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Title. Advertising of over-the-counter codeine-containing medicines in the EU: Differences in the regulation of advertising between Member States

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Abstract

Introduction: The availability of over-the-counter (OTC) medicines containing codeine has generated worldwide debate with increased focus on its safe use. Medicine agencies across the European Union (EU) have responded to the public health concern by placing restrictions and warnings on codeine medicines sold OTC in high street and internet pharmacies. These restrictions include direct-to-consumer advertising, however there are few published studies examining conditions of advertising across member states.

Methods: A review of the conditions of advertising was conducted by accessing information pertaining to each medicines regulatory agency allowing the sale of codeine in the EU. Each agency was asked to respond to three questions and data were collated and tabulated in Excel to demonstrate its position on OTC codeine advertising.

Results: In the EU, 12 countries allow the sale of OTC codeine, while 16 do not. Of the 12 countries permitting its sale OTC, 4 countries prohibited direct-to-consumer advertising of codeine. The majority of the countries permitting advertisements did not have any additional or special restrictions or warnings for codeine-containing products with the exception of the UK where advertising codeine was only permitted under certain restrictions including product endorsement and special warnings including its indication of use for a maximum of three days.

Conclusion: There is wide disparity in advertising of OTC codeine in the EU. Safeguards for OTC codeine use are likely to continue to remain a priority in the interest of public safety.

Key points

- There is wide disparity in the direct-to-consumer advertising of codeine sold over-the-counter (OTC) across the EU
- Countries allowing direct-to-consumer advertising may not effectively communicate the risk of developing a substance use disorder (SUD) due to codeine use
- Research is needed to examine the conditions of sale of OTC codeine and its relationship to developing a SUD

1.0 Introduction

The availability of over-the-counter (OTC) medicines containing codeine has generated worldwide debate with increased focus on its safe use (1-3). Data on codeine use and misuse across the EU remains scant and confined to French and Norwegian studies with some statistics available on SUD treatment in the UK and Ireland (4-7). In the UK in 2013-2014, 2.2% of individuals attending specialist addiction treatment services did so for codeine. In Ireland over a defined 5-year period, 1.7% of all people attending treatment did so for codeine.

Codeine is an appropriate medicine used in the short term treatment of mild-to-moderate pain; however, due to risk of developing an addiction, use for chronic pain in the longer term may result in the consumption of higher than recommended doses for longer than is medically advisable (8). There is also risk of harmful effects resulting from prolonged or over use of paracetamol, ibuprofen and aspirin contained in many combination codeine products (9-11). The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM V) currently defines 'addiction' under the term substance use disorder (SUD). Under this term the diagnosis of an SUD is based on a set of behaviours related to the use of that substance and falls into four main categories. These categories included impaired control, social impairment, risky use and pharmacological indicators such as tolerance and withdrawal.

National medicine agencies across the European Union (EU) have responded to the public health concern by placing restrictions and warnings on codeine medicines sold OTC in high street and internet pharmacies. These restrictions include the availability of codeine for self-selection (without requesting it directly from the pharmacist), limits on quantities purchased in a single transaction and drug potency (12). Previous research in 2015 has shown that 12 of the 28 EU member states allowed the sale of OTC codeine in solid dosage form (Bulgaria, Cyprus, Denmark, Estonia, Ireland, Latvia, Lithuania, Malta, Poland, France, Slovenia and the United Kingdom) and two countries (the Netherlands and Hungary) as a codeine cough linctus only. Denmark was the only member state allowing the sale of OTC codeine in supermarkets and convenience stores (behind the counter).

Recently, direct-to-consumer advertising of OTC codeine has come under the spotlight as having the potential to influence buying behaviour (2). Advertising of medicine is defined in medical law as "any form of door to door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products"(13). This specifically includes advertising to the general public, supply of samples, inducements to prescribe or supply by the gift, offer or promise of a bonus, monetary remuneration in any form, and sponsorships including travel or accommodation associated with medical conferences or medicine selling.

Direct-to-consumer advertising of OTC medicines remains controversial (14, 15). Some argue it is specifically designed to convince the consumer that the product is worth buying and will have a beneficial effect on health, with opponents claiming it misleads consumers into buying drugs they may not necessarily need or want. Counter claims to the debate argue that advertising of OTC medicines add a highly valued source of information to allow consumers to make informed decisions about self-care for pain relief (15).

Direct-to-consumer advertising of prescription drugs is illegal in the EU. However, it is suggested that consumers often access online content and view branded drug websites in the United States and New Zealand where direct-to-consumer advertising of prescription drugs is legal (16).

To date there has been limited research examining regulatory conditions related to the advertising of OTC medicines containing codeine to the public across the EU. The aim of this study was to describe the regulatory position on the advertising of codeine for sale OTC in each of the EU member states permitting its sale to the public without a medical prescription, specifically to (i) identify which countries allowed direct advertising of OTC medicines containing codeine and (ii) if the harms imposed by codeine consumption were adequately communicated and aimed to prevent unnecessary patient exposure to risk of developing a SUD.

2.0 Methods

Data were collected between September 2017 and February of 2018. Initially, current regulation on the sale of OTC codeine was established for each of the EU member states. First, the website of each of the relevant medicines agencies was searched over a 2 week period at the beginning of the study. Each website was screened using the English language option. The objective of the web search was to establish if codeine was permitted for sale OTC and to check for information relating to the advertising of OTC medicines. Second, agencies were contacted by e-mail to obtain specific information related to direct-to-consumer advertising of codeine. Medicines agencies not responding by e-mail within a 6-week time frame (Denmark, France, Bulgaria and Slovenia) were followed up by telephone call by one of the research team members. All medicines agencies made a reply giving a 100% response rate.

A topic guide was devised to guide the data collection and to ensure that comparisons could be made. Three subject areas were included: 1) Level and type of restrictions placed on all forms of direct-to-consumer advertising of OTC medicines containing codeine. 2) Labelling criteria on packaging including indication related to the risk of addiction and any other patient information specific to codeine. 3) Complaints received by the medicines agency related to direct consumer advertising of OTC medicines containing codeine.

Data were collated and summarised and entered into an Excel® spreadsheet. Two members of the research team independently tabulated the data under each of the three main questions. The content of this information was discussed, crosschecked and agreed before compiling into two tables (17). A third member of the research team checked the content of the final table and reviewed the data against the written content received by eleven of the twelve countries. One country (Bulgaria) had not provided a written response so verbal responses noted by the researcher were checked in this case.

3.0 Results

3.1 Conditions of codeine advertising across the EU

Table 1 shows the permitted sales of OTC codeine medicines in the EU. Recent rescheduling of codeine has occurred in two European countries. In 2015 Hungary removed the sale of codeine cough mixture for sale without a medical prescription and in 2017 France restricted codeine to prescription only (18). Twelve countries allow the sale of OTC codeine, while 16 do not. Table 2 shows the conditions of advertising, packaging requirements of OTC codeine and if complaints were received by the medicine agency. Of the 12 countries permitting its sale OTC, 4 countries prohibited direct-to-consumer advertising of codeine. All countries highlighted that direct-to-consumer advertising of medicines was stipulated in the countries Medicines Act.

The majority of the countries permitting advertisements did not have any additional or special restrictions or warnings for codeine-containing products with the exception of the UK where advertising codeine was only permitted under certain restrictions relating to product endorsement and special warnings, including its indication of use for a maximum of 3 days. Equally, the UK was the only country stipulating advertising warnings with respect to the risk of developing an addiction. The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK was the only agency indicating advertising complaints made by members of the public. This was related to two OTC codeine products, Syndol® and Solpadeine® Max. It was claimed that promotional materials for Syndol® were inadequate and the latter complaint relating to Solpadeine ®Max suggested that warnings around use of codeine were not clearly presented. In both cases the MHRA did not uphold the complaint, however did make recommendations resulting in changes to advertising of both products.

4.0 Discussion

The study found wide disparity in direct-to-consumer advertising of OTC codeine across the EU. It is likely that countries banning the advertising of codeine perceive the risks to be greater than those that did not, including the potential for consumers to develop a SUD from inappropriate codeine use. For some countries like Denmark and the UK, allowing direct-to-consumer advertisement may hold the opposite viewpoint, either that adequate

structures are already in place to prevent excessive use, or that the levels of codeine contained in OTC formulations are too small to induce a SUD (2).

Across EU member states, there appears to be a lack of evidence to evaluate the effects of codeine advertising on consumers decision to purchase , consumption patterns or levels of SUD. However, television advertisements are considered to be an important promotional tool on potential buyers of medicines, particularly analgesics. Non-opioid analgesics are some of the most popular OTC medicines purchased across Europe and studies have shown that television advertising has a significant impact on purchase decisions (15). Marketing strategies such as that adopted by Purdue Pharma ® for promoting OxyContin® directly to doctors was shown to play a huge role in the opioid epidemic in the United States (19). The concern would be that promoting codeine directly to the public through any form of advertisement may play a role in medicine use and subsequently development of a SUD. Additionally, online promotional advertising of prescription medicines accessible globally presents additional challenges for national regulatory agencies not permitting direct-to-consumer advertising of medicines either prescription or OTC. While traditional print and broadcast media can be controlled to a certain extent, online promotions have the ability to cross national boundaries through various media platforms to countries when it is not legal (16).

Of the countries allowing direct-to-consumer advertising, the UK appear to be the most comprehensive in communicating risk of developing an addiction in advertising materials to the public, although some complaints were received. While the impact of such communication remains unquantifiable, other countries permitting direct-to-consumer advertising should consider improvements in communication to highlight the risks of SUD in the interest of public health. Studies have shown that content contained in advertisements can change perceptions surrounding the drug's efficacy, risk and benefit (20). The current study did not review if the advertisements met the conditions of the competent authorities and while it was stipulated that all advertising materials must be comprehensive, valid and include information like the product name, active ingredients, adverse drug reactions, precautions and contraindications, it is likely that inclusions of health warnings on packaging and improvements in patient-information leaflets (PILs) could further educate the public on safe use and potential risk of SUD. It should be noted that all medicines must, under EU regulation, include PILs providing information on the safe and appropriate use of the medicine. However, studies have shown that patients' often fail to read and/or understand the information provided in the PIL (21). It is also important in the future to establish if direct sale of OTC codeine in countries with fewer restrictions of sale correlate with national figures for codeine-specific SUD, adverse drug reactions, intoxication and mortality. Codeine consumption resulting in SUD is now recognised around the world as a serious problem (22) and shows the importance of reviewing and challenging current regulation. From the perspective of drug safety and risk management, it is important to investigate fully the impact of codeine advertising on developing a SUD.

One of the limitations of the study is that it did not evaluate the advertising materials from the eight countries permitting the advertising of codeine OTC. Therefore we are unable to comment directly on the content of advertising in each member state. All countries were accessed in the English language and there is some possibility that information could have been lost through translation other relevant information may have been available published in the local language. However all responses given by the competent authority in each country were done through the English language.

5.0 Conclusions

The condition of sale and advertising of OTC codeine and its association with developing a SUD is likely to remain a subject of popular debate into the future. Safeguards are likely to continue to remain a priority in the interest of public safety in many EU member states and worldwide. Strengthening medicine safety is a key priority for the European Medicines Agency and direct-to-consumer advertising of codeine in countries allowing its sale without direct medical supervision needs to be further examined to ensure it is adequate and is not placing consumers at increased harm.

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Compliance with Ethical standards:

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest: MF, PK, AK and PD have no conflicts of interest to declare

Ethical approval: Ethical approval was not required for the study as this study met the criteria for service evaluation.

Table 1: Sale of over-the-counter codeine-containing medicines according to EU member states

Country	**National Competent Authorities**	**Permitted to sell medicines containing codeine over-the-counter without a medical prescription (Yes/No)**
Austria	Austrian Agency for Health and Food	No
Belgium	Federal Agency for Medicine and Health products	No
Bulgaria	Bulgarian Drug Agency	Yes
Croatia	Agency for Medicinal Products and Medical Devices of Croatia	No
Cyprus	Ministry for Health	Yes
Czech Republic	State Institute for Drug Control	No
Denmark	Danish Medicines Agency	Yes
Estonia	State Agency of Medicines	Yes
Finland	Finnish Medicines Agency	No
France	French National Agency of Medicine and Health Products Safety	No
Germany	Federal Agency for Drug and Medical Devices	No
Greece	National Organisation for Medicines	No
Hungary	National Institute for Pharmacy	No
Ireland	Health Products Regulatory Authority	Yes
Italy	Italian Medicines Agency	No
Lativa	State Agency of Medicines of the Republic of Latvia	Yes
Lithuania	The State Medicines Control Agency of Lithuania	Yes
Luxembourg	Ministry of Health	No
Malta	Medicines Authority of Malta	Yes
Netherlands	Medicines Evaluation Board	Yes (Cough linctus only)
Poland	Main Pharmaceutical Inspectorate	Yes
Portugal	National Authority of Medicines and Health Products	No
Romania	National Agency for Medicines and Medical devices	No
Slovakia	State Institute for Drug Control	No
Slovenia	Agency for Medicinal products and Medical devices of the Republic of Slovenia	Yes
Spain	Spanish Agency for Medicines and Health products	No
Sweden	Medical Products Agency	No
United Kingdom	Medicine and Healthcare products Regulatory Authority	Yes

Table 2. Conditions of advertising for over-the-counter (OTC) codeine-containing medicines

Country permitting sale of OTC codeine	**Permitted direct to the consumer advertising of medicines containing codeine OTC without a medical prescription**	**Advertising conditions for OTC codeine sales**	**Packaging requirements related to risk of addiction**	**Advertising complaints received**
Bulgaria	Yes	Advertising of codeine is permitted for OTC combination products. Expert council of advertising draws expertise on the advertising of medicines and all advertisements and promotions must be approved by the Bulgarian Drug Agency (BDA). The BDA monitors pharmaceutical promotion of OTC drugs	No requirement to include any special warning indicating the risk of addiction	None
Cyprus	No			
Denmark	Yes	Advertising is permitted for OTC codeine and must comply with rules for advertising of medicine stipulated in the Danish Medical Act (2014). Advertisements must be comprehensive and valid and cannot be misleading or exaggerate the abilities of the medicine	Packaging does not need to carry a label indicating the risk of addiction or any additional special warnings	None
Estonia	Yes	Advertising is permitted and must comply with the Medicinal Products Act of Estonia, Chapter 4 Division 1. Advertising of the product to the general public must contain sufficient information for the correct and safe use of the product	No requirement for labelling or warnings with respect to codeine addiction	None
Ireland	No			
Lativa	No			
Lithuania	Yes	Advertising of OTC codeine is not prohibited according to the Law on Pharmacy of Lithuania. Must follow the general rules outlined for advertisement of medicines to the general public	No special requirements on packaging	None
Malta	Yes	Medicine containing codeine may be advertised to the general public by virtue of their composition and purpose and in line with regulation (2005). The advertisement should not be misleading and encourage the rational use of medicine by presenting it clearly and objectively	No special requirements	None
Netherlands	Yes (Cough linctus only)	Advertisements must be in accordance with the Dutch Medicines Act and code for pharmaceutical advertising (CGR) that governs the advertising of medical products to the public. They must contain the name of the product and the information necessary for correct use of the medicine	There are no special warnings on the label required to illustrate the risk of addiction. However it is mentioned in the Patient Information Leaflet (PIL)	None
Poland	No			
Slovenia	Yes	Medicines containing codeine available without a prescription in Slovenia have no restrictions regarding advertising to the public. Advertising must contain sufficient information for correct and safe use	No requirements to carry additional warnings of addiction	None
United Kingdom	Yes	Permitted to advertise codeine under restriction and all advertising materials must be submitted and approved by the Proprietary Association of Great Britain. Advertisements of codeine cannot appear to exaggerate the abilities of the medicine or appear to be endorsed by a healthcare professional	Labelling and packaging must adhere to contain conditions. Must indicate that the medicine is for 3 days use only and can cause addition. Straplines must not refer to the power or strength of the medicine. Packaging materials must also host a critical health panel. This panel provides information for self-assessment of symptoms and signs of addiction	Two complaints received by the Medicines and Healthcare products Regulatory Agency (MHRA) regarding the advertisement of OTC codeine

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