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"The Dog ate my Script"- Perceptions of medical professionals on prescribed and over the counter medicines containing codeine.

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Title: "The Dog ate my Script" - A study of medical professionals perspectives on prescribed and over the counter medicines containing codeine

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ABSTRACT

Objectives:

To explore prescribing practitioners' perspectives on prescribed codeine use, their ability to identify dependence and their options for treatment in the United Kingdom.

Design:

Cross sectional design using a questionnaire containing closed and open ended items.

Setting:

A nationally representative sample of prescribing professionals working in the United Kingdom

Participants:

Three hundred prescribing professionals working in primary care and pain settings.

Results:

Participants stated that they regularly reviewed patients prescribed codeine, understood the risks of dependence and recognised the potential for codeine to be used recreationally. Over half the participants felt patients were unaware of the adverse health consequences of high doses of combination codeine medicines. One quarter of participants experienced patient resentment when asking about medicines containing codeine. Just under 40% of participants agreed that it was difficult to identify problematic use of codeine without being informed by the patient and did not feel confident in identification of codeine dependence. Less than 45% of all participants agreed that codeine dependence could be managed effectively in general practice. Slow or gradual withdrawal was the most popular suggested treatment in managing

dependence. Education and counselling was also emphasised in managing codeine dependant patients in primary care.

Conclusions:

Communication with patients should involve assessment of patient understanding of their medication, including risk of dependence. There is a need to develop extra supports for professionals including patient screening tools for identifying codeine dependence. The support structure for managing codeine dependant patients in primary care requires further examination.

Article Summary

- This is the first study examining medical professionals perceptions of medicines containing codeine across the UK
- The study used a questionnaire design with closed and open ended items relating to both prescribed and over the counter medicines containing codeine and included questions on dependence and treatment options in practice
- Professionals involved in the prescribing of codeine were accessed across the UK using the principles of stratified random sampling
- Reponses rates were lower than expected and the study was unable to access the full population of nurse prescribers
- This study is cross-sectional and therefore does not describe how the situation might change over time

INTRODUCTION

Pain is a common reason for accessing primary care services. It is estimated that 14 million people in the UK suffer from long term pain,(1) with patients complaining of headaches thought to account for one in twenty five of primary care consultations,(2) and musculoskeletal pain accounting for one in seven.(3) Opioids are widely used in pain management with codeine being the second most widely prescribed opioid medicine in general practice.(4) In 2012, it was estimated that 640 codeine prescriptions per 1000 patients were dispensed in the UK.(5) Additionally, medicines containing codeine can be purchased over the counter (OTC) in pharmacies albeit with restrictions (6). However, the nature and extent of OTC codeine use and misuse in the UK is not widely reported.

Treatment with opioid medication is thought to be effective in the treatment of non-cancer pain for acute and short periods of less than six months.(7) Current scientific evidence measuring the efficacy of codeine over other alternative medications for chronic and longer term pain remains inconclusive.(8) There are limited studies examining the efficacy of low doses of codeine found in many prescribed and OTC medicines (less than 12.5mg per unit dose). While several Cochrane reviews have evaluated the efficacy of codeine, these are principally confined to acute postoperative pain at high doses (60mg). Some studies show codeine as clinically useful in some patients, but only 10% of patients reported to achieve effective pain relief with codeine when compared to those having the same dose of paracetamol alone. Although codeine was found to extend the duration of analgesia by approximately one hour.(9) A recent Cochrane review found that the combination of ibuprofen 400mg plus codeine 25.6mg to 60mg demonstrated effective analgesic efficacy in post-operative pain, however very limited data suggests that the combination is better than

the same dose of either drug alone.(10) Equally, the use of codeine containing syrups in supressing cough appears to lack positive scientific basis and is not widely discussed in the current literature.

Whilst codeine is considered a weak opiate, it carries an identified abuse potential. Development of tolerance on regular or excessive use appears within a short timeframe.(11) Literature reports increasing trends in the misuse use of codeine, including over the counter preparations, which appears to incur significant negative epidemiologic, social and economic consequences.(12-16) Related harms in terms of morbidity and mortality are documented,(12) along with monetary costs associated with indirect effects on healthcare, prevention and treatment.(17)

Treatment of codeine dependence is varied and does not appear to be well documented in the literature. Guidance on options for opioid dependence is evident but appears non-specific to weak opioids such as codeine. Summary statistics for codeine dependence obtained from treatment providers in the UK, suggest that codeine as the primary substance of misuse is extremely low.(18) These statistics may give an impression that codeine dependence is not an issue warranting attention compared to other substances of misuse; however treatment for codeine dependence conducted in primary care does not appear in national treatment surveillance systems. What is of particular concern is that codeine dependent patients appear to function well within the range of perceived normality, carrying out the functions of normal daily living.(19) Evaluating as to whether medical professionals are equipped to detect and manage patients presenting with codeine dependence is therefore an area of considerable importance.

Studies have called for further research on the experiences and concerns of medical professionals around use of medicines containing codeine, with particular focus on their

experiences, challenges, perspectives and practices.(20) The aim of the study was to garner information regarding prescribing practitioners' perspectives on prescribed and OTC codeine use, their ability to identify dependence and options for treatment in the UK. This study was part of a larger study examining both OTC and prescribed misuse of codeine medicines in the Republic of Ireland, UK and South Africa and was funded by the European Commission (www.codemisused.org).

METHOD

Recruitment of participants and study procedures

The study involved a cross-sectional design and took place between May 2014 and April 2015 using an online questionnaire. 2,000 GP practices were chosen using stratified random sampling (number of GPs located in England, Scotland, Northern Ireland and Wales). GP practices were contacted by e-mail and asked to select at least one GP or prescriber from their respective practice to complete the questionnaire. In addition, a pre-existing list of 150 specialist pain nurses involved in prescribing in the UK, obtained from a previous study (21), were also invited to take part. The link to the online survey was supplied to those agreeing to partake in the research. All methods of data collection were followed up with a two week reminder. The online questionnaire detailed the information on the study and participants were required to provide consent before proceeding online. Dissemination activities, including circulars and newsletters were used to encourage participation in the study. Ethical approval was granted by King's College London Ethics Committee (PNM/13/14-75).

Data collection methods

We collected the data using an online questionnaire using the survey tool www.onlinesurveys.ac.uk. Questions were developed to bridge gaps in knowledge following a comprehensive search of the literature.(4) Eight questions were added to collect

demographic information in order to establish the representativeness of the respondents. The questionnaire comprised of a combination of closed and open ended items, including triggers for suspecting codeine misuse, managing codeine dependent patients and reasons for referral. Participants were provided with an opportunity to add additional comments at the end of the questionnaire including knowledge of innovations on preventing medicine misuse.

Data Analysis

Data analysis was conducted using SPSS version 21. Data were downloaded directly from the online data capture page and data were screened and checked for errors. Data were then examined descriptively using frequency and percentage. Suspected occurrence of dependence problems as identified by participants were calculated using median scores and were computed as a rate using the numbers of patients per 100 consultations per average month. Referrals were calculated and presented as an overall percentage of participants' referrals to secondary care.

The open-ended questions were downloaded into a separate Excel® sheet. Content was examined and then coded by one researcher into broad themes. The themes were discussed by the research team and categories were applied for the next level of coding. Three researchers independently coded the data (two academics and one pharmacist). Inter-coder reliability of the data was conducted by dialogue between three members of the research team. Each item was checked for both agreement and non-agreement with the thematic categories. Where discrepancies were identified or non-agreement with the coding the researchers discussed the content. This was then resolved when two or more researchers were in agreement. Data were presented as an overall percentage of those who responded to the questions.

RESULTS

Three hundred medical professionals involved in prescribing codeine were recruited to the study. Table 1 details the demographic information. The mean age of participants was 47 years (25-68). The average years of practice were 19.52 years (1-48).

Table 1 – Demographic details and information pertaining to profession, location and specialist training

	N=300 Frequency (f)	%
Gender		
Male	140	46.7
Female	160	53.3
Profession		
General Practitioner	238	79.3
Independent/Supplementary prescriber	23	7.7
Specialist in family medicine	31	10.3
Specialist in Pain Management	0	0
Other	8	2.7
County		
England		
Wales		
Scotland		
Northern Island		
Location		
Urban	166	55.3
Rural	40	13.3
Mix of both	94	31.3
Specialist training in substance misuse		
Yes	89	29.7
No	208	69.3

Prescribed codeine

Table 2 shows the results for questions examining medical professionals' experiences of prescribing codeine. Frequencies and percentages were used to describe the results of each statement.

Table 2 – Statement items on medical proffesionals' experiences of prescribing codeine.

Statement	Strongly Agree f (%)	Agree f (%)	Neutral f (%)	Disagree f (%)	Strongly Disagree f (%)
I routinely review patients who are prescribed medicines containing codeine	110 (36.7)	130 (43.3)	34 (11.3)	23 (7.7)	1 (0.3)
I believe that patients resent me asking about their use of medicines containing codeine	20 (6.7)	60 (20.0)	71 (23.7)	123 (41.0)	24 (8.0)
I feel awkward about asking patients about their codeine use because they will think I am accusing them of having a problem	3 (1.0)	25 (8.3)	42 (14.0)	168 (56.0)	61 (20.3)
Patients are aware of adverse health consequence associated with high doses of combination codeine preparations	8 (2.7)	57 (19.0)	73 (24.3)	128 (42.7)	33 (11.0)
It is unlikely that prescribed medicines containing codeine are used as recreational drugs	1 (0.3)	26 (8.7)	28 (9.3)	149 (49.7)	96 (32.0)
Patients' requests for prescribed medicines containing codeine is increasing	31 (10.3)	116 (38.7)	82 (27.3)	59 (19.7)	10 (3.3)
I would avoid prescribing medicines containing codeine with other drug groups that also produce a depressant effect on the central nervous system	24 (8.0)	138 (46.0)	82 (27.3)	47 (15.7)	7 (2.3)
I would generally prescribe medicines containing codeine following unsuccessful treatment with non-opioid analgesics	43 (14.3)	204 (68.0)	24 (8.0)	23 (7.7)	4 (1.3)
I would generally prescribe codeine linctus following unsuccessful treatment of cough with non-codeine containing cough suppressants	7 (2.3)	31 (10.3)	42 (14.0)	110 (36.7)	110 (36.7)
Doses of less than 30mg of codeine phosphate (compounded or uncompounded) are not very effective for treating mild to moderate pain	8 (2.7)	51 (17.0)	36 (12.0)	173 (57.7)	32 (10.7)

Fifty percent of participants showed some level of agreement that the requests for prescribed codeine was increasing. In relation to prescribing practices, 54% of participants implied that they avoided the prescribing of codeine with other depressant drugs. Eighty two percent of participants agreed to some extent that they prescribed codeine following unsuccessful treatment with non-opioid analgesics. Only 12.6% of participants agreed to prescribe codeine cough linctus following unsuccessful treatment of cough with non-codeine based medicine. One third of participants agreed that low doses of codeine, less than 30mg, are not effective in treating mild to moderate pain. Eighty percent of professionals agreed to routinely reviewing patients who are prescribed codeine. One quarter experienced patient resentment when asking about medicines containing codeine (26.7%). However, most professionals disagreed with the statement in respect to 'feeling awkward' around questioning patients about their codeine use (76.6%). Furthermore, over half showed a level of disagreement (53.7%) with the statement "patients are aware of the adverse health consequences of high dose of combination codeine medicines". Participants recognised the potential for codeine to be used recreationally.

Over the counter codeine

Seventy six percent of those responding to the questionnaire were found to routinely ask about patients' use of OTC codeine medicine, and 71% indicated that they documented the use of OTC medicines in the patients' medical notes. Concern about availability of OTC codeine in pharmacies was recorded at 45.8%. Concern about the availability of OTC codeine on the internet slightly higher a 64%. However, the vast majority of practitioners agreed to some extent that the potential to buy codeine from multiple sources added significantly to the potential for misuse (86.9%). Thirty five percent showed some level of agreement that medicines containing codeine should be regulated to a prescription only medicine. Sixteen

percentage of participants felt that patient were given sufficient information and there was agreement that patients were not fully aware of the risks of dependence with consumption of OTC codeine medicines (83.8%) and believed them to be safe (86.3%). Only 23% of practitioners agreed (or strongly agreed) that codeine was more effective than non-opioid analgesics. The potential to extract codeine from compounded formulation showed mixed levels of agreement (see also table 3 below).

Table 3 – Statement items for OTC codeine

Statement	Strongly Agree f (%)	Agree f (%)	Neutral f (%)	Disagree f (%)	Strongly Disagree f (%)
I routinely ask patients about their use of over the counter medicines	63 (21.1)	164(54.8)	24 (8.0)	46 (15.4)	2 (0.7)
I document the use of over the counter medicine in a patient's medical notes	53(17.8)	159(53.5)	41(13.8)	39(13.1)	5(1.7)
I am concerned about the availability of over the counter medicines containing codeine in pharmacies	38(12.8)	98(33.0)	84(28.0)	74(24.9)	3(1.0)
The availability of medicines containing codeine on the internet is a growing concern for the medical profession	61(20.5)	129(43.3)	89(30.0)	12(4.0)	6(2.0)
The potential to buy medicines containing codeine from multiple sources adds significantly to the potential for misuse	108(36.2)	151(50.7)	25(8.4)	11(3.7)	3(1.0)
Patients are given sufficient information on use of over the counter medicines containing codeine	7(2.3)	41(13.7)	108(36.0)	105(35.0)	36(12.0)
Medicines containing codeine should be regulated to a prescription only medicine (POM)	27(9.1)	78(26.4)	83(28)	96(32.4)	12(4.0)
Over the counter medicines containing codeine give patients better choice for pain relief	10(3.4)	171(57.6)	69(23.2)	40(13.5)	7(2.4)
Over the counter mixtures containing codeine gives patients better choice for treating cough	2(0.7)	53(17.8)	70(23.6)	111(37.0)	61(20.5)
Over the counter medicines containing codeine are more effective than non-opioid analgesics such as paracetamol and ibuprofen in treating mild to moderate pain	4(1.3)	64(21.3)	81(27.1)	184(46.3)	18(6.0)
The potential for misuse of over the counter medicines containing codeine is minimal	2(0.7)	19(6.4)	38(12.8)	166(55.7)	73(24.5)
Over the counter medicines containing codeine have greater potential for inappropriate use compared to prescribed medicines containing codeine	22(7.4)	93(31.2)	61(20.5)	111(37.2)	11(3.7)
Codeine is easily extracted from compounded formulations (e.g. Cocodamol) increasing its abuse potential	6(2.0)	37(12.5)	198(66.9)	48(16.2)	2(0.5)
It is likely that over the counter codeine medicines could be used as recreational drugs	42(14%)	175(58.9)	49(16.5)	27(9.1)	4(1.3)
Codeine misuse is as serious a problem to society as misuse of stronger opioids	28(9.4)	119(39.9)	88(29.5)	54(18.1)	9(3.0)
Patients do not fully understand the risk of dependence in taking over the counter medicines containing codeine	63(21.2)	186(62.6)	35(11.8)	13(4.4)	0
Patients believe that over the counter medicines containing codeine are safe	55(18.5)	202(67.8)	35(11.7)	5(1.7)	1(0.3)

Dependence, screening and treatment

Table 4 shows responses to the various items for, dependence, screening and treatment.

Disagreement with the view that patients were not at risk of codeine dependence from

prescribed medication use was indicated by 83.3% of respondents. The majority agreed to some extent that patients did not fully understand the risk of dependence when taking prescribed medicine containing codeine (82%). Over 40% agreed difficulty in identification of problematic use of codeine without being informed by the patient. This corresponded with relatively high percentages of those who did not feel confident in identification of codeine dependence. 70% indicated that they would like further instruction on prescribing potentially addictive medicines. When asked if women were at higher risk of development of codeine dependence only 20.8% agreed. Forty five percent of all participants agreed that codeine dependence could be managed effectively in general practice with 27% agreeing to have adequate services in place to manage codeine dependent patients.

Table 4 – Statement items for codeine dependence, screening and treatment

Statement	Strongly Agree f (%)	Agree f (%)	Neutral f (%)	Disagree f (%)	Strongly Disagree f (%)
Patients who take their codeine medication as prescribed are not at risk of developing a codeine dependence	5 (1.7)	20 (6.7)	25 (8.4)	194 (64.9)	55 (18.4)
Patients do not fully understand the risk of dependence when taking prescribed medicines containing codeine	45 (15.1)	200 (66.9)	33 (11.0)	17 (5.7)	4 (1.3)
I find it difficult to identify problematic use of medicines containing codeine (including OTCs) without the patient first telling me	11 (3.7)	115 (38.5)	64 (21.4)	99 (33.1)	10 (3.3)
I am confident that I can identify codeine dependence in my patients	6 (2.0)	75 (25.1)	95 (31.8)	116 (38.8)	7 (2.3)
Females are at higher risk of developing a codeine dependence than their male counterparts	8 (2.7)	54 (18.1)	188 (62.9)	47 (15.7)	2 (0.7)
Codeine dependence can be managed effectively in general practice	15 (5.0)	119 (39.8)	92 (30.8)	64 (21.4)	9 (3.0)
I have suitable screening methods that I use to identify inappropriate use of medicines containing codeine	6 (2.0)	59 (19.8)	61 (20.5)	151 (50.7)	21 (7.0)
Support services are readily available in my area to help those with a codeine dependence problem	10 (3.4)	73 (24.5)	47 (15.8)	117 (39.3)	51 (17.1)
I am fully aware of best practice in managing codeine misuse and dependence	14 (4.7)	67 (22.6)	81 (27.3)	126 (42.4)	9 (3.0)
I would like more instruction on prescribing potentially addictive medications	47 (15.8)	162 (54.5)	66 (22.2)	21 (7.1)	1 (0.3)

Managing codeine dependence

The median number of patients suspected of being codeine dependent was calculated as being three patients per 100 consultations. Only 13.6% of participants did not suspect any cases of codeine dependence. 73% of participants indicated that they had not made any referral to secondary care for codeine dependence. Where referrals were indicated, the median number was one patient per month.

Patient behaviours, treatment options and referral reasons

Practitioners were asked to describe the typical patient behaviours triggering their suspicion of codeine misuse. Figure 1 shows thematic categories of indicators of codeine dependence displayed as a total percentage of those who responded. Patient behaviours that triggered suspicion of codeine misuse and dependency included requesting codeine specifically by name, early requests and refills and calling the surgery at inappropriate times to request codeine medicines. Lost prescriptions or medicines were also perceived to be an indicator for dependence and practitioners used anecdotes to describe patient situations such as “the dog ate my script” “I lost my medication on the bus” or “on holiday”. Unresolved pain was indicated as a further trigger in suspicion of dependence and situations of hypersensitivity to pain were described in terms of headache, inadequate pain relief and indications of chronic pain not being helped by the current medication regime. Aberrant behaviours were described and included aggression, demanding codeine, reluctance to change medication and becoming very keen to obtain a script. Physical signs of misuse included restricted pupils, anxiety, constipation, gastric disturbances and irritability. Other indicators included history of co-morbidity and history of additions. Some professionals also mentioned social and economic factors including taking excessive sick leave and unemployment. The person’s gender was indicated as trigger for a minority of respondents but was principally identified as female.

Various treatments for codeine dependence were described by practitioners (see figure 2). A large proportion of respondents mentioned slow or gradual withdrawal as the suggested treatment in managing dependence. Education and counselling was also emphasised and was more often suggested with gradual withdrawal and restricted prescriptions. Restricted prescriptions were described in terms of giving limited amounts of codeine in doses of up to three days or a one week supply. Other suggested treatments include substitution using non-opioid analgesics, substitution with other drugs including amitriptyline and benzodiazepines, other opiates, methadone and buprenorphine. Some respondents indicated that the main treatment they used was 'cold turkey'. Referral to specialist care was also indicated including, drug and alcohol services, rehabilitation centres, psychologists, psychiatrists and pain specialists.

The primary reasons for referral are reported in Figure 1 and were indicated as the inability to manage the patient effectively in primary care or that the patient was a complex case requiring specialist care. Complex cases were described as those with multiple issues including other drugs and alcohol misuse, pregnant patients and other co-morbidities, usually related to mental health. Patient's request to be referred for specialist treatment was also a common response. Indications were also that referrals to specialist care were as a result of the lack of resources, or time during the consultation and lack of knowledge with regard to best practice.

Additional comments related to codeine use, misuse and dependence were expressed by participants. Many respondents spoke of codeine as a problem in society and something that required significant attention.

> *"It is very difficult to control patients' codeine use as they may use multiple pharmacies, buy from friends or online. I don't think we have fully woken up to the*

scale of the problem of opiate dependence. Especially when opiates are prescribed by pain clinics for chronic, non-cancer pain". (GP participant)

"Have advised colleagues many times that this is a time-bomb (not wishing to be melodramatic!) If evidence is promoted or the Daily Mail decides to champion a codeine scare we will be on the back-foot managing the fall-out and patient distress". (GP participant)

Some expressed their views on codeine in terms of other drug and poly-substance misuse problems:

"Whilst codeine is misused, I am more concerned with heroin and cocaine misuse". (GP participant)

"We also have big problems with dihydrocodeine, oxycodone, tramadol, pregabalin and gabapentin". (GP participant)

Popular comments raised by participants related to its availability from pharmacies and multiple sources and on repeat dispensing. Some suggested the introduction of national databases for dispensing, the role of advertising, and efforts to control repeat prescribing;

"We worry about codeine abuse, etc., yet Solpadeine is very heavily advertised, but it does serve a purpose in self-medication for moderate pain. In my experience patients are started too early on high strength codeine painkillers and simply parked there via repeat prescriptions. Little effort seems to be given to follow up and monitoring usage before the patient becomes addicted to the codeine as opposed to suffering pain". (GP participant)

"Big problem. We struggle to monitor repeat prescriptions closely enough. Hospital hand out codeine and tramadol like smarties. Difficult to know how best to tackle

OTC access as primary care does not have the capacity to pick up seeing all those people who self-treat appropriately with OTC meds". (GP participant)

Several comments were also made about the area of practitioner training in managing misuse problems.

"It would be helpful to have some teaching on misuse of OTC products and management there of". (GP participant,)

Concerns were expressed with patient knowledge of codeine containing medication and the requirements for patient education, especially in relation to toxicity from combination preparations.

"I am very concerned about the number of people I see who take products containing a combination of codeine and paracetamol at levels that put them at high risk of liver damage as they often do not realise that taking large amounts for the psychoactive effects of the codeine means that they are likely to be unintentionally overdosing on the paracetamol". (GP participant)

Some additional comments were made related to the requirement to share information across sectors and to obtain information on OTC product sales in pharmacies and the lack of resources available to manage problem of codeine dependence.

"There is a gap between practicing perfect medicine where patients' drug use is explored in depth and the practicalities of managing time and workload. I feel that to a certain extent, exploring drug misuse in patients who are pre-contemplative is not necessarily the most effective use of time (although of course would be done in an ideal world)". (GP participant)

DISCUSSION

The current study exhibited high levels of agreement that patients' prescribed codeine were routinely reviewed by their medical professional. Half of all those who responded felt that the request for codeine medicines was increasing and is substantial in raising some concern. The increasing requests for codeine may be directly as a result of newer restrictions imposed on OTC supply, forcing patients to obtain a steady source on prescription.(21) While there is no specific evidence to verify this, a level of caution should be exercised by the prescriber when a medicine is requested specifically by name. Content analysis of the open ended questions showed that one of the most common triggers for suspecting misuse was when codeine was requested specifically by its name or brand name.

Views regarding the effectiveness of 30mg of codeine showed some notable variation. The efficacy of low doses of codeine is not well documented in the literature and a greater evidence base is required to further develop indications for codeine use.(22) Codeine appeared used in response to unsuccessful treatment with non-opioid analgesics. However, the complexity of pain management has drawn significant attention over recent years with limited options for prescribers to avoid unpleasant side effects.(23, 24) Newer drugs acting at the GABA receptors have gathered some momentum in the treatment of chronic neuropathic pain; however, they also carry significant side effects and serious risk of misuse.(25) The difficulty for any prescriber is to balance these risks and it is feasible that codeine is considered to have lower abuse liability due to its weak opioid status.(26)

There is concern regarding patients' use of OTC codeine containing medicine and a large number of respondents in the current study believe that patients were unaware of the health consequences associated with high doses of combination codeine preparations. Equally, the respondents were of the view that patients do not understand the risk of dependence when taking prescribed medicines containing codeine. This concurs with evidence reported in the

literature.(27, 28) Further research should identify the level and type of information patients require to make informed decisions surrounding their medicine use both prescribed and over the counter. Rescheduling of codeine has drawn significant debate and some suggestion was made in the current study to remove sales of OTC codeine altogether (24). However, without actual prevalence rates of misuse and harm, it is difficult to draw definitive conclusions. Additionally, several countries across the EU do not permit the sale of OTC codeine (25) and there is little evidence that restricting this provision has any impact on harms associated with its use. The rescheduling to a prescription only medicine is likely to place additional pressure of GPs for self-limiting conditions and shift diversionary patterns.

Risk of development of a codeine dependence in spite of taking codeine as prescribed was identified by the majority of professionals in the UK and shows that prescribers are aware of potential risks associated with its use. Detection of codeine dependence in patients appears to be problematic, with low levels of confidence expressed in detection of codeine dependence, highlighting the need for specific screening tools.(29) Equally, adequate screening tools for identification of patient at risk appears lacking in practice and practitioners indicated the desire for further training activities on prescribing potentially addictive medicines. Education of professionals on the abuse potential of codeine and the ability for individuals to extract paracetamol from compounded formulations is also warranted to enhance existing knowledge.

In the current study an overwhelming majority of respondents indicated that they used the process of gradual withdrawal including tapering of the dose, restricting and reducing patients' prescriptions coupled with education and counselling techniques as strategies to address misuse of and dependence on codeine. This may well be the foundation on which to build some guidance for prescribers and pharmacists in managing detoxification, however, taking into consideration that each patient will have their own individual needs. Due to the

fact that several of the prescribers mentioned the toxicity associated with paracetamol and ibuprofen, initial treatment to reduce this risk should be the first consideration.(11) The education and counselling offered and expressed by professionals in the open ended questions could be further evaluated for its content, applicability and effectiveness in the treatment process.

Levels of referral to secondary care appear low and reflect the levels of patients entering addiction treatment indicated by the National Drug Treatment Monitoring Service,(18) and may indicate that a high proportion of patients are being effectively managed in primary care, or more seriously, not being detected at all. If this is the case then actual prevalence rates of misuse are under reported in the national figures. The reporting of codeine misuse by general practice outside of secondary care may actually help in the estimation and prevalence of not only codeine, but also other substances of misuse in populations who remain outside of addiction services. Professionals in the current study identified a lack of support services for those identified with problems related to their codeine use. The acknowledgement of poor support requires further investigation in the context of the development of adequate services for patients within primary care, community and inpatient settings.

LIMITATIONS

There are several limitations with respect to this study. The recruitment of participants to this online survey was challenging and therefore resulted in a lower than expected response rate The study is cross-sectional in nature and therefore cannot describe how the situation might change over time. It is also feasible that those experiencing problem with codeine dependence in their practice may have been more likely to participate in the study. However, the study responds to the increasing demand for greater information regarding codeine misuse and dependence found in the UK.

IMPLICATIONS FOR PRACTICE

Greater sources of information are required to develop policy on codeine use, misuse and treatment options in the interest of public health. This study has shed light on medical professional's experiences in the UK and has highlighted areas of concern regarding medicines containing codeine and the need to develop specific patient screening tools. It is important to note that medicines containing codeine have utility when used appropriately, however greater research is required to examine its' indications for use in longer term pain management. Further education and training is required in the area of prescribing addictive medicines at all levels of practice. Similarly specialist training on recognition of the signs and symptoms drawing from the responses of professionals in this study could help with early detection of codeine dependence. The reporting of cases of codeine dependency outside of addiction services into national registers should be considered. It is important to identify as accurately as possible the prevalence of codeine misuse and dependence in the population so that services can be adequately provided and needs addressed appropriately.

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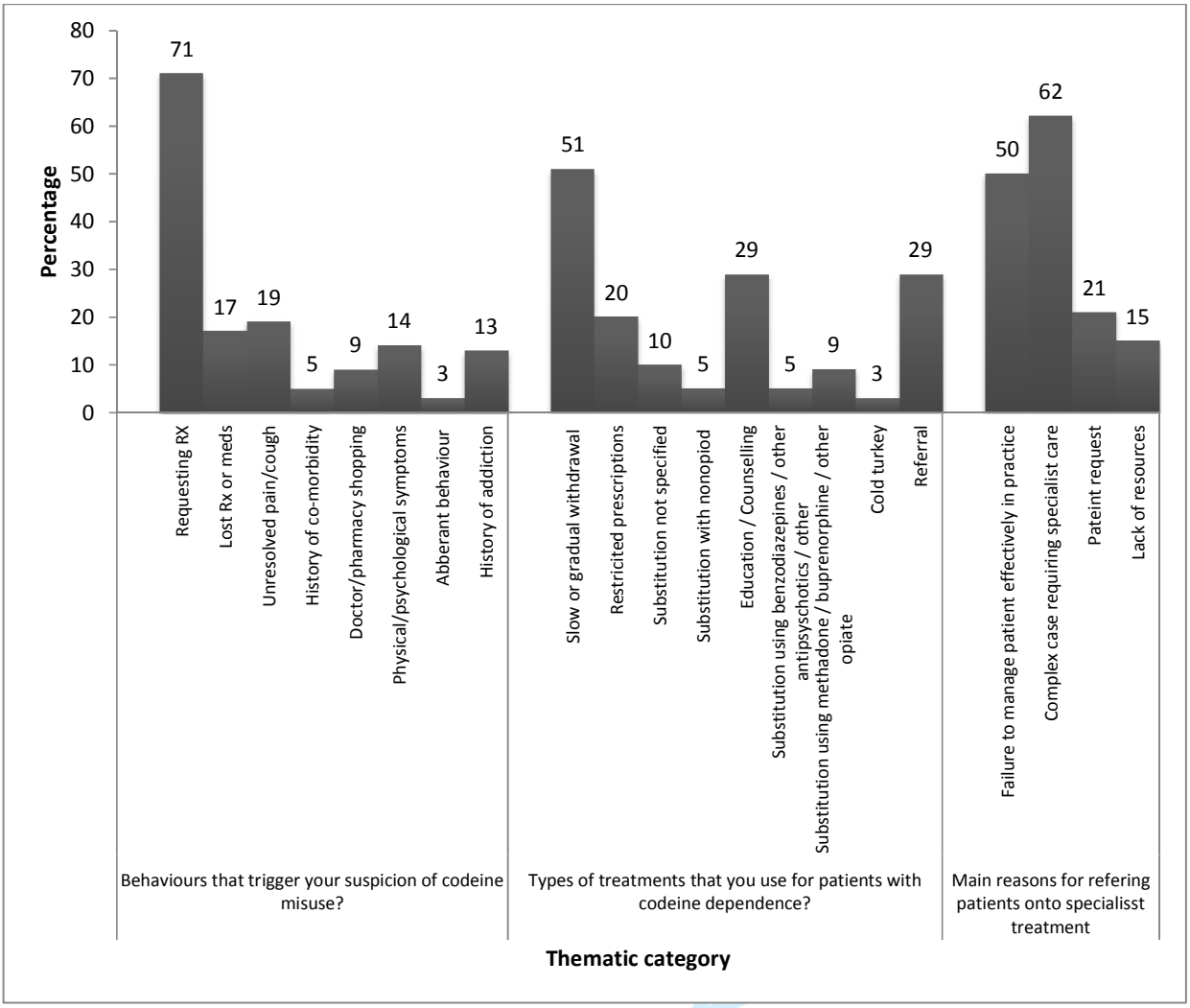
Figure 1 – showing thematic categories from open-ended questions



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Medical professionals' perspectives on prescribed and over the counter medicines containing codeine: A cross-sectional study

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Title: - Medical professionals' perspectives on prescribed and over the counter medicines containing codeine: A cross-sectional study

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ABSTRACT

Objectives:

To explore prescribing practitioners' perspectives on prescribed codeine use, their ability to identify dependence and their options for treatment in the United Kingdom.

Design:

Cross sectional design using a questionnaire containing closed and open ended items.

Setting:

A nationally representative sample of prescribing professionals working in the United Kingdom

Participants:

Three hundred prescribing professionals working in primary care and pain settings.

Results:

Participants stated that they regularly reviewed patients prescribed codeine, understood the risks of dependence and recognised the potential for codeine to be used recreationally. Over half the participants felt patients were unaware of the adverse health consequences of high doses of combination codeine medicines. One quarter of participants experienced patient resentment when asking about medicines containing codeine. Just under 40% of participants agreed that it was difficult to identify problematic use of codeine without being informed by the patient and did not feel confident in identification of codeine dependence. Less than 45% of all participants agreed that codeine dependence could be managed effectively in general practice. Slow or gradual withdrawal was the most popular suggested treatment in managing

dependence. Education and counselling was also emphasised in managing codeine dependant patients in primary care.

Conclusions:

Communication with patients should involve assessment of patient understanding of their medication, including risk of dependence. There is a need to develop extra supports for professionals including patient screening tools for identifying codeine dependence. The support structure for managing codeine dependant patients in primary care requires further examination.

Article Summary

- This is the first study examining medical professionals perceptions of medicines containing codeine across the UK
- The study used a questionnaire design with closed and open ended items relating to both prescribed and over the counter medicines containing codeine and included questions on dependence and treatment options in practice
- Professionals involved in the prescribing of codeine were accessed across the UK using the principles of stratified random sampling
- Reponses rates were lower than expected and the study was unable to access the full population of nurse prescribers
- This study is cross-sectional and therefore does not describe how the situation might change over time

INTRODUCTION

Pain is a common reason for accessing primary care services. It is estimated that 14 million people in the United Kingdom (UK) suffer from long term pain,(1) with patients complaining of headaches thought to account for one in twenty five of primary care consultations,(2) and musculoskeletal pain accounting for one in seven.(3) Opioids are widely used in pain management with codeine being the second most widely prescribed opioid medicine in general practice.(4) In 2012, it was estimated that 640 codeine prescriptions per 1000 patients were dispensed in the UK.(5) Additionally, medicines containing codeine can be purchased over the counter (OTC) in pharmacies albeit with restrictions (6). Medicines containing codeine (up to 12.8mg per unit dose) may only be sold in the UK under the supervision of a qualified pharmacist. There are restrictions on the quantity of tablets permitted for sale in a single transaction and the product is not available for self-selection, although advertising of codeine containing medicines are permitted both in the pharmacy and on national media. A sale may be refused if there is suspicion that the buyer is misusing codeine. Currently, the nature and extent of OTC codeine use and misuse in the UK is not widely reported.

Treatment with opioid medication is thought to be effective in the treatment of non-cancer pain for acute and short periods of less than six months.(7) Current scientific evidence measuring the efficacy of codeine over other alternative medications for chronic and longer term pain remains inconclusive.(8) There are limited studies examining the efficacy of low doses of codeine found in many prescribed and OTC medicines (less than 12.8mg per unit dose). While several Cochrane reviews have evaluated the efficacy of codeine, these are principally confined to acute postoperative pain at high doses (60mg). Some studies show codeine as clinically useful in some patients, but only 10% of patients reported to achieve

effective pain relief with codeine when compared to those having the same dose of paracetamol alone. Although codeine was found to extend the duration of analgesia by approximately one hour.(9) A recent Cochrane review found that the combination of ibuprofen 400mg plus codeine 25.6mg to 60mg demonstrated effective analgesic efficacy in post-operative pain, however very limited data suggests that the combination is better than the same dose of either drug alone.(10) Equally, the use of codeine containing syrups in supressing cough appears to lack positive scientific basis and is not widely discussed in the current literature.

Whilst codeine is considered a weak opiate, it carries an identified abuse potential. Development of tolerance on regular or excessive use appears within a short timeframe.(11) Literature reports increasing trends in the misuse use of codeine, including over the counter preparations, which appears to incur significant negative epidemiologic, social and economic consequences.(12-16) Related harms in terms of morbidity and mortality are documented,(12) along with monetary costs associated with indirect effects on healthcare, prevention and treatment.(17)

Treatment of codeine dependence is varied and does not appear to be well documented in the literature. Guidance on options for opioid dependence is evident but appears non-specific to weak opioids such as codeine. Summary statistics for codeine dependence obtained from treatment providers in the UK, suggest that codeine as the primary substance of misuse is extremely low.(18) These statistics may give an impression that codeine dependence is not an issue warranting attention compared to other substances of misuse; however treatment for codeine dependence conducted in primary care does not appear in national treatment surveillance systems. What is of particular concern is that codeine dependent patients appear to function well within the range of perceived normality, carrying out the functions of normal daily living.(19) Evaluating as to whether medical professionals are equipped to detect and

manage patients presenting with codeine dependence is therefore an area of considerable importance.

Studies have called for further research on the experiences and concerns of medical professionals around use of medicines containing codeine, with particular focus on their experiences, challenges, perspectives and practices.(20) The aim of the study was to garner information regarding prescribing practitioners' perspectives on prescribed and OTC codeine use, their ability to identify dependence and options for treatment in the UK. This study was part of a larger study examining both OTC and prescribed misuse of codeine medicines in the Republic of Ireland, UK and South Africa and was funded by the European Commission (www.codemisused.org).

METHOD

Recruitment of participants and study procedures

The study involved a cross-sectional design and took place between May 2014 and April 2015 using an online questionnaire. A nationally representative sample of medical practitioners in the UK was facilitated through Specialist Info, a medical directory specialist. A random list of 1000 practice managers was generated by strata using proportionate numbers of GPs present in each county (Wales n=48, Northern Ireland n=36, Scotland n=98, England n=818). Each practice manager was asked to recruit at least one GP from their respective practice to participate in the study. Each practice manager was sent a reminder approximately two to four weeks later. 150 Pain Specialist e-mail records were also retrieved from Specialist Info and these were subsequently sent the link to the survey. In order to have representation from Pain Specialist Nurses, a previous distribution list was utilised (21). These participants were asked to indicate their agreement to be added to the e-mail distribution list. 54 agreed to participate and the link to the survey was then provided. In total

this process resulted in 136 participants completing the online questionnaire. A further 65 GPs were recruited through GP target sessions. A second random sample of 1000 practice managers was generated checked for duplicates and e-mailed as previously described. A follow up reminder was distributed four to six weeks later. This resulted in the completion of a further 98 questionnaires. The indicated time to complete the questionnaire was approximately 10 minutes and this was specified in the e-mail correspondence and prior to proceeding with the questionnaire. Information on the study was provided and informed consent was obtained prior to proceeding online. Participants were advised to complete the questionnaire only once. Dissemination activities, including circulars and newsletters were used to encourage participation in the study. Ethical approval was granted by King's College London Ethics Committee (PNM/13/14-75).

Data collection methods

We collected the data using an online questionnaire using the survey tool www.onlinesurveys.ac.uk. Questions were developed to bridge gaps in knowledge following a comprehensive search of the literature.(4) Eight questions were added to collect demographic information in order to establish the representativeness of the respondents. The questionnaire comprised of a combination of closed and open ended items, on prescribed and over the counter medicines containing codeine and included questions on triggers for suspecting codeine misuse, managing codeine dependent patients and reasons for referral. Participants were provided with an opportunity to add additional comments at the end of the questionnaire and knowledge of innovations on preventing medicine misuse (see supplementary information for full details of questionnaire).

Data Analysis

Data were downloaded directly from the online data capture page to SPSS version 21. Data were screened and checked for errors. Data were then examined descriptively using

frequencies and percentage. The data was summarised to create two categories by combining levels of agreement and disagreement for reporting purposes. The occurrence of codeine dependence was estimated using the approximate numbers of patients suspected of having codeine dependence as indicated in the questionnaire divided by the number of consultations indicated by professionals in an average month. Referrals were estimated using the numbers indicated by participants in the questionnaire and this figure was presented as an overall percentage of the total number of participants' referrals to secondary care for codeine dependence.

The open-ended questions were downloaded into a separate Excel® sheet for content analysis. This data was examined and individual categories were created for each of the open-ended questions based on common features and dominant subjects identified in the text. The categories were discussed by two senior members of the research team and agreed. Three researchers independently coded the data (two academic researchers and one pharmacist). This was achieved by labelling each field where the content matched the associated thematic category. Inter-coder reliability of the data was conducted by dialogue between three members of the research team. Each item was checked for both agreement and non-agreement with the thematic categories. Where discrepancies were identified or disagreement with the category placing occurred the researchers discussed the illustrated content. This was then resolved when two or more researchers were in agreement. Data were presented as an overall percentage of those who responded to the open-ended questions.

RESULTS

Three hundred medical professionals involved in prescribing codeine were recruited to the study, giving an overall response rate of approximately 12.5%. Table 1 details the

demographic information. The mean age of participants was 47 years (Range = 25-68 years). The average years of practice were 19.52 years (Range = 1-48 years).

Table 1 -Demographic details and information pertaining to profession, location and specialist training

	N=300 Frequency (f)	%
Gender		
Male	140	46.7
Female	160	53.3
Profession		
General Practitioner	238	79.3
Independent/Supplementary /Nurse prescriber[1]	23	7.7
Specialist in family medicine	31	10.3
Specialist in Pain Management	0	0
Other	8	2.7
County		
England	253	84.6
Wales	15	5.0
Scotland	23	7.7
Northern Island	9	2.7
Location		
Urban	166	55.3
Rural	40	13.3
Mix of both	94	31.3
Specialist training in substance misuse		
Yes	89	29.7
No	208	69.3

[1] Currently nurses, pharmacists, optometrists, physiotherapists, chiropodists or podiatrists, radiographers and community practitioners may undertake further professional training to qualify as non-medical prescribers. Independent prescribers are responsible and accountable for the assessment of patients with undiagnosed and diagnosed conditions and for decisions about the clinical management required, including prescribing.
Supplementary prescribers may prescribe any medicine (including controlled drugs), within the framework of a patient-specific clinical management plan, which has been agreed with a doctor. Nurses, pharmacists, physiotherapists, chiropodists or podiatrists, radiographers and optometrists may train and register as a supplementary prescriber.

Prescribed codeine

Figure 1 illustrates statement items examining medical professionals' experiences of prescribing codeine. Percentage agreement and disagreement were used to describe the results. Fifty percent of participants showed some level of agreement that the requests for prescribed codeine was increasing. In relation to prescribing practices, 54% of participants implied that they avoided the prescribing of codeine with other depressant drugs. Eighty two percent of participants agreed to some extent that they prescribed codeine following unsuccessful treatment with non-opioid analgesics. Only 12.6% of participants agreed to prescribe codeine cough linctus following unsuccessful treatment of cough with non-codeine based medicine. One third of participants agreed that low doses of codeine, less than 30mg, are not effective in treating mild to moderate pain. Eighty percent of professionals agreed to routinely reviewing patients who are prescribed codeine. Twenty seven percent of those responding believed that patients resented them for asking about their use of medicines containing codeine. However, most professionals disagreed with the statement in respect to 'feeling awkward' around questioning patients about their codeine use (76.6%).Furthermore, over half showed a level of disagreement (53.7%) with the statement "patients are aware of the adverse health consequences of high dose of combination codeine medicines". Participants recognised the potential for codeine to be used recreationally.

Over the counter codeine

Figure 2 shows statement items examining medical professionals' experiences of over the counter codeine. Percentage agreement and disagreement were used to describe the results. Seventy six percent of those responding to the questionnaire were found to routinely ask about patients' use of OTC codeine medicine, and 71% indicated that they documented the use of OTC medicines in the patients' medical notes. Concern about availability of OTC

codeine in pharmacies was recorded at 45.8%. Concern about the availability of OTC codeine available on the internet was slightly higher at 64%. However, the vast majority of practitioners agreed to some extent that the potential to buy codeine from multiple sources added significantly to the potential for misuse (86.9%). Thirty five percent showed some level of agreement that medicines containing codeine should be regulated to a prescription only medicine. Sixteen percentage of participants felt that patient were given sufficient information and there was agreement that patients were not fully aware of the risks of dependence with consumption of OTC codeine medicines (83.8%) and believed them to be safe (86.3%). Only 23% of practitioners agreed (or strongly agreed) that codeine was more effective than non-opioid analgesics. The potential to extract codeine from compounded formulation showed mixed levels of agreement.

Dependence, screening and treatment

Figure 3 shows responses to the various statement items examining codeine dependence. Only 8% of participants agreed that patients were not at risk of codeine dependence when they took their codeine medicine as prescribed. The majority agreed to some extent that patients did not fully understand the risk of dependence when taking prescribed medicine containing codeine (82%). Over 40% agreed difficulty in identification of problematic use of codeine without being informed by the patient. This corresponded with relatively high percentages of those who did not feel confident in identification of codeine dependence. When asked if women were at higher risk of development of codeine dependence only 20.8% agreed. Forty five percent of all participants agreed that codeine dependence could be managed effectively in general practice.

21% of participants agreed to have suitable screening methods to identify if codeine was being used inappropriately. 27% of participants agreed that adequate services in place to manage codeine dependent patients. While only 28% agreed to be fully aware of best

practice in managing codeine misuse and dependence. A high proportion of participants, (70.3%) would like more instruction on the prescribing of potentially addictive medicines.

Managing codeine dependence

The median number of patients suspected of being codeine dependent was calculated as being three patients per 100 consultations. Only 13.6% of participants did not suspect any cases of codeine dependence. When asked if they had referred a patient to specialist care for codeine dependence, 73% of participants indicated that they had not made any referrals to secondary/specialist care. Where referrals were indicated, the median number was one patient in a monthly period.

Patient behaviours, treatment options and referral reasons

Practitioners were asked to describe the typical patient behaviours triggering their suspicion of codeine misuse. Table 2 shows thematic categories of results displayed as a frequency and as a percentage of the total responses. Patient behaviours that triggered suspicion of codeine misuse and dependency included requesting codeine specifically by name, early requests and refills and calling the surgery at inappropriate times to request codeine medicines. The potential to obtaining codeine from multiple sources was expressed. Additional comments reflected the difficulties in managing patients' codeine use.

> *"It is very difficult to control patients' codeine use as they may use multiple pharmacies, buy from friends or online. I don't think we have fully woken up to the scale of the problem of opiate dependence. Especially when opiates are prescribed by pain clinics for chronic, non-cancer pain".* (GP participant)

> *"Have advised colleagues many times that this is a time-bomb (not wishing to be melodramatic!) If evidence is promoted or the Daily Mail decides to champion a*

codeine scare we will be on the back-foot managing the fall-out and patient distress". (GP participant)

Lost prescriptions or medicines were also perceived to be an indicator for dependence and practitioners used anecdotes to describe patient situations such as *"the dog ate my script" "I lost my medication on the bus" or "on holiday"*. Unresolved pain was indicated as a further trigger in suspicion of dependence and situations of hypersensitivity to pain were described in terms of headache, inadequate pain relief and indications of chronic pain not being helped by the current medication regime. Aberrant behaviours were described and included aggression, demanding codeine, reluctance to change medication and becoming very keen to obtain a script. Physical signs of misuse included restricted pupils, anxiety, constipation, gastric disturbances and irritability. Other indicators included history of co-morbidity and history of addiction. Some professionals also mentioned social and economic factors including taking excessive sick leave and unemployment.

Various treatments for codeine dependence were described by practitioners (see table 2). A large proportion of respondents mentioned slow or gradual withdrawal as the suggested treatment in managing dependence. Education and counselling was also emphasised and was more often suggested with gradual withdrawal and restricted prescriptions. Additional comments were also made about the area of practitioner training in managing misuse and the requirement to improve patient knowledge on codeine consumption.

"It would be helpful to have some teaching on misuse of OTC products and management there of". (GP participant)

"I am very concerned about the number of people I see who take products containing a combination of codeine and paracetamol at levels that put them at high risk of liver damage as they often do not realise that taking large amounts for the psychoactive

effects of the codeine means that they are likely to be unintentionally overdosing on the paracetamol". (GP participant)

Restricted prescriptions were described in terms of giving limited amounts of codeine in doses of up to three days or a one week supply. One GP spoke of the role of advertising and efforts to control repeat prescribing while another also spoke of problems of monitoring of repeat prescriptions.

"*We worry about codeine abuse, etc., yet Solpadeine is very heavily advertised, but it does serve a purpose in self-medication for moderate pain. In my experience patients are started too early on high strength codeine painkillers and simply parked there via repeat prescriptions. Little effort seems to be given to follow up and monitoring usage before the patient becomes addicted to the codeine as opposed to suffering pain".* (GP participant)

"Big problem. We struggle to monitor repeat prescriptions closely enough. Hospitals hand out codeine and tramadol like smarties. Difficult to know how best to tackle OTC access as primary care does not have the capacity to pick up seeing all those people who self-treat appropriately with OTC meds". (GP participant)

Other suggested treatments include substitution using non-opioid analgesics, substitution with other drugs including amitriptyline and benzodiazepines, other opiates, methadone and buprenorphine. Some respondents indicated that the main treatment they used was 'cold turkey'. Referral to specialist care was also indicated including, drug and alcohol services, rehabilitation centres, psychologists, psychiatrists and pain specialists.

The primary reasons for referrals are reported in table 2 and were indicated as the inability to manage the patient effectively in primary care or that the patient was a complex case

requiring specialist care. Complex cases were described as those with multiple issues including other drugs and alcohol misuse, pregnant patients and other co-morbidities, usually related to mental health. Some sentiment was also expressed about other drugs of misuse

> *"Whilst codeine is misused, I am more concerned with heroin and cocaine misuse".* (GP participant)

> *"We also have big problems with dihydrocodeine, oxycodone, tramadol, pregabalin and gabapentin".* (GP participant)

Patient's request to be referred for specialist treatment was also a common response. Indications were also that referrals to specialist care were as a result of the lack of resources, or time during the consultation and lack of knowledge with regard to best practice.

Some additional comments were made related to the lack of resources available to manage problem of codeine dependence.

> *"There is a gap between practicing perfect medicine where patients' drug use is explored in depth and the practicalities of managing time and workload. I feel that to a certain extent, exploring drug misuse in patients who are pre-contemplative is not necessarily the most effective use of time (although of course would be done in an ideal world)".* (GP participant)

Table 2 – Showing main thematic categories and frequency of responses

N=300	Frequency of responses (%)
Can you describe the patient behaviours that trigger your suspicion of codeine misuse?	
Requesting prescriptions for codeine	212 (71)
Aberrant behaviour	89(30)
Unresolved pain/cough	78(19)
Lost prescriptions or medications	52(17)
Physical or psychological symptoms	41(14)
History of addiction	38(13)
Doctor/pharmacy shopping for codeine medicines	28(9)
History of co-morbidity	14(5)
Socio-economic status	14(5)
Sex	3(1)
Can you describe the types of treatments that you use for patients with codeine dependence?	
Slow or gradual withdrawal	153(51)
Education / Counselling	87(29)
Referral to secondary or specialist care	87(29)
Restricted prescriptions	60(20)
Substitution with another drug (drug not specified)	30(10)
Substitution using methadone / buprenorphine / other opiate drug	27(9)
Substitution with non-opioid medication	15(5)
Substitution using benzodiazepines / other antipsychotics / other	15(5)
Cold turkey	9(3)
What were the main reasons for referring patients onto specialist treatment?	
Failure to manage patient effectively in practice	150(50)
Complex case requiring specialist care	186(62)
Patient request for referral	63(21)
Lack of resources	45(15)

DISCUSSION

The current study exhibited high levels of agreement that patients' prescribed codeine were routinely reviewed by their medical professional and included questioning around OTC codeine use. Half of all those who responded felt that the request for codeine medicines was increasing and is substantial in raising some concern. The increasing requests for codeine may be directly as a result of newer restrictions imposed on OTC supply, forcing patients to obtain a steady source on prescription.(21) Other factors contributing to the perceived increase in codeine requests may relate to changes in scheduling of other prescription opioids such as Tramadol (22). In the UK, Tramadol must only be supplied in quantities that do not exceed 30 days and must not be dispended on 'batch' repeat prescriptions, making refills more difficult to obtain. Codeine is currently not bound by these restrictions. While there is no specific evidence to verify that codeine consumption is increasing, a level of caution should be exercised by the prescriber when a medicine is requested specifically by name. Content analysis of the open ended questions showed that one of the most common triggers for suspecting misuse was when codeine was requested specifically by its name or brand name.

Views regarding the effectiveness of 30mg of codeine showed some notable variation. The efficacy of low doses of codeine is not well documented in the literature and a greater evidence base is required to further develop indications for codeine use.(23) Codeine appeared used in response to unsuccessful treatment with non-opioid analgesics. However, the complexity of pain management has drawn significant attention over recent years with limited options for prescribers to avoid unpleasant side effects.(24, 25) Newer drugs acting at the GABA receptors have gathered some momentum in the treatment of chronic neuropathic pain; however, they also carry significant side effects and serious risk of misuse.(26) The

difficulty for any prescriber is to balance these risks and it is feasible that codeine is considered to have lower abuse liability due to its weak opioid status.(27)

There is concern regarding patients' use of OTC codeine containing medicine and a large number of respondents in the current study believe that patients were unaware of the health consequences associated with high doses of combination codeine preparations. Equally, the respondents were of the view that patients do not understand the risk of dependence when taking prescribed medicines containing codeine. This concurs with evidence reported in the literature.(28, 29) Further research should identify the level and type of information patients require to make informed decisions surrounding their medicine use both prescribed and over the counter. Rescheduling of codeine has drawn significant debate and some suggestion was made in the current study to remove sales of OTC codeine altogether (24). However, without actual prevalence rates of misuse and harm, it is difficult to draw definitive conclusions. Equally, other prescription opioids, including codeine, are also misused so removal of OTC codeine is unlikely to eliminate the problem entirely. Additionally, several countries across the EU do not permit the sale of OTC codeine (25) and there is little evidence that restricting this provision has any impact on harms associated with its use. The rescheduling to a prescription only medicine is likely to place additional pressure of GPs for self-limiting conditions and shift diversionary patterns.

Risk of development of a codeine dependence in spite of taking codeine as prescribed was identified by the majority of professionals in the UK and shows that prescribers are aware of potential risks associated with its use. Detection of codeine dependence in patients appears to be problematic, with low levels of confidence expressed in detection of codeine dependence, highlighting the need for specific screening tools.(30) Equally, adequate screening tools for identification of patient at risk appears lacking in practice and practitioners indicated the desire for further training activities on prescribing potentially addictive medicines.

Education of professionals on the abuse potential of codeine and the ability for individuals to extract paracetamol from compounded formulations is also warranted to enhance existing knowledge.

Currently, there are no specific clinical guidelines in managing codeine detoxification, although clinical guidance does exist under the broad umbrella of opioid detoxification.(31) In the current study an overwhelming majority of respondents indicated that they used the process of gradual withdrawal including tapering of the dose, restricting and reducing patients' prescriptions coupled with education and counselling techniques as strategies to address misuse of and dependence on codeine. A minority of participants mentioned that they would prescribe benzodiazepines and other medicines to manage codeine dependent patients. They basis of this decision should be investigated further in light that some of the drugs mentioned come with a high abuse potential. The methods offered by respondents may well be the foundation on which to build some guidance for prescribers and pharmacists in managing detoxification, however, taking into consideration that each patient will have their own individual needs. Due to the fact that several of the prescribers mentioned the toxicity associated with paracetamol and ibuprofen, initial treatment to reduce this risk should be the first consideration.(11) The education and counselling offered and expressed by professionals in the open ended questions could be further evaluated for its content, applicability and effectiveness in the treatment process.

Levels of referral to secondary care appear low and reflect the levels of patients entering addiction treatment indicated by the National Drug Treatment Monitoring Service,(18) and may indicate that a high proportion of patients are being effectively managed in primary care, or more seriously, not being detected at all. If this is the case then actual prevalence rates of misuse are under reported in the national figures. The reporting of codeine misuse by general practice outside of secondary care may actually help in the estimation and prevalence

of not only codeine, but also other substances of misuse in populations who remain outside of addiction services. Professionals in the current study identified a lack of support services for those identified with problems related to their codeine use. The acknowledgement of poor support requires further investigation in the context of the development of adequate services for patients within primary care, community and inpatient settings.

LIMITATIONS

There are several limitations with respect to this study. The recruitment of participants to this online survey was challenging and therefore resulted in a lower than expected response rate. The targeting of GPs practice managers rather than GPs directly may have impacted on the response rate. However, due to the level of e-mail correspondence GPs receive filtering it in this manner may have been beneficial. There may be some criticism of the methods used to boost response; however, as a professional group it is unlikely that participants answered the questionnaire more than once. The study is cross-sectional in nature and therefore cannot describe how the situation might change over time. It is also feasible that those experiencing problem with codeine dependence in their practice may have been more likely to participate in the study. It is possible that term misuse and dependence may have different meanings to specific responders and while specific definitions were provided these were contained within an additional information dropdown menu. However, one of the major strength of the study is the fact that it responds to the increasing demand for greater information regarding codeine misuse and dependence found in the UK and provides information that can be utilised in future studies.

IMPLICATIONS FOR PRACTICE

Greater sources of information are required to develop policy on codeine use, misuse and treatment options in the interest of public health. This study has shed light on medical

professional's experiences in the UK and has highlighted areas of concern regarding medicines containing codeine and the need to develop specific patient screening tools. It is important to note that medicines containing codeine have utility when used appropriately, however greater research is required to examine its' indications for use in longer term pain management. Further education and training is required in the area of prescribing addictive medicines at all levels of practice. Similarly specialist training on recognition of the signs and symptoms drawing from the responses of professionals in this study could help with early detection of codeine dependence. The reporting of cases of codeine dependency outside of addiction services into national registers should be considered. It is important to identify as accurately as possible the prevalence of codeine misuse and dependence in the population so that services can be adequately provided and needs addressed appropriately.

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Authorship: All the authors contributed substantially to the study conception and design; MF, ER and CP conducted the analysis, and interpretation of data. MF and PD recruited the participants. MF drafted the work and TC, MCVH and PD revised it critically for important intellectual content. All Authors gave final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributions: We would like to acknowledge the CODEMISUSED project secondees who assisted with this study during their secondment periods.

Data sharing: No additional data is available

Ethical approval: Ethical approval by King's College London Research Ethics Committee prior to recruitment of participants (8 April 2014).

Transparency statement: MF affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Figure 1 – showing the level of agreement and disagreement with statements related to prescribed codeine medicine

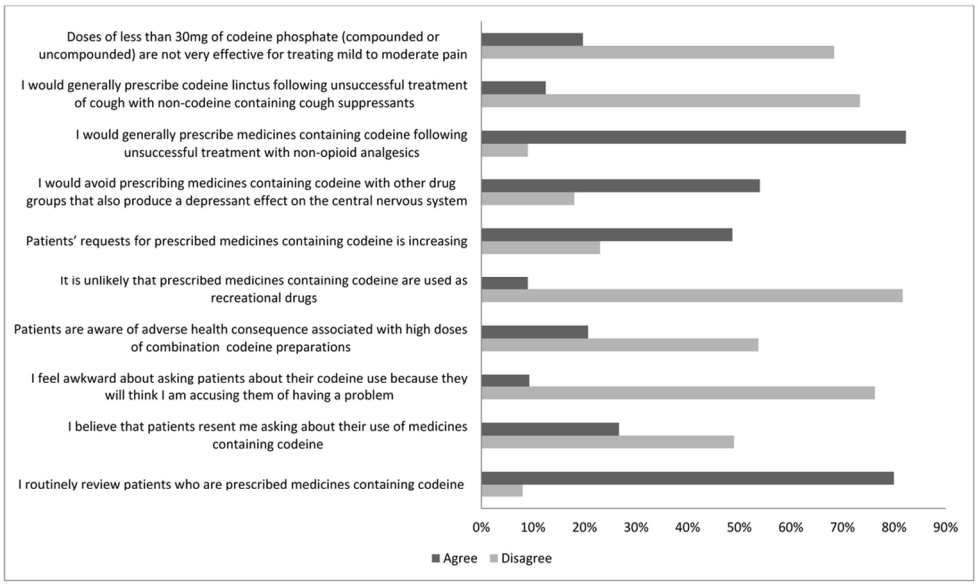

Figure 1
110x70mm (300 x 300 DPI)

Figure 2 – Showing percentages of agreement and disagreement with each of the statements related to over the counter codeine

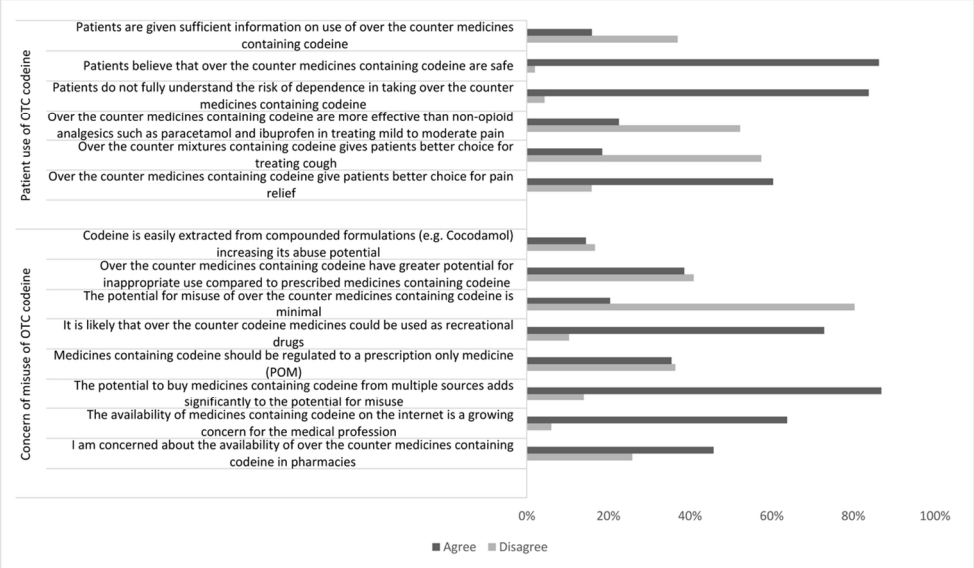

Figure 2
115x76mm (300 x 300 DPI)

Figure 3 – Showing levels of agreement and disagreement for statement items related to codeine dependence.

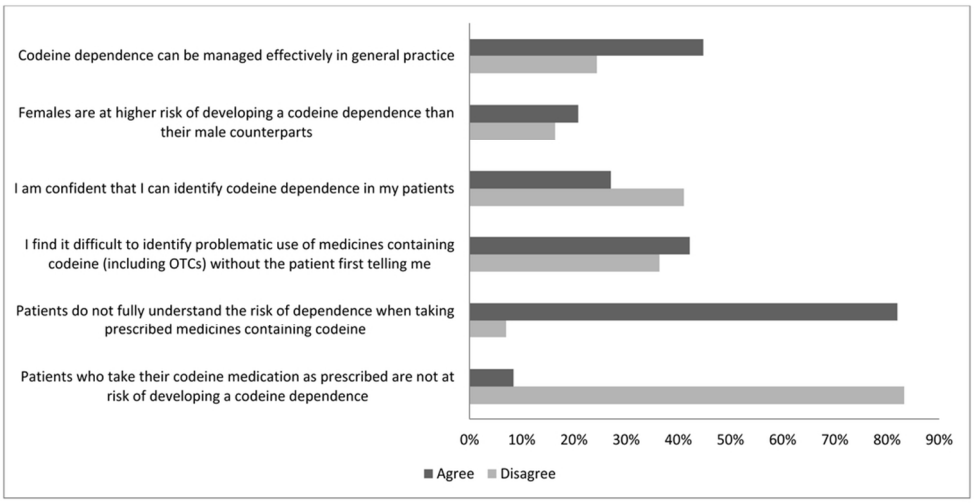

Figure 3
96x53mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1√	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2√	Explain the scientific background and rationale for the investigation being reported
Objectives	3√	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4√	Present key elements of study design early in the paper
Setting	5√	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls √*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7√	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*√	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9√	Describe any efforts to address potential sources of bias
Study size	10√	Explain how the study size was arrived at
Quantitative variables	11√	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		√(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed √*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*√	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*√	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		√*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17√	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18√	Summarise key results with reference to study objectives
Limitations	19√	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20√	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21√	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22√	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

The following statements examine codeine dependence; can you please indicate your agreement with the following statements;

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Patients who take their codeine medication as prescribed are not at risk of developing a codeine dependence					
Patients do not fully understand the risk of dependence when taking prescribed medicines containing codeine					
I find it difficult to identify problematic use of medicines containing codeine (including OTCs) without the patient first telling me					
I am confident that I can identify codeine dependence in my patients					
Females are at higher risk of developing a codeine dependence than their male counterparts					
Codeine dependence can be managed effectively in general practice					

The following statements examine screening, support services and training in managing codeine dependence; can you please indicate you level of agreement with the following;

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
I have suitable screening methods that I use to identify inappropriate use of medicines containing codeine					
Support services are readily available in my area to help those with a codeine dependence problem					
I am fully aware of best practice in managing codeine misuse and dependence					
I would like more instruction on prescribing potentially addictive medications					

In an average month approximately how many patients have you suspected of having a codeine dependence problem? (insert number) ☐

Can you describe the type of patient behaviours that trigger your suspicion of codeine misuse?

Can you describe types of treatments that you use for patients with codeine dependence?

In the past month approximately how many patients with a codeine dependence have you referred on to a specialist addiction service? (insert number) ☐

What were the main reasons for referring patients onto specialist treatment?

We would like to know if you are aware of any new approaches, good practices or innovations in relation to the prevention, identification (e.g. screening), monitoring and/or management of the misuse of over the counter medications in general or codeine in particular. Please give the name/s and contact details of people from whom we could obtain further information;

Are there any other comments you wish to add in relation to codeine misuse and dependence not covered in this questionnaire?

Waterford Institute of Technology
INSTITIÚID TEICNEOLAÍOCHTA PHORT LÁIRGE

MARIE CURIE ACTIONS

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CODEMISUSED

CODEINE USE MISUSE DEPENDENCE

Questionnaire

The survey is completed anonymously, and takes approximately **10 minutes** to complete

Can you please return this questionnaire along with your consent form in the freepost envelope provided

Thank you for agreeing to complete this Questionnaire.

The research leading to these results has received funding from the European Community's Seventh Framework Programme FP7/2007-2013 under grant agreement no 611736.

Can you please provide us with some information about yourself;

Demographics section

Are you?
Male ☐ Female ☐

How old are you? (insert number here) ☐

Which of the following best describes your profession? Please circle

1. General practitioner
2. Independent/supplementary prescriber
3. Specialist in Family medicine
4. Specialist in Pain management
5. Other ___Please Specify _____

How many patients do you consult with in an average week? (insert number here) ☐

How many years have you been a qualified practitioner? (insert number here) ☐

Which country do you work in?

England ☐ Wales ☐ Scotland ☐ Northern Ireland ☐

Which best describes the location of the practice you work in?

Urban ☐ Rural ☐ Mix of both ☐

Do you have any specialist training in substance misuse?

Yes No _____if yes please specify _____

The following questions examine your experiences of prescribed codeine; can you please indicate your level of agreement with the following statements;

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
I routinely review patients who are prescribed medicines containing codeine					
I believe that patients resent me asking about their use of medicines containing codeine					
I feel awkward about asking patients about their codeine use because they will think I am accusing them of having a problem					
Patients are aware of adverse health consequences associated with high doses of codeine phosphate					
It is unlikely that prescribed medicines containing codeine are used as recreational drugs					
Patients' requests for prescribed medicines containing codeine is increasing					
I would avoid prescribing medicines containing codeine with other drug groups that also produce a depressant effect on the central nervous system					
I would generally prescribe medicines containing codeine following unsuccessful treatment with non-opioid analgesics					
I would generally prescribe codeine linctus following unsuccessful treatment of cough with other non-codeine containing cough suppressants					
Doses of less than 30mg of codeine phosphate(compounded or uncompounded) are not very effective for treating mild to moderate pain					

The following questions are specific to Over the Counter Codeine; can you please indicate your level of agreement with the following statements;

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
I routinely ask patients about their use of over the counter medicines					
I document the use of over the counter medicine in a patient's medical notes					
I am concerned about the availability of over the counter medicines containing codeine in pharmacies					
The availability of medicines containing codeine on the internet is a growing concern for the medical profession					
The potential to buy medicines containing codeine from multiple sources adds significantly to the potential for misuse					
Patients are given sufficient information on use of over the counter medicines containing codeine					
Medicines containing codeine should be regulated to a prescription only medicine (POM)					
Over the counter medicines containing codeine give patients better choice for pain relief					
Over the counter mixtures containing codeine gives patients better choice for treating cough					
Over the counter medicines containing codeine are more effective than non-opioid analgesics such as paracetamol and ibuprofen in treating mild to moderate pain					
The potential for misuse of over the counter medicines containing codeine is minimal					
Over the counter medicines containing codeine have greater potential for inappropriate use compared to prescribed medicines containing codeine					
Codeine is easily extracted from compounded formulations (e.g. Co-codamol) increasing its abuse potential					
It is likely that over the counter codeine medicines could be used as recreational drugs					
Codeine misuse is as serious a problem to society as misuse of stronger opioids					
Patients do not fully understand the risk of dependence in taking over the counter medicines containing codeine					
Patients believe that over the counter medicines containing codeine are safe					

The following statements examine your opinion surrounding 'patients' use of codeine medications outside of normal medical practice; can you please indicate your agreement with the following statements;

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Patients who knowingly take medicines containing codeine for non-medical reasons may do so to enhance a positive experience or emotion					
Patients who knowingly take medicines containing codeine outside of normal medical practice may do so to reduce illicit opiate withdrawals					
Patients who knowingly take medicines containing codeine outside of normal medical practice may do so to reduce withdrawal headaches associated with consecutive longer term codeine use					
Patients who knowingly take medicines containing codeine outside of normal medical practice may choose to ignore the risk associated with their use					
Patients who misuse other opiates are more likely to request medicines containing codeine than other patients					
Patients who are prescribed other drugs that have a depressant effect on the central nervous system are more likely to request medicines containing codeine than other patients					
Patients with a history of problematic alcohol use are more likely to request medicines containing codeine than other patients					

BMJ Open

Medical professionals' perspectives on prescribed and over the counter medicines containing codeine: A cross-sectional study

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Primary Subject Heading:	Addiction
Secondary Subject Heading:	Public health, Addiction
Keywords:	Codeine, over the counter, dependence, PRIMARY CARE

Title: - Medical professionals' perspectives on prescribed and over the counter medicines containing codeine: A cross-sectional study

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Telephone (+) 353 51 845593Key words: Codeine, dependence, prescribing, primary care, pain management, over the counter

Word count: 3,765

ABSTRACT

Objectives:

To explore prescribing practitioners' perspectives on prescribed codeine use, their ability to identify dependence and their options for treatment in the United Kingdom.

Design:

Cross sectional design using a questionnaire containing closed and open ended items.

Setting:

A nationally representative sample of prescribing professionals working in the United Kingdom

Participants:

Three hundred prescribing professionals working in primary care and pain settings.

Results:

Participants stated that they regularly reviewed patients prescribed codeine, understood the risks of dependence and recognised the potential for codeine to be used recreationally. Over half the participants felt patients were unaware of the adverse health consequences of high doses of combination codeine medicines. One quarter of participants experienced patient resentment when asking about medicines containing codeine. Just under 40% of participants agreed that it was difficult to identify problematic use of codeine without being informed by the patient and did not feel confident in identification of codeine dependence. Less than 45% of all participants agreed that codeine dependence could be managed effectively in general practice. Slow or gradual withdrawal was the most popular suggested treatment in managing

dependence. Education and counselling was also emphasised in managing codeine dependent patients in primary care.

Conclusions:

Communication with patients should involve assessment of patient understanding of their medication, including risk of dependence. There is a need to develop extra supports for professionals including patient screening tools for identifying codeine dependence. The support structure for managing codeine dependent patients in primary care requires further examination.

Article Summary

- This is the first study examining medical professionals perceptions of medicines containing codeine across the UK
- The study used a questionnaire design with closed and open ended items relating to both prescribed and over the counter medicines containing codeine and included questions on dependence and treatment options in practice
- Professionals involved in the prescribing of codeine were accessed across the UK using the principles of stratified random sampling
- Reponses rates were lower than expected and the study was unable to access the full population of nurse prescribers
- This study is cross-sectional and therefore does not describe how the situation might change over time

INTRODUCTION

Pain is a common reason for accessing primary care services. It is estimated that 14 million people in the United Kingdom (UK) suffer from long term pain,(1) with patients complaining of headaches thought to account for one in twenty five of primary care consultations,(2) and musculoskeletal pain accounting for one in seven.(3) Opioids are widely used in pain management with codeine being the second most widely prescribed opioid medicine in general practice.(4) In 2012, it was estimated that 640 codeine prescriptions per 1000 patients were dispensed in the UK.(5) Additionally, medicines containing codeine can be purchased over the counter (OTC) in pharmacies albeit with restrictions (6). Medicines containing codeine (up to 12.8mg per unit dose) may only be sold in the UK under the supervision of a qualified pharmacist. There are restrictions on the quantity of tablets permitted for sale in a single transaction and the product is not available for self-selection, although advertising of codeine containing medicines are permitted both in the pharmacy and on national media. A sale may be refused if there is suspicion that the buyer is misusing codeine. Currently, the nature and extent of OTC codeine use and misuse in the UK is not widely reported.

Treatment with opioid medication is thought to be effective in the treatment of moderate pain for acute and short periods of less than six months.(7) Current scientific evidence measuring the efficacy of codeine over other alternative medications for chronic and longer term pain remains inconclusive.(8) There are limited studies examining the efficacy of low doses of codeine found in many prescribed and OTC medicines (less than 12.8mg per unit dose). While several Cochrane reviews have evaluated the efficacy of codeine, these are principally confined to acute postoperative pain at high doses (60mg). Some studies show codeine as clinically useful in some patients. A Cochrane review using 14 studies

comprising of 926 participants compared the use of single dose oral paracetamol plus codeine with the same dose of paracetamol alone for postoperative pain in adults .The review concluded that the addition of codeine provided effective pain relief to approximately 10% more participants than the same dose of paracetamol alone. The use of codeine in combination with paracetamol was found to extend the duration of analgesia by approximately one hour.(9) A recent Cochrane review found that the combination of ibuprofen 400mg plus codeine 25.6mg to 60mg demonstrated effective analgesic efficacy in post-operative pain, however very limited data suggests that the combination is better than the same dose of either drug alone.(10) Equally, the use of codeine containing syrups in supressing cough appears to lack positive scientific basis and is not widely discussed in the current literature.

Whilst codeine is considered a weak opiate, it carries an identified abuse potential. Development of tolerance on regular or excessive use appears within a short timeframe.(11) Literature reports increasing trends in the misuse use of codeine, including over the counter preparations, which appears to incur significant negative epidemiologic, social and economic consequences.(12-16) Related harms in terms of morbidity and mortality are documented,(12) along with monetary costs associated with indirect effects on healthcare, prevention and treatment.(17)

Treatment of codeine dependence is varied and does not appear to be well documented in the literature. Guidance on options for opioid dependence is evident but appears non-specific to weak opioids such as codeine. Summary statistics for codeine dependence obtained from treatment providers in the UK, suggest that codeine as the primary and secondary substance of misuse is extremely low at 2.2% (4,248 individuals) of all those entering addiction treatment services in the period 2013-2014 .(18) These statistics may give an impression that codeine dependence is not an issue warranting attention compared to other substances of

misuse; however treatment for codeine dependence conducted in primary care does not appear in national treatment surveillance systems. What is of particular concern is that codeine dependent

patients appear to function well within the range of perceived normality, carrying out the functions of normal daily living.(19) Evaluating as to whether medical professionals are equipped to detect and manage patients presenting with codeine dependence is therefore an area of considerable importance.

Studies have called for further research on the experiences and concerns of medical professionals around use of medicines containing codeine, with particular focus on their experiences, challenges, perspectives and practices.(20) The aim of the study was to garner information regarding prescribing practitioners' perspectives on prescribed and OTC codeine use, their ability to identify dependence and options for treatment in the UK. This study was part of a larger study examining both OTC and prescribed misuse of codeine medicines in the Republic of Ireland, UK and South Africa and was funded by the European Commission (www.codemisused.org).

METHOD

Recruitment of participants and study procedures

The study involved a cross-sectional design and took place between May 2014 and April 2015 using an online questionnaire (see Figure 1). A nationally representative sample of medical practitioners in the UK was facilitated through Specialist Info, a medical directory specialist. A random list of 1000 practice managers was generated by strata using proportionate numbers of GPs present in each country (Wales n=48, Northern Ireland n=36, Scotland n=98, England n=818). Each practice manager was asked to recruit at least one GP

from their respective practice to participate in the study. Each practice manager was sent a reminder approximately two to four weeks later. 150 Pain Specialist Physicians e-mail records were also retrieved from Specialist Info and these were subsequently sent the link to the survey. In order to have representation from Nurse Prescribers, a previous distribution list of 98 Pain Specialist Nurses was utilised (21). These participants were asked to indicate their agreement to be added to the e-mail distribution list. 54 agreed to participate and the link to the survey was then provided. In total this process resulted in 136 participants completing the online questionnaire. A further 65 GPs were recruited through GP target sessions. A second random sample of 1000 practice managers was generated checked for duplicates and e-mailed as previously described. A follow up reminder was distributed four to six weeks later. This resulted in the completion of a further 98 questionnaires. The indicated time to complete the questionnaire was approximately 10 minutes and this was specified in the e-mail correspondence and prior to proceeding with the questionnaire. Information on the study was provided and informed consent was obtained prior to proceeding online. Participants were advised to complete the questionnaire only once. Dissemination activities, including circulars and newsletters were used to encourage participation in the study. Ethical approval was granted by King's College London Ethics Committee (PNM/13/14-75).

Data collection methods

We collected the data using an online questionnaire using the survey tool www.onlinesurveys.ac.uk. Questions were developed to bridge gaps in knowledge following a comprehensive search of the literature.(4) Eight questions were added to collect demographic information in order to establish the representativeness of the respondents. The questionnaire comprised of a combination of closed and open ended items, on prescribed and over the counter medicines containing codeine and included questions on triggers for suspecting codeine misuse, managing codeine dependent patients and reasons for referral.

Participants were provided with an opportunity to add additional comments at the end of the questionnaire and knowledge of innovations on preventing medicine misuse (see supplementary information for full details of questionnaire). A paper edition of the questionnaire was made available at GP target sessions in two separate locations (Continuing professional development). GPs had the option to complete the questionnaire online via the survey link or complete the paper copy and return to the researcher at the end of the target session. GP were also informed that they could return by post and were provide with a return envelope on request.

Data Analysis

Data were downloaded directly from the online data capture page to SPSS version 21. Data captured in paper format were entered manually and combined with the data captured online. Data were screened and checked for errors. Data were then examined descriptively using frequencies and percentage. The data was summarised to create two categories by combining levels of agreement and disagreement for reporting purposes. The occurrence of codeine dependence was estimated using the approximate numbers of patients suspected of having codeine dependence as indicated in the questionnaire divided by the number of consultations indicated by professionals in an average month. Referrals were estimated using the numbers indicated by participants in the questionnaire and this figure was presented as an overall percentage of the total number of participants' referrals to secondary care for codeine dependence.

The open-ended questions were downloaded into a separate Excel® sheet for content analysis. This data was examined and individual categories were created for each of the open-ended questions based on common features and dominant subjects identified in the text. The categories were discussed by two senior members of the research team and agreed. Three researchers independently coded the data (two academic researchers and one pharmacist).

This was achieved by labelling each field where the content matched the associated thematic category. Inter-coder reliability of the data was conducted by dialogue between three members of the research team. Each item was checked for both agreement and non-agreement with the thematic categories. Where discrepancies were identified or disagreement with the category placing occurred the researchers discussed the illustrated content. This was then resolved when two or more researchers were in agreement. Data were presented as an overall percentage of those who responded to the open-ended questions.

RESULTS

Three hundred medical professionals involved in prescribing codeine were recruited to the study, giving an overall response rate of approximately 12.5%. Table 1 details the demographic information. The mean age of participants was 47 years (Range = 25-68 years). The average years of practice were 19.52 years (Range = 1-48 years).

Table 1 -Demographic details and information pertaining to profession, location and specialist training.

	N=300 Frequency (f)	%
Gender		
Male	140	46.7
Female	160	53.3
Age	Median (Md) 48years Range (25-68 years)	
Profession		
General Practitioner	238	79.3
Independent/Supplementary/Nurse prescriber[1]	23	7.7
Specialist in family medicine	31	10.3
Specialist in Pain Management	0	0
Other	8	2.7
Number of years as a qualified practitioner	20 years (Md) Range (1-48 years)	
Number of consultations in an average week	100 (Md) Range (7-500)	
Country		
England	253	84.6
Wales	15	5.0
Scotland	23	7.7
Northern Island	9	2.7
Location		
Urban	166	55.3
Rural	40	13.3
Mix of both	94	31.3
Specialist training in substance misuse		
Yes	89	29.7
No	208	69.3
Did not indicate	3	1.0
Type of substance misuse training		
Certificate in substance misuse	42	47.2
Postgraduate qualification in substance misuse	13	14.6
Continuing professional development (CPD)	12	13.4
Other	5	6.3
Did not indicate	17	19.1

[1] Currently nurses, pharmacists, and community practitioners in the UK may undertake further professional training to qualify as non-medical prescribers. Independent prescribers are responsible and accountable for the assessment of patients with undiagnosed and diagnosed conditions and for decisions about the clinical management required, including prescribing of medicines from a predetermined list. Supplementary prescribers may prescribe any medicine (including controlled drugs), within the framework of a patient-specific clinical management plan, which has been agreed with a doctor. Nurses, pharmacists, physiotherapists, chiropodists or podiatrists, radiographers and optometrists may train and register as a supplementary prescriber.

Prescribed codeine

Figure 2 illustrates statement items examining medical professionals' experiences of prescribing codeine. Percentage agreement and disagreement were used to describe the results. Fifty percent of participants showed some level of agreement that the requests for prescribed codeine was increasing. In relation to prescribing practices, 54% of participants implied that they avoided the prescribing of codeine with other depressant drugs. Eighty two percent of participants agreed to some extent that they prescribed codeine following unsuccessful treatment with non-opioid analgesics. Only 12.6% of participants agreed to prescribe codeine cough linctus following unsuccessful treatment of cough with non-codeine based medicine. Less than 20% of participants agreed that low doses of codeine, less than 30mg, are not very effective in treating mild to moderate pain. Eighty percent of professionals agreed to routinely reviewing patients who are prescribed codeine. Twenty seven percent of those responding believed that patients resented them for asking about their use of medicines containing codeine. However, most professionals disagreed with the statement in respect to 'feeling awkward' around questioning patients about their codeine use (76.6%).Furthermore, over half showed a level of disagreement (53.7%) with the statement "patients are aware of the adverse health consequences of high dose of combination codeine medicines". Participants recognised the potential for codeine to be used recreationally (81.7%).

Over the counter codeine

Figure 3 shows statement items examining medical professionals' experiences of over the counter codeine. Percentage agreement and disagreement were used to describe the results. Seventy six percent of those responding to the questionnaire were found to routinely ask about patients' use of OTC codeine medicine, and 71% indicated that they documented the

use of OTC medicines in the patients' medical notes. Concern about availability of OTC codeine in pharmacies was recorded at 45.8%. Concern about the availability of OTC codeine available on the internet was slightly higher at 64%. However, the vast majority of practitioners agreed to some extent that the potential to buy codeine from multiple sources added significantly to the potential for misuse (86.9%). Thirty five percent showed some level of agreement that medicines containing codeine should be regulated to a prescription only medicine while a similar percentage (36%) did not or had no opinion (28%). Sixteen percentage of participants felt that patient were given sufficient information and there was agreement that patients were not fully aware of the risks of dependence with consumption of OTC codeine medicines (83.8%) and believed them to be safe (86.3%). Only 23% of practitioners agreed (or strongly agreed) that codeine was more effective than non-opioid analgesics. The potential to extract codeine from compounded formulation showed mixed levels of agreement.

Dependence, screening and treatment

Figure 4 shows responses to the various statement items examining codeine dependence. Only 8% of participants agreed that patients were not at risk of codeine dependence when they took their codeine medicine as prescribed. The majority agreed to some extent that patients did not fully understand the risk of dependence when taking prescribed medicine containing codeine (82%). Over 40% agreed difficulty in identification of problematic use of codeine without being informed by the patient. This corresponded with relatively high percentages of those who did not feel confident in identification of codeine dependence (41%). When asked if women were at higher risk of development of codeine dependence only 20.8% agreed, while 16% showed a level of disagreement. Forty five percent of all participants agreed that codeine dependence could be managed effectively in general practice.

21% of participants agreed to have suitable screening methods to identify if codeine was being used inappropriately. 27% of participants agreed that adequate services in place to manage codeine dependent patients. While only 28% agreed to be fully aware of best practice in managing codeine misuse and dependence. A high proportion of participants, (70.3%) would like more instruction on the prescribing of potentially addictive medicines.

Managing codeine dependence

Eight six percent of the total participants had suspected cases of codeine dependence in practice. The median number of patients suspected of being codeine dependent was calculated as being three patients per 100 consultations. When asked if they had referred a patient to specialist care for codeine dependence in the past month, 27%of participants indicated referrals to secondary/specialist care. Where referrals were indicated, the median number was one patient in a monthly period.

Patient behaviours, treatment options and referral reasons

Practitioners were asked to describe the typical patient behaviours triggering their suspicion of codeine misuse. Table 2 shows thematic categories of results displayed as a frequency and as a percentage of the total responses. Patient behaviours that triggered suspicion of codeine misuse and dependency included requesting codeine specifically by name, early requests and refills and calling the surgery at inappropriate times to request codeine medicines. The potential to obtaining codeine from multiple sources was expressed. Additional comments reflected the difficulties in managing patients' codeine use.

> *"It is very difficult to control patients' codeine use as they may use multiple pharmacies, buy from friends or online. I don't think we have fully woken up to the scale of the problem of opiate dependence. Especially when opiates are prescribed by pain clinics for chronic, non-cancer pain".* (GP participant)

> *"Have advised colleagues many times that this is a time-bomb (not wishing to be melodramatic!) If evidence is promoted or the Daily Mail decides to champion a codeine scare we will be on the back-foot managing the fall-out and patient distress*". (GP participant)

Lost prescriptions or medicines were also perceived to be an indicator for dependence and practitioners used anecdotes to describe patient situations such as *"the dog ate my script" "I lost my medication on the bus" or "on holiday"*. Unresolved pain was indicated as a further trigger in suspicion of dependence and situations of hypersensitivity to pain were described in terms of headache, inadequate pain relief and indications of chronic pain not being helped by the current medication regime. Aberrant behaviours were described and included aggression, demanding codeine, reluctance to change medication and becoming very keen to obtain a script. Physical signs of misuse included restricted pupils, anxiety, constipation, gastric disturbances and irritability. Other indicators included history of co-morbidity and history of addiction. Some professionals also mentioned social and economic factors including taking excessive sick leave and unemployment.

Various treatments for codeine dependence were described by practitioners (see table 2). A large proportion of respondents mentioned slow or gradual withdrawal as the suggested treatment in managing dependence. Education and counselling was also emphasised and was more often suggested with gradual withdrawal and restricted prescriptions. Additional comments were also made about the area of practitioner training in managing misuse and the requirement to improve patient knowledge on codeine consumption.

> *"It would be helpful to have some teaching on misuse of OTC products and management there of".* (GP participant)

> *"I am very concerned about the number of people I see who take products containing a combination of codeine and paracetamol at levels that put them at high risk of liver damage as they often do not realise that taking large amounts for the psychoactive effects of the codeine means that they are likely to be unintentionally overdosing on the paracetamol".* (GP participant)

Restricted prescriptions were described in terms of giving limited amounts of codeine in doses of up to three days or a one week supply. One GP spoke of the role of advertising and efforts to control repeat prescribing while another also spoke of problems of monitoring of repeat prescriptions.

> "*We worry about codeine abuse, etc., yet Solpadeine is very heavily advertised, but it does serve a purpose in self-medication for moderate pain. In my experience patients are started too early on high strength codeine painkillers and simply parked there via repeat prescriptions. Little effort seems to be given to follow up and monitoring usage before the patient becomes addicted to the codeine as opposed to suffering pain".* (GP participant)

> *"Big problem. We struggle to monitor repeat prescriptions closely enough. Hospitals hand out codeine and tramadol like smarties. Difficult to know how best to tackle OTC access as primary care does not have the capacity to pick up seeing all those people who self-treat appropriately with OTC meds".* (GP participant)

Other suggested treatments include substitution using non-opioid analgesics, substitution with other drugs including amitriptyline and benzodiazepines, other opiates, methadone and buprenorphine. Some respondents indicated that the main treatment they used was 'cold turkey'. Referral to specialist care was also indicated including, drug and alcohol services, rehabilitation centres, psychologists, psychiatrists and pain specialists.

The primary reasons for referrals are reported in table 2 and were indicated as the inability to manage the patient effectively in primary care or that the patient was a complex case requiring specialist care. Complex cases were described as those with multiple issues including other drugs and alcohol misuse, pregnant patients and other co-morbidities, usually related to mental health. Some sentiment was also expressed about other drugs of misuse

> *"Whilst codeine is misused, I am more concerned with heroin and cocaine misuse".* (GP participant)

> *"We also have big problems with dihydrocodeine, oxycodone, tramadol, pregabalin and gabapentin".* (GP participant)

Patient's request to be referred for specialist treatment was also a common response. Indications were also that referrals to specialist care were as a result of the lack of resources, or time during the consultation and lack of knowledge with regard to best practice.

Some additional comments were made related to the lack of resources available to manage problem of codeine dependence.

> *"There is a gap between practicing perfect medicine where patients' drug use is explored in depth and the practicalities of managing time and workload. I feel that to a certain extent, exploring drug misuse in patients who are pre-contemplative is not necessarily the most effective use of time (although of course would be done in an ideal world)".* (GP participant)

Table 2 – Showing main thematic categories and frequency of responses

N=300	Frequency of responses (%)
Can you describe the patient behaviours that trigger your suspicion of codeine misuse?	
Requesting prescriptions for codeine	212 (71)
Aberrant behaviour	89(30)
Unresolved pain/cough	78(19)
Lost prescriptions or medications	52(17)
Physical or psychological symptoms	41(14)
History of addiction	38(13)
Doctor/pharmacy shopping for codeine medicines	28(9)
History of co-morbidity	14(5)
Socio-economic status	14(5)
Sex	3(1)
Can you describe the types of treatments that you use for patients with codeine dependence?	
Slow or gradual withdrawal	153(51)
Education / Counselling	87(29)
Referral to secondary or specialist care	87(29)
Restricted prescriptions	60(20)
Substitution with another drug (drug not specified)	30(10)
Substitution using methadone / buprenorphine / other opiate drug	27(9)
Substitution with non-opioid medication	15(5)
Substitution using benzodiazepines / other antipsychotics / other	15(5)
Cold turkey	9(3)
What were the main reasons for referring patients onto specialist treatment[2]?	
Failure to manage patient effectively in practice	150(50)
Complex case requiring specialist care	186(62)
Patient request for referral	63(21)
Lack of resources	45(15)

[2]Although only 27% of participants indicated referral in the past month, all respondents went on to indicated the main reasons for referring patients onto specialist care outside of the previous month. This data were considered highly relevant and was therefore calculated as proportionate to the total cohort.

DISCUSSION

The current study exhibited high levels of agreement that patients' prescribed codeine were routinely reviewed by their medical professional and included questioning around OTC codeine use. Half of all those who responded felt that the request for codeine medicines was increasing and is substantial in raising some concern. The increasing requests for codeine may be directly as a result of newer restrictions imposed on OTC supply, forcing patients to obtain a steady source on prescription.(21) Other factors contributing to the perceived increase in codeine requests may relate to changes in scheduling of other prescription opioids such as Tramadol (22). In the UK, Tramadol must only be supplied in quantities that do not exceed 30 days and must not be dispended on 'batch' repeat prescriptions, making refills more difficult to obtain. Codeine is currently not bound by these restrictions. While there is no specific evidence to verify that codeine consumption is increasing, a level of caution should be exercised by the prescriber when a medicine is requested specifically by name. Content analysis of the open ended questions showed that one of the most common triggers for suspecting misuse was when codeine was requested specifically by its name or brand name.

Views regarding the effectiveness of 30mg of codeine showed some notable variation. The efficacy of low doses of codeine is not well documented in the literature and a greater evidence base is required to further develop indications for codeine use.(23) Codeine appeared used in response to unsuccessful treatment with non-opioid analgesics. However, the complexity of pain management has drawn significant attention over recent years with limited options for prescribers to avoid unpleasant side effects.(24, 25) Newer drugs acting at the GABA receptors have gathered some momentum in the treatment of chronic neuropathic pain; however, they also carry significant side effects and serious risk of misuse.(26) The

difficulty for any prescriber is to balance these risks and it is feasible that codeine is considered to have lower abuse liability due to its weak opioid status.(27)

There is concern regarding patients' use of OTC codeine containing medicine and a large number of respondents in the current study believe that patients were unaware of the health consequences associated with high doses of combination codeine preparations. Equally, the respondents were of the view that patients do not understand the risk of dependence when taking prescribed medicines containing codeine. This concurs with evidence reported in the literature.(28, 29) Further research should identify the level and type of information patients require to make informed decisions surrounding their medicine use both prescribed and over the counter. Rescheduling of codeine has drawn significant debate and some suggestion was made in the current study to remove sales of OTC codeine altogether (24). However, without actual prevalence rates of misuse and harm, it is difficult to draw definitive conclusions. Equally, other prescription opioids, including codeine, are also misused so removal of OTC codeine is unlikely to eliminate the problem entirely. Additionally, several countries across the EU do not permit the sale of OTC codeine (25) and there is little evidence that restricting this provision has any impact on harms associated with its use. The rescheduling to a prescription only medicine is likely to place additional pressure of GPs for self-limiting conditions and shift diversionary patterns. This may explain differences observed in the current study regarding rescheduling of codeine to a prescription only medicine.

Risk of development of a codeine dependence in spite of taking codeine as prescribed was identified by the majority of professionals in the UK and shows that prescribers are aware of potential risks associated with its use. Detection of codeine dependence in patients appears to be problematic, with low levels of confidence expressed in detection of codeine dependence, highlighting the need for specific screening tools.(30) Equally, adequate screening tools for identification of patient at risk appears lacking in practice and practitioners indicated the

desire for further training activities on prescribing potentially addictive medicines. Education of professionals on the abuse potential of codeine and the ability for individuals to extract paracetamol from compounded formulations is also warranted to enhance existing knowledge.

Currently, there are no specific clinical guidelines in managing codeine detoxification, although clinical guidance does exist under the broad umbrella of opioid detoxification.(31) In the current study an overwhelming majority of respondents indicated that they used the process of gradual withdrawal including tapering of the dose, restricting and reducing patients' prescriptions coupled with education and counselling techniques as strategies to address misuse of and dependence on codeine. A minority of participants mentioned that they would prescribe benzodiazepines and other medicines to manage codeine dependent patients. They basis of this decision should be investigated further in light that some of the drugs mentioned come with a high abuse potential. The methods offered by respondents may well be the foundation on which to build some guidance for prescribers and pharmacists in managing detoxification, however, taking into consideration that each patient will have their own individual needs. Due to the fact that several of the prescribers mentioned the toxicity associated with paracetamol and ibuprofen, initial treatment to reduce this risk should be the first consideration.(11) The education and counselling offered and expressed by professionals in the open ended questions could be further evaluated for its content, applicability and effectiveness in the treatment process.

Levels of referral to secondary care appear low and reflect the levels of patients entering addiction treatment indicated by the National Drug Treatment Monitoring Service,(18) and may indicate that a high proportion of patients are being effectively managed in primary care, or more seriously, not being detected at all. If this is the case then actual prevalence rates of misuse are under reported in the national figures. The reporting of codeine misuse by

general practice outside of secondary care may actually help in the estimation and prevalence of not only codeine, but also other substances of misuse in populations who remain outside of addiction services. Professionals in the current study identified a lack of support services for those identified with problems related to their codeine use. The acknowledgement of poor support requires further investigation in the context of the development of adequate services for patients within primary care, community and inpatient settings.

LIMITATIONS

There are several limitations with respect to this study. The recruitment of participants to this online survey was challenging and therefore resulted in a lower than expected response rate. The targeting of GPs practice managers rather than GPs directly may have impacted on the response rate. However, due to the level of e-mail correspondence GPs receive filtering it in this manner may have been beneficial. There may be some criticism of the methods used to boost response; however, as a professional group it is unlikely that participants answered the questionnaire more than once. The study is cross-sectional in nature and therefore cannot describe how the situation might change over time. It is also feasible that those experiencing problem with codeine dependence in their practice may have been more likely to participate in the study. It is possible that term misuse and dependence may have different meanings to specific responders and while specific definitions were provided these were contained within an additional information dropdown menu. However, one of the major strength of the study is the fact that it responds to the increasing demand for greater information regarding codeine misuse and dependence found in the UK and provides information that can be utilised in future studies.

IMPLICATIONS FOR PRACTICE

Greater sources of information are required to develop policy on codeine use, misuse and treatment options in the interest of public health. This study has shed light on medical professional's experiences in the UK and has highlighted areas of concern regarding medicines containing codeine and the need to develop specific patient screening tools. It is important to note that medicines containing codeine have utility when used appropriately, however greater research is required to examine its' indications for use in longer term pain management. Further education and training is required in the area of prescribing addictive medicines at all levels of practice. Similarly specialist training on recognition of the signs and symptoms drawing from the responses of professionals in this study could help with early detection of codeine dependence. The reporting of cases of codeine dependency outside of addiction services into national registers should be considered. It is important to identify as accurately as possible the prevalence of codeine misuse and dependence in the population so that services can be adequately provided and needs addressed appropriately.

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Competing interests: "We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests."

Authorship: All the authors contributed substantially to the study conception and design; MF, ER and CP conducted the analysis, and interpretation of data. MF and PD recruited the participants. MF drafted the work and TC, MCVH and PD revised it critically for important intellectual content. All Authors gave final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributions: We would like to acknowledge the CODEMISUSED project secondees who assisted with this study during their secondment periods.

Data sharing: No additional data is available

Ethical approval: Ethical approval by King's College London Research Ethics Committee prior to recruitment of participants (8 April 2014).

Transparency statement: MF affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Funding: The research leading to these results has received funding from the European Community's Seventh Framework Programme FP7/2007-2013 under grant agreement no 611736.

Figure 1 - Showing recruitment of participants to the study

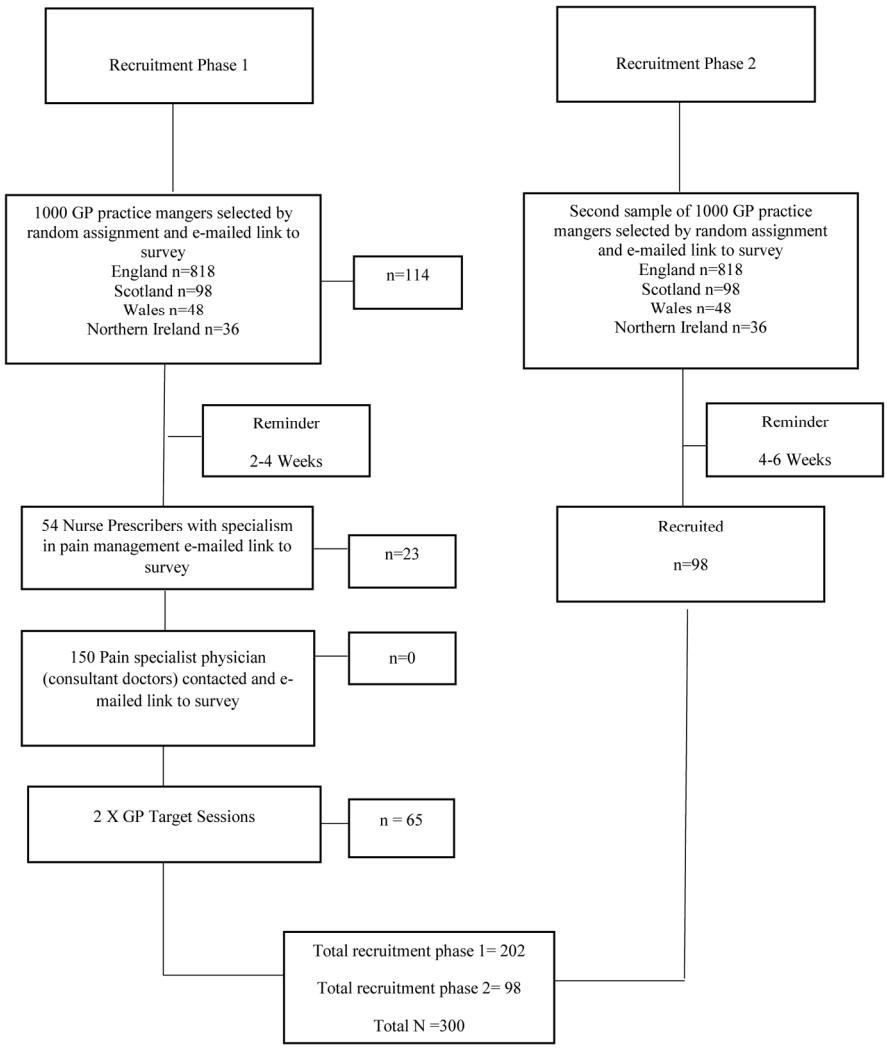

Figure 1
203x254mm (300 x 300 DPI)

Figure 2 – showing the level of agreement (agree strongly, agree) and disagreement (disagree strongly, disagree) and neutral responses with statements related to prescribed codeine medicine

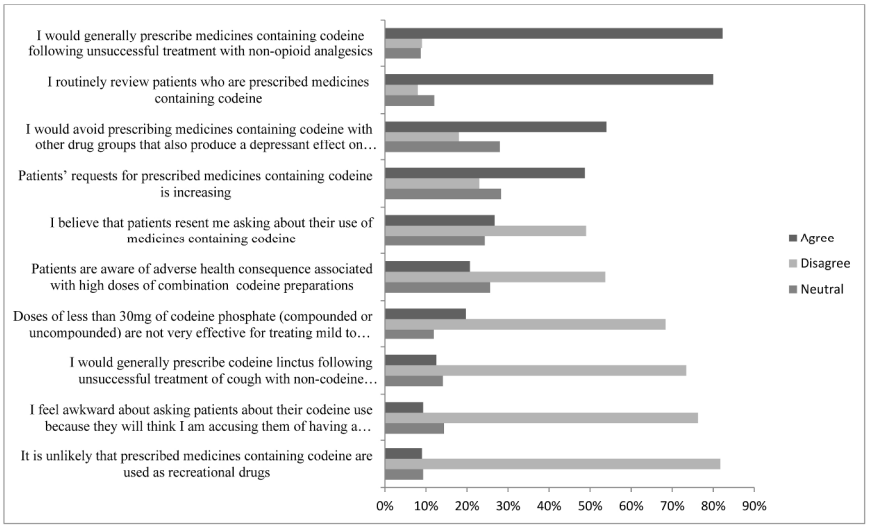

Figure 2
249x147mm (300 x 300 DPI)

Figure 3 – Showing percentages of agreement (strongly agree, agree), disagreement (strongly disagree, disagree) and neutral responses with each of the statements related to over the counter codeine

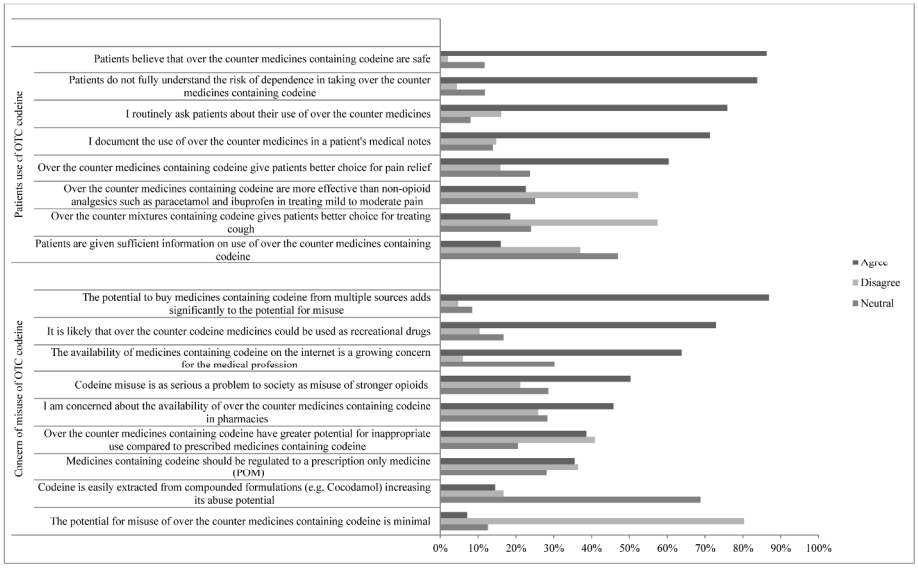

Figure 3
254x158mm (300 x 300 DPI)

Figure 4 – Showing levels of agreement (strongly agree, agree) and disagreement (strongly disagree, disagree) and neutral statements for statement items related to codeine dependence and treatment.

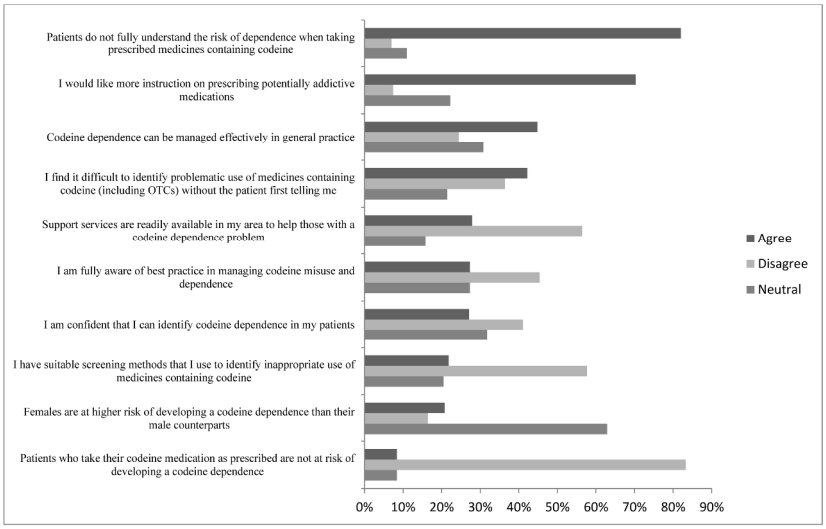

Figure 4
249x146mm (300 x 300 DPI)

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MARIE CURIE ACTIONS

PEOPLE

WELDRICKS PHARMACY
weldricks.co.uk
"Committed to Community Healthcare"

CODEMISUSED
CODEINE USE MISUSE DEPENDENCE

Questionnaire

The survey is completed anonymously, and takes approximately **10 minutes** to complete

(Paper Format)

(Where applicable) Can you please return this questionnaire along with your consent form in the freepost envelope provided

Thank you for agreeing to complete this Questionnaire.

The research leading to these results has received funding from the European Community's Seventh Framework Programme FP7/2007-2013 under grant agreement no 611736.

Can you please provide us with some information about yourself;

Demographics section

Are you?
Male ☐ Female ☐

How old are you? (insert number here) ☐

Which of the following best describes your profession? Please circle

1. General practitioner
2. Independent/supplementary prescriber
3. Specialist in Family medicine
4. Specialist in Pain management
5. Other ___Please Specify _____

How many patients do you consult with in an average week? (insert number here) ☐

How many years have you been a qualified practitioner? (insert number here) ☐

Which country do you work in?

England ☐ Wales ☐ Scotland ☐ Northern Ireland ☐

Which best describes the location of the practice you work in?

Urban ☐ Rural ☐ Mix of both ☐

Do you have any specialist training in substance misuse?

Yes No _____if yes please specify _____

The following questions examine your experiences of prescribed codeine; can you please indicate your level of agreement with the following statements;

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
I routinely review patients who are prescribed medicines containing codeine					
I believe that patients resent me asking about their use of medicines containing codeine					
I feel awkward about asking patients about their codeine use because they will think I am accusing them of having a problem					
Patients are aware of adverse health consequences associated with high doses of combination codeine preparations					
It is unlikely that prescribed medicines containing codeine are used as recreational drugs					
Patients' requests for prescribed medicines containing codeine is increasing					
I would avoid prescribing medicines containing codeine with other drug groups that also produce a depressant effect on the central nervous system					
I would generally prescribe medicines containing codeine following unsuccessful treatment with non-opioid analgesics					
I would generally prescribe codeine linctus following unsuccessful treatment of cough with other non-codeine containing cough suppressants					
Doses of less than 30mg of codeine phosphate(compounded or uncompounded) are not very effective for treating mild to moderate pain					

The following questions are specific to Over the Counter Codeine; can you please indicate your level of agreement with the following statements;

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
I routinely ask patients about their use of over the counter medicines					
I document the use of over the counter medicine in a patient's medical notes					
I am concerned about the availability of over the counter medicines containing codeine in pharmacies					
The availability of medicines containing codeine on the internet is a growing concern for the medical profession					
The potential to buy medicines containing codeine from multiple sources adds significantly to the potential for misuse					
Patients are given sufficient information on use of over the counter medicines containing codeine					
Medicines containing codeine should be regulated to a prescription only medicine (POM)					
Over the counter medicines containing codeine give patients better choice for pain relief					
Over the counter mixtures containing codeine gives patients better choice for treating cough					
Over the counter medicines containing codeine are more effective than non-opioid analgesics such as paracetamol and ibuprofen in treating mild to moderate pain					
The potential for misuse of over the counter medicines containing codeine is minimal					
Over the counter medicines containing codeine have greater potential for inappropriate use compared to prescribed medicines containing codeine					
Codeine is easily extracted from compounded formulations (e.g. Co-codamol) increasing its abuse potential					
It is likely that over the counter codeine medicines could be used as recreational drugs					
Codeine misuse is as serious a problem to society as misuse of stronger opioids					
Patients do not fully understand the risk of dependence in taking over the counter medicines containing codeine					
Patients believe that over the counter medicines containing codeine are safe					

The following statements examine your opinion surrounding 'patients' use of codeine medications outside of normal medical practice; can you please indicate your agreement with the following statements;

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Patients who knowingly take medicines containing codeine for non-medical reasons may do so to enhance a positive experience or emotion					
Patients who knowingly take medicines containing codeine outside of normal medical practice may do so to reduce illicit opiate withdrawals					
Patients who knowingly take medicines containing codeine outside of normal medical practice may do so to reduce withdrawal headaches associated with consecutive longer term codeine use					
Patients who knowingly take medicines containing codeine outside of normal medical practice may choose to ignore the risk associated with their use					
Patients who misuse other opiates are more likely to request medicines containing codeine than other patients					
Patients who are prescribed other drugs that have a depressant effect on the central nervous system are more likely to request medicines containing codeine than other patients					
Patients with a history of problematic alcohol use are more likely to request medicines containing codeine than other patients					

The following statements examine codeine dependence; can you please indicate your agreement with the following statements;

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Patients who take their codeine medication as prescribed are not at risk of developing a codeine dependence					
Patients do not fully understand the risk of dependence when taking prescribed medicines containing codeine					
I find it difficult to identify problematic use of medicines containing codeine (including OTCs) without the patient first telling me					
I am confident that I can identify codeine dependence in my patients					
Females are at higher risk of developing a codeine dependence than their male counterparts					
Codeine dependence can be managed effectively in general practice					

The following statements examine screening, support services and training in managing codeine dependence; can you please indicate you level of agreement with the following;

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
I have suitable screening methods that I use to identify inappropriate use of medicines containing codeine					
Support services are readily available in my area to help those with a codeine dependence problem					
I am fully aware of best practice in managing codeine misuse and dependence					
I would like more instruction on prescribing potentially addictive medications					

In an average month approximately how many patients have you suspected of having a codeine dependence problem? (insert number)
Can you describe the type of patient behaviours that trigger your suspicion of codeine misuse?
Can you describe types of treatments that you use for patients with codeine dependence?
In the past month approximately how many patients with a codeine dependence have you referred on to a specialist addiction service? (insert number)
What were the main reasons for referring patients onto specialist treatment?

We would like to know if you are aware of any new approaches, good practices or innovations in relation to the prevention, identification (e.g. screening), monitoring and/or management of the misuse of over the counter medications in general or codeine in particular. Please give the name/s and contact details of people from whom we could obtain further information;

Are there any other comments you wish to add in relation to codeine misuse and dependence not covered in this questionnaire?

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1√	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2√	Explain the scientific background and rationale for the investigation being reported
Objectives	3√	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4√	Present key elements of study design early in the paper
Setting	5√	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls √*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7√	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*√	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9√	Describe any efforts to address potential sources of bias
Study size	10√	Explain how the study size was arrived at
Quantitative variables	11√	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		√(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed √*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*√	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*√	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		√*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17√	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18√	Summarise key results with reference to study objectives
Limitations	19√	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20√	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21√	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22√	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.