# Trends in polypharmacy and potentially inappropriate medication (PIM) in older and middle-aged people treated for diabetes

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## Abstract

Objective Polypharmacy is common in people with diabetes and associated with the use of potentially inappropriate medication (PIM). This study aimed to assess trends in prevalence of polypharmacy and PIM in older and middle-aged people with diabetes. Methods A repeated cross-sectional study using the University Groningen IADB.nl prescription database was conducted. All people [?]45 years treated for diabetes registered in the period 2012-2016 were included. PIMs were assessed using Beers criteria for people [?]65 years old, and PRescribing Optimally in Middle-aged People's Treatments (PROMPT) criteria for 45-64 years old. Chi-square tests and regression analysis were applied. Results The prevalence of polypharmacy increased from 56.5% to 58.2% during the study period. In 2016, the prevalence of polypharmacy was 36.9% in the group of 45-54 years old, 50.3% in 55-64 years old, and 66.2% in [?]65 years old. All age-groups showed significant increases. The prevalence of older people with at least one PIM decreased around 3%, while in the middle-aged group this prevalence increased around 1% with a highest level in 2015. The most common PIMs in both age groups were the use of long-term high-dose proton-pump-inhibitors, benzodiazepines, and strong opioids without laxatives. Of those, only benzodiazepines showed a decreasing trend. Conclusions Polypharmacy increased in older and middle-aged people with diabetes. While the prevalence of PIM decreased over time in older age, this trend was not observed in middle-aged people with diabetes. Efforts are needed to decrease the use of PIMs in populations already burdened with many drugs, notably at middle age

## 1. Introduction

Polypharmacy is the concurrent use of multiple medications and is commonly defined as the chronic use of five or more medications daily [1]. Older people are often seen as a high-risk group but polypharmacy is not restricted to the age. Significant increases in polypharmacy prevalence have also been observed in middle-aged people [2-4]. With increasing polypharmacy, the risk of medication-related harm increases. On the other hand, the use of multiple medications can provide clinical benefit and may be needed, especially for people with comorbidities [5,6]. Polypharmacy is common in people with diabetes, and having diabetes is a risk factor for polypharmacy [7,8]. Many diabetes patients are prescribed more than eight different drugs to treat their diabetes and related diseases [5].

In general, polypharmacy is associated with more use of potentially inappropriate medication (PIM) [9]. Not much is known about polypharmacy in relation to PIM in people with diabetes. It seems that PIM use is more common in older people with diabetes as compared to younger people with diabetes or older people with hypertension [10,11]. There is a worrying increase in the prevalence of diabetes in younger age groups [12]. The extent of polypharmacy and PIM use have not been investigated in detail in this age group. Better

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insights into the trends of polypharmacy and PIM in older and middle-aged people with diabetes are needed to guide the development of medication optimization interventions.

The aim of our study was to assess (1) the trends in polypharmacy in older and middle-aged people treated for diabetes, and (2) the trends of PIM in those patients on polypharmacy.

## 2. Methods

### 2.1 Study design and data source

We carried out a repeated cross-sectional study over five years (2012-2016) to assess trends in polypharmacy and the prevalence of PIM in patients with polypharmacy in the Netherlands. The data were obtained from the University of Groningen community pharmacy database IADB.nl. This database contains anonymized information of dispensed prescriptions, including the Anatomical Therapeutic Chemical code (ATC code) of the drug, the date of dispensing, the number of units dispensed, and the prescribed daily dose. The IADB.nl does not include information on medical conditions or on medication dispensed during hospitalization. The IADB.nl has been validated and used for many studies in the pharmacoepidemiology field [13,14]. Ethical approval is not required for studies using anonymous data in The Netherlands.

### 2.3 Study population

The study population consists of all adults known in the IADB.nl database, aged 45 years or older in 1 January of each study year and receiving at least two prescriptions for medication used for diabetes treatment (ATC codes: [A10A, insulin and analogues] and/or A10B [blood glucose lowering drugs, excluding insulin]) in the calendar year, and with follow-up data for at least 12 months.

### 2.4 Polypharmacy Definition

Polypharmacy was defined as the chronic use of at least five drugs concurrently [15]. Chronic use was defined as a drug being dispensed for at least 90 days or at least three times in a four-month period between 1 September and 31 December in the study year. Given the definition of the Dutch guideline [15], all drugs intended for topical use, contrast media, radiopharmaceuticals, surgical dressings, and general nutrients (ATC codes belonging to D, V, Y, Z), as well as records with invalid ATC codes were excluded from the calculation of polypharmacy prevalence. To determine the number of different drugs for chronic use, the third level of the ATC code (ATC3), which describes pharmacological subgroups, was used following the Dutch guideline on polypharmacy [15]. This implies that dispensing of different substances within the same pharmacological subgroup, e.g. beta-blocking agents, are counted as one chronic drug.

### 2.5 Potentially inappropriate medication (PIM) Criteria

We used the American Geriatrics Society (AGS) Beers 2015 criteria for assessment of PIM for patients of 65 years and older [16], and the PRescribing Optimally in Middle-aged People's Treatments (PROMPT) criteria for patients 45-64 years old [17]. We included only those criteria for the assessment of a PIM that can be applied in a pharmacy database without clinical information. Beers criteria consist of a list of therapeutic classes and individual drug substances which should be avoided in people aged 65 and older in most circumstances or with some specified medical conditions [16]. The PROMPT criteria were in part derived from the Beers criteria but in addition include criteria related to drug-drug interactions [17]. Since such drug-drug interactions are not included in Beers, we excluded them from our PIM assessment. In total, 14 criteria from Beers and nine criteria from PROMPT were excluded because: (a) they could not be assessed with information available in the IADB database, (b) the drugs were not available on the Dutch market during the study period, or (c) they concerned drug-drug interactions. This resulted in a total of 15

PIMs for therapeutic classes and 15 PIMs for individual drug substances from Beers and PROMPT criteria that were used in our study (Figure 1). There were 24 PIMs from Beers applied for patients of 65 years and older, and 13 PIMs from PROMPT applied for patients between 45 and 64 years of age. In addition, there were nine PIMs from PROMPT that were not part of the Beers criteria, which we considered also of relevance for older patients. For comparison, these nine PIMs were also applied for patients of 65 years and older (Appendix Table 1).

## 2.6 Outcome

The primary outcome was polypharmacy prevalence per calendar year, stratified by age (45-54 years, 55-64 years and [?]65 years). Secondary outcomes were the prevalence of any PIM and the prevalence of the individual PIMs in polypharmacy patients. For the outcome of any PIM, patients were categorized as having no PIM or at least one PIM, using the 24 PIM criteria from Beers, and the 13 PIM criteria from PROMPT.

## 2.7 Analysis

The prevalence of polypharmacy and PIM were assessed for each year and expressed as percentages with 95% Confidence Intervals (CI). Additionally, absolute differences in these prevalences over the study period are presented. The prevalence of polypharmacy was calculated by dividing the number of people with diabetes on polypharmacy (numerator) by the total number of diabetes patients in each year (denominator). The prevalence of PIM was calculated by dividing the number of people with diabetes and polypharmacy who had at least one PIM by the total number of people with diabetes and polypharmacy. Linear-by-linear association with Chi-square analysis and regression analysis were used to test for significant linear or quadratic trends of the prevalence rates. Statistical significance was evaluated at the 2-sided $\alpha$=0.05 level. All statistical analyses were carried out using SPSS software (version 23.0; IBM, Armonk, NY, USA).

# 3. Results

## 3.1 Study Population

The number of patients treated for diabetes included in this study ranged from 27,845 in 2012 to 24,809 in 2016. The percentage of people with diabetes out of the total population was around 8-9% throughout the study period. Among the people with diabetes, around 14% were 45-54 years, around 25% were 55-64 years, and around 61% were 65 years or older. From 2012 to 2016, the percentage in the oldest age group slightly increased from 59.1% to 61.5% (Table 1).

## 3.2 Trends of polypharmacy in people with diabetes

Overall, the prevalence of polypharmacy increased from 56.5% (95% Confidence Interval [CI] 55.9-57.1) in 2012 to 58.2% (95% CI: 57.6-58.8) in 2016 (p-value for trend <0.001), with the highest prevalence in 2015 of 58.8% (95% CI: 58.2-59.3) (Figure 2). In the oldest age group, the highest prevalence was 66.2% in 2016 (95% CI: 65.5-67.0). In the same year, the prevalence was 50.3% (95% CI: 49.0-51.5) in the 55-64 years old, and 36.9% (95% CI: 35.3-38.5) in the 45-54 years old (Figure 2, Appendix Table 2). The absolute increase over the study period was 1.0% in the [?]65 years old, 2.0% in the 55-64 years old, and 1.4% in the 45-54 years old (p-values for linear trend for all age groups <0.001).

## 3.3 Trends in PIM in older people with diabetes and polypharmacy

In patients of 65 years and older with polypharmacy, the percentage with at least one PIM according to the 24 Beers criteria decreased from 28.0% in 2012 to 24.9% in 2016 (p-value for linear trend <0.001). The majority

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received one PIM (21-24%) and the highest number of PIMs was five (Table 2). The highest prevalence was observed for long-term high-dose use of proton-pump-inhibitors (PPI) (17-18%), for benzodiazepines (9-10%), for strong opioids without laxatives (7-8%), and for tricyclic antidepressants (TCAs) (6%) (Table 3).

At individual PIM level, also looking at the additional PROMPT criteria, absolute increases of at least 0.1% during the study period were seen for the use of strong opioids without laxatives (0.9%), TCAs (0.6%), long-term high-dose use of PPIs (0.5%), and sliding scale insulins (0.2%). Meanwhile absolute decreases of at least 0.1% were seen for the use of benzodiazepines (-1.7%), dipyridamole (-0.8%), long-acting sulfonylureas (-0.7%), long-term corticosteroids without biphosponates (-0.7%), high-dose digoxin (-0.4%), first generation antihistamines (-0.4%), nonsteroidal anti-inflammatory drugs (NSAIDs) without PPI or misoprostol (-0.4%), high-dose acetylsalicylic acid (-0.2%), and antispasmodics (-0.2%) (Table 3).

### 3.4 Trends in PIM in middle-aged people with diabetes and polypharmacy

In middle-aged patients with polypharmacy, the percentage with at least one PIM from the 13 PROMPT criteria increased gradually from 36.9% in 2012 to 39% in 2015. In 2016, the percentage decreased to 37.8% (p-value for quadratic trend <0.05). The majority received one PIM (27-30%), and the highest number of PIMs was five (Table 2). The highest prevalences were seen for the use of long-term high-dose PPI (22-23%), long-term benzodiazepines (11%), and strong opioids without laxatives (9-10%) (Table 3).

At individual PIM level, absolute increases during the study period were seen for long-term high-dose use of PPIs (0.7%), strong opioids without laxatives (0.6%), long-term corticosteroids without biphosponate (0.3%), long-term non-benzodiazepines (0.2%). Conversely, NSAIDs long-term without PPIs or misoprostol (0.4%), long-term benzodiazepines (0.4%), long-acting sulfonylureas (-0.2%), dipyridamole monotherapy (-0.2%), stimulant laxative no long-term, except with opioid (-0.2%) showed absolute decreases in prevalence (Table 3).

## 4. Discussion

### 4. 1 Principal findings and their relationship with the literature

The prevalence of polypharmacy in people treated for diabetes increased from 56.5% in 2012 to 58.2% in 2016. Significant increases were seen in all age groups with the highest absolute increase in the group of 55-64 years old. The prevalence of older people with at least one PIM decreased around 3% in the study period. In the middle-aged group, the prevalence increased around 2% from 2012 to 2015, then it decreased 1% afterwards. The use of long-term high-dose PPI, benzodiazepines, and strong opioids without laxatives were the most common PIMs in people with diabetes in both age groups, with gradual increases over time for PPIs and opioids without laxatives, and decreases for benzodiazepines. Furthermore, the use of TCAs was common in the older age group, with an increase over time.

The findings of this study confirm that polypharmacy is a concern in people with diabetes, with the highest rate in older-age patients [8,18,19]. The increasing trend of polypharmacy in the diabetes population was similar to the trend in the general population [2,3]. The polypharmacy prevalences in people with diabetes, ranging from 36% in the 45-54 years old to 65% in those aged [?]65 years in 2012, were substantially higher than the prevalence seen in the general population at that time [2]. Previously, an increase of polypharmacy was seen in the middle-aged people [2,3], and likewise we observed this in people with diabetes. A noteworthy finding was that the absolute increase in the 55-64 years old was larger than in the group of 65 years and older. This may indicate an increase in the number of co-morbidities in this age group, which is followed by an increase in prescribing of medication. Whether less increase in the older age group means less increase in co-morbidities or more restrictive prescribing remains unknown. For middle-aged patients, prescribers may

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not yet see polypharmacy as a large burden or problem. So far, attention for polypharmacy management is more focused on older than middle-aged people [20].

Our study showed that while polypharmacy increased for people with diabetes between 2012 and 2016, the prevalence of PIM in older patients with polypharmacy decreased in this period. This suggests that the continuing attention and many initiatives to decrease inappropriate polypharmacy in older patients have had an effect in this population [21]. Studies in the general population using Beers criteria also showed decreasing trends in the annual PIM prevalence between 1995 and 2004 in France [22], and between 2007 and 2014 in US [23]. Interestingly, a slight increase in PIM was observed in the beginning of our study period in the middle-aged people with polypharmacy, with the highest PIM prevalence of 39% in 2014. In 2015, there was a slight decrease and the significant quadratic trend may indicate the beginning of a decline in PIM in this middle-aged group. Further data from recent years are needed to support this finding. The PIM prevalences of 37-39% we observed in middle-aged diabetes patients with polypharmacy are of concern. Other studies which used PROMPT criteria in middle-aged people showed PIM prevalences ranging from 21% to 43% in community-dwelling people [24,25]. Although these numbers are difficult to compare due to differences in setting and assessment of the PROMPT criteria, they underline the importance of focussing on inappropriate polypharmacy in the middle-aged group.

The use of long-term high-dose PPIs, benzodiazepines, and strong opioids without laxatives was common in both age groups. The prevalence rates when applying the same PROMPT criteria were around 1-2% higher in the younger as compared to the older patients. Similar common PIMs have been found in a general middle-aged population using PROMPT criteria [25]. In the general older-age population, benzodiazepines were also among the most prevalent PIMs, with the prevalence rates ranging from 0.74% to 3.9% [22,26]. The other most common PIMs when assessed using Beers criteria were from opioid group, antidepressant group, and digoxin [22,23,26]. Our findings indicate that prescribers appear not to be more cautious with prescribing these PIMs in older people with or without having diabetes. Apparently, substantial numbers of people with diabetes require these drugs according to their physicians. Chronic insomnia and anxiety are highly prevalent in people with diabetes [27,28], and benzodiazepines can be prescribed to treat those problems. Proton-pump inhibitors are considered as well-tolerated drug classes for treating and preventing acid-related disorders. However, the use of PPIs above maintenance dosage was identified to increase the risk of chronic kidney disease in diabetic population [29]. The reason for not adding a laxative in diabetes patients using opioids is also of concern, since they may already have a higher risk for constipation [30]. A possible reason for not prescribing laxatives could be that patients are sufficiently managed with dietary measures or over-the-counter (OTC) drugs, or that patients experience insufficient benefits from laxatives [31]. Benzodiazepines were frequently prescribed but the prevalence decreased in the study period. This may be part of a downward trend seen in the use of these drugs in the general population in the Netherlands [2]. Since 2009, reimbursement for benzodiazepines has been restricted in the Netherlands to discourage overuse of these drugs. On the other hand, for the other common PIMs -i.e., long-term high-dose PPIs, strong opioids without laxatives, and TCAs in older patients- some increases were seen, despite recommendations in the Dutch national guidelines against such use [32]. It is disappointing that in people with diabetes, who already have a high medication burden, we do not see a more restricted use in the study period.

## Strength and limitation

This study is unique in providing detailed insights into the prevalence of polypharmacy and PIM in older and middle-aged people with diabetes. A large pharmacy database was used which includes all outpatient prescriptions for people registered with the participating pharmacies. In the Netherlands, most people collect their medication from one pharmacy, where they are registered. There are some limitations. First of all, some PIM criteria, particularly from the Beers list, require clinical information which is not available in a pharmacy database. This is likely to lead to lower estimates of the overall PIM prevalence compared to other studies. On the other hand, many different PIM lists have been developed, and usually adaptations and selections have to be made depending on the setting and the medication available in a country [33]. Second,

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the pharmacy database provides information about dispensed drugs, which may not reflect actual use and thus exposure to the PIM, and does not provide data on drugs used during hospitalisation. Finally, we do not know whether patients used OTC drugs, which might include laxatives. We expect, however, that for chronic use such laxatives would be dispensed on prescription, allowing for reimbursement.

### 4.3 Implication for policy and practice

Polypharmacy can be considered as an indicator for medication burden, although it does not indicate inappropriate medication. In older people with diabetes, we observed a small decrease in patients with any PIM among an increasing population with polypharmacy. Despite this trend, more than a quarter of older people with diabetes and polypharmacy received at least one PIM. Notably, in the middle-aged group the prevalence of PIM appears to be higher and did not decrease. One should be aware, however, that comparing the absolute prevalence rates between the groups is restricted by the use of different PIM lists for different age groups. Importantly, at individual PIM level many PIMs were not decreasing in older nor middle-aged people with diabetes.

It is therefore important not only to focus on older patients with PIM. To decrease inappropriate polypharmacy, attention should be paid to specific PIMs and to specific high-risk populations, such as those with diabetes. Multifaceted, patient-centered interventions have shown to be effective at reducing inappropriate medication in the general older population [34,35]. Developing such interventions for middle-aged people with diabetes may be necessary. More research is needed to assess the benefits versus harms caused by PIMs in middle-aged populations.

### 5. Conclusion

Polypharmacy is common in both older and middle-aged people with diabetes, with increasing trends in the study period, particularly in patients between 55-64 years of age. Despite an increase in polypharmacy, we observed a decrease in PIM prevalence in patients of 65 years and older with polypharmacy. No decrease was seen for middle-aged patients with polypharmacy. The most common PIMs in people with diabetes were similar to those seen in the general population. Further efforts are needed to decrease the use of PIMs in populations already burdened with many drugs.

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# Conflict of interest statement

All authors have nothing to disclose.

# Funding Information

# Data availability statement

The data that support the findings of this study are available from the affiliations of corresponding author upon reasonable request. The University Groningen Research and Data Management Plan (RDMP) only allows access to health care data via a password protected environment requested to Prof. dr. Bob Wilffert (email: b.wilffert@rug.nl), head of the unit PharmacoTherapy,-Epidemiology& -Economics and of the IADB.nl database.

# Author contributions

M.P.O conceptualized the research, researched data, wrote and edited the manuscript. S.D.A validated data research and reviewed the manuscript. C.C.M.S-V conceptualized methods and reviewed the manuscript, H.J.B validated data research and organized database. K.T conceptualized methods and reviewed the manuscript. E.H supervised the research and reviewed the manuscript. P.D conceptualized the research, supervised the research, reviewed and edited the manuscript.

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# Tables

Table 1. Number of people with diabetes stratified by age in IADB 2012-2016

Table 2. Trends in PIM prevalence in people with diabetes and polypharmacy 2012-2016

Table 3. Prevalence of PIM according to Beers (B) and PROMPT (P) criteria 2012-2016, stratified by age

| Table 1. Number of people with diabetes stratified by age in IADB 2012-2016 | Table 1. Number of people |
|---|---|
| Years | Overall No. of diabetes patients |
| 2012 | 27845 |
| 2013 | 28483 |
| 2014 | 28804 |
| 2015 | 28873 |
| 2016 | 24809 |

| Table 2. Trends in PIM prevalence in people with diabetes and polypharmacy 2012-2016 | Table 2. Trends |
|---|---|
| Age group | Year |
| 45-64 years | 2012 |
| | 2013 |
| | 2014 |
| | 2015 |
| | 2016 |
| 65 years | 2012 |
| | 2013 |
| | 2014 |
| | 2015 |
| | 2016 |

**Table 3. Prevalence of PIM according to Beers (B) and PROMPT (P) criteria 2012-2016, stratified by age**

**Year**

**PIM Identification**

Antihistamines, first generation (B)

Antihistamines, first generation as first-line (P)

Corticosteroids long-term without bisphosphonate (P)

Tricyclic antidepressants (B)

Tricyclic antidepressants as first-line (P)

Benzodiazepines (B)

Benzodiazepines long-term (P)

Nonbenzodiazepines (B)

Nonbenzodiazepines long-term (P)

Strong opioid without laxatives (P)

Sulfonylureas, long-acting (B, P)

PPI long-term high-dose (P)

PPI long-term high-dose, except with NSAID or corticosteroid (P adapted)

Stimulant laxative no long-term, except with opioid (P)

NSAIDs long-term without PPI or misoprostol (P)

NSAIDs without PPI or misoprostol (B)

Dipyridamole monotherapy (P)

Dipyridamole (B)

Theophylline monotherapy (P)

Acetylsalicylic acid >150 mg/day (P)

Skeletal muscle relaxants (B)

Antispasmodics, anticholinergic (B)

Estrogen (B)

Insulin sliding scale (B)

Disopyramide (B)

Indomethacin (B)

Digoxin high-dose (B)

Nifedipine, immediate release (B)

Pentazocine (B)

B: Beers criteria P: PROMPT criteria Barbiturates, Meprobamate, Ergoloid mesylates, Desiccated thyroid, Megestrol, Mine

# Figures legends
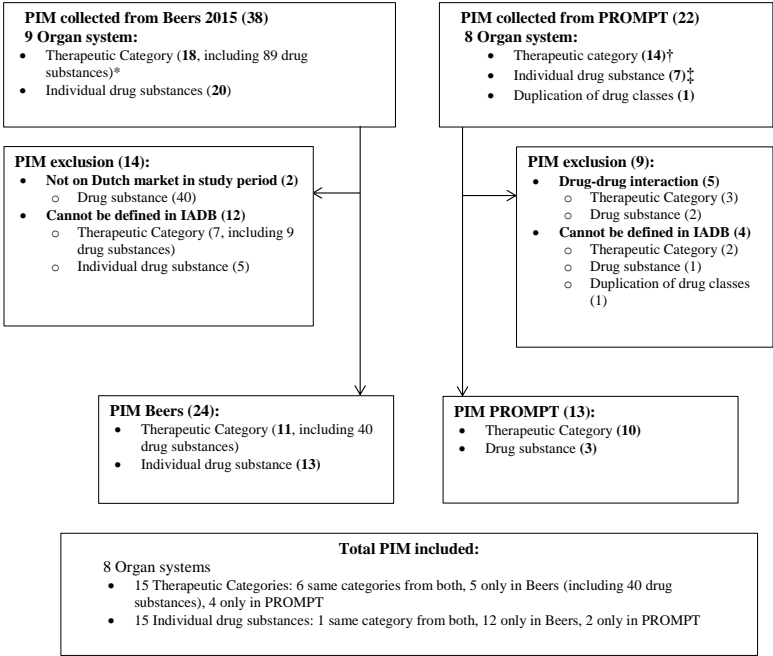
**Figure 1. Flow chart of included PIM**

*According to the Beers list; additional substances belonging to these categories were on the Dutch market in the study period

+ 1 therapeutic category (NSAIDs) includes 2 PIMS

++ 1 PIM including 2 drug substances (esomeprazole/omeprazole)

Bold in brackets are number of PIMs

**Figure 2. Trends in polypharmacy in people with diabetes 2012-2016**

# Appendices

Appendix Table 1. Beers and PROMPT criteria definition according to IADB database

Appendix Table 2. Trends in polypharmacy in people with diabetes 2012-2016 with confidence interval (CI)



**Figure 1.** Flow chart of included PIM