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Opioid purchases and expenditure in nine western European countries: 'Are we killing off morphine?'

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Background: In clinical practice the major role of opioid drugs is the management of malignant and nonmalignant pain. The primary aim of this study is to evaluate the trend in sales of four opioid analgesic drugs (codeine, tramadol, morphine, fentanyl), from wholesalers to community pharmacies, as an indicator of opioid consumption in nine European countries in 2001, 2002 and 2003. Secondary aims are to compare: (a) the amount of each drug purchased by different countries in 2003; (b) the average price for each drug in the different countries in 2003; and (c) the total expenditure for each opioid from 2001 to 2003. **Methods:** Data from the Statistical Report on drugs purchased by pharmacies was supplied by IMS Health, an internationally accepted information provider for the pharmaceutical and health care industries. **Finding:** In the period 2001–2003, while the percentage increase of purchases of fentanyl and tramadol was considerable, that of morphine was the lowest in most of the nine countries. The largest consumer of codeine was the UK and of tramadol was Belgium. The consumption of morphine was the lowest reported in all the countries together and was three times lower than that of transdermal fentanyl. There was a high variability in the costs of the opioids among the different countries. In 2003, the total expenditure on fentanyl reached the total expenditure on tramadol, followed by codeine. Morphine presents the lowest expenditure in all nine countries and over all three years. **Interpretation:** These results open up many questions. What factors influence opioid purchasing and costs in these European countries? It would be interesting to have the answers from those people who know the actual situation in the individual countries. *Palliative Medicine* 2005; **19:** 179–184

Key words: codeine; European countries; fentanyl; morphine; opioid expenditure; opioid purchases; tramadol

Introduction

Opioid drugs are mainly used for treating pain. According to the World Health Organization (WHO) and the European Association for Palliative Care (EAPC), as far as cancer-related pain is concerned, opioids are the mainstay of adequate analgesic therapy and morphine is the drug of first choice for treating moderate to severe pain.[1–3]

Opioid analgesics have been proved to be effective, without overt evidence of tolerance and intolerable toxicity, even in selected patients with nonmalignant acute and chronic pain, and in particular when used as elements in a multimodality strategy.[4–6]

The global manufacture, stocks, consumption and utilization of opioids from 1983 to 2002 are reported by the International Narcotics Control Board (INCB),[7] but for the purposes of our study we could not use the INCB data because tramadol consumption is not reported, the expenditure of the opioids are not considered and the data regarding 2003 are not available yet.

The primary aim of this study is to evaluate the trend in the sales amount of four opioid drugs (codeine, tramadol, morphine, fentanyl), from wholesalers to pharmacies, as an indicator of opioid consumption, in nine European countries in 2001, 2002 and 2003, with particular attention to morphine compared to the others. Secondary aims are to compare: (a) the amount of each drug purchased by the different countries in 2003; (b) the average price (wholesaler purchase price) for each drug in the different countries in 2003; and (c) the total expenditure for each opioid from 2001 to 2003.

Methods

For each year considered (2001, 2002, 2003), the amount of purchases (in kilograms) and expenditure (in Euros) by pharmacies of four opioid analgesics, in nine western European countries, was taken from the Statistical Report on drugs purchased by community pharmacies,

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which was supplied to us by IMS Health (International Medical Statistics), an internationally accepted information provider concerning the pharmaceutical and health care industries.

The following European countries, for which data was available, were investigated: Belgium, Germany, Ireland, Italy, the Netherlands (NL), Norway, Portugal, Spain and the UK. We also gathered data from France but decided not to present them because they were based on only a 2% sample of pharmacies.

Among all the opioids contained in the Statistical Report, only the sales of codeine and tramadol (as weak opioids), and morphine and fentanyl (as strong opioids) were considered, because of their availability for analgesic purposes in all the nine countries, unlike other opioids such as oxycodone and hydromorphone, which are not yet available everywhere. Methadone was excluded because although it is available in many countries as an analgesic, it is, however, used above all for the treatment of drug-addicted patients.

The amounts of opioids purchased by community pharmacies were considered instead of the final consumption data both because of the easier and less expensive access to them and because they can be considered as a good proxy of the latter.

Data gathering methods were different in the various countries due to the different market structures. Table 1 shows the sample of community pharmacies or wholesalers for community pharmacies for each country involved in the survey. As shown, the sampling coverage of the total market is very high for all countries. Raw data were corrected by projection factors depending upon sample size, collaboration and sample data quality; hence all data reported are on a national basis.

Data elaboration

For the years 2002 and 2003, the percentage variation with respect to the previous year of the amount of each opioid purchased was calculated for each country.

In order to compare the consumption of the different opioids in 2003, raw data (in milligrams) have been transformed into the number of defined daily doses per 1000 people (DDD/1000 people). DDD is defined by WHO as the 'assumed average maintenance dose per day for a drug used for its main indication in adults'.[8] Table 2 shows the conversion rules into DDD for each drug considered.[8]

Data on the number of inhabitants for each country on 1 January 2001 are those reported by EUROSTAT.[9] 2003 expenditure data were converted into cost data (Euros/gram), dividing the former by the 2003 amount of opioid purchased, thus obtaining the price paid by community pharmacies to wholesalers (wholesaler price).

All data are graphically presented by means of paired bar charts to facilitate comparisons between the different countries or the different drugs.

Table 1 Countries involved in the survey and sample of community pharmacies or wholesalers for each country

Belgium	96% wholesalers and 12.3% of all pharmacies in the country
Germany	100% of wholesalers and 14.8% of all pharmacies in the country
Italy	96% of wholesalers and 7% of all pharmacies in the country
NL	100% of wholesalers
Norway	100% of all pharmacies in the country
Spain	90% of all pharmacies in the country
UK	97% of all pharmacies in the country
Ireland	93% of wholesaler census data
Portugal	96% of the total market

Results

Figure 1 shows the percentage purchasing variations by pharmacies in 2002 with respect to 2001 (black bars), and in 2003 with respect to 2002 (grey bars), for each country and lastly for all the countries involved.

As regards all the countries considered, a yearly increase of about 7% in sales of morphine in both periods is observed. The morphine purchases vary from the maximum increase in Norway (+15% in 2002 versus 2001) to the maximum decrease in Ireland (−11% in 2002 versus 2001). Fentanyl purchases register global increases of +25% and +15% in the two periods (all countries together), and reach a maximum in Italy (+70% and +35%), followed by Spain (+37% and +14%) and the UK (+29% and +19%). It can also be observed that the percentage increase of fentanyl purchase is lower in the second period in all countries except the NL.

As regards the percentage purchase variations of weak opioids in all the countries considered as a whole, codeine purchase shows a slight increase similar to morphine in 2003 versus 2002. However, there is a drop in codeine purchases in 2002 versus 2001 and an increase in 2003 versus 2002 in Belgium (−48% and +7%), in Germany (−8% and +9%) and in Spain (−8% and +17%).

On the other hand, tramadol purchases show a substantial increase in all the countries together (+11%

Table 2 DDD for different drugs and administration routes (Ref. 8)

Drug	Administration route (*)	DDD (mg)
Codeine	O	150
Tramadol	O, P, R	300
Morphine	O	100
Fentanyl	TD, SC	0.6

*O, oral; P, parenteral; R, rectal; TD, transdermal; SC, subcutaneous

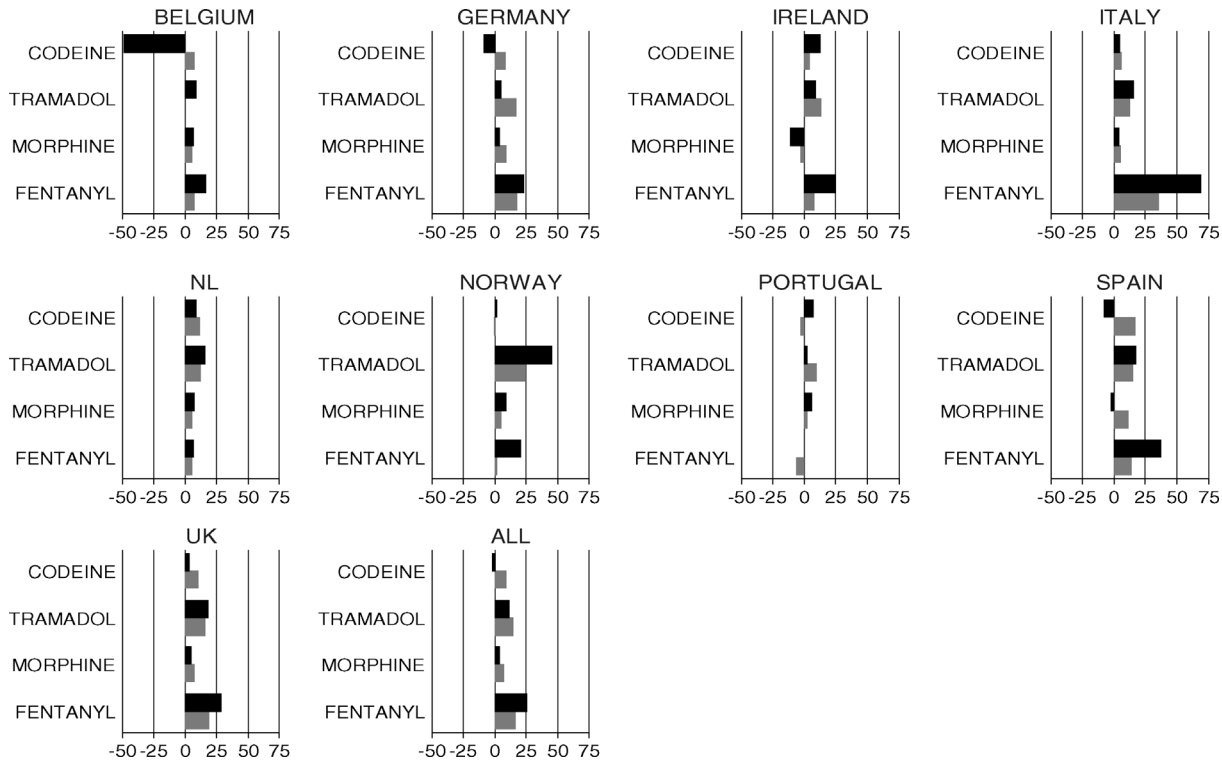

Figure 1 The percentage purchase variation in 2002 and 2003 with respect to the previous year for each country and all the countries together. Black bars indicate 2002 versus 2001 variation; grey bars indicate 2003 versus 2002 variations. Positive variations indicate an increase in the drug purchase, while the negative ones indicate a decrease.

and +16%), with a marked increase in Norway (+45% and +24%) and moderate increases (from +15% to +18%) in Italy, the NL, Spain and the UK. Portugal shows a substantial stability of all opioids purchase data.

Figure 2 shows the number of DDD/1000 people of the four opioids purchased in 2003. Considering all the countries put together, the DDD/1000 of codeine reported is 316 with a minimum of 26 DDD/1000 in Italy, and a maximum of 1003 DDD/1000 in the UK. Instead, tramadol consumption is more homogeneous among the 10 countries in 2003. Its highest consumption is reported in Belgium (389 DDD/1000), whereas the lowest consumption is reported in Italy (39 DDD/1000) and in Portugal (88 DDD/1000).

The consumption of morphine is the lowest reported in all the countries put together (53 DDD/1000). Norway presents the highest consumption of morphine (109 DDD/1000) followed by the UK (96 DDD/1000); whereas Italy and Portugal report the lowest consumption (7 and 5 DDD/1000 respectively). On the other hand, in the nine countries put together, fentanyl consumption (177 DDD/1000) is three times more than that of morphine. The highest fentanyl consumption is in Germany (332 DDD/1000), followed by Belgium (243 DDD/1000) and the NL (187 DDD/100). Once again, Italy and Portugal report the lowest consumption (66 and 8 DDD/1000 respectively). It can be seen that in Italy fentanyl is the most consumed opioid; it is used about 10 times more than morphine.

Figure 3 shows the wholesaler price of drugs (Euros/grams) by country in 2003. The cost of tramadol is highest in Italy (5.95 Euros/g) and lowest in Norway (2.54 Euros/g). Italy is also the country where codeine is the most expensive (14.9 Euros/g) and Norway the country in which the opioids considered are always among the cheapest.

Figure 3 also shows a high variability in the costs of strong opioids among the different countries: morphine cost ranges from 32.33 Euros/g in Germany to 8.7 Euros/g in Norway; fentanyl from 2909.00 Euros/g in Germany to 1701.30 Euros/g in Italy.

Figure 4 shows the total expenditure in Euros (considering wholesale prices) for each opioid in 2001–2003 in the countries considered all together. The trend of expenditure (which depends on both the cost and the quantity consumed) shows a reverse in tendencies. In the year 2001 the highest expenditure was for codeine (81.40 billion Euros) followed by tramadol (73.26 billion Euros) and fentanyl (64.40 billion Euros). In the year 2002, expenditure for those three drugs was equivalent (about 80 billion Euros for each one), whereas in the year 2003 expenditure for codeine was lower with respect to tramadol and fentanyl, having both reached the highest levels (respectively 93.56 billion Euros and 92.95 billion

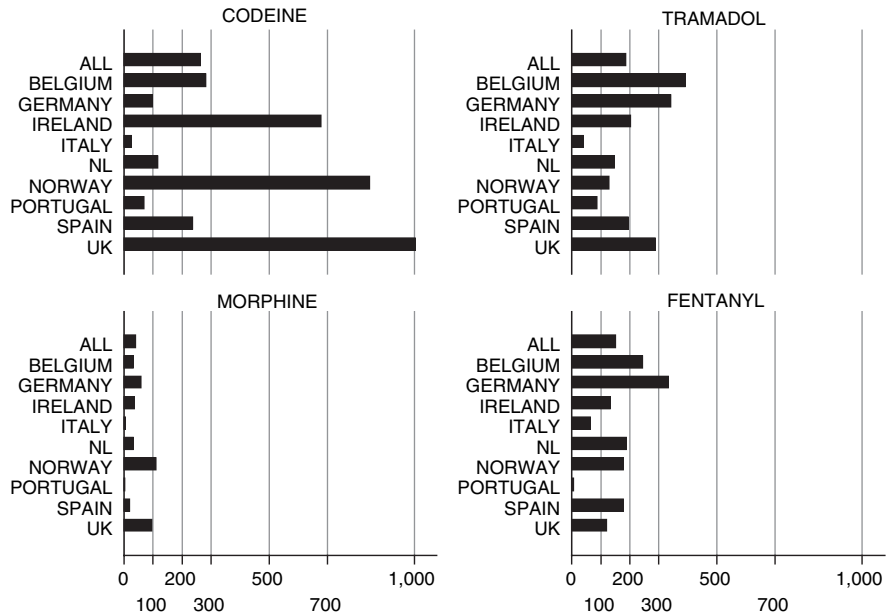

Figure 2 The number of DDDs per 1000 people in 2003 for each country

Euros). The expenditure for morphine is the lowest in all the three years considered (from 31.02 to 33.01 billion Euros) and corresponds to about one-third of expenditure on the other three opioids (Figure 3).

Discussion

The results presented show that, in the period 2001–2003 in the nine countries considered, the trend of community pharmacies purchasing (and consequently of final consumption) is different among the different opioids. In particular, a significant increase in the consumption of tramadol and transdermal fentanyl was registered versus only a slight increase in the consumption of morphine and codeine. These results are also consistent with the trend in the total expenditure data which show that fentanyl has reached the total expenditure of tramadol, while morphine and codeine remain substantially unmodified. The consumption of opioids was compared

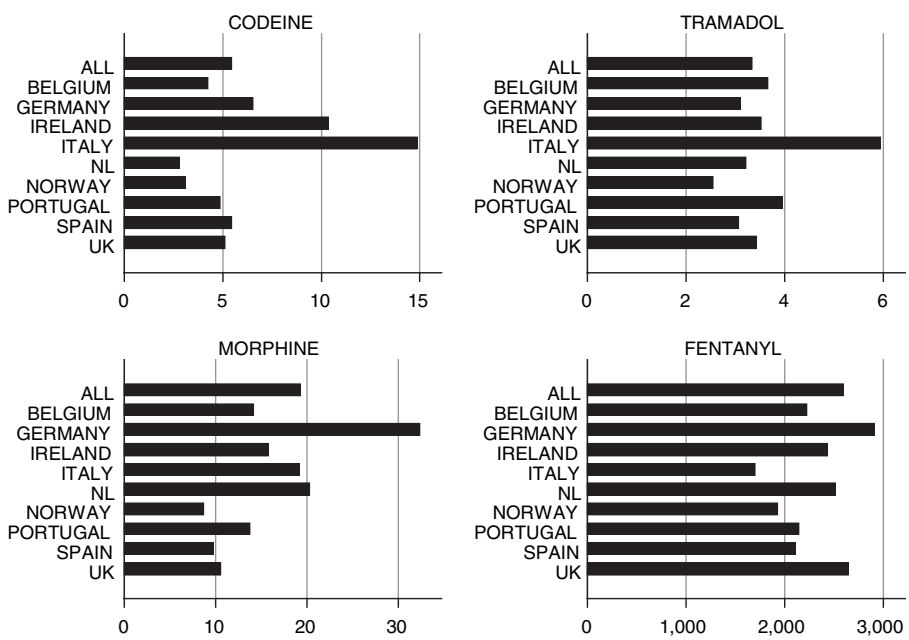

Figure 3 The wholesale price (Euros/g) of four opioid drugs by country in 2003

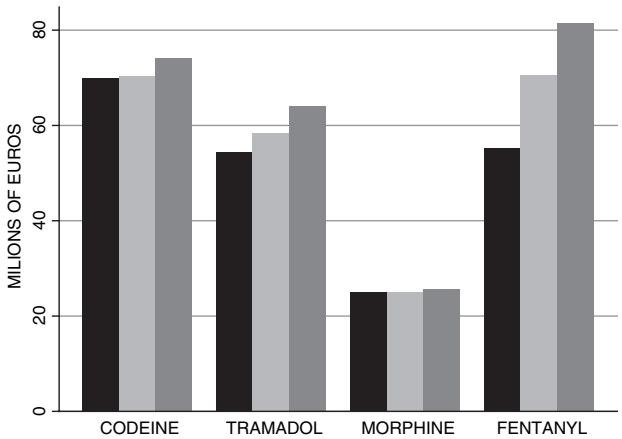

Figure 4 The total expenditure (wholesale cost) in Euros in 2001 (black bars), 2002 (light grey bars) and 2003 (dark grey bars) for each opioid in the nine European countries considered

also in terms of DDD/1000 people and the results are consistent in showing a major consumption of fentanyl in respect to morphine.

The study presents some limitations. Our own data on consumption quantity and prices do not allow the distinction by route of opioid administration or by the type of release (short, immediate, slow), which are all important aspects for their influence on drug usage. Our results allow a global and comparative vision of the comprehensive use of four different classes of opioids and their various costs in the nine countries under study.

Moreover, the use of DDD has certain limits as an indicator of consumption when comparing the different drugs and their different costs. It should be considered that, notwithstanding that the use of DDD allows the possibility of comparing the quantity of the different drugs consumed, the DDDs defined by WHO[8] are not really equipotent doses in clinical practice, because the DDD does not take into account the potency of the drugs but the most frequently used dose of each drug. Thus it would be more appropriate to consider the equipotency ratios instead of DDD when comparing different strong opioids. For example, Table 2 shows that the DDD for morphine is equal to 100 mg and DDD for fentanyl is equal to 25 mcg/h.[8] In clinical practice 25 mcg/h of transdermal fentanyl (thus 0.6 mg/day of fentanyl) is less potent than 100 mg of oral morphine. On the grounds of these considerations, the data shown in Figure 2 could overestimate the quantity of fentanyl consumed expressed in DDD/1000.

If a DDD of transdermal fentanyl equal to 50 mcg/h (1.2 mg/day) is used, which is closer as potency to 100 mg of oral morphine, the difference in consumption between morphine and fentanyl would be lower: all the bars shown in Figure 2 would be halved. In all countries together, considering the DDD for fentanyl (50 mcg/h), the number of fentanyl DDD would still be superior to that of morphine (89 versus 53). However, we have decided to use the DDD according to the WHO definition[8] so that our data may be comparable to others.

As far as the costs are concerned, we preferred to present the data as cost/gram, underlying that they have to be considered according to the different potency of each opioid.

The results of this investigation lead to few certainties and, at the same time, open up many questions. One certainty is that these nine countries, all of which live under the common banner of Europe, have different and often incomprehensible data regarding both consumption as well as the cost of the same drug. Another certainty is that the percentage purchase variation and the consumption (DDD/1000 people) of weak and strong opioids in Italy and Portugal are the lowest among all the considered countries.

For the Italian authors of this article, this fact is disheartening and discouraging if all the educational efforts that have been made over the last 20 years to promote the use of opioids in treating malignant and nonmalignant pain are considered.

Another certainty is the fact that morphine, considered the gold standard drug for pain management, the most studied drug, and the one having the highest number of publications, has the lowest consumption in respect to the other opioids.

Are we killing off morphine? Why? Is it perhaps because the name still evokes unjustified fears (addiction, abuse, adverse effects, impending death etc.), or because everybody knows that it is an opioid drug, unlike other opioids that have trade names not linkable to the chemical compound, or because there is less interest in marketing due to its low cost?

And yet morphine has never been shown to be less analgesic and/or more toxic than other opioids. Once 'opiophobia' was talked about,[10,11] however, looking at the data of this study it seems that the appropriate term, today, would be 'morphinephobia'.

The questions left open regard the reasons why the percentage of purchase of transdermal fentanyl has increased and the consumption (DDD/1000) is high in all the investigated countries. Is this due to the fact that the fentanyl patch in particular is a relatively new formulation and thus what we have observed over these three years is only the tail of an event of novelty? This does not seem to be the answer if we consider that transdermal fentanyl has been on the market longer: Belgium and Italy from 1996; Ireland, Norway and the NL from 1995; the UK and Germany from 1994; with the exception of Portugal and Spain where it could be found since 1999 and 1998 respectively.

Is it due to the fact that the transdermal formulation is easy to use and to prescribe because it is 'simply a patch'

or that most patients do not know that fentanyl is an opioid and much more potent than morphine, or is it because its marketing is very intense in European countries?[12] Or could it be the fact that fentanyl causes less constipation in respect to morphine[13,14] or that it is safer in renal impairment?

Other questions are, for example, why is codeine consumption so high in the UK, Norway and Ireland in respect to the other countries?

Why is tramadol used more than morphine in all the nine countries notwithstanding the many adverse-event reports classified under the coding terms 'drug interactions', 'drug dependence', 'drug withdrawal' or 'drug abuse' in association with tramadol, even in cases where there was no history of drug/substance abuse.[15–19]

Also, the question regarding the difference of cost of the same drug in the different countries is intriguing. Why do morphine and fentanyl cost so much in Germany and why does codeine and tramadol cost more in Italy (when at the time they were not yet reimbursable by the Health Care System) than in any other country? Why in Norway is the cost of all four opioids less than the average?

What factors influence opioid purchasing in these European countries? Is it influenced by scientific literature or by cultural, educational, political, legislative and economic factors such as the cost of the drugs and their reimbursement. Or is it influenced by more or less aggressive marketing, by patient compliance, by information given to the patients and their families?

How much do these factors weigh in opioid purchasing? How much do these factors taken singularly or as a whole influence opioid purchasing? We do not know, but we would like to!

We believe there should be a common language concerning opioids, taking into consideration scientific and educational factors, regulation and monitoring of the marketing, uniformity of prescription, and cost and reimbursement of these opioids under a European concept. In such a way, we hope soon to have Europe free from pain and free from factors that might influence opioid purchasing without considering above all the real needs of the patients.

It would be interesting to receive answers to the questions put forward from the people who know what the actual situation is in the individual countries.

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