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# Drug-related problems (DRPs) in geriatric patients with type 2 diabetes mellitus (T2DM): a review

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**ABSTRACT**

Diabetes mellitus (DM) is a degenerative disease affecting 10 million people in Indonesia, with a prevalence higher than 6.2 %. In 2006, WHO reported that Indonesia ranked 4th in the world in terms of the number of diabetes cases after India, China, and the United States. In 2030, DM cases in Indonesia are expected to increase from 7 to 12 million. Drug related problems (DRPs) are unfavorable events that occur in the patients as a result of drug therapy and have the potential to interfere with the desired therapeutic outcomes. The geriatric population at high risk to DRPs due to physiological changes, comorbid conditions which lead to polypharmacy, and irrational drug therapy. Identification of DRPs is crucial not only for increasing the efficacy of drug therapy, but also improving the quality of life patient. This article aimed to identify the types of DRPs in geriatric patients with type 2 diabetes mellitus (T2DM). The information obtained is expected to describe the pattern, to prevent the incidence of DRPs in geriatrics patients, and to be used as basis of further research.

**ABSTRAK**

Diabetes melitus (DM) merupakan penyakit degeneratif yang diderita 10 juta orang Indonesia dengan prevalensi lebih 6,2 persen. Pada 2006 WHO melaporkan, Indonesia menempati urutan ke-4 negara dengan kasus DM terbesar di dunia, setelah India, China, dan Amerika Serikat. Pada 2030 di Indonesia, diperkirakan DM akan meningkat dari 7 juta menjadi 12 juta kasus. *Drug related problems* (DRPs) adalah kejadian yang tidak diinginkan pada pasien akibat terapi obat dan berpotensi mempengaruhi hasil terapi yang diinginkan. Pasien geriatri memiliki peningkatan risiko DRP karena perubahan fisiologis tubuh, kondisi komorbiditas yang mengarah ke polifarmasi, atau terapi obat yang tidak rasional. Identifikasi DRP sangat penting tidak hanya untuk meningkatkan keberhasilan terapi, tetapi juga dapat meningkatkan kualitas hidup pasien. Artikel ini bertujuan untuk mengidentifikasi jenis DRPs pada pasien geriatri diabetes melitus tipe 2 (DMT2). Informasi yang didapat dapat membantu menentukan jenis dan mencegah DRP pada geriatri dan dijadikan sebagai dasar untuk penelitian selanjutnya.

## INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by high blood glucose levels and caused by abnormalities in insulin secretion/or action.[1] Diabetes mellitus is a highly prevalent disease worldwide. According the latest The International Diabetes Federation (IDF) data published in 2021, 537 million people lived with DM worldwide.[2] Indonesia ranks 5th in DM cases in the world with a prevalence rate of 6.2% or more than 10 million DM cases. In 2019, 10.7 million people with DM was reported and it is estimated to increase to be 16.6 million in 2045. In 2017, DM was one of the top 3 causes of death in Indonesia. Approximately 90% of people with DM is type 2 diabetes

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mellitus (T2DM).[3-5]

Drug problems that involve actual or potential pharmacotherapy and can influence expected health outcomes are called drug related problems (DRPs).[6] Geriatric patients with T2DM have a higher incidence of DRP, with an average of four DRPs per patient.[1,7] A study in Indonesia found DRPs in 78.2% of hospitalized geriatric patients.[8] At least two reasons why the geriatric population is susceptible to DRP, namely 1) in geriatric, physiological changes occur in body which affect the pharmacokinetic and pharmacodynamic parameters of a drug and, 2) the existence of co-morbidities, medication adherence, and the use of multiple drugs called polypharmacy.[4,9] It may also be due to geriatric patients receiving multiple medications and treatments via multiple routes of administration that exceed clinical indications for controlling their medical condition.

This article reviewed the types of DRPs in geriatric patients with T2DM. The information obtained from this article is expected could be used to determine the pattern of DRPs in geriatrics patients with DM, preventing the occurrence of DRPs, and as preliminary data for future research.

## MATERIALS AND METHODS

Articles from PubMed, Science Direct, JAMA and Google Scholar databases published form December 2003 to November 2019 were gathered in order to collect the data. The search strategy was designed to identify relevant studies of DRPs in elderly patients with DM. The following keywords were used including DRPs, DM, geriatrics, and elderly patients.

## RESULTS AND DISCUSSION

Types of DRPs in patients with T2DM were identified in this review which were 1) adverse drug reaction (ADRs); 2) dose too low (under dose); 3) dose to high (over dose); 4) therapy without indications (unnecessary therapy); 5) indication without therapy; 6) inappropriate drug selection; 7) adherence problem (non-compliance); 8) drug interaction; and 9) polypharmacy.

### Adverse drug reactions (ADRs)

Adverse drug reaction is an unintended and perilous response to a drug therapy. It is encountered in the usual dosages used for treatment, prophylaxis and diagnosis in human beings. Age is one of the risk factors which increases ADR events. The elderly patient has more risk factors to experience ADR.[10] Another risk factor of ADRs is gender. A study conducted in Dr. H. Moch. Ansari District Hospital, Banjarmasin, Indonesia reported that women tends to have DM (90 %) than men, and age more than 55 y.o. has more likely to have T2DM (55%).[11] Women are affected twice more than men, which is because of a combination of pharmacodynamic and pharmacokinetic factors.[12]

The most prevalent ADR in geriatrics with T2DM was hypoglycemia (63.72 %), followed by gastroenteritis (6.86 %) especially with insulins and gastrointestinal events for biguanides and meglitinides.[13] Sulfonylureas are drugs also associated with hypoglycemic events. Hypoglycemia can cause confusion, loss of consciousness, extreme fatigue, tachycardia, disorientation, even death.[14] Lactic acidosis was frequently reported in metformin-associated lactic acidosis (MALA) cases. High serum lactate concentration can increase mortality in septic shock patients.[12]

A study conducted on elderly Japanese patients with T2DM reported higher prevalence of ADRs associated with ipragliflozin administration. An estimated 10.06 % ADRs occurred in patients that were given ipragliflozin in a year, and 0.61 % of ADRs were classified as severe. The most prevalent ADRs were skin disorders (2.27 %), renal and urinary infection (1.67 %), general disorders and administration site problems (1.12 %),

and digestive disorders (1.02 %).[15]

**Dose too low (under dose)**

Under dose is a very small dose that it fails to achieve the desired response. A study concerning medication errors including under dose drugs in the elderly with chronic disease in Austria reported that metformin has 5.1 % over or under dose.[16] However, in another retrospective study geriatric patients with T2DM at Kalooran GMIM Amurang Hospital, North Sulawesi, Indonesia, and Gedong Air Public Health Center in Lampung, Indonesia indicated the most DRPs were drug interaction, contraindicated medication, and drugs without indication. Furthermore, the underdose event was not found in those studies.[17,18]

For some years, we have given comprehension starting treatment from the lowest dose, especially for elderly patients. The advantages of choosing a very low initial dose are a) it could minimize the possibility of ADRs; b) it may involve patients in determining the optimal dose for them; and c) it could offer placebo effects.[19] Nevertheless, the very low dose has a weakness. It can cause medication ineffectiveness and it also affects the adherence of the patient. If using under dose medication and its effect does not achieve the best result, the patient would not be satisfied and discontinue taking the medications. Adherence is one of the keys to achieve the best treatment for elderly patients with chronic diseases, such as DM.[20]

**Dose too high (overdose)**

An overdose can be defined as if there is an excessive amount of drug or medicine. It could be toxic or poisonous to the body and life-threatening. A case report about metformin overdose was found in a diabetic woman of 79 y.o. with poor nutritional intake. Metformin reduces blood glucose levels by preventing glycogen breakdown and decreases gluconeogenesis. Metformin also reduces the rate of glucose absorption from the gastrointestinal tract and increased intestinal lactate production. The most commonly reported ADRs of metformin include hypoglycemia and lactic acidosis.[21]

Patients 80 y.o. and up had the greatest rate of emergency department visits and hospitalization due to insulin-related hypoglycemia errors (IHEs). The risk of hypoglycemic in the elderly should be considered in prescribing antidiabetic oral and intensifying insulin. Meal planning accompanied with appropriate antidiabetic oral and insulin dose are the best way for hypoglycemia prevention. Insulin is one of DM treatments and it is still difficult to manage and poses a severe risk of hypoglycemia. IHEs in emergency department visits by taking the wrong insulin were documented, combining long-acting and rapid-acting insulin is the most common error reported.[22]

Hypoglycemia could be defined as low fasting blood glucose levels measured precisely. Hypoglycemia threshold is commonly around 70 mg/dL. Severe hypoglycemia is defined as a plasma glucose level of 40–50 mg/dL. In geriatric patients, hypoglycemia is related to morbidity and death. In order to reduce hypoglycemia, clinicians should do health education programs often and monitor patient condition closely to those diabetic patients with severe hypoglycemia.[23]

**Therapy without indications (unnecessary therapy)**

Administration of drugs without proper indication not only increases the cost of therapy but also has adverse consequences for the patient. The following factors can lead to the administration of drugs without indication a) patient taking drugs that are not in line with the disease's current indications; b) non-drug therapy (lifestyle modification) is more effective in treating the patient's medical condition; c) patients are given treatment to manage undesirable effects produced by other drugs that should be substituted

with drugs that have fewer side effects; d) patients gets multiple drugs for conditions where single-drug therapy is enough based on indications; e) there is duplication of therapy.[24]

**Indication without therapy**

The patient is suffering from a disease which needs therapeutic interventions but patient disease is left untreated. Some examples of indication which need therapy are a) patients with a new medical condition need new drug therapy accordingly; b) patients suffering from chronic diseases need follow-up drug therapy; c) patients with health conditions that require combination pharmacotherapy to achieve a synergistic or potentiating effect; d) patients at risk of developing a new medical condition that can be prevented by the use of prophylactic drugs.[25]

**Inappropriate drug selection**

Inappropriate drug use has emerged as a serious problem among geriatric patients. Inappropriate drug administration increases the incidence of ADEs, treatment failure, hospitalization, death, and medical costs.[26] If a drug is not the best choice according to the patient's clinical condition and needs or the drug is more likely to be harmful than useful, it is deemed inappropriate.[26] A study conducted in India reported that 7.42% of the patients received inappropriate drugs while 23% of patients had at least one prescription of the inappropriate drug.[27] Another study conducted in the geriatric population of the United States and Canada found a significant incidence of inappropriate drug use in the range of 14% to 34% of the general elderly population.[28]

Inappropriate drug usage involves the following; a) inappropriate drug, dose, frequency of administration, or length of therapy; b) overlapping treatment; c) drug interactions and proper drug indications are not taken into account; e) even after the acute illness is resolved, the appropriate therapy for the illness continues to be administered inappropriately; f) when a patient is treated with a drug that is effective but expensive in the presence of a drug that is equally effective but cheap; g) when a patient is allergic to a given therapy; h) combination therapy instead of effective single-drug therapy; i) effective but expensive therapy as compared to other alternative drug options; j) patients develop resistance to the given therapy.[25]

Some drug classes are of particular concern in the elderly and should be stopped or used in certain situations with close monitoring.[29] American Geriatrics Society introduced Beers Criteria to identify the drugs that are potentially inappropriate in geriatric patients. The physicians must assess the benefits and risks of treatment on an individual patient basis. Despite the presence of evidence-based guidelines, geriatric patients are still being prescribed inappropriate drugs. In such patients, the incidence of undesirable consequences is higher.[30]

Elderly people often have non-pharmacological treatments (eg, physical activity, massage, diet)[31] or drugs that cause adverse effects on mild clinical symptoms (including harmful effects of other drugs). Drugs (typically analgesics, $H_2$ receptor antagonists, sleeping pills, or laxatives) are prescribed, even if lower doses of the drug may provide better treatment. Initiating the administration of supplementary medication is usually unnecessary; benefits are little, the cost is high, and supplementary medication can increase the risk of lethal effects.

Avoiding short-listed drugs and paying attention to the categories of drug that require attention is not enough to fix the issues of improper medicine use in the geriatric patients. In addition to potential benefits versus hazards, a patient's overall treatment plan should also be evaluated on a regular basis to assess the drug's long - term use.

**Adherence problem (non-compliance)**

Term adherence is defined by the

WHO as the extent to which a person follows agreed instructions from healthcare professionals in terms of taking drugs, following the diet plan, and/or improving his lifestyle.[32] Lack of adherence usually affects drug efficacy in geriatric patients. Many factors affect adherence, and age is one of them. Half of the elderly do not take the medication as prescribed and generally take less than the recommended dose (poor adherence). Patients who adhere to their treatment plan have a lower risk of hospitalization and mortality. In a study, researchers found that the rate of hospitalization in non-adherent patients was two times higher, while the rate of mortality was 3 times higher than those who showed adherence to their therapy[33]. Patients with DM must adhere to drug therapy, exercise, and healthy food in order to minimize acute and chronic complications.[34]

The following factors play a role in non-adherence; a) economic and physical constraints can make drug purchase difficult[35]; b) cognitive issues that might make it difficult to take medication as prescribed; c) polypharmacy; d) taking medication more than once a day, or in a certain way; e) lack of knowledge about the drugs (benefits) purpose or how to identify and manage the adverse effects; f) prescribed medications contradicting the patient's health beliefs[36]; g) the unpleasant taste of dosage form.

Regimes that are administered regularly or infrequently, polypharmacy regimens, or both, which may be too complex for patients to understand. Physicians evaluate the patient's health literacy and ability to follow medication regimens (e.g., dexterity, hand strength, cognition, visual acuity), easy-to-use containers, bold print drug labels, and instructions. Attempts should be made to meet their limitations by organizing and proposing a container with an alarm to avoid missed doses, a daily medicine container, a confirmation phone call, or medical support.[37] Pharmacists and nurses may help by providing education each time they meet an elderly patient and reviewing prescription instructions together.[38] It is important to guide patients about the complications that can arise if diabetes is not appropriately managed.[39] The pharmacist may be able to detect the problem by noticing that the patient is replenishing the medication on time, or that the prescription is not irrational. Many pharmacies have the ability to monitor drug replenishment trends and notify patients and/or prescribers if prescription medicine replenishment is not completed at the required intervals.

**Drug interaction**

Drug interaction can be defined as a reaction between two or more drugs, with foods, herbal and supplements, beverages, or alcohol which results in unwanted effects. High proportion of prescription drugs in geriatric (taking an average of five drugs in one prescription) increases the chances of drug interactions. Interaction can occur at pharmacodynamic and/or pharmacokinetic levels.[40] A study investigated the potential drug interaction between rebamipide, diclofenac and celecoxib by monitoring the effects on plasma concentrations. It was found that rebamipide concentration were significantly altered in rats after oral administration followed by diclofenac orally, compared to rebamipide only and rebamipide plus celecoxib combination.[41]

Combination of glimepiride and insulin can increase risk of hypoglycemia. A randomized controlled trial compared the efficacy and safety parameters of glimepiride when given in combination with morning insulin gargline, bedtime insulin gargline, and bedtime neutral protamine hagedorn (NPH) in T2DM patients. The given dose of glimepiride was 3 mg and to achieve fast blood glucose levels of 5.56 mmol/L, the dose of insulin was titrated by using predefined regimen. Patients with hypoglycemia events was higher in glimepiride combined with bedtime NPH insulin than bedtime insulin gargline and

morning insulin gargline. Hypoglycemia is one of adverse effect that should be monitored closely especially for elderly population.[42]

**Polypharmacy**

The Centers for Medicare and Medicaid Services (CMS) defines polypharmacy as the simultaneous taking of prescriptions for the use of inappropriate drugs, drugs without clinical indications, or patients receiving 3 to 5 or more medications. Polypharmacy is a common practice in elderly population because they suffer from complicated diseases that require more than one drug for treatment.[43] Polypharmacy results in irrational drug use, adverse drug events, poor health outcomes and excessive use of resources. The complexity of health management in elderly patients continues to increase. Comorbidity and polypharmacy are linked closely. Healthcare providers must play an active role in eradicating drug-related problems by continuing to assess and seek treatment of patients for secondary problems due to polypharmacy to optimize outcomes.[44]

There are many drug guidelines for elderly patients to treat common complicated diseases such as hypertension, DM, and heart failure. In a study on diabetic patients, most patients ended up being treated with one to four drugs along with several daily glucose monitoring tests. The findings revealed that, only few individuals adopt definite lifestyle modifications and performed activities to improve their treatment goals with less drug possibilities. Analysis showed that age, presence of comorbidities and ADRs, year of diagnosis with DM, and physician communication and awareness about the patient's disease management all appeared to be prognostic factors for polypharmacy.[45]

## CONCLUSION

Geriatric population at high risk to DRPs due to physiological changes, comorbid conditions which lead to polypharmacy, and irrational drug therapy. Geriatric patients with T2DM have a higher incidence of DRP, with an average of four DRPs per patient. The most prevalent of DRPs in geriatric patients with T2DM are adverse drug reaction (ADRs); dose too low (under dose); dose to high (over dose); therapy without indications (unnecessary therapy); indication without therapy; inappropriate drug selection; adherence problem (non-compliance); drug interaction; and polypharmacy. Coordination and collaboration among physicians, pharmacists, and other healthcare professionals are needed to minimize the DRPs events and to enhance the quality of pharmaceutical care services for patients to achieve desired therapeutic outcomes.

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