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Deaths of opiate/opioid misusers involving dihydrocodeine, UK, 1997–2007

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Dihydrocodeine (DHC) is an opioid analgesic sometimes prescribed as an alternative to other medications (e.g. methadone and buprenorphine) for opioid misuse. Its effectiveness is, however, still controversial.
- DHC prescription rates seem to be related to levels of DHC fatalities, possibly in relation to levels of disregard of the availability of supervised or interval dispensing of opioids, but no large-scale analysis of DHC fatalities has been carried out.
- We analysed here involvement of DHC in fatalities that occurred between 1997 and 2007 among individuals with a history of opiate/opioid misuse reported to the National Programme on Substance Abuse Deaths (np-SAD).

WHAT THIS STUDY ADDS

- DHC, either alone or in combination, was identified in 584 fatalities. Typical cases identified were males in their early thirties. In accidental overdoses, DHC, which had been prescribed to 45% of the victims, was typically identified in combination with other drugs, such as heroin/morphine, methadone and hypnotics/sedatives. Both paracetamol and antidepressants were more typically identified in combination with DHC in suicides.
- Opiate/opioid misusers should be educated about risks associated with polydrug intake and prescribers should carefully consider a pharmacological intervention alternative to DHC (e.g. methadone, buprenorphine) when managing and treating opiate addiction.

AIMS

Although its effectiveness is somewhat controversial, it appears that dihydrocodeine (DHC) is still prescribed in the UK as an alternative to both methadone and buprenorphine for the treatment of opiate addiction.

METHODS

Data covering the period 1997–2007 voluntarily supplied by coroners were analysed. All cases pertaining to victims with a clear history of opiate/opioid misuse and in which DHC, either on its own or in combination, was identified at post-mortem toxicology and/or implicated in death, were extracted from the database.

RESULTS

Dihydrocodeine, either alone or in combination, was identified in 584 fatalities meeting the selection criteria. In 44% of cases it was directly implicated in the cause of death. These cases represented about 6.8% of all opiate/opioid-related deaths during this period. Typical DHC cases identified were White males in their early thirties. Accidental deaths (96%) were likely to involve DHC in combination with other psychoactives, mainly heroin/morphine, hypnotics/sedatives and methadone. Both paracetamol and antidepressants were found in proportionately more suicide cases than in accidental overdoses. DHC had been prescribed to the decedent in at least 45% of cases.

CONCLUSIONS

Opiate/opioid misusers should be educated about risks associated with polydrug intake. More in particular, co-administration of DHC with heroin, methadone and benzodiazepines may increase the risk of accidental fatal overdose. Prescribers should carefully consider pharmacological intervention alternative to DHC (e.g. methadone, buprenorphine) when managing and treating opiate addiction. More resources are required to do prospective research in this area.

Introduction

Dihydrocodeine (DHC) is a semi-synthetic opioid [1] licensed in most countries to treat moderate to severe pain. However, DHC is sometimes prescribed as well as an alternative to other medications (e.g. methadone and buprenorphine) in substitution or detoxification treatment of opioid misuse [2]. In the UK, DHC is a controlled drug and any preparation containing more than 1.5% (as a base) of the substance or a maximum dose of 10 mg is a prescription only medicine (POM). DHC is not licensed in the UK for the treatment of opiate dependence and should not normally be used for such purposes [3]. The effectiveness of DHC for opiate addiction treatment is still controversial. In Germany, Krausz *et al*. [4] carried out both a retrospective and a prospective study assessing the effects of the codeine-based substitution in heroin abusers (n = 416). In terms of a number of parameters, including physical and psychological health, social integration, criminal activities and consumption patterns, a general improvement was noticed, and results were similar to those reported with standard opioid agonist treatment. Similarly, Robertson *et al*. [2] from the UK, suggested that DHC maintenance regimes showed comparable improvements with those of methadone (n = 235). Conversely, Elias's [5] earlier observations identified a lower compliance with DHC than that observed with methadone. Although DHC has been suggested as a useful tool for detoxification from methadone [6], a recent randomized controlled trial concluded that DHC should not be prescribed for opiate detoxification [7]. In fact, DHC might be less effective than both buprenorphine [8] and methadone [9] for opiate/opioid detoxification purposes. In the UK, both general practitioners and community pharmacists occupy a pivotal position in relation to providing treatment for opiate addiction. Strang *et al*. [10] found that 8.5% of general practitioners in England and Wales declared they had previously prescribed DHC for treatment of opioid misuse at some point. Furthermore, Matheson *et al*. [11] pointed out that 26% of pharmacists in Scotland dispensed DHC and Pearson *et al*. [12] observed that DHC is the most common medication given to opiate misusers to manage opiate withdrawal symptoms in police custody in seven London areas.

On the other hand, it is an issue of concern that DHC prescription rates seem to be related to levels of DHC fatalities in both Scotland [13] and Germany [14]. This is possibly in relation to levels of disregard of the availability of supervised or interval dispensing of opioids, which in turn may increase the risk of diversion to the black market and hence their availability for recreational abuse [10]. Misuse of DHC itself has been widely reported [15–17]. Recently, Cicero *et al*. [18, 19] emphasized how recreational abuse of opioid analgesics is becoming an increasing phenomenon, albeit predominantly occurring in a context of polydrug abuse [15].

Opiate analgesics in general, and DHC in particular, are often identified in studies focusing on drug-related deaths in addicts [13, 14, 20–22]. It is thought that in recent years improvements have occurred in the quality of treatment of addiction, and DHC prescriptions for opiate management have dropped in several areas [23]. However, DHC-related deaths continue to be a risk for addicts in the UK [24].

In order to have a better understanding of this important phenomenon, we analysed levels of involvement of DHC in deaths that occurred between 1997 and 2007 among individuals with a history of opiate/opioid misuse reported to the National Programme on Substance Abuse Deaths (np-SAD) at St George's, University of London.

Methods

The National Programme on Substance Abuse Deaths (np-SAD) was established after the Home Office Addicts Index closed in 1997 and, since then, it has regularly received information from coroners on a voluntary basis on deaths related to drugs in both addicts and non-addicts in England and Wales, Northern Ireland, the Channel Islands and the Isle of Man. Since 2004, information has been received from the Scottish Crime and Drug Enforcement Agency and the General Register Office for Northern Ireland. To date, details of some 23 000 deaths have been received. The data presented here relate to those 1997–2007 cases which had already been entered in the database by 1 June 2009.

To be recorded in the np-SAD database as a drug-related death, at least one of the following criteria must be met: (i) presence of one or more psychoactive substances directly implicated in death, (ii) history of dependence or abuse of drugs and (iii) presence of controlled drugs at post-mortem. Alcohol is included only when implicated in combination with other qualifying drugs. The response rate from Coroners in England and Wales has been as high as 95% [24].

When Coroners' inquests are complete, cases are 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. We extracted all cases in which victims had a clear history of opiate/opioid misuse. The following criteria also had to be met: (i) DHC or metabolites identified in the post-mortem toxicology and (ii) DHC considered as implicated in death. Deaths were classified as either intentional (e.g. suicide) or accidental in line with the Coroner's verdict. As heroin is chiefly metabolized to morphine, there are difficulties in distinguishing heroin (i.e. diacetylmorphine) from morphine intoxication cases at post-mortem [25]. For the purpose of this study, those victims in whom either heroin

or morphine, or both, were identified were included in the heroin/morphine category.

Statistical analysis

Analyses were performed using the Statistical Package for Social Sciences (SPSS), 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 Fisher's exact test if appropriate. The results for statistical tests were regarded as significant at or below the 5% probability level.

Results

There were 646 cases identified as DHC-related deaths in this opiate/opioid misusers' population (Table 1). In 62 cases, the cause of death was considered by the Coroner to be unascertained and hence those cases were excluded from the statistical analyses. DHC was specifically mentioned in 44% of all cases and found in the post-mortem toxicology results of 96% of cases. Basic demographic information of the sample is summarized in Table 1. White victims were more represented in accidental deaths than victims from other ethnic groups ($P = 0.013$). Accidental death victims were younger than the intentional death ones (mean age 35.3 *vs*. 38.8 years, $P = 0.013$). Females were more represented in the intentional death subgroup ($P = 0.036$).

Most (489, 96.1%) victims died from polydrug intake (see Table 2), with a mean of 3.30 (SD = 1.25) substances found at post-mortem. A significant difference in the number of drugs ingested between the accidental and intentional deaths groups was identified (3.37 *vs*. 2.80 respectively, $P < 0.001$). Heroin/morphine ($P < 0.001$), methadone ($P = 0.006$) and hypnotics/sedatives ($P = 0.012$) were more likely to be identified in accidental deaths. Conversely, both paracetamol ($P = 0.043$) and antidepressants ($P = 0.046$) were more frequently identified in the intentional deaths subgroup. DHC was more frequently identified as the only drug at post-mortem in the suicidal subgroup ($P < 0.0001$).

Complete information on prescribed medication was made available for 450 cases only (see Table 3). Prior to death, DHC was regularly prescribed to 202 (44.9%) subjects. In comparison to those prescribed with DHC, victims in which illicit DHC was identified were more likely to have been prescribed with methadone ($P < 0.0001$) but presented as well with a higher proportion of deaths due to both street/illicit methadone ($P = 0.002$) and hypnotics/sedatives ($P = 0.029$). Conversely, victims prescribed with DHC were more likely to have been prescribed with hypnotics/sedatives ($P < 0.0001$) as well. In this subgroup, illicit antidepressants were more likely to be identified at post-mortem ($P = 0.006$). In 14 cases, a concurrent prescription of methadone and DHC was identified.

Discussion

To the best of our knowledge, the present report constitutes the largest available collection of DHC mortality data pertaining to victims with a clear history of opiate/opioid misuse. DHC was identified, either alone or in combination, in about 4.5% of total cases held in the np-SAD database between 1997 and 2007, or 6.8% of all opiate/opioid-related deaths. Victims of accidental and

Table 1

Deaths of opiate/opioid misusers involving dihydrocodeine UK, 1997–2007. Victims' basic socio-demographics and comparisons between accidental and intentional death subgroups (*)

	Number of valid cases ($n = 584$)	Accidental ($n = 509$)	Intentional ($n = 75$)	Total	Chi square (two-tailed)	P†
Gender	**584**					
Male		**407** (80.0%)	**52** (69.3%)	**459** (78.6%)	$\chi^2 = 4.389$	**0.036**
Female		**102** (20.0%)	**23** (30.7%)	**125** (21.4%)		
Ethnicity	**512**					
White		**438** (97.8%)	**59** (92.2%)	**497** (97.1%)	$\chi^2 = 6.132$	**0.013**†
Other		**10** (2.2%)	**5** (7.8%)	**15** (2.9%)		
Employment status	**544**					
Unemployment; inability to work; sickness		**355** (75.2%)	**47** (65.3%)	**402** (73.9%)	$\chi^2 = 3.196$	0.074
Employed or other defined working condition		**117** (24.8%)	**25** (34.7%)	**140** (26.1%)		
Living arrangements	**543**					
Alone/other		**263** (55.3%)	**32** (47.8%)	**293** (54.3%)	$\chi^2 = 1.328$	0.249
With others		**213** (44.7%)	**35** (52.2%)	**248** (45.7%)		
Mean age (SD) (years)	**584**	**35.3** (9.5)	**38.8** (11.2)	**35.8** (9.8) min = 16.0; max = 70.7	$t = -2.858$	**0.013**

Bold figures are statistically significant. *All subjects here described had a clear history of opiate/opioid misuse; t = Student's t-test; χ^2 = chi-squared test; † = Fisher's correction.

Table 2

Deaths of opiate/opioid misusers involving dihydrocodeine UK, 1997–2007. Substances identified at post-mortem and comparisons between accidental and intentional subgroups (*)

	Accidental deaths (*n* = 509)	Intentional deaths (*n* = 75)	Total sample (*n* = 584)	Statistics	*P*†
Mean number of substances	**3.37** (SD = 1.25)	**2.80** (SD = 1.36)	**3.30** (SD = 1.28 min = 1;max = 7	*t* = 3.661	**0.000**
Dihydrocodeine only	**20** (3.9%)	**14** (18.7%)	**34** (5.8%)	χ^2 = 25.894	**0.000†**
Dihydrocodeine in combination with other substances	**489** (96.1%)	**61** (81.3%)	**550** (94.2%)		
Other psychoactive substances					
Alcohol in combination	**154** (30.3%)	**15** (20.0%)	**169** (28.9%)	χ^2 = 3.343	0.067
Heroin/morphine	**289** (56.8%)	**22** (29.3%)	**311** (53.3%).	χ^2 = 19.778	**0.000**
Methadone	**128** (25.1%)	**8** (10.7%)	**136** (23.3%)	χ^2 = 7.673	**0.006**
Opiate analgesics	**122** (24.0%)	**20** (26.7%)	**142** (24.3%)	χ^2 = 0.259	0.611
Cannabis	**37** (7.3%)	**2** (2.7%)	**39** (6.7%)	χ^2 = 2.222	0.136
Psychostimulants	**83** (16.3%)	**8** (10.7%)	**91** (15.6%)	χ^2 = 1.581	0.209
Hypnotics/sedatives	**262** (51.5%)	**27** (36.0%)	**289** (49.5%)	χ^2 = 6.261	**0.012**
Antidepressants	**76** (14.9%)	**18** (24.0%)	**94** (16.1%)	χ^2 = 3.981	**0.046**
Paracetamol	**22** (4.3%)	**8** (10.7%)	**30** (5.1%)	χ^2 = 5.339	**0.043**†

Bold figures are statistically significant. *All subjects here described had a clear history of drug addiction; *t* = Student's *t*-test; χ^2 = chi-squared test; † = Fisher's correction.

Table 3

Deaths of opiate/opioid misusers involving dihydrocodeine (DHC) UK, 1997–2007. Psychoactive medication prescribed, substances identified at post-mortem and comparisons between prescribed and non-prescribed DHC subgroups (*)

	DHC not prescribed (*n* = 248)	DHC prescribed (*n* = 202)	Total (*n* = 450)	Statistics	*P*†
Demographics					
Mean age (SD) (years)	**36.06** (10.09)	**36.16** (9.63)	**36.10** (9.87) min = 18.0; max = 70.7	*t* = 0.106	0.916
Gender					
Female	**58** (23.4%)	**47** (23.3%)	**105** (23.3%)	χ^2 = 0.001	0.976
Male	**190** (76.6%)	**155** (76.7%)	**345** (76.7%)		
Cause of death					
Accidental	**213** (85.9%)	**163** (80.7%)	**376** (83.6%)	χ^2 = 2.186	0.139
Intentional	**35** (14.1%)	**39** (19.3%)	**74** (16.4%)		
Psychoactive substances prescribed					
Hypnotics/sedatives	**98** (39.5%)	**141** (69.8%)	**239** (53.1%)	χ^2 = 41.003	**0.000**
Antidepressants	**57** (23.0%)	**63** (31.2%)	**120** (26.7%)	χ^2 = 3.832	0.050
Methadone	**50** (20.2%)	**14** (6.9%)	**64** (14.2%)	χ^2 = 15.974	**0.000**
Opiate analgesics – other than DHC	**16** (6.5%)	**18** (8.9%)	**34** (7.6%)	χ^2 = 0.964	0.326
Other psychoactive substances	**35** (14.1%)	**39** (19.3%)	**74** (16.4%)	χ^2 = 2.186	0.139
Non-prescribed substances implicated					
Alcohol in combination	**77** (31.0%)	**52** (25.7%)	**129** (28.7%)	χ^2 = 1.533	0.216
Hypnotics/sedatives	**138** (55.6%)	**91** (45.0%)	**229** (50.9%)	χ^2 = 5.001	**0.029**†
Heroin/morphine	**132** (53.2%)	**97** (48.0%)	**229** (50.9%)	χ^2 = 1.207	0.272†
Antidepressants	**32 (**12.9%)	**46** (22.8%)	**78** (17.3%)	χ^2 = 7.567	**0.006**
Methadone	**71** (28.6%)	**33** (16.3%)	**104** (23.1%)	χ^2 = 9.466	**0.002**
Cannabis	**20** (8.1%)	**12** (5.9%)	**32** (7.1%)	χ^2 = 0.760	0.383
Psychostimulants	**43** (17.3%)	**28** (13.9%)	**71** (15.8%)	χ^2 = 1.013	0.314
Other psychoactive substances	**14** (5.7%)	**6** (2.9%)	**20** (4.4%)	χ^2 = 1.960	0.161
Other opiate/opioid analgesics (i.e. not heroin/morphine)	**68** (27.4%)	**42** (20.8%)	**110** (24.4%)	χ^2 = 2.647	0.104

Bold figures are statistically significant. *All subjects here described had a clear history of drug addiction; *t* = Student's *t*-test; χ^2 = chi-squared test; † = Fisher's correction.

intentional fatalities presented differences in terms of both demographic features and patterns of drugs involved. As in previous reports [26], most (87.2%) deaths were here considered to be accidental and typically occurring following the ingestion of a combination of substances [20, 24]. Conversely, in line with previous reports [27], DHC fatal mono-intoxications occurred rarely and were more frequently identified in suicides ($P = 0.001$).

Accidental and intentional subgroups presented with different demographic characteristics. Typical accidental victims were White males in their thirties and two-thirds of them were in receipt of state benefits, reflecting these clients' levels of social vulnerability [28].Those of non-White ethnicity were more represented in suicidal victims, in line with previous studies which show that being part of a minority community could be a risk factor for suicide [29]. In contrast with the rest of the sample, typical suicidal victims were females and older. Although not invariably [30, 31], there is evidence that female addicts are more at risk than their male counterparts for suicide [32, 33], and especially so for those suffering from depression [34]. With ageing, addicts tend to decrease their drug use levels but present with a range of issues, such as alcohol misuse [35], physical illness [36] and pain [37, 38]. All of the above factors are considered to be associated with higher suicidal rates.

There was a significantly higher proportion ($P < 0.0001$) of intentional deaths compared with accidental overdoses, where DHC as a sole substance was found in the post-mortem toxicology results. The average number of post-mortem substances was also lower in this group. These findings suggest that accidental overdoses are more likely to occur as a result of poly-substance use and that deliberate overdoses are more commonly achieved by taking a fatal dose of a single opioid drug.

Differences in patterns of drug misuse between accidental and intentional deaths may confirm the possible role of depression as a risk factor for suicide. Present data indeed showed that antidepressants were identified in almost a quarter of suicidal victims. Antidepressants have been frequently reported as a major means of self-poisoning over the years [39, 40]. The use of paracetamol was also frequently identified in intentional death victims, with its use for suicidal purposes being a well-known phenomenon in the UK [22, 41, 42].

Conversely, in line with previous reports [43], accidental deaths included here a relevant proportion of heroin/morphine (almost six out of 10 cases), methadone (one case out of four) and hypnotics/sedatives (one case out of two) related fatalities. DHC may have been used by opioid addicts as an alternative opiate preparation at times of heroin shortage or may have been part of an attempt at self-detoxification [44]. Use of alternative opiates (i.e. morphine) in areas where heroin is less available has been also described [45].

Differences in prescription patterns between accidental and intentional deaths were identified as well. In our sample, information on the prescribing of DHC to the deceased was only available for about 45% of cases, therefore it is likely that it was illicitly obtained in over a half of cases. In the UK it seems that DHC, similarly to remaining opiate/opioid analgesics [22], is most likely obtained illicitly from friends/relatives or from the streets [10] rather than from Internet websites. These victims were instead more frequently prescribed with methadone and non-prescribed hypnotic/sedatives were also more likely identified at post-mortem. In order to prevent fatalities, users should be educated about risks associated with polydrug misuse and more effective strategies to minimize diversion of prescribed opiates/opioids and tranquillizers should be implemented. When prescribing methadone, clinicians must consider that low dosages of either buprenorphine or methadone are less effective in retaining patients and in controlling concurrent drug abuse [46–48].

Conversely, DHC was prescribed in about 45% of cases, and in a limited number of cases ($n = 14$) DHC and methadone were concurrently prescribed prior to death. Given that all the victims presented with a clear history of opiate/opioid misuse, one could conclude that DHC, although unlicensed for this use, was actually prescribed for the treatment of opiate addiction itself. DHC maintenance treatment deserves more attention compared with methadone or other opioids, as DHC has weaker pharmacological effects [4] and studies about the effectiveness of DHC as a treatment for addiction are limited [49].

An examination of deaths related to buprenorphine between 1980 and 2002 also found that an important proportion of these cases involved suicide (28%). However, most of these did not have a history of drug misuse or dependence [50]. Buprenorphine as a sole drug was found in about one-sixth of these cases (7/43), a larger proportion than that for DHC (6%) found in the present study, and for methadone cases (6%) reported to the np-SAD in 2009 [24]. Where heroin/morphine and methadone were prescribed to individuals 77% and 65%, respectively, had had it implicated in death, compared with a lower proportion for other opiates/opioid analgesics (60%) [24]. These findings support the suggestion [4] that DHC has weaker pharmacological effects than some other opioids.

Interestingly, among those prescribed DHC there were high rates of victims prescribed both hypnotics/sedatives (almost 70%) and antidepressants (about one case out of three). In opiate/opioid-treated addicts, this finding may suggest the presence of either poorly medicated withdrawal symptoms [51, 52], or a co-morbid anxiety/depression problem [53, 54]. In these cases, higher maintenance dosages of buprenorphine/methadone should probably be considered instead [55].

In a subsample of the present study population, DHC may have been prescribed as a painkiller. Even when detoxified [56], opiate addicts may indeed frequently seek help for pain control reasons. Opiate misusers may suffer from altered pain perception [57], with pain distress possibly being correlated with drug cravings [58]. Further studies are needed to analyse better treatment options for multiple co-morbid (i.e. substance misuse, pain, psychiatric problems) addicts.

Limitations of this study may include variations in coroners' reporting rates over time, lack of total geographical coverage of coroner's jurisdictions, incomplete

information relating to prescription of psychoactive medications in almost one case out of four and lack of information on the concentration of DHC detected in body fluids, so that some victims might have had only traces of the substance. As mortality rates (e.g. number of deaths out of number of DHC prescriptions) were not here calculated, it may be difficult to determine the true extent of risks associated with DHC consumption. Furthermore, the sample did not include deaths related to the prescription of other substitution therapies, so one may be unable to determine whether the DHC prescription was in fact associated with an increased risk of death relative to other modalities. The paper represents a retrospective analysis of deaths notified voluntarily to a Special Mortality Register. Such studies are easier and cheaper to undertake than setting up large-scale prospective studies with long periods of follow-up. However, the findings reported here are based on several hundred cases and may hopefully provide a solid basis for the conclusions drawn. Further studies of a similar nature should be conducted on other populations to see if the patterns described in this paper are confirmed. It would also be instructive to make a comparison of deaths for those with a history of DHC use/misuse with those without such a history. This would throw light on the role of the drug as a pain-killer in contrast to its use as a treatment for opiate/opioid dependence.

Notwithstanding the possible biases outlined above, mortality rates reported here may suggest caution when prescribing DHC to opiate addicts for either maintenance or detoxification therapy.

Competing Interests

There are no competing interests to declare.

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REFERENCES

1 Klepstad P, Kaasa S, Cherny N, Hanks G, de Conno F, Research Steering Committee of the EAPC. Pain and pain treatments in European palliative care units. A cross sectional survey from the European Association for Palliative Care Research Network. Palliat Med 2005; 19: 477–84.

2 Robertson JR, Raab GM, Bruce M, McKenzie JS, Storkey HR, Salter A. Addressing the efficacy of dihydrocodeine versus methadone as an alternative maintenance treatment for opiate dependence: a randomized controlled trial. Addiction 2006; 101: 1752–9.

3 Strang J, Bridge J, Day E, Farrell M, Gerada C, Gilvarry E, Harris L, Howard J, Keen J, Kidd B, Myles J, Oretti R, Raistrick D, Robertson R, Steventon N, Walker H, Wardle I, Wright N, Zador D. Drug Misuse and Dependence – UK Guidelines on Clinical Management. London: Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive, 2007 Available at http://www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf (last accessed 22 May 2010).

4 Krausz M, Degkwitz P, Wernecke A, Verthein U, Chorzelski G, Behrendt K. Drug substitution treatment of heroin dependent patients with codeine preparations – treatment effects from the viewpoint of the physicians and patients. Psychiatr Prax 1995; 22: 179–85.

5 Elias H. Substitute drug-assisted treatment of drug dependent patients in general practice. Fortschr Med 1990; 108: 256–8.

6 Banbery J, Wolff K, Raistrick D. Dihydrocodeine: a useful tool in the detoxification of methadone-maintained patients. J Subst Abuse Treat 2000; 19: 301–5.

7 Sheard L, Wright NM, El-Sayeh HG, Adams CE, Li R, Tompkins CN. The Leeds Evaluation of Efficacy of Detoxification Study (LEEDS) prisons project: a randomised controlled trial comparing dihydrocodeine and buprenorphine for opiate detoxification. Subst Abuse Treat Prev Policy 2009; 4: 1.

8 Wright NM, Sheard L, Tompkins CN, Adams CE, Allgar VL, Oldham NS. Buprenorphine versus dihydrocodeine for opiate detoxification in primary care: a randomised controlled trial. BMC Fam Pract 2007; 8: 3.

9 Backmund M, Meyer K, Eichenlaub D, Schutz CG. Predictors for completing an inpatient detoxification program among intravenous heroin users, methadone substituted and codeine substituted patients. Drug Alcohol Depend 2001; 64: 173–80.

10 Strang J, Sheridan J, Hunt C, Kerr B, Gerada C, Pringle M. The prescribing of methadone and other opioids to addicts: national survey of GPs in England and Wales. Br J Gen Pract 2005; 55: 444–51.

11 Matheson C, Bond CM, Hickey F. Prescribing and dispensing for drug misusers in primary care: current practice in Scotland. Fam Pract 1999; 16: 375–9.

12 Pearson R, Robertson G, Gibb R. The identification and treatment of opiate users in police custody. Med Sci Law 2000; 40: 305–12.

13 Seymour A, Black M, Jay J, Oliver JS. The role of dihydrocodeine in causing death among drug users in the west of Scotland. Scott Med J 2001; 46: 143–6.

14 Penning R, Fromm E, Betz P, Kauert G, Drasch G, von Meyer L. Drug death autopsies at the Munich Institute of Forensic Medicine (1981–1992). Forensic Sci Int 1993; 62: 135–9.

15 Friessem DH, Taschner KL. Codeine and dihydrocodeine as substitute and alternative drugs. Fortschr Neurol Psychiatr 1991; 59: 164–9.

16 Swadi H, Wells B, Power R. Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. Br Med J 1990; 300: 1313.

17 Ulmer A. Dihydrocodeine in substance dependence. Fortschr Med 1990; 108: 261.

18 Cicero TJ, Inciardi JA, Munoz A. Trends in abuse of Oxycontin and other opioid analgesics in the United States: 2002–2004. J Pain 2005; 6: 662–72.

19 Cicero TJ, Dart RC, Inciardi JA, Woody GE, Schnoll S, Munoz A. The development of a comprehensive risk-management program for prescription opioid analgesics: Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS-R). Pain Med 2007; 8: 157–70.

20 Hickman M, Carrivick S, Paterson S, Hunt N, Zador D, Cusick L, Henry J. London audit of drug-related overdose deaths: characteristics and typology, and implications for prevention and monitoring. Addiction 2007; 102: 317–23.

21 Reith D, Fountain J, Tilyard M. Opioid poisoning deaths in New Zealand (2001–2002). NZ Med J 2005; 118: 1293.

22 Schifano F, Zamparutti G, Zambello F, Oyefeso A, Deluca P, Balestrieri M, Little D, Ghodse AH. Review of deaths related to analgesics and cough suppressant-opioids; England and Wales 1996–2002. Pharmacopsychiatry 2006; 39: 185–91.

23 Strang J, Manning V, Mayet S, Ridge G, Best D, Sheridan J. Does prescribing for opiate addiction change after national guidelines? Methadone and buprenorphine prescribing to opiate addicts by general practitioners and hospital doctors in England, 1995–2005. Addiction 2007; 102: 761–70.

24 Ghodse H, Corkery J, Oyefeso A, Schifano F, Ahmed K, Naidoo V. Drug-related deaths in the UK: Annual Report 2009. Drug-related deaths reported by Coroners in England, Wales, Northern Ireland, Guernsey, Jersey and the Isle of Man; Police forces in Scotland; & the Northern Ireland Statistics and Research Agency – Annual Report January – December 2008. London: International Centre for Drug Policy, St George's University of London. September 2009. Available at http://www.sgul.ac.uk/research/projects/icdp/pdf/np-SAD%2011th%20annual%20report%20Final.pdf (last accessed on 22 May 2010).

25 Nakamura GR. Toxicologic assessments in acute heroin fatalities. Clin Toxicol 1978; 13: 75–87.

26 Darke S, Ross J. The relationship between suicide and heroin overdose among methadone maintenance patients in Sydney, Australia. Addiction 2001; 96: 1443–53.

27 Shields LB, Hunsaker DM, Hunsaker JC 3rd, Ward MK. Toxicologic findings in suicide: a 10-year retrospective review of Kentucky medical examiner cases. Am J Forensic Med Pathol 2006; 27: 106–12.

28 March JC, Oviedo-Joekes E, Romero M. Drugs and social exclusion in ten European cities. Eur Addict Res 2006; 12: 33–41.

29 Crawford MJ, Kuforiji B, Ghosh P. The impact of social context on socio-demographic risk factors for suicide: a synthesis of data from case-control studies. J Epidemiol Community Health 2010; 64: 530–4.

30 Bakken K, Vaglum P. Predictors of suicide attempters in substance-dependent patients: a six-year prospective follow-up. Clin Pract Epidemiol Ment Health 2007; 3: 20.

31 Trémeau F, Darreye A, Staner L, Corrêa H, Weibel H, Khidichian F, Macher JP. Suicidality in opioid-dependent subjects. Am J Addict 2008; 17: 187–94.

32 Darke S, Ross J, Lynskey M, Teesson M. Attempted suicide among entrants to three treatment modalities for heroin dependence in the Australian Treatment Outcome Study (ATOS): prevalence and risk factors. Drug Alcohol Depend 2004; 73: 1–10.

33 Britton PC, Conner KR. Suicide attempts within 12 months of treatment for substance use disorders. Suicide Life Threat Behav 2010; 40: 14–21.

34 Phillips J, Carpenter KM, Nunes EV. Suicide risk in depressed methadone-maintained patients: associations with clinical and demographic characteristics. Am J Addict 2004; 13: 327–32.

35 Schneider B. Substance use disorders and risk for completed suicide. Arch Suicide Res 2009; 13: 303–16.

36 Rajaratnam R, Sivesind D, Todman M, Roane D, Seewald R. The aging methadone maintenance patient: treatment adjustment, long-term success, and quality of life. J Opioid Manag 2009; 5: 27–37.

37 Ratcliffe GE, Enns MW, Belik SL, Sareen J. Chronic pain conditions and suicidal ideation and suicide attempts: an epidemiologic perspective. Clin J Pain 2008; 24: 204–10.

38 Ilgen MA, Zivin K, McCammon RJ, Valenstein M. Pain and suicidal thoughts, plans and attempts in the United States. Gen Hosp Psychiatry 2008; 30: 521–7.

39 Neeleman J, Wessely S. Drugs taken in fatal and non-fatal self-poisoning: a study in south London. Acta Psychiatr Scand 1997; 95: 283–7.

40 Staikowsky F, Theil F, Candella S. Trends in the pharmaceutical profile of intentional drug overdoses seen in the emergency room. Presse Med 2005; 34: 842–6.

41 Hawton K, Fagg J, Simkin S, Mills J. The epidemiology of attempted suicide in the Oxford area, England (1989–1992). Crisis 1994; 15: 123–35.

42 Hawton K, Bergen H, Simkin S, Brock A, Griffiths C, Romeri E, Smith KL, Kapur N, Gunnell D. Effect of withdrawal of Co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis. BMJ 2009; 338: b2270.

43 Coffin PO, Galea S, Ahern J, Leon AC, Vlahov D, Tardiff K. Opiates, cocaine and alcohol combinations in accidental drug overdose deaths in New York City, 1990–98. Addiction 2003; 98: 739–47.

44 Strang J, Farrell M, Meadows G. Misuse of dihydrocodeine tartate (DF 118) among opiate addicts. BMJ 1990; 301: 119.

45 Degenhardt L, Black E, Breen C, Bruno R, Kinner S, Roxburgh A, Fry C, Jenkinson R, Ward J, Fetherston J, Weekley J, Fischer J. Trends in morphine prescriptions, illicit morphine use and associated harms among regular injecting drug users in Australia. Drug Alcohol Rev 2006; 25: 403–12.

46 Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. Cochrane Database Syst Rev 2003; (3): CD002208.

47 Van den Brink W, Hasen C. Evidence-based treatment of opioid dependent patients. Can J Psychiatry 2006; 51: 635–46.

48 Wittchen HU, Apelt SM, Soyka M, Gastpar M, Backmund M, Golz J, Kraus MR, Tretter F, Schafer M, Siegert J, Scherbaum N, Rehm J, Buhringer G. Feasibility and outcome of substitution treatment of heroin-dependent patients in specialized substitution centres and primary care facilities in Germany: a naturalistic study in 2694 patients. Drug Alcohol Depend 2008; 95: 245–57.

49 Hall WD, Mattick RP. Clinical update: codeine maintenance in opioid dependence. Lancet 2007; 370: 550–2.

50 Schifano F, Corkery J, Gilvarry E, Deluca P, Oyefeso A, Ghodse AH. Buprenorphine mortality, seizures and prescription data in the UK, 1980–2002. Hum Psychopharmacol 2005; 20: 343–8.

51 Gossop M, Marsden J, Stewart D. Remission of psychiatric symptoms among drug misusers after drug dependence treatment. J Nerv Ment Dis 2006; 194: 826–32.

52 Gowing L, Ali R, White J. Buprenorphine for the management of opioid withdrawal. Cochrane Database Syst Rev 2000; (3): CD002025.

53 Ross J, Teesson M, Darke S, Lynskey M, Ali R, Ritter A, Cooke R. The characteristics of heroin users entering treatment: findings from the Australian treatment outcome study (ATOS). Drug Alcohol Rev 2005; 24: 411–8.

54 Phillips GT, Gossop M, Bradley B. The influence of psychological factors on the opiate withdrawal syndrome. Br J Psychiatry 1986; 149: 235–8.

55 Maremmani I, Pacini M, Lubrano S, Perugi G, Tagliamonte A, Pani PP, Gerra G, Shinderman M. Long-term outcomes of treatment-resistant heroin addicts with and without DSM-IV axis I psychiatric comorbidity (dual diagnosis). Eur Addict Res 2008; 14: 134–42.

56 Larson MJ, Paasche-Orlow M, Cheng DM, Lloyd-Travaglini C, Saitz R, Samet JH. Persistent pain is associated with substance use after detoxification: a prospective cohort analysis. Addiction 2007; 102: 752–60.

57 Pud D, Cohen D, Lawental E, Eisenberg E. Opioids and abnormal pain perception: new evidence from a study of chronic opioid addicts and healthy subjects. Drug Alcohol Depend 2006; 82: 218–23.

58 Ren ZY, Shi J, Epstein DH, Wang J, Lu L. Abnormal pain response in pain-sensitive opiate addicts after prolonged abstinence predicts increased drug craving. Psychopharmacology (Berl) 2009; 204: 423–9.