Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Review

The association between polypharmacy and adverse health consequences in elderly type 2 diabetes mellitus patients; a systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 13 June 2019
Received in revised form
22 July 2019
Accepted 29 July 2019
Available online 31 July 2019

Keywords:
Type 2 diabetes mellitus
Polypharmacy
Elderly
Multimorbidity

ABSTRACT

Aim: To summarize the existing literature concerning the association between polypharmacy and adverse health consequences in elderly patients with type 2 diabetes mellitus.
Methods: We searched four literature databases (PubMed/Medline, ScienceDirect and Web of Science) through April 2019. We included all studies that addressed the association between polypharmacy and all-cause of mortality, glycemic control, macrovacular complications, hospitalization, potentially inappropriate medicines, drug-drug interactions and fall. A statistical program OpenMeta [Analyst] was used. The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with a random effects model. I^2 statistics was performed to assess heterogeneity.
Results: Out of sixteen studies, three studies were used for meta-analysis. A statistically significant association was found between polypharmacy and all-cause mortality (OR = 1.622, 95% CI (1.606–1.637) P < 0.001), and myocardial infarction (OR = 1.962, 95% CI (1.942–1.982), P < 0.001. Non-statistically significant association with evidence of moderate heterogeneity was found between polypharmacy and stroke (OR = 1.335; 95% CI (0.532–3.346), P = 0.538, I^2 = 45%), and hospitalization (OR = 1.723; 95% CI (0.983–3.021), P = 0.057, I^2 = 57%).
Conclusions: Pooled risk estimates reveal that polypharmacy is associated with increased all-cause mortality, macrovacular complications and hospitalization using categorical definitions. These findings assert the need for interventions that optimize the balance of benefits and harms in medicines prescribing.

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https://doi.org/10.1016/j.diabres.2019.107804
0168-8227/

Contents

1. Introduction

Type 2 diabetes mellitus is highly prevalent chronic condition among adults, being estimated that more than 500 million people diagnosed in 2018 worldwide with gradual elevation with aging and life expectancy [1]. Elderly patients are usually associated with more chronic conditions such as hypertension, dyslipidemia, coronary heart disease, and chronic kidney disease [2,3].

Polypharmacy appears to be highly prevalent and important lineament. A cross-sectional study in Canada found that (48%) of elderly frail patients with type 2 diabetes mellitus were taking $\geq$ 9 medications daily [4]. Another study in Greece found that (43.4%) were using $\geq$ 7 medications daily [5]. Since multiple medications are needed to control the disease and associated comorbid conditions, those patients often require to take more than dozen of different classes of medications [6].

Polypharmacy can be associated with adverse outcomes, such as increase the risk of hypoglycemia, decline in medication adherence, risk of drug-drug interactions, and probability of worsen quality of life which can result in higher risk of hospitalization, mortality rate and healthcare costs [7].

Management of those patients is a complex process due to patients characteristics, which require individualize medication regimen to balance the pressing to control the diabetes as well as other comorbid conditions and/or complications and minimizing and/or preventing medications related risks [8].

The international diabetes federation (IDF) guideline recommends to consider reducing polypharmacy, suggesting to perform comprehensive medication review, consider deprescribing when its safe and possible, dose titration, identify adherence difficulties, apply medications lists such as Beer's or (STOPP) and screening tool to alert to right treatment (START), implementation of non-pharmacological options, providing individualized medication education, and involve family/caregivers in the care plan [8].

On the other hand, the American diabetes association guideline recommends the avoidance of polypharmacy and undergoing deintensification of complex regimen whenever possible, taking into consideration special attention while prescribing and monitoring of pharmacological therapies, medications costs and presence of other comorbidities [9,10].

When researching the literature on adverse health consequences of polypharmacy, it was noteworthy that there is no available synthesis of data examining multiple patient outcomes. It is therefore important to examine the available literature to determine the risk of adverse health consequences from polypharmacy among those patients [8]. Greater knowledge about this problem is important, and early interventions should be designed and implemented [9].

1.1. *Aim*

To summarize the existing literature concerning the association between Polypharmacy and adverse health consequences in elderly type 2 diabetes mellitus patients.

1.2. *Methods*

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used to standardize the conduct and reporting of this systematic review and meta-analysis [11].

Study Characteristics: observational studies (cross-sectional studies, cohort studies, case series, and case-control studies), interventional studies (randomized

controlled trials, and quasi-experimental studies) designs were considered. Only studies published in English were included.

Types of Participants: Participants who were aged ≥ 65 -years old and diagnosed with type 2 diabetes mellitus. We included studies that defined polypharmacy as a discrete definition and studies using categorical thresholds [12,13].

1.3. Primary outcomes

All-cause of mortality (risk of death)

Glycemic control, for the purpose of the this review we considered the following categories of elderly patients' glycemic target according to IDF global guideline for managing older people with type 2 diabetes mellitus. (A) Functionally independent (HbA1c target is 7.0–7.5%), sub-category (A) frail (HbA1c target up to 8.5%). (B) Functionally dependent (HbA1c target is 7.0–8.0%), sub-category (B) dementia (HbA1c target up to 8.5%) [8].

Macrovascular complications which including coronary artery diseases (CAD), heart failure (HF), cerebrovascular disease (CVD) and stroke [10].

Hospitalization or hospital Re-admission (including all-cause hospital admissions and unplanned re-hospitalization) [14].

1.4. Secondary outcomes

Studies were reported the association between polypharmacy and potentially inappropriate medicines [15], drug–drug interaction [16], and fall or fall risk [17].

1.5. Information sources

Studies were identified by searching electronic databases of PubMed/Medline, ScienceDirect, and Web of Science, through April 2019. No limit was set for the study setting or time frame. No limitation was considered for date of acceptance or publication.

Search Strategy the full search strategy is included in Supplementary Data 2.

1.6. Study selection

All titles and abstracts identified in the databases above were screened for eligibility by one author (L.M). Two review authors independently evaluated full texts of all potentially eligible studies for appropriateness for inclusion without prior consideration of the results (AP.M, L.M). Any disagreements were resolved by discussion or feedback from a third and fourth authors (JF. R, C.T).

1.7. Data item

The following information was extracted: author name, publication year, study design, study setting, study location, study outcomes, definition of Polypharmacy, participants demographic data: age groups (if applicable), gender, sample size, study duration and statistical model used.

1.8. Quality (Risk of Bias) assessment for the individual studies

Two review authors independently assessed the quality for each study. Any disagreements were resolved by discussion or a third author (JF. R). We used the Newcastle-Ottawa Scale (NOS) for observational cohort and modified version for cross-sectional studies which was used in previous studies [18]. Using a point" Star" system to judge on the three broad perspectives, a maximum of one 'star' for each h item within the 'Selection' and 'Exposure/Outcome' categories; maximum of two 'stars' for 'Comparability' for cohort studies.

For the modified tool for cross-sectional studies, a maximum five stars for the selection category, two stars for the comparability category and three stars for outcome category. The scale scores varied depending on the study design: for cross-sectional studies it ranged from 0 (lowest grade) to 9 (highest grade) and for cohort studies from 0 (lowest grade) to 10 (highest grade), Studies with scores above the median were classified as good quality studies, for cross-sectional studies > 5 and for cohort studies > 6.

1.9. Data synthesis

Individual data for prevalence of polypharmacy were derived either directly or indirectly from each study. To address the association of polypharmacy with adverse health consequences, we calculated the odd ratio (OR) and their respective 95% confidence intervals, and P value was set to be < 0.05. Meta-analysis was implemented when there were two or more studies with same design identified the same outcome using random-effect model, and I2 test was used to identify the heterogeneity. OpenMeta[Analyst] a cross-platform software for meta-analysis was used [19].

2. Results

2.1. Study selection

The search of the electronic databases provided a total of 1859 citations. After screening the titles and abstracts for duplicates, 1823 were remained. Of these, 1663 were removed due to either the full text copy was not available, or the papers did not publish in English. The full texts of the remaining 160 citations were examined in more detail. Of these, 143 studies did not meet the inclusion criteria. Finally, sixteen studies were included in the systematic review and three studies were included in the meta-analysis (Fig. 1).

The studies publication date was 2018 (n = 1), 2017 (n = 1), 2016 (n = 3), 2015 (n = 5), 2013 (n = 3), 2012 (n = 2), and 2010 (n = 1). The studies duration was between 4 months to 10 years. The studies conducted mainly in USA (n = 7), Australia (n = 2), Malaysia (n = 2), UK (n = 1), Chile (n = 1), Brazil (n = 1), Italy (n = 1), and Japan (n = 1).

The total number of patients included in this review was 1,205,821, in which 50.22% of these were females. 1,179,325 (97.80% of the total number of patients) were elderly. The most common definition of polypharmacy was using five or more medications found in 50% of the studies and the preva-

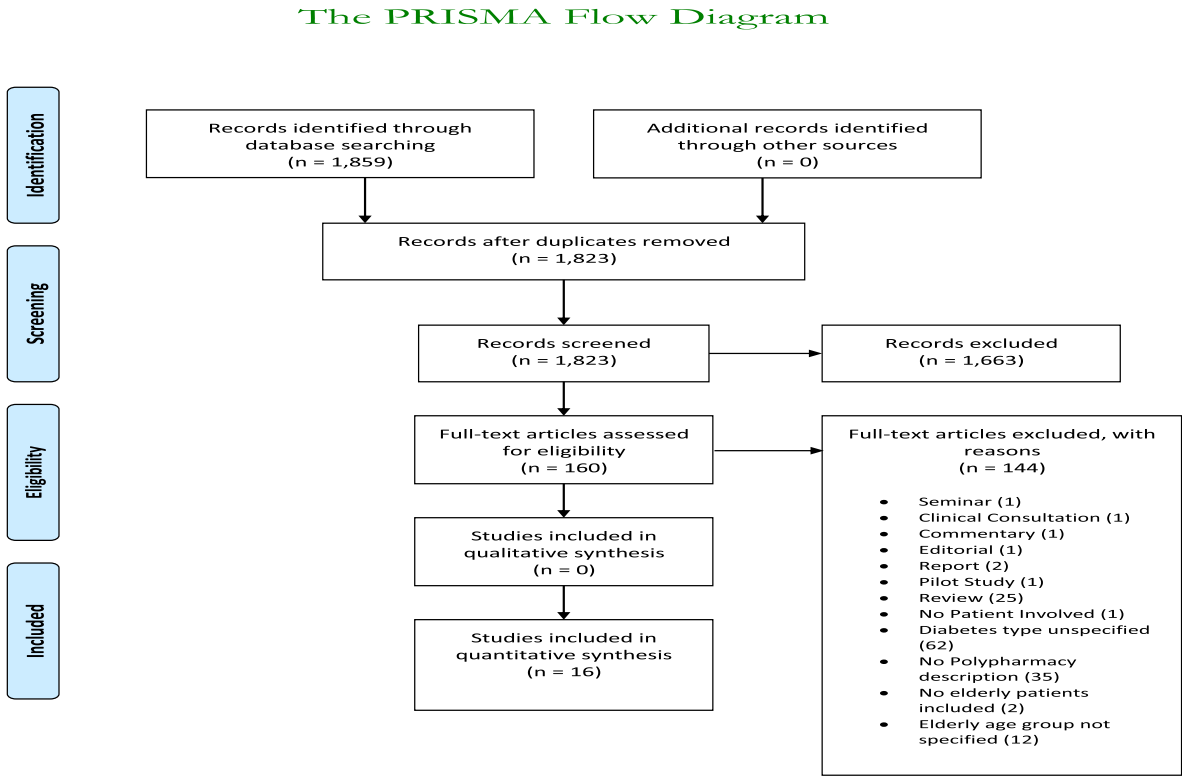

Fig. 1 – the PRISMA flow diagram for the included studies.

Table 3 – ORs and 95% CIs for the association between polypharmacy with all-cause mortality, myocardial infarction, stroke and hospitalization.

Outcome	Study reference	Study design	Odd ratio (95% CI)
All-cause mortality	Yashkin et al. 2018	Cohort	1.622 (1.606–1.637)
	Patel et al. 2012	Cohort	1.169 (0.468–2.918)
	Noale et al. 2016	Cross-sectional	4.569 (3.056–6.829)
Myocardial infarction	Yashkin et al. 2018	Cohort	1.962 (1.942–1.982)
	Patel et al. 2012	Cohort	1.544 (0.526–4.596)
	Noale et al. 2016	Cross-sectional	4.67 (3.01–7.25)
Stroke	Yashkin et al. 2018	Cohort	1.718 (1.701–1.735)
	Patel et al. 2012	Cohort	0.559 (0.109–2.860)
	Noale et al. 2016	Cross-sectional	1.56 (0.96–2.52)
Hospitalization	Raval et al. 2015	Cohort	1.438 (1.371–1.509)
	Patel et al. 2012	Cohort	2.714 (1.197–6.149)

lence was between (6.25–93.4%). The extracted data summarized in Supplementary table 1.

The review found that between 26% and 48.7% of elderly diabetes type 2 patients had HbA1c between (8.0% to ≥8.5%) despite receiving treatment intensification. Median time to treatment intensification was shorter in those on polypharmacy (18.5 months) than those without polypharmacy (20.4 months). No association found between HbA1c and polypharmacy [20–22].

The prevalence of potentially inappropriate (PIMs) medicines was varied among the studies, ranging from 22.7% to 79% using Beer's and 48% using STOPP criteria. The most commonly identified PIMs were using of metformin in elderly patients with type 2 diabetes mellitus aged ≥85 years old, benzodiazepines, tricyclic anti-depressants, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and beta-blockers. Polypharmacy was associated with presence of PIMs [23–25].

Severe hypoglycemia was reported from the interaction between sulfonylureas (glyburide and glipizide) with co-trimoxazole antibiotic more in patients on polypharmacy. Interactions between oral hypoglycemic agents (metformin, glyburide, metformin plus glyburide and acarbose) with hydrochlorothiazide, furosemide, angiotensin-converting

enzyme inhibitors (ACEIs), simvastatin and prednisolone were also reported [26,27]. No association was reported between fall or fall risk and polypharmacy [28].

2.2. Risk of bias assessment

Assessment of risk of bias is found in Supplementary table 2.

Table 3 summarizes the estimated ORs (95% CIs) obtained from each study for the association between polypharmacy with all-cause mortality, myocardial infarction, stroke and hospitalization.

The association between polypharmacy and all-cause of mortality was reported in two cohort studies [29,30] and one cross-sectional study [31]. When combining the estimated effects based on cohort studies, polypharmacy was significantly associated with all-cause mortality (pooled OR, 1.622; 95% CI 1.606 to 1.637, P < 0.001, I2 = 0%) Supplementary figure 2. Including the cross-sectional study, a non-statistically significant association with evidence of high heterogeneity was observed (pooled OR, 2.151; 95% CI 0.971 to 4.765, P = 0.059, I2 = 92%).

The association between polypharmacy and myocardial infarction was reported in two cohort [29,30] and one cross-sectional study [31]. When combining the estimated effects based on cohort studies, polypharmacy was significantly associated with myocardial infarction (pooled OR, 1.962; 95% CI 1.942 to 1.982, P < 0.001, I^2 = 0%) Supplementary figure 3. Including the cross-sectional study, a significant association was also observed, with evidence of level of heterogeneity (pooled OR, 2.790; 95% CI 1.140 to 6.828, P = 0.025, I2 = 94%).

Data on the association between polypharmacy and stroke was reported in two cohort [29,30] and one cross-sectional study [31]. When combining the estimated effects based on cohort studies, a non-significant association between polypharmacy and stroke was observed (pooled OR, 1.335; 95% CI 0.532 to 3.346, P = 0.538, I2 = 45%) Supplementary figure 4. Including the cross-sectional study, a significant association was observed, with evidence of high level of heterogeneity (pooled OR, 1.929; 95% CI 1.164 to 3.199, P = 0.011, I2 = 76%).

Data regarding the association between polypharmacy and hospitalization was reported in two cohort studies [30,32]. When combining the estimated effects of these studies, a non-significant association between polypharmacy and hospitalization with moderate evidence of heterogenity was observed (pooled OR, 1.723; 95% CI 0.983 to 3.021, P = 0.057, I2 = 57%) Supplementary figure 5.

3. Discussion

The increase in categorical threshold from 5 or more medicines was associated with high risk of by 62% in all-cause mortality, 96% with myocardial infarction and 71% with stroke. The risk did not increased in dose-dependent manner, which can be explained by low number of elderly patients with type 2 diabetes mellitus using 10 or more medicines per day [33,34]. In addition, hospitalization was 71% in those using 10 or more medicines compared 44% in those using 13 or more medicines.

These findings were not agreed with previous systematic reviews, which found that the association between polypharmacy and mortality [33], as well as dementia [35] increased in a dose-dependent patterns when the threshold values for the number of medicines defining polypharmacy increased.

A meta-analysis of five prospective randomized controlled trials of intensive glucose lowering therapy (but not polypharmacy) effect on cardiovascular outcomes and death in elderly patients with type 2 diabetes mellitus found that, 17% reduction in events of non-fatal MI (OR = 0.83, 95% CI (0.75–0.93), 15% reduction in events of coronary heart disease (OR = 0.85, 95% CI (0.77–0.93) and no significant effect on events of stroke (OR = 0.93, 95% CI (0.81–1.06) or all-cause mortality (OR = 1.02, 95% CI (0.87–1.19) [36].

The review found between 26% and 48.7% of elderly diabetes mellitus type 2 patients received treatment intensification. Despite that, these patients mostly had higher HbA1c value between (8.0% to ≥8.5%).

Large real-world observational study of 17,493 type 2 diabetes mellitus patients, found that treatment intensification was less likely the older the patient, and more likely the higher the first HbA1c value, up to an HbA1c threshold of 9% [37].

Clinical inertia, which is defined as the failure to initiate or intensify therapy in a timely manner according to evidence-based clinical guidelines, greater comorbidity, long duration of diabetes, aging, and higher use of oral hypoglycemic agents can be a key reason for uncontrolled hyperglycemia [38]. It can be also applied for the failure of clinician to stop or reduce therapy no longer needed (reverse clinical inertia) [39].

A review found that clinical inertia can be occur at all stages of diabetes treatment. Medication non-adherence to glucose lowering medicines may range from 53% to 65% at 1 year, can be responsible for higher HbA1c values in about 23% of cases [40].

Our findings agreed with clinical guidelines for the treatment of older adults with Type 2 diabetes mellitus in which the HbA1c in those population should be up to 8.5% whenever appropriate, treatment intensification should be used at appropriate time with caution especially with elderly to avoid the risk of hypoglycemia and other adverse events [38].

Polypharmacy was also found associated with risk of potentially inappropriate medicines, with prevalence between 22.7% and 79% Beer's criteria and 48% using STOPP criteria. These results in agreement with previous reviews conducted in Europe and United States [41–43]. Principle PIMs identified were similar to those found in previous reviews [43,44].

The review did not found any association between polypharmacy and fall or fall risk only in one study. Previous review and large cohort study found that older adults with type 2 diabetes mellitus are associated with greater risk of falls, especially in insulin-treated patients, without measuring the impact of polypharmacy [45,46].

Another large cohort study of type 2 diabetes mellitus found that using four or more (not a definition of polypharmacy in the study) can be associated increasing risk of fall, with no specific glucose lowering drug involvement in fall risk. The study revaled that examining the relationship between medications and falls would benefit from using for-

mal definition of polypharmacy and what mechanisms link polypharmacy to adverse events [47].

Even most of studies included in this review were of good quality, these studies are observational, and number of medications cannot be assigned to patients, since those who are on polypharmacy are associated with adverse health consequence more than those who are taking fewer medicines.

Therefore, risk of confounding, follow up, and sampling bias cannot be ignored and particularly important. However, other types of bias may be present. Presence of these biases result in apparent evidence of heterogeneity in the studies used in meta-analysis.

Because of concerns regarding confounding and complexity between polypharmacy and adverse health outcomes, it is more suggested to conduct randomized controlled trials that may provide more definitive solutions regarding to these issues.

The meta-analysis has several limitations; the quality of meta-analysis was affected by the quality of included studies. Firstly, studies used several definitions of polypharmacy and non-polypharmacy (for example: in non-polypharmacy definition, patients may be classified as using 4 or less, 5 or less, less than 13 medicines), based on the definition of polypharmacy.

The definition of polypharmacy that most studies used did not provide any information on duration, definition of number of medications and if non-prescription medicines were used. Moreover, information regarding all comorbid conditions and/or diabetes complications was not fully reported, also some studies were excluded patients had specific complications, and presence of other risk factors can also affect these associations.

The number of studies that involved in meta-analysis for assessment of overall effect of the association between polypharmacy and adverse health consequences in elderly with type 2 diabetes melllitus was low; this can be associated with several explanation, little information is available in the literature about such associations in those population, most of studies evaluated these adverse health consequences did not consider polypharmacy as risk factor.

Poor representation of elderly population in clinical trials, even they are more prone to adverse effects due to comorbidities and polypharmacy. Moreover, a few large prospective cohort studies seek to overcome these limitations from clinical trials which can be considered as representative of patients on polypharmacy, but they were limited by either small sample size or follow up periods.

In addition, studies weighted with high percentage were accounted for the overall effect of meta-analysis, as well as using of unadjusted estimates of risk of association with polypharmacy can exceeded the adjusted estimates. Many studies were excluded for this review because either reported exposure or outcome, were not of interest.

4. Conclusion

Distinguishing the potential risks of polypharmacy in elderly type 2 diabetes mellitus patients is clinically important. Our goal was to summarize the existing knowledge regarding this topic, which may reveal support for a statistical association between polypharmacy and several adverse health outcomes.

Polypharmacy has been and always will be common among those patients due to the need to control diabetes and other comorbid conditions. Unfortunately, with this increase in the use of multiple medicines may come with an increased risk for negative health outcomes.

The results of this systematic review were mixed, with some studies demonstrated the association between polypharmacy and adverse health consequences, and other studies failed to find this association.

This can raise the question of whether polypharmacy is solely a marker of inappropriate medicines use, and whether it is also a marker of underprescribing, which may lead to underuse of appropriate medicines, and increase the risk of adverse health consequences in those population, in addition to Multimorbidity, aging, scarcity of scientific evidence, risk of adverse events and economic issues [48].

Appropriate monitoring should be implemented, including necessary laboratory testing and patient education regarding how to monitor themselves for potential adverse events and what to do when they occur. Interventions designed for improvement of medication appropriateness, which includes a deprescribing, are generally effective at improving surrogate clinical markers, but the effect on long-term outcomes, such as mortality, is not well established.

Funding

This review did not receive any funding.

Declaration of Competing Interest

All authors declare that there is no conflict of interests.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107804.

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