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Complete List of Authors:	Lee, Cia Sin; SingHealth Polyclinics, Sengkang Polyclinic Tan, Jane Hwee Mian; SingHealth Polyclinics Sankari, Usha; SingHealth Polyclinics Koh, Yi Ling Eileen; SingHealth Polyclinics Tan, Ngiap Chuan; Duke NUS Medical School, ; SingHealth Polyclinics, Research
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TITLE PAGE

Title

Assessing oral medication adherence amongst patients with type 2 diabetes mellitus treated with polytherapy in a developed Asian community: a cross-sectional study

Authors

Cia Sin, LEE[1]

Hwee Mian Jane, TAN[1]

Sankari Usha[1]

Yi Ling Eileen, KOH[1]

Ngiap Chuan, TAN[1,2]

[1]SingHealth Polyclinics, Singapore

[2]Duke-NUS Medical School, Singapore

Corresponding author

Cia Sin Lee;

Singhealth Polyclinics – Sengkang,

Sengkang Square, #01-04,

Singapore 54025

Email: lee.cia.sin@singhealth.com.sg

Tel: (65) 6315 3501

ABSTRACT

Objectives:

The disease burden of type 2 diabetes mellitus (T2DM) is rising due to prevalent suboptimal glycemic control leading to vascular complications. Medication adherence (MA) directly influences glycemia control and clinical consequences. This study aimed to assess the MA of patients with T2DM and identify its associated factors.

Design:

Data analysis from a cross-sectional survey and electronic medical record.

Setting:

Primary care outpatient clinic.

Participants:

Adult patients with type 2 diabetes mellitus.

Main outcome measures:

Medication adherence to each prescribed oral hypoglyceamia agents (OHA) was measured using the 5-questions Medication Adherence Report Scale (MARS-5). Low MA is defined as MARS-R score of <25. Demographic data, clinical characteristics, and investigation results were collected to identify factors that are associated with low MA.

Results:

The study population comprised 382 patients with slight female predominance (53.4%) and mean (SD) age of 62.0±10.4 years. 57.1% of them had low MA to at least one OHA. Univariate analysis showed that patients who were younger, of Chinese ethnicity, married or windowed, self-administering their medications and were taking fewer (4 or less) daily medications tended to have low MA to OHA. Logistic regression revealed that younger age (OR=0.97; 95%CI:0.95, 0.99), Chinese ethnicity (OR=2.80; 95%CI:1.53, 5.15) and poorer glycaemic control (HbA1c) [OR=1.27; 95%CI:1.06, 1.51] were associated with low MA to OHA respectively.

Conclusions:

Younger patients with T2DM and of Chinese ethnicity were susceptible to low MA to OHA, which were associated with poorer glycaemic control. Polytherapy was not associated with low MA.

Strengths and limitation of this study

- Medication adherence directly influences glycemic control and this study used a simple self-administered tool to measure medication adherence to each oral hypoglycemia agents among adult patients with type 2 diabetes mellitus.
- This study identified factors associated with low medication adherent.
- Potential of selection bias as case-encounter sampling method employed in this study which may restrict the extrapolation of the results to the general population.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disease with staggering increase in prevalence and disease burden globally.[1] One of these countries, which reported this spiral rise in prevalence is Singapore, a developed nation with a mature healthcare system serving a population of increasing longevity. [2] Gravely, increasing numbers of the local multi-ethnic Asian population on the island-state are suffering from T2DM and associated complications over longer life spans. Singapore is thus a favorable microcosm to study the impact of T2DM on the community as most of the patients have access to treatment in primary care. 45% of them are currently treated in local public primary care clinics, where medications for diabetic treatment are dispensed to patients from the in-house pharmacies conveniently at subsidized costs.[2]

While medical treatment is readily available to manage the disease in primary care in Singapore, glycaemic control remains suboptimal in 32% of local patients with T2DM [2]. The mean HbA1c of patients with T2DM in a primary care clinic was 7.7% (SD 1.7%) in a recent cohort study.[3] To achieve glycaemic control, patients are prescribed multiple oral hypoglycemic agents (OHA) and add on insulin therapy in the context of the natural progression of the disease. Aside from polytherapy, medication adherence (MA) directly influences the glycemic control and clinical consequences. Factors associated with MA tend to be complex due to the interaction between patient, physician, healthcare team and medication factors.[4]

Measurement of MA can be assessed in several ways but using questionnaires and scales is easier to integrate into clinical practice [5-7]. Instruments, such as the 5-item Medication Adherence Report Scale (MARS-5) or the 4- or 8-item Morisky Medication Adherence Scale (MMAS) have been used to assess MA.[8-11] These scales rely on subjects to self-report their adherence to specific medication.

Earlier studies have reported low MA to single oral hypoglycaemia agents (OHA) but the rate varied from 36% to 42% pending on the OHA.[12,13] The MA assessment becomes more complicated if a patient is on polytherapy or combination therapy with several oral medications to curb dysglycemia. Little research has been carried out to assess MA amongst patients on polytherapy to achieve disease control. A systematic review has just commenced to address the issue and no aggregated instrument has been developed for such assessment.[14] This is further complicated if patients are taking concurrent medications for the treatment of other co-morbidities.

One approach is to determine the MA for each of the OHA prescribed to the individual patient on polytherapy. We hypothesized that patients with T2DM differed in their MA to each of their prescribed OHA if they were on polytherapy. For optimal glycaemic control, it is important to understand the MA to specific class of OHA, so that appropriate measure can be introduced to address the reason for low adherence. Cappocia K et al reported low MA was associated with poor tolerance to

medication, frequency of administration beyond twice daily and perverse views about the importance of medication.[15]

Hence, the main objective of this study was to determine the MA of patients with T2DM to their specific OHA using the MARS-5 scale as the primary clinical outcome. This study also aimed to identify the factors influencing their MA in association with their glycaemic control.

METHOD

Study site

A questionnaire survey was administered to patients with T2DM treated with OHA in primary care. The survey was carried out at a typical public primary care clinic (polyclinic) located in SengKang, an estate located in the north eastern region of Singapore. The polyclinic serves a population of over 316,000 multi-ethnic Asian residents living within 20 square kilometres in area and neighbouring Punggol estates.[16]

Study population and recruitment procedure

Patients with known T2DM, as affirmed from their electronic medical records at the study site, were screened by trained research assistants and polyclinic nurses for eligibility for enrolment into this survey. Recruited on a case-encounter basis between June 2015 and March 2016, they included patients aged between 35 to 84 years old, both gender, multi-ethnicity and were followed up at the study site for at least two visits over a minimal period of 6 months.

The subjects were treated with one or more OHA, and included those with medications for the management of other co-morbidities. The OHA included the Sulphonyurea (largely tolbutamide, glipizide and gliclazide), Biguanides (Metformin), Alpha-Glucosidase Inhibitors (AGI such as Acarbose) and Dipeptidyl Peptidase-4 Inhibitor (DPP4, such as Sitagliptin).

Each subject had a minimum of one glycated haemoglobin (HBA1c) as an indicator of their glycaemic control in the past 6 months. Those who were on dietary control alone or were on any form of insulin therapy, and/or with intellectual or cognitive impairment were excluded.

The subjects were provided with participant information sheet which described the study protocol and their written consent was obtained after clarification with the research coordinator. Next they filled the questionnaire, assisted by the research assistant.

Sample size calculation

Based on a low MA rate of 36% from a Malaysian study[13] which has a similar multi-ethnic Asian population, the sample size was computed using a confidence interval of 5% and study power of 95%. Therefore, an estimated sample of 342 eligible subjects would be needed for this study. To allow a withdrawal rate of 10%, the investigator team planned to recruit a total of 380 patients.

Instrument

Existing scales measure adherence to a single specific medication. However, patients with T2DM are often treated with more than one medication to control the hyperglycaemia. Low MA may be specific to a single medication or across multiple medications. To investigate the MA to multiple medications, the scale must be simple, validated, reliable and easy to implement as it has to be repeated for each medication.

The investigators have selected the Medication Adherence Report Scale (MARS-5) in view of its ease of application. MARS-5 has been widely used in studies in a variety of chronic illnesses, including T2DM, hypertension and chronic obstructive pulmonary disease.[10,11,17,18] Approval to use MARS-5 was obtained from the developer.

MARS-5 comprises 5 questions pertaining to “forgetting”, “changing of dosages”, “stopping”, “skipping” and “using medication less than what is prescribed”. Study subjects indicate the frequency (“always”, “often”, “sometimes”, “rarely”, or “never”) for each question, with ascending score from “always” (1 point) to “never” (5 points). Scores for each of the 5 questions are aggregated to give the final score which ranged from 5 to 25 points. A total score of less than 25 points is defined as low adherence to the respective medication.

In addition to MARS-5, the questionnaire also obtained data on the subject’s demographic characteristics (age, gender, sex, marital status, education level, type of housing) and their modes of daily OHA administration. Clinical information were retrieved back-end from subjects’ electronic medical records, including co-morbidities, diabetes related complications, latest glycated haemoglobin (HbA1c) levels, and their other chronic medications.

Definition of low Medication Adherence

A subject treated with multiple OHA and attained a MARS-5 score of 24 and below for any OHA would be regarded as having low MA, even if the respective scores for the other OHA were 25.

Data management and statistical analysis

The data management officer in the investigator team organised, audited and anonymised the data before handling the data set to the biostatistician for data analysis. Data were analysed with the aid of SPSS version 22 (Statistical Package

for the Social Sciences). Descriptive statistics were computed and were expressed as mean with standard deviation (SD) for continuous variables with normal distribution and as median (inter-quartile range: Q1-3) for non-parametric variables. Factors associated with low MA were analysed with univariate analysis, followed by multiple logistic regression analysis, with the relationships reflected in odds ratio (OR) at 95% confidence interval (95% CI) and *p* value of <0.05 was considered statistically significant.

RESULTS

Demographic characteristics of the study population

A total of 382 patients with T2DM participated in this study. The demographic and clinical characteristic of the patients are shown in Table 1. The mean ± SD age of the patients was 62 ± 10.4 years with slight female predominance (53.4%). The majority of the patients were married (77.5%), attained minimally secondary education (60.5%), residing in public housing (94.2%) and managed the medication on their own (94.2%). 44.8% of them had at least one T2DM-related microvascular complication. Their median HbA1c was 7.2% (Q1-Q3: 6.6-7.9%).

Patients were prescribed with an average of 2 OHA (Q1-Q3: 1-2) and majority were prescribed with 5 or more medication for the daily treatment of all their chronic diseases (63.3%). 66.5% of patients had at least 2 other chronic diseases.

Table 1: Demographic characteristics of the study population

	Total	Adherent MARS-5=25	Low MA MARS-5 < 25	p-value
Total	382 (100.0)	164 (42.9)	218 (57.1)	
Age, Mean (SD)	62 (10.4)	63.6 (10.1)	60.4 (10.3)	<0.01*
Gender				0.17
Female	204 (53.4)	81 (39.7)	123 (60.3)	
Male	178 (46.6)	83 (46.6)	95 (53.4)	

Ethnicity				0.02*
Chinese	282 (73.8)	108 (38.3)	174 (61.7)	
Malay	36 (9.4)	19 (52.8)	17 (47.2)	
Indian	59 (15.4)	34 (57.6)	25 (42.4)	
Others	5 (1.3)	3 (60)	2 (40)	
Marital status				0.02*
Single	36 (9.4)	13 (36.1)	23 (63.9)	
Married	296 (77.5)	127 (42.9)	169 (57.1)	
Divorced/Separated	16 (4.2)	3 (18.8)	13 (81.3)	
Widowed	34 (8.9)	21 (61.8)	13 (38.2)	
Highest education				0.38
Up to primary level	151 (39.5)	69 (45.7)	82 (54.3)	
Secondary and above	231 (60.5)	95 (41.1)	136 (58.9)	
Type of Housing				0.99
Public housing	354 (92.7)	152 (42.9)	202 (57.1)	
Condo or Private apartment/ Landed property	28 (7.3)	12 (42.9)	16 (57.1)	
Mode of administration of medication				0.04*
Self-medication	360 (94.2)	150 (41.7)	210 (58.3)	
Assisted by family member or domestic	22 (5.8)	14 (63.6)	8 (36.4)	

helper				
Number of diabetic medications, Median (IQR)	2 (1-2)	2 (1-2)	2 (1-2)	0.08
Total number of regular/daily medications				0.04*
5 or more	243 (63.6)	114 (46.9)	129 (53.1)	
Up to 4	139 (36.4)	50 (36)	89 (64)	
Number of other chronic diseases (co-morbidities)				0.19
3 or more	128 (33.5)	61 (47.7)	67 (52.3)	
Up to 2	254 (66.5)	103 (40.6)	151 (59.4)	
Any diabetic complications				0.25
Yes	171 (44.8)	79 (46.2)	92 (53.8)	
No	211 (55.2)	85 (40.3)	126 (59.7)	
HbA1c, Median (IQR)	7.2 (6.6-7.9)	7 (6.5-7.7)	7.3 (6.7-8.2)	0.01*

*Diabetic complications include nephropathy, retinopathy and neuropathy

#Chronic diseases include hypertension, hyperlipidaemia, ischemic heart disease, stroke, chronic renal failure, obesity, depression, gout, anaemia, asthma, Hypothyroidism

Medication adherence and associated factors

The median MARS-5 score was 24 with the interquartile range between 23 and 25. 57.1% of the study population had MARS-5 score of less than 25 for at least one OHA. (Table 1) Patients who were younger, of Chinese ethnicity, married or windowed, taking their medications on their own and were taking fewer (4 or less) daily medications tended to be less adherent to their OHA. Those who were older, married or widowed, assisted by family members or domestic helper in their medications or were taking 5 or more daily medications seemed to be more adherent to their OHA. Patients who were non-adherent to their OHA had poorer glycaemic control, as reflected in their higher median HbA1c level.

Logistic regression revealed that patients of the younger age group, Chinese ethnicity and poorer glycaemic control (HbA1c) were associated with low MA to OHA. (Table 3)

Table 3. Logistic regression on factors influencing MA to OHA

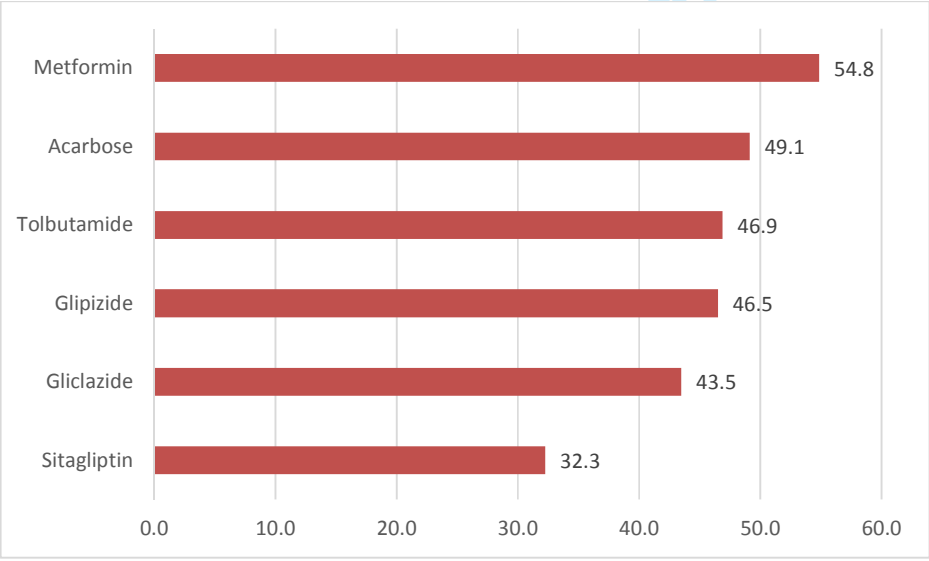
	Low MA (OR , 95% CI)	p-value
Age	0.97 (0.95, 0.997)	0.03*
Ethnicity		
Indian	Reference	-
Chinese	2.80 (1.53, 5.15)	<0.01*
Malay	1.24 (0.52, 2.97)	0.63
Others	1.05 (0.15, 7.50)	0.96
Marital status		
Single	Reference	-
Married	0.95 (0.44, 2.06)	0.89
Divorced/Separated	3.20 (0.73, 14.1)	0.12
Widowed	0.79 (0.26, 2.40)	0.68

Administration of medication		
Self-medication	Reference	-
Assisted by family member or domestic helper	0.47 (0.19, 1.22)	0.12
Total number of daily/regular medications		
Up to 4	Reference	-
5 or more	0.76 (0.48, 1.21)	0.24
HbA1c	1.27 (1.06, 1.51)	0.01*

Low medication adherence to specific oral hypoglycaemic agent

Chart 1 showed the highest low MA amongst patients to Biguanides (54.8%), followed by AGI (Acarbose 49.1%), Sulfonylurea (Tolbutamide 46.9%, Glipizide 46.5%, Gliclazide 43.5%), and DPP4 (Sitagliptin 32.3%).

Chart 1: Low medication adherence to specific OHA*



*Patients could be treated with more than one OHA.

DISCUSSION

This study found that 57.1% of the study population had low MA to at least one of their OHA, reflected in a MARS-5 score of less than 25. The result is comparable to other studies in developed communities with low MA ranging from 56.2% to 61.8% using MARS-5 with similar cut-off points.[8,19]

More younger patients had lower MA to OHA. As they were more likely to be employees, their working hours could have interfered with their MA. Consequently, their glycaemic control was suboptimal: their HbA1c was higher by 27% (Table 3). This observation corresponded to the results in another local primary care study which also showed that younger patients tended to have poorer glycaemic control.[20]

Patients who were single, divorced or separated were less adherent to their OHA, compared to those who were married or widowed. DiMatteo MR in his meta-analysis also reported that MA was higher in patients from cohesive families.[21] Family support is vital in the care of patients with long term illnesses, including their MA. Family members or domestic helper could help to remind the patient of their medication schedule, which reinforce MA (Table 1).

Patients of Chinese ethnicity were more than twice likely to have low MA to OHA compared to those of the other minority ethnic group. Ethnic variation in MA will be explored in a sequel to this study using qualitative research method to probe the context and reasons for this ethnic difference.

The educational level of patients and their socioeconomic status, as reflected by their housing types as a proxy, did not seem to be associated with MA. Jin J et al in their meta-analysis had alluded to the equivocal effect of education level on MA.[4]

The total number of regular medications (OHA and other long term medications) consumed daily did not seem to impact on their medication adherence to OHA. Grant RW et al had similarly revealed the lack of association between the number of chronic medications and their MA.[22]

Biguanide (Metformin) and AGI (Acarbose) were associated with higher proportions of low MA compared to the various Sulfonylureas and Sitagliptin. Donnan et al. found that low MA was associated with Metformin compared to Sulfonylurea.[23] Metformin and AGI are often prescribed in multiple daily doses and are thus susceptible to risk of dose omission. A study done by Peas et al reported that once daily regimes led to higher MA than twice or more daily regime.[24] Furthermore, both Metformin and Acarbose have higher incidences of adverse gastrointestinal effects, which could affect their adherence to these two medications.[25,26] In contrast, the once daily regime of DPP4 (such as Sitagliptin) showed a more favourable adherence rate compared to other multi-dose OHA. When DPP4 is part of the polytherapy, this class of medication showed better MA than Sulphonyureas (SU) and Thiazolidinediones (TZD).[27]

This study highlighted the strong association between MA and glycemic status, after adjustment of confounding factors. Patients with low MA to OHA had higher Hba1c level (median 7.3%, Q1-Q3: 6.7-8.2%) compared to those who adhered to their OHA (median 7%, Q1-Q3: 6.5-7.7%). The findings were similar in other studies.[9,13,28,29]

Whilst there was no association between MA and multiple morbidities, nor was it associated with the presence of T2DM related complications, a longitudinal study design would be more ideal to determine such relationship.

LIMITATIONS

Measurement of MA can be challenging in clinical practice. There is no single measure which can be referred to as the gold standard. A mix-method is perceived to be the most effective way in estimating MA.[30] However, self-reported screening is practical, easy to implement and inexpensive. A study done by McAdam-Marx C et al. showed that MARS-5 was comparable to the more complicated method using modified medication possession ratio (mMPR) which calculates adherence as the total days supplied divided by the number of days from the first claim to the last claim plus the days supplied on the last claim.[9]

Reliance on self-reporting by patients to measure their medication adherence could potentially underestimate the problem. Technology-based tools such as automated counter installed in pill containers have been developed as alternative mode of assessment but the use of such devices can likewise be fraudulent and may not accurately reflect the actual MA.[31]

The case-encounter sampling method employed in this study may restrict the extrapolation of the results to the general population. However this sampling technique is fast, convenient to be implemented at the study site, where targeted subjects are readily available in the busy polyclinic. The medication non-adherence rate from this study will provide a better estimate for sample size computation for a larger ethnicity-stratified community study using epidemiological approach in the near future.

CONCLUSION

Younger patients with T2DM and of Chinese ethnicity were susceptible to low MA. The resultant poorer glycaemic control subjected them to risks of T2DM related complications. The use of sustained-release, once-daily OHA and engaging the family to facilitate MA could potentially alleviate the problem but these measures await evaluation in future studies.

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Conflicts of interest disclosure

None

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Abbreviations

T2DM: Type 2 diabetes mellitus; MARS-5: 5-item Medication Adherence Report Scale; MA: Medication adherence; OHA: oral hypoglycaemia agents; MMAS: Morisky Medication Adherence Scale; CIRB: Centralized Institutional Review Board; SPSS: Statistical Package for the Social Sciences; Q1-3: Lower-Upper quartiles; SD: Standard deviation; OR: Odds ration; CI: Confidence interval.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	
5Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6/7
		(*b*) Describe any methods used to examine subgroups and interactions	6/7
		(*c*) Explain how missing data were addressed	Not applicable as no missing data in this study

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12/13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13/14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Assessing oral medication adherence amongst patients with type 2 diabetes mellitus treated with polytherapy in a developed Asian community: a cross-sectional study

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Keywords:	Type 2 Diabetes Mellitus,, Medication Adherence, oral hypoglycemic agent, polytherapy

TITLE PAGE

Title

Assessing oral medication adherence amongst patients with type 2 diabetes mellitus treated with polytherapy in a developed Asian community: a cross-sectional study

Authors

Cia Sin, LEE[1]

Hwee Mian Jane, TAN[1]

Sankari Usha[1]

Yi Ling Eileen, KOH[1]

Ngiap Chuan, TAN[1,2]

[1]SingHealth Polyclinics, Singapore

[2]Duke-NUS Medical School, Singapore

Corresponding author

Cia Sin Lee;

Singhealth Polyclinics – Sengkang,

Sengkang Square, #01-04,

Singapore 54025

Email: lee.cia.sin@singhealth.com.sg

Tel: (65) 6315 3501

ABSTRACT

Objectives:

The disease burden of type 2 diabetes mellitus (T2DM) is rising due to prevalent suboptimal glycemic control leading to vascular complications. Medication adherence (MA) directly influences glycemia control and clinical consequences. This study aimed to assess the MA of patients with T2DM and identify its associated factors.

Design:

Data analysis from a cross-sectional survey and electronic medical record.

Setting:

Primary care outpatient clinic, Singapore

Participants:

Adult patients with type 2 diabetes mellitus.

Main outcome measures:

Medication adherence to each prescribed oral hypoglyceamia agents (OHA) was measured using the 5-questions Medication Adherence Report Scale (MARS-5). Low MA is defined as MARS-R score of <25. Demographic data, clinical characteristics, and investigation results were collected to identify factors that are associated with low MA.

Results:

The study population comprised 382 patients with slight female predominance (53.4%) and mean (SD) age of 62.0±10.4 years. 57.1% of them had low MA to at least one OHA. Univariate analysis showed that patients who were younger, of Chinese ethnicity, married or windowed, self-administering their medications and were taking fewer (4 or less) daily medications tended to have low MA to OHA. Logistic regression revealed that younger age (OR=0.97; 95%CI:0.95, 0.99), Chinese ethnicity (OR=2.80; 95%CI:1.53, 5.15) and poorer glycaemic control (HbA1c) [OR=1.27; 95%CI:1.06, 1.51] were associated with low MA to OHA respectively.

Conclusions:

Younger patients with T2DM and of Chinese ethnicity were susceptible to low MA to OHA, which were associated with poorer glycaemic control. Polytherapy was not associated with low MA.

Keywords: Type 2 Diabetes Mellitus, Medication Adherence, oral hypoglycemic agent, polytherapy

Strength and limitation of this study

- This study used a simple 5 item questionnaire to measure medication adherence amongst patients with type 2 diabetes mellitus on pharmacotherapy
- The medication adherence assessment of multiple oral hypoglycemic agents used to treat type 2 diabetes mellitus using a common scale in a single patient is novel.
- The case-encounter sampling method employed in this study may restrict the extrapolation of the results to the general population.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disease with staggering increase in prevalence and disease burden globally.[1] One of these countries, which reported this spiral rise in prevalence is Singapore, a developed nation with a mature healthcare system serving a population of increasing longevity. [2] Gravely, increasing numbers of the local multi-ethnic Asian population on the island-state are suffering from T2DM and associated complications over longer life spans. As in June 2016, Chinese formed 74.3% of the resident population in Singapore, followed by Malays and Indian at 13.4% and 9.1% respectively.[3] Singapore is thus a favorable microcosm to study the impact of T2DM on the community as most of the patients have access to treatment in primary care. 45% of them are currently treated in local public primary care clinics, where medications for diabetic treatment are dispensed to patients from the in-house pharmacies conveniently at subsidized costs.[2]

While medical treatment is readily available to manage the disease in primary care in Singapore, glycaemic control remains suboptimal in 32% of local patients with T2DM .[2] The mean HbA1c of patients with T2DM in a primary care clinic was 7.7% (SD 1.7%) in a recent cohort study.[4] To achieve glycaemic control, patients are prescribed multiple oral hypoglycemic agents (OHA) and add on insulin therapy in the context of the natural progression of the disease. Aside from polytherapy, medication adherence (MA) directly influences the glycemic control and clinical consequences. Factors associated with MA tend to be complex due to the interaction between patient, physician, healthcare team and medication factors.[5]

Measurement of MA can be assessed in several ways but using questionnaires and scales is easier to integrate into clinical practice.[6-8] Instruments, such as the 5-item Medication Adherence Report Scale (MARS-5) or the 4- or 8-item Morisky Medication Adherence Scale (MMAS) have been used to assess MA.[9-12] These scales rely on subjects to self-report their adherence to specific medication.

Earlier studies have reported low MA to single oral hypoglycaemia agents (OHA) but the rate varied from 36% to 42% pending on the OHA.[13,14] The MA assessment becomes more complicated if a patient is on polytherapy or combination therapy with several oral medications to curb dysglycemia. Little research has been carried out to assess MA amongst patients on polytherapy to achieve disease control. A systematic review has just commenced to address the issue and no aggregated

instrument has been developed for such assessment.[15] This is further complicated if patients are taking concurrent medications for the treatment of other co-morbidities.

One approach is to determine the MA for each of the OHA prescribed to the individual patient on polytherapy. We hypothesized that patients with T2DM differed in their MA to each of their prescribed OHA if they were on polytherapy. For optimal glycaemic control, it is important to understand the MA to specific class of OHA, so that appropriate measure can be introduced to address the reason for low adherence. Cappocia K et al reported low MA was associated with poor tolerance to medication, frequency of administration beyond twice daily and perverse views about the importance of medication.[16] A local study by Joanne Quah et al revealed that poor adherence to medications was more prevalent amongst younger patients with type 2 diabetes mellitus.[17] Hence, we postulated that demographic and medication related factors could be associated with MA in diabetic treatment.

Therefore, the main objective of this study was to determine the MA of patients with T2DM to their specific OHA using the MARS-5 scale as the primary clinical outcome. This study also aimed to identify the demographic and medication-related factors influencing their MA in association with their glycaemic control.

METHOD

Study site

A questionnaire survey was administered to patients with T2DM treated with OHA in primary care. The survey was carried out at a typical public primary care clinic (polyclinic) located in SengKang, an estate located in the north eastern region of Singapore. The polyclinic serves a population of over 316,000 multi-ethnic Asian residents living in both SengKang and neighbouring Punggol estates, covering an area of about 20 square kilometres.[18] About 9000 patients with T2DM are being followed up at the polyclinic.

Study Population

Inclusion criteria:

The targeted patients are those with known T2DM, as affirmed from their electronic medical records at the study site. They included those with age between 35 to 84 years, both gender, multi-ethnicity and were followed up at the study site for at least two visits over a minimal period of 6 months.

The subjects were treated with one or more OHA, and included those with medications for the management of other co-morbidities. The OHA included the Sulphonyurea (largely tolbutamide, glipizide and gliclazide), Biguanides (Metformin), Alpha-Glucosidase Inhibitors (AGI such as Acarbose) and Dipeptidyl Peptidase-4 Inhibitor (DPP4, such as Sitagliptin).

Each subject had a minimum of one glycated haemoglobin (HBA1c) as an indicator of their glycaemic control in the past 6 months.

Exclusion criteria:

Patients who were on dietary control alone or were on any form of insulin therapy, and/or with intellectual or cognitive impairment as stated in electronic medical record, were excluded.

Recruitment procedure

Potential subjects were screened by multiple trained research assistants and polyclinic nurses for eligibility for enrolment into this survey. They were recruited on a case-encounter basis between June 2015 and March 2016. The study site comprised of a three-storey polyclinic with consultation rooms at level two and three. Patients could move liberally between the three levels to access various service points, such as diabetic eye and feet screening and laboratory services When these subjects were waiting for these services, they were approached by the research assistants and study team members and were provided with information on the study protocol using the approved Patient Information Sheet. Their written consent was obtained after their queries were clarified. Next they filled the questionnaire, assisted by the research assistant. They were shown pictograms of their OHA as references when they used the MARS-5 scale for each OHA.

Sample size calculation

Based on a low MA rate of 36% from a Malaysian study [14] which has a similar multi-ethnic Asian population, the sample size was computed using a confidence interval of 5% and study power of 95%. Therefore, an estimated sample of 342 eligible subjects would be needed for this study. To allow a withdrawal rate of 10%, the investigator team planned to recruit a total of 380 patients.

Instrument

Existing scales measure adherence to a single specific medication. However, patients with T2DM are often treated with more than one medication to control the hyperglycaemia. Low MA may be specific to a single medication or across multiple medications. To investigate the MA to multiple medications, the scale must be simple, validated, reliable and easy to implement as it has to be repeated for each medication.

The investigators have selected the Medication Adherence Report Scale (MARS-5) in view of its ease of application. The MARS-5 was developed by Horne[19] and has

been widely used in studies in a variety of chronic illnesses, including T2DM, hypertension and chronic obstructive pulmonary disease.[11,12,20,21] MARS-5 demonstrated acceptable internal consistency with Cronbach alpha of 0.77.[22] This is first study conducted in Asia using MARS-5 to measure medication adherence in patient with T2DM. Approval to use MARS-5 was obtained from the developer.

MARS-5 comprises 5 questions pertaining to "forgetting", "changing of dosages", "stopping", "skipping" and "using medication less than what is prescribed". Study subjects indicate the frequency ("always", "often", "sometimes", "rarely", or "never") for each question, with ascending score from "always" (1 point) to "never" (5 points). Scores for each of the 5 questions are aggregated to give the final score which ranged from 5 to 25 points. A total score of less than 25 points is defined as low adherence to the respective medication. MARS-5 is administered to each OHA to measure the comparison of MA across different type of OHA.

In addition to MARS-5, the questionnaire also obtained data on the subject's demographic characteristics (age, gender, sex, marital status, education level, type of housing) and their modes of daily OHA administration. MARS-5 and questionnaire on demographic characteristic were self-administered by the subjects or their family member. Clinical information was retrieved back-end from subjects' electronic medical records, including co-morbidities, diabetes related complications, latest glycated haemoglobin (HbA1c) levels, and their other chronic medications.

Definition of low Medication Adherence

A subject treated with multiple OHA and attained a MARS-5 score of 24 and below for any OHA would be regarded as having low MA, even if the respective scores for the other OHA were 25.

Data management and statistical analysis

The data management officer in the investigator team organised, audited and anonymised the data before handling the data set to the biostatistician for data analysis. Data were analysed with the aid of SPSS version 22 (Statistical Package for the Social Sciences). Descriptive statistics were computed and were expressed as mean with standard deviation (SD) for continuous variables with normal distribution and as median (inter-quartile range: Q1-3) for non-parametric variables. Factors that potentially associated with low MA (age, gender, ethnicity, marital status, education level, type of housing, mode of administration of medication, number of diabetic medication, total number of regular daily medications, number of other chronic diseases, association of any diabetic complication and HbA1c level were analysed with univariate analysis in which chi square or fisher exact test were used for categorical variables and mann whitney U test or independent t-test for

continuous variables. Factors shown to be statistically significant in the univariate analysis were included in the multiple logistic regression analysis, with the relationships reflected in odds ratio (OR) at 95% confidence interval (95% CI) and *p* value of <0.05 was considered statistically significant.

Ethical approval

This study was approved by the SingHealth Centralized Institutional Review Board (CIRB approval number: 2015/2062).

RESULTS

Demographic characteristics of the study population

A total of 382 patients with T2DM participated in this study. The demographic and clinical characteristic of the patients are shown in Table 1. The mean ± SD age of the patients was 62 ± 10.4 years with slight female predominance (53.4%). The majority of the patients were married (77.5%), attained minimally secondary education (60.5%), residing in public housing (94.2%) and managed the medication on their own (94.2%). 44.8% of them had at least one T2DM-related microvascular complication. Their median HbA1c was 7.2% (Q1-Q3: 6.6-7.9%).

Patients were prescribed with an average of 2 OHA (Q1-Q3: 1-2), and majority were prescribed with 5 or more medications for the daily treatment of all their chronic diseases (63.3%). 66.5% of patients had at least 2 other chronic diseases.

Table 1: Demographic characteristics of the study population

	Total	Adherent MARS-5=25	Low MA MARS-5 < 25	p-value
Total	382 (100.0)	164 (42.9)	218 (57.1)	
Age, Mean (SD)	62 (10.4)	63.6 (10.1)	60.4 (10.3)	<0.01*

Gender				0.17
Female	204 (53.4)	81 (39.7)	123 (60.3)	
Male	178 (46.6)	83 (46.6)	95 (53.4)	
Ethnicity				0.02*
Chinese	282 (73.8)	108 (38.3)	174 (61.7)	
Malay	36 (9.4)	19 (52.8)	17 (47.2)	
Indian	59 (15.4)	34 (57.6)	25 (42.4)	
Others	5 (1.3)	3 (60)	2 (40)	
Marital status				0.02*
Single	36 (9.4)	13 (36.1)	23 (63.9)	
Married	296 (77.5)	127 (42.9)	169 (57.1)	
Divorced/Separated	16 (4.2)	3 (18.8)	13 (81.3)	
Widowed	34 (8.9)	21 (61.8)	13 (38.2)	
Highest education				0.38
Up to primary level	151 (39.5)	69 (45.7)	82 (54.3)	
Secondary and above	231 (60.5)	95 (41.1)	136 (58.9)	
Type of Housing				0.99
Public housing	354 (92.7)	152 (42.9)	202 (57.1)	
Condo or Private apartment/ Landed property	28 (7.3)	12 (42.9)	16 (57.1)	
Mode of administration of medication				0.04*

Self-medication	360 (94.2)	150 (41.7)	210 (58.3)	
Assisted by family member or domestic helper	22 (5.8)	14 (63.6)	8 (36.4)	
Number of diabetic medications, Median (IQR)	2 (1-2)	2 (1-2)	2 (1-2)	0.08
Total number of regular daily medications				0.04*
5 or more	243 (63.6)	114 (46.9)	129 (53.1)	
Up to 4	139 (36.4)	50 (36)	89 (64)	
Number of other chronic diseases (co-morbidities)				0.19
3 or more	128 (33.5)	61 (47.7)	67 (52.3)	
Up to 2	254 (66.5)	103 (40.6)	151 (59.4)	
Any diabetic complications				0.25
Yes	171 (44.8)	79 (46.2)	92 (53.8)	
No	211 (55.2)	85 (40.3)	126 (59.7)	
HbA1c, Median (IQR)	7.2 (6.6-7.9)	7 (6.5-7.7)	7.3 (6.7-8.2)	0.01*

*Diabetic complications include nephropathy, retinopathy and neuropathy

#Chronic diseases include hypertension, hyperlipidaemia, ischemic heart disease, stroke, chronic renal failure, obesity, depression, gout, anaemia, asthma, Hypothyroidism

Medication adherence and associated factors

The median MARS-5 score was 24 with the interquartile range between 23 and 25. 57.1% of the study population had MARS-5 score of less than 25 for at least one OHA. (Table 1) Patients who were younger, of Chinese ethnicity, married or windowed, taking their medications on their own and were taking fewer (4 or less) daily medications tended to be less adherent to their OHA. Those who were older, married or widowed, assisted by family members or domestic helper in their medications or were taking 5 or more daily medications seemed to be more adherent to their OHA. Patients who were non-adherent to their OHA had poorer glycaemic control, as reflected in their higher median HbA1c level.

Logistic regression revealed that patients of the younger age group, Chinese ethnicity and poorer glycaemic control (HbA1c) were associated with low MA to OHA. (Table 2)

Table 2. Logistic regression on factors influencing MA to OHA

	Low MA (OR , 95% CI)	p-value
Age	0.97 (0.95, 0.997)	0.03*
Ethnicity		
Indian	Reference	-
Chinese	2.80 (1.53, 5.15)	<0.01*
Malay	1.24 (0.52, 2.97)	0.63
Others	1.05 (0.15, 7.50)	0.96
Marital status		
Single	Reference	-
Married	0.95 (0.44, 2.06)	0.89
Divorced/Separated	3.20 (0.73, 14.1)	0.12
Widowed	0.79 (0.26, 2.40)	0.68

Administration of medication		
Self-medication	Reference	-
Assisted by family member or domestic helper	0.47 (0.19, 1.22)	0.12
Total number of daily/regular medications		
Up to 4	Reference	-
5 or more	0.76 (0.48, 1.21)	0.24
HbA1c	1.27 (1.06, 1.51)	0.01*

Medication adherence to specific oral hypoglycaemic agent

Figure 1 showed the highest MA amongst patients to DPP4 (Sitagliptin 367.7%)followed by Sulfonylurea (Gliclazide 56.5%, Glipizide 53.5% and Tolbutamide 53.1%), AGI (Acarbose 50.1%), and Biguanides (45.2%)

DISCUSSION

This study found that 57.1% of the study population had low MA to at least one of their OHA, reflected in a MARS-5 score of less than 25. The result is comparable to other studies in developed communities with low MA ranging from 56.2% to 61.8% using MARS-5 with similar cut-off points.[9,23]

Younger patients had lower MA to OHA. As they were more likely to be employees, their working hours could have interfered with their MA. Consequently, their glycaemic control was suboptimal as reflected in their higher HbA1c (Table 3). This observation corresponded to the results in another local primary care study which also showed that younger patients tended to have poorer glycaemic control.[17]

Patients who were single, divorced or separated were less adherent to their OHA, compared to those who were married or widowed. DiMatteo MR in his meta-analysis also reported that MA was higher in patients from cohesive families.[24] Family support is vital in the care of patients with long term illnesses, including their MA. Family members or domestic helper could help to remind the patient of their medication schedule, which reinforce MA (Table 1).

Patients of Chinese ethnicity were more than twice likely to have low MA to OHA compared to those of the other minority ethnic group. Ethnic variation in MA will be explored in a sequel to this study using qualitative research method to probe the context and reasons for this ethnic difference.

The educational level of patients and their socioeconomic status, as reflected by their housing types as a proxy, did not seem to be associated with MA. Jin J et al in their meta-analysis had alluded to the equivocal effect of education level on MA.[5]

The total number of regular medications (OHA and other long term medications) consumed daily did not seem to impact on their medication adherence to OHA. Grant RW et al had similarly revealed the lack of association between the number of chronic medications and their MA.[25]

Biguanide (Metformin) and AGI (Acarbose) were associated with higher proportions of low MA compared to the various Sulfonylureas and Sitagliptin. Donnan et al. found that low MA was associated with Metformin compared to Sulfonylurea.[26] Metformin and AGI are often prescribed in multiple daily doses and are thus susceptible to risk of dose omission. A study done by Peas et al reported that once daily regimes led to higher MA than twice or more daily regime.[27] Furthermore, both Metformin and

Acarbose have higher incidences of adverse gastrointestinal effects, which could affect their adherence to these two medications.[28,29] In contrast, the once daily regime of DPP4 (such as Sitagliptin) showed a more favourable adherence rate compared to other multi-dose OHA. When DPP4 is part of the polytherapy, this class of medication showed better MA than Sulphonyureas (SU) and Thiazolidinediones (TZD).[30]

This study highlighted the strong association between MA and glycemic status, after adjustment of confounding factors. Patients with low MA to OHA had higher Hba1c level (median 7.3%, Q1-Q3: 6.7-8.2%) compared to those who adhered to their OHA (median 7%, Q1-Q3: 6.5-7.7%). The findings were similar in other studies.[10,14,31,32]

Whilst there was no association between MA and multiple morbidities, nor was it associated with the presence of T2DM related complications, a longitudinal study design would be more ideal to determine such relationship.

LIMITATIONS

Measurement of MA can be challenging in clinical practice. There is no single measure which can be referred to as the gold standard. A mix-method is perceived to be the most effective way in estimating MA.[33] However, self-reported screening is practical, easy to implement and inexpensive. A study done by McAdam-Marx C et al. showed that MARS-5 was comparable to the more complicated method using modified medication possession ratio (mMPR) which calculates adherence as the total days supplied divided by the number of days from the first claim to the last claim plus the days supplied on the last claim.[10]

Reliance on self-reporting by patients to measure their medication adherence could potentially underestimate the problem. Technology-based tools such as automated counter installed in pill containers have been developed as alternative mode of assessment. [34]

The lack of computation of the response rate is another limitation. It was not computed to avoid double counting as potential subjects could be approached multiple times by research assistants at different levels of the study site. The case-encounter sampling method employed in this study would restrict the extrapolation of the results to the general population. However this sampling technique is fast, convenient to be implemented at the study site, where targeted subjects are readily available in the busy polyclinic. The medication non-adherence rate from this study will provide a better estimate for sample size computation for a larger ethnicity-stratified community study using epidemiological approach in the near future.

CONCLUSION

Younger patients with T2DM and of Chinese ethnicity were susceptible to low MA. Medication-related factors were not significantly associated with MA. Low MA associated with poorer glycaemic control subjected them to risks of T2DM related complications. The use of sustained-release, once-daily OHA and engaging the family to facilitate MA could potentially alleviate the problem but these measures await evaluation in future studies.

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None

Conflicts of interest disclosure

None

Contributorship

CSL, HMJ, and TNC were involved in the conception / design of the study. YLK and SU conducted the statistical analysis. CSL and TNC drafted the manuscript. All authors approved the final version of the manuscript.

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Data sharing

No additional data are available.

Abbreviations

T2DM: Type 2 diabetes mellitus; MARS-5: 5-item Medication Adherence Report Scale; MA: Medication adherence; OHA: oral hypoglycaemia agents; MMAS: Morisky Medication Adherence Scale; CIRB: Centralized Institutional Review Board; SPSS: Statistical Package for the Social Sciences; Q1-3: Lower-Upper quartiles; SD: Standard deviation; OR: Odds ration; CI: Confidence interval.

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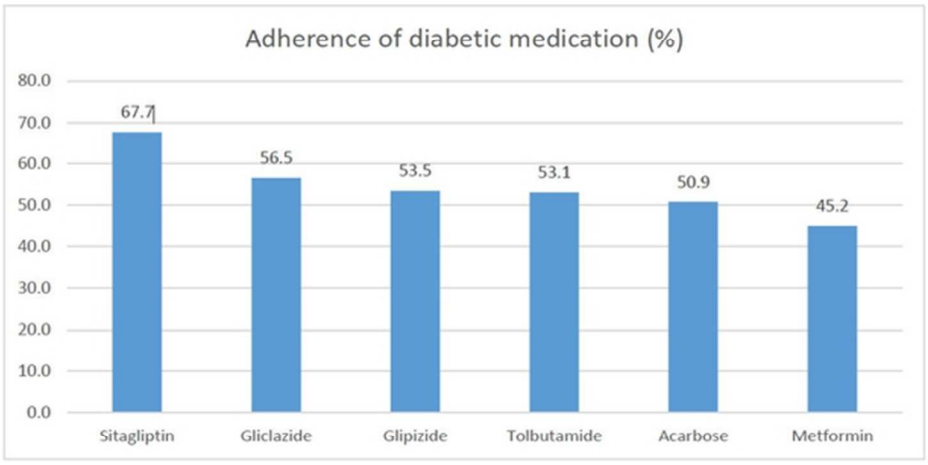
Figure 1: Percentage of Medication adherence to specific OHA*



*Patients could be treated with more than one OHA.

55x33mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	
5Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	15
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	Not applicable as no missing data in this study

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	7-8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15-16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Assessing oral medication adherence amongst patients with type 2 diabetes mellitus treated with polytherapy in a developed Asian community: a cross-sectional study

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TITLE PAGE

Title

Assessing oral medication adherence amongst patients with type 2 diabetes mellitus treated with polytherapy in a developed Asian community: a cross-sectional study

Authors

Cia Sin, LEE[1]

Hwee Mian Jane, TAN[1]

Sankari Usha[1]

Yi Ling Eileen, KOH[1]

Ngiap Chuan, TAN[1,2]

[1]SingHealth Polyclinics, Singapore

[2]Duke-NUS Medical School, Singapore

Corresponding author

Cia Sin Lee;

Singhealth Polyclinics – Sengkang,

Sengkang Square, #01-04,

Singapore 54025

Email: lee.cia.sin@singhealth.com.sg

Tel: (65) 6315 3501

ABSTRACT

Objectives:

The disease burden of type 2 diabetes mellitus (T2DM) is rising due to prevalent suboptimal glycemic control leading to vascular complications. Medication adherence (MA) directly influences glycemia control and clinical consequences. This study aimed to assess the MA of patients with T2DM and identify its associated factors.

Design:

Data analysis from a cross-sectional survey and electronic medical record.

Setting:

Primary care outpatient clinic, Singapore

Participants:

Adult patients with type 2 diabetes mellitus.

Main outcome measures:

Medication adherence to each prescribed oral hypoglyceamia agents (OHA) was measured using the 5-questions Medication Adherence Report Scale (MARS-5). Low MA is defined as MARS-R score of <25. Demographic data, clinical characteristics, and investigation results were collected to identify factors that are associated with low MA.

Results:

The study population comprised 382 patients with slight female predominance (53.4%) and mean (SD) age of 62.0±10.4 years. 57.1% of them had low MA to at least one OHA. Univariate analysis showed that patients who were younger, of Chinese ethnicity, married or windowed, self-administering their medications and were taking fewer (4 or less) daily medications tended to have low MA to OHA. Logistic regression revealed that younger age (OR=0.97; 95%CI:0.95, 0.99), Chinese ethnicity (OR=2.80; 95%CI:1.53, 5.15) and poorer glycaemic control (HbA1c) [OR=1.27; 95%CI:1.06, 1.51] were associated with low MA to OHA respectively.

Conclusions:

Younger patients with T2DM and of Chinese ethnicity were susceptible to low MA to OHA, which were associated with poorer glycaemic control. Polytherapy was not associated with low MA.

Keywords: Type 2 Diabetes Mellitus, Medication Adherence, oral hypoglycemic agent, polytherapy

Strength and limitation of this study

- This study used a simple 5 item questionnaire to measure medication adherence amongst patients with type 2 diabetes mellitus on pharmacotherapy
- The medication adherence assessment of multiple oral hypoglycemic agents used to treat type 2 diabetes mellitus using a common scale in a single patient is novel.
- The case-encounter sampling method employed in this study may restrict the extrapolation of the results to the general population.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disease with staggering increase in prevalence and disease burden globally.[1] One of these countries, which reported this spiral rise in prevalence is Singapore, a developed nation with a mature healthcare system serving a population of increasing longevity. [2] Gravely, increasing numbers of the local multi-ethnic Asian population on the island-state are suffering from T2DM and associated complications over longer life spans. As in June 2016, Chinese formed 74.3% of the resident population in Singapore, followed by Malays and Indian at 13.4% and 9.1% respectively.[3] Singapore is thus a favorable microcosm to study the impact of T2DM on the community as most of the patients have access to treatment in primary care. 45% of them are currently treated in local public primary care clinics, where medications for diabetic treatment are dispensed to patients from the in-house pharmacies conveniently at subsidized costs.[2]

While medical treatment is readily available to manage the disease in primary care in Singapore, glycaemic control remains suboptimal in 32% of local patients with T2DM .[2] The mean HbA1c of patients with T2DM in a primary care clinic was 7.7% (SD 1.7%) in a recent cohort study.[4] To achieve glycaemic control, patients are prescribed multiple oral hypoglycemic agents (OHA) and add on insulin therapy in the context of the natural progression of the disease. Aside from polytherapy, medication adherence (MA) directly influences the glycemic control and clinical consequences. Factors associated with MA tend to be complex due to the interaction between patient, physician, healthcare team and medication factors.[5]

Measurement of MA can be assessed in several ways but using questionnaires and scales is easier to integrate into clinical practice.[6-8] Instruments, such as the 5-item Medication Adherence Report Scale (MARS-5) or the 4- or 8-item Morisky Medication Adherence Scale (MMAS) have been used to assess MA.[9-12] These scales rely on subjects to self-report their adherence to specific medication.

Earlier studies have reported low MA to single oral hypoglycaemia agents (OHA) but the rate varied from 36% to 42% pending on the OHA.[13,14] The MA assessment becomes more complicated if a patient is on polytherapy or combination therapy with several oral medications to curb dysglycemia. Little research has been carried out to assess MA amongst patients on polytherapy to achieve disease control. A systematic review has just commenced to address the issue and no aggregated

instrument has been developed for such assessment.[15] This is further complicated if patients are taking concurrent medications for the treatment of other co-morbidities.

One approach is to determine the MA for each of the OHA prescribed to the individual patient on polytherapy. We hypothesized that patients with T2DM differed in their MA to each of their prescribed OHA if they were on polytherapy. For optimal glycaemic control, it is important to understand the MA to specific class of OHA, so that appropriate measure can be introduced to address the reason for low adherence. Cappocia K et al reported low MA was associated with poor tolerance to medication, frequency of administration beyond twice daily and perverse views about the importance of medication.[16] A local study by Joanne Quah et al revealed that poor adherence to medications was more prevalent amongst younger patients with type 2 diabetes mellitus.[17] Hence, we postulated that demographic and medication related factors could be associated with MA in diabetic treatment.

Therefore, the main objective of this study was to determine the MA of patients with T2DM to their specific OHA using the MARS-5 scale as the primary clinical outcome. This study also aimed to identify the demographic and medication-related factors influencing their MA in association with their glycaemic control.

METHOD

Study site

A questionnaire survey was administered to patients with T2DM treated with OHA in primary care. The survey was carried out at a typical public primary care clinic (polyclinic) located in SengKang, an estate located in the north eastern region of Singapore. The polyclinic serves a population of over 316,000 multi-ethnic Asian residents living in both SengKang and neighbouring Punggol estates, covering an area of about 20 square kilometres.[18] About 9000 patients with T2DM are being followed up at the polyclinic.

Study Population

Inclusion criteria:

The targeted patients are those with known T2DM, as affirmed from their electronic medical records at the study site. They included those with age between 35 to 84 years, both gender, multi-ethnicity and were followed up at the study site for at least two visits over a minimal period of 6 months.

The subjects were treated with one or more OHA, and included those with medications for the management of other co-morbidities. The OHA included the Sulphonyurea (largely tolbutamide, glipizide and gliclazide), Biguanides (Metformin), Alpha-Glucosidase Inhibitors (AGI such as Acarbose) and Dipeptidyl Peptidase-4 Inhibitor (DPP4, such as Sitagliptin).

Each subject had a minimum of one glycated haemoglobin (HBA1c) as an indicator of their glycaemic control in the past 6 months.

Exclusion criteria:

Patients who were on dietary control alone or were on any form of insulin therapy, and/or with intellectual or cognitive impairment as stated in electronic medical record, were excluded.

Recruitment procedure

Potential subjects were screened by multiple trained research assistants and polyclinic nurses for eligibility for enrolment into this survey. They were recruited on a case-encounter basis between June 2015 and March 2016. The study site comprised of a three-storey polyclinic with consultation rooms at level two and three. Patients could move liberally between the three levels to access various service points, such as diabetic eye and feet screening and laboratory services When these subjects were waiting for these services, they were approached by the research assistants and study team members and were provided with information on the study protocol using the approved Patient Information Sheet. Their written consent was obtained after their queries were clarified. Next they filled the questionnaire, assisted by the research assistant. They were shown pictograms of their OHA as references when they used the MARS-5 scale for each OHA.

Sample size calculation

Based on a low MA rate of 36% from a Malaysian study [14] which has a similar multi-ethnic Asian population, the sample size was computed using a confidence interval of 5% and study power of 95%. Therefore, an estimated sample of 342 eligible subjects would be needed for this study. To allow a withdrawal rate of 10%, the investigator team planned to recruit a total of 380 patients.

Instrument

Existing scales measure adherence to a single specific medication. However, patients with T2DM are often treated with more than one medication to control the hyperglycaemia. Low MA may be specific to a single medication or across multiple medications. To investigate the MA to multiple medications, the scale must be simple, validated, reliable and easy to implement as it has to be repeated for each medication.

The investigators have selected the Medication Adherence Report Scale (MARS-5) in view of its ease of application. The MARS-5 was developed by Horne[19] and has

been widely used in studies in a variety of chronic illnesses, including T2DM, hypertension and chronic obstructive pulmonary disease.[11,12,20,21] MARS-5 demonstrated acceptable internal consistency with Cronbach alpha of 0.77.[22] This is first study conducted in Asia using MARS-5 to measure medication adherence in patient with T2DM. Approval to use MARS-5 was obtained from the developer.

MARS-5 comprises 5 questions pertaining to "forgetting", "changing of dosages", "stopping", "skipping" and "using medication less than what is prescribed". Study subjects indicate the frequency ("always", "often", "sometimes", "rarely", or "never") for each question, with ascending score from "always" (1 point) to "never" (5 points). Scores for each of the 5 questions are aggregated to give the final score which ranged from 5 to 25 points. A total score of less than 25 points is defined as low adherence to the respective medication. MARS-5 is administered to each OHA to measure the comparison of MA across different type of OHA.

In addition to MARS-5, the questionnaire also obtained data on the subject's demographic characteristics (age, gender, sex, marital status, education level, type of housing) and their modes of daily OHA administration. MARS-5 and questionnaire on demographic characteristic were self-administered by the subjects or their family member. Clinical information was retrieved back-end from subjects' electronic medical records, including co-morbidities, diabetes related complications, latest glycated haemoglobin (HbA1c) levels, and their other chronic medications.

Definition of low Medication Adherence

A subject treated with multiple OHA and attained a MARS-5 score of 24 and below for any OHA would be regarded as having low MA, even if the respective scores for the other OHA were 25.

Data management and statistical analysis

The data management officer in the investigator team organised, audited and anonymised the data before handling the data set to the biostatistician for data analysis. Data were analysed with the aid of SPSS version 22 (Statistical Package for the Social Sciences). Descriptive statistics were computed and were expressed as mean with standard deviation (SD) for continuous variables with normal distribution and as median (inter-quartile range: Q1-3) for non-parametric variables. Factors that potentially associated with low MA (age, gender, ethnicity, marital status, education level, type of housing, mode of administration of medication, number of diabetic medication, total number of regular daily medications, number of other chronic diseases, association of any diabetic complication and HbA1c level were analysed with univariate analysis in which chi square or fisher exact test were used for categorical variables and mann whitney U test or independent t-test for

continuous variables. Factors shown to be statistically significant in the univariate analysis were included in the multiple logistic regression analysis, with the relationships reflected in odds ratio (OR) at 95% confidence interval (95% CI) and *p* value of <0.05 was considered statistically significant.

Ethical approval

This study was approved by the SingHealth Centralized Institutional Review Board (CIRB approval number: 2015/2062).

RESULTS

Demographic characteristics of the study population

A total of 382 patients with T2DM participated in this study. The demographic and clinical characteristic of the patients are shown in Table 1. The mean ± SD age of the patients was 62 ± 10.4 years with slight female predominance (53.4%). The majority of the patients were married (77.5%), attained minimally secondary education (60.5%), residing in public housing (94.2%) and managed the medication on their own (94.2%). 44.8% of them had at least one T2DM-related microvascular complication. Their median HbA1c was 7.2% (Q1-Q3: 6.6-7.9%).

Patients were prescribed with an average of 2 OHA (Q1-Q3: 1-2), and majority were prescribed with 5 or more medications for the daily treatment of all their chronic diseases (63.3%). 66.5% of patients had at least 2 other chronic diseases.

Table 1: Demographic characteristics of the study population

	Total	Adherent MARS-5=25	Low MA MARS-5 < 25	p-value
Total	382 (100.0)	164 (42.9)	218 (57.1)	
Age, Mean (SD)	62 (10.4)	63.6 (10.1)	60.4 (10.3)	<0.01*

Gender				0.17
Female	204 (53.4)	81 (39.7)	123 (60.3)	
Male	178 (46.6)	83 (46.6)	95 (53.4)	
Ethnicity				0.02*
Chinese	282 (73.8)	108 (38.3)	174 (61.7)	
Malay	36 (9.4)	19 (52.8)	17 (47.2)	
Indian	59 (15.4)	34 (57.6)	25 (42.4)	
Others	5 (1.3)	3 (60)	2 (40)	
Marital status				0.02*
Single	36 (9.4)	13 (36.1)	23 (63.9)	
Married	296 (77.5)	127 (42.9)	169 (57.1)	
Divorced/Separated	16 (4.2)	3 (18.8)	13 (81.3)	
Widowed	34 (8.9)	21 (61.8)	13 (38.2)	
Highest education				0.38
Up to primary level	151 (39.5)	69 (45.7)	82 (54.3)	
Secondary and above	231 (60.5)	95 (41.1)	136 (58.9)	
Type of Housing				0.99
Public housing	354 (92.7)	152 (42.9)	202 (57.1)	
Condo or Private apartment/ Landed property	28 (7.3)	12 (42.9)	16 (57.1)	
Mode of administration of medication				0.04*

Self-medication	360 (94.2)	150 (41.7)	210 (58.3)	
Assisted by family member or domestic helper	22 (5.8)	14 (63.6)	8 (36.4)	
Number of diabetic medications, Median (IQR)	2 (1-2)	2 (1-2)	2 (1-2)	0.08
Total number of regular daily medications				0.04*
5 or more	243 (63.6)	114 (46.9)	129 (53.1)	
Up to 4	139 (36.4)	50 (36)	89 (64)	
Number of other chronic diseases (co-morbidities)				0.19
3 or more	128 (33.5)	61 (47.7)	67 (52.3)	
Up to 2	254 (66.5)	103 (40.6)	151 (59.4)	
Any diabetic complications				0.25
Yes	171 (44.8)	79 (46.2)	92 (53.8)	
No	211 (55.2)	85 (40.3)	126 (59.7)	
HbA1c, Median (IQR)	7.2 (6.6-7.9)	7 (6.5-7.7)	7.3 (6.7-8.2)	0.01*

*Diabetic complications include nephropathy, retinopathy and neuropathy

#Chronic diseases include hypertension, hyperlipidaemia, ischemic heart disease, stroke, chronic renal failure, obesity, depression, gout, anaemia, asthma, Hypothyroidism

Medication adherence and associated factors

The median MARS-5 score was 24 with the interquartile range between 23 and 25. 57.1% of the study population had MARS-5 score of less than 25 for at least one OHA. (Table 1) Patients who were younger, of Chinese ethnicity, married or windowed, taking their medications on their own and were taking fewer (4 or less) daily medications tended to be less adherent to their OHA. Those who were older, married or widowed, assisted by family members or domestic helper in their medications or were taking 5 or more daily medications seemed to be more adherent to their OHA. Patients who were non-adherent to their OHA had poorer glycaemic control, as reflected in their higher median HbA1c level.

Logistic regression revealed that patients of the younger age group, Chinese ethnicity and poorer glycaemic control (HbA1c) were associated with low MA to OHA. (Table 2)

Table 2. Logistic regression on factors influencing MA to OHA

	Low MA (OR , 95% CI)	p-value
Age	0.97 (0.95, 0.997)	0.03*
Ethnicity		
Indian	Reference	-
Chinese	2.80 (1.53, 5.15)	<0.01*
Malay	1.24 (0.52, 2.97)	0.63
Others	1.05 (0.15, 7.50)	0.96
Marital status		
Single	Reference	-
Married	0.95 (0.44, 2.06)	0.89
Divorced/Separated	3.20 (0.73, 14.1)	0.12
Widowed	0.79 (0.26, 2.40)	0.68

Administration of medication		
Self-medication	Reference	-
Assisted by family member or domestic helper	0.47 (0.19, 1.22)	0.12
Total number of daily/regular medications		
Up to 4	Reference	-
5 or more	0.76 (0.48, 1.21)	0.24
HbA1c	1.27 (1.06, 1.51)	0.01*

Medication adherence to specific oral hypoglycaemic agent

Figure 1 showed the highest MA amongst patients to DPP4 (Sitagliptin 67.7%), followed by Sulfonylurea (Gliclazide 56.5%, Glipizide 53.5% and Tolbutamide 53.1%), AGI (Acarbose 50.1%), and Biguanides (45.2%)

Figure 1 Percentage of medication adherence to specific OHA*

DISCUSSION

This study found that 57.1% of the study population had low MA to at least one of their OHA, reflected in a MARS-5 score of less than 25. The result is comparable to other studies in developed communities with low MA ranging from 56.2% to 61.8% using MARS-5 with similar cut-off points.[9,23]

Younger patients had lower MA to OHA. As they were more likely to be employees, their working hours could have interfered with their MA. Consequently, their glycaemic control was suboptimal as reflected in their higher HbA1c (Table 1). This observation corresponded to the results in another local primary care study which also showed that younger patients tended to have poorer glycaemic control.[17]

Patients who were single, divorced or separated were less adherent to their OHA, compared to those who were married or widowed. DiMatteo MR in his meta-analysis also reported that MA was higher in patients from cohesive families.[24] Family support is vital in the care of patients with long term illnesses, including their MA. Family members or domestic helper could help to remind the patient of their medication schedule, which reinforce MA (Table 1).

Patients of Chinese ethnicity were more than twice likely to have low MA to OHA compared to those of the other minority ethnic group. Ethnic variation in MA will be explored in a sequel to this study using qualitative research method to probe the context and reasons for this ethnic difference.

The educational level of patients and their socioeconomic status, as reflected by their housing types as a proxy, did not seem to be associated with MA. Jin J et al in their meta-analysis had alluded to the equivocal effect of education level on MA.[5]

The total number of regular medications (OHA and other long term medications) consumed daily did not seem to impact on their medication adherence to OHA. Grant RW et al had similarly revealed the lack of association between the number of chronic medications and their MA.[25]

Biguanide (Metformin) and AGI (Acarbose) were associated with higher proportions of low MA compared to the various Sulfonylureas and Sitagliptin. Donnan et al. found that low MA was associated with Metformin compared to Sulfonylurea.[26] Metformin and AGI are often prescribed in multiple daily doses and are thus susceptible to risk of dose omission. A study done by Peas et al reported that once daily regimes led to

higher MA than twice or more daily regime.[27] Furthermore, both Metformin and Acarbose have higher incidences of adverse gastrointestinal effects, which could affect their adherence to these two medications.[28,29] In contrast, the once daily regime of DPP4 (such as Sitagliptin) showed a more favourable adherence rate compared to other multi-dose OHA. When DPP4 is part of the polytherapy, this class of medication showed better MA than Sulphonyureas (SU) and Thiazolidinediones (TZD).[30]

This study highlighted the strong association between MA and glycemic status, after adjustment of confounding factors. Patients with low MA to OHA had higher Hba1c level (median 7.3%, Q1-Q3: 6.7-8.2%) compared to those who adhered to their OHA (median 7%, Q1-Q3: 6.5-7.7%). The findings were similar in other studies.[10,14,31,32]

Whilst there was no association between MA and multiple morbidities, nor was it associated with the presence of T2DM related complications, a longitudinal study design would be more ideal to determine such relationship.

The calculated Nagelkerke R square in this study was 12.9%. Other factors which could account for the 87.1% variations in MA include costs and the side effects of medications, complexity of the medication regime, inadequate medication and diabetes-related knowledge.[33-35]

LIMITATIONS

Measurement of MA can be challenging in clinical practice. There is no single measure which can be referred to as the gold standard. A mix-method is perceived to be the most effective way in estimating MA.[36] However, self-reported screening is practical, easy to implement and inexpensive. A study done by McAdam-Marx C et al. showed that MARS-5 was comparable to the more complicated method using modified medication possession ratio (mMPR) which calculates adherence as the total days supplied divided by the number of days from the first claim to the last claim plus the days supplied on the last claim.[10]

Reliance on self-reporting by patients to measure their medication adherence could potentially underestimate the problem. Technology-based tools such as automated counter installed in pill containers have been developed as alternative mode of assessment. [37]

The lack of computation of the response rate is another limitation. It was not computed to avoid double counting as potential subjects could be approached

multiple times by research assistants at different levels of the study site. The case-encounter sampling method employed in this study would restrict the extrapolation of the results to the general population. However this sampling technique is fast, convenient to be implemented at the study site, where targeted subjects are readily available in the busy polyclinic. The medication non-adherence rate from this study will provide a better estimate for sample size computation for a larger ethnicity-stratified community study using epidemiological approach in the near future.

CONCLUSION

Younger patients with T2DM and of Chinese ethnicity were susceptible to low MA. Medication-related factors were not significantly associated with MA. Low MA associated with poorer glycaemic control subjected them to risks of T2DM related complications. The use of sustained-release, once-daily OHA and engaging the family to facilitate MA could potentially alleviate the problem but these measures await evaluation in future studies.

Funding sources

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Conflicts of interest disclosure

None

Contributorship

CSL, HMJ, and TNC were involved in the conception / design of the study. YLK and SU conducted the statistical analysis. CSL and TNC drafted the manuscript. All authors approved the final version of the manuscript.

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Data sharing

No additional data are available.

Abbreviations

T2DM: Type 2 diabetes mellitus; MARS-5: 5-item Medication Adherence Report Scale; MA: Medication adherence; OHA: oral hypoglycaemia agents; MMAS: Morisky Medication Adherence Scale; CIRB: Centralized Institutional Review Board; SPSS: Statistical Package for the Social Sciences; Q1-3: Lower-Upper quartiles; SD: Standard deviation; OR: Odds ration; CI: Confidence interval.

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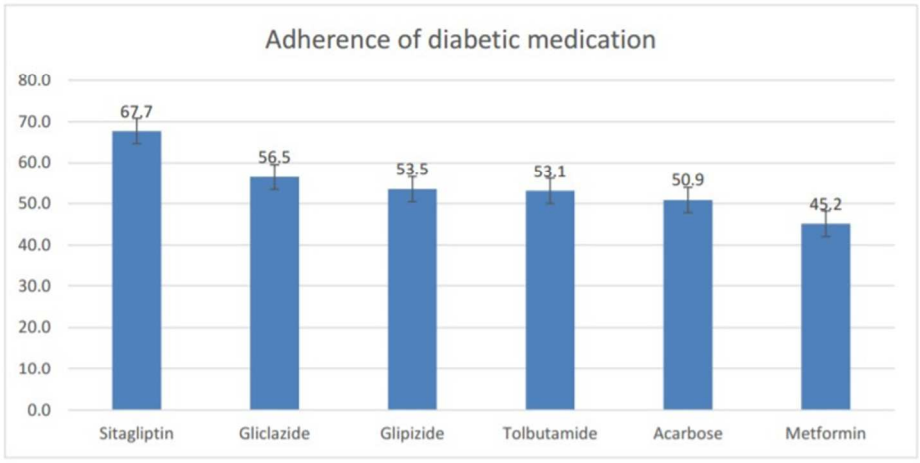
Figure 1: Percentage of Medication adherence to specific OHA*



*Patients could be treated with more than one OHA.

Figure 1: Percentage of medication adherence to specific OHA*

69x47mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	
5Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	15
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	Not applicable as no missing data in this study

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	7-8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15-16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.