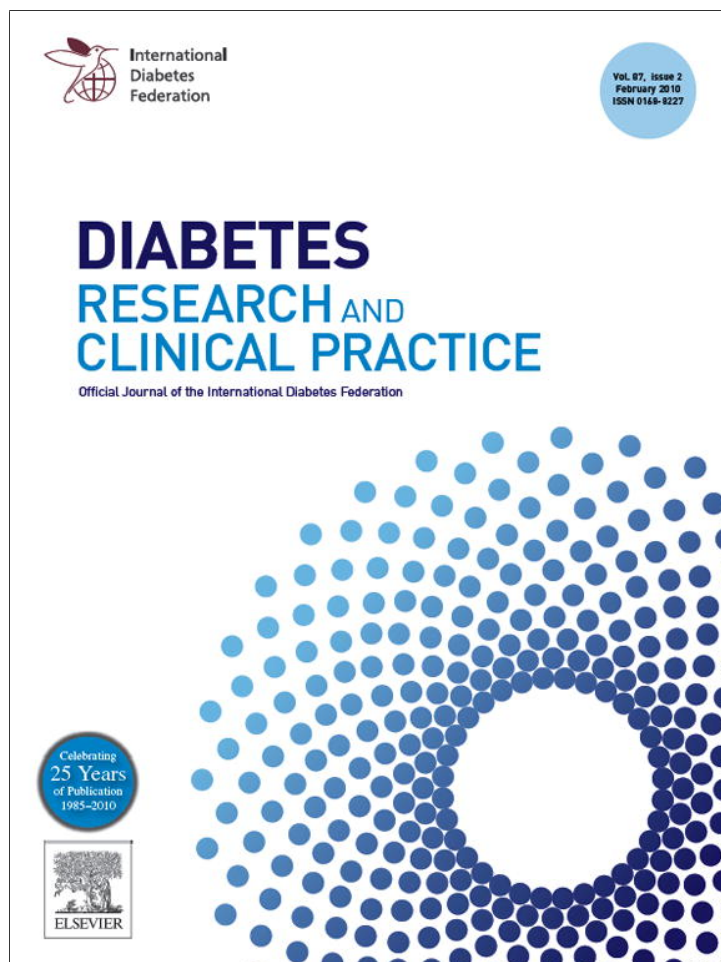


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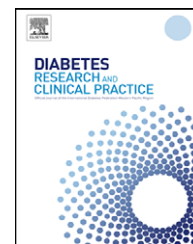


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# Patient-reported tolerability issues with oral antidiabetic agents: Associations with adherence; treatment satisfaction and health-related quality of life<sup>☆</sup>

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### ABSTRACT

**Aims:** The study's aim was to quantify prevalence of tolerability issues among patients with T2DM currently treated with OADs and to assess its association with treatment adherence, satisfaction and health-related quality of life (HRQL).

**Methods:** Data were collected from the 2006–2008 US National Health and Wellness Survey and the Ailment Panel of Lightspeed Online Research, an internet-based questionnaire. Participants (N = 2074) self-reported a diagnosis of T2DM, were >18 years of age and currently taking >1 OADs but not insulin, and spoke English.

**Results:** The majority (71.7%) experienced at least 1 tolerability issue in the past 2 weeks; 49.7% experienced >2. Tolerability issues included signs/symptoms of hypoglycemia (57.2%), constipation/diarrhea (28%), headaches (25.6%), weight gain (22.9%) and water retention (21.0%). There was a significant association between the number of tolerability issues and both the likelihood of non-adherence ( $r = 0.20$ ,  $p < 0.01$ ) and reduced treatment satisfaction ( $r = -0.42$ ,  $p < 0.01$ ). Each additional tolerability issue was associated with 28% greater likelihood of medication non-adherence. Constipation/diarrhea ( $b = -0.02$ ,  $p < 0.01$ ) and symptoms of hypoglycemia ( $b = -0.08$ ,  $p < 0.01$ ) were significantly associated with lower HRQL scores.

**Conclusions:** Optimizing OAD therapy of T2DM by improving tolerability may increase patient satisfaction, medication adherence and HRQL, and may increase the likelihood of attaining treatment goals.

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## 1. Introduction

Diabetes is a chronic progressive condition that if not managed properly can lead to numerous health complications

and disability. The incidence and prevalence of type 2 diabetes (T2DM) are on the rise in the United States and worldwide. It is currently estimated by the American Diabetes Association (ADA) that 8% (23.6 MM) of all Americans have diabetes, of

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which approximately 90% have T2DM [1]. As of 2007, this high rate of diabetes translates to \$ 174 billion annually in direct medical costs and indirect productivity losses to the United States economy. Additionally, many Americans are classified as being pre-diabetic and may be at higher risk for transitioning to T2DM. Such data highlight the continued increasing trend in prevalence and costs associated with T2DM in the foreseeable future [2].

Though the 2009 ADA Standards of Medical Care in Diabetes recommend a comprehensive disease management program that includes lifestyle interventions, the use of prescription oral antidiabetic agents (OADs) has traditionally been a cornerstone of T2DM treatment [3]. The use of multiple OADs – needed to attain or maintain glycemic treatment goals – increases the probability that patients may experience the additive effects and adverse events (AEs) or tolerability issues associated with the various OADs. For instance, sulfonylureas have been associated with weight gain and hypoglycemia, and patients on biguanides report negative gastrointestinal effects, while higher rates of weight gain, edema and fractures have been reported with thiazolidinediones [4,5].

There may be a greater distinction between OAD classes in terms of their tolerability issues and subsequent effects on health-related quality of life (HRQL) and treatment adherence [6]. Although glycemic response can be fairly consistent among OAD therapies, AEs and tolerability issues experienced do vary by treatment, and have been shown to result in patients switching medications or reducing adherence to their prescribed regimen [7–9].

Considering that the screening, diagnosis and treatment costs resulting from adverse drug reactions have been estimated in excess of \$ 76.6 billion annually in the United States [10] and that US poison control centers report an increase in OAD exposures [5], it is becoming increasingly necessary to investigate patient-reported tolerability issues as they relate to treatment with OADs. However, adverse events and tolerability issues associated with OADs have been reported almost exclusively in clinical trials, which may not be reflective of the real-world impact these issues can have on patients' daily lives.

Assessing those tolerability issues that are most burdensome and most frequently experienced may reveal unmet needs in managing T2DM, and provide insight into treatment adherence, satisfaction, and patients' HRQL. The objectives of this study were two-fold; first to quantify the prevalence of self-reported tolerability issues among T2DM patients currently being treated with OADs and to assess the association of tolerability issues with treatment adherence, satisfaction, and HRQL.

### 1.1. Subjects

A total of 10,374 potential study participants that were nationally representative of the general US consumer population were identified through self-reported diabetes responses collected from the 2006–2008 US National Health and Wellness Survey (NHWS) (an annual Internet-based questionnaire developed by Consumer Health Sciences/KantarHealth), and the Ailment Panel of Lightspeed Online Research (a partner organization). Participants were invited via e-mail to participate in this study. Specific criteria for inclusion in the study were: 18

years of age or older; self-reported diagnosis of T2DM made by a healthcare provider; currently taking one or more OADs, but not insulin; ability to read and write English; residence in the United States at the time of the study; and provided informed consent to participate in the study. A study response quota based on the expected prevalence of common tolerability issues for available OADs was set at 2000 participants.

## 2. Materials and methods

### 2.1. Study design

A self-administered, Internet-based survey with patient-reported outcome (PRO) instruments was developed and administered in September 2008 to a cohort of respondents with self-reported T2DM currently using OADs. This cross-sectional survey took approximately 30 min to complete and collected data on demographics, general health, disease and treatment characteristics, resource utilization, and health care access to assess disease symptoms, treatment adherence and satisfaction, and HRQL. The study protocol and questionnaire were reviewed and approved by Essex IRB (Lebanon, NJ, USA).

### 2.2. Study measures

#### 2.2.1. Tolerability issues

Patient-reported tolerability issues were assessed by a combination of direct questions developed for this study and items from existing disease symptom measures. Patients reported their experiences with common tolerability issues over the previous two weeks and rated bothersomeness on a five-point scale, ranging from not at all to extremely bothersome, with higher scores indicating greater bother. Tolerability issues were identified from a comprehensive review of prescribing information for currently available OADs as well as the most frequently occurring events based on expert clinical consultation. Tolerability issues of interest included: constipation or diarrhea, headache, loss of appetite, nausea or vomiting, upper respiratory infection, genital-urinary tract infections, water retention or edema, unintended weight loss, yeast infections, hypoglycemia, weight gain, and cardiovascular (CV) events. Though not a tolerability issue per se, severe CV event AEs were included as part of the survey based on continued interest in CV risk associated with some OAD classes. Bothersomeness was not assessed for CV events.

The 30-item Diabetes Symptom Measure (DSM) [11], measures cognitive and physiological symptoms and was used to assess weight gain and disease symptoms associated with hypoglycemia during the two weeks prior to taking the survey. Frequency of symptoms was assessed on a five-point Likert scale ranging from 'none of the time' to 'all of the time'. Higher scores are associated with greater symptom burden. Since the presence of hypoglycemia symptoms was a composite of item responses, an overall level of bothersomeness for hypoglycemia was not assessed. The signs and symptoms of hypoglycemia were identified as those from the DSM which correspond closely to ADA recognized symptoms; including difficulty thinking or concentrating, irritability, anxiety or nervousness, inability to think as quickly as usual,

inability to stay focused, shakiness or trembling, headaches, breaking into a sweat, feeling unusually hungry, faint, dizzy or light-headed, shivers or cold sweats, feeling weak, uncoordinated or clumsy, symptoms of low blood sugar, and low blood sugars in the middle of the night [12].

### 2.2.2. Medication adherence

Adherence was assessed using the 4-item Morisky Medication Adherence Scale (MMAS) [13]. The MMAS consists of four questions that assess forgetfulness about taking medication, carelessness about taking medication, stopping medication when feeling better, and stopping medication when feeling worse. Respondents with scores  $\geq 2$  are classified as non-adherent; those with scores 0–1 are classified as adherent.

### 2.2.3. Treatment satisfaction

Patient treatment satisfaction was evaluated using the Diabetes Medication Satisfaction (DiabMedSat) tool [11], a 22-item instrument that measures three domains: satisfaction related to burden (e.g., frequency of monitoring blood glucose, frequency of medication dosing), efficacy, and symptoms, each of which is computed as a score. In addition, a total satisfaction score is computed. Each item in the scale uses a 5–7 point Likert scale; overall and domain scores range from 0 to 100, with higher scores indicating greater levels of treatment satisfaction.

### 2.2.4. Health-related quality of life

The EQ-5D is a generic, preference-based utility measure consisting of two parts that was used to measure respondent's HRQL and utility values. The EQ-5D Index is computed from five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses for each of the five dimensions range from "no health problems", to "moderate health problems", and "extreme health problems". A composite EQ-5D score is computed from the five dimensions and ranges from 0 to 1. The EQ-5D questionnaire also includes a visual analogue scale (VAS), which records respondents' self-rated health status on a graduated (0–100) scale, with higher scores for higher HRQoL [14,15].

2.2.5. Demographics, comorbidity, and disease characteristics Gender, race/ethnicity (white vs. non-white), marital status (married vs. not married), and education (college graduate vs. not a college graduate) were assessed as dichotomous variables; age was assessed as a continuous variable. Overall health and disease comorbidity was assessed using the Charlson Comorbidity Index (CCI) [16]. The CCI was computed from an extensive list of health conditions that respondents reported experiencing. Conditions were assigned weights, which were then summed for each respondent, yielding a measure of the degree of comorbidity for each respondent. Psychiatric conditions were assessed as the presence of anxiety, bipolar disorder, or depression. To assess potential severity of T2DM, years since diagnosis of T2DM, years of OAD treatment, knowledge of and values for glucose parameters were also collected.

## 2.3. Statistical analyses

Statistical analyses, including multivariate analysis, were conducted using SPSS software (version 15.0, Chicago, IL,

USA). Univariate frequencies were used to present reported rates of tolerability issues and bothersomeness among OAD users. Pearson correlations were used to assess the unadjusted associations of the number of tolerability issues with medication non-adherence, symptoms, treatment satisfaction, and HRQL. Additionally, chi-square tests were used to assess the unadjusted association of tolerability issues with medication non-adherence, and ANOVA was used to assess unadjusted associations of tolerability issues with patient treatment satisfaction and HRQL [17].

Multivariate regression models were developed to determine the association of tolerability issues with medication non-adherence, treatment satisfaction, and HRQL while controlling for patient demographics, comorbidity, and disease characteristics. Logistic regressions were used to assess medication non-adherence, and linear regressions were used to assess patient treatment satisfaction, EQ-5D Index, and EQ-5D VAS scores.

## 3. Results

### 3.1. Sample characteristics

A total of 2074 respondents met study criteria and completed the survey. The study sample was 47.4% female, 13.3% non-white, had a mean age of 60.1 years (SD = 10.8) with a diagnosis of T2DM for an average of 8.9 years (SD = 7.2). The mean Charlson Comorbidity Index of the sample was 2.0 (SD = 1.8); 71.8% had experienced hypertension, 70.2% had experienced dyslipidemia, and 35.5% had experienced a psychiatric condition. Within the total sample, 95% ( $n = 1977$ ) reported having visited a healthcare provider to measure HbA1c in the past 12 months. Although 48% ( $n = 995$ ) of respondents indicated that their most recent HbA1c value was at or below the target determined by their physician, approximately 72% of these patients did not know the specific value of their most recent HbA1c test. The most commonly used OADs as either monotherapy or in combination were biguanides (77.2%), followed by sulfonylureas (48.5%), thiazolidinediones (TZDs) (27.9%), dipeptidyl peptidase-4 inhibitors (DPP-4s) (12.4%), and other OADs (2.1%). Nearly half (48%) of respondents were currently being treated with one OAD class, 38% with two OAD classes, and 14% with three or more OAD classes. Most (82.5%) of the study respondents recall having initiated an OAD treatment within 6-months of their T2DM diagnosis. Twenty-two percent of the cohort initiated a new OAD, either as an add-on therapy or a switch, within the 12 months prior to the survey.

### 3.2. Tolerability issues

The majority of respondents (71.7%) reported having experienced at least one tolerability issue in the past two weeks, with many patients experiencing multiple tolerability issues (mean = 1.76, SD = 1.61). Specifically, 22.0% experienced one tolerability issue, 19.9% experienced two, 14.1% experienced three, and 15.7% experienced four or more issues. More than half (57.2%) of respondents experienced signs and symptoms of hypoglycemia in the past two weeks. Other commonly reported tolerability issues included: gastrointestinal symptoms (i.e., 28.0% constipation/diarrhea, 7.3% nausea/vomiting,

**Table 1 – Tolerability issues experienced in the past two weeks.**

|                                     | Experienced in past two weeks (%) | Very or extremely bothersome <sup>a</sup> |
|-------------------------------------|-----------------------------------|---|
| Symptoms of hypoglycemia            | 57.2                              | NA  |
| Constipation or diarrhea            | 28.0                              | 34.3%                                     |
| Headache                            | 25.6                              | 24.5%                                     |
| Weight gain                         | 22.9                              | NA  |
| Water retention or edema            | 21.0                              | 35.9%                                     |
| Nausea or vomiting                  | 7.3                               | 37.1%                                     |
| Loss of appetite                    | 5.7                               | 9.3%                                      |
| Upper respiratory infections        | 3.2                               | 54.5%                                     |
| Weight loss (unintended)            | 1.8                               | 8.1%                                      |
| Genital-urinary tract infection     | 1.7                               | 61.1%                                     |
| Yeast infection of the genital area | 1.5                               | 42.0%                                     |
| Cardiovascular event                | 0.4                               | NA  |

<sup>a</sup> 4 or 5 on a 5-point Likert scale; NA—not assessed.

5.7% loss of appetite), headaches (25.6%), weight gain (22.9%), and water retention (21.0%) (Table 1). When asked about the perception of tolerability issues, the level of bothersomeness experienced by respondents varied widely. Among the tolerability issues, where the level of bothersomeness was asked, genital-urinary tract infections were considered the most bothersome, though one of the least reported issues, whereas loss of appetite and unintended weight loss were considered the least bothersome.

**3.3. Tolerability issues and medication adherence**

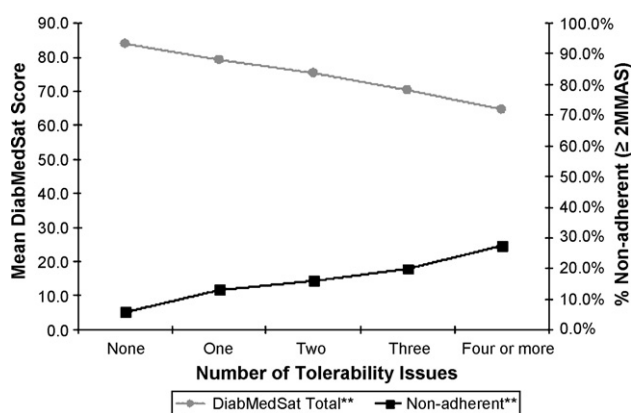
There was a significant association between the number of tolerability issues and likelihood of non-adherence ( $r = 0.20$ ,  $p < 0.01$ ). Of respondents with no tolerability issues, only 6% were considered to be non-adherent, compared with 19.9% of those with three tolerability issues and 27.3% of those with four or more (Fig. 1). Adjusted models demonstrated that each additional tolerability issue was associated with 28% greater likelihood of being non-adherent (OR 1.28,  $p < 0.01$ ) to the T2DM regimen (Table 2). When examined individually, constipation and diarrhea (OR 1.47,  $p < 0.01$ ) and hypoglycemia (OR 1.76,  $p < 0.01$ ) were found to be significantly

associated with increased likelihood of self-reported medication non-adherence (Table 3).

**3.4. Tolerability issues and treatment satisfaction**

A significant association was also observed between the number of tolerability issues reported by study participants and reduced treatment satisfaction ( $r = -0.42$ ,  $p < 0.01$ ). Fig. 1 illustrates the overall relationship between lower treatment satisfaction and greater number of tolerability issues. Mean treatment satisfaction scores ranged from 84.04 (SD = 7.92) for those reporting no tolerability issues over the previous two weeks to 64.69 (SD = 13.23) for study participants reporting four or more tolerability issues. When analyzing each satisfaction domain (burden, efficacy, symptoms) separately, similar relationships were observed between these domains and the presence of tolerability issues.

Even after adjusting for respondent characteristics, experiencing more tolerability issues continued to be



**Fig. 1 – Unadjusted<sup>†</sup> association of number of tolerability issues with patient treatment satisfaction (DiabMedSat) and morisky medication adherence scale (MMAS). <sup>\*</sup> $p < 0.05$ , <sup>\*\*</sup> $p < 0.01$ . <sup>†</sup>Method: chi-square for categorical variables and ANOVA for continuous variables.**

**Table 2 – Adjusted association of number of tolerability issues with medication adherence, patient treatment satisfaction, and EQ-5D.**

| Dependent variable                  | Odds ratio  | 95% CI |       |
|-------------------------------------|-------------|--------|-------|
|                                     |             | Low    | High  |
| Non-adherence <sup>a</sup>          | 1.28**      | 1.18   | 1.39  |
|                                     | Coefficient | Low    | High  |
| Treatment satisfaction <sup>b</sup> |             |        |       |
| Burden                              | -1.76**     | -2.09  | -1.42 |
| Efficacy                            | -4.22**     | -4.75  | -3.69 |
| Symptoms                            | -4.93**     | -5.33  | -4.52 |
| Total score                         | -3.63**     | -3.94  | -3.32 |
| EQ-5D index <sup>b</sup>            | -0.05**     | -0.05  | -0.04 |
| EQ-5D VAS <sup>b</sup>              | -4.36**     | -5.10  | -3.62 |

All model structures adjust for gender, age, race/ethnicity, marital status, education, presence of psychiatric condition, Charlson Comorbidity Index, and years since diagnosis.

<sup>a</sup> Method: Logistic regression model.

<sup>b</sup> Method: Linear regression model.

<sup>\*</sup>  $p < 0.05$ .

<sup>\*\*</sup>  $p < 0.01$ .

**Table 3 – Adjusted association of individual tolerability issues with medication adherence and patient treatment satisfaction.**

|                                     | Non-adherence <sup>a</sup> |              | Treatment satisfaction <sup>b</sup> |                 | EQ-5D index <sup>b</sup> |                | EQ-5D) VAS <sup>b</sup> |                |
|-------------------------------------|----------------------------|--------------|-------------------------------------|-----------------|--------------------------|----------------|-------------------------|----------------|
|                                     | Odds ratio                 | 95% CI       | Coefficient                         | 95% CI          | Coefficient              | 95% CI         | Coefficient             | 95% CI         |
|                                     |                            | [Low, high]  |                                     | [Low, high]     |                          | [Low, high]    |                         | [Low, high]    |
| Cardiovascular event                | 1.04                       | [0.12, 8.84] | -8.74**                             | [-15.37, -2.12] | 0.03                     | [-0.06, 0.13]  | -15.94                  | [-31.96, 0.07] |
| Constipation or diarrhea            | 1.47**                     | [1.11, 1.95] | -3.85**                             | [-4.9, -2.8]    | -0.02**                  | [-0.04, -0.01] | -4.75**                 | [-7.3, -2.2]   |
| Headache                            | 1.15                       | [0.86, 1.53] | -0.87                               | [-1.96, 0.22]   | -0.02**                  | [-0.04, -0.01] | -0.36                   | [-2.99, 2.27]  |
| Loss of appetite                    | 0.98                       | [0.6, 1.61]  | -1.23                               | [-3.23, 0.76]   | -0.06**                  | [-0.09, -0.03] | -0.14                   | [-4.97, 4.69]  |
| Nausea or vomiting                  | 1.3                        | [0.85, 1.98] | -3.95**                             | [-5.76, -2.15]  | -0.02                    | [-0.04, 0.01]  | 0.78                    | [-3.58, 5.14]  |
| Symptoms of hypoglycemia            | 1.76**                     | [1.27, 2.45] | -5.16**                             | [-6.2, -4.11]   | -0.08**                  | [-0.09, -0.06] | -8.78**                 | [-11.3, -6.27] |
| Upper respiratory infections        | 0.87                       | [0.45, 1.71] | -2.2                                | [-4.73, 0.34]   | -0.03                    | [-0.07, 0.01]  | 0.39                    | [-5.74, 6.51]  |
| Genital-urinary tract infection     | 1.53                       | [0.68, 3.47] | -3.54*                              | [-6.89, -0.18]  | -0.03                    | [-0.08, 0.017] | -1.19                   | [-9.31, 6.92]  |
| Water retention or edema            | 1.29                       | [0.95, 1.75] | -2.45**                             | [-3.59, -1.31]  | -0.07**                  | [-0.09, -0.06] | -5.95**                 | [-8.7, -3.2]   |
| Weight gain                         | 1.05                       | [0.78, 1.41] | -6.64**                             | [-7.78, -5.51]  | -0.05**                  | [-0.06, -0.03] | -5.54**                 | [-8.28, -2.8]  |
| Weight loss (unintended)            | 1.33                       | [0.6, 2.96]  | -3.70*                              | [-7.05, -0.34]  | -0.06*                   | [-0.11, -0.01] | -11.09**                | [-19.2, -2.98] |
| Yeast infection of the genital area | 1.04                       | [0.4, 2.67]  | -1.05                               | [-4.7, 2.6]     | -0.04                    | [-0.09, 0.02]  | 0.61                    | [-8.22, 9.43]  |

All model structures adjust for gender, age, race/ethnicity, marital status, education, presence of psychiatric condition, Charlson Comorbidity Index, and years since diagnosis.

<sup>a</sup> Method: logistic regression model.

<sup>b</sup> Method: linear regression model.

\*  $p < 0.05$ .

\*\*  $p < 0.01$ .

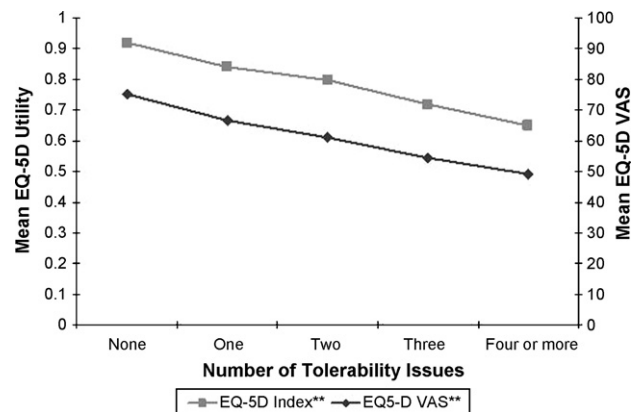
significantly associated with reduced treatment satisfaction. Specifically, each additional tolerability issue was associated with a -3.63 reduction in the total DiabMedSat score ( $p < 0.01$ ) (Table 2). Among the individual tolerability issues, cardiovascular events ( $b = -8.74$ ,  $p < 0.01$ ), unintended weight loss ( $b = -3.70$ ,  $p < 0.05$ ), water retention or swelling ( $b = -2.45$ ,  $p < 0.01$ ), nausea or vomiting ( $b = -3.95$ ,  $p < 0.01$ ), constipation or diarrhea ( $b = -3.85$ ,  $p < 0.01$ ), urinary tract or genital-urinary infection ( $b = -3.54$ ,  $p < 0.05$ ), symptoms of hypoglycemia ( $b = -5.16$ ,  $p < 0.01$ ), and weight gain ( $b = -6.64$ ,  $p < 0.01$ ) were all found to be significantly associated with lower rates of overall treatment satisfaction (Table 3).

### 3.5. Tolerability issues and HRQL

Fig. 2 illustrates the relationship between mean EQ-5D Index and VAS health utility scores and the number of tolerability issues experienced by respondents. Mean EQ-5D scores for those reporting no tolerability issues, one, two, three, and four or more issues were 0.9027 (SD = 0.13164), 0.8605 (SD = 0.14112), 0.8113 (SD = 0.16562), 0.7758 (SD = 0.16339), and 0.6845 (SD = 0.20283), respectively. Similarly, mean VAS scores ranged from 74.16 (SD = 22.992) for those reporting no tolerability issues to 50.56 (SD = 27.177) for study participants with four or more issues. Experiencing more tolerability issues was found to be associated with reduced health utility for both the EQ-5D Index and VAS scores ( $r = 0.52$ ,  $p < 0.01$ ;  $r = 0.34$ ,  $p < 0.01$ , respectively).

Even after adjusting for respondent and disease characteristics, experiencing more tolerability issues was significantly

associated with reduced health utility as measured by the EQ-5D Index and EQ-5D VAS score. Specifically, each additional tolerability issue was found to be associated with a change in EQ-5D Index of -0.05 ( $p < 0.01$ ) and a change in EQ-5D VAS of -4.36 ( $p < 0.01$ ) (Table 2). Individually, headache ( $b = -0.02$ ,  $p < 0.01$ ), constipation or diarrhea ( $b = -0.02$ ,  $p < 0.01$ ), loss of appetite ( $b = -0.06$ ,  $p < 0.01$ ), symptoms of hypoglycemia ( $b = -0.08$ ,  $p < 0.01$ ), water retention ( $b = -0.07$ ,  $p < 0.01$ ), weight gain ( $b = -0.05$ ,  $p < 0.01$ ), and unintended weight loss ( $b = -0.06$ ,  $p < 0.05$ ) were significantly associated with lower EQ-5D Index scores (Table 3). For the EQ-5D VAS scores,



**Fig. 2 – Unadjusted association of number of tolerability issues with EQ-SD. †Method: ANOVA. \*  $p < 0.05$ , \*\*  $p < 0.01$ . ††Method: chi-square for categorical variables and ANOVA for continuous variables.**

constipation or diarrhea ( $b = -4.75$ ,  $p < 0.01$ ), symptoms of hypoglycemia ( $b = -8.78$ ,  $p < 0.01$ ), water retention ( $b = -5.95$ ,  $p < 0.01$ ), weight gain ( $b = -5.54$ ,  $p < 0.01$ ), and unintended weight loss ( $b = -11.09$ ,  $p < 0.01$ ) were significantly associated with lower scores (Table 3).

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#### 4. Discussion

A large proportion of respondents taking OADs for T2DM reported experiencing tolerability issues in the two weeks before this survey; with the most commonly reported issues being hypoglycemia and GI symptoms. Study participants considered all tolerability issues bothersome to some degree; however, genital-urinary infections were considered to be the most bothersome.

As in previous studies, OAD tolerability issues experienced by respondents in this study resulted in an increased likelihood for non-adherence to T2DM medications [18,19], especially if three or more issues were experienced. In addition, significant relationships were observed for outcomes related to treatment satisfaction and patient quality of life. Hypoglycemia and GI symptoms were routinely associated with increased likelihood of medication non-adherence, lower treatment satisfaction, and reduced HRQL. Recognizing and addressing the presence of multiple tolerability issues in patients treated with OADs could decrease bothersomeness of these issues, and thereby improve patient outcomes through higher medication adherence, greater treatment satisfaction levels, and better overall HRQL.

This study has several important limitations. First, all data were self-reported via an online web panel; it is possible that this route of survey administration and clinical information to validate patient responses was not available. In addition, though the NHWS and Ailment Panels are designed to be nationally representative, respondents for the current study may have differed from the general population in several respects, including age, race, and severity of condition, HbA1c testing rates, and utilization of prescription OADs. Caution should be used when generalizing these results to other populations. Furthermore, it is possible that the two-week recall period does not capture important experiences that occurred further in the past.

The cross-sectional design of this study limits our ability to draw conclusions about causality based on the association between patients' perceptions of experiencing medication-related tolerability issues and the outcomes of interest. Our analysis did not examine each drug class separately, and although we controlled for underlying diseases and characteristics, attributing specific tolerability issues or AEs to individual classes would have proven unreliable given that treatment therapies often consisted of multiple OADs. Nevertheless, the study design allowed for collection of relevant and accurate data while establishing a significant association between the presence of tolerability issues and the patient-reported outcomes.

It is also important to note that respondents indicated that they had been on their current treatment regimens for extended durations, which helps minimize the possibility that participants experiencing tolerability issues were early

in their treatment course (and therefore in the process of working with their physician to determine appropriate dosing schedules). Furthermore, the fact that study participants had been diagnosed and continuously treated for an average of >8 years, indicates that tolerability issues can be persistent through the continuum of care received by patients and should not only be considered when initiating new therapies. In addition, a majority (57.2%) of these same patients indicated that they experienced signs and symptoms of hypoglycemia during the previous two weeks. This result among a cohort of respondents with prevalent T2DM does indicate that glucose control maybe lacking even after an average of 8 years of continuous treatment or monitoring by their physician.

Data regarding tolerability issues obtained from the questionnaire administered to respondents with self-reported T2DM indicated that a majority of subjects receiving OADs have recently experienced these treatment-related issues. Reported tolerability issues can also have significant effects on patient HRQL, treatment adherence and satisfaction, and, potentially, affect patients' ability to achieve long-term glucose control. This study highlights the general burden related to tolerability issues and provides important insights into the outcomes of respondents with self-reported T2DM currently taking OADs. Additional studies are needed to determine whether this association persists in other populations and if results are more significant for one particular OAD class or T2DM sub-population. Practitioners should be cognizant of potential treatment-related tolerability issues and how these may affect long-term efforts to successfully manage T2DM.

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#### Conflicts of interest

The authors have a competing interest to declare. The National Health and Wellness Survey (NHWS) is conducted by Consumer Health Sciences/KantarHealth, Princeton, NJ. AstraZeneca, Wilmington, DE and Bristol-Myers Squibb, Plainsboro, NJ, licensed access to NHWS and funded the analysis and preparation of this paper. Mr. Pollack and Dr. Williams are employees of AstraZeneca. Dr. Bolge and Ms. Purayidathil were employees of CHS/KantarHealth at the time of the research.

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