HHS Public Access

Author manuscript

Chronic Illn. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Chronic Illn. 2021 December ; 17(4): 451–462. doi:10.1177/1742395319884096.

Clinical associations of an updated medication effect score for measuring diabetes treatment intensity

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Contributorship

ASA, MJC, and WSY researched literature and conceived of the study. ASA and MJC drafted the initial manuscript. CJC and ASJ assisted with data acquisition, statistical analyses, and helped draft the methods section of the manuscript. All authors assisted with data interpretation. All authors reviewed and edited the manuscript, and approved the final version of the manuscript.

Guarantor

ASA

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

This study was approved by the Durham Veterans Affairs (VA) Medical Center Institutional Review Board in Durham, NC, USA (study ID# 01794), and was completed in accordance with the Helsinki Declaration as revised in 2013.

Informed consent

Written informed consent was obtained from Jump Start study participants.

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Abstract

Objectives: The medication effect score reflects overall intensity of a diabetes regimen by consolidating dosage and potency of agents used. Little is understood regarding how medication intensity relates to clinical factors. We updated the medication effect score to account for newer agents and explored associations between medication effect score and patient-level clinical factors.

Methods: Cross-sectional analysis of baseline data from a randomized controlled trial involving 263 Veterans with type 2 diabetes and hemoglobin AIc levels ≥8.0% (≥7.5% if under age 50). Medication effect score was calculated for all patients at baseline, alongside additional measures including demographics, comorbid illnesses, hemoglobin AIc, and self-reported psychosocial factors. We used multivariable regression to explore associations between baseline medication effect score and patient-level clinical factors.

Results: Our sample had a mean age of 60.7 (*SD* = 8.2) years, was 89.4% male, and 57.4% non-White. Older age and younger onset of diabetes were associated with a higher medication effect score, as was higher body mass index. Higher medication effect score was significantly associated with medication nonadherence, although not with hemoglobin AIc, self-reported hypoglycemia, diabetes-related distress, or depression.

Discussion: We observed several expected associations between an updated medication effect score and patient-level clinical factors. These associations support the medication effect score as an appropriate measure of diabetes regimen intensity in clinical and research contexts.

Keywords

Type 2 diabetes; medication regimen; medication intensity; hemoglobin AIc; adherence

Introduction

Type 2 diabetes is a progressive disease characterized by intensification of therapy over time. Over 17 million patients in the United States are on medication for diabetes, of whom nearly 18% use insulin.[1] While the goal of medication intensification is improved glycemic control, greater regimen complexity may actually reduce medication adherence and ultimately worsen glycemic control.[2–8] Medication escalation may also elicit or exacerbate undesirable effects such as hypoglycemia and weight gain, counteracting the benefits of hemoglobin A1c (HbA1c) reduction.[9–11] Notably, the intensive control arm in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study experienced higher mortality, an effect that was concentrated in a subgroup of patients who remained “resistant” to HbA1c lowering despite protocol-driven regimen intensification.[12,13] This finding highlights the deleterious effects of intensifying therapy in some patients, as well as the need for effective alternatives to medication escalation for improving outcomes in diabetes.

Diabetes medication regimens are often complex, with multiple agents, varied dosages and frequent administration. Furthermore, medication adjustments at clinic visits can be

intricate, with increased dosages of some medications and decreased dosages of others at the same visit. Therefore, validated tools to measure regimen intensity are needed in order to provide a better understanding of medication intensification or de-intensification, and to allow comparison of medication intensity across patients. While it is generally accepted that an increase in the dose of an oral or injectable diabetes medication represents "intensification", evidence-based measures that facilitate reliable, accurate, and reproducible assessment of medication regimen intensity are needed.

The medication effect score (MES) is a measure of overall diabetes regimen intensity, and is based on the dosages of medications used and their potencies. While MES has been successfully utilized in several studies,[14–23] a gap remains in our understanding of how MES relates to patient factors, as well as the correlation of increasing MES with important measures of diabetes care such as HbA1c and medication nonadherence. Understanding how the MES correlates with patient factors expected to align with medication intensity provides assurance in its ongoing use as a measure of diabetes regimen intensity. With an expanding repertoire of diabetes medications, updates to the MES are also required to account for newer therapies, and to enhance its utility and relevance in current diabetes practice.

We sought to provide evidence-based updates to the MES, and to explore associations between the MES and patient-level clinical factors plausibly linked to medication intensity, including duration of diabetes, body mass index (BMI), HbA1c, hypoglycemia, medication nonadherence, diabetes-related distress, and depression.

Methods

We performed a cross-sectional analysis on baseline demographic and survey data from Veterans enrolled in the Jump Starting Shared Medical Appointments for Diabetes with Weight Management (Jump Start) study.[16] Jump Start (Clinicaltrials.gov NCT01973972) is a randomized controlled trial of a novel diabetes management program that delivers intensive weight management via shared (group) medical appointments in patients with uncontrolled type 2 diabetes and overweight or obesity. The study is approved by the Veterans Affairs (VA) Medical Center Institutional Review Board.

Patient population

Patients in Jump Start were recruited from outpatient sites affiliated with the Durham VA Health Care system. All patients had a diagnosis of type 2 diabetes based on International Classification of Diseases (ICD) codes (ICD-9 255.x0, 250.x2, or ICD-10 E11.xxx). Eligible patients had an HbA1c of ≥8.0% at the time of screening, (≥7.5% if age under 50), BMI of ≥27 kg/m^2, interest in losing weight, and agreement to attend visits. Eligible patients also required reliable access to a telephone and means of transportation, and assignment to a VA Medical Center primary care provider. Patients were excluded if they were age ≥75 or had type 1 diabetes, hemoglobinopathy, chronic kidney disease (creatinine ≥1.5 mg/ dL in men, ≥1.3 mg/dL in women), unstable coronary heart disease, dementia, psychiatric illness, or substance abuse. Additional exclusions included pregnancy, breastfeeding, lack of birth control (in premenopausal women), uncontrolled blood pressure (BP ≥160/100 mmHg) and

uncontrolled dyslipidemia at screening (triglycerides ≥600 mg/ dL or serum low-density lipoprotein cholesterol ≥190 mg/dL).

MES measure

The MES was developed as means of assessing the overall intensity of a patient's diabetes pharmacotherapy based on potency and dosages of medications.[14] The MES is calculated for each diabetes medication in a regimen using the following equation: (actual drug dose/ maximum drug dose) × drug-specific adjustment factor. The adjustment factor equates to the expected decrease in HbA1c achieved by the drug as monotherapy. A patient's individual medication effects are then summed to give an overall MES. The MES presumes a linear relationship between medication dosage and HbA1c, and the sum of MES values attributed to individual medications represents the maximum A1c reduction that may be expected by the regimen. For instance, an MES of 2.5 for a drug regimen translates to a maximal expected drop in HbA1c of 2.5%. MES has been used in several studies to monitor change in medication intensity with various interventions.[14–23] Baseline MES was calculated for each participant in Jump Start.

Updating the MES

MES adjustment factors were initially devised based on a consensus statement by the American Diabetes Association (ADA) in 2009, which included expected HbA1c reductions with available diabetes medication classes.[24] Based on interim studies, we updated the MES by reviewing adjustment factors for older classes and included adjustment factors for newer diabetes therapies that were not in use when the score was developed (Table 1). Two of the authors, who are endocrinologists, reviewed the literature to reach a consensus on adjustment factors reflecting best estimates of expected HbA1c reduction with drug monotherapy. Our review focused on randomized controlled trials and systematic reviews reporting expected HbA1c lowering with diabetes medications, and quality of the evidence was considered when deciding on adjustment factors from these studies. MEDLINE search terms included: "type 2 diabetes," "efficacy," "hemoglobin A1c," and the name of drug classes (e.g., "dipeptidyl peptidase-4 (DPP-4) inhibitors"), and individual drug names (e.g., "semaglutide"). When studies were inconsistent regarding degree of HbA1c lowering, the two authors agreed upon adjustment factors within the reported ranges, and this decision was guided by clinical experience, as well as a broader discussion with diabetes experts.

Review of the literature did not support changing the adjustment factors for insulin, metformin, sulfonylureas, or pioglitazone.[24–29]

The 2009 ADA consensus statement reported an expected HbA1c reduction of 0.5–0.8% with DPP-4 inhibitors.[24] However, because a 2011 meta-analysis of randomized controlled trials revealed an HbA1c reduction of 0.69–0.78% for current DPP-4 inhibitors in use,[30] the authors agreed upon an adjustment factor of 0.70.

A systematic review from 2016 provided HbA1c reductions for glucagon-like peptide 1 (GLP-1) receptor agonists,31 with the exception of semaglutide which was not in use at the time. The approximate HbA1c reductions (vs. placebo) reported in this study became the adjustment factors for these agents: 1.20 for dulaglutide, 0.70 for short-acting

exenatide, 1.10 for long-acting exenatide, and 1.15 for liraglutide.[31] The adjustment factor for semaglutide was informed by a 2018 meta-analysis which revealed a 1.38% reduction in HbA1c[32]; an adjustment factor of 1.4 was agreed upon by the authors. The adjustment factors for sodium–glucose transporter 2 (SGLT-2) inhibitors dapagliflozin (adjustment factor 0.70), canagliflozin (adjustment factor 0.90) and empagliflozin (adjustment factor 0.70) were agreed upon based on HbA1c reductions reported in a 2016 meta-analysis assessing safety and efficacy of these agents.[33] Table 1 provides a summary of the adjustment factors used for this study, along with references.

Baseline measures

We examined self-reported patient demographic factors as baseline covariates. We analyzed age at diagnosis as a continuous variable. We also included the following variables in the multivariable model: gender (male vs. female), race (White vs. non-White), ethnicity (Hispanic vs. non-Hispanic), marital status (married vs. not), education level (education beyond high school vs. high school degree or less), employment (employed vs. unemployed, retired or disabled), and annual income (≥$60,000 vs. less).

We also examined baseline clinical factors. Systolic and diastolic BP, BMI, serum creatinine, and HbA1c were all analyzed as continuous variables in the model. We included whether a patient was being seen by an endocrinologist for their diabetes in the model (yes vs. no). Hypoglycemia was assessed at baseline using a procedure modified from Zammitt et al.[34] where hypoglycemia was based on documented blood sugar <70 mg/dL or episodes with typical hypoglycemia symptoms since their previous visit (on average one month prior). Because most patients did not report hypoglycemia at baseline, we dichotomized this variable (any hypoglycemic events versus no hypoglycemic events).

Finally, we examined psychosocial factors. Nonadherence to insulin and noninsulin diabetes therapies was assessed using a validated, 3-item questionnaire that investigates missed doses over the preceding seven days[35] (score of ≥2 indicates nonadherence). Diabetes-related distress was calculated using the Problem Areas in Diabetes (PAID) scale,[36] for which severe diabetes-related distress is categorized as any value ≥40. We examined depressive symptoms using the Patient Health Questionnaire-2 (PHQ-2)[37]; a PHQ-2 score of ≥3 is a positive screen for depression. All three of these psychosocial factors were continuous variables in our multivariable model.

Statistical analysis

Descriptive statistics, including means and standard deviations (*SD*s) for continuous variables and frequencies for categorical variables, were calculated for baseline characteristics and measures. We fit a multivariable linear regression with baseline MES score as the outcome that included patient-level clinical variables described above. Residual plots from the model were examined to assess linearity and normality assumptions. Collinearity was also assessed and no issues were found. Statistical significance was assessed at a conventional alpha level of ≤0.05. Data management and analysis were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

Results

Population characteristics

Table 2 summarizes baseline demographic, clinical and psychosocial factors from 263 patients enrolled in the Jump Start study. The mean age of participants was 61 years; most were male (89%), non-White race (57%), married (61%), and had education beyond a high school degree (81%). Mean HbA1c at baseline was 9.1%. Most patients were on metformin (82.5%), with a large proportion of patients also taking insulin (62%). Nonadherence to diabetes medications was 61%. From the PAID questionnaire, 32% of patients were experiencing severe diabetes-related distress at baseline with a score of ≥40, and 25% of all patients screened positive for depression by PHQ-2 score.

Multivariable analysis of MES

From the multivariable linear regression model, we found that older age, higher BMI and medication nonadherence were associated with higher MES scores (Table 3). Older age of diabetes onset was associated with lower MES scores. We did not find an association of HbA1c, PAID, or PHQ-2 scores with MES.

Discussion

To the best of our knowledge this is the first study exploring the association of diabetes medication regimen intensity—as calculated by MES—with patient-level clinical factors, with a goal of exploring the utility of MES in clinical and research contexts. In our study, we observed an association between increasing MES and greater duration of illness (as evidenced by older age and younger onset of type 2 diabetes), BMI, and medication nonadherence. We did not observe statistically significant associations between MES and HbA1c, hypoglycemia, diabetes-related distress, or depression.

An expected finding in our study is that MES was associated with older age and earlier onset of diabetes. This accurately reflects the disease course of diabetes, as patients with older age and longer disease duration typically experience *beta* cell loss over time, so require progressive medication intensification to maintain glycemic control.

In addition to duration of diabetes, we found higher BMI to be associated with greater MES. This an expected outcome, as weight gain is a well-documented effect of certain diabetes therapies, namely thiazolidinediones, sulfonylureas, and especially insulin.[38,39] Such weight gain with medication intensification can lead to insulin resistance and hyperglycemia, in turn necessitating further treatment intensification in a “vicious cycle.” The GLP-1 receptor agonist and SGLT-2 inhibitor classes are recognized for weight loss effects; we might therefore hypothesize that increasing utilization of these agents might blunt the association between BMI and MES over time. Our study population included relatively few patients on GLP-1 receptor agonists and SGLT2 inhibitors, necessitating continued reevaluation of the MES as patterns of diabetes medication utilization evolve.

While treatment intensification with insulin and sulfonylureas are associated with higher rates of hypoglycemia,[40] we did not observe an association between hypoglycemia and MES

in our study. Furthermore, we did not observe a statistically significant association between HbA1c and MES. The relationship between HbA1c and medication intensity cannot be easily predicted, as medication intensification has the capacity to both improve glycemic control and deter adherence; which can in turn worsen glycemic control.[2–8] Future work should explore this complex, likely bidirectional relationship between HbA1c and diabetes medication intensity.

Medication nonadherence was associated with greater regimen intensity as measured by MES, consistent with previous studies exploring the effects of regimen complexity on nonadherence.[2–8] Polypharmacy as a contributor to nonadherence is an especially central issue in diabetes because patients often have multiple medication-requiring comorbid conditions. Insulin may be a particularly strong driver of the relationship between medication intensity and nonadherence. Several studies have observed that adherence to insulin is as low as 43% using self-reported measures.[41] Poor insulin adherence and persistence can be attributed to a multitude of patient and healthcare-related factors, as well as system factors such as cost, insurance coverage, and approach to care delivery.[41,42] Notably, nonadherence increases with number of daily insulin injections, which consequently impairs attainment of goal HbA1c.[43] Therefore, despite the important role of insulin in improving glycemic control and reducing diabetes complications, the value of regimen intensification with insulin should be weighed against nonadherence, the possibility of declining glycemic control, and weight gain. As a measure of diabetes regimen intensity, the MES does not account for medication adherence, and cannot discern between appropriate medication intensification to improve HbA1c, versus intensification that occurs in the setting of nonadherence. Therefore, while the MES is a helpful tool to quantify medication intensity in diabetes, clinical context is needed for meaningful interpretation in the real-world setting.

We did not observe an association between diabetes-related distress or depression with greater regimen intensity in our study. A study by Delahanty et al. found levels of distress to be higher in insulin-treated patients compared to those on oral medications,[44] which suggests an association with greater medication intensity. However, it is plausible that distress may be less influenced by treatment intensity than by patient-perceived treatment complexity, a related but distinct entity that may exert different influences on outcomes. The medication regimen complexity index (MRCI) is a patient-level measure used in multiple studies to explore the effects of regimen complexity.[45] The MRCI takes into account dose, route, frequency, and administration instructions that can add to the day-to-day challenges of taking a medication (e.g., timing related to food). As such, the MRCI better reflects the complexity of a regimen from the patient's perspective, whereas the MES is a measure of therapy intensity, accounting for medication dosages and potency. While complex regimens are frequently more intensive, these constructs do not always overlap; for example, a patient taking a high dose of a once-daily medication might have high intensity, but lower relative complexity. The interplay between regimen intensity and complexity requires consideration in future studies of associations between regimen composition and patient outcomes.

Our study has some limitations. First, hypoglycemia was self-reported, meaning it relied on adequate detection by the patient, as well as full recollection of events when the

patient filled out a survey several days to weeks later. Journaling of hypoglycemic events was encouraged but incompletely performed. As such, we are unlikely to have captured all hypoglycemic events in this study. Secondly, adjustment factors were based on best available evidence; however when discrepancies existed between studies, authors agreed on adjustment factors within these evidence-based ranges, largely guided by clinical experience and expert opinion. Finally, this study was conducted in a population of Veterans with uncontrolled diabetes and overweight or obesity despite good access to care and medications, so our findings may not generalize to other populations, or to those with well-controlled diabetes and/or lower BMI. Of note, reliable access to care in this study may in fact strengthen the link between regimen intensity and behavioral contributors to nonadherence by minimizing nonadherence stemming from poor access.

Conclusion

Our study identified key associations between the MES and patient-level clinical factors, including medication nonadherence, BMI, age, and diabetes duration. We have updated the MES to reflect current medications used in diabetes care. Our study supports the ongoing use of MES in clinical and research settings.

Acknowledgements

We would like to acknowledge Elizabeth Strawbridge, RD, Jennifer Zervakis, PhD, and Teresa A. Hinton, RN, for their contributions to data collection in this study.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Jump Start study was supported by a grant from the Veterans Affairs Health Services and Research & Development (IIR 13-053). This work was supported by the Durham Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT), (CIN 13-410) at the Durham VA Health Care System. Additionally, research reported in this publication was supported by the National Institutes of Health under Award Number T32DK007012 (ASA and NS). MJC is supported by a Career Development Award from VHA Health Services Research and Development (CDA 13-261), and CIV is supported by a Health Services Research & Development, Research Career Scientist award (RCS 14-443).

References

1. Wang C, Wang X, Gong G, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. Int J Cancer2012; 130: 1639–1648. [PubMed: 21544812]
2. Bailey CJ and Kodack M. Patient adherence to medication requirements for therapy of type 2 diabetes. Int J Clin Pract 2011; 65: 314–322. [PubMed: 21314869]
3. Dailey G, Kim MS and Lian JF. Patient compliance and persistence with antihyperglycemic therapy: evaluation of a population of type 2 diabetic patients. J Int Med Res 2002; 30: 71–79. [PubMed: 11921502]
4. Donnelly LA, Morris AD, Evans JM, et al. Adherence to insulin and its association with glycaemic control in patients with type 2 diabetes. QJM2007; 100: 345–350. [PubMed: 17504861]
5. Pollack M, Chastek B, Williams SA, et al. Impact of treatment complexity on adherence and glycemic control: an analysis of oral antidiabetic agents. J Clin Outcomes Manag2010; 17: 257–265.
6. de Vries ST, Keers JC, Visser R, et al. Medication beliefs, treatment complexity, and non-adherence to different drug classes in patients with type 2 diabetes. J Psychosom Res2014; 76: 134–138. [PubMed: 24439689]

7. Ingersoll KS and Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med 2008; 31: 213–224. [PubMed: 18202907]
8. Egede LE, Gebregziabher M, Echols C, et al. Longitudinal effects of medication nonadherence on glycemic control. Ann Pharmacother2014; 48: 562–570. [PubMed: 24586059]
9. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet1998; 352: 837–853. [PubMed: 9742976]
10. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med2009; 360: 129–139. [PubMed: 19092145]
11. Action to Control Cardiovascular Risk in Diabetes StudyGerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med2008; 358: 2545–2559. [PubMed: 18539917]
12. Group AS, Gerstein HC, Miller ME, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med2011; 364: 818–828. [PubMed: 21366473]
13. Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care2010; 33: 983–990. [PubMed: 20427682]
14. Mayer SB, Jeffreys AS, Olsen MK, et al. Two diets with different haemoglobin A1c and antiglycaemic medication effects despite similar weight loss in type 2 diabetes. Diabetes Obes Metab2014; 16: 90–93. [PubMed: 23911112]
15. Carter Sc PM and Keogh JB. Effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes: a randomized noninferiority trial. JAMA Netw Open 2018; 1(3): e180756.
16. Crowley MJ, Edelman D, Voils CI, et al. Jump starting shared medical appointments for diabetes with weight management: rationale and design of a randomized controlled trial. Contemp Clin Trials2017; 58: 1–12. [PubMed: 28445783]
17. Dorman RB, Serrot FJ, Miller CJ, et al. Case-matched outcomes in bariatric surgery for treatment of type 2 diabetes in the morbidly obese patient. Ann Surg2012; 255: 287–293. [PubMed: 21975321]
18. Kempf K, Altpeter B, Berger J, et al. Efficacy of the telemedical lifestyle intervention program TeLiPro in advanced stages of type 2 diabetes: a randomized controlled trial. Dia Care2017; 40: 863–871.
19. Tay J, Luscombe-Marsh ND, Thompson CH, et al. A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: a randomized trial. Dia Care2014; 37: 2909–2918.
20. Tay J, Luscombe-Marsh ND, Thompson CH, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr2015; 102: 780–790. [PubMed: 26224300]
21. Tay J, Thompson CH, Luscombe-Marsh ND, et al. Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: a 2-year randomized clinical trial. Diabetes Obes Metab2018; 20: 858–871. [PubMed: 29178536]
22. Watson N, Dyer K, Buckley J, et al. Effects of low-fat diets differing in protein and carbohydrate content on cardiometabolic risk factors during weight loss and weight maintenance in obese adults with type 2 diabetes. Nutrients2016; 8(5): E289. [PubMed: 27187457]
23. Watson NA, Dyer KA, Buckley JD, et al. A randomised trial comparing low-fat diets differing in carbohydrate and protein ratio, combined with regular moderate intensity exercise, on glycaemic control, cardiometabolic risk factors, food cravings, cognitive function and psychological wellbeing in adults with type 2 diabetes: Study protocol. Contemp Clin Trials2015; 45: 217–225. [PubMed: 26546883]
24. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care2009; 32: 193–203. [PubMed: 18945920]

25. DeFronzo RA and Goodman AM. Efficacy of metformin in patients with noninsulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med 1995; 333: 541–549. [PubMed: 7623902]
26. Sherifali D, Nerenberg K, Pullenayegum E, et al. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. Diabetes Care2010; 33: 1859–1864. [PubMed: 20484130]
27. Simonson DC, Kourides IA, Feinglos M, et al. The Glipizide Gastrointestinal Therapeutic System Study Group. Efficacy, safety, and dose-response characteristics of glipizide gastrointestinal therapeutic system on glycemic control and insulin secretion in NIDDM. Results of two multicenter, randomized, placebo-controlled clinical trials. Diabetes Care1997; 20: 597–606. [PubMed: 9096986]
28. Wu D, Li L and Liu C. Efficacy and safety of dipeptidyl peptidase-4 inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis. Diabetes Obes Metab 2014; 16: 30–37. [PubMed: 23803146]
29. Herz M, Johns D, Reviriego J, et al. A randomized, double-blind, placebo-controlled, clinical trial of the effects of pioglitazone on glycemic control and dyslipidemia in oral antihyperglycemic medication-naive patients with type 2 diabetes mellitus. Clin Ther2003; 25: 1074–1095. [PubMed: 12809958]
30. Esposito K, Cozzolino D, Bellastella G, et al. Dipeptidyl peptidase-4 inhibitors and HbA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. Diabetes Obes Metab2011; 13: 594–603. [PubMed: 21320267]
31. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. Diabetes Obes Metab2017; 19: 524–536. [PubMed: 27981757]
32. Andreadis P, Karagiannis T, Malandris K, et al. Semaglutide for type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab2018; 20: 2255–2263. [PubMed: 29756388]
33. Zaccardi F, Webb DR, Htike ZZ, et al. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab2016; 18: 783–794. [PubMed: 27059700]
34. Zammitt NN, Streftaris G, Gibson GJ, et al. Modeling the consistency of hypoglycemic symptoms: high variability in diabetes. Diabetes Technol Ther2011; 13: 571–578. [PubMed: 21413888]
35. Voils CI, Maciejewski ML, Hoyle RH, et al. Initial validation of a self-report measure of the extent of and reasons for medication nonadherence. Med Care2012; 50: 1013–1019. [PubMed: 22922431]
36. Snoek FJ, Pouwer F, Welch GW, et al. Diabetes-related emotional distress in Dutch and U.S. diabetic patients: cross-cultural validity of the problem areas in diabetes scale. Diabetes Care2000; 23: 1305–1309. [PubMed: 10977023]
37. Kroenke K, Spitzer RL and Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care 2003; 41: 1284–1292. [PubMed: 14583691]
38. Gross JL, Kramer CK, Leitao CB, et al. Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. Ann Intern Med2011; 154: 672–679. [PubMed: 21576535]
39. Phung OJ, Scholle JM, Talwar M, et al. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA2010; 303: 1410–1418. [PubMed: 20388897]
40. Zammitt NN and Frier BM. Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. Diabetes Care 2005; 28: 2948–2961. [PubMed: 16306561]
41. Davies MJ, Gagliardino JJ, Gray LJ, et al. Real-world factors affecting adherence to insulin therapy in patients with Type 1 or Type 2 diabetes mellitus: a systematic review. Diabet Med2013; 30: 512–524. [PubMed: 23323988]

42. Cooke CE, Lee HY, Tong YP, et al. Persistence with injectable antidiabetic agents in members with type 2 diabetes in a commercial managed care organization. Curr Med Res Opin2010; 26: 231–238. [PubMed: 19921965]

43. Peyrot M, Rubin RR, Kruger DF, et al. Correlates of insulin injection omission. Diabetes Care2010; 33: 240–245. [PubMed: 20103556]

44. Delahanty LM, Grant RW, Wittenberg E, et al. Association of diabetes-related emotional distress with diabetes treatment in primary care patients with Type 2 diabetes. Diabet Med2007; 24: 48–54. [PubMed: 17227324]

45. George J, Phun YT, Bailey MJ, et al. Development and validation of the medication regimen complexity index. Ann Pharmacother2004; 38: 1369–1376. [PubMed: 15266038]

Table 1.

Medications, doses and adjustment factors utilized in the updated medication effect score (MES).

Medication	Maximum dose	Original MES adjustment factors[14]	Updated adjustment factors	References
All insulin	1 unit/kg	2.5	2.5	24
Metformin	2550 mg	1.5	1.5	24
Sulfonylureas				24
Glimepiride	8 mg	1.5	1.5	
Glipizide	40 mg	1.5	1.5	
Glyburide	20 mg	1.5	1.5	
Pioglitazone	45 mg	0.95	0.95	24, 26, 29
DPP4 inhibitors		N/A		24, 30
Sitagliptin	100 mg		0.70	
Saxagliptin	5 mg		0.70	
Linagliptin	5 mg		0.70	
GLP-1 receptor agonists		N/A		24, 31, 32
Liraglutide qD	1.8 mg		1.15	
Exenatide BID	20 mcg		0.70	
Exenatide qW	2 mg		1.10	
Dulaglutide qW	1.5 mg		1.20	
Semaglutide qW	1 mg		1.40	
SGLT2 inhibitors		N/A		33
Dapagliflozin	10 mg		0.70	
Canagliflozin	300 mg		0.90	
Empagliflozin	25 mg		0.70	

DDP4: dipeptidyl peptidase 4; qD: daily; GLP-1: glucagon-like peptide 1; BID: twice daily; SGLT2: sodium–glucose transporter 2; qW: weekly.

Table 2.

Baseline patient demographics and clinical characteristics.

Variable	Overall *n* = 263
Patient demographics	
Mean age (SD)	60.7 (8.2)
Male sex, *n* (%)	235 (89.4)
Race, *n* (%)	
Non-White	151 (57.4)
Ethnicity, *n* (%)	
Hispanic/Latino	5 (1.9)
Married, *n* (%)[a]	160 (60.8)
Highest education, *n* (%)	
High school degree or less	51 (19.4)
Secondary school	99 (37.6)
Undergraduate degree	84 (31.9)
Graduate work	29 (11)
Employment status, *n* (%)	
Employed or student	87 (33.1)
Unemployed or retired	124 (47.1)
Disabled	52 (19.8)
Annual income, *n* (%)[a]	
≤$29,999	71 (27.0)
≥$30,000–59,999	107 (40.7)
≥$60,000	73 (27.8)
Missing	12 (4.6)
Distance to the VA, *n* (%)	
0–20 miles	124 (47.1)
21–40 miles	86 (32.7)
>40 miles	53 (20.2)
Clinical factors	
Mean hemoglobin AIc (SD)	9.1 (1.3)
Mean age of diabetes diagnosis (SD)[a]	47.4 (10.3)
Occurrence of hypoglycemia, *n* (%)[a]	66 (25.1)
Mean number of hypoglycemic events (SD)	1.3 (3.2)
Following with endocrinologist for diabetes, *n* (%)	41 (15.6)
Mean systolic blood	129.4 (17.6)

Variable	Overall *n* = 263
pressure (SD)	
Mean diastolic blood pressure (SD)	78.9 (11.1)
Mean BMI (SD)	35.3 (5.1)
Mean serum creatinine (SD)	1.1 (0.2)
Mean calculated low density lipoprotein (LDL) (SD)	91.3 (31.8)
Mean triglycerides (SD)	167.7 (101.5)
Mean medication effect score (SD)	2.3 (1.1)
Metformin, *n* (%)	217 (82.5)
Sulfonylureas, *n* (%)	119 (45.3)
Thiazolidinediones, *n* (%)	8 (3.0)
DDP4 inhibitors, *n* (%)	10 (3.8)
GLP-1 receptor agonists, *n* (%)	7 (2.7)
SGLT2 inhibitors, *n* (%)	4 (1.5)
Insulin, *n* (%)	162 (61.6)
Basal only	65 (24.7)
Basal + prandial	87 (33)
Premixed	10 (3.8)
Psychosocial factors	
Diabetes Medication non-adherence, *n* (%)[a]	157 (61.0)
PAID score[a]	
Mean score (SD)	30.5 (21.6)
Score ≥40, *n* (%)	84 (32.4)
PHQ-2 score[a]	
Mean score (SD)	1.6 (1.7)
Score ≥3, *n* (%)	62 (24.6)

DDP4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide 1; PAID: Problem Areas in Diabetes; PHQ: Patient Health Questionnaire; SGLT2: sodium–glucose transporter 2.

[a]Variables with missing values included: marital status (*n* = 1), income (*n* = 12), age of diabetes diagnosis (*n* = 23), hypoglycemia (*n* = 6), medication adherence

Table 3.

Results of regression analysis.

Variable	Coefficient (β)	95% CI	*P* value
Patient demographics			
Age	0.035	0.011, 0.059	0.004
Race	0.225	−0.076, 0.525	0.142
Hispanic/Latino ethnicity	−0.252	−1.19, 0.683	0.595
Gender	−0.025	−0.509, 0.459	0.920
Marital status	0.099	−0.206, 0.403	0.524
Education level	−0.217	−0.571, 0.137	0.228
Employment status	0.318	−0.018, 0.653	0.064
Annual income	−0.005	−0.326, 0.317	0.977
Clinical factors			
Hemoglobin AIc	0.099	−0.012, 0.209	0.080
Creatinine	−0.075	−0.724, 0.575	0.821
Age of diabetes diagnosis	−0.030	−0.047,−0.014	<0.001
Occurrence of hypoglycemia	0.181	−0.143, 0.505	0.272
Seeing endocrinologist for diabetes	0.207	−0.177, 0.592	0.289
Systolic blood pressure	0.003	−0.008, 0.014	0.594
Diastolic blood pressure	−0.005	−0.022, 0.012	0.561
BMI	0.035	0.008, 0.061	0.011
Psychosocial factors			
Medication adherence	−0.303	−0.598 −0.009	0.044
PAID score	0.000	−0.007, 0.008	0.985
PHQ-2 score	−0.066	−0.163, 0.032	0.184

PAID: Problem Areas in Diabetes; PHQ: Patient Health Questionnaire.

229 of the 263 observations were used in the multivariable model due to missing values.