities such as hypertension, dyslipidemia, CVD, CKD, and depression often necessitate the use of multiple medications. This widespread use of concurrent medications, commonly termed polypharmacy, is particularly prevalent in the elderly diabetic population. Although polypharmacy may be clinically justified, it can also pose significant challenges in glycemic management, adherence, drug interactions, and adverse effects.

Polypharmacy refers to the use of five or more medications by a patient. In the context of diabetes care, this includes antidiabetic agents (e.g., metformin, insulin, Glucagon-Like Peptide receptor agonists [GLP-1RA], Sodium-Glucose Cotransporter 2 inhibitors [SGLT2i]), antihypertensives, statins, antiplatelets, and medications for coexisting psychiatric, renal, or gastrointestinal conditions. Studies suggest that up to 60-80% of patients with T2DM are exposed to polypharmacy, particularly those over 65 years of age [15].

The impact of polypharmacy on glycemic control could be explained in several ways.

2.1 Medication Adherence and Complexity

Multiple medications increase the risk of non-adherence, especially when regimens are complex or require different dosing schedules. Non-adherence has been associated with poor glycemic control (glycated hemoglobin [HbA1c] >7.0%), which increases the risk of complications. In an interesting study, Gellad et al. found that each additional daily medication reduces adherence by approximately 5% [16].

2.2 Drug-Drug Interactions and Hypoglycemia Risk

Polypharmacy increases the potential for drug-drug interactions. For instance, sulfonylureas combined with NSAIDs or warfarin may precipitate hypoglycemia. Beta-blockers can mask hypoglycemia symptoms. Thiazide diuretics may worsen glycemic control by impairing insulin sensitivity. A meta-analysis by Whitty et al. reported that older adults on more than eight medications had a significantly increased risk of both hyperglycemia and hypoglycemia episodes [17].

2.3 Impact on HbA1c and Clinical Outcomes

While polypharmacy is often associated with poor outcomes, some studies highlight that appropriate medication use can result in better metabolic control. For example, optimized regimens including SGLT2i or GLP-1 RA can improve HbA1c, body weight, and blood pressure. However, the net benefit depends on therapeutic appropriateness rather than the number of medications per se. A recent work reported that polypharmacy deteriorates blood glucose control in elderly patients with T2DM [18]. Hence, polypharmacy should be taken cautiously in this population.

2.4 Deprescribing and Medication Review in T2DM Management

Given the risks associated with polypharmacy, regular medication review is recommended, particularly in older adults and those with multiple comorbidities. Deprescribing, defined as the systematic process of identifying and discontinuing drugs where harms outweigh benefits, has emerged as a key strategy.

Tools such as the Beers Criteria, STOPP/START guidelines, and the Medication Appropriateness Index (MAI) are used to guide safe deprescribing [19,20]. The Beers Criteria is a guideline developed by to identify potentially inappropriate medications (PIMs) that should be used with caution—or avoided altogether—in older adults (≥65 years). Similarly, the STOPP/START criteria are evidence-based tools, similar in purpose to the Beers Criteria, but developed to optimize prescribing in older adults (≥65 years). The MAI is a validated tool used to assess the appropriateness of prescribed medications, particularly in older adults who are at high risk of polypharmacy and adverse drug events. A randomized trial by Scott et al. found that pharmacist-led deprescribing interventions significantly improved HbA1c levels, reduced pill burden, and improved quality of life [21].

Add-on therapy is useful in certain conditions (such as, uncontrolled diabetes, refractory hypertension, or heart failure). It may require the use of additional agents to achieve therapeutic targets. Better disease control (such as, lower HbA1c, improved blood pressure, reduced cardiovascular risk) is achievable with add-on treatment. It also enables adherence to guideline-directed therapy (such as, adding SGLT2 inhibitors in people with diabetes with heart failure or CKD). However, it has some risks in geriatric populations. These include cumulative side effects (hypoglycemia from sulfonylureas/insulin, dizziness from antihypertensives, polyuria from SGLT2 inhibitors), reduced adherence due to complex regimens, and diminished marginal benefit when life expectancy is limited.

2.5 Optimizing Pharmacologic Therapy in T2DM

A patient-centered approach is the key. The 2024 ADA and EASD guidelines emphasize individualized therapy, considering patient age, frailty, renal function, and cardiovascular risk [22]. Simplifying regimens, such as using fixed-dose combinations (e.g., metformin + DPP4i), selecting agents with low hypoglycemia risk, such as SGLT2 inhibitors and GLP-1 RAs, and monitoring renal function for agents like metformin and SGLT2 inhibitors may improve the effects of polypharmacy on diabetic older adults.

Pharmacogenomics and polypharmacy are other points to consider. Emerging research suggests that pharmacogenomics can help predict adverse drug reactions or therapeutic failures in patients taking multiple medications. These data, although not yet used in routine clinical practice, may be valuable for optimizing regimens in patients with complex T2DM.

Elderly and multimorbid patients are special groups in diabetes care. Older adults are more susceptible to the negative consequences of polypharmacy due to reduced renal and hepatic drug clearance, increased sensitivity to central nervous system-active medications, and high prevalence of cognitive impairment or depression. A study by Khezrian et al. found that polypharmacy in elderly diabetics was associated with a higher risk of frailty, functional decline, and mortality [23]. Therefore, periodic medication reconciliation and goal-aligned care (e.g., prioritizing function over strict HbA1c targets) are essential.

Digital health and decision support tools could be helpful in the management of this population. Integration of electronic prescribing systems, clinical decision support tools, and digital health platforms can aid in identifying drug interactions, monitoring adherence, and providing patient education. These tools, combined with team-based care (involving pharmacists, nurses, and dietitians), have been reported to decrease inappropriate polypharmacy and ameliorate diabetes outcomes [24].

3. Polypharmacy and Diabetic Complications

Poor glycemic control in the setting of polypharmacy increases the risk of microvascular (neuropathy, nephropathy, and retinopathy) and macrovascular complications (stroke, and myocardial infarction). Moreover, the use of certain medications such as corticosteroids, antipsychotics (e.g., olanzapine), and immunosuppressants may induce or worsen diabetes. Inappropriate polypharmacy has been associated with increased emergency visits and hospitalizations [25]. Moreover, it is also associated with falls and fractures, especially with sedatives or antihypertensives in the older people. Moreover, polypharmacy has been linked to cognitive decline, which further impairs self-management ability.

Polypharmacy is extremely common among T2DM patients with nephropathy. For example, a study from India in tertiary-care nephrology clinics found that among patients with stage 4–5 nephropathy, 95.3% were on ≥5 medications and 46.7% on ≥10 drugs, with antihypertensives being almost universal [26-30]. In hospitalized patients with diabetic nephropathy, the average number of drugs per prescription was 7.4 (involving antihypertensive, metabolic, and antimicrobial agents) [31].

A cross-sectional Palestinian study (non-T2DM-specific, but relevant) reported that among older adults, taking 5–9 medications increased the chance of renal impairment by 60%, and ≥10 drugs doubled it [32]. A systematic review of CKD populations reported that nearly 69% of CKD patients were exposed to polypharmacy (≥5 medications) [26,29,33,34].

Longitudinal data in Korean CKD patients suggested that increased medication burden correlated with renal hazard events. However, much of this effect was driven by underlying disease burden rather than direct drug nephrotoxicity [30].

Mechanisms linking polypharmacy to nephropathy are various. One of them is increased drug–drug and drug–disease interactions. Multiple medications raise the risk of nephrotoxic effects, especially with over-the-counter NSAIDs, aminoglycosides, and pharmacodynamic interactions [29,35]. Another mechanism is impaired drug clearance and accumulation. Impaired renal function in nephropathy alters the pharmacokinetics of many drugs, which may lead to harmful accumulation, especially for renally cleared agents [26,28-32,34-36]. Another possible pathway is frailty, hospitalizations, and medication cascades. Polypharmacy is linked to increased frailty, hospital admissions, and prescription cascades; conditions that often necessitate more medications, worsening kidney function [26,28,33,34].

Potentially inappropriate medications (PIMs) in diabetic nephropathy (DN) should be checked. Among diabetic nephropathy patients, a significant proportion are prescribed PIMs, which pose extra risks due to impaired kidney function—common culprits include NSAIDs, certain antihypertensives, and sulfonylureas [35]. In a Palestinian cohort, 36.8% of patients with renal impairment were using at least one PIM, with sulfonylureas implicated in 20% of these prescriptions [32].

Collaborative care is indicated for addressing polypharmacy in diabetic subjects. Evidence supports that physician–pharmacist collaboration improves medication adherence and safely reduces inappropriate polypharmacy in patients with diabetic nephropathy [28]. Table 1 summarizes the relationship between polypharmacy and DN.

Table 1. The link between polypharmacy and DN in patients with T2DM.

Aspect	Findings
Prevalence of polypharmacy in DN	≥95% in advanced DN
Renal impairment risk	Increased odds with ≥5 meds; potential doubling with ≥10 meds
Possible Mechanisms	Drug interactions, pharmacokinetic changes, prescription cascades
Prevalence of PIM	36–40% of DN patients on ≥1 PIM
Mitigation strategy	Medication review, deprescribing, pharmacist collaboration

Abbreviations: DN: diabetic nephropathy; PIM: potentially inappropriate medication.

Some studies have identified an association between polypharmacy and increased risk or severity of diabetic neuropathy in elderly diabetic patients. A cross-sectional study showed that polypharmacy was independently associated with a higher prevalence of diabetic peripheral neuropathy, even after adjusting for glycemic control, age, and duration of diabetes [37]. Polypharmacy may contribute to neuropathy through several mechanisms. Neurotoxic drug effects such as statins, some antihypertensives, and certain antibiotics; drug-drug interactions leading to increased toxicity or reduced efficacy of medications managing glucose levels; and poor medication adherence, which may result in suboptimal glycemic control, a known risk factor for neuropathy [38,39]. Reports in literature indicate that elderly patients with multimorbidity and frailty are more prone to both polypharmacy and neuropathy [38]. Frailty can both lead to polypharmacy (due to multiple chronic diseases) and increase susceptibility to nerve damage due to poorer homeostatic reserve.

Statins may have a dual effect in diabetic neuropathy. A small randomized trial in non-insulin-dependent diabetics found atorvastatin (20 mg/day for 6 months) improved motor nerve conduction velocity; a sign of better nerve health [40]. Similar effects of rosuvastatin have also been reported [41]. Animal studies and clinical evidence suggest that statins may exert anti-inflammatory and antioxidant effects that could mitigate diabetic peripheral neuropathy [39,42]. On the contrary, a retrospective cohort in Malaysia reported that T2DM patients on statins had a 22.9% incidence of peripheral neuropathy, compared to 15.5% in non-users; a relative risk increase of ~1.47 [43]. However, larger meta-analyses (including diabetic patients) found no statistically significant association between statin use and neuropathy [42,44].

Polypharmacy has been linked to poorer clinical outcomes in elderly patients with diabetic neuropathy. Reported consequences include a higher risk of falls, stemming from impaired balance due to both neuropathy itself and adverse effects of medications such as sedatives or antihypertensives; cognitive decline, which can further complicate self-management of neuropathy; and a decline in overall quality of life, as demonstrated in studies assessing medication burden in relation to neuropathy symptoms. Moreover, several commonly prescribed drug classes in older adults with diabetes have been associated with either the development of neuropathy or worsening of existing neuropathic symptoms. For example, some studies report an association between statin use and peripheral neuropathy, although findings remain controversial [42,43]. Moreover, antidepressants and anticonvulsants are commonly used for neuropathic pain but they may also contribute to cognitive decline and falls. Additionally, drugs such as beta-blockers may cause peripheral circulation issues, potentially worsening neuropathy symptoms. Therefore, medication review is strongly recommended in elderly diabetic patients, particularly those with neuropathy, to minimize unnecessary drug use and reduce neurotoxic risks [26]. Deprescribing strategies should be considered when appropriate, with careful monitoring for potential withdrawal effects or loss of glycemic control. Clinicians should be encouraged to use comprehensive geriatric assessments to evaluate the risks and benefits of each medication in this vulnerable group.

4. Polypharmacy in T2DM Related Conditions

Diabetes related conditions, such as metabolic syndrome and MASLD, are negatively affected by polypharmacy.

MASLD is strongly linked with metabolic syndrome, obesity, T2DM, hypertension, and dyslipidemia [45-48]. As such, patients often require multiple medications, contributing to polypharmacy. A PubMed observational study found that T2DM patients with MASLD had a high burden of comorbidity and polypharmacy, especially those with severe liver disease (37% had significant fibrosis), emphasizing the complexity of their treatment regimens [49].

Agents commonly used in the treatment of metabolic diseases, such as metformin, statins, antihypertensives, and antidiabetic drugs, can have both protective and harmful effects on the liver. Some medications (e.g., GLP-1 RAs, SGLT-2 inhibitors) may improve MASLD by reducing weight, improving insulin sensitivity, and lowering steatosis [50]. Drug-induced liver injury (DILI) risk is valid for certain medications. Polypharmacy increases the chance of idiosyncratic or cumulative hepatic injury, especially when combined with DILI-prone drugs [51]. A recent framework emphasizes the need to evaluate MASLD for possible drug-induced contributions in polypharmacy contexts [46,48,52].

A MASLD cohort study of diabetic patients confirmed a significant rate of multimorbidity and polypharmacy, correlating with advanced fibrosis and treatment complexity [53-55]. Pharmacological treatments targeting MASLD (e.g., GLP-1 RAs, SGLT-2 inhibitors, resmetirom) may reduce hepatic steatosis but underscore the importance of balancing therapeutic benefits versus hepatic risk [52].

Patients with metabolic syndrome frequently receive multiple medications for its components; diabetes, hypertension, dyslipidemia, and obesity. In adults over 65 with T2DM, the rate of polypharmacy, defined as five or more drugs, reaches up to 60% [26,56-59]. A study of elderly community members found that nearly one-third (28.6%) of those with cardiometabolic diseases were on polypharmacy regimens, particularly involving antihypertensives, antidiabetics, and lipid-lowering agents [58]. Possible causes of metabolic syndrome in polypharmacy patients could be the following:

4.1 Multidisciplinary Treatment Necessity

The coexistence of diabetes, hypertension, dyslipidemia, and obesity often mandates distinct pharmacotherapies (e.g., metformin, ACE inhibitors, statins, anti-obesity agents) [60].

4.2 Side Effects Prompting New Drugs

Medications used can cause adverse effects, leading to prescribing cascades that further amplify polypharmacy (e.g., TZDM-induced edema, central nervous system; active anti-obesity agents) [61].

A systematic review in older adults with diabetes found a pooled polypharmacy prevalence of 50-64%, and identified associations with worse glycemic control, increased risk of hypoglycemia, falls, hospitalizations, and mortality [26]. The combination of multiple metabolic medications raises the risk of drug–drug interactions, adherence issues, and adverse events—factors contributing to suboptimal metabolic outcomes [60].

Both T2DM, obesity, metabolic syndrome, and MASLD are characterized by some degree of inflammation [62-65]. Polypharmacy is associated with both poor diabetic control and high inflammation markers. Hence, polypharmacy affects not only diabetes mellitus patients but also subjects with MASLD or metabolic syndrome.

5. Conclusions

Polypharmacy in patients with T2DM and related conditions is a complex, multifactorial issue. While many patients require multiple medications to control glycemia and manage comorbid conditions, the quality and appropriateness of therapy are more important than the sheer number of drugs. Regular medication review, deprescribing when appropriate, and individualized therapeutic strategies can help optimize glycemic control while minimizing adverse outcomes. Future studies should explore the integration of pharmacogenomics, artificial intelligence, and patient-reported outcomes further to refine diabetes pharmacotherapy in the era of precision medicine.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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