Adverse drug events and overtreatment often found in bariatric polypharmacy patients: an interim analysis of a cross-sectional study on Drug Related Problems after BARiatric surgery (DRePBAR)

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Background: While bariatric surgery is an effective treatment for morbid obesity, anatomical and metabolic changes may pose a risk for drug related problems (DRPs). Polypharmacy patients may be even at higher risk. Thus far, no previous research has been performed on DRPs in bariatric polypharmacy patients in the years after surgery.

Aim: The aim of this study is to determine which DRPs are present in bariatric polypharmacy patients, and what drugs are associated with these DRPs.

Methods: In this single-centre cross-sectional study, polypharmacy patients that underwent a primary sleeve gastrectomy (SG) or Roux-en-Y-gastric bypass (RYGB) in the St. Antonius hospital, Nieuwegein, the Netherlands, in 2018 and 2019, were approached for a medication review. As part of the medication review, a structured telephone interview took place. Outcomes were discussed in multidisciplinary Expert Panel meetings. The number of patients with DRPs, the number of DRPs per patient and the categories of DRPs were assessed. Furthermore, drugs suspected to cause these DRPs were determined both in general and per category of DRPs. A Mann-Whitney U-test was performed to compare the number of DRPs per type of surgery.

Results: In this interim analysis, DRPs are found in all 34 patients (100.0%), with a median of 5.00 (interquartile range (IQR) 3.00-8.00) DRPs per patient. Adverse drug events (ADEs) (n=57, 28.6%) and overtreatment (n=29, 14.6%) are most often found. Calcium (n=35, 14.9%), drugs for peptic ulcer and gastro-oesophageal reflux disorder (GORD), and bariatric multivitamin supplements (both n=24, 10.2%) are most often suspected to cause DRPs in general. Antidepressants (n=8, 11.1%) and antithrombotic agents (n=7, 9.7%) are most often suspected to cause ADEs, drugs for peptic ulcer and GORD and lipid modifying drugs (both n=6, 16.7%) are most often suspected to cause overtreatment. When comparing SG and RYGB, no differences are found in the number of DRPs per patient (5.00 (IQR 3.00-9.25) and 5.00 (IQR 3.00-9.00), respectively, Mann-Whitney U: 3420.00, p=0.385).

Conclusions: Results of this interim analysis imply that DRPs are prevalent in bariatric polypharmacy patients (median of 5.00 DRPs per patient) and indicate an apparent need for standardised medication reviews in this population.

Introduction

Obesity is a serious health condition in which excessive fat accumulation substantially increases the risk of comorbidities like type 2 diabetes, heart disease, psychological disorders and several types of cancers (1–3). The prevalence of obesity is increasing (4), and bariatric surgery has proven to be an effective treatment for morbid obesity (5,6). Additionally, it has been shown to have a positive influence on several obesity-related comorbidities (7–9). The sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are two of the most common types of bariatric surgery. Both procedures substantially influence the anatomy of the gastrointestinal (GI) tract. During SG, the stomach is reduced in size by 80% (10), whilst during RYGB a gastric pouch is created and connected to the jejunum. In patients that underwent a RYGB, intake therefore bypasses the duodenum, whilst the duodenum stays available for transport of digestive fluids (11).

Despite the need for an effective treatment for obesity, bariatric surgery has also introduced new challenges. Clinical practice has shown that patients may experience drug related problems (DRPs) after surgery. According to the Pharmaceutical Care Network Europe (PNCE), DRPs are defined as '*events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes*' (12). Previous studies have shown that DRPs can lead to outpatient visits, hospital (re)admission and even death (13,14). Several studies have been performed on DRPs in different patient populations (15–18). However, to the best of our knowledge, no previous studies have been performed on DRPs in the bariatric population in the years after surgery. In a study on the perioperative period of bariatric surgery, DRPs could be found in 89.1% of the patients, with a median of 2.2 DRPs per patient (19).

However, due to the anatomical changes introduced by bariatric surgery, an increase in the number of DRPs after surgery can be expected. First, it is known that drug metabolism can be influenced by the anatomical changes (20–22). Also, GI problems like diarrhoea and vomiting may occur (23,24). These GI problems may shorten residence time and therefore limit absorption of administered drugs. Moreover, the gastric volume decreases (25), causing restrictions in intake. These restrictions may lead to difficulties with administration of drugs multiple times a day. The necessary intake of proton pump inhibitors (PPIs), mineral supplements, and specialised bariatric multivitamin supplements after surgery (26,27), may contribute to these difficulties. Difficulties with administration may apply especially to polypharmacy patients, because of the already high number of drugs. Apart from difficulties with administration, it is known that a higher number of drugs is associated with the risk for DRPs (28). Hence, bariatric polypharmacy patients may be prone to DRPs even more.

Therefore, the aim of this study is to assess the number of polypharmacy patients that have undergone bariatric surgery and experience DRPs along with the number of DRPs per patient. Furthermore, we aim to assess the category of DRPs, and to gain insight into the types of drugs often suspected to cause DRPs, both in general and per category of DRPs. Apart from that, we aim to examine possible differences in DRPs between SG and RYGB surgery. Moreover, we aim to gain insight into patients' perspective on DRPs. In this manuscript, an interim analysis of this study will be performed.

Ethics approval

This study was performed in line with the Declaration of Helsinki. Approval for this non-WMO study was granted by the Ethics Committee of the St. Antonius Hospital, Nieuwegein, the Netherlands (1 December 2021/ID: W21.214).

Methods

Setting and patient population

In this single-centre cross-sectional study, DRPs of polypharmacy patients that have undergone primary bariatric surgery in the St. Antonius hospital, Nieuwegein, the Netherlands, between 1 January 2018 and 31 December 2019, were assessed. The St. Antonius hospital is located in the centre of the Netherlands. Yearly ~1,000 patients undergo bariatric surgery in this hospital. Prior to and following bariatric surgery, patients receive guidance regarding necessary life style changes through individual and group meetings.

Patients were considered polypharmacy patients when using ≥5 prescription drugs. Drug formulations were assigned prescription drugs when registered in the Medicines Information Bank (MIB) of the Dutch Medicines Evaluation Board (MEB) (29) at the time of this study. All other formulations were assigned non-prescription drugs. For prescription drugs, every individual active pharmaceutical ingredient (API) in a formulation was considered an individual prescription drug. For non-prescription drugs, all formulations were considered a single drug, regardless of the number of APIs.

Inclusion and exclusion criteria

Polypharmacy patients were eligible for inclusion if they had undergone a primary SG or RYGB between 1 January 2018 and 31 December 2019. Medication reconciliation prior to surgery, according to the definition of Karapinar-Çarkit *et al.* (30) was required. All patient communication in this study was performed in Dutch. Therefore, patients that did not possess effective Dutch language skills, apparent through initial contact with the performing researcher, were excluded. This also applied to patients with cognitive decline or impairment, in line with the principles of the Declaration of Helsinki. Furthermore, patients were excluded when conversion from SG to RYGB had taken place, since patient conditions leading to a conversion were expected to introduce bias.

All patients eligible for inclusion were approached via telephone calls between 9.00 A.M. and 6.00 P.M., with a maximum of one attempt per day and three attempts per patient. When willing to participate, patients received study information by post and were asked to provide signed informed consent. Patients were reminded to provide informed consent a maximum of three times, with a maximum of one attempt a day.

Medication review

After receiving informed consent, a medication review was performed. As part of the review, patients were invited for a structured telephone interview. Prior to this study, no questionnaire on DRPs in bariatric patients was available yet. However, a validated questionnaire on DRPs in the geriatric population was available (31). This questionnaire includes questions on physical and practical complaints. The questionnaire was adapted to the bariatric population by adding drug-specific complaints for psychotropics, psychostimulants, levothyroxine, contraceptive drugs, anticonvulsants and antithrombotics. These drugs and drug-specific complaints were based on literature and clinical experience from an Expert Panel consisting of anaesthesiologists, bariatric surgeons, clinical pharmacologists, hospital pharmacists, internist endocrinologists, and specialised bariatric nurses.

As all patient communication was performed in Dutch, the structured telephone interview was as well. Therefore, a translation of the questionnaire can be found in Table A in the Annex. For all physical

complaints, questions regarding the severity of the complaint (mild, moderate or severe), time after surgery to experiencing the complaint, the presence prior to surgery, and if applicable, the severity prior to surgery were part of the questionnaire. These questions can be found in Section 1.1 in Table A in the Annex. All physical complaints and the added drug-specific physical complaints can be found in Section 1.2 and 1.3 in Table A in the Annex, respectively. Questions on practical complaints can be found in Section 2 in Table A in the Annex.

Apart from the structured telephone interview, drugs prior to surgery (extracted from the information on medication reconciliation from the hospital information system) were compared to drugs at the time of the interview. Furthermore, drug use at time of the interview was compared to the most recent guidelines on the associated health conditions and diseases, and the Dutch pharmacy guidelines on drug use after bariatric surgery (32).

Assessment of DRPs

All outcomes of the medication review were reviewed by a fifth-year pharmacy student and two hospital pharmacists, and presented in Expert Panel meetings. In these meetings, DRPs were identified. During identification, the following patient characteristics were taken into account: age, gender, body mass index (BMI) at time of surgery and at time of the interview, type of surgery (SG or RYGB), smoking status, alcohol consumption, and drugs prior to surgery and at time of the interview. Furthermore, the complaints itself and in case of physical complaints, the severity of the complaint, the time to experiencing the complaint, the presence of the complaint prior to surgery and, if applicable, the severity prior to surgery were taken into account. Physical complaints that were equally severe prior to surgery and after surgery were not taken into consideration, except when such complaints were emphatically assigned to a drug by a patient. In this latter situation, these DRPs were also marked as patient-reported DRPs. Furthermore, all practical complaints were marked as patient-reported DRPs.

Classification and categorisation of DRPs

All DRPs were classified on certainty (certain, probable or uncertain). Certain and probable DRPs were considered DRPs with sufficient certainty. Uncertain DRPs were taken into consideration separately. Regardless of certainty, all DRPs were categorised into one of 19 categories. These categories were based on a previous study on DRPs by Huiskes *et al.* in cardiovascular patients (33). Because of the specific features of the bariatric population and its drug use, two categories were added. *DRP 18. Vitamin and/or mineral deficiency* was added since previous studies have shown vitamin and mineral deficiencies are frequently present after surgery, even in patients using bariatric multivitamin supplements (34,35). These bariatric multivitamin supplements contain higher doses compared to regular supplements (27). *DRP 19. High costs* was added since reimbursement of vitamin supplements is not provided by the Dutch health insurance system, and previous research on the bariatric population has described high costs of vitamin supplements as a cause of noncompliance (36). An overview and explanation of all categories of DRPs can be found in Table B in the Annex.

For all DRPs, the suspected (combination of) drugs were discussed and grouped at the World Health Organisations' Anatomical Therapeutic Chemical classification system (ATC) level 3, describing the anatomical, therapeutic and pharmacological subgroups of drugs (37). Furthermore, non-prescription drugs were divided in 'bariatric multivitamin supplements', 'non-bariatric multivitamin supplements', and 'other non-prescription drugs'.

Data selection

Data was collected to describe patient characteristics consisting of age at time of the surgery and at time of the interview, gender, BMI at time of the interview and at time of the surgery, and level of education. Moreover, the number of prescription and non-prescription drugs prior to surgery and at time of the interview, was collected.

Outcomes measures

The primary outcomes were the number of patients that experienced DRPs, the number of DRPs per patient and the categories of DRPs experienced. The secondary outcomes were the types of drugs most often suspected to cause DRPs, in general and per category of DRP, and the number of patient-reported DRPs with which the Expert Panel did agree and did not agree.

Data analysis

To assess the number of DRPs per patient, the median number and interquartile range (IQR) of DRPs were calculated. Furthermore, the number of DRPs per category were determined and frequencies of categories were calculated as percentages (%) of the total number of DRPs. For DRPs in general, the frequencies of drugs suspected to cause DRPs were calculated as percentages (%) of the total number of suspected drugs. For each category, the frequencies of drugs suspected to cause DRPs were calculated as percentages (%) of the total number of suspected drugs in that particular category. To examine the possible differences between types of surgery, the median number of DRPs per patient were assessed per type of surgery (SG and RYGB). Furthermore, the frequency of patient-reported DRPs was determined and calculated as percentage (%) of the total number of DRPs. The number of patient-reported DRPs that the Expert Panel did agree and did not agree on (partly or completely) were determined as well, and calculated as percentages of DRPs (%).

To compare patient characteristics, independent sample T-tests, Mann-Whitney U-tests and a Fisher's Exact test were performed. To compare the number of DRPs per patient per type of surgery (SG or RYGB), a Mann-Whitney U-test was performed. All statistical analyses were performed using IBM SPSS Statistics version 26. A *p*-value of <0.05 was considered as statistically significant.

In data analysis, a distinction was made between classifications of DRPs. All certain and probable DRPs were grouped since both considered DRPs with sufficient certainty, while uncertain DRPs were analysed separately. For uncertain DRPs, no distinctions were made between types of surgery.

Results

From 1 January 2018 – 31 December 2019, 1373 patients underwent bariatric surgery in the St. Antonius Hospital, of which 534 patients (38.9%) were eligible for inclusion. Of these 534 patients, 142 (26.6%) were willing to participate on 9 January 2023. A total of 72 patients (50.7%) have given written informed consent. For 34 patients (47.2%) a medication review has been performed and outcomes have been discussed in Expert Panel meetings. These patients are included in this interim analysis. Figure 1 gives an

overview of the route of inclusion. Patient characteristics of patients included in this study on 9 January 2023 and in this interim analysis, are shown in Table 1.

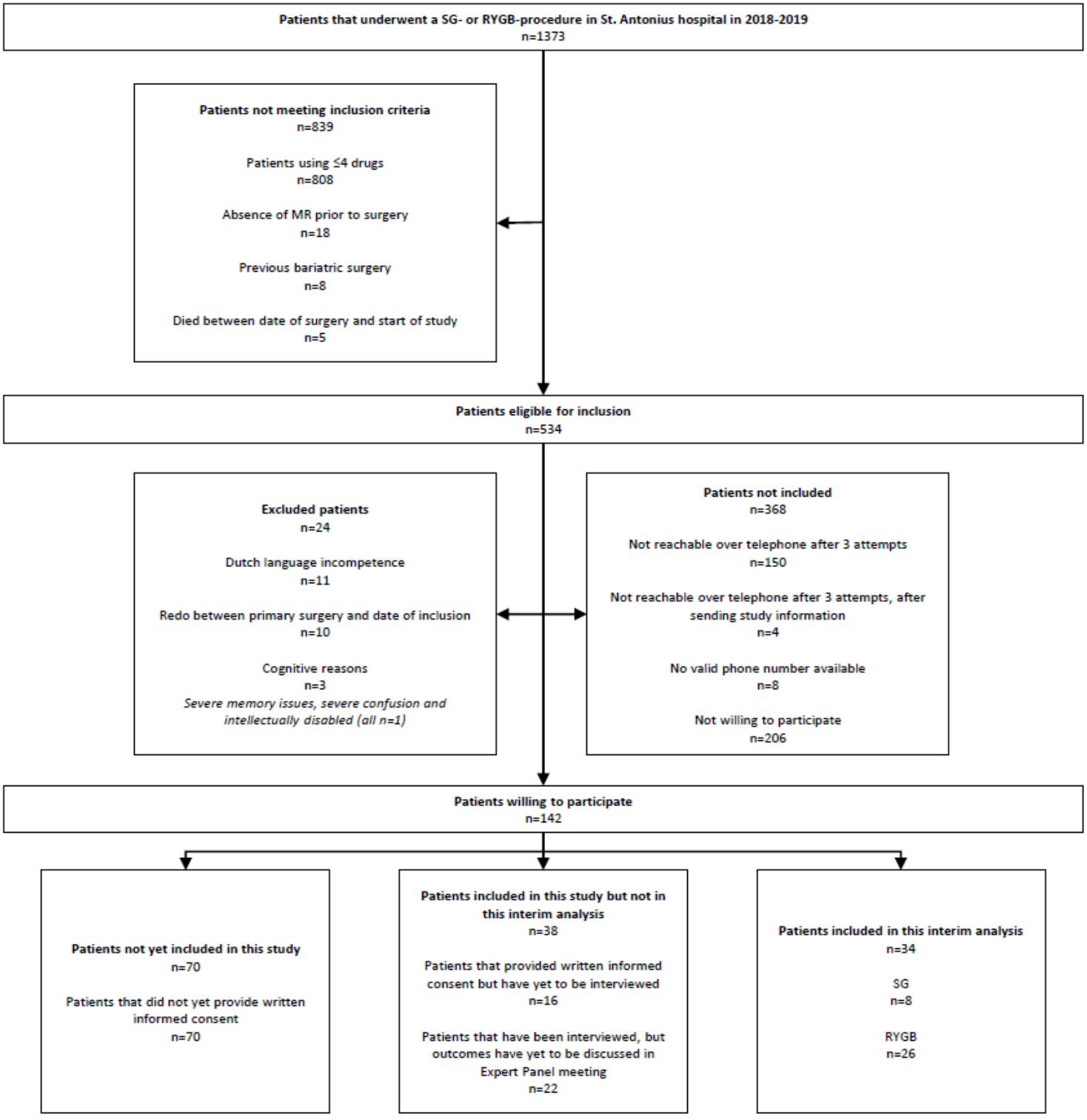

Figure 1. Flowchart of inclusion in the interim analysis. This flowchart shows the route of inclusion of bariatric polypharmacy patients in this single-centre cross-sectional study, and specifically in this interim-analysis. Of the 72 patients included in this study on 9 January 2023, 34 patients are included in this interim analysis. Of these 34 patients, 8 underwent a SG and 26 a RYGB. *MR: medication reconciliation; Redo: revisional weight loss surgery; RYGB: Roux-en-Y-gastric bypass; SG: sleeve gastrectomy.*

Table 1. Patient characteristics of patients included in this study and in this interim analysis. Patient characteristics are described for both patients included in this study on 9 January 2023 (n=72) and for patients included in this interim analysis (n=34). Characteristics of the patients included in this interim analysis are also shown per type of bariatric surgery (SG and RYGB) and compared between these groups.

Patient characteristics	Included patients	Interim analysis	SG	RYGB
Patients, n (% of patients included in this interim analysis)	72	34 (100.0%)	8 (23.5)	26 (76.5)
Number of patients that underwent SG surgery, n (%)	17 (23.6)	8 (23.5)	n/a	n/a
Age at time of surgery, mean ±sd	57.58±8.10	57.82±8.70	57.00±12.1	58.07±7.67
Age at time of interview, mean ±sd	n/a	61.58±8.71	60.72±12.06	61.84±7.70
Female gender, n (% of all patients)	52 (72.2)	25 (73.5)	6 (75.0)	19 (73.1)
BMI at the time of surgery, median (IQR)	41.18 (38.53-44.22)	41.62 (39.61-45.15)	45.00 (42.69-50.80)[*1]	41.00 (39.14-43.43)[*1]
BMI at the time of interview, median (IQR) (missing)	n/a	29.35 (27.03-31.95) (2)	33.15 (31.73-36.63)[*2]	27.91 (26.76-29.72)[*2] (2)
Time to interview, mean ±sd	n/a	3.76±0.221	3.73±0.116[*3]	3.77±0.246[*3]
Number of drugs prior to surgery, median (IQR)	8.00 (7.00-11.00)	8.00 (6.75-11.00)	7.50 (7.00-11.00)	8.50 (6.25-10.75)
Prescription drugs	8.00 (6.00-11.00)	8.00 (6.00-11.00)	7.50 (6.25-11.00)	8.00 (6.25-10.75)
Non-prescription drugs	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Number of drugs at time of interview, median (IQR)	n/a	9.50 (8.00-13.00)	11.00 (7.50-13.75)	9.00 (8.00-17.00)
Prescription drugs	n/a	8.00 (6.00-10.00)	8.50 (6.25-9.75)	8.00 (6.00-10.00)
Non-prescription drugs	n/a	1.50 (1.00-3.00)	2.00 (1.00-3.75)	1.00 (1.00-2.75)
Use of bariatric multivitamins at time of interview, n (%)	n/a	17 (50.0)	3 (37.5)	14 (53.8)
Education, n (% of all patients/*per type of surgery*)	n/a	34 (100.0)	8 (*100.0*)	26 (*100.0*)
Primary education	n/a	7 (20.6)	2 (*25.0*)	5 (*19.2)*
Secondary education	n/a	15 (44.1)	2 (*25.0*)	14 (*53.8*)
Higher education	n/a	12 (35.3)	4 (*50.0)*	7 (*26.9*)

BMI: body mass index (kg/m^2), SG: Sleeve Gastrectomy; RYGB: Roux-en-Y-Gastric Bypass
SG vs. RYGB: [*1] p=0.012; [*2] p=0.001; [*3] p=0.011

Number and categories of DRPs assessed by the Expert Panel

DRPs can be found in all patients (n=34, 100.0%), with a total of 199 DRPs (certain n=73, 36.7%; probable 126, n=63.3%) and median of 5.00 (IQR 3.00-8.00) DRPs per patient. The most abundant category is 'Adverse drug events' (ADEs) (n=57, 28.6%), followed by 'Overtreatment' (n=29, 14.6%) and 'No effect' (n=17, 8.5%). Frequencies of all categories can be found in Table 2.

Drugs suspected to cause DRPs

A total of 235 drugs are suspected. Overall, calcium (n=35, 14.9%), drugs for peptic ulcer and gastro-oesophageal reflux disorder (GORD), bariatric multivitamin supplements (both n=24, 10.2%), antidepressants (n=16, 6.8%) and antithrombotic agents (n=12, 5.1%) are suspected most often. Figure 2 displays an extended overview of the most often suspected types of drugs. For 13 DRPs, no specific drug is suspected. An overview of these 13 DRPs can be found in Table C in the Annex.

For 'ADEs', antidepressants (n=8, 11.1%) are the most often suspected type of drugs. For both 'Overtreatment' and 'No effect', drugs for peptic ulcer and GORD (n=6, 16.7% and n=8, 44.4%, respectively) are the most often suspected types of drugs. Table 3 provides a more detailed overview of the drugs most often suspected to cause the most prevalent categories of DRPs. An extended overview, including all categories of DRPs, can be found in Table D in the Annex.

Table 2. Overview of the overall number of drug related problems and frequencies of categories of drug related problems This table provides an overview of the number of all certain and probable drug related problems, the median number per patient and the frequencies of the categories. Categories are sorted from most to least prevalent.

Median number of DRPs (IQR)	5.00 (3.00-8.00)
Number of DRPs, n (% of total)	199 (100.0%)
DRP 5. Adverse drug events	57 (28.6)
DRP 6. Overtreatment	29 (14.6)
DRP 10. No effect	17 (8.5)
DRP 2. Undertreatment	15 (7.5)
DRP 18. Vitamin or mineral deficiency	13 (6.5)
DRP 3. Inappropriate formulation	10 (5.0)
DRP 8. Nonadherence	9 (4.5)
DRP 9. Dose too low	9 (4.5)
DRP 7. Package problem	8 (4.0)
DRP 4. Insufficient drug monitoring	7 (3.5)
DRP 1. Incorrect use	6 (3.0)
DRP 14. Education	6 (3.0)
DRP 11. Dose too high	4 (2.0)
DRP 12. Contraindication	4 (2.0)
DRP 16. Irrational pharmacotherapy	4 (2.0)
DRP 17. Administrative problems	1 (0.5)
DRP 13. Interaction	0 (0.0)
DRP 15. Allergies/intolerance	0 (0.0)
DRP 19. High costs	0 (0.0)

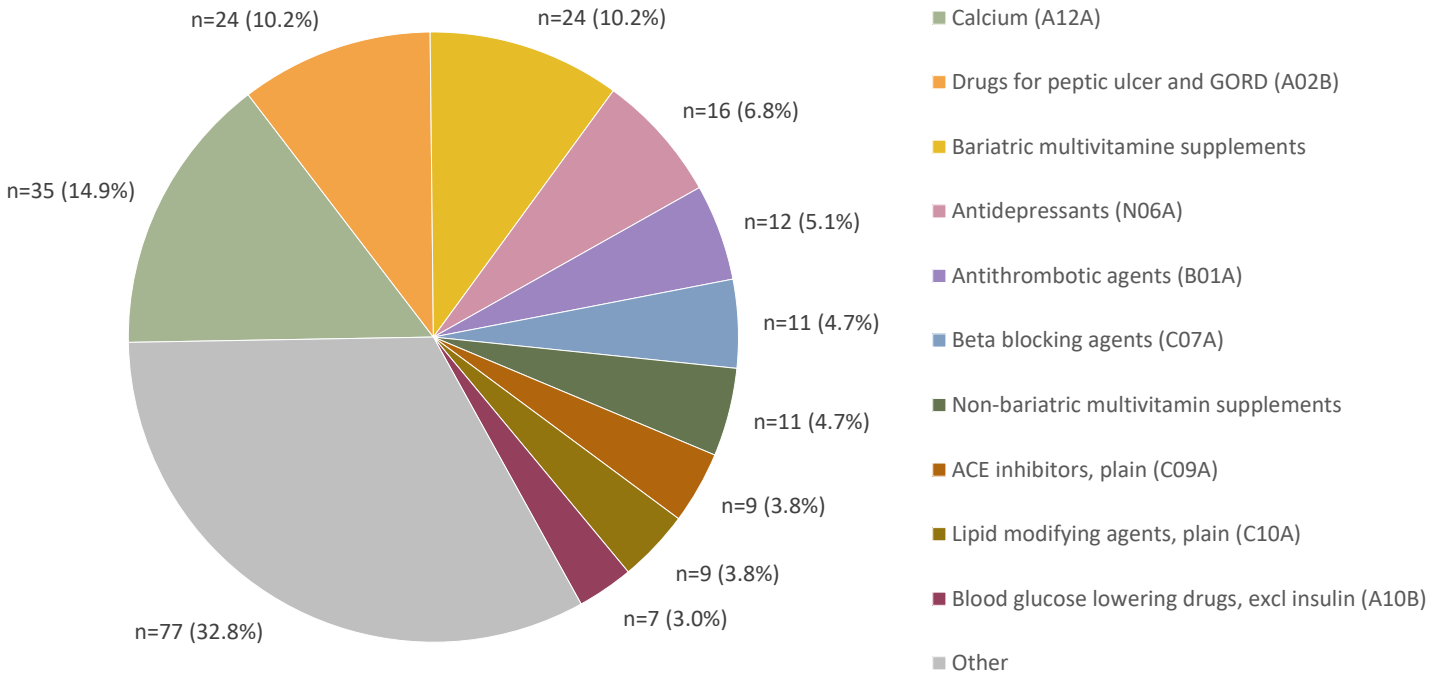

Figure 2. Overview of the types of drugs most often suspected to cause drug related problems. The pie chart displays and overview of the types of drugs most often suspected to cause certain and probable DRPs in 34 polypharmacy patients that underwent SG (n=8) and RYGB (n=26). Drugs are categorised on ATC 3 level. For non-bariatric multivitamin supplements and bariatric multivitamin supplements, no ATC-code is available, since these are non-prescription drugs. *ACE: angiotensin converting enzyme; ATC: Anatomical Therapeutic Chemical classification system; GORD: gastro-oesophageal reflux disease.*

Table 3. Overview of the types of drugs most often suspected to cause the three most prevalent categories of drug related problems. For all certain and probable DRPs, categories of DRPs and suspected types of drugs per category of DRP are presented from most frequent to least frequent. Types of drugs are organised on ATC level 3, describing the anatomical, therapeutic and pharmacological subgroup of drugs. *The number of suspected drugs per category of DRP were 73 for DRP 5. Adverse drug events, 36 for DRP 6. Overtreatment and 18 for DRP 10. No effect.

Categories of DRPs	Type of drugs (ATC level 3)	n (% of all drugs suspected to cause this category of DRPs*)
DRP 5. Adverse drug events	Antidepressants (N06A)	8 (11.1)
	Antithrombotic agents (B01A)	7 (9.7)
	Drugs for peptic ulcer and GORD (A02B)	6 (8.3)
	ACE inhibitors, plain (C09A)	6 (8.3)
DRP 6. Overtreatment	Drugs for peptic ulcer and GORD (A02B)	6 (16.7)
	Lipid modifying agents (C10A)	6 (16.7)
	Beta blocking agents (C07A)	4 (11.1)
DRP 10. No effect	Drugs for peptic ulcer and GORD (A02B)	8 (44.4)
	Antidepressants (N06A)	3 (16.7)
	Other analgesics and antipyretics (N02B)	2 (11.1)

ACE: angiotensin converting enzyme; ATC: Anatomical Therapeutic Chemical classification system; DRPs: drug related problems; GORD: gastro-oesophageal reflux disease.

Differences between SG and RYGB

The median number of DRPs per patient (SG: n=50 (25.1%); RYGB: n=149 (74.9%)), does not differ per type of surgery (median SG 5.00 (IQR 3.00-9.25); RYGB 5.00 (IQR 3.00-9.00); Mann-Whitney U: 3420.00, *p*=0.385).

Patient-reported DRPs

Of the 199 DRPs, 92 DRPs (46.2%) are also patient-reported. For 84 DRPs (91.3%), the Expert Panel agrees that the DRP is caused by the drug assigned by the patient, whilst for 8 DRPs (8.7%) the Expert Panel suspects a different drug than the one assigned by the patient. A total of 29 patient-reported DRPs were not considered DRPs by the Expert Panel. Therefore, these were not classified on certainty.

Uncertain DRPs

DRPs classified as uncertain are found in 23 patients (67.7%), with a total of 61 DRPs and median of 4.00 (IQR 2.00-7.00) DRPs per patient. The most abundant category is 'ADEs' (n=33, 54.1%), followed by 'No effect' (n=10, 16.4%) and 'Dose too low' and Vitamin and/or mineral deficiency' (both n=4, 6.6%). Frequencies of all categories can be found in Table E in the Annex.

A total of 64 drugs are suspected. Overall, lipid modifying agents (n=8, 12.5%), antidepressants (n=7, 10.9%) and bariatric multivitamin supplements (n=5, 7.8%) are suspected most often. For 5 DRPs, no specific drug is suspected. An overview of these 5 DRPs can be found in Table F in the Annex.

For 'ADEs', antidepressants (n=8, 20.5%) are the most often suspected type of drugs. For 'No effect', drugs for peptic ulcer and GORD (n=4, 4.4%) are the most often suspected type of drugs. For 'Dose too low' and 'Vitamin and/or mineral deficiency', non-bariatric multivitamin supplements (n=4, 100.0%) and bariatric multivitamin supplements (n=4, 100.0%) are the most often suspected type of drugs, respectively. An overview of all suspected types of drugs, including all categories of DRPs, can be found in Table G in the Annex.

Of the 61 DRPs, 10 DRPS (16.4%) are also patient-reported. For 8 DRPs (80.0%), the Expert Panel agrees that the DRP is caused by the drug assigned by the patient, whilst for 2 DRPs (20.0%), the Expert Panel suspects a different drug than the one assigned by the patient.

Discussion

In this interim analysis, all patients experienced DRPs, with a total of 199 DRPs (median 5.00 (IQR 3.00-8.00) with sufficient certainty. Half of these DRPs are also patient-reported. ADEs, overtreatment and no effect are most frequently found. Overall, calcium, drugs for peptic ulcer and GORD and bariatric multivitamin supplements are most frequently associated with DRPs.

When comparing the findings of this interim analysis with the study on perioperative DRPs in the bariatric population from Wang *et al.,* the percentage of patients is higher (89.1% versus 100.0%), as well as the number of DRPs per patient (median 2.20 versus 5.00 DRPs per patient). This may indeed imply an increase in DRPs in the years after surgery. However, due to differences in patient characteristics, these results cannot directly be compared. First, polypharmacy was no inclusion criterion in the study by Wang *et al*. Furthermore, mean age in this interim analysis is 57.8 years, while the mean age in the study by Wang *et al.* was 32.2 years (19). When comparing the age of our study population with the median age of primary bariatric surgery world-wide (42 years) and in the Netherlands (45 years) (38), age in our population appears to be quite high as well. This is important, since it is known that the number of drugs and higher age may be predisposing factors for DRPs (39). The relatively high age of the patients included in this interim analysis could be due to approaching patients and performing the structured telephone interviews during office hours. It can be expected that younger people are more likely to be at work themselves during office hours, making them less able to participate. Thereby, the number of DPRs in this interim analysis could be an overestimation of the situation in daily clinical practice.

However, when comparing the findings of this interim analysis with studies on geriatric polypharmacy populations, the number of DRPs per patient in our population in relatively high as well. A study from Chau *et al.* on DRPs in elderly polypharmacy patients (mean age 78 years), retrieved DRPs via medication reviews from 318 community pharmacies. In this study, a median of 2.00 (IQR 1.00-4.00) DRPs was found (17). Finkers *et al.* performed a study on DRPs in nursing home settings (mean age 80 years), in which a mean of 3.5 DRPs per patient was found (18). Even though the mean age in both studies was higher, the number of DRPs are lower compared to our findings. This could be explained by the expected influence of bariatric surgery on DRPs and the specific patient characteristics of this population. However, this could also be partly due to the use of the questionnaire on specific complaints during the structured telephone interview, since the use of such questionnaire was not implemented in the design of the mentioned studies.

While ADEs were most often found in this interim analysis (28.6%), this category of DRPs made up for only 8.1% and 3.1% of the DRPs in the studies from Chau *et al.* and Finkers *et al.*, respectively. This relatively high number of ADEs could in theory be explained by altered drug metabolism (20). However, for antidepressants, the most often suspected type of drugs for ADEs, this cannot be supported by literature. Previous studies show a lower absorption of antidepressants (20,40,41), which would logically lead to therapy failure and no effect, rather than ADEs. Therefore, other factors seem to contribute to the abundance of ADEs. One of these could be the assessment of DRPs via questions on complaints, instead of asking patients if they experienced adverse drug reactions.

Overall, calcium, drugs for peptic ulcer and GORD (which include PPIs) and bariatric multivitamin supplements are most often suspected to cause DRPs. All these drugs are standard of care after bariatric surgery. It could be thought that the high prevalence of use can contribute to these findings. However, at the time of the interview only 50.0% of the patients were using bariatric multivitamin supplements. And while PPIs are indicated after surgery to prevent stomach ulceration, this is only for the first months after surgery (26). It is known that the prevalence of unnecessary use of PPIs in the western population is increasing (42). The results of this interim analysis imply this also applies to the bariatric polypharmacy population, since drugs for peptic ulcer and GORD are often suspected to cause overtreatment.

Strengths and limitations

This is the first study on DRPs in the bariatric polypharmacy population. In this study, DRPs were thoroughly assessed via patient interviews, which have shown to contribute to identification of DRPs (43). Furthermore, a questionnaire focused on DRPs in the bariatric population was used. Moreover, outcomes of the medication reviews were discussed in multidisciplinary meetings. However, this study also has its limitations. First, the outcomes may be affected by volunteer bias. Patients with complaints regarding their drugs may be more likely to participate. This could lead to an overestimation of the median number of DRPs per patient. Second, the outcomes may also be affected by recall bias. Since the median time between surgery and the structured telephone interview was 3.76 years, patients sometimes needed to make an estimation of the time of occurrence and seriousness of complaints. This was partly dealt with by offering patients to answer 'I don't know' during the interview. Third, information on medication reviews that could have been performed in the community pharmacy, prior to inclusion in this study, was not available. Because of the possibility of DRPs having been solved during these reviews, this could have led to an underestimation of DRPs. Last, these results are only part of an interim analysis, with a yet relatively low number of patients included. This makes it difficult to establish firm conclusions.

Clinical implications

The results of this interim analysis imply that DRPs are prevalent in polypharmacy patients with a history of bariatric surgery. Even though the relatively high age of our study population may contribute to the high number of DRPs, this does not seem to be the only explanation. Therefore, the results of this interim analysis imply the need for implementation of medication reviews in bariatric polypharmacy patients. During these reviews, special attention should be paid to drugs introduced after surgery as part of standard of care. While eventual analysis may strengthen the outcomes of this interim analysis, it may also provide further insight into types of drugs less frequently found due to a low numbers of users. It is important to engage younger bariatric polypharmacy patients as well to participate, to assure representative outcomes for clinical practice. Further research should focus on the best moment to perform medication reviews, to ensure prevention of DRPs and possible consequences.

Conclusions

This is the first study on DRPs in bariatric polypharmacy patients in the years after surgery. While the results of the final report are still to be awaited, the results of this interim analysis highlight the presence of DRPs in this population. ADEs, overtreatment and no effect are most often found. Additionally, the drugs introduced as standard of care after bariatric surgery are most often suspected to cause DRPs. This combination of findings indicate an apparent need for medication reviews in polypharmacy patients following bariatric surgery.

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Annex

Table A. Translation of the Dutch questionnaire to assess drug related problems in bariatric polypharmacy. Questions (Section 1.1) regarding general physical complaints (Section 1.2) were asked. Questions (Section 1.1) regarding drug-specific complaints (Section 1.3) were asked when prior to surgery and/or at time of the interview, patients were using certain drugs. These drugs (with ATC code) are stated in italics below the specific type of drug (e.g. 'Anticonvulsants': *Antiepileptics (N03A)*). All possible answers were mutually exclusive, except when stated differently ('*Not mutually exclusive*'). '[complaint]' means one of the complaints described in Section 1.2 or (if applicable) in Section 1.3. '[open]' means the patient could name any kind of drug. This questionnaire is adjusted to the bariatric population from a questionnaire on drug related problems the geriatric population by Ponjee *et al.* (31).

Section 1.1 Questions regarding physical complaints	
Did you experience [complaint] after surgery?	1. Yes 2. No
If 'Yes': to what extent?	1. Mild 2. Moderate 3. Severe
When did you experience [complaint]? *Not mutually exclusive*	1. <1 year after surgery a. Within 1 month after surgery b. Within 1-3 months after surgery c. Within 3-6 months after surgery d. Within 6-12 months after surgery e. I don't know 2. >1 year after surgery a. 1-2 years after surgery b. 2-3 years after surgery c. 3-4 years after surgery d. I don't know 3. At the moment 4. I don't know
Do you think [complaint] is caused by (a) drug{s})?	1. Yes a. What drug(s)? [open] 2. No 3. I don't know
Did you also experience [complaint] prior to surgery?	1. Yes 2. No
If 'Yes': to what extent?	1. Mild 2. Moderate 3. Severe
Section 1.2 General physical complaints	
Pain	1. Headache 2. Sore throat 3. Abdominal pains 4. Back pain 5. Pain in extremities 6. Muscle strains 7. Joint pain 8. Other pains a. What kind of pain? [open]
Eating/drink	1. Decreased appetite 2. Nausea and/or vomiting 3. Heartburn and/or belching

	4. Stomach ulcer (proven) 5. Dry mouth and/or frequently thirsty 6. Excessive burping
Stool problems	1. Diarrhoea 2. Obstipation 3. Black stools 4. Bloated feeling
Problems urinating	1. Urinating less often 2. Urinating more often 3. Incontinence
Muscles	1. Muscle stiffness 2. Muscle spasms and/or cramps 3. Muscle tremors
Balance and movement	1. Falling without any apparent reason 2. Dizziness or vertigo 3. Feeling of weakness 4. Fatigue
Sleep	1. Somnolence and/or drowsiness 2. Insomnia
Heart and lungs	1. Couching 2. Shortness of breath 3. Chest pain 4. Palpitations 5. Swollen ankles and/or legs
Skin	1. Skin reaction (itching and/or rash) 2. Bruising
Miscellaneous complaints	1. Nosebleeds 2. Eye irritation 3. Poor vision (blurry sight and/or double vision)
Temperature	1. Fever 2. Infections 3. Excessive sweating 4. Hot flashes 5. Excessive blushing
Section 1.3 Drug specific physical complaints	
Psychotropics *Antipsychotics (N05A); Anxiolytics (N05B); Hypnotics and sedatives (N05C); Antidepressants (N06A)*	1. Sombre mood 2. Mood swings 3. Fear 4. Agitation (feeling restless/rushed) 5. Blood pressure fluctuations
Psychostimulants *Psychostimulants, agents used for ADHD and nootropics (N06B)*	1. Hallucinations 2. Difficulty concentrating 3. Fear 4. Agitation (feeling restless/rushed)
Immunosuppressants *Immunosuppressants (L04A)*	1. Acne 2. Thrombosis 3. Flares inflammatory disease
Levothyroxine *Thyroid preparations (H03A)*	1. Insults (in case of epilepsy) 2. Menstrual disorders 3. Hyperthyroidism

	4. Hypothyroidism
Contraceptive drugs *Hormonal contraceptives for systemic use (G03A); Contraceptives for topical use (G02B)*	1. Breakthrough bleedings 2. Amenorrhea
Anticonvulsants *Antiepileptics (N03A)*	1. Insults
Antithrombotics *Antithrombotic agents (B01A)*	1. Bleeding 2. Increased menstrual bleeding 3. Thrombosis 4. Dark urine
Section 2. Practical complaints	
Are you having trouble taking your drugs as prescribed by your doctor? *Not mutually exclusive*	1. No 2. Yes, because it are many drugs at the same time 3. Yes, because one or more of the drugs do not work 4. Yes, because I don't know why I take them 5. Yes, because I experience side effects 6. Yes, because I am afraid of side effects 7. Yes, because I don't feel like it 8. Yes, because I have difficulties keeping the drugs apart 9. Yes, because of other reasons a. Namely [open]
If 'Yes', to what drug(s) does this apply?	[open]
Do you sometimes forget to take your drugs?	1. Yes 2. No
If 'Yes', how often does this happen?	1. Once a month 2. A couple of times a month 3. Once a week 4. A couple of times a week 5. Daily
Do you have practical difficulties with taking your drugs? *Not mutually exclusive*	1. No 2. Yes, because it are many drugs at the same time 3. Yes, because I have difficulties with the times of the day 4. Yes, because I have difficulties with swallowing the drug 5. Yes, because I have difficulties with opening the package 6. Yes, because I have difficulties with reading and/or understanding the instructions on the package 7. Yes, because the taste is bad 8. Yes, because I have difficulties with administering the drug (for example inhalation drugs or eye drops) 9. Yes, because I have to perform an additional action before I can take them (e.g. opening of the package, breaking or dissolving tablets) 10. Other reasons a. Namely [open]
If 'Yes', to what drug(s) does this apply?	[open]
What problems did you face the most concerning drug use following bariatric surgery? *Not mutually exclusive*	10. No problems 11. Stopping drugs 12. Change of drugs 13. Change in dosage form

	14. Change in dose 15. Intake of drugs 16. Starting new drugs
Which changes in drugs did you face since bariatric surgery? *Not mutually exclusive*	1. No changes 2. Change in dose 3. Change in dosage form 4. Change in products 5. Starting new drugs 6. Stopping drugs 7. Other

ATC: Anatomical Therapeutic Chemical classification system.

Table B. Description of categories of DRPs used to categorise drug related problems assessed in polypharmacy patients that underwent bariatric surgery. According to the definitions by Huiskes *et al.* (33). Adjustments and additions made in this study are shown in bold.

Categories of DRP		Description of categories of DRP
1.	Incorrect use	e.g. following standard instructions for use that apply to proper use of the medicine or not feasible for the patient. **In addition: if the patient finds it hard to follow instructions on a particular formulation (e.g. chewing on slow release tablets).**
2.	Undertreatment	e.g. patient suffers from conditions not being treated, or patient does not use protective medication that is needed for safe use of other medication – e.g. gastroprotective agents in combination with NSAIDs, laxative agents in combination with opioids
3.	Inappropriate formulation	e.g. patient has problems administering the drug or slow release tablet is indicated. **In addition: if the patient indicates the formulation tastes bad.**
4.	Insufficient drug monitoring	Monitoring of laboratory values (e.g. electrolytes, renal function) are insufficiently performed or not within range.
5.	Adverse events	Patient experiences adverse events from medication.
6.	Overtreatment	Patient uses medicines without a clear indication.
7.	Package problem	Patients experiences problems concerning the opening of the packaging
8.	Nonadherence	Patient does not take medication as prescribed by physician (e.g. patient takes less or more medication than prescribed). **In this study in particular, nonadherence was defined as missing ≥1 intake per week.**
9.	Dose too low	The dosage prescribed and/or taken is too low according to prescribing guidelines.
10	No effect	The patient experiences no or insufficient effect from a medicine.
11	Dose too high	The dosage prescribed and/or taken is too high according to the prescribing guidelines.
12	Contraindication	Patient suffers from a condition that is a contraindication for 1 or more drugs he/she is taking.
13.	Interaction	The patient uses a drug that negatively affects the efficacy or toxicity of another drug they are using.
14.	Education	Questions from patients about their medication.
15.	Allergies/intolerance	
16.	Irrational pharmacotherapy	
17.	Administrative problem	
18.	**Vitamin or mineral deficiency**	**Despite of the use of specific bariatric supplements, the patient uses (an) additional supplement(s) according to prescribing guidelines after bariatric surgery and/or the patient notices symptoms that could be related to vitamin or mineral deficiency (muscle pains, muscle tremor, muscle cramps, feeling weak or tiredness) (unless there is another suitable reason).**
19.	**High costs**	**The patient decides to choose for another, less suitable, supplement, due to high costs.**

Table C. Overview of the certain and probable drug related problems for which no specific drug was suspected. These drug related problems are grouped on type of drug. For some drug related problems, this was not suitable. These DRPs are indicated with 'no specific drug assigned'. For example: DRP 2. Undertreatment, suspected to be caused by lack of pain medication. It was clear pain medication would be appropriate, but not what pain medication would be most suitable.

Category of DRP (n)	**Description of type of drug (n)**
DRP 2. Undertreatment (9)	Laxatives (5) No specific type of drug (2) Antithrombotics (1) Pain medication (1)
DRP 10. No effect (3)	Antibiotics (3)
DRP 17. Administrative problem (1)	No specific type of drug (1)

Table D. Overview of the types of drugs most often suspected to cause certain and probable drug related problems, per category of DRPs. The three most frequent suspected types of drugs are presented from most frequent to least frequent. Types of drugs are organised on ATC level 3, describing the anatomical, therapeutic and pharmacological subgroup of drugs. For DRPs categories 2, 10 and 17, no/not all DRPs were assigned to (a) suspected drug(s). These DRPs can be found in Table C in this Annex. DRP categories 13, 15 and 19 are not included in this table, since no 'Certain' and 'Probable' DRPs were found in these categories.

Categories of DRPs	Type of drugs (ATC level 3)	n (% of all drugs suspected to cause this category of DRPs*)
DRP 5. Adverse drug events	Antidepressants (N06A) Antithrombotic agents (B01A) Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B) ACE inhibitors, plain (C09A)	8 (11.1) 7 (9.7) 6 (8.3) 6 (8.3)
DRP 6. Overtreatment	Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B) Lipid modifying agents (C10A) Beta blocking agents (C07A)	6 (16.7) 6 (16.7) 4 (11.1)
DRP 10. No effect	Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B) Antidepressants (N06A) Other analgesics and antipyretics (N02B)	8 (44.4) 3 (16.7) 2 (11.1)
DRP 2. Undertreatment	Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B) Calcium (A12A) Antithrombotic agents (B01A) Decongestants and other nasal preparation for topical use (R01A) Adrenergics (R03A) Non-bariatric multivitamin supplements	1 (16.7) 1 (16.7) 1 (16.7) 1 (16.7) 1 (16.7) 1 (16.7)
DRP 18. Vitamin or mineral deficiency	Calcium (A12A) Bariatric multivitamin supplements	4 (30.7) 9 (69.2)
DRP 3. Inappropriate formulation	Calcium (A12A) Bariatric multivitamin supplements Antacids (A02A) Antidepressants (N06A)	5 (50.0) 3 (30.0) 1 (10.0) 1 (10.0)
DRP 8. Nonadherence	Calcium (A12A) Non-bariatric multivitamin supplements Bariatric multivitamin supplements Other non-prescription drugs	7 (70.0) 1 (10.0) 1 (10.0) 1 (10.0)
DRP 9. Dose too low	Non-bariatric multivitamin supplements Calcium (A12A) Antiepileptics (N03A) Beta blocking agents (C07A	6 (66.7) 1 (11.1) 1 (11.1) 1 (11.1)
DRP 7. Package problem	Calcium (A12A)	5 (22.7)

	Lipid modifying agents (C10A)	2 (9.1)
	Other non-prescription drugs	2 (9.1)
DRP 4. Insufficient drug monitoring	Antidepressants (N06A)	5 (71.4)
	Antiarrhythmics, class I and III (C01B)	1 (14.3)
	Thyroid preparations (H03A)	1 (14.3)
DRP 1. Incorrect use	Calcium (A12A)	4 (50.0)
	Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B)	1 (12.5)
	Beta blocking agents (C07A)	1 (12.5)
	Thyroid preparations (H03A)	1 (12.5)
	Bariatric multivitamin supplements	1 (12.5)
DRP 14. Education	Bariatric multivitamin supplements	4 (36.4)
	Calcium (A12A)	3 (27.3)
	Blood glucose lowering drugs, excl. insulins (A10B)	2 (18.2)
DRP 11. Dose too high	Calcium (A12A)	2 (50.0)
	Bariatric multivitamin supplements	2 (50.0)
DRP 12. Contraindication	Anti-inflammatory and anti-rheumatic products, non-steroids (M01A)	2 (50.0)
	Antithrombotic agents (B01A)	1 (25.0)
	Drugs affecting bone structure and mineralization (M05B)	1 (25.0)
DRP 16. Irrational pharmacotherapy	Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B)	1 (25.0)
	Drugs for constipation (A06A)	1 (25.0)
	High-ceiling diuretics (C03C)	1 (25.0)
	Hypnotics and sedatives (N05C)	1 (25.0)
DRP 17. Administrative problems	No specific drugs suspected, see table C.	n/a

*ATC: Anatomical Therapeutic Chemical classification system; DRPs: drug related problems. *The number of suspected drugs per category of DRPs: DRP 1: 8; DRP 2: 6; DRP 3: 10; DRP 4: 7; DRP 5: 73; DRP 6: 36; DRP 7: 22; DRP 8: 10; DRP 9: 9; DRP 10: 18; DRP 11: 4; DRP 12: 4; DRP 14: 11; DRP 16: 4; DRP 18: 13.*

Table E. Overview of the overall number of drug related problems and frequencies of categories of drug related problems. This table provides an overview of the number of DRPs with certainty level 'Certain' and 'Probable', the median number of DRPs per patient and the frequencies of the categories of DRPs. Categories are sorted from most frequent to least frequent.

Median number of DRPs (IQR)	4.00 (5.00)
Number of DRPs, n (% of total)	61 (100.0%)
DRP 5. Adverse drug reactions	33 (54.1)
DRP 10. No effect	10 (16.4)
DRP 9. Dose too low	4 (6.6)
DRP 18. Vitamin or mineral deficiency	4 (6.6)
DRP 1. Incorrect use	3 (4.9)
DRP 2. Undertreatment	3 (4.9)
DRP 6. Overtreatment	2 (3.3)
DRP 3. Inappropriate formulation	1 (1.6)
DRP 11. Dose too high	1 (6.6)

Table F. Overview of the uncertain drug related problems for which no specific drug was suspected. These drug related problems are grouped per type of drug. For some drug related problems, this was not suitable. These DRPs are indicated with 'no specific drug assigned'. For example: DRP 2. Antidepressants, possibility of undertreatment of depression, without clear indication which antidepressant would be most suitable.

Category of DRP (n)	**Description of type of drug (n)**
DRP 1. Incorrect use (1)	No specific type of drug (1)
DRP 2. Undertreatment (3)	Antidepressants (1) Drugs to prevent osteoporosis (1) Dermatics (1)
DRP 10. No effect (1)	Antibiotics (1)

Table G. Overview of the types of drugs most often suspected to cause different categories of uncertain drug related problems. The most frequent suspected types of drugs are presented from most frequent to least frequent. Types of drugs are organised on ATC level 3, describing the anatomical, therapeutic and pharmacological subgroup of drugs. For DRP categories 1, 2 and 10, no/not all DRPs were assigned to (a) suspected drug(s). These DRPs can be found in Table F in this Annex. DRP categories 4, 7, 8, 12-17 and 19 are not included in this table, since no 'Uncertain' DRPs with this were found in these categories.

Categories of DRPs	Type of drugs (ATC level 3)	n (% of all drugs suspected to cause this category of DRPs*)
DRP 5. Adverse drug events	Antidepressants (N06A)	8 (20.5)
	Lipid modifying agents (C10A)	7 (18.0)
	Blood glucose lowering drugs, excl. insulins (A10B)	3 (7.7)
DRP 10. No effect	Drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B)	4 (44.4)
	Vasodilators used in cardiac diseases (C01D)	1 (11.1)
	Urologicals (G04B)	1 (11.1)
	Muscle relaxants, centrally acting agents (M03B)	1 (11.1)
	Hypnotics and sedatives (N05C)	1 (11.1)
	Antihistamines for systemic use (R06A)	1 (11.1)
DRP 9. Dose too low	Non-bariatric multivitamin supplements	4 (100.0)
DRP 18. Vitamin or mineral deficiency	Bariatric multivitamin supplements	4 (100.0)
DRP 1. Incorrect use	Calcium (A12A)	2 (100.0)
DRP 2. Undertreatment	No specific drugs suspected, see table E.	n/a
DRP 6. Overtreatment	Low-ceiling diuretics, thiazides (C03A)	1 (20.0)
	Beta blocking agents (C07A)	1 (20.0)
	Selective calcium channel blockers with mainly vascular effects (C08C)	1 (20.0)
	ACE inhibitors, plain (C09A)	1 (20.0)
	Lipid modifying agents (C10A)	1 (20.0)
DRP 3. Inappropriate formulation	Hypnotics and sedatives (N05C)	1 (100.0)
DRP 11. Dose too high	Calcium (A12A)	1 (100.0)

*ATC: Anatomical Therapeutic Chemical classification system; DRPs: drug related problems. *The number of suspected drugs per category of DRPs: DRP 1: 2; DRP 3: 1; DRP 5: 39; DRP 6: 5; DRP 9: 4; DRP 10: 9; DRP 11: 1; DRP 18: 4.*