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Managing diabetes mellitus in a complex world: navigating the challenges of polypharmacy

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ABSTRACT

Diabetes mellitus (DM) presents complex challenges for both patients and healthcare providers. DM can lead to a range of complications and often coexists with other comorbidities. The need to effectively manage these complications, coupled with the presence of comorbidities, contributes to polypharmacy in DM patients. Polypharmacy can increase the risk of adverse drug events and drug interactions. As most serious adverse effects of polypharmacy in DM patients arise from drug interactions, the importance of careful medication management is paramount. Physicians must consider individual patient factors and conduct thorough pharmacological assessments in order to prevent unwanted effects. Furthermore, medication errors are a significant concern, particularly in elderly diabetic patients who are often prescribed multiple drugs due to comorbidities. Adhering to the Beers Criteria as well as regular monitoring for drug-drug and drug-food interactions, side effects, and medication appropriateness is essential for the optimization of the treatment and the reduction of the risk of adverse events in DM patients.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder that presents complex challenges for both patients and healthcare providers. It is one of the leading global health concerns, ranking as the eighth leading cause of death and disability worldwide. Currently, 537 million adults are living with diabetes; a number that is expected to rise to 783 million by 2045[1]. DM can lead to a range of complications, including both macrovascular and microvascular issues, and often coexists with other comorbidities[2]. Around 50% of individuals with DM also experience comorbidities, such as heart

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disease, hypertension, and dyslipidaemia. These conditions, along with the risk of cardiovascular, renal, gastrointestinal, neurological, endocrine, and ophthalmological complications, result in a significantly reduced quality of life compared to those without DM[3].

The need to manage these complications, coupled with the presence of comorbidities, contributes to polypharmacy in DM patients. Although polypharmacy has been an important factor in reducing the incidence of type 2 DM-related complications and all-cause mortality, it can increase the risk of adverse drug events and drug interactions. Furthermore, managing complications with additional medications further complicates adherence to treatment plans, thereby increasing the likelihood of non-compliance. It is also important to note that the risk of adverse events rises by approximately 50% when five drugs are used, and by over 95% when eight or more drugs are prescribed.

2. Pharmacological treatment of type 2 DM

A variety of drug classes are used to treat type 2 DM, including insulin, biguanides, sulfonylureas, meglitinides, sodium-glucose transport protein-2 (SGLT-2) inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, amylin analogues, dipeptidyl peptidase-4 inhibitors, and incretin mimetics. Each class works through different mechanisms, but all come with potential adverse reactions. Severe side effects, as outlined in the summary of product characteristics, include haematological disorders (e.g., leukopenia, agranulocytosis, thrombocytopenia), anaphylactic reactions, severe skin reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis), and the potential for pancreatitis, among other serious conditions.

Certain adverse reactions require special attention: (i) euglycemic diabetic ketoacidosis (a serious and potentially life-threatening reaction associated with SGLT-2 inhibitors)[4], (ii) Fournier's gangrene (although extremely rare, it is particularly dangerous), (iii) medullary thyroid cancer (MTC; the incidence of MTC is slightly elevated in patients using semaglutide; the latter should be avoided in individuals with a family history of MTC and it should be used cautiously in those with nodular goiter), (iv) bladder cancer (the risk of bladder cancer associated with pioglitazone is time- and dose-dependent), (v) bone fractures (an increased risk of fractures, particularly in postmenopausal women, is linked to pioglitazone), and (vi) adverse reactions related to tirzepatide (still under evaluation).

3. Lipid management in DM patients

For DM patients with established coronary artery disease, maintaining low-density lipoprotein (LDL) levels is crucial. LDL levels should be reduced to less than 55 mg/dL or to less than 35 mg/dL if heart attacks persist despite treatment. Common medications used to achieve these targets include statins, ezetimibe, bempedoic acid, and combinations of these drugs. Additional therapies, such as PCSK9 (proprotein convertase subtilisin / kexin type 9) inhibitors, colesevelam, or fish oil derivatives, may also be used[5].

However, lipid-lowering drugs, particularly statins, are not without risks. Serious, albeit rare, side effects include skin reactions like the Stevens-Johnson syndrome and the DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome. Patients should also be monitored for muscle-related issues, including myopathy, rhabdomyolysis, and severe necrotizing myopathy[6]. Additionally, statins may exacerbate conditions like myasthenia gravis and have been linked to an increased risk of developing DM. Other rare side effects of lipid-lowering medications, particularly of rosuvastatin, include tubular proteinuria.

4. Hypertension and diabetic comorbidity

Hypertension is a common comorbidity in individuals with type 2 DM. Treatment often begins with a combination of two or three medications, depending on the severity of hypertension. First-line therapies include diuretics (e.g., hydrochlorothiazide or furosemide), angiotensin II receptor antagonists or

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angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (e.g., amlodipine), and beta-blockers (e.g., bisoprolol).

It is essential to monitor for potential adverse effects associated with antihypertensive and diuretic medications. Key concerns include electrolyte disturbances and cardiovascular symptoms, such as angina pectoris, atrioventricular block (1st, 2nd, or 3rd degree), sinus bradycardia, sinus pause, malleolar oedema, palpitations, and tachycardia. Additionally, rare but serious adverse reactions like the DRESS syndrome have been reported with furosemide. ACE inhibitors may also cause mood changes, including depression, while the relationship between calcium channel blockers and depression remains unclear.

5. Drug interactions and considerations

Most serious adverse effects result from drug interactions, and can be classified as either pharmacokinetic or pharmacodynamic[7]. Some notable examples of drug interactions include the co-administration with: (i) hypoglycaemic drugs (this can lead to significant hypoglycaemia), (ii) drugs metabolized by cytochrome P450 enzymes (particular attention is needed for drugs metabolized by these enzymes, such as sulfonylureas and pioglitazone; significant pharmacokinetic interactions can occur with inducers or inhibitors of cytochrome P450; cytochrome P450 inhibitors include ketoconazole, itraconazole, ritonavir, clarithromycin, erythromycin, amiodarone, diltiazem, verapamil, fluconazole, and grapefruit juice; cytochrome P450 inducers include rifampicin, carbamazepine, phenytoin, phenobarbital, and St John's wort)[8,9], (iii) contraceptives (requires caution due to the potential for reduced contraceptive effectiveness; for example, tirzepatide significantly reduces the plasma concentration of oral contraceptives), (iv) verapamil or quinidine (this combination can be harmful for patients with hypertrophic obstructive cardiomyopathy, potentially leading to pulmonary oedema), (v) dicoumarin anticoagulants (close monitoring of the international normalized ratio / INR levels is essential for safe anticoagulation), (vi) digitalis or lithium (close monitoring of drug levels is essential due to the risk of toxicity), and (vii) antihypertensives and nonsteroidal anti-inflammatory drugs (caution is advised, particularly in patients with compromised renal function, as this combination can further impair kidney function).

6. Conclusion

Most serious adverse effects arise from drug interactions, thereby highlighting the importance of careful medication management. Physicians must consider individual patient factors and conduct thorough pharmacological assessments in order to prevent unwanted effects. Furthermore, medication errors are a significant concern, particularly in elderly DM patients who are often prescribed multiple drugs due to comorbidities. Adhering to the Beers Criteria for prescribing can help minimize adverse drug reactions and improve patient outcomes[10]. Regular monitoring for drug-drug and drug-food interactions, side effects, and medication appropriateness is essential for the optimization of the treatment and the reduction of the risk of adverse events.

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Conflicts of interest

None exist.

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