

DOI: <https://doi.org/10.36489/saudecoletiva.2021v11i68p7787-7798>

# Clinical pharmacology and the lack of non-quantitative effectiveness of drugs for diabetes mellitus II: evaluation of criteria related to pharmaceutical chemistry and drug use habits

Farmacología clínica y falta de efectividad no cuantitativa de los medicamentos para la diabetes mellitus II: evaluación de criterios relacionados con la química farmacéutica y los hábitos de uso de medicamentos

Farmacologia clínica e a falta de efetividade não quantitativa de fármacos para diabetes mellitus II: avaliação de critérios relativos à química farmacéutica e aos hábitos de uso de medicamentos

## ABSTRACT

Objective: to problematize and alert to non-quantitative issues involving non-therapeutic success in patients with Diabetes Mellitus II (DM II). Method: the study carried out in two Basic Family Health Unit Centers, in Joinville city, Santa Catarina State, Brazil. The studied population corresponded to users of chronic DM II drugs; under drug treatment and registered in medical records. Data collection took place through interviews and analysis of medical records. Results: A total of 222 patients, between 42 and 82 years old, were selected in the study. The analysis of the presence of factors that lead to lack of non-quantitative effectiveness (FLNQE) resulted in an average of 3.09 causes of non-effectiveness per patient. Conclusion: FLNQE are present, especially in newly diagnosed and polypharmacy patients, also with age as a contributing factor. New studies have helped to better understand this phenomenon.

**DESCRIPTORS:** Diabetes Mellitus; Evaluation of the Efficacy-Effectiveness of Interventions; Drug Therapy; Unified Health System.

## RESUMEN

Objetivo: problematizar y alertar sobre cuestiones no cuantitativas que implican el éxito no terapéutico en pacientes con Diabetes Mellitus II (DM II). Método: estudio realizado en dos Unidades Básicas de Salud de la Familia (UBSF), ubicadas en la ciudad de Joinville, Santa Catarina - Brasil. La población estudiada correspondió a usuarios de fármacos DM II crónicos; en tratamiento de drogas y registrado en registros médicos. La recolección de datos se realizó a través de entrevistas y análisis de historias clínicas. Resultados: Se seleccionaron en el estudio un total de 222 pacientes, entre 42 y 82 años. El análisis de la presencia de factores que conducen a la falta de efectividad no cuantitativa (FFENC) resultó en un promedio de 3.09 causas de no efectividad por paciente. Conclusión: Los FFENC están presentes, especialmente en pacientes recién diagnosticados y polifarmacia, también con la edad como factor contribuyente. Nuevos estudios han ayudado a comprender mejor este fenómeno.

**DESCRIPTORES:** Diabetes Mellitus; Evaluación de Eficacia-Efectividad de Intervenciones; Quimioterapia; Sistema Único de Salud.

## RESUMO

Objetivo: problematizar e alertar para as questões não quantitativas envolvendo o não sucesso terapêutico em pacientes com Diabetes Mellitus II (DM II). Método: o estudo realizado em duas Unidades Básicas de Saúde da Família (UBSF), localizadas na cidade de Joinville, Santa Catarina - Brasil. A população estudada correspondeu à usuários de medicamentos crônicos de DM II; em tratamento medicamentoso e com registro em prontuários de atendimentos. A coleta de dados se deu por meio de entrevista e análise de prontuário. Resultados: Um total de 222 pacientes, entre 42 e 82 anos foram selecionados no estudo. A análise da presença de fatores que levam à falta de efetividade não quantitativa (FFENQs) resultou em uma média de 3,09 causas de não efetividade por paciente. Conclusão: FFENQs estão presentes, principalmente em pacientes recém diagnosticados e em situação de polifarmácia, também tendo a idade como fator contribuinte. Novos estudos ajudaram a melhor compreensão deste fenômeno.

**DESCRIPTORES:** Diabetes Mellitus; Avaliação de Eficácia-Efetividade de Intervenções; Tratamento Farmacológico; Sistema Único de Saúde.

RECEIVED ON: 04/14/2021 APPROVED ON: 04/28/2021

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**INTRODUCTION**

The lack of effectiveness of medications is a chronic problem that affects most medication users.<sup>1</sup> This can be divided into quantitative and non-quantitative. The first concerns the lower dosage that the patient needs; while the latter is a phenomenon reported in situations where there is adequate concentration and dosage, but different factors prevent the desired therapeutic result. Both conditions in patients with adherence to drug treatment have been called failures in pharmacotherapy.<sup>1</sup>

The lack of non-quantitative effectiveness can have many origins and causes; and it is based on the fact that the concentration and dosage indicated would be correct, but handling, storage, conservation, food interference, among other factors, could interfere with the therapeutic result.<sup>1</sup>

Knowing these conditions, as well as ranking them as to their influence on drug treatments, becomes essential for health actions to be more appropriate and resolute; always aiming to achieve

the desired therapeutic result with regard to pharmacological interventions.<sup>1</sup>

In this work, we investigated Factors that lead to the Non-Quantitative Lack of Effectiveness (FNQLE) as a factor that may contribute to the non-therapeutic result, listing issues such as age, treatment time or number of drugs used, as well as chemical stability of drugs affected by incorrect storage; in which these conditions may or may not contribute to this phenomenon, and to a certain extent. Such observations about FNQLEs are not limited only to their physiological and pharmacological part, which refer to dose adjustments, but are also linked to the patients' routine, which include conservation, time of use in relation to food, among others; and that affect the result of the drugs, either by loss of chemical and molecular integrity of the drug, or by preventing correct absorption, or by habits that favor the pathological state, limiting the drug's spectrum of action.

Among the therapies that present FNQLEs is Diabetes mellitus type II (DM II).<sup>3</sup> The treatment of this clinical condition prioritizes the achievement

of glycemic goals determined by several references of values and prognostics. In Brazil, the country where the research was carried out, – the glycemic target adopted is 100 mg/dl; and glycosylated hemoglobin (HbA1c) of <7%; being the values adopted in the Unified Health System (SUS) of this country to avoid complications such as kidney and vision, among others.<sup>4,5</sup>

Several situations can compromise the glycemic control of DMII 4; as [1] the influence of beta-blocker drugs,<sup>6,7</sup> [2] the adoption of an inadequate diet for the diabetic,<sup>8,9</sup> [3] inadequate conservation of drugs,<sup>10</sup> [4] use of foods that compromise drug absorption 6 and, [5] incorrect use of drugs compared to recommended. These are five conditions considered as factors that lead to non-quantitative ineffectiveness; dealing with predictable and preventable issues.

This work aims to problematize and raise awareness of non-quantitative issues involving therapeutic failure in patients with DM II, contrasting the almost common practice of changing medication or simply increasing the dose as the only

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Pinto, L.H.; Santos, M.B.P.; Simões, T.L.; Bitencourt, M.F.; Martins, H.H.; Kartens, L.F.;

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way to circumvent negative results in pharmacotherapy.

## METHOD

Study conducted in two Basic Family Health Units (UBSF), located in the city of Joinville, state of Santa Catarina - Brazil. This is a practice scenario that receives interns from health care courses at the University of the Region of Joinville (UNIVILLE).

The population studied corresponded to users of previously diagnosed chronic DM II medications; in drug treatment and registered in medical records. Patients using the medication indicated by the physician were selected, but when they underwent exams, the results were not within the normal range. That is, there was good adherence recorded in the medical record; however, these patients were considered “difficult to control” regarding the use of drug

treatment, with at least three consecutive measurements of blood glucose and HbA1c above the recommended level. Patients with DM of secondary origin, with non-adherence proven in medical records and without the ability to communicate effectively, were excluded from the study.

Patients who used the medication indicated by the doctor, but when they underwent tests, the results were not within the normal range.

This was an observational, cross-sectional study, with document analysis and interviews (Figure 1). Data collection took place in two situations: [a] interview and [b] medical record analysis. Data were registered in a standard form developed by the researchers, inspired by a pre-existing form.<sup>12</sup>

The data and information collected corresponded to: [1] Patient characteristics: age / gender / previous illnesses / family history; [2] Treatment characteristics: blood glucose values / medications in use / eating habits / treatment time / specific complaints related to the medication; followed by [3] Analysis of the FNQLEs: administration of medicines / time of administration of medicines / place where they are kept / eating habits / presence of medicines interfering with blood glucose.

The last analysis was performed according to the script in Figure 2.

As it involves human beings, this project was submitted to the Research Ethics Committee (CEP) of UNIVILLE, being approved and obtaining protocol number 01717418.0.0000.5366.

Figure 1: Study carried out in 6 steps. [1] Definition of the study UBSFs, [2] definition of the population and sample, with inclusion and exclusion criteria and ethical procedures, [3] access to medical records for sample selection and subsequent interview with them, [4] collection of data of interest to research, [5] systematization of data for analysis and [6] analysis facing the research question.

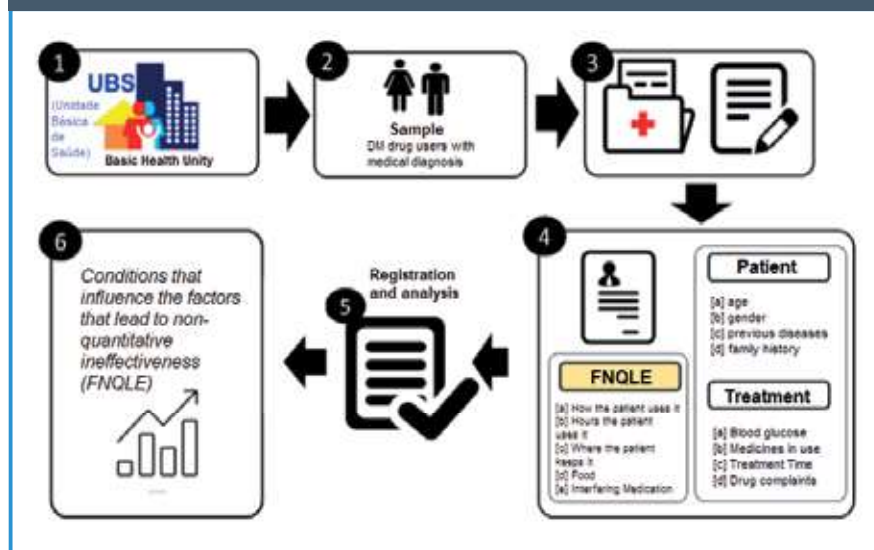
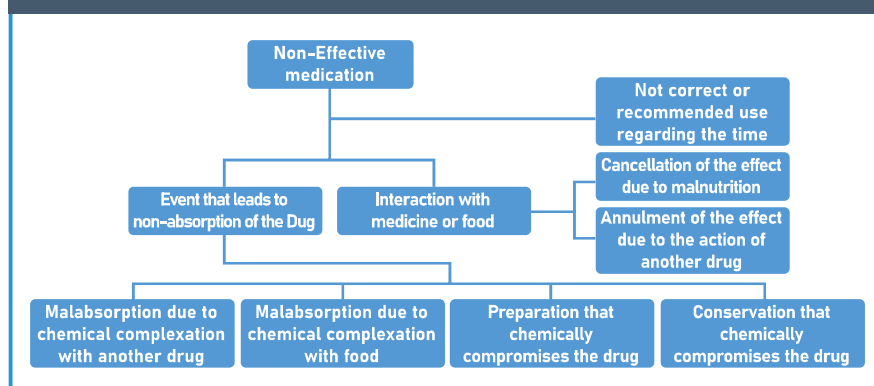


Figure 2: Flowchart of the evaluation of FNQLEs. Developed by authors based on the scientific literature contained in the reference of this research. Considering this research only as “suspicious” for the unexpected outcome.



Source: The authors

## RESULTS AND DISCUSSIONS

There were 446 registered DM-II diabetics in the UBSFs under study. A total of 222 patients - 95 men and 127 women - met the inclusion and exclusion criteria. Ages ranged between 42 and 82 years. The time of diagnosis ranged from 1 year to 30 years. The mean value of fasting blood glucose in the last exam of each patient was 164.4 mg/dL, and the mean

value of HbA1c was 8.1%. Diabetes drug regimens are listed in Table 1.

As for the presence of other diseases, 198 patients had some other type of chronic disease. The total average of medications used was 3 per patient, ranging from 2 medications and reaching 9 types of medications in total for various clinical conditions. All 222 present in the sample had a family history of chronic diseases. The frequency of medical appointments and visits to the UBSF Pharmacy were regular, and in the medical records and pharmacy records there was a record of adherence to the use of medications. The analysis of the presence of FNQLEs resulted in a total of 688 records of possible situations that

would be the cause of non-effectiveness, giving an average of 3,09 per patient.

### Presence of FNQLEs in diabetic drug users in the study

The distribution of FNQLEs in general is described in Figure 4. Among the factors that could contribute to the lack of effectiveness, the most frequent was related to inadequate nutrition for the treatment of DM II, present in 42,4% of the patients analyzed.

### Percentage of FNQLEs found in the sample

Of the total, only one patient claimed to undergo some type of nutritional mo-

onitoring. The other participants obtained information about adequate food from the doctor or another non-specific source; but they claimed not to follow them. Some participants reported that their financial situation had an impact on the adoption of more adequate food.

It's noteworthy that the relationship between healthy eating and glycemic control is well established in clinical practice.<sup>13</sup> Studies show that the reduction in HbA1c resulting from the change in eating habits can match or even surpass the reduction in values resulting from the current drug therapy for DM II after 3 to 6 months of follow-up.<sup>4,14</sup> But the issue of adopting eating habits also comes up against the issue of difficult access to habits considered healthy, such as financial, cultural and family.<sup>4</sup> The food routine of a family is not always adapted to a member who has a chronic disease, showing that this issue is not just a matter of patient guidance, but in many cases, a family member.<sup>14</sup>

The second most present factor was; "incorrect or non-recommended use regarding time and dosage", which appeared in 30,3% of the patients studied. These FNQLEs relate to non-compliance with medical recommendations regarding hours, intervals and mode of use. This situation, in which patients adhered to the drugs, but not their correct form of use.<sup>15</sup>

The origin of the non-compliance with the recommendations stems from the personal interpretation about the use, without any scientific support. Failure to comply with the medical prescription is a factor of considerable relevance for the manifestation of non-effectiveness. In a study that evaluated the use of prescription drugs, about 63% of patients did not use them properly.<sup>15</sup> WHO estimates that about 50% of drug users do not comply with the treatment as instructed by the health professional, exposing themselves to the risks of an uncontrolled chronic disease.<sup>16</sup>

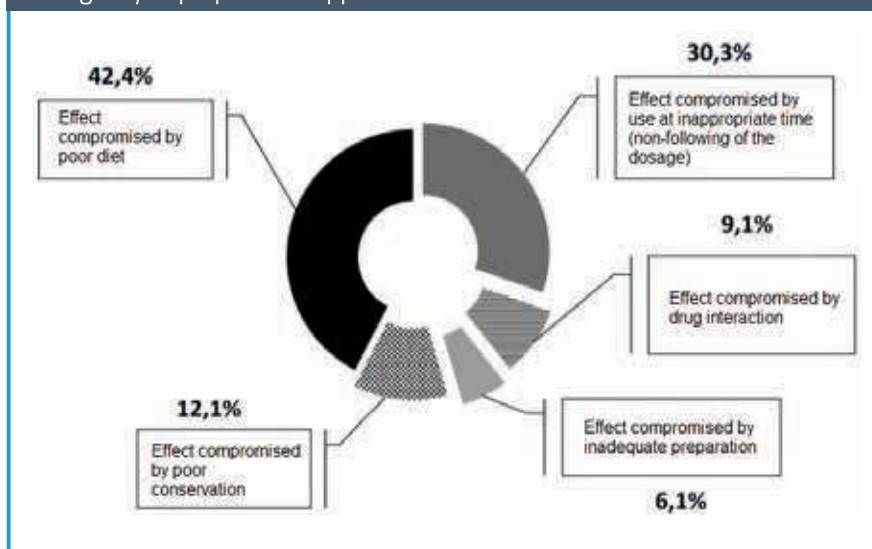
Among the other situations suspected of lack of effectiveness, there were

Table 1: Patients and drug regimens used in DM II. Source: Medical records of SMS UBSF patients

DM II DRUG REGIMEN	NUMBER OF PATIENTS	PERCENTAGE %
Glibenclamide	16	7,2
Glyazide	26	11,7
Metformin	12	5,4
Glibenclamide + Metformin	72	32,4
Glibenclamide + Metformin	96	43,2
Total	222	100

Source: Joinville SMS service record

FIGURE 3: Most frequent occurrences of FNQLEs: there is the incorrect and non-recommended use of the medication and the nullification of the effect by adopting a non-recommended diet for DM II. Complexation with food and wrong way of preparation appears less.





conditions linked to “inadequate conservation” (12,1%); potential drug interactions (9,1%) and “mistaken way of preparation” (6,1%), as shown in Figure 3. Inadequate conservation corresponds to that carried out in places that generally suffer variations in humidity and temperature, such as the kitchen and bathroom. It is known that the incorrect storage of the drug can lead to loss of efficacy and compromise its pharmacotherapy, due to molecular alterations that affect the pharmacophoric group of the molecule, as well as its activity structure.<sup>21</sup> The wrong way, on the other hand, referred to crushing tablets, solubilization, among other non-recommended ways of use, in which the loss of the integrity of the pharmaceutical form implies and influences the drug’s bioavailability, also involving chemical-pharmaceutical changes that alter its expected effectiveness; with risk of formation of disulfide bridges between molecules that contain sulfur, as is the case of sulfonyleureas.<sup>21</sup>

The most relevant interactions were those that included beta-blockers.

About 47% of patients had systemic arterial hypertension (SAH) and used this class of medication (propranolol or atenolol). These medications have the potential to exacerbate blood glucose levels and alter the treatment of DM II.<sup>7</sup> The American Association of Endocrinology recommends avoiding the use of this class of drugs in the initial treatment options for SAH in diabetic patients and when use is really necessary, opting for newer beta-blockers, such as Carvedilol, 7 available at the Basic Health Unit, but rarely prescribed in the sample (7% of those using beta-blockers).

**Conditions that influenced the FNQLEs: Patient age, treatment time and number of medications.**

Once the FNQLEs were identified, it was analyzed whether the patient’s age or length of treatment had any influence on the occurrence of such a phenomenon. The number of FNQLEs and the average by age group and treatment time were then evaluated (Figure 4).

Relative frequency of FNQLEs by influence conditions

Note that age and number of medications imply an increase in the frequency of FNQLEs when analyzed separately. With regard to age, it is known that it is a predictive factor for having difficulty in handling medications due to motor changes, cognitive losses, visual complications, among others.<sup>18,19</sup> The caregiver’s presence could even reverse this therapeutic result.<sup>23</sup> The absence of a caregiver (formal or informal) appeared in the glucose concentration range above 200 mg/dl. According to the patients’ reports, some had difficulty in understanding the use and needed help to identify and plan the medication administration routine.

Polymedication, in turn, also implies greater risks of inappropriate use due to the multiplicities of information, requiring special guidance for correct use.<sup>24</sup>

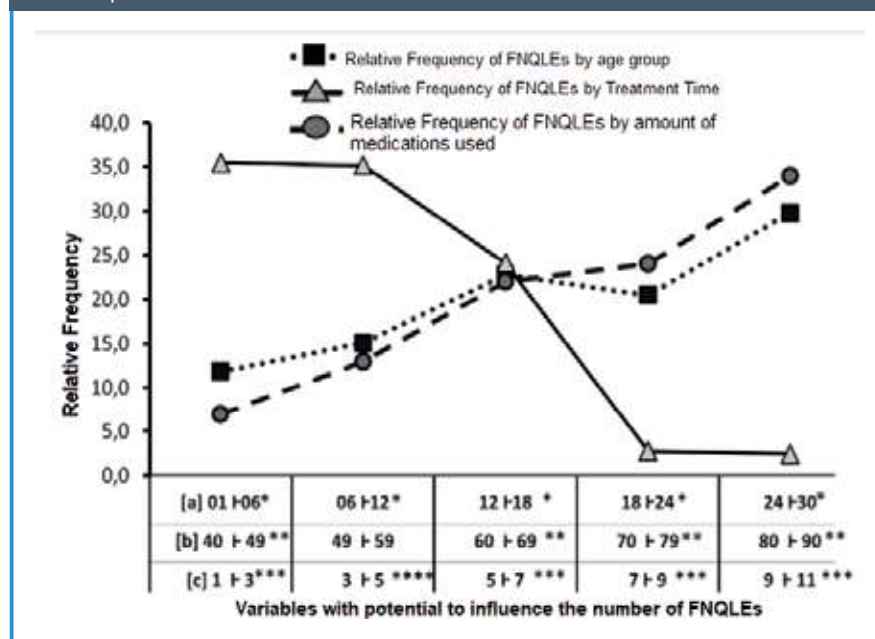
With respect to time, FNQLEs become less frequent in patients with a longer time of diagnosis. Newly diagnosed patients require more attention with regard to self-care and health information. A systematic review highlighted that health education is essential for self-care; and that health education practices aimed at newly diagnosed DM patients are essential, as they improve the learning of the disease and reduce the difficulties of daily life.<sup>25</sup>

**CONCLUSION**

Based on what was found in these studies, the factors that lead to non-quantitative ineffectiveness (FNQLE) are present in the universe of patients with decompensated DM II, and may be the reason for this condition. Further studies are needed to confirm this relationship demonstrated here. The conditions, age and number of medications used indicate that they are predictive of this mistake in the use of medication, deserving attention from health professionals.

On the other hand, the length of treatment proves to be a condition that contributes to the drop in FNQLEs, pointing out that newly diagnosed pa-

Figure 4: Conditions that imply a greater number of FNQLEs. Establishment of 5 classes of study, with subsequent calculation of the relative frequency for comparison.



tients deserve special attention for the beginning of treatments regarding the medication to be used.

In terms of contribution to the medi-

cal field in general, care for the patient's age (which includes assessing the need to have someone to help them) and polypharmacy should be included as

important parameters for the success of drug therapy. And further studies need to be carried out to better understand this phenomenon. ■

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