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Factors Affecting Non-Insulin Antidiabetic Drug Adherence in Patients with Type 2 Diabetes: A Systematic Review

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Abstract

Objective: To identify factors associated with medication non-adherence in patients with type 2 diabetes using non-insulin anti-diabetic medication.

Methods: PubMed, EMBASE/MEDLINE, and Cochrane Library databases were searched from January to March 2017. Studies were included if they used medication possession ratio (MPR) or proportion of days covered (PDC) to evaluate adherence associated with factors, were published in the last 10 years, and did not include insulin in the adherence calculations. The factors were grouped based on the five dimensions previously shown to affect medication adherence as defined by the World Health Organization.

Results: Of the 25 articles included in the review, the major factors reported to be associated with non-insulin anti-diabetic medication were younger age, female, non-Caucasian race, not using mailed prescriptions, cancer diagnosis, lower number of comorbidities, and a smaller pill burden.

Conclusion: The systematic review showed that younger age, racial minorities, female gender, fewer comorbidities, diagnosis of cancer and decreased pill burden is associated with medication nonadherence to non-insulin anti-diabetic drugs.

Keywords: Medication adherence; Non-insulin antidiabetic drugs; Type 2 diabetes; Medication possession; Glucagon-like peptide-1; General practitioner; Healthcare providers

Abbrevations: T2DM: Type 2 Diabetes Mellitus; NIAD: Non-Insulin Anti-Diabetic Drugs; MNA: Medication Nonadherence; WHO: World Health Organization, SR: Systematic Review; MPR: Medication Possession Ratio; PDC: Proportion of Days Covered, PQA: Pharmacy Quality Alliance; GLP1: Glucagon-Like Peptide-1; NIH: National Institute of Health; GP: General Practitioner; HCPs: Healthcare Providers

Introduction

As of 2014, there were 29.1 million Americans diagnosed with diabetes mellitus and it is estimated that type 2 diabetes mellitus (T2DM) accounts for 90 to 95% of these cases [1]. Approximately 70% of patients with diabetes control their glucose with a non-insulin anti-diabetic drugs (NIAD) [2]. Glycemic control is important because it decreases the risk of micro- and macro-vascular complications, as well as all-cause mortality [3]. However, glycemic control is achieved in only about 50% of patients, with the primary cause being non-adherance [4]. It is estimated that only between 30.4% to 70.6% of people using NIAD are adherent to their medication [5]. It has been found that when patients are adherent to metformin alone, the probability of achieving glycemic control is up to 28% higher [6].

Understanding the factors associated with Medication Non Adherence (MNA) is essential for developing interventions to increase adherence. The World Health Organization (WHO) describes adherence as an interplay of five dimensions, which include: social and economic factors, health care team and system related factors, condition-related factors, therapy related factors, and patient related factors [7,8]. WHO explains that many interventions to increase adherence fail because there is a tendency to focus only on one of the listed factors. Therefore, it is important to understand and quantify the specific factors associated with MNA in diabetes in order to design more effective interventions [7]. There have been numerous studies evaluating associations with MNA in patients with T2DM. The most notable

systematic review (SR) conducted by the WHO found the factors that most negatively contributed to MNA were high cost of care, concurrent depression, long duration of the disease, and complex treatment [7]. However, there has not yet been a SR to quantify the effect of factors associated with MNA. To help address this information gap, this review aimed to quantify the effect of factors associated with MNA in patients with T2DM using NIAD.

Methods

Search methods for identification of studies

A systematic search of electronic databases was conducted to identify observational studies that evaluated factors associated with adherence to anti-diabetic medication in T2DM patients. The following databases were searched: PubMed, EMBASE/MEDLINE, and Cochrane Library. The search was conducted between January 29th 2017 and March 23rd 2017. The search filters included: full text, English language, and published from January 2007 and onwards. The data was quantified using the two most common methods to measure adherence: medication possession ratio (MPR) and proportion of days covered (PDC). The key terms 'proportion of days covered' and 'medication possession ratio' were combined with the medical subject headings "diabetes mellitus, type 2" and "medication adherence." These concepts were all related using the Boolean operators. Additional studies were retrieved through references of other articles included in this review.

Inclusion and exclusion criteria

Observational studies were included in this review if they met the following four criteria (1) participants had type 2 diabetes, (2) used non-insulin anti-diabetic medication, (3) adherence was measured using PDC or MPR, and (4) evaluated a specific patient characteristic and its possible association with adherence. Insulin products were excluded from the study because the Pharmacy Quality Alliance (PQA), which endorses the PDC method, does not consider insulin feasible to measure due to the complexity of measuring adherence to this injectable [3]. However, the injectable glucagon-like peptide-1 (GLP1) agonists are endorsed and therefore were included [9]. The majority of the studies excluded focused on interventions to improve patient's adherence, strategies to measure compliance, and the outcome of non-compliance. These studies were excluded because they did not report adherence as MPR or PDC.

Data Extraction and Analysis

Studies were first screened based on title and abstract using the described inclusion and exclusion criteria. Then, the relevant studies were evaluated for the characteristics associated with non-adherence to NIAD. The associations were summarized and recorded with their PDC and MPR. The strength of data was then assessed by how the PDC was calculated. The reported PDCs that followed the PQA calculation (for the corresponding year) were considered to be strong. The studies were also evaluated for bias using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies by the National Institute of Health (NIH). Studies were rated based on 14 criteria that examined the research question, study population and size, eligibility criteria, level of exposure (e.g. more than one medication), assessment, outcome, follow up, and statistical analysis. Based on these criteria the quality can either be rated as 'good' 'fair' or 'poor.'

Results

The search result yielded 106 articles. After applying exclusion and inclusion criteria, 25 retrospective cohorts were included. Figure 1 depicts the data abstraction process.(Table 1) shows the detailed description of the adherence studies included in this study.[10-34] There were 19 studies that used MPR as their compliance measurement [10-29] and 6 studies that used PDC [30-34]. The cut-off value for MPR and PDC was ≥80%. The statistical analysis used to assess the effect of various factors on NIAD adherence was a multilevel logistic model because PDC and MPR are continuous variables. There were 13 good studies, 6 fair studies, and 5 poor studies. (Table 1) describes the studies included in this review.

Table 1: Characteristics of the included studies.

Source	Country	Duration	Database	Patient Population	Sample Size	Age	Medication	Adherence Measures	Factors Analyzed	Mean Adherence 95	Study Strength
Briesacher et al. [101	USA	5 years	Market Scan Research	Initiated new drug therapy in previous year	105,225	57.7(0.02)	Any oral	MPR	Age, pill burden, disease duration, comorbidities	65.84%	fair

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Calip et al. [11]	USA	19 yea rs	Group Health Cooperative	Women from COMBO cohort diagnosed with early stage (I,II) Invasive breast cancer	509	65	MET, SUA	MPR	Adherence before, at, and after breast cancer diag-nosis	Pre-cancer 80.6, post cancer 49%	fair
Cho, et al. [12]	Canada [British Colum-bia)	10 years	PharmNet	South-Asian, Chinese and white people aged ≥35 years	37,243	NA	higuan ides, SUA T2Ds	MPR	race ethnicity, comorbid conditions, socio-eco-nomic status, medication type	NA	good
Cohen et al. [13]	USA	-	11995EIU Benefit and Pensions Fund	mufti-ethnic, lower income, Insured adults in NYC, age >30	526	55.5(7.3)	Any Oral	MPR	sex, age, duration of disease, marital status, income, edu-cation level	NA	poor
Dijk et al. [14]	Neth-erlands	1 year	Dutch gen-eral practice registration database & dispensing registration database	Patients from a Dutch general practice regis-tration	2,428	Nonadherent: 66.6(13.4); Adher-ent:65.8(11.9)	biguan ides, SUA	MPR	sex, age, edu-cation, marital status, cor-norbidities, healthcare contact	NA	fair
Egede et al. [15]	USA	5 years	Linked Vet-erans Health Administra-tion National Patient Carr and Pharmacy Benet. Manage-ment databases	National cohort of veterans	479,248	65.7(11.28)	Any Oral	MPR	sex, age, race/ ethnicity, lo-cation, marital status	80.86.%	poor
Guenetre et al. [16]	Canada (Que-bec)	9 years	Quebec health insurance board (RAMQ)	New users of OADs in Que-bec in a plan that covers ages 65 or above, welfare recipients and those without access to private health insurance	119,832	NA	Any Oral	MPR	age, sex, resi-dential region, socioeco-nomic status, specialty of prescriber, medication, history of hospitaliza-tion, physician visits, pill burden	86.3(16.2)	poor
Hansen et al. [17]	USA	3 years	MEDSTAT MarketScan Research data-bases	age 18-90 years, taking metformin, pioglitazone or a sulfonylu rea, ≥2 outpatient claims or ≥1 inpatient claim	108,592	54(11)	MET, SUA, PIO	MPR	Age, sex, in-surance type, cornorbidites, medication type	metformin: 66.7%, pioglitazone: 61.3%, sulfonylurea: 67.5%	good
Haupt et al. [18]	Swe-den	1 year	Swedish pre-scribed drug register	Age >40 years having ≥2 dis-pensing of one or more OAD	171,220	NA; mode of age range was 75-84 yrs	My Oral	MPR	Age, sex, med-ication type, pill burden, specialty of prescriber, indication written on rx	107%	good

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Jha et al. [19]	USA	4 years	Medco Health Solutions	Nationwide cohort age >18, majority covered by medicare	135,639	NA	My Oral or GIP-1	MPR	Age, sex, comorbidities Income, education, race	NA	good
Kirkman et al. [20]	USA	1 year	Information warehouse of Medco Health Solutions	Patients using no more than two oral a antidiabetic medications, patients from all 50 states including Puerto Rico, Virgin islands, Guam, age >8	218,384	64.9(4.8)	Any Oral or GLP-1	MPR	Substance abuse disorder, schizophrenia, depression, pill burden, age, sex, race, homelessness, marital status, copayment, days supply	NA.	2
Kreyenbuhl et al. [21]	USA	2 years	VA's National Psychosis Registry	Veterans with and without schizophrenia	22,014	Diabetes with schizophrenia: 55.7(10.7); diabetes without schizophrenia 65 4(10 6)	Any Oral	MPR	Age, sex, race, marital status, homelessness, depression, PTSD, comorbidities, hospitalization in past year, health care contact, mailed prescriptions, copay,	NA	good
Piette et al. [22]	USA	1 year	VA's, Nation, Psychosis Registry	Veterans with schizophrenia, diabetes, and hypertension_ Mostly unmarried males	1,686	54.9(10.8)	Any Oral	MPR	Concurrent schizophrenia, hypertension, and days supply	16%	good
Rolnick et al. [23]	USA	2 years	Pharmac administrative database	Midwestern, >18. with at least one of eight comorbid conditions	4631	NA	any oral or GIP 1	MPR	age, sex; race, education, comorbiditie, pill burden	81%	good
Rozenfield et al. [24]	USA	3 years	Pharmacy claims from a managed care plan in oregan	>18 yo living in Oregon who recently initiated oral antidiabetic	2741	54(11)	MET, SUA, TZD	MPR	medication class, age, sex, comorbiditie, pill burden	rnet-formin:80.7(21.6), sulfonylurea:11.8(21.7), TZD: 82(21.4), total 81.3(21.6)	poor
Schoenthaler et al. [25]	USA	2 years	physician orders in electronic health records	at least 4 office visits in pst 2 years, at least one oral hypoglycemic, ages >30 and <75. majority were male and retired, mean duration of time with diabetes: 5 years	608	62.1 (9.2)	Any Oral	MOO	age, sex, duration of disease, knowledge of diabetes,	-	good

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Tan et al. [26]	USA	2 years	MarkeScan Commercial Claims and Encounters Database	Age 13-64 with concomitmant diagnoses of canoer [breast, prostate, colon or long) and type 2 diabetes	1918	56.7	Any Oral	MPR	age sex, cancer type, location, comorbidities, medication type, pharmacy type, diabetes. complications	60(0.32)	poor
Wong et al. [27]	China	35 years	Clinical Data Analyses and Reporting System (CDARS)	Chinese adult patients. Majority were male, fee payers, lived in uran areas, and few comorbidities	26,782	>60	MET, SUA	MPR	age, se; payment, service type, comorbidities., drug class		fair
Zanders et al. [28]	USA	9 years	Eindhoven Cancer Registry, PHARMO Database	Age 30 years and over with any cancer type (except melanoma) and matched with non- cancer controls	15,231	67.7 (9.8) for cancer and 67.5 (9.7) for controls	Any Oral	MOO	age, sex; cancer diagnosis, cancer type, medication class	baseline not given, average 6.3% drop after cancer diagnosis (max:-15.2%)	good
Huber et 212016 1291	Switzerland	3 years	Helsana Group	aged ≥18 years with diabetes and treated with at least 1 oral a antidiabetic	26,713	69(12)	My Oral	PDC	sex, age, copay, preceding hospitalization, dispensing channel, number of comorbidities, drug therapy,	68%	fair
Huber et al. [30]	Switzerland	3 years	Helsana Group	aged ≥8 years with diabetes and treated with at least 1 oral a Antidiabetic	26,722	69(12)	My Oral	PDC	sex, age, cope, preceding hospitalization, number of comorbidities, drug therapy, dispensing channel	70%	good
Juarez et al. [31]	USA (Hawali)	4 years	Hawali health plan	adult patients with diabetes enrolled in health plan in Hawali for 4 years	23,450	60(13)	Any Oral	PDC	age, sex, number of comorbidities and type, ethnicity, pill burden	55%	good
Stuart et al. [32]	USA	1 year	Chronic Conditions Data Warehouse (CCW)	5% random sample of Medicare part D beneficiaries with type 2 diabetes. Patients who had newly diagnosed cancer wet compared to cancer-free control	32755	NA	Any Oral and GLP-1 agonists	PDC	cancer diagnosis	Pre-cancer: 80.8, post cancer: 73.8	good

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Turret et al. [33]	USA	3 years	Truven Health MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases	aged ≥8 years with diabetes who represent nationally comercially insured population who have both medicare and supplemental coverage	113,449	60.7(12.6)	Any Oral	PDC	age, pill burden, disease duration, dosing regimen, sex, copayrnent	75%	fair
Yang et al. [34]	USA	1 year	Medicare Part D Prescription claims data	Medicare Part D enrollees from 6 dispersed states (Alabama, California, Florida, Mississpi, New York, Ohio)	1,888,632	71.6(11.6)	My Oral	PDC	age, sex, race, comorbidities	65.%	good

All patient populations in the studies had T2DM and used at least one NIAD. The majority of the studies measured adherence to any oral hypoglycemic [10,13,18,21,22,25,26,28-31,33,34], while 4 broadened their coverage to include GLP-1 agonists [19,20,23,32], and 7 only included specific oral hypoglycemics [11,12,14,17,24,27,32]. The average age of the study population ranged from 56-84 [13,18]The studies were performed in various countries including the United States [10,11,13,15,17-26,31-34], Canada [12,16], Netherlands [14], Sweden [18], China [27], and Switzerland [29,30]. The study duration ranged from 1 year to 19 years [11,14,18,20,22,32,34].The sample size ranged from 509 to 1,888,682 people.[11,34]. Some unique patient populations studied were those with cancer [11,26,28,32], schizophrenia [21,22], and veterans[15,21,22].

Factors associated with medication adherence

The factors contributing to MNA were grouped based on the pre-established dimensions of medication adherence found by WHO (Table 2). These dimensions include: 1) social and economic-related factors; 2) health care team and system-related factors; 3) condition-related factors; 4) therapy related factors; and 5) patient related factors [7].

Table 2: Factors contributing to medication non-adherence categorized based on pre-established dimensions of medication adherence found by world health organization (WHO).

Factors	Studies with Positive Association with Adherence	Studies with Negative Association with Adherence	Studies with no Significant Association with Adherence
Social and economic-related factors			
Increasing age	15 [10,16,17,18,19,20,23,24, 26,27,29,30,31,33,34]	2[15,28]	2[21,25]
Gender, male	10[15,19,20,23,25,29,30,31 ,33,34]	3[13,18,27]	5 [14,16,21,24,26]
Non-caucasian		8 [12,13,15,19,21,23,31,34]	
Higher Education	2 [19,20]		2 [14,23]
Low income status	2 [12, 16]	2 [19,20]	1 [23]
Homelessness		1 [21]	
Rural resident	2[15, 16]		2 [26,27]
Married	1 [15]	1 [14]	1 [21]
Low copayment	4 [20,21,30,33]		1[27,34]
Health care team and system-related factors			
shared decision making with physician	1[25]		
Increased time spent with physician	1[25]		

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Indication written on the rx	1[18]		
GP as Initial prescriber	2[16,20]		2[18,24]
Average days' supply >60	1[22]		1[21]
Mailed prescriptions.	3[20,21,26]	1[30]	
dispensing channel			
Condition-related factors			
hospitalization in past year	1 [16]	3[21,29,30]	
Long duration of diabetes	4 [10,13,20,33]		
Severity of diabetes related complications		2 [15,25]	1 [26]
Number of comorbldities	7 [12,16,24,27,29,30,31]		2[14,26]
frequent healthcare visits	3[11,16,27]	4 [17,21,23,34]	1 [14]
Cancer Diagnosis		3[26,28,32]	
Cancer type		more severe: 213,32	1 [26]
Coronary Artery Disease		1 [31]	
Congestive heart failure		1[31]	
hypertension	1[22]		
Substance Abuse Disorder		1 [21]	
Schizophrenia	1[21]	1 [22]	
Depression		1 [21]	
Therapy-related factors			
Metformin	5[12,16,18,26,29]		3[14,24,271
Sulfonylurea	2[17,18]	4 [12,16,26,28]	3[14,24,27]
Other medication type		5[12,16,17,18,261	1[24]
Pill burden	8 [10,16,20,21,24,29,30,33]	4 [11,14,23,26]	2[14,27]
Patient-related factors			
increased diabetes related knowledge		1[25]	
agree dependent on medications		1[25]	

Social and economic-related factors

Many studies supported that increasing age [10,16-20,23,24,26,27,29-31,33,34], and male gender[15,19,20,23,25,29,30,31,33,34], were the most associated with NIAD adherence. Non-Caucasian race consistently showed decreased adherence compared to Caucasians, except for the Japanese [31]. The races evaluated that showed lower adherence were Hispanic [13,15,23,34], non-Hispanic black [13,15,19,21,23,34]

, Chinese [12,27], South-Asian descent, [12] and Filipino [31]. The associations between NIAD adherence with income, copayment, education level, marital status, and rural residence were equivocal due to the number and quality of studies that supported the associations.

Health care team and system-related factors

The most prevalent health system-related factors that were observed were the specialty of the prescriber and the use of mailed prescriptions. Patients are more likely to be adherent to their NIAD if their initial prescriber was a general practitioner (GP) or endocrinologist, rather than another specialist such as an internist [16,20].

Condition-related factors

Conditions consistently associated with MNA were a hospitalization in the past year [21,29,30], infrequent physician visits [11,16,27], and a diagnosis of cancer [26,28,32]. However, Guénette et al found that when the physician consultations exceeded 18, the odds of adherence decreased (OR:0.93, 95% CI: [xx,xx]) [16]. Also, the type of cancer diagnosis is also significant

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as more severe cancers lead to more profound drop in MPR or PDC than with breast or prostate cancer [28,32]. The association between NIAD adherence with duration of the disease as well as the presence of comorbidities is difficult because there are multiple studies that have found positive and negative relationships with both these conditions. Huber et al found an interesting relationship with the number of comorbidities and proportion of adherent patients. In a sample 26,713 patients, the proportion of adherent patients with 0-1, 2-4, and ≥5 comorbidities was 24%, 58.4%, and 17.6%, respectively.[29] This suggests that having 2-4 comorbidities is associated with increased adherence.

Therapy-related factors

In regard to medication regimen, patients prescribed metformin [12,16,18,26,29], and who have a higher pill burden are more likely to be adherent [10,16,20,21,24,29,30,33].

Patient-related factors

The only study that analyzed WHO defined patient related-factors was a study by Schoenthaler et al,. Interestingly, they found a negative relationship between patients' diabetes-related knowledge and adherence [25].

Discussion

This SR identified studies reporting associations with MNA in T2DM patients using NIAD. Previous SRs have studied MNA factors, but this is the first SR that utilized MPR and PDC to characterize MNA and to group the factors based the five WHO dimensions of MNA [7]. WHO recognized that cost of care was the primary social and economic related factor associated with MNA. This study identified only two studies that supported this finding and two studies that did not [12,16,19,20]. Both articles that showed a positive association were graded as 'poor' quality and therefore based on the strength of evidence this not considered a social and economic related factor. Social and economic related-factors that were not previously analyzed were: age[10,15-21,23-31,33,34],gender [13-16,18-21,23-27,29-31,33,34], race/ethnicity, [12,13,15,19,21,23,31,34] education level [14,19,20,23], income status [12,16,19,20,23], area of residence [15,16,26,27], homelessness, [21] and marital status [15,21]. Of these factors listed, the highest strength of evidence based on the number and quality of studies were the first three. The clinical implication of racial minorities being MNA is profound. Poor glycemic control achieved by racial minorities due to NIAD MNA has shown a strong association with increased mortality [35,36]. It is postulated that MNA in racial minorities is attributed to language barriers [37], low health literacy [38], and preference of alternative medicine [39]. The poor adherence observed in the Asian population [12,23,31], except for the Japanese [31] may have been primarily influenced by use of traditional medicine. Wilson et al found that 33% of south Asians with T2DM preferentially used alternative medicine for glycemic control [40]. Therefore, it is imperative that healthcare providers (HCPs) inquire about alternative medicine and work with the patients to determine which supplements can be used to compliment prescribed therapy. It is also important that HCPs recognize that younger patients, especially under 54 years old, are more likely to be MNA [16]. The only health care team and system related factors that WHO identified was a poor relationship between the patient and physician [7]. Only one study was found that supported this association, therefore an association cannot be determined [25]. The only major factor observed for this dimension was mailed prescriptions [20,21,26]. The association may be attributed to increased day's supply, lower price, and convenient telephone consultations provided by the service [41].

The condition-related factors associated with MNA identified by WHO were depression and increased duration of disease [7]. No articles that met the inclusion criteria for this SR analyzed the association with depression. However, this association was found in studies that included insulin [42,43]. In contrast to WHO's findings, this SR presents that adherence may be associated with longer duration of diabetes rather than shorter [10,13,20,33]. However, this factor needs further investigation as this information is unavailable to some studies [15,25], and there was one good and one poor quality study that supported the contrary [15,25]. The most clinically useful information for HCPs regarding condition-related factors would be the association of MNA with cancer diagnosis [26,28,32] and comorbidities [12,16,17,21,23,24,26,27,29-31], MNA following a cancer diagnosis, especially in patients with a worse prognosis[28,32], was consistent with the finding that major life events with psychological stressors leads to a significant drop anti-diabetic medication adherence [44]. However, it is imperative that cancer patients continue their NIAD, especially metformin, as it has been shown to improve breast cancer prognosis as well as inhibit tumor growth [45-47]. There may be a relationship between fewer comorbidities, younger age, newer to diabetes, and on fewer medications as described by Kirkman et al, [20]. Venturini suggested that this is because younger patients have less comorbidities and sequentially less complex therapies and therefore do not perceive their health to be dependent on their medicine [48]. Therefore, this population should be especially targeted for interventions of adherence. Regarding therapy-related factors, WHO found that MNA was associated with complex treatment and increased pill burden [7], which is contrary to the relationship described by Kirkman and Venturini [20,47]. Although there were studies that showed decreased adherence with increased pill burden [11,18,26], there were twice the number of studies, which observed the contrary[10,16,20,21,24,29,30,33], and three of which were higher quality [10,21,30]. Therefore, HCP should be especially cognizant of the potential of MNA with patients who are on monotherapy. The patient-related factors identified by WHO that were associated by MNA in diabetic patients were depression, stress, alcohol abuse, and poor self-esteem/self-

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efficacy [7]. Arguably, these factors should have been placed under condition-related factors, as the author explains that condition related factors include comorbidities, such as depression, HIV, and substance abuse. The patient-related factors consist of attitudes, beliefs, and perceptions [7]. Fitting this criterion, the only patient related factors were reported in a study by Schoenthaler et al, [25], which showed MNA was associated with increased diabetes related knowledge and decreased perceived dependence on their medication [25]. The latter is consistent with the medication dependence conclusion made by Venterini et al, [48] However, HCP should be careful when interpreting these associations as this study was only graded as fair due to the sample size and low external validity.

There are several limitations to this study. Firstly, insulin was not included in this SR and there was a disproportionately lower number of studies that included GLP-1 agonists. This is significant because there are differences in medication-use behaviors for oral vs. injectable drugs [26]. Secondly, the degree a factor was associated with MNA could not be compared across studies because some studies reported their results with odds ratios, in text, or the percentage of MPR or PDC achieved. Thirdly, there was clearly a correlation between concomitant medications, age, and health status but the exact relationship was not determined. Fourthly, the data can only show associations but not causality. Fifthly, there are assumptions that are made with claims data that do not always hold true, which include: the NIAD were picked up in a timely manner, the NIAD were used by the patient and intended patient only, and that the prescriptions filled were accurately captured in the data set [26]. Finally, the PDC is preferred over MPR for measuring adherence, which is the standard measurement for CMS [49]. However, there were not enough studies that used PDC to measure adherence which is why studies using MPR were also included.

Conclusion

The SR showed that MNA to NIAD as measured by PDC and MPR is associated with younger age, racial minorities, female gender, fewer comorbidities, diagnosis of cancer and decreased pill burden. More studies are needed which include GLP-1 agonists, use PDC to measure adherence, and examine the relationship between age, comorbidities, and pill burden.

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