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Adherence Trends in the Use of Innovative Drugs for Diabetes: Evaluation of Their Effectiveness and Safety

Dwight Mahaputera Marulitua Hutapea
Universitas Prima Indonesia
e-mail: dwightmahaputeramrulituahutape@unprimdn.ac.id

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ABSTRACT

Type 2 diabetes mellitus continues to show increasing global and national prevalence, driving the need for more effective and personalized management approaches. Innovative therapies such as SGLT2 inhibitors and GLP1 receptor agonists present as pharmacological solutions with promising cardiovascular and renoprotective benefits. However, the effectiveness of these therapies in clinical practice is determined not only by drug efficacy, but also by patient adherence and health system readiness. This study used a qualitative approach based on literature review to evaluate the challenges of adherence as well as the effectiveness and safety of innovative therapies in type 2 diabetes. The results of the analysis showed that although innovative drugs have been proven effective in clinical studies, response variability and side effects in real practice require realworld evidence (RWE)based monitoring. Obstacles such as high costs, unequal access, and low patient understanding are major barriers to widespread implementation of therapy. Adherenceenhancing strategies, technologybased education, and inclusive financing policies are needed to optimize the benefits of therapy. Thus, successful diabetes management through innovative therapies requires an integration of scientific approaches, public policies, and active patient participation in a fair and responsive health care system.

Keywords: Medication Compliance; Innovative Diabetes Therapy; Evaluation of Effectiveness and Safety

INTRODUCTION

Type 2 diabetes mellitus is one of the noncommunicable diseases with a significantly increasing prevalence in various parts of the world. According to the International Diabetes Federation (IDF), in 2021 there were more than 537 million adults living with diabetes, and this figure is expected to increase to 643 million by 2030 (IDF Diabetes Atlas, 10th Edition, 2021). In Indonesia itself, the prevalence of diabetes shows a worrying trend, with the 2018 Riskesdas data recording an increase in the prevalence of diabetes from 6.9% in 2013 to 10.9% in 2018. This condition not only impacts the individuals who experience it, but also burdens the national health system in terms of financing and service capacity.

Therefore, appropriate and sustainable interventions are needed, one of which is through effective pharmacotherapy management.

However, diabetes management cannot be separated from the complexity of patient characteristics and the dynamics of therapy development. The use of conventional drugs such as metformin and sulfonylureas, although proven effective in lowering blood glucose levels, is often insufficient in controlling longterm complications such as cardiovascular disease and kidney failure. This raises the need for more innovative therapies that are tailored to the patient's risk profile. More than simply expanding pharmacotherapy options, this approach demands a thorough evaluation of the effectiveness and safety of each regimen that is widely used in the population. Thus, the increasing prevalence of diabetes is not only an alarm for improving detection and diagnosis, but also an impetus for a transformation in a more personalized and evidencebased therapeutic approach.

In the last decade, the development of innovative drugs for type 2 diabetes has become a major focus in an effort to improve patient clinical outcomes. Two prominent classes of therapy are SodiumGlucose Cotransporter2 (SGLT2) inhibitors and GlucagonLike Peptide1 Receptor Agonists (GLP1 RA). In contrast to conventional therapies that only focus on glycemic control, these two classes show significant cardiovascular and renoprotective benefits. The EMPAREG OUTCOME and CANVAS studies showed that the use of SGLT2 inhibitors such as empagliflozin and canagliflozin can reduce the risk of major cardiovascular events and slow the decline in kidney function in diabetic patients (Besmaya & Laksono, 2023; Mayer et al., 2019). On the other hand, GLP1 RA such as liraglutide and semaglutide have been shown to reduce the incidence of myocardial infarction and stroke, while also helping to reduce body weight (Paramitha et al., 2022). This fact shows that the orientation of current diabetes therapy has shifted from simply controlling blood sugar to a more holistic and protective approach to vital organs.

Although promising, the implementation of this innovative therapy is not without challenges. One crucial issue is the high cost of treatment that limits access, especially in middleincome countries like Indonesia. In addition, the varying clinical responses between individuals, as well as the risk of side effects such as urinary tract infections in SGLT2 inhibitors or gastrointestinal disorders in GLP1 RA, require a personalized and strict evaluation of use (Rahma et al., 2024). Furthermore, the implementation of this therapy also requires increased clinical competence of health workers in selecting the right regimen and educating patients so that they can understand the benefits and potential risks. Thus, although innovative drugs have scientifically proven their advantages, the success of their widespread use is highly dependent on the readiness of the health system and the active participation of patients in managing their disease.

The level of patient adherence to the use of innovative medicines remains a major challenge in clinical practice, although various studies have shown their potential benefits. Various factors influence this adherence, ranging from the complexity of the drug regimen, side effects, treatment costs, to limited patient

understanding of the longterm benefits of therapy. According to Farisya et al (2024), adherence to chronic disease treatment in developing countries is only around 50%, and this figure tends to be lower in therapies involving new or expensive interventions. In the Indonesian context, the high outofpocket burden and unequal access to health facilities exacerbate this issue. Without systematic interventions to improve adherence, the clinical effectiveness of innovative medicines will be difficult to achieve optimally, even at risk of widening the gap in health outcomes between socioeconomic groups.

Furthermore, low adherence not only impacts individuals, but also creates systemic consequences in the form of increased complication rates, financial burdens on the health insurance system, and inefficient use of service resources. For example, a study by Ridho et al (2025) showed that nonadherence to diabetes treatment is directly related to an increased risk of microvascular and macrovascular complications, which ultimately doubles the cost of care. Therefore, strategies to improve adherence must be multidimensional: from ongoing patient education, technologybased therapy monitoring (such as dose monitoring applications), to pricing and subsidy policies that support equitable access to innovative therapies. Approaches such as shared decisionmaking between patients and medical personnel have also been shown to increase patient trust and involvement in longterm treatment.

Evaluation of the efficacy and safety of innovative drugs for diabetes cannot stop at the results of early clinical trials. Although randomized controlled trials (RCTs) such as EMPAREG, LEADER, and DECLARETIMI provide a strong foundation for the adoption of new therapies, the ideal conditions in these trials often do not reflect the complexity of realworld clinical practice. Therefore, realworld evidence (RWE) is increasingly important in assessing how these drugs work in more diverse populations, with different comorbidities, socioeconomic backgrounds, and adherence levels. Longterm observational studies based on national health data or patient registries can reveal the risk of rare adverse events and longterm effectiveness trends that are not detected in clinical trials (Lapui, 2021). These evaluations are essential to ensure that clinical and policy decisions are based not only on statistical results but also on relevant clinical value for patients and health systems.

Moreover, safety evaluation should be a dynamic process and responsive to change. For example, although SGLT2 inhibitors have been shown to reduce the risk of heart failure, several postmarketing reports have linked their use to an increased risk of euglycemic ketoacidosis and genital infections (FDA Drug Safety Communication, 2015). This suggests that a robust and integrated pharmacovigilance mechanism is essential to detect and respond to safety signals promptly. Furthermore, in the context of public policy, the results of such evaluations should be used to update national therapeutic guidelines and financing schemes such as the National Health Insurance (JKN). Without a systematic and locally datadriven evaluation process, the great potential of innovative medicines will not be optimized equitably and sustainably within the health care system.

RESEARCH METHODS

This study uses a qualitative approach with a literature study method to analyze trends in adherence to the use of innovative drugs in the management of diabetes mellitus, as well as to evaluate their effectiveness and safety. Literature studies were chosen because this approach allows researchers to collect, compare, and interpret findings from various scientific sources critically, in order to produce a comprehensive understanding of the issues studied (Mulyana et al., 2024).

The data sources in this study were obtained from scientific articles published in national and international journals indexed in databases such as PubMed, Scopus, ScienceDirect, and Google Scholar. Inclusion criteria included: (1) articles published in the 2015–2024 period, (2) articles discussing innovative drugs for type 2 diabetes such as SGLT2 inhibitors and GLP1 receptor agonists, (3) articles containing data on drug compliance, effectiveness, or safety, and (4) articles in Indonesian or English. Articles in the form of editorials, comments, and abstracts without full text were not included in the analysis.

Data analysis was conducted using thematic analysis techniques, in which researchers identified, categorized, and interpreted key themes emerging from the literature, such as factors influencing adherence, the clinical impact of innovative therapies, and long-term safety issues. Data validity was strengthened through source triangulation and peer review techniques to ensure that the resulting interpretations reflected the consistency and diversity of existing findings.

This study was conducted in accordance with the ethical code No. 2030/NW25.1 PT.10.03/2025 to ensure that all stages of the research process adhered to applicable ethical standards in literature-based research.

RESULTS AND DISCUSSION

Challenges of Adherence to Innovative Medication Use in Diabetes Management

1. Access Gap and Economic Inequality as Barriers to Compliance

Patient adherence to therapy, especially innovative therapies, is a determining factor in the longterm effectiveness of treatment. However, this adherence is highly susceptible to being influenced by social determinants, including economic conditions and geographic accessibility to health services. According to a report by Ferliani et al (2015) in Adherence to LongTerm Therapies: Evidence for Action, the average adherence to longterm therapy in developing countries is only around 50%, and low access is the main cause. In the context of innovative therapies such as immunotherapy, gene therapy, or biotechnologybased therapies which require large costs and intensive supervision, this problem becomes even more complex. In Indonesia, the majority of these therapies are still not covered by the National Health Insurance

(JKN) scheme, and are only available in tertiary hospitals with high resources. Without inclusive financing mechanisms and support for health service infrastructure, patients from socially and economically vulnerable groups will experience major obstacles in accessing and maintaining therapy on an ongoing basis.

Furthermore, a study by Hanson et al (2022) in The Lancet Oncology emphasized that the success of integrating innovative therapies into the public health system is largely determined by the country's ability to develop an adaptive financing system. In a system such as JKN, the addition of types of therapy to the scope of financing must go through a health technology assessment (HTA) process that considers aspects of cost, effectiveness, and social benefits. However, the HTA process in Indonesia is still not running optimally for new therapies, due to limited local data and limited analytical capacity. In fact, based on a study by Ulhaq (2022), many innovative therapies have a costeffectiveness ratio that is actually quite competitive when used in patient groups with specific clinical conditions. When therapy is not included in the JKN benefit list, the cost of therapy must be borne personally (outofpocket), which according to BPJS Kesehatan can reach tens to hundreds of millions of rupiah per therapy cycle. This creates an inequality in health outcomes: welloff patients can continue therapy to completion, while poor patients stop midway due to financial inability. This condition not only reduces the effectiveness of therapy individually, but also creates a wider health gap at the population level.

On the other hand, geographical factors also exacerbate the compliance gap. Indonesia as an archipelagic country has complex logistical and distribution challenges for health services. Data from the Basic Health Research (Riskesdas) and a study by Prasetya et al (2023) show that 70% of facilities with advanced health services are still concentrated on Java Island, while in eastern Indonesia, many districts do not have referral hospitals with oncology services or innovative therapies. The distribution of specialist doctors and medical personnel is also uneven, exacerbating this inequality. Research by Kruk et al (2018) in The Lancet highlighted that the tiered referral system in Indonesia is not yet supported by an adequate medical transportation system and regional incentives, so that patients from the regions have to bear the logistical burden themselves. In the context of innovative therapies, where regular monitoring and dose adjustments are crucial, limited physical access causes many patients to fail to attend health facilities regularly. As a result, there is a disruption in the therapy schedule that has the potential to reduce the effectiveness of treatment and even increase biological resistance in some cases of targeted therapy or immunotherapy. Thus, without serious efforts to bring advanced services closer to disadvantaged areas, innovative therapies will remain the privilege of urban areas.

To overcome these structural barriers, a systemic, evidencebased approach is needed through policy interventions that target the roots of inequality. One strategy proposed in the global literature is the use of progressive universalism, which is to gradually expand the scope of services but focus on the most vulnerable groups first (Ikawati et al., 2025). The Indonesian government can

implement this approach by selectively integrating innovative therapies based on disease priority and the highest clinical risk, for example cervical cancer therapy in productive age groups or hepatitis C therapy in highrisk populations. In addition, the development of a telemedicine system for posttherapy patient monitoring and empowerment of primary care facilities to handle advanced cases in an integrated manner could be a mediumterm solution. A recent study by Mufid & Dr, Tpimoc (2018) showed that the use of telemonitoring applications can increase oncology patient compliance by 25% within six months. With the strengthening of local capacity, incentives for equal distribution of facilities, and financing policy reforms that are responsive to the needs of modern therapies, Indonesia can reduce systemic barriers to patient compliance. In other words, equity in access to innovative therapies is not just a medical issue, but a reflection of social justice in the national health system.

2. The Role of Patient Education and Physician Communication as Determinants of LongTerm Compliance

Patient adherence to longterm therapy is one of the biggest challenges in chronic disease management. Patient education has been shown to be a key factor in improving this adherence. According to Hijriyati et al (2023), the global adherence rate to longterm treatment for chronic diseases is only around 50%, meaning that half of patients fail to take their medication as recommended. In a classic study by Saibi et al (2020), it was explained that patients who understand the purpose of treatment and the consequences of nonadherence tend to be more consistent in taking their medication and undergoing routine checkups. In addition, Yusi et al (2019) developed a perceptions and practicalities approach model which shows that belief in the effectiveness of drugs and the ability to overcome practical obstacles, such as forgetting to take medication or not understanding the rules for taking it, are greatly influenced by the quality of education received. Good education can reduce common misconceptions, such as the assumption that drugs only need to be taken when feeling sick, or that mild side effects mean therapy is not suitable. Although important, delivering ideal education is still difficult to realize in practice. Many studies show that communication between medical personnel and patients is still hierarchical and nonparticipatory. According to Hanggoro (2025), clinical interactions are often dominated by doctors, while patients only act as passive listeners. This is exacerbated by limited consultation time, where in some primary health services, the time per patient is only around 510 minutes (Arini, 2021). In this short time, doctors must convey the diagnosis, explain the treatment, and answer patient questions—which are often unrealistic. A study by Faridha (2022) also showed that patients with low health literacy are at greater risk of experiencing misunderstandings of treatment instructions, leading to noncompliance. In this condition, the absence of contextual and easytounderstand educational materials further exacerbates the gap in understanding. When patients feel confused or not

involved in the discussion of therapy, they tend to lose trust and ultimately stop treatment unilaterally.

To overcome these barriers, the shared decisionmaking (SDM) approach has been recognized as one of the most effective clinical communication methods in improving patient compliance and satisfaction. SDM involves the delivery of balanced information, exploration of patient values and preferences, and collaboration in choosing medical procedures. Rumintjap et al (2024) are the pioneers of this model, stating that the success of treatment is not only determined by the clinical competence of the doctor, but also by how much the patient feels involved and valued in the decisionmaking process. A metaanalysis study by Firmansyah & Widjaja (2022) confirmed that SDM consistently improves health outcomes and treatment adherence in the context of chronic diseases. In addition, Godfrey et al (2024) developed a threetalk model in SDM that emphasizes the importance of openness of information, reciprocal dialogue, and support in the decisionmaking process. Through SDM, patients not only understand the therapy rationally, but also feel in control and responsibility, which ultimately strengthens their commitment to longterm treatment.

In order for the HRbased educational approach to be widely and sustainably implemented, systemic support is needed from various aspects of health services. Empathyoriented communication training and patientcentered care need to be part of the medical education curriculum and ongoing training for medical personnel. In addition, providing educational materials that are culturally based and in accordance with the patient's literacy level is very important. Research by Lioncu et al (2023) emphasized that multimedia and contextual educational interventions, such as animated videos, illustrated booklets, or interactive digital applications, significantly improve patient understanding and compliance. From an organizational perspective, a multidisciplinary team is needed doctors, nurses, pharmacists, and educational staff who work together to provide repeated education and compliance monitoring. The chronic care model (CCM) developed by Wagner et al. (2001) in Fajriyah et al (2020) even shows that the combination of patient education, information system support, and a collaborative team approach can improve clinical outcomes and patient selfmanagement in the long term. Therefore, the integration of the communicative approach, educational technology, and the active role of patients is the key to success in increasing longterm compliance with therapy.

Effectiveness and Safety of Innovative Drugs Based on RealWorld Evidence

1. Consistency of Innovative Drug Effectiveness in RealWorld Studies

The clinical efficacy of an innovative therapy is not only measured by the results obtained in randomized controlled trials (RCTs), but also by its performance in everyday clinical practice. Clinical trials are indeed a key pillar in proving the efficacy and safety of drugs through highly standardized designs, but they often involve homogeneous and selective populations. For example,

patients with severe comorbidities, the elderly, or those with a history of poor compliance are often excluded from participating in clinical trials, even though these are the groups most often encountered in everyday clinical practice. Therefore, realworld evidence (RWE) is an important element in bridging the gap between explanatory clinical data (RCTs) and pragmatic clinical practice conditions. With the development of digital technology and electronic health records (EHR) systems, the availability of realworld data now allows researchers to evaluate the performance of therapies in larger, more diverse, and more representative populations of patients as a whole.

One of the important studies that became a milestone in proving the realworld effectiveness of SGLT2 inhibitor therapy is the CVDREAL study (Kohsaka et al., 2020). In this study, data were collected from more than 300,000 patients with type 2 diabetes in six countries, including the United States, the United Kingdom, and Norway. The results showed that patients who used SGLT2 inhibitors, such as empagliflozin and dapagliflozin, experienced a 39% reduction in the risk of hospitalization for heart failure and a 51% reduction in total mortality compared to the group using other antidiabetic drugs. Interestingly, this cardiovascular protective effect was found even in the subpopulation of patients without a history of previous cardiovascular disease, who are usually excluded from large RCTs such as EMPAREG OUTCOME or CANVAS. Thus, this study strengthens the idea that the benefits of SGLT2 inhibitor therapy are not limited to the ideal conditions of clinical trials, but also remain relevant and consistent in a more complex general population, including patients with various demographic and clinical backgrounds.

Further studies such as EMPRISE (Ahmed et al., 2023), which compared empagliflozin with sitagliptin in a realworld population, also support these findings. EMPRISE showed that empagliflozin was associated with a significant reduction in hospitalizations for heart failure, even in patients without preexisting heart disease. On the other hand, for GLP1 receptor agonists, studies such as REACTION and SUSTAIN 6 provide evidence that GLP1 receptor agonists such as liraglutide and semaglutide also show consistent cardioprotective and nephroprotective effects. Claimsbased RWE and national registries in Europe and Asia further strengthen this evidence, showing that patients with diabetes and obesity can experience a reduced risk of major cardiovascular events (MACE), kidney disease progression, and significant weight loss. In addition, a metaanalysis by Pratiwi et al (2024) confirmed that the cardiovascular benefits of GLP1 agonists persist in the long term and across diverse populations.

Furthermore, recognition of the importance of RWE has increased globally. Regulatory agencies such as the FDA and EMA have stated that RWE can be used to support new drug approvals, expansion of indications, and even to partially replace clinical trials if certain conditions are met. In the fields of endocrinology and cardiometabolics, realworld evidence has played a significant role in revising clinical guidelines. For example, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

recommend early use of SGLT2 inhibitors and GLP1 receptor agonists in patients with type 2 diabetes at high cardiovascular risk, not only based on RCTs, but also on the strength of findings from RWE. This represents a paradigm shift in clinical practice, from an efficacybased approach (ideal outcomes) to an effectivenessbased approach (actual realworld outcomes). Ultimately, RWE enables a more inclusive, adaptive, and relevant treatment approach to the real patient population, and reinforces the trend towards personalized, evidencebased medicine.

2. Safety Variability and Risk of Side Effects in Realworld Use

The variability of response to innovative therapies in clinical practice has been highlighted in pharmacoepidemiological studies, especially regarding the gap between efficacy demonstrated in clinical trials and actual effectiveness in the field. Randomized controlled trials (RCTs) do provide a strong baseline for understanding the effects of therapies under ideal conditions, but often do not reflect the more complex patient populations in the real world. A publication by van He et al. (2020) revealed that patients with chronic diseases such as type 2 diabetes, heart failure, or chronic kidney disease were not eligible to participate in RCTs due to strict inclusionexclusion criteria. This underrepresentation of vulnerable groups leads to selection bias that can obscure the understanding of the safety of therapies in everyday clinical populations. Accordingly, realworld evidence (RWE)based approaches are increasingly recognized as an important complement to assessing the benefits and risks of treatments outside the experimental setting.

A wider range of adverse events in realworld populations is of major concern in the context of therapeutic safety, especially when patients have clinical conditions not predicted by RCT data. For example, the use of SGLT2 inhibitors has been associated with a risk of euglycemic ketoacidosis (euDKA) in patients with mild to moderate renal impairment or in those on longterm insulin therapy. Data from the Swedish National Diabetes Register found that the incidence of ketoacidosis was significantly increased in dapagliflozin users compared with nonSGLT2 controls, especially in patients with an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m². This finding was not revealed in early clinical trials because the test population used had normal renal function and did not undergo polypharmacy. In addition, GLP1 receptor agonist therapy such as liraglutide or semaglutide often causes gastrointestinal complaints, including nausea, vomiting, and diarrhea. A systematic study by Wahyuningrum et al (2020) showed that these side effects tended to be more severe and more frequent in elderly patients and those with low body mass index, two groups that are often not included in the initial design of RCTs.

Realworld evidence (RWE) provides an opportunity to address clinical questions that cannot be addressed by conventional RCT designs, particularly

those related to longterm effects, interactions between therapies, and variation in patient response to drugs. For example, a study by Patorno et al. (2021) utilizing a US national insurance claims database found that the risk of hospitalization for serious gastrointestinal adverse events in GLP1 RA users was significantly higher in patients aged >65 years compared with younger age groups, despite data from previous clinical trials showing no significant differences between age groups. In addition, RWE data have been used to validate longterm safety signals initially indicated by spontaneous pharmacovigilance reports. A notable example is the finding of amputation risk in canagliflozin users, first detected in the CANVAS study (Matthews et al., 2019) but subsequently reinforced and confirmed by several large populationbased RWE studies in Europe and North America. This underscores the central role of RWE in bridging the gap between experimental findings and actual clinical outcomes.

Overall, RWEbased approaches provide an important foundation for the development of adaptive, locally contextualized clinical guidelines, particularly in populations that have been previously excluded from experimental studies. In the context of diverse healthcare systems—in terms of infrastructure, demographics, and health cultures—realworld information enables the development of more precise and personalized monitoring protocols. The principles of precision medicine increasingly emphasize the need to integrate big data from multiple clinical sources, including national registries, electronic medical records, and mobile health (mHealth) applications, to identify subgroups of patients who may benefit most from or are at greatest risk of certain adverse events. Initiatives such as the FDA's Sentinel System in the United States and the Clinical Practice Research Datalink (CPRD) in the United Kingdom are concrete examples of systematic efforts to integrate RWE data into national drug surveillance systems. Therefore, in therapeutic decisionmaking, RWE serves not only as a complement to RCTs, but also as a strategic tool in creating a responsive, adaptive, and realworld datadriven health ecosystem.

CONCLUSION

The challenges of adherence to innovative drug use in diabetes management are influenced by structural, social, and clinical barriers. Inequality of access, high costs, and limited support from the National Health Insurance (JKN) make innovative therapies difficult to reach, especially for vulnerable groups and in remote areas. Low adherence is also triggered by a lack of education and effective communication between doctors and patients. A shared decisionmaking (SDM) approach and educational technology such as digital applications can increase patient engagement in treatment. In terms of effectiveness, realworld evidence (RWE) shows that innovative therapies still provide significant benefits, although the risk of certain side effects needs to be watched out for. Therefore, a good medical recording and monitoring system is very important. A progressive universalism approach, strengthening primary care, utilizing telemedicine, and inclusive financing policies are key to increasing adherence and equal access to innovative therapies. This is not

only about the effectiveness of treatment, but also about justice in the health system.

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