Abstract

Objective To develop an evidence-based checklist to identify potential drug related problems (PDRP) in patients with type 2 diabetes. Setting The evidence based checklist was applied to records of ambulatory type 2 diabetes patients in New South Wales, Australia. Method After comprehensive review of the literature, relevant medication groups and potential drug related problems in type 2 diabetes were identified. All the relevant information was then structured in the form of a checklist. To test the utility of the evidence-based checklist a cross-sectional retrospective study was conducted. The PDRP checklist was applied to the data of 148 patients with established type 2 diabetes and poor glycaemic control. The range and extent of DRPs in this population were identified, which were categorized using the PCNE classification. In addition, the relationship between the total as well as each category of DRPs and several of the patients’ clinical parameters was investigated. Main outcome measure: Number and category of DRPs per patient. Results The PDRP checklist was successfully developed and consisted of six main sections. 682 potential DRPs were identified using the checklist, an average of 4.6 (SD = 1.7) per patient. Metabolic and blood pressure control in the study subjects was generally poor: with a mean HbA1c of 8.7% (SD = 1.5) and mean blood pressure of 139.8 mmHg (SD = 18.1)/81.7 mmHg (SD = 11.1). The majority of DRPs was recorded in the categories ‘therapy failure’ (n = 264) and ‘drug choice problem’ (n = 206). Potentially non-adherent patients had a significantly higher HbA1c than patients who adhered to therapy (HbA1c of 9.4% vs. 8.5%; \( P = 0.01 \)). Conclusion This is the first tool developed specifically to detect potential DRPs in patients with type 2 diabetes. It was used to identify DRPs in a sample of type 2 diabetes patients and demonstrated the high prevalence of DRPs per patient. The checklist may assist pharmacists and other health care professionals to systematically identify issues in therapy and management of their type 2 diabetes patients and enable earlier intervention to improve metabolic control.

Keywords Type 2 diabetes · Drug related problems · Drug therapy · Evidence-based medicine · Evidence-based pharmacy · Diabetes · PCNE DRP classification

Impact of findings on practice

- An evidence-based checklist can be used specifically in patients with type 2 diabetes, to assist pharmacists and other healthcare professionals in systematically identifying DRPs.
- There is a high prevalence of DRPs in the population of patients with type 2 diabetes and poor glycaemic control.
- The most important DRPs in type 2 diabetes patients in New South Wales seem to be therapy failure and drug choice problems.

Introduction

Type 2 diabetes is a chronic metabolic disorder characterised by both defects in insulin secretion and/or tissue
sensitivity to insulin. The latter is known as insulin resistance and forms part of a cluster of cardiovascular risk factors seen in a high proportion of patients with type 2 diabetes. It is known as the metabolic syndrome and also includes central obesity, hypertension and/or dyslipidaemia. Evidence suggests that a targeted, intensified, multifactorial intervention which includes lifestyle modifications and multiple pharmacotherapy is required to reduce or prevent macrovascular and microvascular complications [1, 2].

The optimal use of medications therefore plays a key role in achieving treatment targets for glucose, blood pressure and lipids. The efficacy of a medication regimen, however, may be limited by a range of drug related problems (DRPs) including adverse drug reactions, interactions, contra-indications and non-adherence [3]. Since patients with type 2 diabetes generally use multiple medications, DRPs are likely to occur in this population and these can negatively influence diabetes control. Research has shown that a substantial proportion of DRPs that exist within the health care system are related to patients with diabetes [4]. Nevertheless, there is currently no specific tool available that can be used by pharmacists or other healthcare professionals to help detect DRPs in patients with type 2 diabetes.

**Aim**

Our aim was to develop an evidence-based PDRP (potential drug related problems) checklist that may be used to review a patient’s clinical status and medication regimen to identify potential DRPs in type 2 diabetes.

**Method**

**Development of the checklist**

The development of the PDRP checklist followed a systematic process which is outlined in Fig. 1. Initially, a MEDLINE search of English-language articles published between 1997 and 2007 with the terms ‘type 2 diabetes mellitus’ and ‘drug therapy’ was conducted to identify published literature on the subject. The available literature was comprehensively reviewed to provide up to date information on the pharmacological management of type 2 diabetes and the risk management of its related complications. In addition, current standards in the therapeutic management of type 2 diabetes were obtained by reviewing several recently published guidelines [5–8]. According to all guidelines, the current recommended targets for type 2 diabetes for glycaemic control and cardiovascular risk reduction are HbA1c ≤7%, blood pressure <130/80 mmHg (125/75 mmHg in case of proteinuria >1 g/day). With respect to lipids, Australian guidelines recommend total cholesterol <4 mmol/l; LDL-C <2.0 mmol/l; HDL-C >1.0 mmol/l; triglycerides <1.5 mmol/l [7]. In the US and Europe the recommended levels for lipids are expressed in mg/dl (LDL-C <100 mg/dl; HDL-C >40 mg/dl; triglycerides <150 mg/dl) [5].

Based on this, the therapeutic targets and the drug groups to be included in the PDRP checklist were selected (displayed in Table 1) and the potential DRPs related to each group were identified. All the relevant information was then structured in the form of a checklist. To enable easy application in clinical practice, the checklist must be relatively short and concise. Therefore, very rarely used agents (e.g. bile acid binding resins and nicotinic acid for the treatment of dyslipidaemia), were excluded. In addition, only the most common and/or most severe adverse effects, contra-indications and significant interactions were listed [9]. (i.e., drug interactions with a significance rating of 1 or 2 in the Drug Interaction Facts software) [10]. Dosage information for each agent was derived from the Australian Medicines Handbook [9]. After the checklist had initially been developed by the authors, it was extensively reviewed by a panel of experts and corrected hereafter (see Acknowledgements).

**Using the PDRP checklist**

In the literature, there are several systems available for the classification of DRPs [11]. The characteristics of each
system were examined to select the most suitable for classifying the outcomes of the PDRP checklist. The PCNE classification proved to be the most appropriate one to apply in this study [12]. It is based on a clear definition, has a hierarchical problem classification and its validation has been published [11]. The outcomes of the checklist appeared to be easily categorized into one of the six primary domains of this classification: adverse reactions, drug choice problems, dosing problems, drug use problems, interactions and others. In this study, the primary domain called ‘others’ was renamed to ‘therapy failure’ because that is the only type of DRP in this domain that was investigated in this study.

A cross-sectional retrospective study design was used. Study subjects were patients from New South Wales, Australia who participated in the Pharmacy Diabetes Care Program in 2004 [13]. These were all patients with established type 2 diabetes and poor glycaemic control (HbA1c ≥ 7.0%). Full patient medication records and other data collected in the study, including BMI, HbA1c, systolic and diastolic blood pressure, lipid profile and medication adherence were available. Adherence was assessed using the Brief Medication Questionnaire (BMQ), a validated self-report tool that is used to indicate potential non-adherence [13, 14]. No further data from the patients’ perspective were available. The PDRP checklist was used to review each patient’s data to determine the prevalence of identified DRPs.

Data analysis

For each type of DRP identified in the review process, the cumulative frequencies and, if relevant, the nature of the problem was reported. All the DRPs were categorized according to their primary domain in the PCNE classification. Next, the relationship between the total number and category of DRPs and several clinical parameters was investigated using either the Spearman’s rank correlation coefficients (for continuous or ordinal variables) or the independent-samples Student’s t-tests for comparing means of two groups. The DRPs in the ‘therapy failure’ category were not included in this analysis, since the occurrence of a DRP in this category is logically related to poor control of blood glucose levels, blood pressure and/or lipid levels. All the statistical analyses were carried out using SPSS for Windows (version 15.0; SPSS Inc, Chicago, IL, USA).

Results

The PDRP checklist

The checklist (see Appendix) consists of six main sections: lifestyle management, glycaemic control, blood pressure control, lipid control, platelet control and medication adherence. Whilst the main focus of the checklist is on the detection of potential DRPs in the patient’s current medications, including missing therapy and the appropriateness of the prescribed agents, lifestyle management issues are also relevant in the overall management of type 2 diabetes and were therefore included.

Sample description

A total of 148 patients with established type 2 diabetes were included in the study. The demographics and clinical parameters of these study subjects are displayed in Table 2. In total, the study subjects were using 599 medications of the four main groups that were included in the checklist. Of these 599 medications, 258 (43.1%) were anti-diabetics, 200 (33.4%) were anti-hypertensives, 80 (13.4%) were lipid lowering drugs and 61 (10.2%) were anti-platelet agents (Table 3).

Distribution of drug related problems

A total of 682 DRPs were identified using the PDRP checklist. This represents an average of 4.6 (SD = 1.7) DRPs per patient. The distribution of the recorded DRPs is presented in Table 4.
Adverse reactions

43 patients (29.1%) reported having experienced at least one episode of hypoglycaemia of any kind in the 1 month period prior to enrollment in the study. All these patients were using a sulphonylurea or insulin, therefore this was considered a potential adverse effect of their drug therapy.

Drug choice problem

This category of DRP was recorded 206 times, resulting in an average of 1.4 drug choice problem per patient. By far the most recorded drug choice problem ($n = 182$) was that of missing therapy despite a clear indication being present. A total of 90 patients (60.8%) were not receiving anti-platelet therapy although they were at increased cardiovascular risk, 71 patients (48.0%) were missing lipid lowering therapy, 20 patients (13.5%) were missing anti-hypertensive therapy and 1 patient (0.7%) was not prescribed any blood glucose lowering therapy at the point of data collection.

Also, drugs that were not the most appropriate treatment option were prescribed in 19 cases. These were all related to the use of a non-preferred agent as monotherapy for the treatment of hypertension: diltiazem or verapamil was recorded 12 times, a non-selective $\beta$-blocker was recorded 6 times and 1 patient only used a selective $\alpha$-antagonist to treat high blood pressure.

Dosing problem

In total, a dosing problem was recorded 40 times. Underutilization of a drug was recorded when the prescribed dose was below the recommended range or when the dosing regimen was inappropriately infrequent. This was seen 13 times, with the most prevalent being aspirin ($n = 4$) or ACE inhibitors ($n = 4$). Overutilization was recorded 27 times. In 15 of these cases, sulphonylureas were responsible for this type of DRP. Sulphonylureas ($n = 9$) and metformin ($n = 3$) were the next most frequently overutilized drugs.

Drug use problem

Potential non-adherence was categorized as a drug use problem and occurred in 17.6% ($n = 26$) of the study subjects.
Table 4 Drug related problems in the study subjects (n = 148)

| Type of drug related problem                  | n  | Percentage of total DRPs |
|-----------------------------------------------|----|--------------------------|
| 1. Adverse reaction                           | 43 | 6.3                      |
| 2. Drug choice problem                        | 206| 30.2                     |
| Inappropriate/not most appropriate drug       | 19 | 2.8                      |
| Duplication of therapeutic group              | 1  | 0.1                      |
| Contra-indication                             | 4  | 0.6                      |
| No drug prescribed but clear indication       | 182| 26.7                     |
| 3. Dosing problem                             | 40 | 5.9                      |
| Drug dose too low or regimen not frequent     | 13 | 1.9                      |
| Drug dose too high or regimen too frequent    | 27 | 4.0                      |
| 4. Drug use problem                           | 26 | 3.8                      |
| Potential non-adherence                       | 26 | 3.8                      |
| 5. Interactions                               | 103| 15.1                     |
| 6. Therapy failure                            | 264| 38.7                     |
| Total                                         | 682| 100.0                    |

Interactions

A total of 103 potential interactions were identified with the use of the checklist. The most recorded type of potential interaction was the combination of an ACE inhibitor with either a sulphonylurea (n = 32) or insulin (n = 14). The so-called ‘triple whammy’, defined as the use of a thiazide diuretic and an ACE inhibitor or angiotensin II antagonist in combination with an NSAID, was observed 15 times [15]. Other repeatedly reported potential interactions were the concomitant use of low-dose aspirin and another NSAID (n = 7); atorvastatin or simvastatin and a macrolide antibiotic (n = 6); a sulphonylurea and an antimalarial drug (n = 6); and an ACE inhibitor as well as an angiotensin II antagonist (n = 6).

Therapy failure

This was the largest category of DRPs (n = 264), accounting for 38.7% of all problems. Therapy failure was assumed to be present when blood glucose levels, blood pressure or lipid levels weren’t controlled adequately despite receiving drug therapy to treat these metabolic disorders. The underlying causes of the DRPs in this category are unknown; potential causes are ineffectiveness of medications (e.g. secondary failure of sulphonylureas), missing therapy (e.g. patients requiring more than one antihypertensive to control their blood pressure), incorrect administration of drugs and undetected non-adherence. Therefore, not reaching therapeutic targets while receiving drug therapy was recorded as a separate DRP in this category. Blood glucose levels were above recommended levels in 133 patients (89.9%), blood pressure was elevated in 69 patients (46.6%) and lipid levels failed to reach the treatment goals in 62 patients (41.9%).

To investigate whether there was a relationship between the prevalence of DRPs and the therapeutic status of the patient; Spearman’s correlation coefficients were calculated between the number of total DRPs (minus the ‘therapy failure’ category) and several clinical parameters. A significant correlation was observed between systolic blood pressure and the total number of DRPs minus ‘therapy failure’ (Spearman’s correlation n = 0.19; P = 0.028). Potentially non-adherent patients had a significantly higher HbA1c than the other patients (HbA1c of 9.4 vs. 8.5; 95% CI: −1.50 to −0.20).

Discussion

In this study, an evidence-based checklist for the detection of DRPs in type 2 diabetes has successfully been developed. The checklist was used to identify DRPs in a population of patients with type 2 diabetes. A total of 682 DRPs were detected, which were classified in six different categories.

The high average of 4.6 DRPs (SD = 1.7) per patient showed that the early identification and resolution of DRPs is important in the therapeutic management of patients with type 2 diabetes. An earlier study found a comparable average of 4.1 DRPs per patient with type 2 diabetes, albeit using a different method of detecting (by qualitative interviews) and classifying DRPs [16]. Collectively, these findings demonstrated that the prevalence of DRPs in these patients is relatively high. This can partly be explained by the fact that patients with type 2 diabetes generally use many medications, but it also emphasizes the need for adequate medication management in these patients.

One of the major issues identified by the PDRP checklist was the large proportion of patients who were missing therapy for clear indication. This was especially the case for anti-platelet therapy. Approximately 60% of all the patients were not taking aspirin in spite of being at increased cardiovascular risk. Also, nearly half of all the patients were not receiving any lipid lowering drugs although lipid levels were not adequately controlled in these patients. This is a concern, especially since the benefits of anti-platelet and lipid lowering therapy in patients with type 2 diabetes have clearly been established in earlier large randomized clinical trials [17–19].

A high proportion of patients in this study had poor glycaemic control, an expected finding since this was a selection criterion for entry into study [13]. It suggests, however, that pharmacotherapy may need to be intensified for many poorly controlled patients with type 2 diabetes, assuming they have been adherent to their diabetes.
management regimen [5]. The findings also highlight the need for self monitoring of blood glucose by all type diabetes patients on medication therapy.

Blood pressure control among this cohort was also suboptimal. Nearly half of the patients had an elevated blood pressure (46.6%) as well as suboptimal lipid control (41.9%). Thus, notwithstanding the availability of a wide range of pharmacotherapy, achieving metabolic control in type 2 diabetes continues to be a major challenge.

Another notable result was that 16% of all patients in this study on sulphonylurea therapy were prescribed a dose that was higher than recommended. The desirability of this prescribing behaviour is questionable, since it is well known that the risk of hypoglycaemia is enhanced with increased dosages of sulphonylureas [20]. Also, approximately a third of all patients reported having experienced at least one episode of hypoglycaemia of any kind in the month before entry into the study. It is not possible, though, to conclude what proportion of these episodes was directly induced by sulphonylureas from the retrospective patient data. Information on other adverse effects was not available from the patient data, so the number of DRPs collected in this category may have been underestimated. Also, there was no information available from the original data on the patient’s renal and hepatic function; so it was not possible to detect possible contra-indications related to these parameters.

Several potential interactions were identified with the use of the PDRP checklist. A large proportion (44.7%) related to the combination of an ACE inhibitor with either a sulphonylurea or insulin. Although the combination of these agents is unavoidable in the therapeutic management of type 2 diabetes for many patients, the increased risk of hypoglycaemia requires careful monitoring [21, 22]. This is also true for the potential impairment in renal function when using the so-called ‘triple whammy’ combination, which was prescribed in 14.6% of patients. Overall, ACE inhibitors were involved in 63 of all 103 potential interactions (61.2%), suggesting that patients taking these agents should be monitored carefully.

An interesting observation was the significant difference in HbA1c between adherent and potentially non-adherent patients. An earlier observational study demonstrated a significant relationship between adherence to insulin therapy and glycaemic control, but this relationship has not been established previously for other anti-diabetic medications [23]. Since 17.6% of the study subjects were potentially non-adherent, an improvement in medication adherence is highly likely to contribute to improving glycaemic control in type 2 diabetes as has been shown in earlier studies [24, 25]. It should be noted that the PDRP checklist does not detect potential non-adherence, but information on this was available from the patient data. In these data, potential non-adherence had previously been assessed by the use of a self-report tool [13]. Considering the importance of adherence in type 2 diabetes, a tool of that kind should be integrated in the checklist in the future to enable full completion and improve convenience.

The total number of DRPs (minus the ‘therapy failure’ category) correlated significantly with systolic blood pressure but not with any other clinical parameters. A possible explanation for this is that blood glucose and lipid levels are influenced to a greater extent by non-medication related factors, such as environmental and lifestyle aspects, than is systolic blood pressure.

Certain limitations to this study, however, are due to its retrospective nature. While the statistical analyses showed a relationship between the prevalence of DRPs in a patient and the control of several metabolic parameters, they do not demonstrate causality. Also, it is unsure whether the results of this study are representative for all patients with type 2 diabetes, since nearly all the study subjects had poor glycaemic control.

Another important factor that should be considered is that we studied the prevalence of potential DRPs instead of actual DRPs. Therefore it is unknown whether patients with more potential DRPs actually had worse clinical outcomes during follow-up. As a result, the clinical significance of the detected DRPs cannot be established. This is moreover true because no information on the patients’ perspective was included.

The PDRP checklist is the first tool developed specifically to detect potential DRPs in patients with type 2 diabetes and was able to identify DRPs from previously collected patient data. However, the development of an electronic version will be necessary to allow efficient future use. The development of this checklist represents an important first step in developing a tool that can be applied in clinical practice. A broad review on the correctness and completeness by specialists is needed to further determine the contents of the checklist. After this, an additional study on the implementation in practice should be undertaken. For efficient implementation, collaboration between pharmacists and physicians is needed; for example in carrying out the interventions.

The high average of DRPs per patient demonstrates the importance of the early identification and resolution of DRPs in patients with type 2 diabetes. Therapy failure was the most frequently recorded DRP, which suggests that to achieve treatment goals in type 2 diabetes identifying the cause of therapy failure is a critical step. For example if non adherence is the issue, behavioural modification strategies may be needed. If failure of therapy is due to beta cell failure then earlier intensification of therapy is likely to be required [5]. Missing therapy, especially for anti-platelet and lipid lowering medications, was also common which
shows that cardiovascular risk was not adequately addressed in this population.

**Conclusion**

In conclusion, the wide range of DRPs detected by the checklist shows that optimal medication management in type 2 diabetes remains a major challenge in clinical practice. The use of the PDRP checklist may assist pharmacists and other health care professionals to systematically identify issues in therapy and management of their type 2 diabetes patients and enable earlier intervention to improve metabolic control. Whether this will translate into better health outcomes in the longer term, remains to be proven in the near future.

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**Conflicts of interest** None.

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**Appendix**

**PDRP checklist: medications in type 2 diabetes**

This tool is meant to be used by pharmacists in order to detect possible drug related problems and/or potential interventions in patients with type 2 diabetes. It is primarily focused on a patient’s medications, and includes the most commonly used agents for the treatment of hyperglycaemia, hypertension, dyslipidaemia and hypercoagulability. Throughout the tool, several footnotes are used. These refer to the following information:

1. Dietary guidelines for Australian adults are provided by the NHMRC. These can be accessed through http://www.nhmrc.gov.au/publications/synopses/_files/n33.pdf.

2. The Australian Physical Activity guidelines recommend at least 30 minutes of moderate-intensity physical activity on most, preferably all, days. These can be accessed through http://www.ausport.gov.au/fulltext/1999/feddep/physguide.pdf.

3. Renal impairment is defined by the creatinine clearance, which is calculated using the Cockroft-Gault formula:

\[ \text{Creatinine clearance} = \left( \frac{140 - \text{age}}{\text{weight}} \times \text{constant} \right) / \text{plasma creatinine} \]

- Creatinine clearance \(<10\text{ ml/min} = \) severe renal impairment
- Creatinine clearance \(10–25\text{ ml/min} = \) moderate renal impairment
- Creatinine clearance \(25–50\text{ ml/min} = \) mild renal impairment

4. Hepatic impairment is present when transaminase levels are \(>2.5\) times the upper limit of normal.

5. The advised amounts from the NHMRC guidelines are:
   - For men: an average of no more than 4 standard drinks a day, and no more than 28 standard drinks a week; not more than 6 standard drinks in any one day.
   - For women: an average of no more than 2 standard drinks a day, and no more than 14 standard drinks a week; not more than 4 standard drinks in any one day.
   - For both men and women, one or two alcohol free days each week are recommended.

6. Heart failure is classified as:
   - NYHA Class I: no limitation is experienced in any activities; there are no symptoms from ordinary activities
   - NYHA Class II: slight, mild limitation of activity; the patient is comfortable at rest or with mild exertion
   - NYHA Class III: marked limitation of any activity; the patient is comfortable only at rest
   - NYHA Class IV: any physical activity brings on discomfort and symptoms occur at rest

The Australian Medicines Handbook (AMH Pty Ltd. July, 2007) was used for the information on dosages.

Drug Interaction Facts on disc v1.0 (1999 Facts and Comparisons, Medifor Inc, July 2007 edition) was used for the information on interactions.

Further information was provided by the literature review.
Lifestyle management

1. Is the patient overweight?  
   - Yes: BMI ≥ 25.0 kg/m²  
   - No: BMI < 25.0 kg/m²  
   Discuss strategies with the patient to try to lose weight

2. Is the patient following a healthy diet?  
   - Yes  
   - No  
   Discuss strategies with the patient to modify his/her diet

3. Is the patient getting regular physical activity?  
   - Yes  
   - No  
   Discuss strategies with the patient to increase the amount of physical activity

4. Is the patient a smoker?  
   - Yes  
   - No  
   Discuss strategies with the patient to try to quit smoking

Glycaemic control

5. What is the patient’s current glycaemic control?  
   - HbA₁c ≥ 7.0%  
   - HbA₁c > 7.0%  
   Patient’s glycaemic control is good

6. Is the patient using:  
   - High-dose beta-blockers  
   - Antipsychotics  
   - Glucocorticoids  
   - Combined oral contraceptives  
   - Glucose metabolism might increase blood glucose concentrations  
   - Antibiotics  
   - Immunosuppressants  
   - Hormone replacement therapy  
   - Isotretinoin  
   - Phenytoin  
   Check how long these agents have been used and how long blood glucose has been elevated; also monitor changes in therapy

7. Is the patient using:  
   - A sulphonylurea  
   - No sulphonylurea  
   Ask patient about the monitoring of side effects: weight gain and hypoglycaemia

8. Check if the patient:  
   - Has renal impairment  
   - Has hepatic impairment  
   - Has irregular eating habits  
   - Consumes more alcohol than advised  
   - Is over 65 years of age  
   Continue to question 11

9. Is the daily dose within the recommended range?  
   - Glibenclamide: 2.5 – 20 mg in 1 – 2 doses  
   - Glimepiride: 1 – 4 mg in 1 dose  
   - Gliclazide: 40 – 320 mg in 1 – 2 doses  
   - (controlled release): 30 – 120 mg in 1 dose  
   - Glipizide: 2.5 – 40 mg in 1 – 3 doses  
   - if not  
   Contact prescriber to adjust dose / frequency

10. Is the patient also using:  
    - Rifamycins  
    - High-dose aspirin  
    - ACE inhibitors  
    - Co-trimoxazole  
    - Closely monitor blood glucose concentrations. Sulphonylurea dose may need to be increased

11. Is the patient using:  
    - Metformin  
    - No metformin  
    Ask patient about side effects: nausea, vomiting, abdominal pain and diarrhea. Check for vitamin B₁₂ deficiency

Continue to question 14
12. Check if the patient:
- Has heart failure NYHA Class III or IV
- Has moderate to severe renal impairment
- Has hepatic impairment
- Is over 85 years of age
- Consumes more alcohol than advised

Patient is at increased risk of lactic acidosis → Contact prescriber: metformin might not be the appropriate agent in these conditions

13. Is the daily dose within the recommended range?

Metformin: 500 – 3000 mg in 1 – 3 doses → if not

Contact prescriber to adjust dose / frequency

14. Is the patient using:
- A thiazolidinedione
- No thiazolidinedione

Continue to question 18

15. Is the patient suffering from:
- Heart failure NYHA Class III or IV
- Hepatic impairment

Contact prescriber: thiazolidinediones are contra-indicated in these conditions

16. Is the daily dose within the recommended range?

Rosiglitazone: 4 – 8 mg in 1 – 2 doses
Pioglitazone: 15 – 45 mg in 1 dose → if not

Contact prescriber to adjust dose / frequency

17. Is the patient also using:
- Gemfibrozil
- Insulin
- NSAIDs
- Rifamycins

Increased risk of adverse effects such as fluid retention and heart failure → Use these combinations with caution

Thiazolidinedione metabolism may be increased → Closely monitor blood glucose levels

18. Is the patient using:
- Acarbose
- No acarbose

Ask patient about side effects: flatulence, diarrhea and abdominal pain

Continue to question 21

19. Is the patient suffering from:
- Inflammatory bowel disease
- Renal impairment
- (Partial) intestinal obstruction

Contact prescriber: acarbose is contra-indicated in these conditions

20. Is the daily dose within the recommended range?

Acarbose: 50 – 600 mg in 1 – 3 doses → if not

Contact prescriber to adjust dose / frequency

21. Is the patient using:
- Repaglinide
- No repaglinide

Ask patient about side effects: hypoglycaemia, nausea, diarrhea, vomiting

Continue to question 24

22. Is the daily dose within the recommended range?

Repaglinide: 1.5 – 16 mg in 3 doses → if not

Contact prescriber to adjust dose / frequency

23. Is the patient also using:
- Gemfibrozil
- Cyclosporin
- Macrolides (e.g. erythromycin)
- Rifamycins

Repaglinide metabolism may be inhibited → Closely monitor blood glucose concentrations: Repaglinide dose may need to be decreased

Repaglinide metabolism may be increased → Closely monitor blood glucose concentrations: Repaglinide dose may need to be increased

24. Is the patient using:
- Exenatide
- No exenatide

Ask patient about side effects: nausea, diarrhea, vomiting and hypoglycaemia

Continue to question 27
**Blood pressure control**

31. Check if the patient has renal impairment:
   - Yes
   - No

32. What is the patient’s blood pressure?
   - Blood pressure ≤ 125/75 mm Hg
   - Blood pressure > 125/75 mm Hg

33. What is the patient’s blood pressure?
   - Blood pressure ≤ 130/80 mm Hg
   - Blood pressure > 130/80 mm Hg

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25. Is the daily dose within the recommended range?
   - Exenatide: 10 – 20 µg in 2 doses
     - if not
     - Contact prescriber to adjust dose / frequency

26. Is the patient suffering from:
   - Moderate to severe renal impairment

27. Is the patient using:
   - Insulin
     - No insulin

28. Check if the patient:
   - Has renal impairment
   - Has hepatic impairment
   - Has irregular eating habits
   - Consumes more alcohol than advised
   - Is over 65 years of age

29. Is the patient also using:
   - High-dose aspirin
   - ACE inhibitors

30. When is the patient’s blood glucose out of the target range?
   - The target range is 3.9 – 7.2 mmol / L

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Contact prescriber: exenatide is contra-indicated in this condition

Ask patient about side effects: hypoglycaemia and weight gain

Use insulin with caution

Patient is at increased risk for hypoglycaemia

Closely monitor blood glucose concentrations. Insulin dose may need to be adjusted

Continue to question 31

Contact prescriber to adjust dose / frequency

Contact prescriber: reduce bedtime insulin dose

Contact prescriber: add rapid-acting insulin at breakfast or rapid-acting insulin at lunch

Contact prescriber: add intermediate-acting insulin at breakfast or rapid-acting insulin at lunch

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Continue to question 32

Continue to question 33

Continue to question 34

Continue to question 35 if the patient is using one or more antihypertensive(s), otherwise continue to question 61

Continue to question 35 if the patient is using one or more antihypertensive(s), otherwise continue to question 61

Continue to question 34
34. Is the patient using:
- One or more antihypertensive agent(s)
- No antihypertensive agents

Patient might be in need of an additional antihypertensive agent

Missing therapy: Patient is in need of an antihypertensive agent. ACE inhibitors and angiotensin II antagonists are the preferred agents in type 2 diabetes. Continue to question 61

35. Is the patient using:
- NSAIDs (including COX-2 inhibitors)
- Sibutramine
- Corticosteroids
- Oral decongestants
- MAO inhibitors
- Venlafaxine
- Cyclosporin
- Hormone replacement therapy
- Combined oral contraceptives
- Haemopoietics

These medications might cause an increase in blood pressure: check how long these agents have been used and how long blood pressure has been elevated; also monitor changes in therapy

36. Is the patient using:
- A thiazide diuretic
- No thiazide diuretic

Thiazide diuretics are ineffective in this condition

Continue to question 40

37. Is the patient suffering from:
- Severe renal impairment

Contact prescriber: thiazide diuretics are contraindicated in severe renal impairment

38. Is the daily dose within the recommended range?

- Chlorthalidone: 12.5 – 25 mg in 1 dose
- Hydrochlorothiazide: 12.5 – 25 mg in 1 dose
- Indapamide: 1.25 – 2.5 mg in 1 dose

if not

Contact prescriber to adjust dose / frequency

39. Is the patient also using:
- An ACE inhibitor / angiotensin II antagonist
- An NSAID (including aspirin)

When using both of these: increased risk of renal impairment; monitor renal function carefully

40. Is the patient using:
- A β-blocker
- No β-blocker

Ask patient about side effects: nausea, diarrhea, bronchospasm, hypotension, cold extremities, dizziness, fatigue

Continue to question 45

41. Is the patient suffering from:
- Bradycardia
- Severe asthmatic disease

Contact prescriber: β-blockers are contraindicated in these conditions

42. Which β-blocker is the patient using:
- Atenolol
- Metoprolol
- Carvedilol
- Labetalol
- Oxprenolol
- Pindolol
- Propranolol

Non-selective β-blockers

These agents can mask the symptoms of hypoglycaemia to a greater extent than selective ones: recommend atenolol or metoprolol instead

43. Is the daily dose within the recommended range?

- Atenolol: 25 – 100 mg in 1 dose
- Carvedilol: 12.5 – 50 mg in 1 dose
- Labetalol: 200 – 800 mg in 2 doses
- Metoprolol: 50 – 200 mg in 1 – 2 doses
- Oxprenolol: 80 – 320 mg in 2 doses
- Pindolol: 10 – 30 mg in 2 – 3 doses
- Propranolol: 40 – 320 mg in 2 – 3 doses

if not

Contact prescriber to adjust dose / frequency
44. Is the patient also using:
   - Verapamil
   - Diltiazem
   - Rifamycins

   Antihypertensive effects of β-blockers might be decreased

   Closely monitor blood pressure

45. Is the patient using:
   - An ACE inhibitor
   - No ACE inhibitor

   ACE inhibitors may worsen renal function

   Monitor renal function and use with caution. Dosage adjustments might be necessary. Risk of hyperkalaemia is also increased: monitor potassium levels

46. Is the patient suffering from:
   - Renal impairment

   ACE inhibitors may worsen renal function

   Monitor renal function and use with caution. Dosage adjustments might be necessary. Risk of hyperkalaemia is also increased: monitor potassium levels

47. Is the daily dose within the recommended range?

   | Drug            | Dose Range          |
   |-----------------|---------------------|
   | Captopril       | 25 – 100 mg in 2 doses |
   | Enalapril       | 5 – 40 mg in 1 – 2 doses |
   | Fosinopril      | 10 – 40 mg in 1 dose |
   | Lisinopril      | 5 – 40 mg in 1 dose |
   | Perindopril     | 4 – 8 mg in 1 dose |
   | Quinapril       | 5 – 40 mg in 1 or 2 doses |
   | Ramipril        | 2.5 – 10 mg in 1 or 2 doses |
   | Trandolapril    | 1 – 4 mg in 1 dose |

   if not

   Contact prescriber to adjust dose / frequency

48. Is the patient also using:
   - Potassium-sparing diuretics
   - Potassium supplements
   - Angiotensin II antagonists
   - Lithium

   Increased risk of hyperkalaemia

   Monitor potassium concentrations

   Lithium toxicity might occur

   Monitor serum lithium levels

49. Is the patient using:
   - An angiotensin II antagonist
   - No angiotensin II antagonist

   Ask patient about side effect: dizziness. Check for hyperkalaemia

   Continue to question 53

50. Is the patient suffering from:
   - Renal impairment

   ACE inhibitors may worsen renal function

   Monitor renal function and use with caution. Dosage adjustments might be necessary. Risk of hyperkalaemia is also increased: monitor potassium levels

51. Is the daily dose within the recommended range?

   | Drug            | Dose Range          |
   |-----------------|---------------------|
   | Candesartan     | 8 – 16 mg in 1 dose |
   | Eprosartan      | 400 – 800 mg in 1 dose |
   | Irbesartan      | 75 – 300 mg in 1 dose |
   | Losartan        | 25 – 200 mg in 1 dose |
   | Telmisartan     | 20 – 80 mg in 1 dose |

   if not

   Contact prescriber to adjust dose / frequency

52. Is the patient also using:
   - Potassium-sparing diuretics
   - Potassium supplements
   - Angiotensin II antagonists
   - Lithium

   Increased risk of hyperkalaemia

   Monitor potassium concentrations

   Lithium toxicity might occur

   Monitor serum lithium levels
53. Is the patient using:
   - A calcium channel blocker
   - No calcium channel blocker

   Ask patient about side effect: flushing, headache, ankle edema

Continue to question 59

54. Which calcium channel blocker is the patient using?
   - Amlodipine
   - Felodipine
   - Lercanidipine
   - Nifedipine
   - Diltiazem
   - Verapamil

   Antihypertensive effect less strong than other calcium channel blockers: check indication and recommend a dihydropyridine instead if used for hypertension. Continue to question 56

Continue to question 58

55. Is the patient also using:
   - Rifamycins
   - Phenytion
   - Pioglitazone
   - Carbamazepine
   - Grapefruit juice
   - Norfloxacin
   - Imidazoles (e.g. fluconazole)
   - None of these

   Antihypertensive effects of calcium channel blockers might be decreased

Monitor blood pressure. Continue to question 58

56. Is the patient suffering from:
   - Heart failure NYHA Class I – IV
   - Bradycardia

   Contact prescriber: diltiazem and verapamil are contra-indicated in these conditions

Continue to question 58

57. Is the patient also using:
   - Macrolides (e.g. erythromycin)
   - Digoxin

Increased risk of cardiac toxicity

Monitor cardiac function

Digoxin toxicity might occur

Monitor digoxin levels and clinical status

58. Is the daily dose within the recommended range?

- Amlodipine: 2.5 – 10 mg in 1 dose
- Felodipine: 5 – 20 mg in 1 dose
- Lercanidipine: 10 – 20 mg in 1 dose
- Nifedipine: 20 – 80 mg in 2 doses (controlled release): 20 – 120 mg in 1 dose
- Diltiazem: 180 – 360 mg in 1 dose
- Verapamil: 120 – 480 mg in 1 dose

if not

Contact prescriber to adjust dose / frequency

59. Is the patient using:
   - A selective α-blocker
   - No selective α-blocker

   Not the preferred agent in the hypertension management of type 2 diabetes

Check medication history: consider recommending another antihypertensive agent

Continue to question 61

60. Is the daily dose within the recommended range?

- Prazosin: 12.5 – 25 mg in 2 or 3 doses
- Terazosin: 12.5 – 25 mg in 1 dose

if not

Contact prescriber to adjust dose / frequency

Lipid control

61. What’s the patient’s lipid profile?
   - Total cholesterol > 4.0 mmol/L
   - LDL cholesterol > 2.5 mmol/L
   - HDL cholesterol < 1.0 mmol/L
   - Triglycerides > 1.5 mmol/L
   - None of the above

Patient’s cholesterol levels are poorly controlled

A dose change or additional lipid-lowering agent might be needed

Patient’s triglyceride levels are poorly controlled

Check glycaemic control: high blood glucose levels can cause high triglycerides

Patient’s lipid levels are well controlled
62. Is the patient suffering from:
- Hypothyroidism
- Obstructive liver disease
- Nephrotic syndrome

These might be secondary causes of dyslipidaemia
Make sure these disorders are being treated adequately

63. Is the patient using any lipid-lowering medications?
- Yes
- No

Nearly all patients with type 2 diabetes should be using lipid-lowering medication(s)
Check for missing therapy. Continue to question 77

64. Is the patient using:
- A statin
- No statin

Ask patient about side effects: gastrointestinal upset, headache and especially muscle aches (for risk of rhabdomyolysis)
Continue to question 70

65. Is the patient suffering from:
- Hepatic impairment

Increased risk of hepatotoxicity
Carefully monitor liver function, consider discontinuing the statin and changing therapy if impaired

66. Is the daily dose within the recommended range?
- Atorvastatin: 10 – 80 mg in 1 dose
- Simvastatin: 10 – 80 mg in 1 dose
- Fluvastatin: 40 – 80 mg in 1 or 2 doses
- Pravastatin: 20 – 80 mg in 1 or 2 doses
- Rosuvastatin: 5 – 40 mg in 1 dose

if not
Contact prescriber to adjust dose / frequency

67. Which statin is the patient using?
- Atorvastatin
- Simvastatin
- Fluvastatin
- Pravastatin
- Rosuvastatin

Continued to question 68

68. Is the patient also using:
- Imidazoles (e.g. fluconazole)
- Macrolides (e.g. erythromycin)
- Protease inhibitors
- Rifamycins
- Carbamazepine
- Fibrates

Atorvastatin or simvastatin levels may be increased: higher risk of adverse effects
Monitor the patient’s clinical response

69. Is the patient also using:
- Cyclosporin
- Fibrates

Increased risk of myopathy
Carefully monitor for clinical symptoms

70. Is the patient using:
- A fibrate
- No fibrate

Ask patient about side effects: dyspepsia and abdominal pain
Continue to question 74

71. Is the patient suffering from:
- Severe renal impairment
- Hepatic impairment

Contact prescriber: fibrates are contra-indicated in these conditions

72. Is the daily dose within the recommended range?
- Fenofibrate: 145 mg in 1 dose
- Gemfibrozil: 1200 mg in 2 doses

if not
Contact prescriber to adjust dose / frequency

73. Is the patient also using:
- Warfarin

Increased risk of bleeding
Avoid combination or monitor INR frequently
74. Is the patient using:
   - Ezetimibe
   - No ezetimibe
   - Cyclosporin
   - levels of ezetimibe as well as cyclosporine might be elevated

75. Is the daily dose within the recommended range?
   - Ezetimibe 10 mg in 1 dose
   - if not
   - Contact prescriber to adjust dose / frequency

76. Is the patient also using:
   - Platelet control
   - Ask patient about side effects: myopathy, headache and diarrhea
   - Continue to question 77

Platelet control
77. Is the patient using any anti-platelet medications?
   - Yes
   - Nearly all patients with type 2 diabetes should be using anti-platelet medication(s)
   - Continue checklist
   - Check for missing therapy. Continue to question 88
   - No

78. Is the patient using:
   - Low-dose aspirin (< 150 mg)
   - No low-dose aspirin
   - Ask patient about side effects: gastrointestinal irritation and increased bleeding time
   - Continue to question 81

79. Is the patient suffering from:
   - Active peptic ulceration
   - Allergy to aspirin or NSAIDs
   - A bleeding disorder
   - Severe renal impairment
   - Hepatic impairment
   - Increased risk of bleeding
   - Carefully monitor aspirin use
   - Contact prescriber: aspirin is contra-indicated in these conditions

80. Is the daily dose within the recommended range?
   - Aspirin 75 – 150 mg in 1 dose
   - if not
   - Contact prescriber to adjust dose / frequency

81. Is the patient also using:
   - Clopidogrel
   - Carefully monitor concomitant use
   - Increased risk of bleeding
   - Contact prescriber: clopidogrel is contra-indicated in this condition
   - Other NSAIDs
   - Carefully monitor concomitant use
   - Corticosteroids
   - Efficacy of aspirin might be reduced; increased risk of gastrointestinal irritation
   - Dipyridamole
   - Ask patient about side effects: (gastrointestinal) bleeding, diarrhea and rash
   - No dipyridamole

82. Is the patient using:
   - Clopidogrel
   - No clopidogrel
   - Continue to question 86

83. Is the patient suffering from:
   - An active internal bleeding
   - Hepatic impairment
   - Increased risk of bleeding
   - Carefully monitor clopidogrel use

84. Is the daily dose within the recommended range?
   - Clopidogrel 75 mg in 1 dose
   - if not
   - Contact prescriber to adjust dose / frequency

85. Is the patient also using:
   - NSAIDs
   - Increased risk of bleeding
   - Carefully monitor concomitant use

86. Is the patient using:
   - Dipyridamole
   - No dipyridamole
   - Ask patient about side effects: headache, diarrhea, nausea and hypotension
   - Continue to question 86

87. Is the daily dose within the recommended range?
   - Dipyridamole 400 mg in 2 doses
   - if not
   - Contact prescriber to adjust dose / frequency

Adherence
88. Is the patient adherent to his / her medications?
   - Yes
   - Discuss strategies with the patient to try to improve adherence
   - No
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