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Opioid availability statistics from the International Narcotics Control Board do not reflect the medical use of opioids: comparison with sales data from Scandinavia

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Abstract

Objectives: Opioid analgesics are essential in clinical practice, but their excessive use is associated with addiction risk. Increases in opioid prescription rates have fuelled an epidemic of opioid addiction in the USA, making statistics on medical opioid use a critical warning signal. A dramatic 150% increase in Swedish opioid access 2001–2013 was recently reported based on data from the International Narcotics Control Board (INCB; Berterame et al. 2016) in conflict with other studies of opioid use in the Nordic countries. This article aims to analyse to what degree published INCB statistics on opioids in Scandinavia (Denmark, Norway and Sweden) reflect actual medical use and study the methodological reasons for putative discrepancies.

Methods: Data on aggregated total national sales of opioids for the whole population, including hospitals, were collected from the Swedish e-Health Authority. Total sales data for Denmark and drugs dispensed at pharmacies in Norway are publicly available through the relevant authorities' websites.

Results: INCB opioid statistics during the period 2001–2013 were markedly inconsistent with sales data from

Scandinavia, calling the reliability of INCB data into question. INCB-data were flawed by (a) over-representing the volume of fentanyl, (b) under-reporting of codeine, and (c) by not including tramadol.

Conclusions: Opioid availability, as expressed by INCB statistics, does not reflect medical opioid use. It is crucial to underline that INCB statistics are based on the manual compilation of national production, import and export data from manufacturers and drug companies. This is not the same amount that is prescribed and consumed within the health care system. Moreover, there are methodological problems in the INCB reports, in particular concerning fentanyl, codeine and tramadol. We suggest that INCB should carefully review the quality of their data on medical opioids.

Keywords: analgesics; chronic pain; opioids; pharmacoepidemiology; prescription drugs.

Introduction

In the USA, the last decades' opioid epidemic has been paralleled by a dramatic increase in opioid-related mortality [1, 2]. The problem of opioid dependence and addiction is, however, by no means new. The disastrous consequences of the widespread use of morphine had become clear in the West at the end of the 19th century, ultimately leading to strict legal regulations and to a situation of restrictive use and “opiophobia” [3]. A landmark in the gradual turn from opiophobia to the more liberal view prevalent in the West today was the publication of the World Health Organization (WHO) analgesic ladder for cancer pain in 1986 [4]. In many parts of the world, however, there is still a worrying lack of opioid availability for the treatment of cancer-related and end-of-life pain [5].

The Anatomical Therapeutic Chemical (ATC) classification system for drugs, and Defined Daily Dose (DDD) as a measuring unit, are curated by the WHO Collaborating

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Centre for Drug Statistics Methodology in Oslo, Norway, and are the gold standard for international drug utilisation monitoring and research [6]. ATC and DDD are further described in *Methods*. Since the DDDs of different opioids are not based on equipotency, one DDD for a particular opioid can have a dramatically different effect compared to one DDD for another opioid. Ideally, dosages should be recalculated from DDD to oral morphine equivalents (OMEQ) [7]. Equianalgesic conversion tables for OMEQs are not standardised and thus open to discussion [8]. Moreover, opioids differ in their pharmacokinetic profiles, a short “time to peak” being associated with higher addictive potential.

The global imbalance in opioid availability is reflected in the statistics published by the INCB, statistics that formed the backbone of an editorially commented *Lancet* paper by Berterame et al. in 2016 [9, 10]. A reported increase in opioid use of 150% in Sweden during the decade between 2001–2003 and 2011–2013 (henceforward referred to as 2001–2013) sparked interest among Swedish decision-makers and healthcare professionals, as this would indicate an on-going “opioid epidemic”. However, the reported increase is not congruent with national sales data on opioids dispensed at pharmacies in Sweden, according to which the yearly prevalence of opioid users is stable, and the use of prescribed opioids expressed in OMEQ/1,000 inhabitants and day or in DDD/1,000 inhabitants is stable or decreasing, respectively [11]. These findings have been confirmed in a recent report from the Swedish Medical Products Agency [12], and in a recent peer-reviewed paper analysing data from three Nordic countries [13].

Methodologically, it is important to be aware that different studies include different opioids, study different age intervals, differ in their data gathering methodology, and that different statistical measures can be used (cf., DDD vs. OMEQ). INCB statistics can have a considerable influence over governments and policymakers worldwide, and because of this, the data reported by INCB must be reliable and correctly interpreted. The present study aimed to compare published INCB statistics (mainly as reported by Berterame et al. [10]) on what these authors define as the use of opioids in three Scandinavian countries with national total sales statistics on the medical use of opioids in these countries, and to discuss methodological reasons for discrepancies.

Methods

For this study’s purpose, opioids were defined according to the ATC-code system (version 2019 [6]) as all substances within N02AA

opioid + R05AD03 hydrocodone + R05AD04 codeine. Following Berterame et al. [10], drugs classified as *N07BC Drugs used in opioid dependence* (specific formulations of buprenorphine isolated or in fixed combinations, and methadone) were not included, except when necessary for comparison with INCB special reports data (see below).

INCB methodology

The 12 opioids studied in the INCB-based paper of Berterame et al. [10] (codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, ketobemidone, morphine, oxycodone, pethidine, tilidine, and tramperidine), either as isolated substances or as fixed combinations, were coded according to the ATC-code system (except for tramperidine that lacks a defined ATC-code and does not have marketing approval in the countries in this study) and are referred to in this article as **INCB-opioids**. Berterame et al. studied the above-mentioned opioids, but only reported the *total* of opioid DDD, i.e. they did not report the particular DDD values of each opioid.

Importantly, opioids tabulated in yearly so-called technical reports from INCB are not exactly the same as the ones reported by Berterame et al. [10, 14, 15]. For instance, the technical reports include methadone [14, 15], and some also buprenorphine [15]. In contrast, Berterame et al. exclude methadone and buprenorphine “because their use for pain relief cannot be distinguished from their predominant use in the treatment of dependence” [10]. The special reports intermittently published by INCB also differ somewhat in their choice of reported opioids [16]. In addition to INCB data published by Berterame et al., we also retrieved data from two INCB technical reports and two special reports [14–17].

INCB uses a non-standardised measurement unit of “*Defined Daily Doses for statistical purposes*”, S-DDD. According to Berterame et al., “*levels of use, expressed in S-DDD per million inhabitants per day, are calculated with the following formula: annual use divided by 365 days, divided by the population in millions of the country or territory during the year, divided by the DDD*” [10]. What the authors call “*annual use*” will be extensively discussed and problematised later in the present paper.

ATC and DDD

In the ATC-classification, a specific substance can have several ATC-codes for different formulations with different therapeutic use. Morphine, for instance, is classified in group A07D Antipropulsives as fixed combinations as A07DA52; in group N02AA Natural opium alkaloids as only morphine N02AA01 in oral, parenteral and rectal formulations and as fixed substances N02AA51; and in N02AG Opioids in combination with antispasmodics as N02AG01 in fixed combinations of morphine and antispasmodics [6].

DDD is an administrative measure and denotes the assumed average maintenance dose per day for a drug used for its main indication in adults. The advantage of DDD is that, with only one DDD assigned per ATC code and route of administration (e.g. oral formulation), it provides a fixed unit of measurement independent of price, currencies, package size and strength, thus enabling researchers to assess trends in drug consumption and perform comparisons between population groups [6].

Different DDDs can be defined when the bioavailability is substantially different for various administration routes (e.g. oral and

parenteral administration of morphine) or if the dosage forms are used for different indications. When parenteral formulations represent only a minor fraction of the total use for a specific indication, these products have normally not received a separate DDD. The DDD for combination products can be established based on different principles, for instance, based on the substance deemed the main active ingredient. Another way is to base the DDD on the average number of dosing intervals per day, i.e. two tablets is the DDD for combinations given twice daily, and three tablets is the DDD for combinations given three times daily and so forth. In this case, the assigned DDDs may differ from the DDD assigned for the main active ingredient. Also, it is possible to have local adaptations of DDD [6].

Importantly, DDD does not necessarily reflect neither recommended nor equipotent doses. If a change in use over time encompasses switches between substances where assigned DDD do not reflect equipotent doses, then a methodological confound might be introduced. This issue is a significant problem in opioid statistics.

National drug sales statistics

Aggregated data on total statistics over the legal sale of medical opioids, including sale to hospitals, were collected from the Swedish e-Health Authority which maintains a database with aggregated sales data (i.e. dispensed at pharmacies + used in hospitals + over-the-counter (OTC)). The data are publicly available as aggregated statistics without the need for approval by an ethical review board. In the present study, opioid national data were retrieved for the total population in Sweden. Total sales data for Denmark and drugs dispensed at pharmacies in Norway are publicly available through the relevant authorities' web-sites [18, 19]. Total sales data for Norway are available and can be applied for, however in this study we chose to use only the publicly available data from the Norwegian Prescription Database (prescription opioids constituting the vast majority of sales statistics).

For fixed combinations of drugs, the DDD assigned to the fixed combination can be either one DDD/unit or a DDD that represents one of the substances. In the Scandinavian countries, the DDD for fixed combinations with opioids reflects the amount of the opioid. A common fixed combination in Scandinavia is 30 mg of codeine combined with paracetamol or acetylsalicylic acid. In the national drug consumption statistics in Sweden, Denmark and Norway, such a fixed combination is registered with a DDD of 0.3, reflecting that 100 mg of codeine is defined as one DDD.

Of the 28 member states of EU, 13 permitted the sale of codeine OTC in 2014 [20]. No opioids were available OTC in Sweden and Norway during the study period. In Denmark, where codeine combinations with 10 mg codeine per tablet are sold OTC, a nationally specified DDD for codeine in these tablets is 60 mg based on a usual daily dose of 6 tablets. Depending on whether a codeine combination tablet is sold as a prescribed drug or OTC, different DDD definitions will thus be used in the national statistics. The fraction of the total sale of fixed combinations of codeine as OTC was, however, less than 10% during the studied period. Because of this, no correction was applied to the data.

Time periods and chronology

Berterame et al. studied the total availability of opioids in the period 2001–2003 compared with 2011–2013 [10], and we have therefore

compiled Scandinavian sales data accordingly. To enable a more in-depth study per substance of INCB data, an INCB special report covering 2007–2009 (i.e. in the middle of the above-mentioned period) was compared to sales data; see Annex 1, pp 63–63, in the INCB special report for details [16]. Also, in order to enable a better appreciation of long-term trends, we retrieved Scandinavian sales data for a broader time frame (2001–2016).

Results

According to INCB statistics published by Berterame et al. [10], the use of INCB-opioids (whether expressed as S-DDD per 1,000 inhabitants and day or as the total amount in DDD) increased substantially in Scandinavia between 2001 and 2013: in Denmark, the total sales volume of INCB-opioids increased with 112%, in Norway with 140%, and in Sweden with 150% (Table 1). A special report of INCB covering the same period also reported substantial increases in the Scandinavian countries [17]. However, according to national sales statistics of medical opioids, the total sales volume in DDD/1,000 inhabitants and day *decreased* by 25% in Denmark and by 28% in Sweden during the same time interval (Table 1). There was a substantial difference between volumes expressed as S-DDD (INCB statistics) and as DDD (national drug consumption statistics), the former being lower in all three countries during both periods (Table 1). Moreover, focusing on national drug consumption statistics, there was a discrepancy between the volumes of INCB-opioids and the volumes of all opioids (Table 1).

Detailed national opioid consumption statistics in Scandinavia 2001–2016 are tabulated in Table 2; notably, the discrepancy mentioned above between volumes of INCB-opioids and all opioids is mainly because that tramadol is not included in the INCB-opioids. Notable trends over time were less use of codeine and dextro-propoxyphene, and an increase in use of fentanyl, oxycodone, and tramadol in all three countries (except for tramadol in Sweden) (Table 2).

DDD is not always defined for all different formulations; this is for instance true for opioid anaesthetics (N01AH) and especially relevant for parenteral formulations alone or in combinations with fentanyl (N01AH01 & N01AH51). Also, some other formulations such as morphine in combination with spasmolytics (N02AG01) have no officially assigned DDD. The total sale volumes of fentanyl, morphine, oxycodone and hydromorphone with no DDD assigned in Sweden in 2008 was 22.8 million SEK, representing 4% of the total sales of all opioids.

The amount of N02AB03 fentanyl as transdermal, buccal and oral formulations measured in DDD increased in

Table 1: Volume of opioids (S-DDD/1,000 inhabitants and day, recalculated from original reporting as S-DDD/1,000,000 inhabitants and day) average over three years in the Scandinavian countries according to INCB statistics (reported volume in DDD of production + import – export) compared with national drug consumption statistics (DDD/1,000 inhabitants and day). Total sales for Denmark and Sweden, for Norway only drugs dispensed at pharmacies. As the Norwegian Prescription Database was established in 2004, sales statistics for 2001–2003 are missing for Norway.

	Opioids	Data source	2001–2003	2011–2013	% Change
Denmark	INCB-opioids*	INCB statistics***	7.09	15.06	+112%
	INCB-opioids*	National drug sales statistics	23.47	17.67	–25%
	All opioids**	National drug sales statistics	30.07	28.17	–6%
Norway	INCB-opioids*	INCB statistics***	3.61	8.67	+140%
	INCB-opioids*	National drug sales statistics		13.39	
	All opioids**	National drug sales statistics		16.73	
Sweden	INCB-opioids*	INCB statistics***	3.34	8.34	+150%
	INCB-opioids*	National drug sales statistics	17.53	12.60	–28%
	All opioids**	National drug sales statistics	22.99	18.89	–18%

*Opioids reported by Berterame et al. [10]: codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, ketobemidone, morphine, oxycodone, pethidine, tilidine, and trimeperidine. See text. **All opioids according to the authors: N02A opioids + R05AD03 hydrocodone + R05AD04 codeine. N07BC drugs used in opioid dependence are not included. ***As published by Berterame et al. (10), see text.

Sweden with 102 % from 2001–2003 to 2015–2016 (Table 2) while the use of N01AH01 + N02AH51 fentanyl as a parenteral opioid anaesthetic decreased between 2005 and 2015 (–16% in the number of orders, –32% in delivered units).

Finally, a detailed comparison between INCB statistics retrieved from an INCB “special report” [16] and national consumption data was made for different opioids during 2007–2009, i.e., in the middle of the period studied by Berterame et al. The results are depicted in Figure 1, with details available in Web Extra Material 1. Notably, INCB statistics did *not* cover tramadol, and reported no availability of codeine in Denmark and Sweden and a low availability in Norway. This is in conflict with national sales statistics where tramadol and codeine were the most commonly used opioids in Denmark, Norway and Sweden, constituting respectively 36–65% and 13–34% of the total volume of all opioids measured in DDD according to national sales statistics (percentages computed from data in Web Extra Material 1). Also, fentanyl constituted 68–70% of INCB-opioids according to INCB measured in S-DDD, while constituting only 3–6% of all opioids measured in DDD according to national sales statistics. The absolute volumes of fentanyl were 4.4–7.9 larger in the INCB report than in the national drug consumption statistics.

Discussion

We have shown that the use of opioids reported from INCB for the Scandinavian countries is not congruent with legal sales of opioids in these countries’ healthcare system. According to INCB the use of opioids in the three

Scandinavian countries increased substantially between 2001 and 2013. However, when studying legal sales within the healthcare, the volume of opioids decreased during that period in both Denmark and Sweden expressed as DDD/1,000 inhabitants and day (no data publicly available for Norway in 2001–2003). These sales data are well in line with what has been reported in previous studies, for Sweden [11, 12] but also for the Scandinavian countries in general [13]. A few things are worth pointing out concerning the marked discrepancies between INCB data and actual sales data from Scandinavia.

Consumption or availability

First, Berterame et al. claim they are studying opioid “use”, while INCB reports alternate between the terms “availability” (in the text) and “consumption” (in the figures) [15, 16]. The methodology used by INCB is challenging to follow. Our interpretation is that the annual use reported by INCB is equivalent to the administrative difference between the reported sum of *national production + import* and the *national export* of the 12 opioids as mentioned above. According to Berterame et al., the INCB methodology seems to consist of two stages. In stage 1, countries provided data on “the amounts that each country’s competent national authority estimates are needed and used annually, including reporting of medicines destroyed, losses during manufacture, and so on” [10].

According to INCB, Swedish data were provided by representatives from the Swedish Medical Products Agency (personal communication, Berterame). As stated in a

Table 2: Detailed national opioid consumption statistics in Scandinavia 2001–2016 in DDD/1,000 inhabitants and day. Including buprenorphine both as analgesic (N02AE01) and included in N07BC drugs used in treatment of opioid dependence (in order to be comparable to production data used by INCB), but excluding methadone (N07BC02). Total sales for Denmark and Sweden, for Norway only drugs dispensed at pharmacies. As the Norwegian Prescription Database was established in 2004, sales statistics for 2001–2003 are missing for Norway.

	Denmark				Norway				Sweden			
	2001–2003	2007–2009	2011–2013	2015–2016	2001–2003	2007–2009	2011–2013	2015–2016	2001–2003	2007–2009	2011–2013	2015–2016
Codeine + combinations	16.07	12.90	10.23	7.10		11.60	10.15	8.88	9.53	7.82	8.15	7.04
	N02AA59 + N02AA79 + N02AJ06 + N02AJ07 + N02AJ08 + N02AJ09 + R05DA04											
Morphine + combinations	2.50	1.97	3.00	3.05		0.96	0.78	0.72	1.06	0.90	1.09	0.93
	A07DA52 + N02AA01 + N02AA51 + N02AG01 + R05DA05											
Ketobemidon	1.87	1.00	0.60	0.30		0.14	0.14	0.12	0.54	0.20	0.16	0.08
Fentanyl	1.17	1.77	1.70	1.75		0.67	0.79	0.88	0.58	1.09	1.20	1.17
	N02AB03 + N01AH01 ^{††} + N01AH51 ^{††}											
Dextro-propoxyphene + combinations	0.83	0.33	0.03	0.00		0.70	0	0	5.51	2.30	0.06	0
	N02AC04 + N02AC54											
Oxycodone + combinations	0.73	2.53	1.97	2.15		1.05	1.47	1.93	0.26	1.15	1.53	2.30
	N02AA05 + N02AA55											
Pethidine	0.10	0.10	0.07	0		0.03	0.03	0.03	0	0	0	0
	N02AB02											
Hydromorphone + combinations	0	0.10	0.07	0.05		0.01	0.05	0.13	0.05	0.45	0.42	0.39
	N02AA03 + N02AG04 + N02AA53											
Tramadol + combinations	6.00	8.40	9.70	10.40		2.40	3.31	4.02	5.38	6.39	5.71	3.93
	N02AX02 + N02AJ13 + N02AJ14 + N02AJ15											
Other opioids incl. buprenorphine	0.70	1.13	1.30	1.10		1.22	1.68	1.96	0.20	0.62	1.11	1.41
	N02AA02 + N02AJ13 + N02AJ14 + N02AJ15											
Total INCB-opioids*	23.47	20.80	17.67	14.40		15.15	13.42	12.70	17.53	13.91	12.60	11.92
Total opioids	30.17	30.33	28.67	25.90		18.77	18.41	18.68	23.11	20.92	19.43	17.27

*Codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, ketobemidon, morphine, oxycodone, pethidine, tilidine, and trimeperidine. ^{††}Fentanyl as an anaesthetic for parenteral administration (N02AH01 as a single substance, and N02AH51 combined with bupivacaine) has no assigned DDD.

technical report, “the analysis ... is based on statistical data furnished by Government”, and “the quality of the analysis depends on the data provided” [15]. Then, in stage 2, “this information was verified by the INCB using data from export and import notifications” [10]. Hence, the verification principle used by INCB seems to focus on the difference between export and import. However, if this is the case, Berterame et al.’s claim that their study provides “an assessment of changes to opioid analgesic use worldwide” (emphasis added) [10] is debatable at best. Availability expressed as the difference between the sum of gross production and the import vs. the export, is not the same as actual legal use in healthcare.

INCB data are, at least for Sweden (personal communication with Swedish Medical Products Agency) based on manually compiled data from pharmaceutical companies on the national level. This way of collecting data is necessary for many countries without validated national drug consumption statistics globally. However, it introduces many possible errors and inaccuracies. A better term would be “reported availability”. It should neither be confused with the legal drug consumption in healthcare nor with the illegal use in the society (also comprising illegal production and smuggling and Internet sale of opioids). As a contrast, the publicly available Scandinavian national drug consumption statistics that we present reflect the volume of opioids prescribed/dispensed within the healthcare.

Tramadol

Secondly, neither Berterame et al. nor the two INCB special reports reported data on tramadol. Tramadol is an opioid used to treat moderate to severe pain, and there is a genuine and increasing problem with addiction and illegal abuse. During the studied period, it increased to almost a third of the total use of legally prescribed opioids in Denmark and Sweden, and one-fifth of the opioids dispensed at pharmacies in Norway. Tramadol was classified as a restricted narcotic drug in Sweden in March 2007 after reports of drug dependence [21]. In Denmark, this restriction was imposed in 2017 [22]. By not including tramadol, a methodological flaw is introduced that makes it impossible to compare countries with different use of tramadol and distort the national trends in opioid use.

Codeine

Thirdly, according to INCB, codeine is almost not available for consumption in the Scandinavian countries.

Nevertheless, according to public drug statistics, it is the dominant opioid in these countries (whether studied as a fraction of INCB-opioids or all opioids). The majority of codeine prescribed in healthcare in Scandinavia is in fixed combinations with paracetamol (N02AJ06) or with acetylsalicylic acid (N02AJ07). During the studied period, codeine constituted more than half of the DDD for INCB-opioids in all Scandinavian countries, and more than one-third of all opioids, but in the INCB-reports the amount of codeine is almost zero.

In Denmark, codeine (R05DA04) as a single substance constitutes more than one-fourth of the total amount of codeine prescribed, while it is a negligible part of the codeine prescribed in Norway and Sweden. In 2014, codeine was also available over the counter in 14 of the 28 countries in the European Union [20]. In Denmark, but not in the rest of Scandinavia, codeine is available over the counter (OTC) in a fixed combination of 10 mg codeine together with either acetylsalicylic acid or propyphenazone [23].

For the rest of Europe, the availability of codeine 2007–2009 according to the INCB special report [16] varies from 0 to 4,818, expressed in S-DDD. Most countries however are below 100, while Iceland is an extreme outlier in the world reporting 4,818, which is more than 6 times as much as Canada with 783 (USA reports less than 1).

Fentanyl

Fourthly, the highly lipophilic and potent opioid fentanyl is the dominant opioid in the Scandinavian countries according to INCB, constituting approximately two-thirds of the amount in DDD/1,000 inhabitants of the opioids studied by INCB in 2007–2009. In national drug consumption statistics for the same period, fentanyl measured in DDD made up only 4–9% of the 12 opioids studied by INCB and 4–6% of all opioids. Fentanyl as a parenteral opioid anaesthetic (N01AH01 + N01AH51) lacks an assigned DDD in national consumption statistic, but the use measured in delivered orders and units have decreased over time, not increased.

Prescribed fentanyl is mainly used in patches. A transdermal patch can be assigned one DDD per unit or a DDD that reflects the substance’s bioavailability. In national drug consumption statistics, the amount of DDD per patch is based on the bioavailability or amount absorbed into the body over the number of days the patch is used. Since only 34–63% of the fentanyl in the patches will diffuse into the body (see Web Extra Material 2), the DDD in national drug consumption statistics will be lower than the total amount fentanyl in the patch. However, this

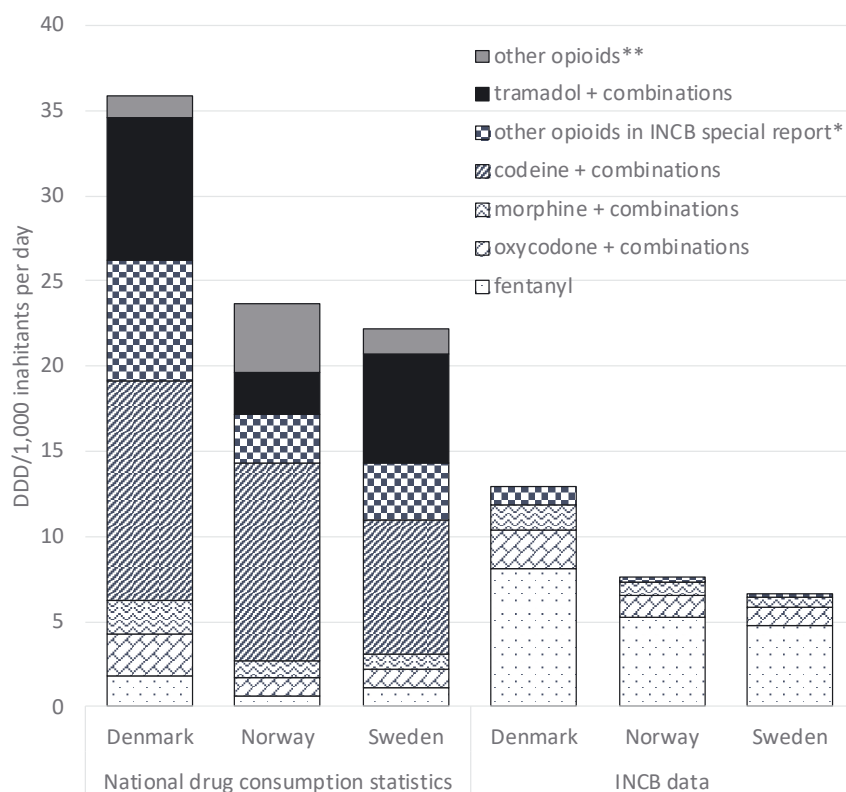


Figure 1: National drug consumption statistics for all opioids in Scandinavia, the average for 2007–2009 (total sales for Denmark and Sweden, for Norway only drugs dispensed at pharmacies) compared with availability reported by INCB in a special report including N07BC02 methadone [16]. Opioids covered by the INCB special report bar with pattern. Opioids not covered in the report (including tramadol) filled bars. National consumption statistics in DDD/1,000 inhabitants and day. INCB data in S-DDD/1,000 inhabitants and day recalculated from original reporting as S-DDD/1,000,000 inhabitants and day.

*pethidine, hydromorphone + combinations, hydrocodone, dextropropoxyphene + combinations, dihydrocodeine, ketobemidone, methadone, tilidine. **all other opioids, including buprenorphine, in national drug consumption statistics not included as opioids in the INCB special report. Tramadol and combinations, also not included as opioids in the INCB special report, reported separately as not INCB.

discrepancy between available and absorbed fentanyl cannot explain the 4–8-fold higher volume of fentanyl in the INCB-data.

Recent data published by INCB point to a dramatic increase of fentanyl availability worldwide from 1997 to 2016, the availability of fentanyl (expressed as S-DDD) in 2016 being more than five times higher than for *any* other opioid [24]. All in all, this strikes us as *prima facie* incorrect, and we suggest that INCB carefully review the quality of their data in general and of fentanyl in particular.

Drugs used in opioid dependence

Fifth, methadone and buprenorphine are two opioids commonly used in treatment of opioid dependence. Preparations intended for this purpose are classified in the ATC-system in N07BC Drugs used in opioid dependence,

more specifically N07BC01 and N07BC51 for buprenorphine and N07BC02 for methadone. For buprenorphine, preparations intended for treatment of pain are classified as N02AE01. In national drug consumption statistics, it is thus possible to separate buprenorphine prescribed for different indications. This is of course not possible when using the INCB-method gathering data over production, import and export of substances.

While the article by Berterame et al. does not include methadone or buprenorphine (neither for pain relief nor for treatment of opioid dependence), the INCB special report covering 2007–2009 does include methadone, but not buprenorphine.

DDD vs. oral morphine equivalents

Sixth, although reporting OMEQ is more appropriate than DDD for opioids, calculating DDD irrespective of

equianalgesic effects is acceptable for the purposes of the present paper. For Sweden, we have elsewhere shown that the decrease in total DDD over time shown in Table 2 corresponds to an initial rise in OMEQ with 22% from 2000 to 2006, followed by a slight rise of 3% from 2007 to 2015 [11]. Hence, given the high equianalgesic ratio of fentanyl, and the relatively low equianalgesic ratio of tramadol and codeine, fentanyl would be expected to figure more prominently if Figure 1 was in OMEQ, whereas tramadol and codeine would be expected to be less prominent.

Accessibility to opioids in healthcare

The above-mentioned discrepancies pertain to the situation in Scandinavia. From a global point of view, a few things are worth underlining. It is important to remember that access to medical opioids is scarce in many countries because of strict regulations [5], even for palliative care patients. This is highly problematic, and we do of course agree with Berterame et al. when they write that impediments to use “urgently need to be addressed by governments and international agencies” [10] concerning certain regions such as for instance Africa and Asia. This kind of advocacy is an important endeavour. However, it is essential that such advocacy is based on solid facts. Sadly, the discrepancies we have described call the overall reliability of INCB data into question, also globally. Once again, we do not doubt that there is a dramatic underuse of medical opioids in many parts of the world, e.g. concerning end-of-life pain [25]. But this fact does not in itself automatically validate the methodology used by INCB.

Methodological limitations

As stated in the Methods section, for Norwegian data we chose to use the Norwegian Prescription Database. Although prescription data cover the main volume of sales statistics of opioids, this is nonetheless a limitation.

However, this has hardly influenced the main findings of this paper. Moreover, this also led to missing data for Norway before 2004, which is the year when the Norwegian Prescription Database was established.

Conclusion

The present study highlights two crucial facts that must be borne in mind when interpreting INCB data:

- (1) Opioid availability (as expressed by INCB statistics) is not the same as legal opioid use in the health care system. It is crucial to underline that INCB statistics are based on the manual compilation of the national production levels and import and export data from manufacturers and drug companies. This net volume is not the same amount that is prescribed and consumed within the health care system.
- (2) There are methodological problems in the INCB reports, in particular concerning fentanyl, codeine and tramadol, INCB-data being flawed by (a) grossly over-representing the volume of fentanyl, (b) a significant under-reporting of codeine in at least Denmark, Norway and Sweden, and (c) by not including tramadol in the reports. For the Scandinavian countries, the reported amount will be too low, and the trend of opioid “use” will be more or less a reflection of an unreliable trend in fentanyl “use” and not a true representation of changes in consumption of opioids.

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Web Extra Material 1

National drug consumption statistics for all opioids in Scandinavia, the average for 2007–2009 (total sales for Denmark and Sweden, for Norway only drugs dispensed at pharmacies) compared with opioids reported by INCB in a special report including N07BC02 methadone [16]. National consumption statistics in DDD/1,000 inhabitants and day. INCB data in S-DDD/1,000 inhabitants and day recalculated from original reporting as S-DDD/1,000,000 inhabitants and day.

		Denmark		Norway		Sweden	
		National drug consumption statistics	INCB data	National drug consumption statistics	INCB data	National drug consumption statistics	INCB data
Opioids included in the INCB special report							
Fentanyl	N02AB03 + N01AH01 + N01AH51	1.77	8.08	0.67	5.28	1.09	4.76
Oxycodone + combinations	N02AA05 + N02AA55 + N02AA56 [†] + N02AJ17 [†] + N02AJ18 [†] + N02AJ19 [†]	2.53	2.30	1.05	1.23	1.15	1.07
Morphine + combinations	A07DA52 [†] + N02AA01 + N02AA51 + N02AG01 + R05DA05 [†]	1.97	1.52	0.96	0.81	0.90	0.58
Pethidine	N02AB02 + N02AG03* + N02AB52 [†] + N02AB72 [†]	0.10	0.08	0.03	0.03	0	0
Hydromorphone + combinations	N02AA03 + N02AG04 + N02AA53 [†]	0.10	0.07	0.01	0.01	0.45	0.20
Hydrocodone	R05DA03	0	0	0.01	0.01	0	0
Codeine + combinations	N02AA59 + N02AA79 [†] + N02AJ06 + N02AJ07 [†] + N02AJ08 + N02AJ09 + R05DA04	12.90	0	11.60	0.02	7.82	0
Other opioids in INCB special report*		7.03	0.99	2.91	0.24	3.34	0.19
Total INCB special report opioids		26.40	13.04	17.24	7.63	14.75	6.82
Opioids not included in the INCB special report							
Tramadol + combinations	N02AX02 + N02AJ13 + N02AJ14 [†] + N02AJ15 [†]	8.40	n.a.	2.40	n.a.	6.39	n.a.
Other opioids**		1.23	n.a.	4.12	n.a.	1.46	n.a.
Total opioids not included in the INCB special report		9.63	n.a.	6.52	n.a.	7.85	n.a.

*dextropropoxyphene + combinations, dihydrocodeine, ketobemidone, methadone, tilidine. **All other opioids, including buprenorphine, in national drug consumption statistics not included as opioids in the INCB special report. [†] No sales during the study period in Denmark, Norway and Sweden.

Web Extra Material 2

Percentage of fentanyl remaining in a 12 µg/h patch after 3 days. Available fentanyl patches on the Swedish market, as of April 25, 2018.

	Total amount of fentanyl contained in the patch when first applied, µg	Total dose delivered to the patient during 3 days, µg	Amount of fentanyl remaining in patch after 3 days, µg	Percentage of fentanyl remaining in the patch after 3 days, %
Durogesic® (Janssen)	2,100	864	1,236	59%
Fentanyl actavis® (Teva)	2,550	864	1,686	66%
Fentanyl lavipharma® (Bluefish pharma)	1,375	864	511	37%
Fentanyl mylan® (Mylan)	2,100	864	1,236	59%
Fentanyl orion® (Orion pharma)	2,550	864	1,686	66%
Fentanyl ratiopharm® (Teva)	2,063	864	1,199	58%
Fentanyl sandoz® (Sandoz AS)	2,100	864	1,236	59%
Matrifen® (Takeda pharma)	1,380	864	516	37%

The following URLs were accessed April 25, 2018. These are the Swedish Summary of Products Characteristics (SPCs) from the Medicinal Products Agency for these products.

Durogesic® (Janssen)	http://fass.se/LIF/product?userType=0&nplld=20040916000958&docType=6&focus=tab_produktnesume&autoScroll=true&scrollTop=300
Fentanyl actavis® (Teva)	http://fass.se/LIF/product?userType=0&nplld=20140801000138&docType=6&focus=tab_produktnesume&autoScroll=true&scrollTop=392
Fentanyl lavipharm® (Bluefish pharma)	http://fass.se/LIF/product?userType=0&nplld=20121113000047&docType=6&focus=tab_produktnesume&autoScroll=true&scrollTop=689.5999755859375
Fentanyl mylan® (Mylan)	http://fass.se/LIF/product?userType=0&nplld=20110302000111&docType=6&focus=tab_produktnesume&autoScroll=true&scrollTop=689.5999755859375
Fentanyl orion® (Orion pharma)	http://fass.se/LIF/product?userType=0&nplld=20080809000016&docType=6&focus=tab_produktnesume&autoScroll=true&scrollTop=796.7999877929688
Fentanyl rationpharm® (Teva)	http://fass.se/LIF/product?userType=0&nplld=20061129000108&docType=6&focus=tab_produktnesume&autoScroll=true&scrollTop=689.5999755859375
Fentanyl sandoz® (Sandoz AS)	http://fass.se/LIF/product?userType=0&nplld=20070609000057&docType=6&focus=tab_produktnesume&autoScroll=true&scrollTop=689.5999755859375
Matrifen® (Takeda pharma)	http://fass.se/LIF/product?userType=0&nplld=20050719000017&docType=6&focus=tab_produktnesume&autoScroll=true&scrollTop=689.5999755859375

Note: The above is based on the SPC of the official Swedish formulary FASS.

References

- Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers—United States, 1999–2008. *MMWR Morb Mortal Wkly Rep* 2011;60:1487–92.
- Centers for Disease Control and prevention (CDC). CDC grand rounds: prescription drug overdoses - a U.S. epidemic. *MMWR Morb Mortal Wkly Rep* 2012;61:10–3.
- Rhodin A. The rise of opiophobia: is history a barrier to prescribing? *J Pain Palliat Care Pharmacother* 2006;20:31–2.
- WHO. Cancer Pain Relief: with a guide to opioid availability, 2nd ed. Geneva: World Health Organization; 1996.
- Kunnumpurath S, Julien N, Kodumudi G, Kunnumpurath A, Kodumudi V, Vadivelu N. Global supply and demand of opioids for pain management. *Curr Pain Headache Rep* 2018;22:34.
- WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index; 2021. Available at: https://www.whocc.no/atc_ddd_index/.
- Svendsen K, Borchgrevink P, Fredheim O, Hamunen K, Mellbye A, Dale O. Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. *Palliat Med* 2011;25:725–32.
- Shaheen PE, Walsh D, Lasheen W, Davis MP, Lagman RL. Opioid equianalgesic tables: are they all equally dangerous? *J Pain Symptom Manag* 2009;38:409–17.
- Cleary JF, Husain A, Maurer M. Increasing worldwide access to medical opioids. *Lancet* 2016;387:1597–9.
- Berterame S, Erthal J, Thomas J, Fellner S, Vosse B, Clare P, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *Lancet* 2016;387:1644–56.
- Bäckryd E, Heilig M, Hoffmann M. Dynamiken i förskrivningen av opioider i Sverige 2000–2015 – markanta omfördelningar inom opioidgruppen, men ingen “epidemi”. *Lakartidningen* 2017;114:EFUE.
- Läkemedelsverket. Förskrivning av opioider i Sverige: Läkemedel, doser och diagnoser; 2020. Available at: <https://www.lakemedelsverket.se/49e69f/globalassets/dokument/publikationer/lakemedelsprodukter-och-narkotika/forskrivning-av-opioider-i-sverige-2020-1.pdf> [Accessed 16 April 2021].
- Muller AE, Clausen T, Sjogren P, Odsbu I, Skurtveit S. Prescribed opioid analgesic use developments in three Nordic countries, 2006–2017. *Scand J Pain* 2019;19:345–53.
- International Narcotics Control Board (INCB). Estimated world requirements for 2005. Statistics for 2003. New York: United Nations; 2005.
- International Narcotics Control Board (INCB). Estimated world requirements for 2015. Statistics for 2013. New York: United Nations; 2015.
- International Narcotics Control Board (INCB). Report of the International Narcotics Control Board on the availability of Internationally Controlled Drugs: ensuring adequate access for medical and scientific purposes. New York: United Nations; 2011.
- International Narcotics Control Board (INCB). Report of the International Narcotics Control Board on the availability of Internationally Controlled Drugs: ensuring adequate access for medical and scientific purposes. New York: United Nations; 2016.
- Sundhedsdatastyrelsen/National Health Data Authority; 2021. Available at: www.medstat.dk.
- Nasjonalt folkehelseinstitutt/Norwegian Institute of Public Health; 2021. Available at: www.norpd.no.
- Foley M, Harris R, Rich E, Rapca A, Bergin M, Norman I, et al. The availability of over-the-counter codeine medicines across the European Union. *Public Health* 2015;129:1465–70.
- Läkemedelsverket. Substansen tramadol nu narkotikaklassad på samma sätt som kodein och dextropropoxifen; 14 maj 2008. Available from: <https://lakemedelsverket.se/Alla-nyheter/NYHETER-2008/Substansen-tramadol-nu-narkotikaklassad-pa-samma-satt-som-kodein-och-dextropropoxifen/> [Accessed 2 September 2016].
- Nissen SK, Pottegard A, Ryg J. Trends of opioid utilisation in Denmark: a nationwide study. *Drugs Real World Outcomes* 2019; 6:155–64.

23. Sundhedsdatastyrelsen/National Health Data Authority. Nationalt tildelte DDK-værdier; 2019. Available at: <https://sundhedsdatastyrelsen.dk/da/tal-og-analyser/analyser-og-rapporter/laegemidler/atc-og-ddd> [Accessed 25 June 2019].
24. International Narcotics Control Board (INCB). Progress in ensuring adequate access to internationally controlled substances for medical and scientific purposes. Vienna: United Nations; 2019.
25. Connor SR, Gwyther E. The worldwide hospice palliative care alliance. *J Pain Symptom Manag* 2018;55 (2 Suppl): S112–6.