Concomitant Use of Oxycodone and Clarithromycin in the Netherlands

A utilization study using the IADB

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Abstract

Oxycodone is a widely used analgesic opioid. In the Netherlands it is used for chronic pain management and short-term pain reduction, such as after an operation. In 2020, the Netherlands counted 390.920 oxycodone users. Oxycodone is metabolized by CYP3A4 into its inactive metabolites. The antibiotic, clarithromycin blocks the CYP3A4 enzymes, causing a decreased clearance of oxycodone and an increased chance of side effects. Therefore, this study aimed to investigate the extent of concomitant use of clarithromycin and oxycodone in the Netherlands.

The data used in this study was retrieved from the IADB, a pharmaceutical database with patient and prescription data from patients in the northern Netherlands. This data is representative of the Dutch population. In this study chronic oxycodone users over the age of 18 were evaluated, investigating the period of use of oxycodone, concomitant use of oxycodone and clarithromycin and dosage changes after this concomitant use between 2001 and 2020. An incidence was formulated as concomitant use per 1,000 oxycodone users. Chi square test was used to test differences in concomitant use between the sexes. Dosage change was evaluated using a one sample t-test on a logarithmic scale.

In this studies population, 616 counts of concomitant use were found, this equaled an incidence of 11.68 per 1,000 oxycodone users. The incidence of concomitant use has a declining trend over the years. The incidence of men and women differ significantly. The dosage change seems to be increasing after concomitant use, however more research is advised. Overall, it can be concluded that concomitant use has become less likely to occur on an individual level between 2001 and 2020, which can be considered an improvement.

Introduction

Oxycodone is a widely used analgesia used for moderate to severe pain treatment; it is part of the opioid family (Moradi et al., 2012). In 2017 6% of the total population in the Netherlands was prescribed an opioid (Bedene et al., 2019). Between 2008 and 2017, the number of oxycodone users in the Netherlands quadrupled, from 574 to 2568 per 100 000 inhabitants (Kalkman et al., 2019). In the same timeframe, oxycodone overdosing has gone up six-fold, from 43 to 280 people in total (DutchNews.nl, 2018). These increases are because oxycodone is now being prescribed, not only to terminal patients, but also for other pain relief, such as after breaking a bone. In 2020, the Netherlands counted 390.920 oxycodone users (GIPdatabank, *N02AA05: Oxycodon*).

Another commonly used drug is Clarithromycin. It is an antibiotic against a range of bacteria, including gram-positive, gram-negative aerobic and many anaerobic bacteria (Vázquez-Laslop & Mankin, 2018) (DrugBank, *Clarithromycin*). Clarithromycin is mostly used for several skin and airway infections, most commonly chronic bronchitis, mild pneumonia, acute sinusitis, and otitis media (Farmacotherapeutisch Kompas, *Claritromycine*). Clarithromycin treatment ranges from five to fourteen days. In 2020 the Netherlands counted 79.378 users of clarithromycin (GIPdatabank, *J01FA09: Claritromycine*).

Adverse Drug Reactions

Since clarithromycin is an antibiotic for common infections and oxycodone use is increasing rapidly, co-prescription between the drugs is to be expected. Unfortunately, concomitant use can lead to adverse drug reactions (Farmacotherapeutisch Kompas, *Oxycodon*) (Apotheek.nl, *Oxycodon*). Clarithromycin is a Cytochrome 450p3A (CYP3A) inhibitor, which is important in general drug metabolism (Farmacotherapeutisch Kompas, *Claritromycine*). CYP3A is responsible for oxidative biotransformation of drugs in the liver and intestine (Wilkinson, 1996). This oxidation can activate, deactivate, or help breakdown drugs in the system. Inhibition of CYP3A can have increasing effects on drug bioavailability.

Oxycodone has two active forms, oxycodone and as a metabolite. Oxycodone is metabolized in the liver via multiple pathways: glucuronidation, reduction or demethylation via CYP2D6 or CYP3A4/5 (Kalso, 2005). Via CYP2D6 around 19% of oxycodone is O-demethylated into oxymorphone, an active metabolite (Lalovic et al., 2005). Oxycodone and Oxymorphone are agonists for the μ-opioid receptor, leading to pain relief. Via CYP3A4 and CYP3A5 around 45% of oxycodone is N-demethylated into noroxycodone, an inactive metabolite. Both metabolites can be glucuronidated, reduced or be transformed into noroxymorphone via CYP6D2 and CYP3A4 (for oxymorphone only). This can be seen in the illustration below.

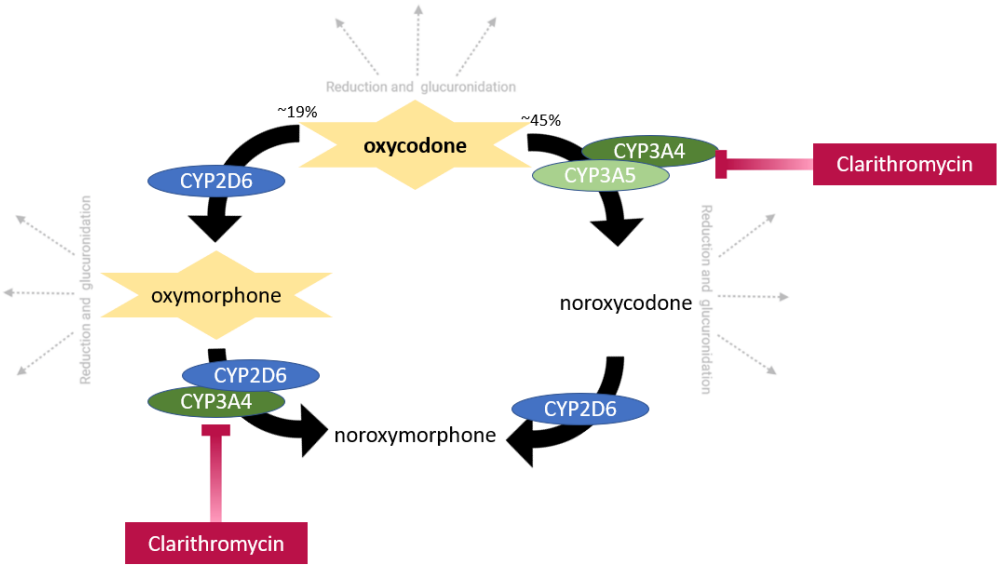

Figure 1: Oxycodone metabolism showing the locations of clarithromycin inhibition

It is well known that CYP3A inhibitors cause adverse drug reactions when concomitantly used with oxycodone, however there is not a lot of research for clarithromycin specifically. No concomitant utilization studies have been done so far. It was found in a 2-phase crossover study that oxycodone clearance decreased by clarithromycin in both young and elderly subjects, by respectively 53% and 48% (Liukas et al., 2011). The formation of the inactive metabolite, noroxycodone, decreased by 74% in young and 71% in elderly during clarithromycin treatment. The oral bioavailability simultaneously increased, which resulted in a prolonged elimination half-life and an increased mean area under the plasma concentration-time curve.

The pharmacological response of oxycodone is not significantly influenced by clarithromycin, however adverse effects can rise in sensitive patients (Liukas et al., 2011). This increased concentration can cause stronger side effects, the most common being nausea, vomiting, constipation, drowsiness, headaches, and itching (Farmacotherapeutisch Kompas, *Oxycodon*) (Apotheek.nl, *Oxycodon*). Sensitive patients can be classified as elderly or patients with hepatic or renal impairment (Kirvela et al., 1996).

Oxycodone metabolism also differs by sex. It was found that women have a 2-fold higher levels of CYP3A4 in hepatocytes than men (Wolbold et al., 2003). This gives rise to sex-dependent differences in oxycodone drug-clearance. Women were also found to have lower oxycodone serum concentrations after the same dose as men (Andreassen et al., 2010).

Guidelines oxycodone use

Oxycodone is an addictive drug. Guidelines surrounding oxycodone are mostly focused on reducing opioid abuse. The United Nations implemented guidelines to reduce opioid addiction whilst still being able to use the opioids for pain relief (Wetten.nl, *Enkelvoudig Verdrag Inzake Verdovende Middelen*). These guidelines are from the Single Convention on Narcotic Drugs in 1961. To combat abuse, the WHO created an analgesic ladder (Ventafridda et al., 1985). On this three-step ladder, pain treatment options are categorized, from NSAIDs to weak opioids, and eventually into potent opioids such as oxycodone. These steps are to be followed for treatment of chronic cancer pain.

In the Netherlands, in 2013, the guidelines for postoperative pain reduction from 2003 were changed (Houweling et al., 2013). Oxycodone was added to the list of potential painkillers after operations. The general guidelines to prescribe opioids as pain treatment relaxed in 2013 as well. According to the Dutch Farmacotherapeutisch Kompas oxycodone should only be used for chronic pain management if NSAIDs do not provide enough pain relief (Farmacotherapeutisch Kompas, *Oxycodon*).

Guidelines concomitant use of oxycodone and clarithromycin

When using oxycodone and a macrolide antibiotic simultaneously, it can lead to clinically relevant interaction (Farmacotherapeutisch Kompas, *Oxycodon*). When oxycodone is simultaneously used with a CYP3A inhibitor, monitoring is advised, and possible dose adjustments might be necessary.

Guidelines in the Netherlands state that with the use of oxycodone, physicians and pharmacists must be mindful of drug interaction (Richtlijnendatabase, *Geneesmiddeleninteracties Met Opioïden Bij Pijn Bij Kanker)*. Most interactions get caught via an automated interaction signaling through the "G-standaard" from the KNMP (KNMP, *Wat Is De G-Standaard*). When prescribing oxycodone with a CYP3A inhibitor, consultation between physician, pharmacist and the G-standaard database is advised.

Study aims

The aim of this study is to investigate to what extent oxycodone and clarithromycin are used simultaneously in the Netherlands. Secondary goals are to determine the incidence of concomitant use over time and whether oxycodone concentrations are adjusted after concomitant prescription. An explorative goal is to determine whether there are differences in concomitant use between sexes.

Given the lack of literature around this subject, only one hypothesis can be formulated. It is hypothesized that when concomitant use takes place, we expect to see a dosage decrease of oxycodone. The incidence of concomitant use cannot be predicted on the available information. Differences in concomitant use between sexes will be explored.

Method

Setting
This utilization study was performed using the University of Groningen IADB.nl pharmacy prescription database (IADB). The IADB contains prescription data of approximately 1,120,000 patients and is found to be representative of the Dutch population as a whole (*IADB*). The IADB contains patient information, such as age, gender and health insurance, and prescription data. The prescription data consists of information such as the Anatomical Therapeutic Chemical (ATC) codes, quantities, dosage, and dispensing dates. All data can be compiled by using patient specific identifiers. Prescription data from hospital and over the counter drugs are not included.

Study population
The study population consists of all patients over the age of 18 in the IADB having had at least two oxycodone (N02AA05) prescriptions within a month between 1994 and 2020. The two prescriptions together should have a theoretical period of oxycodone use of at least 28 days. These inclusion criteria were also used to determine which patients to define as being a user in each single calendar year.
To only test the outcomes of concomitant use of clarithromycin on oxycodone, patients using other strong CYP3A4 inhibitors during the theoretical period of oxycodone usage were excluded from the study population. This includes the use of erythromycin (J01FA01), ketoconazole (J02AB02), itraconazole (J02AC02), voriconazole (J02AC03), posaconazole (J02AC04), saquinavir (J05AE01), ritonavir (J05AE03) atazanavir (J05AE08), darunavir (J05AE10) and lopinavir (J05AR10) (Apotheek.nl, *Oxycodon*) (Busti & Herrington, 2015).

Concomitant use
Concomitant use was determined by having a prescription for clarithromycin during the theoretical period of use of oxycodone. Concomitant use was evaluated by calculating incidence of concomitant use per 1.000 patients using oxycodone for every calendar year in the studied period. The total concomitant use was also separately determined for men and women.

Dosage reduction
As a result of concomitant use, dose reduction is expected. To determine this outcome, concomitant users were evaluated. The dosage of oxycodone was determined by dividing the defined daily dose (DDD) by the theoretical period of use to create the DDD per day. The DDD per day of the prescription before or on the prescription date of clarithromycin are compared to the DDD per day of the first oxycodone prescription after concomitant use. A ratio was calculated by dividing DDD per day after concomitant use by the DDD per day before concomitant use. Only patients with a prescription of oxycodone within a month after concomitant use were included in these calculations.

Statistical analysis
First the theoretical periods of total oxycodone use of the study population over the entire period were calculated and visualized using a histogram. The theoretical period of use is counted for all these prescriptions even though they can cover the same period.

The incidence of concomitant use per 1,000 patients for every year was calculated and visualized for the total study population, and men and women separately. A linear trendline was calculated for each group. The Chi-square test was used to test if concomitant use differed between the sexes, using a significance level of 0.05.

Lastly, the DDD per day ratios were log transformed (Ln), because the data was not normally distributed. Whether or not any dosage adjustments on the population average took place was determined using a simple T-test using SPSS (comparing the difference in ratios to 0 with a significance level of 0.05). If not significant, the mean ratio will give an indication of dosage reduction or increase.

Results

Whilst filtering patients for data extraction, it was observed that oxycodone use in the Netherlands started in 2001. The rest of the results are therefore only looking at the period 2001 to 2020.

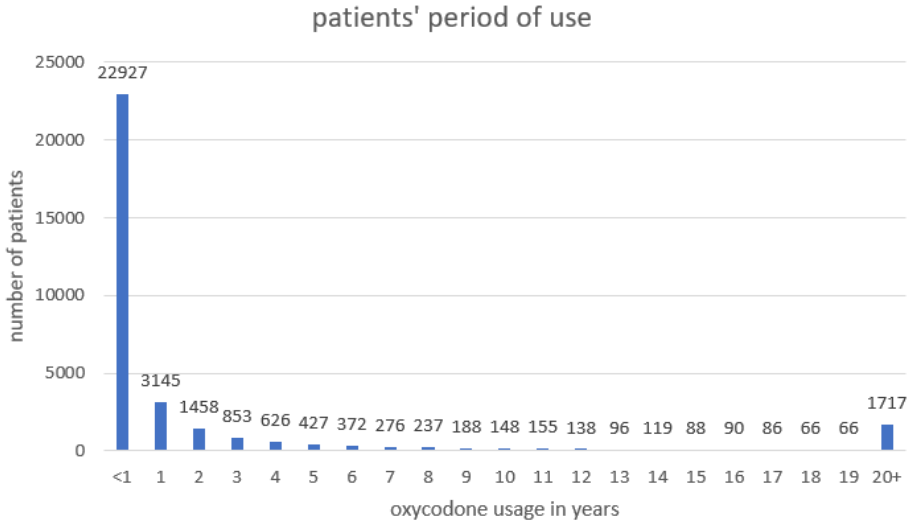

Figure 2: Histogram showing the number of patients by their total theoretical periods of oxycodone use between 2001 and 2020.
n = 33,278.

The study population consists of 33,278 patients. The theoretical periods of use in the period 2001-2020 for all patients is shown in a histogram (figure 2). As can be seen in the histogram, there are 1,717 patients (5.16%) with a theoretical period of use which is longer than the period evaluated, 20 years.

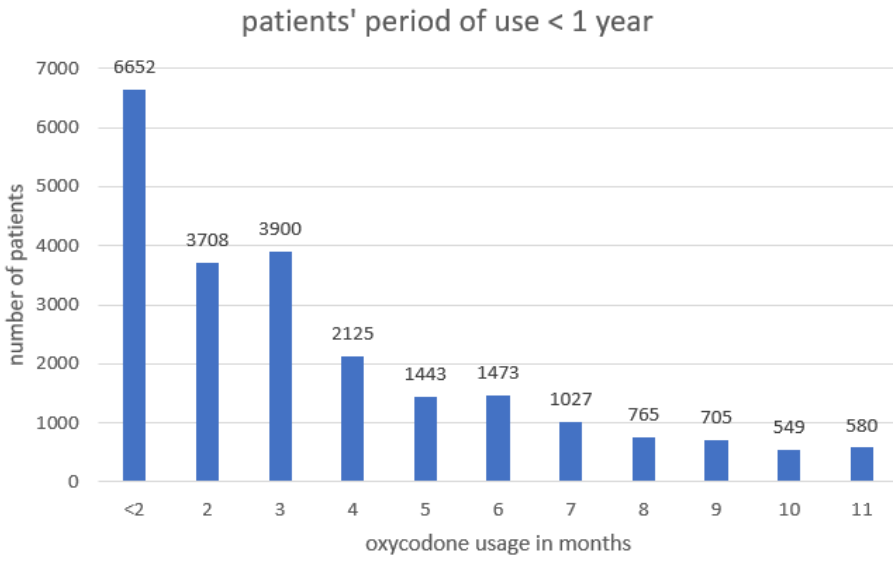

Figure 3: Histogram showing the number of patients and their total theoretical periods of oxycodone use between 2001 and 2020 for which the period of use is less than one year. n = 22,927

The majority of oxycodone users (n=22,927; 68.90%) have a period of use under a year. An additional histogram was created to show the distribution of these patients (figure 3). It is found that most patient (n=6,652; 19.99% of total) used oxycodone for no longer than two month.

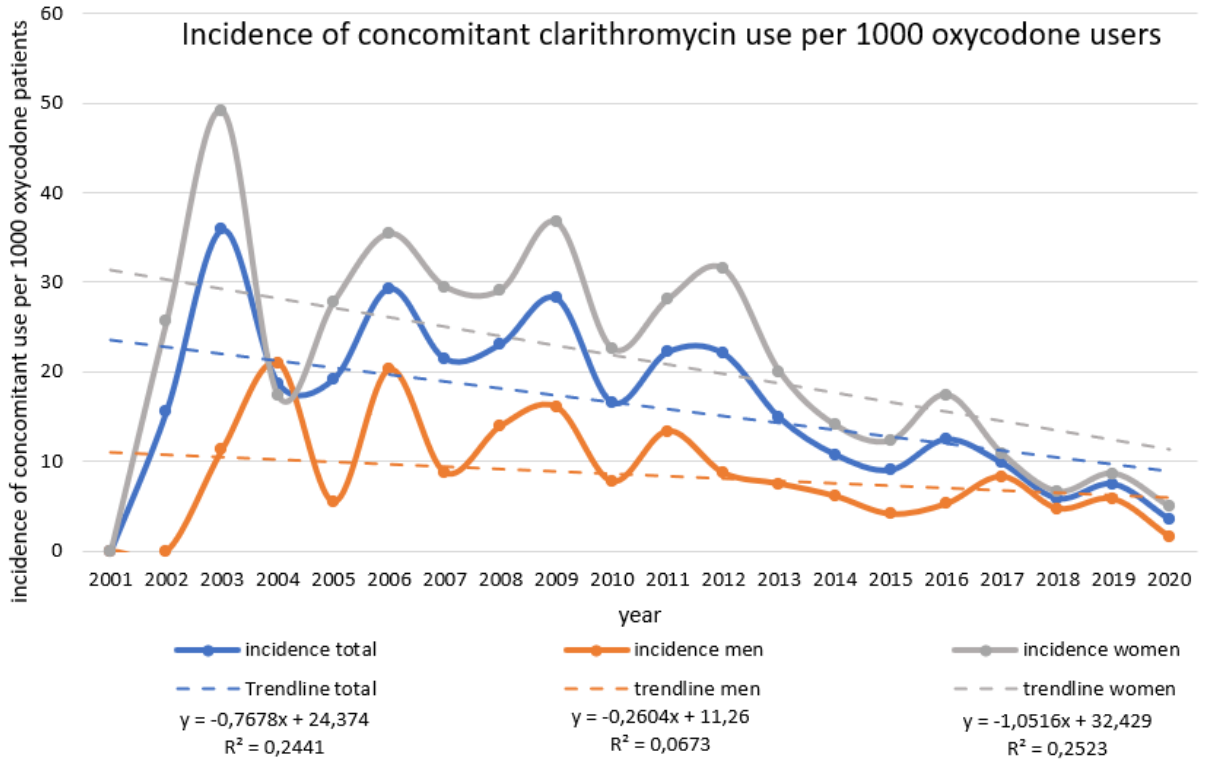

Figure 4: Incidence of concomitant use per 1,000 patients for every year for all patients combined, men and women. Trendlines of concomitant use for all patients and by sex.

Concomitant use was found 616 times in this studies population. Over the whole period, an incidence of concomitant use per 1,000 oxycodone users of 11.68 was found (n= 52,764). For men (n= 21,731) and women (n= 30,992) the combined data gave an incidence of concomitant use equal to, respectively, 6.67 and 15.19 per 1,000 patients. A Chi square test showed that the concomitant use of men and women differed significantly with a p value of lower than 0.001.

After calculating the incidence of concomitant use of oxycodone and clarithromycin per year, these values were visualized in figure 4. This data can be found in table 1 in the appendix. It can be seen that the incidences in females was higher than that of males throughout the years, and that the incidences decreased over time. For all categories, all patient, men and women, a trendline was created with y being the incidence of concomitant use, and x the time per year. The trendline for the incidences in all patients was equal to $y = -0.7678x + 24.374$ and had a R^2 of 0.2441. The equation of the trendline of men and women were respectively $y = -0.2604x + 11.26$ ($R^2 = 0.0673$) and $y = -1.0516x + 32.429$ ($R^2 = 0,2523$). The decline in incidence of the trendline of women is steeper (1.05) than in men (0.26).

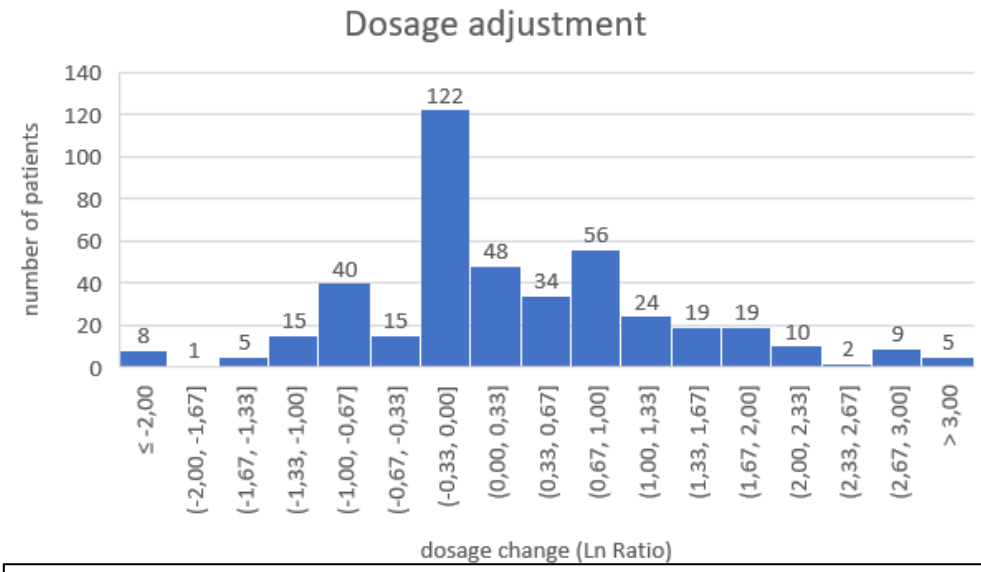

Figure 5: histogram of the dosage adjustment in Ln ratios. Ln ratio > 0 represent a dosage increase. Ln ratio < 0 represent a dosage decrease. n = 432.

After calculations, the dosage adjustment Ln ratios were made visible in a histogram as seen above (figure 5). A Ln ratio > 0 represents a dosage increase and < 0 represents a dosage reduction. The number of patients used for this calculation was 432 patients with an oxycodone prescription within one month after the clarithromycin prescription. As can be seen, the most prevalent Ln ratios were between -0.33 and 0. This count is divided over 122 patients < 0 (28.24%), 88 patients = 0 (20.37%) and 222 patients > 0 (51.39%). Next a simple T-test was used to test the hypothesis that there was no dosage adjustment, meaning the Ln ratio is 0. By specifying the t-test in this way, this after/before comparison is equal to a paired samples t-test for ratios. A p value of lower than 0.0001 was found, therefore the hypothesis of no dosage adjustment was rejected. The mean difference was equal to 0.3238. When converted back to the start ratios, the mean was equal to 1.38 (= e^0.3238) which indicates that the dosage on average increased with 38% after concomitant use. More information on the T-test can be found in table 2 (appendix).

Discussion

The aim of this study was to investigate to what extent oxycodone and clarithromycin are used simultaneously in the Netherlands. This was accomplished by determining the differences in concomitant use between men and women, determining the incidence of concomitant use over time and determining dosage adjustments after concomitant use.

It was found that concomitant use was significantly higher in women, compared to men. The incidence of concomitant use of oxycodone and clarithromycin was found to be 11.68 per 1,000 oxycodone users. The incidence of concomitant use has declining time trend between 2001 and 2020. After concomitant use a dosage increase 38% was found.

Inclusion and exclusion

The first recorded use of oxycodone in the IADB in the Northern part of the Netherlands is from 2001. This coincides with the introduction of Oxycodone on the Dutch market in 2001.

For this research, patients under eighteen were excluded from the database. On the label of oxycodone, it says that children older than twelve years old can be prescribed oxycodone for severe pain. Children from the age of six also receive oxycodone prescriptions off-label. On top of that, not all forms of clarithromycin can be prescribed to children under the age of twelve (Farmacotherapeutisch Kompas, *Claritromycine*). For these reasons, patients under eighteen might have altered the results if included. Therefore, the conclusions are only valid for adult oxycodone users.

This study zooms in on chronic users. Chronic users were defined as having had at least two prescriptions within a month which have a combined theoretical period of use of at least 28 days. In Dutch literature, chronic users have multiple definitions. The Instituut Verantwoord Medicijngebruik defined chronic users as using oxycodone for more than two weeks, whereas Nivel uses the definition of using oxycodone for more than three months (de Metz & Lambooij, 2020) (Weesie et al., 2016). The definition chosen in this research was chosen as a combination of both, using parameters available in the IADB. Two prescription per patient were included in the definition to increase the chance of retrieving usable data for the dosage adjustment ratios.

Period of use of oxycodone

Out of 33,278 chronic oxycodone users, 68.90% had a total theoretical period of use under one year between 2001 and 2020. 19.99% out of all patients had a total theoretical period of use up to two months. 5.16% of all patients had a total theoretical period longer than the investigated 20 years. The theoretical period of use is not representative of the actual period of use. This is because patients can receive multiple prescription in one day of which the period of use is stacked, even though it covers the same period. This leads to an overestimation of the period of use of oxycodone. It does, however, give an indication that more than 68.90% patients used oxycodone for less than a year and that around 5% have used oxycodone almost continuously for around 20 years.

Incidence

Clarithromycin treatment generally last no longer than five to fourteen days (Farmacotherapeutisch Kompas, *Claritromycine*). Due to this short time frame all events of concomitant use were counted per patient. All counts of concomitant use are used to create the incidence instead of the number of patients with concomitant use. Instead of creating an incidence rate, the incidence of concomitant

use per thousand patients was calculated. To use the theoretical period of use to create concomitant use per patient-time, would give unrepresentative results because the patients' total theoretical period of use is the sum of all prescriptions, and is therefore not necessarily equal to the actual period of use. An incidence rate would give rise to an underestimation of concomitant use.

In this study, a linear regression was used to create trendlines, however the data is not in line with prerequisites of this statistical method. For the observed decline in concomitant use, the exact regression coefficients should therefore be interpreted with caution. In future comparable research a time series analysis is advised.

It was found that the concomitant use differs significantly between men and women, where women have higher levels of concomitant use. As mentioned before, women's oxycodone metabolism differs from men (Wolbold et al., 2003) (Andreassen et al., 2010). Theoretically having higher CYP3A4 levels in women and lower concentrations of oxycodone after the same dosage compared to men, may lower the chance on side effects because of concomitant use. It is possible that physicians and pharmacists feel that concomitant use of oxycodone and clarithromycin is safer in women for that reason.

It was observed that the incidence of concomitant use, in both men and women and all patients together, declined with time. This decrease in incidence of concomitant use per year could be explained by multiple developments. Over the years, more and more research about oxycodone and CYP3A inhibitors was published. For example, in 2014 a new strategy was found to evaluate the impact of co-prescription of CYP inhibitors on oxycodone (Marsousi et al., 2014).

Another explanation for decreasing incidence can be improved medication monitoring. In 2005 it was found that medication monitoring was not up to par and recommendation were formulated, such as implementing an electronic coupling of all pharmacies (Vervolgonderzoek Dienstapotheken: Medicatiebewaking Nog Verre Van Sluitend, 2009. In 2008 medication monitoring was found to still not be all encompassing, lacking in information management, non-functioning information systems and insufficient information sharing. After this report, all pharmacies were put on an improvement program. These implementations could have improved signaling of concomitant use of oxycodone and a CYP3A inhibitor, leading to less concomitant use and therefore a lower incidence.

A third explanation is a decreased use of clarithromycin. It was observed in the GIP databank that clarithromycin usage has decreased between 2017 and 2020 (GIPdatabank, *J01FA09: Claritromycine*). The number of users went from 109,810 to 79,378 in four years, this means a decrease of 28% in users. With less clarithromycin users, it can be expected that the simultaneous usage with oxycodone will also decrease, giving a lower incidence. A decrease of 28% is not sufficient to fully explain the 63% reduction in incidence of concomitant use that can be found between 2017 and 2020.

Dosage reduction

Patients with a prescription for other strong CYP3A4 inhibitors were excluded from this study to only test the influence of clarithromycin dosage adjustment. It should however be noted that moderate and low CYP3A4 inhibitors were not excluded. These drugs could still influence the dosage adjustment measure.

Oxycodone metabolism also uses the Cyp2D6 isomer. Cyp2D6 inhibitors were not excluded from the study. These drugs might also have influenced the dosage adjustment measure, by effecting the oxycodone metabolism and pharmaceutic effects as well.

According to the guideline, dosage adjustment should occur on a case-by-case basis. The dosage adjustment measure was used to investigate whether this occurred. The dosage adjustment measure looks at one prescription before concomitant use and one after. The problem arises that patients can receive multiple prescription on one day. In these cases, only one prescription was used in the calculations.

When patients want to terminate oxycodone usage, they must undergo tapering (Lambooij et al., 2021). The oxycodone concentrations are lowered around once a week as long as the pain is still bearable, and the withdrawal symptoms are not too strong. This weekly lowering of the concentration means that part of the dataset may be patients undergoing tapering instead of dosage adjustment after concomitant use. In future research these patients could be filtered out by studying trends of decline and discontinuation of oxycodone per user.

Chronic oxycodone users can have trouble with drug habituation (Farmacotherapeutisch Kompas, *Oxycodon*). To continuously cause the desired pain-relieving effect, oxycodone dosage will have to be increased. This might be the cause of some of the dosage increases that were found.

The study set up might have skewed the results as well. In the ratio calculation, only one prescription was used. It is however very possible that multiple prescriptions were dispensed on the same date as part of the same oxycodone treatment, as mentioned before. The dosage of oxycodone after concomitant use was only included if the prescription was within a month of the dispensing date of clarithromycin. This is however quite a long period for this study set up. Clarithromycin has a period of use of five to fourteen days and dosage reduction due to concomitant use would be expected to fall only in the period of the simultaneous period of use. Future studies should narrow down this window of investigation more than preformed in this study and determine better values for the dosage adjustment. Future studies might also want to investigate dosage change in shorter time intervals to see whether trends can be found.

Conclusion

The incidence of concomitant use of oxycodone and clarithromycin was 11.68 per 1,000 oxycodone users. Concomitant use was higher in women and declined over time for both men and women. It can be inferred that the decline in incidence is partly caused by a reduction of clarithromycin users in the Netherlands. Other contributing factors were expected to be research developments and improvements in drug monitoring in the Netherlands.

It can be concluded that from these findings that concomitant use of clarithromycin and oxycodone seems to become less likely to happen on an individual basis over the years. This should be considered an improvement of concomitant use in the Netherlands.

No clear conclusion regarding dosage adjustment can be drawn because of methodological limitations, including multiple prescriptions and other CYP inhibitors. Further research will be required to test this study's findings of an increase in oxycodone dosage after clarithromycin use.

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Appendix

	incidence of concomitant use per 1,000 users			N conco men	N oxy users men	N conco women	N oxy users women
jaar	**all patients**	**men**	**women**				
2001	0,00	0,00	0,00				
2002	15,63	0,00	25,64			1	39
2003	35,86	11,36	49,08	1	88	8	163
2004	18,72	20,98	17,32	3	143	4	231
2005	19,19	5,52	27,78	1	181	8	288
2006	29,32	20,24	35,42	5	247	13	367
2007	21,44	8,75	29,47	3	343	16	543
2008	23,11	13,95	29,14	6	430	19	652
2009	28,22	16,06	36,68	7	436	23	627
2010	16,57	7,78	22,58	4	514	17	753
2011	22,22	13,39	28,06	12	896	38	1354
2012	22,05	8,72	31,48	10	1147	51	1620
2013	14,90	7,53	20,07	10	1328	38	1893
2014	10,77	6,16	14,07	10	1624	32	2274
2015	9,04	4,17	12,32	8	1919	35	2840
2016	12,47	5,29	17,45	12	2268	57	3267
2017	9,83	8,33	10,89	22	2642	41	3765
2018	5,86	4,78	6,64	13	2722	25	3764
2019	7,48	5,84	8,66	14	2399	29	3350
2020	3,57	1,66	5,00	4	2404	16	3202
Total				145	21731	471	30992

Table 1: The incidences of concomitant use of clarithromycin and oxycodone per 1,000 oxycodone users for every year.

One-Sample Statistics

	N	Mean	Std. Deviation	Std. Error Mean
VAR00001	432	,3239	1,01766	,04896

One-Sample Test

Test Value = 0

	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
VAR00001	6,615	431	,000	,32387	,2276	,4201

Table 2: Results of the one-sample T-test in SPSS used for the dosage adjustment calculations.