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Review of Deaths Related to Analgesic- and Cough Suppressant-opioids; England and Wales 1996–2002

Objective: The data on England and Wales voluntarily supplied by Coroners to the National Programme on Substance Abuse Deaths for the August 1996-December 2002 time frame were analyzed. **Methods:** All cases in which at least one analgesic- and cough suppressant-opioid other than heroin/morphine, methadone or buprenorphine was identified were extracted from the database. We hypothesized that: a) populations of addicts and non-addicts presented differences in patterns of drugs involved; and b) within the population of addicts and non-addicts, intentional and non-intentional deaths presented different patterns of substance consumption. **Results:** A total of 2024 deaths related to selected opioids, either alone or in combination, were included in the analysis. Typically, non-addicts were older than 45 and died as a result of intentional poisoning whilst majority of addicts were young, males and victims of accidental deaths. In about 93 % of cases the selected opioids were reported in combination with another substance. Most frequently identified narcotics were propoxyphene, codeine and dihydrocodeine. Co-proxamol, Co-codamol and Co-dydramol were typically prescribed for non-addicts, whilst dihydrocodeine was mostly given to addicts. In non-addicts, alcohol was mostly represented in accidental deaths and antidepressants were typically represented in intentional deaths. Conversely, illicit drugs and hypnotics/sedatives were typically reported in addicts' accidental deaths. **Conclusions:** The present report constitutes the largest available collection of analgesic- and cough suppressant-opioid mortality data in the UK. Users should be educated about risks associated with polydrug misuse.

Introduction

The opioid preparation group is huge [15] and includes illicitly-used compounds (e.g. heroin) as well. Methadone and buprenorphine are widely used for the treatment of opioid dependence, while most of the remaining compounds, including dextropropoxyphene, dextromoramide, dihydrocodeine, dipipanone, fentanyl, meptazinol, tramadol, and oxycodone are usually

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None declared

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FS wrote the manuscript and coordinated the study. GZ and FZ collected the data. PD and DL carried out the statistical analysis. All Authors participated in interpreting the results. FS is guarantor. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication

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prescribed as narcotic analgesics. A few of them, e.g. codeine phosphate, may be acquired as over-the-counter analgesic medications, whilst others (e.g. dextromethorphan, pholcodine) are administered as cough-suppressants. Dextropropoxyphene, codeine and dihydrocodeine are available in the UK market in combination with paracetamol with the propriety names, Coproxamol, Co-codamol and Co-dydramol, respectively. Opioid abuse potential may be considerable; tolerance and dependence may develop quickly and cross-tolerance exists between virtually all the compounds of this class [15].

At present, there is only one special mortality register in the UK that publishes information on drug related deaths, the National Programme on Substance Abuse Deaths (np-SAD) at St George's, University of London. The np-SAD database was started in July 1997; information from this database is published in both 6–monthly and annual reports on cases notified voluntarily by Coroners in England and Wales. Coroners in Northern Ireland, the Isle of Man and the Channel Islands, as well as some Procurators Fiscal in Scotland, have recently started submitting information to the Programme [14].

Although the overdose effects of the compounds which are traditionally linked to the drug addiction scene, e.g. heroin [20] and methadone [6], have already been commented on, there is still a lack of information regarding the analgesic- and cough suppressant-opioids' mortality data. Furthermore, the role of intentionality in fatalities involving the prescription of opioid analgesics is a cause of concern. Schifano et al. [28] recently reported that buprenorphine, mostly prescribed as analgesic, was implicated in forty-three fatalities in the UK during the period 1980–2002. Twenty-eight percent of cases were suicides; most of them were over 45 and none was known as drug addict.

The aim of this research was to achieve a better understanding of the issue of deaths related to analgesic- and cough suppressant-opioids. We aimed at focussing on England and Wales np-SAD figures for the August 1996–December 2002 time frame. We hypothesized that: a) populations of addicts and non-addicts presented differences in patterns of drugs involved; and b) within the population of addicts and non-addicts, intentional and non-intentional deaths presented different patterns of substance consumption.

Methods

Deaths were included on the np-SAD database if, according to the formal Coroner's verdict, one or more psychoactive substances were directly implicated in death, if the patient had a history of dependence on or misuse of psychoactive drugs, or if controlled drugs were found during necropsy. Alcohol was included only when implicated in combination with other qualifying drugs. When Coroners' inquests were complete, cases were reported by demographic characteristics, time and place of death, whether they were prescribed medication(s), history of drug addiction, psychoactive substances found at post-mortem (including alcohol), causes of death and any other information that Coroners considered to be relevant. By December 31, 2003, the np-SAD database included a total of 8,209 drug-related deaths occurring in England and Wales in the time frame August 1996–December 2002. We extracted all cases in which at least one analgesic- and cough suppressant-opioid was identified by Coroners. Cases in which heroin/morphine, methadone or buprenorphine were identified were included only if these molecules were in association with a qualifying analgesic- and cough suppressant-opioid. There are difficulties in distinguishing heroin- from morphine-intoxication cases at post mortem [13]. For the purpose of this study, those victims in which either heroin, or morphine, or both were identified, were assembled together in the heroin/morphine category.

For further analysis, the cases involving analgesic- and cough suppressant-opioids were divided into two subgroups: addicts and non-addicts. A drug abuser/addict case was identified when one or more of the following criteria were met: a) reported as a known illicit drug user by the Coroner, based on evidence obtained at inquest; b) prescribed substitute medication for drug dependence; c) presence of an illicit drug at post mortem, where not prescribed, or d) presence of any additional information on the Coroner's report suggestive of a history of drug abuse and where such a history fulfilled ICD-10 [32] criteria.

Deaths were also classified as either intentional (e.g. suicide) or accidental in line with the Coroner's verdict. To test for possible differences between subgroups of intentional and accidental deaths, cases of fatalities where the cause of death was unascertained were excluded from the analysis.

Statistical Analysis

Analyses were performed using the Statistical Package for the Social Sciences, version 10 for Windows. Demographic details, risk factors and categorical data were expressed as percentages within groups, and compared with the Pearson chi-squared test (two-tailed) or Fischer's exact test if appropriate. The results for statistical tests were regarded as significant at or below the 5 % probability level.

Results

A total of 2024 deaths (24. 7 % of all fatalities) related to analgesic- and cough suppressant-opioids, either alone or in combination, were included in the analysis. Selected opioids were mentioned either in the toxicological post-mortem analysis (574, 28.4 %) or in the Coroner's verdict (415, 20.5 %) or in both (1035, 51.2 %). Number of deaths related to analgesic- and cough suppressant-opioids showed a peak in 2001, with 441 related fatalities recorded. Most of non-addicts were older than 45 and died as a result of an intentional poisoning whilst majority of addicts were young, males and victims of accidental deaths (Table **1**).

In about 93 % of cases the analgesic- and cough suppressant-opioids were reported in combination with another substance (either psychoactive or not), with polydrug ingestion being significantly more represented in addicts (Table **2**). Most frequently identified narcotic analgesic was dextropropoxyphene/propoxy-

Table **1** Deaths related to analgesic- cough suppressant-opioids, England and Wales, 1996–2002. Gender, age and cause of death; comparisons between non addict and addict subgroups

	Total Sample (N = 2024)	*Non-addicts (N = 1114)*	*Addicts (N = 910)*	*p Values*
Gender				
Male	1345 (66.5%)	601 (53.9%)	744 (81.8%)	$\chi^2 = 173.740$, df = 1, p < .001
Female	679 (33.5%)	513 (46.1%)	166 (18.2%)	
Age group				
< 24	264 (13%)	103 (9.2%)	161 (17.7%)	$\chi^2 = 357.081$, df = 5, p < .001
25–34	577 (28.5%)	199 (17.9%)	378 (41.5%)	
35–44	482 (23.8%)	244 (21.9%)	238 (26.2%)	
45–54	299 (14.8%)	205 (18.4%)	94 (10.3%)	
55–64	165 (8.2%)	140 (12.6%)	25 (2.7%)	
> 65	237 (11.7%)	223 (20.0%)	14 (1.5%)	
Cause of death				
accidental	1242 (61.4%)	486 (43.6%)	756 (83.1%)	$\chi^2 = 333.168$, df = 2, p < .001
suicide	633 (31.3%)	516 (46.3%)	117 (12.9%)	
unascertained	149 (7.4%)	112 (10.1%)	37 (4.1%)	

χ^2 = Pearson's chi square value; p = significance.

Table **2** Deaths related to analgesic- cough suppressant-opioids, England and Wales, 1996–2002. Selected opioids and psychoactive substances identified; comparisons between non addicts and addicts (please note that totals do not equal number of cases due to multiple drugs implicated in most cases)

	Total sample (N = 2024): number of deaths in which the index opioid was identified	*Non-addicts subgroup (N = 1114): number of deaths in which the index opioid was identified*	*Addicts subgroup (N = 910): number of deaths in which the index opioid was identified*	*p values (df = 1)*
Index analgesic- and cough suppressant-opioid in combination with another opioid and/or with another substance	1878 (92.8%)	988 (88.7%)	890 (97.8%)	$\chi^2 = 62.143$, p < .001
Analgesic- and cough suppressant-opioid alone Index analgesic- and cough suppressant-opioids	146 (7.2%)	126 (11.3%)	20 (2.2%)	
Dextro-propoxyphene containing compounds	891 (44.0%)	726 (65.2%)	165 (18.1%)	$\chi^2 = 449.718$, p < .001
Codeine containing compounds	563 (27.8%)	126 (11.3%)	437 (48.0%)	$\chi^2 = 336.186$, p < .001
Dihydrocodeine containing compounds	556 (27.5%)	246 (22.1%)	310 (34.1%)	$\chi^2 = 36.099$, p < .001
Tramadol	75 (3.7%)	47 (4.2%)	28 (3.1%)	$\chi^2 = 1.831$, p = .176
Others (each represented in less than 2% of total number of cases): dipipanone; pethidine; dextromoramide; meptazinol; pholcodine; noscapine; dextromethorphan; fentanyl; pentazocine; alfentanil; oxycodone	90 (4.4%)	39 (3.5%)	51 (5.6%)	$\chi^2 = 5.22$, p = .0224
Psychoactive substances associated Alcohol	721 (35.6%)	394 (35.4%)	327 (35.9%)	$\chi^2 = .070$, p = .791
Hypnotics/sedatives	598 (29.6%)	198 (17.8%)	400 (44.0%)	$\chi^2 = 164.942$, p < .001
Opiates (i.e.: morphine and/or heroin/morphine and/or methadone)	722 (35.7%)	47 (4.2%)	675 (74.2%)	$\chi^2 = 1068.190$, p < .001
Antidepressants	325 (16.1%)	203 (18 .2%)	122 (13.4%)	$\chi^2 = 8.619$, p = .003
Antipsychotics	42 (2.1%)	23 (2.1%)	19 (2.1%)	$\chi^2 = .001$, p = .971
Psychostimulants (i.e. ecstasy, cocaine, amphetamine)	163 (17.9%)	0	163 (17.9%)	$\chi^2 = 217.018$, p < .001
Cannabis	92 (4.5%)	0	92 (10.1%)	$\chi^2 = .117.987$, p < .001

χ^2 = Pearson's chi square value; p = significance.

phene, which was mostly identified in non-addicts. Conversely, codeine and dihydrocodeine were equally identified in both addicts and in non-addicts. Most frequent associated psychoactive substance in both groups was alcohol, identified in about 36% of cases. Antidepressants were mostly identified in non-addicts; less frequently reported narcotics (including dextromoramide and the cough-suppressants pholcodine, noscapine and dextromethorphan) were mostly identified in addicts, together with heroin/morphine; methadone; hypnotics/sedatives; stimulants and cannabis. In addicts, heroin/morphine was associated with codeine in 405 cases (93.0% of codeine-related deaths in addicts).

Analgesic- and cough suppressant-opioids were prescribed in 772 cases (38.1% of the total sample), with a prescription being given more frequently to non-addicts than to addicts (Table **3**).

Table **3** Deaths related to analgesic- cough suppressant-opioids, England and Wales, 1996-2002. Prescribed opioids identified and comparisons between non addicts and addicts (please note that the totals do not equal number of cases due to multiple drugs implicated in most cases)

	Total sample (N = 2024): number of deaths in which the identified opioid resulted to be prescribed	*Non-addicts subgroup (N = 1114) number of deaths in which the identified opioid resulted to be prescribed*	*Addicts subgroup (N = 910) number of deaths in which the identified opioid resulted to be prescribed*	*p values (df = 1)*
Prescribed analgesic- and cough suppressant-opioids	772 (38.1%)	542 (48.6%)	230 (25.3%)	$\chi^2 = 119.675$, $p < .001$
Co-proxamol	376 (50.9%)	322 (28.9%)	54 (5.9%)	$\chi^2 = 174.720$, $p < .001$
Co-codamol	52 (18.6%)	38 (3.4%)	14 (1.5%)	$\chi^2 = 7.025$, $p = .03$
Co-dydramol	19 (0.9%)	16 (1.4%)	3 (0.3%)	$\chi^2 = 6.595$, $p < .01$
Dihydrocodeine	238 (11.8%)	114 (10.2%)	124 (13.6%)	$\chi^2 = 5.557$, $p = .018$

χ^2 = Pearson's chi square value; p = significance.

Table **4** Deaths related to analgesic- cough suppressant-opioids, England and Wales, 1996-2002. Comparisons between accidental and intentional deaths in both non addicts and addicts in terms of psychoactive substances identified. (Please note that only statistically significant results are here provided)

	Non-addicts			*Addicts*		
	Non-addicts accidental deaths (N = 486)	*Non-addicts intentional deaths (N = 516)*	*p values (df = 1)*	*Addicts accidental deaths (N = 756)*	*Addicts intentional deaths (N = 117)*	*p values (df = 1)*
Selected analgesic- and cough suppressant-opioid in combination with another opioid and/or with another substance	307 (63.2%)	281 (54.5%)	$\chi^2 = 7.833$, $p = .005$	722 (95.5%)	99 (84.6%)	$\chi^2 = 21.439$, $p < .001$
Dextro-propoxyphene-containing compounds	304 (62.6%)	335 (68.8%)	$\chi^2 = 4.338$, $p = .037$	111 (14.7%)	42 (35.9%)	$\chi^2 = 31.549$, $p < .001$
Alcohol	195 (40.1%)	154 (29.8%)	$\chi^2 = 11.649$, $p = .001$			
Antidepressants	80 (16.5%)	111 (21.5%)	$\chi^2 = 4.138$, $p = .042$			
Codeine-containing compounds				390 (51.6%)	35 (29.9%)	$\chi^2 = 19.050$, $p < .001$
Illicit drugs (i.e.: heroin/morphine; psycho-stimulants; cannabis)				605 (80%)	49 (41.9%)	$\chi^2 = 78.451$, $p < .001$
Hypnotics/sedatives				348 (46%)	38 (32.5%)	$\chi^2 = 7.545$, $p = .006$

χ^2 = Pearson's chi square value; p = significance.

For the whole sample, the most frequently identified prescribed compound was Co-proxamol, followed by dihydrocodeine. Co-proxamol, Co-codamol and Co-dydramol were mostly prescribed for non-addicts, whilst dihydrocodeine was mostly prescribed for addicts.

Polydrug ingestion was mostly observed in accidental deaths, in both addicts and non-addicts (Table **4**). In non-addicts, alcohol was mostly represented in accidental deaths and antidepressants were typically represented in intentional deaths. Dextropropoxyphene-containing compounds were mostly represented in intentional deaths in both groups. Conversely, codeine-containing compounds; illicit drugs and hypnotics/sedatives were typically reported in addicts' accidental deaths.

Discussion

To the best of our knowledge, the present report constitutes the largest available collection of analgesic- and cough suppressant-opioid mortality data in the UK. Index opioids were identified, either alone or in combination, in well about 25 % of total cases flagged in the 1996–2002 np-SAD data base. Consistent with our hypotheses, it was found here that populations of addicts and non-addicts presented differences in patterns of drugs involved. Furthermore, within the population of addicts and non addicts, intentional and non intentional deaths presented with different patterns of substance intake.

Data from the 2002 US Drug Abuse Warning Network (DAWN) report on drug abuse-related Medical Examiner cases [25] seem to be consistent with high rates of identification of analgesic- and cough suppressant-opioids given here. In fact, a narcotic analgesic ranked in the top 3 most frequently DAWN reported drugs in most important US cities, including New York, New Orleans, Atlanta, Buffalo and San Francisco.

Similarly to previous literature [7], most (83 %) addicts died here as a result of accidental deaths. Conversely, and in parallel with previous UK observations of deaths related to narcotic analgesics

(e.g. buprenorphine; [28]), the number of intentional poisoning cases was considerably high (46 %) in non-addicts. Most frequently identified compounds were those containing dextropropoxyphene, which were reported in 44 % of cases examined. Codeine and dihydrocodeine were reported in about 28 % of cases each and a smaller number of deaths were related to other narcotic analgesics, e.g. tramadol.

Co-proxamol clearly accounted here for most prescriptions. Reports of poisoning with compounds containing dextropropoxyphene have been frequently reported in the literature [17], probably due to their predominance in the market [22]. Antidepressants and dextropropoxyphene-containing compounds were here mostly represented in non-addicts' intentional deaths. Dextropropoxyphene was arguably prescribed for pain control and one might hypothesize a possible association between chronic pain and depression [2], which may in turn have led to suicide. It has been suggested that restriction of Co-proxamol availability could have an important role in suicide prevention [31]; the compound is being gradually withdrawn from the UK market [23].

Cases with a history of drug addiction accounted for 45 % of cases studied. Dihydrocodeine was typically given to addicts and one could wonder if prescription occurred for the treatment of drug addiction itself. Although in contrast with indications issued in the Department of Health guidelines [9], dihydrocodeine is frequently prescribed by individual physicians for harm reduction purposes [27]. In combination with a general acceptance for this drug as a substitute for methadone amongst Scottish general practitioners, in the Strathclyde region an increase in the number of drug related deaths over a five-year period has been reported [30].

Although codeine-containing compounds were here mostly *prescribed* to non-addicts, codeine was typically *identified* in addicts. Polydrug users may report a preference for codeine [11], but one should take also into account that the toxicological analysis of a 'heroin' dose can present an association of heroin, morphine and codeine [13]. Consistently with this, heroin/morphine was here associated with 93 % of codeine related-deaths in addicts.

In about 93 % of cases, analgesic- and cough suppressant-opioids were reported in combination with another substance, with polydrug ingestion being significantly more represented in addicts. Almost exclusively, deaths associated with opiates/opioids also involve a cocktail of drugs, such as alcohol and benzodiazepines [15, 18]. In confirming this, alcohol and hypnotics/sedatives were here respectively identified in about 36 % and 30 % of the whole sample of described fatalities. Sedatives may enhance the respiratory depressive effects of opioids and together form a fatal combination [6]. Conversely, antidepressants were mostly identified in association with opioids in non-addicts. The phenylpiperidine series of opioids, including pethidine, tramadol, dextromethorphan and propoxyphene, appear to be weak serotonin re-uptake inhibitors and may be involved in serotonin toxicity reactions, including some fatalities, in association with serotonergic antidepressants [16].

One could wonder about the reasons behind high rates of identification of opioids in combination with other drugs found here. Whilst in opiate addicts high rates of drug combination patterns may be explained by their medication-seeking behaviour, the 89 % drug combination rate found in non-addicts is an intriguing issue. Furthermore, the medical reasons behind opioid prescription itself to non-addict victims were unclear here. Opioid analgesics might be appropriately prescribed in cancer-related painful conditions only; in fact, available evidence indicates that oral opioids generally achieve only modest reductions in pain levels in patients with chronic non-cancer pain [24]. Although we did not aim here at identifying cancer prevalence figures in victims prescribed with opioid analgesics, occurrence of meaningful rates of neoplasms in the present sample should be considered very unlikely. In fact, in the 'cause of death' section of Coroners' reports, rates of cancer recording as a contributory factor were negligible indeed. On the other hand, present data are consistent with observation of rising prescription rates of opioids in non-malignant conditions in other countries, including the US [3, 4], and Sweden [19], and especially so in older adults. One out of 2 of non-addict victims were here older than 45. Apart from cancer, frequently observed painful conditions in this age range include facet joint arthritis (causing low back pain), polymyalgia rheumatica, neuropathies, peripheral vascular disease and coronary disease [8]. On the other hand, uncritical prescription of narcotic analgesics may be the reason of serious concern. Though the use of opioid analgesics for the treatment of acute pain appears to be generally benign, long-term administration of opioids has been associated with clinically meaningful rates of abuse or addiction [4]. Furthermore, it has been suggested that pain intensity is not consistent with opioid prescription; age, depression, personality disorder, and history of substance abuse was closely linked to the use of opioids for the treatment of back pain in preference to nonsteroidal anti-inflammatory drugs alone [1]. Opioid choices necessitate an understanding of pharmacology to ensure safe administration and avoidance of drug interactions. Possible multifaceted solutions exist to improve physicians' ability to treat patients appropriately. Examples include comprehensive, practical multidimensional guidelines on the evaluation and treatment of chronic non-malignant pain; enhanced continuing medical education and pregraduate training; and multispecialty coordinated care of patients [26].

A possible limitation of the present study is given by our definition of deaths *related* to analgesic- and cough suppressant-opioids, which was as comprehensive as possible. On a number of cases here presented, in fact, index opioids were mentioned in the coronial documents even if their role in the final cause of death was unclear. It has been suggested that in cases of multiple drug fatalities cause of death should not be attributed to any single drug. Rather, the unique combination of drugs, the pattern of drug use/abuse, and individual factors, such as tolerance to the respiratory depressant effects of opioids, must be taken into account in the formulation of a valid cause of death statement [5]. This possibly 'overinclusive' methodological approach [14] has been chosen to add as much information as possible to the very limited knowledge available on opioid administration safety issues in the UK. Although we feel confident that all opioid-related deaths that have been so diagnosed and appro-

priately reported by Coroners have been identified with the chosen data collection methods, changes in reporting over time should be taken into account here to interpret these findings. In fact, although in the last few years the response rate from Coroners in England and Wales has been estimated to have been as high as about 95 % [14,15], in 1996–1998 the np-SAD Coroners' response rate was of only about 50 %. One can think that Coroners' determinations may have been subject to biases. In fact some Coroners, in deciding whether a person was an addict or not, and whether a death was intentional or not, may consciously or unconsciously have used information on the nature and dose of drugs ingested. Furthermore, some Coroners may have preferred, where possible, to spare families the added anguish of a verdict of suicide. As a consequence, the frequency of intention may have been underestimated here. Another potential limitation of the present study is given by the lack of presentation of comprehensive toxicology data. On the other hand, post mortem toxicology examination is *not* routinely carried out in all cases in the UK [28,29]. Positivity of opioids in the toxicology results was not the only criterion used here to define an opioid-related death, since Coroners may have had access to other information, including evidence from the scene, witnesses' statements and list of prescribed medications, to make their own final and formal judgement. Finally, a number of medications here commented (i.e. Co-proxamol, Co-codamol etc), are typically available in the UK but not necessarily in other countries and this may limit the generalisation of present data.

Although there are numerous deaths associated with opioids each year, many of them are preventable. It may be concluded from here that much still needs to be done in educating the users about the risks associated with polydrug use, especially of mixing opioids, alcohol, benzodiazepines and antidepressants [16,18]. Index opioids implicated in deaths were here prescribed in only about half of non-addicts and in about one fourth of addicts. Although low prescription rates shown here may be accounted by possible inconsistencies in information written in Coroners' reports, one could wonder how most victims accessed their opioids. The opioid source may be a family member or partner [18], but over the counter (OTC) availability of some of the opioids here commented may be a cause of concern. In the UK, pharmacists perceive abuse and misuse of OTC products to be occurring in practice [21] and current methods employed for dealing with it are felt to be inadequate [12].

Improvements in the monitoring of opioid prescribing and dispensing, especially while treating chronic pain patients [10], should help to reduce in the UK the number of deaths involving these compounds. Analgesic- and cough suppressant-opioids, like any other compound, may be toxic if not taken appropriately. They have to be administered in the right amount, to the right individuals and for the correct indication.

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