PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pharmacist Intervention for Glycemic Control in the Community (The RxING study)
AUTHORS	Al Hamarneh, Yazid; Charrois, Theresa; Lewanczuk, Richard; Tsuyuki, Ross

VERSION 1 - REVIEW

REVIEWER	Professor Ines Krass Faculty of Pharmacy University of Sydney I have no competing interests - I have not previously collaborated with the authors
REVIEW RETURNED	11-Jun-2013

THE STUDY	The absence of a control or comparison group undermines the strength of evidence provided by the study. Why was this a single group study? This needs justification. The exclusion criteria are extensive and it is unclear how some of these criteria were determined. For example was a cognitive assessment conducted? How did the pharmacist access information on any psychiatric diagnosis? How was the serum creatinine measurement obtained? Were the tests ordered by pharmacists? Why was there no measure of HRQoL or a diabetes specific HRQoL? Page 8 lines 27-29 state that “The intervention also included patient education regarding insulin use, dose titration and self-monitoring. This is very scant information – how was this education conducted what training were the pharmacists given to equip them to educate patients about SMBG? For the example were all or some of the pharmacists already accredited diabetes educators? If they were not how were they educated to ensure consistency of instruction for patients. Sample size: what was the rationale for choosing an effect size of 0.4% reduction in HbA1C? Previous studies have shown that with the introduction of insulin – much higher reductions in A1C are achieved.
RESULTS & CONCLUSIONS	It is unclear whether it was the pharmacist and/or GP who initiated the changes to oral medication therapy – if it is unknown whether some changes were made by the GP this should be acknowledged as a limitation.
GENERAL COMMENTS	Thank you for the opportunity to review this novel intervention trial using community pharmacists to introduce and manage basal insulin therapy for patients with suboptimal glycaemic control. The study highlights the opportunities offered by expansion in the scope of pharmacists practice in some Canadian provinces i.e., granting of

	prescribing rights for credentialed pharmacists. The article is generally well written and presents some preliminary evidence for the benefits of the community pharmacist's role in the intensification of diabetes therapy. However the absence of a control or comparison group undermines the strength of this evidence. I have several other concerns and specific comments which I will detail below by section. Abstract: Line 10; I think the design is more appropriately described as a single group repeated measures design. Line 41: "of which" should be "of whom" Lines 48-53: the changes in HbA1c and FPG should also be reported as the mean difference and the 95% CI for the difference. For example it is unclear whether the changes to oral anti-hyperglycemic therapy were implemented by the pharmacists Introduction: One barrier to insulin use in T2DM is physician reluctance by physicians to prescribe, however patients are also reluctant to use insulin. There should be mention of the patient barriers to insulin commencement, with appropriate references. We also need to understand if and how this pharmacist intervention was designed to overcome patient barriers. Paragraph 4: The argument for the feasibility of pharmacists taking on the role of identifying poorly controlled people with type 2 diabetes can be supported by citations from the literature More information is needed about the nature of the care that pharmacists have delivered to people with type 2 diabetes and the types of impact. The statement about changing scope of practice needs to be geographically situated – eg some provinces in Canada, UK, and parts of the US – it is not universal. Methods: This section needs some subheadings: study sample; study protocol; sample size; data analysis Why was this single group study? This needs justification. The exclusion criteria are extensive and it is unclear how some of these criteria were determined. For example was a cognitive assessment conducted? How did the pharmacist access information on any psychiatric diagnosis? How was the serum creatinine measurement obtained? Were the tests ordered by pharmacists? Why was there no measure of HRQoL or a diabetes specific HRQoL? Page 8 lines 27-29 state that "The intervention also included patient education regarding insulin use, dose titration and self-monitoring. This is very scant information – how was this education conducted what training were the pharmacists given to equip them to educate patients about SMBG? For the example were all or some of the pharmacists already accredited diabetes educators? If they were not how were they educated to ensure consistency of instruction for patients. Sample size: what was the rationale for choosing an effect size of 0.4% reduction in HbA1C? Previous studies have shown that with the introduction of insulin – much higher reductions in A1C are achieved. Data analysis- this is unclear – If Students t-test was conducted this should have been a paired t-test- it is unclear how you adjusted for demographic and clinical

	variables – this would not have been a simple t-test. Results: Table 1: gives extensive demographic information some of which is immaterial to this intervention as it post intervention data on dietary, exercise or stress were not collected. However what is lacking is information about patients/ diabetes history; eg duration of diabetes, comorbidities, complications – More information about the medication regimens of the subjects is needed – for example what combinations of medication were the patients taking? What proportion were on 1, 2, 3 or more medications. Were there any differences in A1C between those who were on 1, 2 or 3 or more medication's? This would allow you to discuss the possibility of other approaches to optimising glycaemic control eg intensifying with another oral agent and acknowledge that adding insulin especially if the A1C <9% is not the only strategy. . Page 11: You state "Nearly half of the patients (48%) had their oral hypoglycemic regimen altered (Table 2); the most frequent alterations were stopping sulfonylurea (46%) followed by initiating meglitinides(23%), stopping metformin (21%) and stopping thiazolidinedione and DPP4 inhibitors (19%)." It is unclear whether it was the pharmacist and/or GP who initiated these changes to therapy – if it is unknown whether some changes were made by the GP this should be acknowledged as a limitation. Figures 1 and 2: Include the sample size – expand titles to include the study population The bars – are they SE or 95% CI – they seem too wide – please check. Discussion In reference to information on baseline medication regimens you need to expand the discussion to acknowledge other strategies to improve glycemic control. A key limitation is the study design – this needs to be acknowledged.

REVIEWER	Robert Rushakoff, MD Professor of Medicine Division of Endocrinology and Metabolism University of California, San Francisco
REVIEW RETURNED	06-Jul-2013

THE STUDY	Methods should be more compete to indicate the algorithm for altering the oral agents. Was this done in conjunction with the patient's primary care provider? How were these decisions made.
GENERAL COMMENTS	Study has pharmacists screening for patients in poor diabetes control and then initiating glargine insulin, titrating the insulin dose and adjusting oral agents. Patients had significantly improved glucose control. 1. Study shows that when patients are given titration guidelines, insulin can be titrated to goal. This has been shown in the several published studies where patients have been given the algorithms and glucose levels are achieved, much like this study. So the issue is not really about titration as mush as starting the insulin with appropriate orders. With that, a limitation of the study is that patients

	who were not willing to start insulin were not included. In a real world situation, these patients would need to be started if appropriate. 2. It is not clear if other treatment options, such as GLP1 agonists were considered. 3. Why was metformin discontinued for some patients? Was that appropriate? 4. How were the patients co morbidities considered in applying goals. 5. As there is no common alhgorithm indicated, were there differences between the sites? 6. How many of the patients has significant cardiac disease and how were orders changed to avoid hypoglycemia.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Professor Ines Krass
Faculty of Pharmacy
University of Sydney

I have no competing interests - I have not previously collaborated with the authors

The absence of a control or comparison group undermines the strength of evidence provided by the study.
Why was this a single group study? This needs justification.

- There were concerns about withholding insulin from this high risk group (Mean HbA1c at baseline was 9.1 mmol/l). Those concerns were based on the Canadian Diabetes Association guidelines and the evidence from the literature, for example, the INSIGHT trial (Gerstein 2007)

Page 8, paragraph 2: " We chose the before-after design because we had concerns about withholding insulin from this high risk group. Those concerns were based on guidelines recommendations (8) and the evidence from studies such as INSIGHT (7)."

The exclusion criteria are extensive and it is unclear how some of these criteria were determined. For example was a cognitive assessment conducted? How did the pharmacist access information on any psychiatric diagnosis?

- Those were left to the pharmacist judgment. The patients recruited were already within the pharmacist's practice, and as such, the pharmacist would already know the patient and whether he/she would be able to complete the study.

How was the serum creatinine measurement obtained? Were the tests ordered by pharmacists?

- The value of serum creatinine was obtained from the patient's healthcare records, where the pharmacist used the most recent value (pharmacists in Alberta have full access to all laboratory tests online).

Page 8, paragraph 5, page 8, paragraph 1: " We excluded patients who were unwilling to use insulin, previously or currently using insulin (confirmed by the patient's medication records), had a history of ketoacidosis (confirmed by the patient's healthcare records), were pregnant, worked night shifts, had renal impairment (serum creatinine of ≥ 124 mmol/l for females or ≥ 133 mmol/l for males) (confirmed by the patient's healthcare records), were clinically unstable (based on the pharmacist's judgment),

were unwilling or unable to attend follow-up visits, or felt to be unlikely to adhere to study procedures due to cognitive limitations (based on the pharmacist's judgment), severe psychiatric disorders or alcoholism (confirmed by the patient's healthcare records)."

Why was there no measure of HRQoL or a diabetes specific HRQoL?

- We tried to measure the quality of life and the diabetes treatment satisfaction using ADDQOL, DTSQ and DTSQc but the response rate was not sufficient for drawing conclusions Only 40 patients returned the questionnaires 30 of which were analyzable.

Page 8 lines 27-29 state that "The intervention also included patient education regarding insulin use, dose titration and self-monitoring.

This is very scant information – how was this education conducted what training were the pharmacists given to equip them to educate patients about SMBG? For the example were all or some of the pharmacists already accredited diabetes educators? If they were not how were they educated to ensure consistency of instruction for patients.

- All the participating pharmacists attended training session conducted by the study team. The training material was based on the most recent Canadian guidelines and recommendations. Although not a requirement, all of the pharmacists were either certified diabetes educators (CDE) or were preparing to be CDE

Page 8, paragraph 3: "All participating pharmacists, who were either certified diabetes educators (CDE) or preparing to be CDE, received face to face training by the study team. The training material was based on the most recent Canadian guidelines and recommendations (7,8). They also received a manual of operations to help them conduct the study."

Sample size: what was the rationale for choosing an effect size of 0.4% reduction in HbA1C? Previous studies have shown that with the introduction of insulin – much higher reductions in A1C are achieved.

- Yes, we agree that our effect size assumptions were conservative. We chose this very conservative reduction in HbA1c for several reasons. First, we anticipated that some patients might not be compliant with their insulin regimen (which would reduce the overall effect size). Secondly, we thought that pharmacists might be less aggressive with insulin titration, leading to a lower effect size.

It is unclear whether it was the pharmacist and/or GP who initiated the changes to oral medication therapy – if it is unknown whether some changes were made by the GP this should be acknowledged as a limitation.

- Adjustments to the oral hypoglycemic agent(s) were made by the pharmacist who then informed the family physician about the action(s).

Page 13, Paragraph 2: " Those alterations were made by the pharmacists who then informed the

patients' family physicians."

Thank you for the opportunity to review this novel intervention trial using community pharmacists to introduce and manage basal insulin therapy for patients with suboptimal glycaemic control. The study highlights the opportunities offered by expansion in the scope of pharmacists practice in some Canadian provinces i.e., granting of prescribing rights for credentialed pharmacists. The article is generally well written and presents some preliminary evidence for the benefits of the community pharmacist's role in the intensification of diabetes therapy. However the absence of a control or comparison group undermines the strength of this evidence. I have several other concerns and specific comments which I will detail below by section.

Abstract:

Line 10; I think the design is more appropriately described as a single group repeated measures design.

- We consider the design before and after because we specified one primary outcome at 6 months

Line 41: "of which" should be "of whom"

- Issue addressed as requested

Page 2, Results section: " We screened 365 patients of whom 111 were eligible."

Lines 48-53: the changes in HbA1c and FPG should also be reported as the mean difference and the 95% CI for the difference.

- Issue addressed as requested

Page 2, Results section: " HbA1c was reduced from 9.1% (SD 1) at baseline to 7.3% (SD 0.9) a change of 1.8% (95% CI 1.4-2, p<0.001). Fasting plasma glucose was reduced from 11 mmol/l (SD 3.3) to 6.9 mmol/l (SD 1.8), a change of 4.1 mmol/l (95% CI of 3.3-5, p= 0.007)."

Introduction:
One barrier to insulin use in T2DM is physician reluctance by physicians to prescribe, however patients are also reluctant to use insulin. There should be mention of the patient barriers to insulin commencement, with appropriate references. We also need to understand if and how this pharmacist intervention was designed to overcome patient barriers.

- A paragraph regarding 'psychological insulin resistance' has been added.

Page 6, paragraph 4, page 7, paragraph 1: "Clinicians' reluctance to initiating insulin due to unfamiliarity with the treatment or using it as a last resort (9) plays a major role in influencing the patient's decision to commence insulin treatment regimen. It has been reported that many patients

have ‘psychological insulin resistance’ where they are unwilling to take insulin because of certain beliefs that insulin will not be beneficial and in some cases it may even be harmful. Personal experience and messages from different healthcare professionals can also affect the patient’s decisions regarding insulin treatment regimen (6, 10)."

Pharmacists are highly trusted by the public and we thought that their communications skills would help patients overcome some of these barriers.

Paragraph 4:
The argument for the feasibility of pharmacists taking on the role of identifying poorly controlled people with type 2 diabetes can be supported by citations from the literature
More information is needed about the nature of the care that pharmacists have delivered to people with type 2 diabetes and the types of impact.
The statement about changing scope of practice needs to be geographically situated – eg some provinces in Canada, UK, and parts of the US – it is not universal.

- Information on the nature of the interventions, the type of impact and citations has been added to this paragraph. And ‘Alberta’ was added to the statement regarding the scope change.

Page 7, paragraph 2: " In community settings, pharmacists have demonstrated that they are capable of identifying poorly controlled patients, educate patients regarding diabetes, medications and self-monitoring of plasma glucose, provide adherence support, identify and resolve diabetes problems and complications and setting goals in order reduce the patients’ HbA1c, plasma glucose and improve their quality of life and other co-morbidities (4, 12 - 16). Moreover, the scope of practice for pharmacists in Alberta is changing, allowing pharmacists to prescribe medications and order laboratory tests. As such, there is an unprecedented opportunity to identify and improve glycemic control in patients with type 2 diabetes."

Methods:
This section needs some subheadings: study sample; study protocol; sample size; data analysis

- Issue addressed, subheadings were added as requested

Why was this a single group study? This needs justification.

- There were concerns about withholding insulin from this high risk group (Mean HbA1c at baseline was 9.1 mmol/l). Those concerns were based on the Canadian Diabetes Association guidelines and the evidence from the literature, for example, the INSIGHT trial (Gerstein 2007)

Page 8, paragraph 2: " We chose the before-after design because we had concerns about withholding insulin from this high risk group. Those concerns were based on guidelines recommendations (8) and the evidence from studies such as INSIGHT (7)."

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psychiatric diagnosis?

- Those were left to the pharmacist judgment. The patients recruited were already within the pharmacist's practice, and as such, the pharmacist would already know the patient and whether he/she would be able to complete the study.

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- Yes, we agree that our effect size assumptions were conservative. We chose this very conservative reduction in HbA1c for several reasons. First, we anticipated that some patients might not be

compliant with their insulin regimen (which would reduce the overall effect size). Secondly, we thought that pharmacists might be less aggressive with insulin titration, leading to a lower effect size.

Data analysis- this is unclear –
If Students t-test was conducted this should have been a paired t-test

- Issue addressed, paired t-test was added as requested

Page 11, Paragraph 1: "The mean HbA1c between baseline and 26 weeks was compared using a paired t-test. Secondary outcomes were analyzed using paired t-tests and basic frequencies."

it is unclear how you adjusted for demographic and clinical variables – this would not have been a simple t-test."

- Linear regression was used to adjust for the patient's demographic and clinical characteristics

Page 11, paragraph 1: " Linear regression was used to adjust for the patients' demographics and clinical characteristics."

Results:
Table 1: gives extensive demographic information some of which is immaterial to this intervention as it post intervention data on dietary, exercise or stress were not collected. However what is lacking is information about patients/ diabetes history; eg duration of diabetes, comorbidities, complications –

- The information regarding diet, exercise and stress has been taken out from the manuscript and Table 1. Information regarding hypertension and cholesterol level has been added to the text and table 1. Diabetes duration has been reported as a mean (standard deviation) in the manuscript.

Page 12, paragraph 2: " The demographic and clinical characteristics of the patients are reported in Table 1. The mean age was 64 years (Standard Deviation (SD) 10.4) and had a diabetes duration of 10.2 years (SD 7). Fifty-eight percent of the patients were male, 77% were married and 90% reported having at least high school education. Nearly half of the patients (48%) were retired, almost ninety percent (89%) were white (ethnicity was self reported) and nearly half (47%) have a government medication coverage. Around one quarter of the patients (22%) reported that they were smokers, and more than half (54%) reported occasional consumption of alcohol (e.g. 1-3 drinks/week). Nearly two thirds of the patients had elevated blood pressure (63%) and elevated cholesterol (64%) (hypertension and high cholesterol were self reported). "

Table 1 Demographic and clinical characteristics of the patients (N=100)
Characteristic Frequency
Gender
Male 58
Female 42
Marital status
Single 8
Married 77
Divorced 9
Widowed 6
Education
Grade School 10
High School 36

Some post secondary education 26
Post secondary education 28
Employment
Caring for family 1
Working for profit/pay 36
Unemployed/looking for a job 6
Retired 48
Other 9

Self reported Ethnicity
Aboriginal/first nation 1
White 89
South Asian 1
Oriental 4
Other 4
Declined 1
Medication coverage
Private 29
Government 47
Out of pocket 15
Private and government 7
Private and out of pocket 2
Smoking status
Smoker 22
Ex-smoker 41
Non-smoker 37
Alcohol consumption
No Alcohol 43
Occasional alcohol (e.g. 1-3 drinks/week) 54
1-2 alcohol drinks per day 3

Self reported Hypertension
Yes 63
No 36
Unknown 1
Self reported high cholesterol
Yes 64
No 33
Unknown 3

More information about the medication regimens of the subjects is needed – for example what combinations of medication were the patients taking? What proportion was on 1, 2, 3 or more medications. Were there any differences in A1C between those who were on 1, 2 or 3 or more medication's? This would allow you to discuss the possibility of other approaches to optimising glycaemic control eg intensifying with another oral agent and acknowledge that adding insulin especially if the A1C <9% is not the only strategy.

- Table 2 which contains the number of oral agents and the mean HbA1c for each group has been added. Also a paragraph regarding the most widely used combinations has been added to the results

section.

Page 13, paragraph 2: "Fifty one percent of the patients achieved the target HbA1c of ≤ 7% at the end of the study. At baseline, two thirds (66%) of the patients were taking two or more medications (Table 2), the most widely used combination was metformin and gliclazide, followed metformin and glyburide and metformin and repaglinide. Nearly half of the patients (48%) had their oral hypoglycemic regimen altered (Table 3); the most frequent alterations were stopping sulfonylurea (46%) followed by initiating meglitinides (23%), stopping metformin (21%) and stopping thiazolidinedoine and DPP4 inhibitors (19%)."

Table 2 Number of oral hypoglycemic agents used by patients and Mean HbA1c
Number of oral agents Frequency Mean HbA1c (SD)
1 34 8.7 (0.9)
2 56 9.1 (0.9)
3 7 9.8 (1.6)
4 3 8.7 (0.7)

Page 11:
You state
“Nearly half of the patients (48%) had their oral hypoglycemic regimen altered (Table 2); the most frequent alterations were stopping sulfonylurea (46%) followed by initiating meglitinides(23%), stopping metformin (21%) and stopping thiazolidinedione and DPP4 inhibitors (19%).”

It is unclear whether it was the pharmacist and/or GP who initiated the changes to oral medication therapy – if it is unknown whether some changes were made by the GP this should be acknowledged as a limitation.

- Adjustments to the oral hypoglycemic agent(s) were made by the pharmacist who then informed the family physician about the action(s).

Page 13, Paragraph 2: " Those alterations were made by the pharmacists who then informed the patients’ family physicians."

Figures 1 and 2: Include the sample size – expand titles to include the study population
The bars – are they SE or 95% CI – they seem too wide – please check.

- Issue addressed as requested

Discussion
In reference to information on baseline medication regimens you need to expand the discussion to acknowledge other strategies to improve glycemic control.

- A paragraph acknowledging that adding insulin to the oral agents is not the only available option has been added to the limitation section

Page 17, Paragraph 2: "We acknowledge that adding insulin to the oral hypoglycemic agent(s) regimen is one of the options which are available to improve glycemic control; however this choice was based on the insulin’s efficacy and safety profile."

A key limitation is the study design – this needs to be acknowledged.

- A paragraph explaining the study design choice has been added to the methods section

Page 8, Paragraph 2: " We chose the before-after design because we had concerns about withholding insulin from this high risk group. Those concerns were based on guidelines recommendations (8) and the evidence from studies such as INSIGHT (7)."

Reviewer: Robert Rushakoff, MD
Professor of Medicine
Division of Endocrinology and Metabolism
University of California, San Francisco

Methods should be more compete to indicate the algorithm for altering the oral agents. Was this done in conjunction with the patient's primary care provider? How were these decisions made.

- Adjustments to the oral hypoglycemic agent(s) were made at the discretion of the treating pharmacist based on the most recent Canadian guidelines who then informed the family physician about the action(s). If the combination with insulin was not approved in Canada, oral hypoglycemic agent was discontinued (e.g. Thiazolidinedione).

Page 9, Paragraph 3: "All patients remained on their previously prescribed oral hypoglycemic agent(s). If the combination with insulin was not approved in Canada, the oral hypoglycemic agent was discontinued (e.g., thiazolidinedione). Adjustments were made at the discretion of the treating pharmacist based on the most recent Canadian guidelines (8)."

Page 13, Paragraph 2: " Those alterations were made by the pharmacists who then informed the patients' family physicians."

Study has pharmacists screening for patients in poor diabetes control and then initiating glargine insulin, titrating the insulin dose and adjusting oral agents. Patients had significantly improved glucose control.

1. Study shows that when patients are given titration guidelines, insulin can be titrated to goal. This has been shown in the several published studies where patients have been given the algorithms and glucose levels are achieved, much like this study. So the issue is not really about titration as mush as starting the insulin with appropriate orders. With that, a limitation of the study is that patients who were not willing to start insulin were not included. In a real world situation, these patients would need to be started if appropriate.

- A paragraph regarding not including patients who were not willing to start insulin has been added to the limitations section. Patients willingness to use insulin was high in the pilot project leading to this study and during the screening process. The proactive and systematic approach that we used in this also helped in identifying patients who could benefit from insulin

Page 17, Paragraph 2: " Patients who were unwilling to use insulin were excluded from the study; however patients' willingness to use insulin was high in our pilot study (4) and also during the screening process. The proactive and systematic approach that we used in this study also helped in identifying patients who could benefit from insulin."

2. It is not clear if other treatment options, such as GLP1 agonists were considered.

- The study's intervention was based on the Canadian Diabetes Association 2008 guidelines. Those guidelines recommend adding insulin as one of the second line agents in patients who are receiving

one or more oral agents and not achieving the recommended targets. They also recommend initiating insulin as one of the first line agents in patients who has HbA1c ≥ 9%. For the purposes of this study adjusting the oral agent(s) dose and adding insulin glargine were the only treatment options considered

3. Why was metformin discontinued for some patients? Was that appropriate?

- Metformin was discontinued in those patients mainly because of the side effects.

4. How were the patients co morbidities considered in applying goals.

- The HbA1c goal for this study was based on the Canadian Diabetes Association 2008 guidelines. Those guidelines had only one HbA1c target (HbA1c ≤ 7%) regardless of the patient's co-morbidities

5. As there is no common algorithm indicated, were there differences between the sites?

- The insulin treatment algorithm was to start with 10 units at bedtime and increase the dose by 1 unit/day to achieve a fasting plasma glucose of ≤ 5.5 mmol/l. All the participating pharmacists attended training session conducted by the study team. The training material was based on the most recent Canadian guidelines and recommendations. The pharmacists also received a manual of operations to help them conducting the study. There were differences in the number of recruited patients between the sites

Page 8, Paragraph 3: "All participating pharmacists, who were either certified diabetes educators (CDE) or preparing to be CDE, received face to face training by the study team. The training material was based on the most recent Canadian guidelines and recommendations (7,8). They also received a manual of operations to help them conduct the study."

6. How many of the patients have significant cardiac disease and how were orders changed to avoid hypoglycemia.

- None of participating patients had a significant cardiac disease