Flemish opioid prescribing trends in primary care

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Master of Family Medicine
Masterthesis family medicine
2017-2019

Abstract

BACKGROUND Around the world there has been a dramatic increase in the use of prescription opioids. At the forefront we currently find the United States, which is undergoing a crippling opioid epidemic. Disconcerning is the similiar trend observed in certain European countries. We aim to quantify the trends in opioid prescribing in Flemish Primary Care.

METHODS We obtained the prevalence of opioid prescriptions in the Flemish Primary Care between January 2005 and December 2015 using data from the Intego database. The proportion of patients per year receiving at least one opioid prescription, at least three opioid prescriptions and at least one tramadol or fentanyl prescription were calculated for different subgroups.

RESULTS The yearly prevalence of opioid prescriptions significantly increased from 4.87% in 2005 to 6.54% in 2015 (chi-square $p<0.01$). During these ten years the increase was seen to be relatively greater with women (36.84%) than with men (30.73%). In the population with an oncological history no significant temporal trend and no gender differences were observed. The evolution in the prevalence of tramadol and fentanyl showed a significant relative increase in the non-oncological group, 61% and 121% respectively (chi-square $p<0.01$). In the population with an orthopaedic diagnosis a significant increase in the prevalence was seen with 8.13% in 2005 to 10.43% in 2015 (chi-square $p<0.01$) and with 5.77% in 2005 to 7.30% in 2015 (chi-square $p<0.01$) in women and men respectively. In each year the presence of psychiatric problems, social problems or benzodiazepine use, was significantly associated with higher opioid prescribing prevalence.

CONCLUSION The prescription of opioids in Flanders has consistently increased over the last years. The growth is clearly driven by the non-cancer population. Notable is the increase in tramadol en fentanyl prescriptions which is significantly higher than that of opioids in general. Additionaly it is clear that patients at increased risk for opioid misuse or abuse are more inclined to receive opioid prescriptions. Opioid management therefore needs to be given the proper attention by healthcare providers and health authorities.

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Preface

During the completion of this master thesis we received the help and guidance of a lot people, for which we want to express our deepest gratitude. We would like to mention some people in particular because without them this thesis would not have been possible.

Foremost we would like to thank our promotor dr. Cathy Mathei. Throughout the completion of this master thesis she has always been reliable and available for communication and professional feedback. Secondly, we would like to thank everyone from INTEGO and especially P. Mamouris for helping us in gathering all the data needed to write this thesis. Finally, we want to thank all general practitioners who participate with INTEGO.

Thank you.

Introduction

For most of the 20th century opioid use was kept at a fairly steady level, until about 30 years ago. Since then, opioids became widely used in acute settings such as trauma care or in postoperative care. This group of molecules has also played a prominent role in combating cancer-related chronic pains for many years. Recently, the spectrum of indications for which doctors prescribe these drugs has become much broader. Patients use more opioids and they use them more often in the context of chronic non-cancer related pains, such as low back pain and other orthopaedic problems (1-3).

Given the high prevalence of these chronic non-cancer related pains, there has been a dramatic increase in the use of these analgesics worldwide. Since the 1990s, the number of prescriptions has increased six fold. This increase is mainly due to countries with a high development index, with the United States being the absolute leader in terms of number of prescriptions per capita (4-6). Nevertheless, a similar trend in prescribing behaviour was observed in several European countries (7,8), including Belgium (9).

The opioid group of medication is indispensable in modern medicine, but it has important side effects too. These vary from bothersome (nausea and constipation) to potentially dangerous (sedation, euphoria, physical and psychological dependence) and even lethal (respiratory depression) (10). Especially the euphoria and the risk of dependence ensure that there is also important misuse and abuse of opioids in addition to pure medical use. Certain patient characteristics are associated with higher risk of addiction, abuse or overdose, such as psychiatric illness or misuse of other prescription drugs (11, 12).

This study aims on the one hand to map the evolution in the prescription of opioids in primary care in Flanders, distinguishing cancer and non-cancer populations, as well as populations with or without an orthopaedic diagnosis. On the other hand, prescription rates for short term use are compared to those for longer duration, as well as differences between tramadol and fentanyl use as the most prescribed weak and strong opioid respectively (9). At last it is looked into whether demographic or patient-related factors are linked to a higher prescription rate of opioids.

Methodology

Study population and design

Data was obtained using INTEGO, a Flemish general practice-based morbidity registration network at the Department of General Practice of the University of Leuven. The Intego procedures were approved by the ethical review board of the Medical School of the University of Leuven (N° ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079). In 2013, 111 general practitioners (GPs) collaborated in the Intego project, all using the medical software Medidoc®. These GPs worked in 48 practices evenly spread over Flanders, the Northern part of Belgium. They applied for inclusion in the registry. Before their data was accepted, registration performance was audited by using a number of algorithms comparing their results with those of all other applicants. Only the data of the practices with an optimal registration performance were included in the database. These Intego GPs prospectively and routinely registered new diagnoses, as well as drug prescriptions, laboratory test results and some background information (including gender and year of birth), using computer-generated keywords internally linked to codes. New data were coded and collected from these GPs' personal computers using specially framed extraction software and entered into a central database. The registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to an elaborate thesaurus, which was automatically linked to the International Classification of Primary Care (ICPC-2). Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.

The current study is a retrospective cohort study that used Intego data from January 1, 2005 till December 31, 2015. In every yearly contact group (patients in contact with their GP for either reason during a year) patients of 18 years and older were selected.

The research questions had to be reformulated in ICPC-2 and ATC codes to extrapolate data from INTEGO. A list of relevant ICPC-2 and ATC codes was made by only including those of a diagnosis, symptoms and treatments were excluded. A second list of ICPC-2 and ATC codes was made to exclude some data (e.g. cancer related pain). The data from INTEGO was then further organised according to the year of prescription and the sex of the patient.

Clinical characteristics

Demographics

Data on age and sex were collected for all included patients

Morbidity

Diagnoses of cancers were collected in order to distinguish opioid prescribing for cancer-related pain from opioid prescribing for other indications. Diagnoses of orthopaedic disorders prior to the first opioid prescription were also collected since they are known to represent a major indication for opioid prescribing (13). Furthermore, data on the presence of social problems and psychiatric problems prior to the first opioid prescription were registered as these conditions have been related to a higher opioid prescribing/consumption rate (14).

Pharmacotherapy

Data were collected on the prescription of opioids (ATC codes) and benzodiazepines (ATC codes) in every yearly contact group. Patients receiving opioids prescriptions on 3 or more contacts were defined as chronic users.

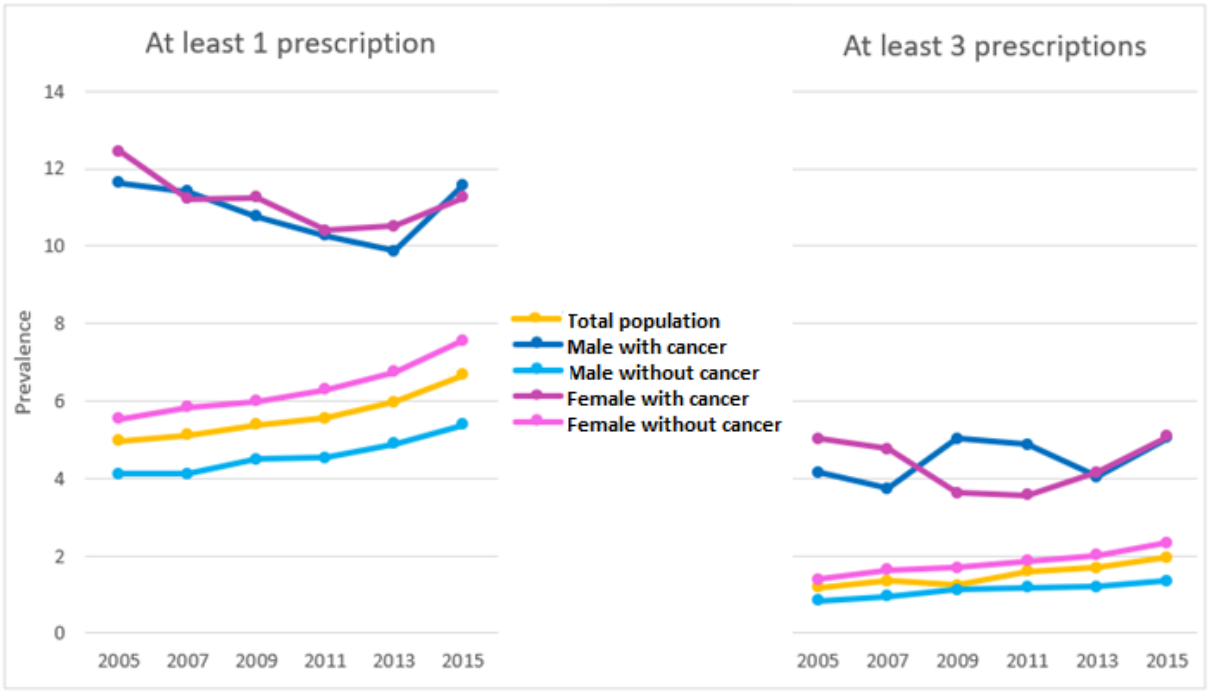
Statistical analysis

Rates of opioid prescriptions were calculated and presented as the portion per thousand patients receiving at least one opioid prescription per year. The chi-squared test for trends was applied to investigate for linear temporal trends in opioid prescribing, in the total population and in subgroups. Rates were calculated for all opioids and for tramadol and fentanyl separately. The chi-squared test was used to assess differences in prevalence rate of opioid prescribing across groups of patients. A p-value $\leq$ 0.05 was considered statistically significant (15, 16).

All analyses were then repeated for patients who received a single opioid prescription and patients who received 3 or more opioid prescriptions in the same year separately. The limit was set at 3 or more because databank analysis using INTEGO showed that patients who received 3 prescriptions generally received much more prescriptions afterwards. Therefore patients who received at least 3 prescriptions in one year could be considered as chronic users. Furthermore, were also done for patients who received one or more prescriptions of Fentanyl and patients who received one or more prescriptions for tramadol separately. Fentanyl and tramadol were chosen because they were the most prescribed molecules in the class of strong and weak opioids respectively (9).

Results

General opioid prescribing trends



Graph 1. The percentage of patients receiving at least 1 and > 3 opioid prescriptions in the general population, the male and female population and the non-cancer population, during the period 2005-2015.

General opioid prescribing trends

The proportion of patients receiving at least one opioid prescription significantly increased in the general population from 4.87% in 2005 to 6.54% in 2015 (Chi-square for trend, p<0.01).

In the female and male population, without an oncological history (≤ 5y), a similar significant linear trend was observed with 5.53% in 2005 to 7.56% in 2015 (p<0.01) and 4.12% in 2005 to 5.39% in 2015 (p<0.01) respectively. There was a significant difference in prevalence between the female and male population in the year 2005 (p<0.01). In the years that followed, this significant difference in prevalence between men and women remained (p<0.01). During these ten years, the prevalence

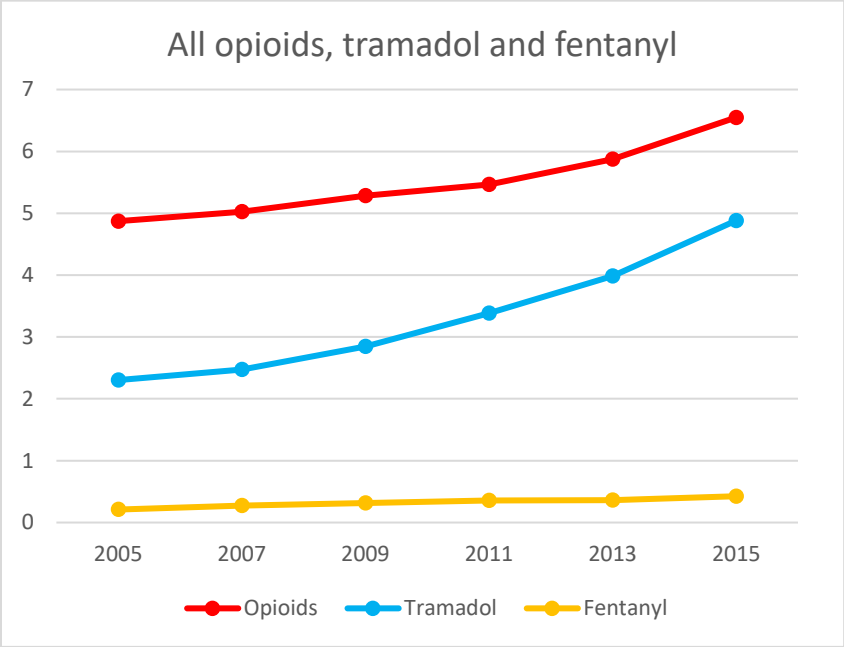
increased by 36.84% for women versus 30.73% for men. The relative prevalence of an opioid prescription was 40.42% higher in women compared to men in 2015.

The prevalence of at least 1 opioid prescription in the female population with an oncological history (≤ 5y) showed no significant linear trend from 2005 to 2015 (p=0.94). In the male population, with the same criteria, there was no significant linear trend either (p=0.68).

General opioid prescribing trends for patients frequently receiving opioid prescriptions

The proportion of patients in the total population and in the non-cancer population that received at least 3 opioid prescriptions showed a significant increasing trend over time (p<0.01). This trend was significant both in women and men but each year women received significantly more prescriptions than men (p<0.01). In contrast, the male and female populations with an oncological history (≤ 5y), showed no significant linear trend (male p=87, female p=93).

General tramadol and fentanyl prescribing trends



Graph 2. The percentage of patients receiving at least 1 opioid prescription, fentanyl and tramadol during the period 2005-2015.

The proportion of patients receiving at least 1 tramadol prescription or at least 1 fentanyl prescription both showed a significant increasing linear trend during the period 2005 to 2015 (2.30% in 2005–4.88% in 2015) (p<0.01) and (0.21% in 2005 - 0.42% in 2015) (p<0.01).

Distinguishing between cancer and non-cancer patients these findings were confirmed in the latter group. Among cancer patients the proportion of patients receiving at least 1 tramadol prescription and at least 1 fentanyl prescription remained stable throughout the study period. In the non-cancer group a significant linear increase of 121% (p<0.01) and 61% (p<0.01) with fentanyl and tramadol respectively was observed. This in contrast with the population with an oncological history (≤ 5y), the fentanyl and tramadol respectively showed no significant linear trend (fentanyl p=0.94, tramadol p=0.26).

	2005	2007	2009	2011	2013	2015	p-value*
Tramadol	2.30	2.47	2.84	3.38	3.99	4.88	<0,01
Cancer	4.93	3.96	3.83	4.13	4.37	4.22	0,94
Non-cancer	1.79	1.78	1.93	2.06	2.39	2.91	<0,01
Fentanyl	0.21	0.28	0.32	0.36	0.36	0.43	<0,01
Cancer	3.40	3.48	3.16	2.67	2.28	2.76	0,26
Non-cancer	0.16	0.23	0.27	0.31	0.31	0.36	<0,01

Table 1. The percentage of patients receiving at least 1 prescription fentanyl, tramadol during period 2005-2015 for cancer and non-cancer population.*Chi-squared test for trends

Opioid prescribing trends for patients with and without an orthopaedic diagnosis

From now on only patients without cancer (≤ 5) prior to opioid prescribing were included.

Patients with and without an orthopaedic indication receiving opioids

In the female and male population, with an orthopaedic diagnosis (≤ 10y), the prevalence of at least one opioid prescription showed a significant linear trend with 8.13% in 2005 to 10.43% in 2015 ($p<0.01$) and with 5.77% in 2005 to 7.30% in 2015 ($p<0.01$) respectively. The proportion per thousand patients receiving at least one opioid was each year significantly higher in women as compared to men ($p<0.01$).

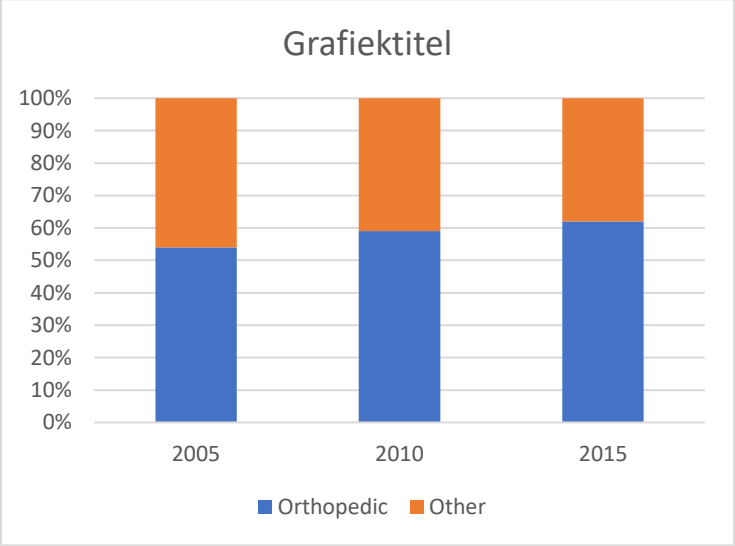
Among the male population without an orthopaedic diagnosis, no significant temporal trends were observed ($p=0.22$). In contrast, among women without an orthopaedic indication the proportion receiving an opioid prescription significantly rose ($p<0.05$).

Patients with and without an orthopaedic diagnosis frequently receiving opioids

Looking at the evolution of the prevalence in the female and male population with at least 3 opioid prescriptions with an orthopaedic diagnosis, a significant linear increasing trend over the years was observed (male $p<0.01$, female $p<0.01$).

In both the female and male population without an orthopaedic indication, there was no significant linear trend over the years 2005 to 2015 (male $p=0.90$, female $p=0.35$).

Relative prevalence of opioid prescribing for patients with and without an orthopaedic indication



Graph 3. Percentagewise distribution of patients who were prescribed at least 1 opioid, with and without an orthopaedic problem in the medical history during the period 2005-2015.

The proportion of patients receiving at least one opioid prescription with a prior orthopaedic diagnosis significantly increased from 54% in 2005 to 62% in 2015 ($p<0.01$).

Tramadol and fentanyl prescribing trends *for patients with and without an orthopaedic indication*
The proportion of patients with an orthopaedic diagnosis (≤10y) receiving at least 1 tramadol prescription or at least 1 fentanyl prescription both showed a significant increasing linear trend during the period 2005 to 2015 (2.77% in 2005– 4.04% in 2015) (p<0.01) and (0.23% in 2005 - 0.48% in 2015) (p<0.01).

Age differences in opioid prescribing trends

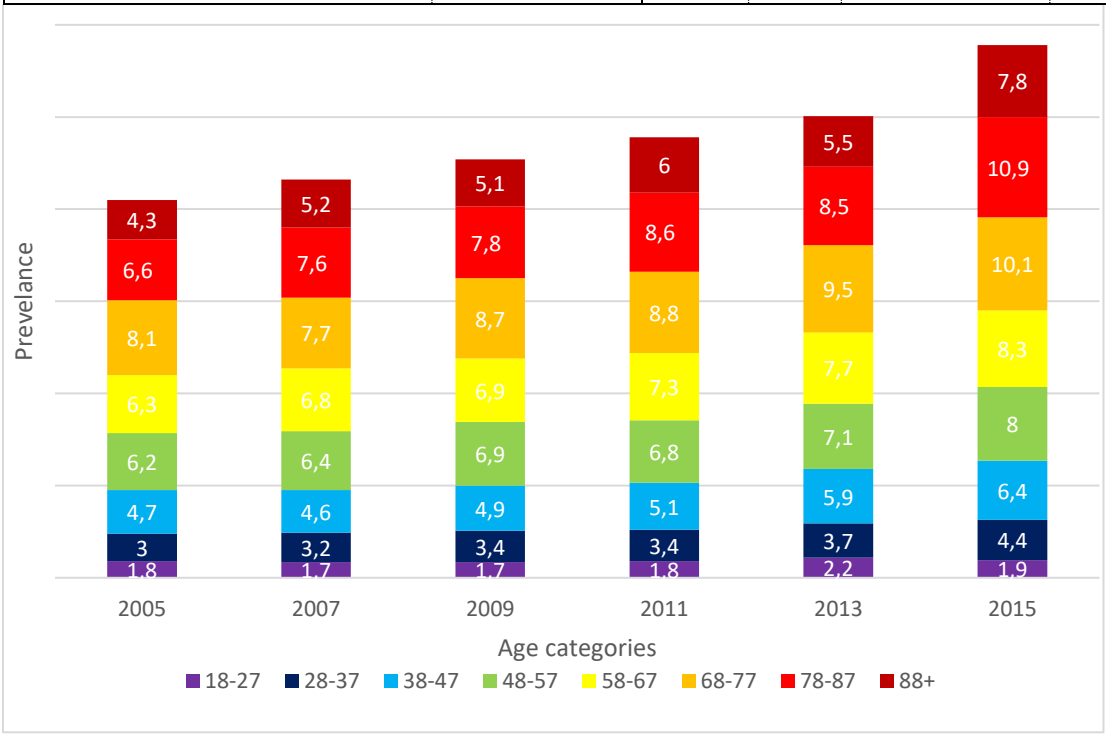
Age differences for general opioid prescribing trends

The proportion of patients receiving at least one opioid prescription significantly increased in each age group during the years 2005 to 2015 (table 2).

The proportion of patients receiving at least on opioid prescription consistently increased with age, reaching a peak 68-77y group until 2015, when the peak shifted to the 78-87y group (table 2).

Table 2. Prevalence of at least 1 opioid prescription for every age category from 2005 to 2015.
***chi-square for trends all showed a p-value <0.05**

	2005	2010	2015	Increase in 10y *		2005	2010	2015	Increase in 10y *
Men	4.12	4.66	5.39	30.73%	Women	5.53	6.12	7.57	36.85%
18-27	1.53	1.48	1.63	6.39%	18-27	2.04	2.09	2.18	6.66%
28-37	2.67	3.31	3.65	36.58%	28-37	3.37	3.48	5.14	52.52%
38-47	4.21	4.54	5.84	38.72%	38-47	5.17	5.68	6.99	35.14%
48-57	5.50	5.90	6.93	26.11%	48-57	6.79	7.70	9.09	33.86%
58-67	5.50	6.27	6.84	24.61%	58-67	7.08	8.38	9.60	35.57%
68-77	5.82	7.02	7.61	30.73%	68-77	9.93	9.76	12.34	24.31%
78-87	5.10	6.52	7.55	48.19%	78-87	7.57	9.52	13.31	75.89%
88+	3.97	4.59	5.92	49.28%	88+	4.51	6.95	8.715	93.41%



Graph 4. Prevalence of at least 1 opioid prescription for every age category from 2005 to 2015

Opioid prescribing trends in different subpopulations

	2005	2010	2015	Increase in 10y	P-value*
Psychiatric	8.28	9.18	10.50	26.72%	<0.01
Non-psychiatric	4.16	4.49	5.34	28.32%	<0.01
	P<0.05	P<0.05	P<0.05		
Social	6.43	8.3	8.16	26.76%	<0.01
Non-social	4.79	5.25	6.42	34.12%	<0.01
	P<0.05	P<0.05	P<0.05		
Benzodiazepines	15.72	17.38	22.23	60.13%	<0.01
No benzodiazepines	4.09	4.63	5.40	31.96%	<0.01
	P<0.05	P<0.05	P<0.05		

Table 3. Prevalence of at least 1 prescription opioids in patients with a history (≤10y) of psychiatric or social problems or benzodiazepine prescription respectively. $chi-square for trends

The prevalence of at least 1 opioid prescription in the subpopulation with a psychiatric history (<10y), a history of social problems (<10y) or receiving a benzodiazepine prescription during the same year was significantly higher over time than in the subpopulation without these patient-related factors. Moreover, the prevalence showed a significantly increasing linear trend in all subpopulations over time (table 3).

Frequent opioid prescribing trends populations considered to have a weakness for misuse and abuse

When looking at which patients received at least 3 opioid prescriptions during a year, it was observed that female patients, patients with psychiatric/neurological/social problem and benzodiazepine users had a higher prevalence. Overall the same trends were observed. The age distribution was also similar to that of patients with at least 1 prescription.

Tramadol and fentanyl prescribing trends in populations considered to have a weakness for misuse and abuse

Tramadol

In 2005 the prevalence/100 for at least 1 tramadol prescription was 2.10 with women and 1.45 with men. In 2015 it rose to 3.32 and 2.43 respectively. Psychiatric problems, social problems and the use of prescription benzodiazepines also gave a higher prevalence from 2005 to 2015 than in the absence thereof. The same trends are observed in the prevalence of tramadol as in that of opioids in general.

Fentanyl

When looking at the number of patients that received at least 1 fentanyl prescription, the prevalence/100 appeared to be higher in women (0.20 - 0.49) than in men (0.11 - 0.21). Psychiatric problems (0.31 - 0.58), neurological problems (0.33 - 0.55), social problems (0.18- 0.42) and use of prescription benzodiazepines (0.83- 1.84) were again found to give a higher prevalence than in their absence. The same trends are thus observed in the prevalence of fentanyl as in the prevalence of opioids in general.

Discussion

The strength of the study is the large amount of data available through INTEGO. This resulted in very reliable trends. Due to the large bulk of data and only one INTEGO analyst, risk factors could not be looked for in this cross-sectional study, in contrast to other prospective studies. From the prevalence data obtained, this study could only describe trends in the prescription of opioids in certain subpopulations. Nevertheless, this was the first study to describe the relationship between patient characteristics and diagnoses concerning opioid prescribing.

The analysis was done by a single analyst with sufficient experience in analyzing the database. This enabled data to be retrieved from INTEGO efficiently. However, no third-party verification by an independent analyst was performed.

As previously stated, the medical practices that participate in INTEGO are screened for their coding method. Previous analyses have shown that there is still a considerable discrepancy between the total number of pathologies diagnosed and the portion that is effectively coded with ICPC-2. Moreover, there's probably an important proportion of prescriptions for opioids that are delivered on home visits of which there is no coded registration in the medical file.

Analysis of the data showed that patients who received at least 3 different prescriptions for opioids were very likely to receive a lot more. However, we cannot derive any abuse or chronic use from this. The extracted data were limited to 1 year each time, but analysis showed that these patients continued to receive opioids in the following years.

Criteria for identifying opioid abuse and aberrant drug behavior have been identified in various studies as: >2 general practitioners, >2 pharmacies, obtaining drugs illegally, etc. Because INTEGO only contains data about legally prescribed medication under the supervision of one general practitioner, no information on this subject could be obtained.

The prevalence of prescription opioid use in the general adult Flemish population increased consistently, from 4.86% in 2005 to 6.55% in 2015, or a relative increase of 34.77% in ten years. This in contrast to the prevalence in the subpopulation with a recent history of cancer, which did not change significantly. Although the prevalence within the cancer population was much higher and therefore included a significant proportion of users, the overall increase is therefore due to the increase in the non-cancer population.

In addition, there was a noticeable difference between the sexes within the non-cancer population. The prevalence of opioid use there was clearly higher among women than among men. There was hardly any difference within the cancer population. A possible explanation for this is that women are more eloquent in mentioning their pain to doctors (17, 18). For example, female patients are more likely to raise the issue of 'pain' than men, where showing pain is seen as a sign of weakness. This is not necessarily true in an oncological setting. In this setting physicians will actively inquire if there is a pain complaint, thus lowering the threshold for talking about the subject.

Moreover, the prevalence of at least 1 prescription was three times higher than that of at least 3 prescriptions. This shows that the majority of patients who are prescribed an opioid use it only for a short time. The difference was less prominent in the cancer population, which is to be expected given the rather chronic nature of the pain in this group.

It also appears that the increase in prevalence of at least 1 prescription for tramadol or fentanyl was much greater than that of opioids in total. This shows that these 2 products have become much more popular in recent years at the expense of the alternatives. The phenomenal increase in fentanyl use in the non-cancer group is particularly striking. It is therefore clear that these powerful opioids are increasingly used outside the context of cancer than before.

The prevalence of opioid use was higher in the population with orthopaedic problems than in the general population, and was also higher among women. Moreover, the prevalence increased and this

difference was greater in the higher age categories. This may possibly be explained by the fact that many opioids are prescribed to geriatric patients, who have a high prevalence of osteoarthritis-related pains. This population has a larger proportion of women since they have a greater average life expectancy than men. It also appears that within the population of cancer-free opioid users, the proportion of patients with an orthopaedic diagnosis increased. This suggests that the importance of orthopedic problems in prescribing opioids is therefore increasing. The prevalence of opioid use was higher in the older age categories, which seems logical given the more frequent occurrence of pain problems within these groups. The peak also moved to the older age groups. A possible explanation is on the one hand the prevalence of contraindications for alternative classes of analgesics according to the WHO pain ladder, in particular the NSAIDs: use of antithrombotics, heart failure, renal insufficiency... These are clearly linked to an increasing age. GPs may be reluctant to prescribe NSAIDs for this reason, although this fear is shown be unfounded if used responsibly (19). On the other hand, there's probably an important proportion of patients who started using opioids chronically in one age category and who have moved up to an older age category over the years.

Although neither psychiatric or social problems nor use of benzodiazepines is an indication for opioids, it appears that non-cancer patients in the presence of these factors had a higher prevalence of opioid use. It is possible that these factors are accompanied by a higher prevalence of orthopedic problems, but this seems unlikely to explain the observed prevalence of opioid use within these groups.

It seems more likely that these are characteristics of a population that has a certain vulnerability to being prescribed opioids, since similar characteristics have already been associated with an increased risk of opioid abuse and addiction (11, 12). Given the risk profile of opioids, it is therefore necessary for the 21st century physician to be aware of the vulnerability of this population in order to avoid prescribing opioids without proper indication and to protect this vulnerable population from side effects. We are of the opinion that Flemish GPs cannot fall back sufficiently on practical support regarding medication abuse in general and opioid abuse in particular, partly due to the lack of guidelines on responsible prescribing and insufficient depth about addiction problems in education (20).

Conclusion

The results of this study show an increasing trend for prescribing opioids to patients without cancer. Orthopaedic problems are the main reason for this increase. When comparing sexes, it is seen that women receive more opioid prescriptions. Furthermore this study shows that patients with psychiatric and social problems and patients who received benzodiazepine prescriptions were seen to receive more opioid prescriptions over the years and that they received more prescriptions than those without these patient-related factors. When looking at all opioids, tramadol and fentanyl show the greatest increase. Patients with a diagnosis of cancer receive more fentanyl whereas patients without cancer receive more tramadol. These results could lead to a better understanding of opioid prescription patterns and better healthcare for patients at risk for misuse or abuse of opioids. We hope that it may contribute to the development of a guideline for safe opioid prescribing.

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Appendix 1: Positive advice ethical commission

DEFINITIVE FAVOURABLE ADVICE

Dear Cathy Matheï
Dear David Berthels, Vince Demeur, Tomas Van Tilborg, Jeroen Budo

The Research Ethics Committee UZ/KU Leuven hereby grants favourable advice to the proposed study, as it was described in the protocol. The Commission is of the opinion that from an ethical standpoint there are no objections to the proposed study. The study was approved on 25-03-2019

De Commissie keurt de aanvraag goed en heeft geen verdere opmerkingen.

Given that the study takes the form of a Master's thesis within the Group Biomedical Science, the application to the Research Ethics Committee UZ/KU Leuven was submitted to the Educational-Support Committee.

The Committee has no objection to the project on the basis of confidential treatment of the data and compliance with the Belgian legislation concerning privacy. The Research Ethics Committee UZ/KU Leuven wishes for the head researcher / promoter of the study to be aware of their responsibilities with regard to the privacy of personal / patient details, when in contact with living persons, patients, and / or contained within electronic medical records, including the correct implementation by employees and students.

This favorable advice concerns the submission of 12-03-2019 and is given for the duration of the Master's thesis of the student(s) concerned. Any amendment to the protocol will invalidate this favorable advice. In that case, you must submit an amendment for advice to the committee that previously approved your file.

The Committee confirms that they work in accordance with the ICH-GCP principles (International Conference on Harmonisation Guidelines on Good Clinical Practice), with the most recent verison of the Helsinki Declaration, and with applicable laws and regulations.

The Committee confirms that in case of a conflict of interest, the members concerned have not participated in decision regarding the study.

Kind regards,

Prof. dr. Minne Casteels
President / Chairperson
Research Ethics Committee UZ/KU Leuven

Prof. dr. Pascal Borry
President / Chairperson
Education-Support Committee for Medical Ethics KU Leuven

Appendix 2: Master paper protocol

MASTER PAPER PROTOCOL: RETROSPECTIVE STUDY

1. APPLICANTS

Protocol - full title	Veilig en verantwoord voorschrijven van de opioïden in de eerste lijn
Version 1: Date submission	Date:11/03/2019
Version 2: Date resubmission	(to add in case of resubmission) Date:Click here to enter a date.
Version 3: Date third submission	(to add in case of third submission) Date:Click here to enter a date.
Principal Investigator – Promoter	Name: Professor Catharina Matheï
	Telephone: Tel: 016/33270; Gsm: 0475/57 16 75
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Sub-investigator – Student(s)	Name: Tomas Van Tilborg
	Name: Jeroen Budo
	Name: Vince Demeur
	Name: David Berthels

2. BACKGROUND AND RATIONALE

By opioids we mean molecules that bind to opioid receptors and thus produce an effect similar to that of morphine (1). In the medical sector they are mainly used as a powerful analgesic, but also as a cough inhibitor and in the treatment of opioid dependence (2). Morphine, fentanyl, codeine and methadone are included in the most recent list of essential medicines from the World Health Organization (3).

This group of medication can no longer be ignored from modern medicine, but it has important side effects too. These vary from bothersome (nausea and constipation) to potentially dangerous (sedation, euphoria, physical and psychological dependence) and even lethal (respiratory depression) (4). Especially the euphoria and the risk of dependence ensure that there is also important recreational use of opioids in addition to pure medical use. This includes both legal drugs and illegal drugs such as heroin.

Data from American studies suggest that not only morbidity and mortality due to opioid use but also recreational use strongly correlate with the volume of these preparations that doctors prescribe to the population (5-6). This makes sense, as increased availability encourages the spread of opioids in society and their use without medical advice.

Since they entered the pharmaceutical market, opioids have been widely used in acute settings such as trauma care or in postoperative care. This group of molecules has also played a prominent role in combating cancer-related chronic pains for many years. Recently, the spectrum of indications for which doctors prescribe these drugs has become much broader. Patients use

more opioids and they use them more often in the context of chronic non-cancer related pains, such as low back pain, headache and fibromyalgia (7-9).

Given the high prevalence of the latter illnesses, there has been a dramatic increase in the use of these analgesics worldwide. Since the 1990s, the number of prescriptions has increased sixfold. This increase is mainly due to countries with a high development index, with the United States being the absolute leader in terms of number of prescriptions per capita (10-12). Nevertheless, a similar trend in prescribing behavior was observed in several European countries (13-14).

This study aims on the one hand to map the evolution in the prescription of opioids in Flanders and to compare these with data from the rest of the world. On the other hand, it is being investigated whether demographic or patient-related factors are linked to a higher prescription rate of opioids. At last, it is looked into whether these factors are related to single versus multiple prescriptions per annum and to tramadol or fentanyl use as the most prescribed weak and strong opioid respectively (15).

3. STUDY OBJECTIVES

This study aims on the one hand to map the evolution in the prescription of opioids in Flanders and to compare these with data from the rest of the world. On the other hand, it is being investigated whether demographic or patient-related factors are linked to a higher prescription rate of opioids.

4. RESEARCH METHOD

First a literatury study was performed to find information about the current use and abuse of opioids and the difference between countries. Risk factors leading to an increase in opioid usage was the main focus of this literatury study. Using PUBMED, the following MESH terms were used “RISK ASSESSMENT” “RISK FACTORS” “ANALGESICS, OPIOID” and this led to 16 relevant articles.

After performing this literatury study, the research questions were formulated and further looked into .

A databank analysis was then performed, using the INTEGO network to answer these research questions. INTEGO was chosen because of the need for representative data in Flanders and opioid prescriptions. Data includes diagnosises, prescriptions and laboratory information.
The research questions had to be reformulated in ICPC-2 and ATC codes to extrapolate data from INTEGO. A list of relevant ICPC-2 and ATC codes was made, a second list of ICPC-2 and ATC codes was made to exclude some data (eg. Cancer related pain). To optimize data extrapolation and maximize the potential of INTEGO these new research questions were discussed and formulated in cooporation with members from INTEGO. The data from INTEGO was then further organised according to the year of prescription and the sex of the patient.
Afterwards a retrospective population study was performed using the data from INTEGO. The data used in this study was limited to the period 2005 - 2015 to improve relevance. The use of every opioid was investigated and was not restricted.

5. DATA COLLECTION

Data was obtained using INTEGO, a Flemish general practice-based registration network at the Department of General Practice of the University of Leuven. INTEGO provides representative information for the Flemish (Belgian region) population. This population consists out of patients from registrated general practitioner practices evenly spread all over Flanders and is representative for age, sex and average income. Every year 2-3 practices leave the network and are replaced by new practices. At the end of 2015, patient information from 50 general practitioner practices were used by INTEGO. This leads to data from 440140 different patients, 4.4 million diagnoses and 16.7 million prescriptions. INTEGO is currently undergoing a transition because of a change in EMD (Medidoc no longer exists) and the revision of data collection and anonimisation. INTEGO codes patient data anonymously.

INTEGO codes diagnoses to the International Classification of Primary Care- 2nd Edition (ICPC-2) and the International Statistical Classification of Diseases and Related Health Problems – 10th Revision (ICD-10). Drugs coding is done according to the Anatomical Therapeutic Chemical (ATC) classification system.

Patients age was restricted to 18 – 80+ and patients diagnosed with cancer were also retained.

6. ANALYSIS

To optimize data extrapolation and maximize the potential of INTEGO these new research questions were discussed and formulated in cooporation with members from INTEGO. This resulted in the following set of questionaires:

Extract the following data from the Intego database: the prevalence of at least 1 prescription opioid (ATC N02) during the period of 2005->2015 devided per year [1 january – 31[for the population of:

1) *18 years and older*
2) *18 years and older, and male*
3) *years and older, and female*
4) *18 years and older, and at least one of the following ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71)*
5) *18 years and older, without any of the following ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71)*
6) *18 years and older, and at least one of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), and male*
7) *18 years and older, without any of the followin cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), and male*
8) *18 years and older, and at least one of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), and female*
9) *18 years and older, without any of the followin cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), and female*
10) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with at least one of the follow orthopedic ICP codes (L0-L20; L72-L90)*
11) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without any of the following ICP codes (L0-L20; L72-L90)*
12) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with at least one of the follow orthopedic ICP codes (L0-L20; L72-L90), and male*
13) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without any of the following ICP codes (L0-L20; L72-L90), and male*

14) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with at least one of the follow orthopedic ICP codes (L0-L20; L72-L90), and female*
15) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without any of the following orthopedic ICP codes (L0-L20; L72-L90), and female*
16) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with one of the following psyhiatric ICP codes (P01; P02; P03; P04; P05; P06; P07; P08; P15; P16; P17; P18; P19; P74; P75; P76; P77; P78 P79; P80;Z29.01)*
17) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without one of the following psychiatric ICP codes (P01; P02; P03; P04; P05; P06; P07; P08; P15; P16; P17; P18; P19; P74; P75; P76; P77; P78 P79; P80;Z29.01)*
18) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with at least one of the following neurologic ICP codes (N01-03; N79-99)*
19) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without any of the following neurologic ICP codes (N01-03; N79-99)*
20) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with at least one of the social problems ICP codes (Z01-Z28)*
21) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without any of the following social problems ICP codes (Z01-Z28)*
22) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with at least one prescription of benzos (ATC N05BA)*
23) *18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without any prescription of benzos (ATC N05BA)*

Next he was asked to extract the following data from the Intego database: the prevalence of at least 1 prescription opioids (ATC N02) during the period of 2005->2015 devided per year [1 january – 31[devided in age categories of 10 years starting with [18-27[.
Next he was asked to repeat the previous steps for people who received at least 3 opioid prescription, tramadol and fentanyl. The 3 opioid prescriptions was defined as at least 3 moments of opioids prescribed by a doctor.

This would lead to us receiving approximately 92 tables with a certain sample size looking as following:

Year	Population	Opioids	Prevalence
2005			
…			

7. DATA HANDLING AND MANAGEMENT

7.1 Data storage and management

INTEGO retrieves it's information from EMD (Medidoc no longer exists) of several GP practices and codes patient data anonymously. A member of INTEGO then analysed this data giving us no more information than the total number of opioids prescribed for a certain population in a certain year. This way we can calculate a population specific prevalence for that year. These printouts will be stored on a USB drive, and later be visible in the appendix of our article.

7.2 Declaration of Confidentiality and Careful Management of Information and Personal Data

In the framework of his / her Master's thesis, the student(s) will have access to all kinds of data, information, results and documents, including personal data which is not exclusively limited to patient data (the "Information"). In order to ensure the confidentiality of this Information and the privacy of those involved, within the framework of his / her Master's thesis the student(s) should always deal with the Information with the greatest care and discretion.

Data collected in the framework of a Master's thesis, in particular research related to patients and including the collection and analysis of personal data, requires the utmost of care and discretion. Therefore, at all times the student must observe complete confidentiality with respect to the Information he / she has collected during the course of his / her Master's thesis.

In performing this research, the student(s) commit(s) him/herself to the following confidentiality obligations:

- *He / she accepts, during and after the completion of the Master's thesis, the obligation to strictly observe the confidentiality of the Information he / she has collected and the activities to which he / she has participated, and regarding the patients, healthy volunteers and the staff members with whom he / she comes into contact;*
- *He / she will only process and collect data that is relevant and necessary for his / her Master's thesis;*
- *He / she will not share information with persons not directly involved within the framework of his / her research;*
- *He / she will take all necessary steps to protect the confidentiality of Information and the privacy of those involved;*
- *He / she will handle with care and responsibility the Information and the access granted to him/her to information systems and digital media.*

  All investigators shall treat all information and data relating to the study as confidential and shall not disclose such information to third parties or use such information for any purpose other than the performance of the study. The collection, processing and disclosure of personal data, such as participants' health and medical information, is subject to compliance with applicable personal data protection legislation.

8. APPROVAL

Hereby we confirm that data collection is performed with approval of the head of the respective unit(s) or department(s) where data collecting is taking place.

9. PUBLICATION POLICY

Publications will be coordinated by the Principal Investigator. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective journal.

10. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

The investigator(s) and the institution(s) will permit study-related monitoring, audits, ethical review and regulatory inspections (where appropriate) by providing direct access to source data.

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Appendix 3: Research questions

Frist the analyst should extract following data from the Intego database: the prevalence of at least 1 prescription opioid (ATC N02) during the period of 2005->2015 devided per year [1 january – 31[for the population of:

1) 18 years and older
2) 18 years and older, and male
3) 18 years and older, and female
4) 18 years and older, and at least one of the following ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71)
5) 18 years and older, without any of the following ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71)
6) 18 years and older, and at least one of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), and male
7) 18 years and older, without any of the followin cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), and male
8) 18 years and older, and at least one of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), and female
9) 18 years and older, without any of the followin cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), and female

10) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with at least one of the follow orthopedic ICP codes (L0-L20; L72-L90)
11) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without any of the following ICP codes (L0-L20; L72-L90)
12) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with at least one of the follow orthopedic ICP codes (L0-L20; L72-L90), and male
13) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without any of the following ICP codes (L0-L20; L72-L90), and male
14) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with at least one of the follow orthopedic ICP codes (L0-L20; L72-L90), and female
15) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without any of the following orthopedic ICP codes (L0-L20; L72-L90), and female
16) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with one of the following psyhiatric ICP codes (P01; P02; P03; P04; P05; P06; P07; P08; P15; P16; P17; P18; P19; P74; P75; P76; P77; P78 P79; P80;Z29.01)
17) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without one of the following psychiatric ICP codes (P01; P02; P03; P04; P05; P06; P07; P08; P15; P16; P17; P18; P19; P74; P75; P76; P77; P78 P79; P80;Z29.01)
18) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with at least one of the following neurologic ICP codes (N01-03; N79-99)
19) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without any of the following neurologic ICP codes (N01-03; N79-99)

20) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with at least one of the social problems ICP codes (Z01-Z28)
21) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without any of the following social problems ICP codes (Z01-Z28)
22) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), with at least one prescription of benzos (ATC N05BA)
23) 18 years and older, without any of the following cancer ICP codes (T71; D76; Y77; U77; U75, R84;D74;A79;Y78;T73;N74;B74;S77;R85;D77;L71), without any prescription of benzos (ATC N05BA)

Next the analyst should extract the following data from the Intego database: the prevalence of at least 1 prescription opioids (ATC N02) during the period of 2005->2015 devided per year [1 january – 31[devided in age categories of 10 years starting with [18-27[.

Next the analyst should repeat the previous steps for people who received at least 3 opioid prescription. The definition of 3 opioid prescriptions is of course still defined at: at least 3 moments of opioid prescribed by a doctor.

Finally the analyst should redo the previous steps twice. Once with only tramadol, and once with only fentanyl.