Pre- Review Report:

Preparations of codeine listed in Schedule III of the 1961 Single Convention on Narcotic Drugs

Acetyldihydrocodeine
  Codeine
Dihydrocodeine
Ethlymorphine
Nicocodine
Nicodidodine
Norcodeine
Pholcodine

Expert Committee on Drug Dependence
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This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization
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References
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Executive Summary

Preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs include a variety of compounds: acetyldihydrocodeine, codeine, dihydrocodeine, ethylmorphine, nicocodine (nicocodine), nicodicodine (nicodicodine), norcodeine and pholcodine. The Schedule also includes these compounds when formulated with one or more other ingredients containing not more than 100 milligrams of the drug per dosage and with a concentration of not more than 2.5 per cent in undivided preparations.

The preparations are all opioids (derived from a natural opiate or of a synthetic origin); one norcodeine is a non-active metabolite. Some such as nicocodine and nicodicodine (nicodicodine) were discovered in 1904, and acetyldihydrocodeine in Germany in 1914. Most if not all have been marketed as antitussive medicines (cough suppressants), and to provide analgesia for mild to moderate pain (acetyldihydrocodeine, ethylmorphine, nicocodine, nicodicodine). Pholcodine helps suppress unproductive coughs and acts as a mild sedative effect, but little or no analgesic effects.

Some, notably acetyldihydrocodeine (a very close relative derivative of Thebacon), nicocodine, an ester of codeine closely related to dihydrocodeine and nicodicodine are not commonly used. Norcodeine is the N-demethylated a metabolite of codeine and has relatively little opioid activity in its own right. Whereas codeine and dihydrocodeine either alone or compounded with paracetamol or a nonsteroidal anti-inflammatory drug such as aspirin or ibuprofen are commonly used worldwide.

In the main, preparations listed in Schedule III are administered orally. Both codeine and dihydrocodeine products can be purchased over the counter in many European and Pacific Rim countries and generally contain from 2 to 30 mg per dosing unit. As weak opioid drugs the Schedule III preparations (except norcodeine) reduce the sensitivity of the respiratory centre to carbon dioxide, which may result in decreased tidal volume and decreased respiratory rate. The triad of coma, pinpoint pupils, and respiratory depression apply to these substances as evidence of toxicity.

The preparations are thought to show stereochemistry (certainly codeine and dihydrocodeine) and are metabolised by the genetically polymorphic enzyme CYP2D6, although the clinical significance of this activity remains unresolved even for codeine and dihydrocodeine. Pholcodine is an exception with regards its pharmacokinetics, the others being short acting compounds.

It is difficult to estimate the prevalence of use of the preparations listed in Schedule III because of the variation in regulations governing the different formulations of the drugs. However, abuse of over the counter (OTC) antitussives containing codeine, dihydrocodeine and pholcodine is a continuing problem in the United States and throughout the world. The continuing problem is thought to be due to increasing availability, social acceptance and the perception, especially among the young that pharmaceutical drugs are safe. With legislative activity, educational, and economic initiatives there may have been a shift to abuse to easily attainable cough and cold preparations.

Codeine and dihydrocodeine misuse and dependence has been described. Codeine dependence was associated with daily use of codeine, faking or exaggerating symptoms to
get a prescription for codeine and 'pharmacy shopping', while dependence arose with dihydrocodeine through treatment of pain and cough.
1. Substance identification

A. International Non-proprietary Name (INN)

Acetyldihydrocodeine (O-Acetyldihydrocodeine)
Codeine
Dihydrocodeine
Ethylmorphine (chlorhydrate de Codethylaine, codethyline)
Nicocodine (nicocodeine)
Nordicodine (nicodicodine)
Norcodeine
Pholcodine (β-4-morpholinylethylmorphine, homocodeine, pholcodin; pholcodinum).

B. Chemical Abstract Service (CAS) Registry Number

<table>
<thead>
<tr>
<th>Substance</th>
<th>Registry Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetyldihydrocodeine</td>
<td>0003861-72-1</td>
</tr>
<tr>
<td>Codeine¹</td>
<td></td>
</tr>
<tr>
<td>Codeine base (anhydrous)</td>
<td>76-57-3</td>
</tr>
<tr>
<td>Codeine base (monohydrate)</td>
<td>6059-47-8</td>
</tr>
<tr>
<td>Codeine hydrochloride</td>
<td>1422-07-7</td>
</tr>
<tr>
<td>Codeine phosphate (anhydrous)</td>
<td>52-28-8</td>
</tr>
<tr>
<td>Codeine phosphate (hemihydrate)</td>
<td>41444-62-6</td>
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<tr>
<td>Codeine phosphate (sesquihydrate)</td>
<td>5913-76-8</td>
</tr>
<tr>
<td>Codeine sulfate (anhydrous)</td>
<td>1420-53-7</td>
</tr>
<tr>
<td>Codeine sulfate (trihydrate)</td>
<td>6854-40-6</td>
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<tr>
<td>Dihydrocodeine</td>
<td>125-28-0</td>
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<tr>
<td>Dihydrocodeine bitartrate</td>
<td>5965-13-9</td>
</tr>
<tr>
<td>Dihydrocodeine hydrochloride</td>
<td>36418-29-8</td>
</tr>
<tr>
<td>Dihydrocodeine hydroiodide</td>
<td>5965-15-1</td>
</tr>
<tr>
<td>Dihydrocodeine phosphate</td>
<td>24204-13-5</td>
</tr>
<tr>
<td>Ethylmorphine</td>
<td>0000076-58-4</td>
</tr>
<tr>
<td>Nicocodine</td>
<td>3688-66-2 or 58263-01-7 (HCl)</td>
</tr>
<tr>
<td>Nicodicodine</td>
<td>808-24-2</td>
</tr>
<tr>
<td>Norcodeine</td>
<td>Not available: metabolite of codeine</td>
</tr>
<tr>
<td>Pholcodine</td>
<td>509-67-1</td>
</tr>
</tbody>
</table>

C. Other Chemical Names

Acetyldihydrocodeine
4,5-Epoxy-3-methoxy-9a-methylmorphinan-6-yl acetate
3-O-Methyl-6-O-acetylmorphine

¹ http://www.inchem.org/documents/pims/pharm/codeine.htm#SectionTitle:3.2%20Chemical%20structure
acetylcodone dihydrocodeine 6-acetate, dihydrothebacone,

**Codeine**

\((5α,6α)-7,8\)-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol

**Dihydrocodeine**

4,5α-epoxy-3-methoxy-17-methyl-morphinan-6α-ol.
\((5α,6α)-3\)-Methoxy-17-methyl-4,5-epoxymorphinan-6-ol

**Ethylmorphine**

3-ethylmorphine
Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-etoxy-17-metyl, \((5α,6α)-3\)-Ethoxy-17-methyl-7,8-didehydro-4,5-epoxymorphinan-6-ol

**Nicocodine**

6-nicotinylcodeine
\((5α,6α)-7,8\)-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-yl pyridine-3-carboxylate hydrochloride

**Nicodicodine**

6-nicotinylidihydrocodeine
Dihydrocodeine 6-nicotinate;4,5α-Epoxymorphinan-6α-ol 3-pyridinecarboxylate
\((5α,6α)-3\)-Methoxy-17-methyl-4,5-epoxymorphinan-6-yl nicotinate

**Norcodeine**

N-demethylcodeine
\((5α,6α)-3\)-Methoxy-7,8-didehydro-4,5-epoxymorphinan-6-ol

**Pholcodine**

3-(2-(4-Morpholinyl)ethyl)morphine
\(β\)-morfolinoetilmorfin
7,8-didehydro-4,5-alpha-Epoxy-17-methyl-3-(2-morpholinoethoxy) morphinan-6-alpha-ol
\((5α,6α)-17\)-Methyl-3-[2-(4-morpholinyl)ethoxy]-7,8-didehydro-4,5-epoxymorphinan-6-ol
6-hydroxy-N-methyl-3-(2-morpholinoethoxy)-4,5 epxymorphinen-7
3-(2-morfolinoetossi)-4,5-eorrisi-N-metil-7-morfinene

D. **Trade Names (including combinational medicinal products)**[1]

**Acetyldihydrocodeine**

Logicin

**Codeine**

Abitran, Actifed, Adibeta, Afebralgo, Aferin, Algiespas, Amiorel, Anakod, Antigrippine, APC, Apex, Asedok, Benamine Expectorans, Benzokodin, Bislolvon Compositum, Bromocod N, Bromocodeina, Bronchocodine, Bronchofluid, Broncoton, Bronquibasol, Bronchotussine, Brosol, Buscalginol, Cerebro, Cimex, Co-Efferalgan, Co Dafalgan, Codasel, Codeidol, Codeinol, Codelasa, Codepal, Codioxal, Codipront, Codol, Coedefen, Coldeks, Corex, Coveral, Dafalgan Codeina, Codeine Linctus, Codis, Codeinum, Codicept, Coducept,

With paracetamol (co-codamol): e.g., brands Paracod, Panadeine Tylenol-with-codeine series, including Tylenol 3 and 1,2, and 4) With aspirin (co-codaprin);
With ethylmorphine, Codenur, Fenekodin, Jucodine, Kodineks, Kodipen, Kodis, Kodulumine, Koludine, Ludicodine, Neocodin/e
With ibuprofen (Nurofen Plus).
With phenacetin (Emprazil with codeine No. 1, 2, 3, 4, 5)
With naproxen, indomethacin, diclofenac
More complex mixtures:
Aspirin + paracetamol + codeine ± caffeine ± antihistamines (e.g., Synalgos-DC)

Dihydrocodeine

Etheylmorphine
Codetilina Eucalipto Hè, Clarix 0,1%, Codethylin, Coselan, codethyline, dionine)Dinacode N, Dionina, Grippil, Mindol Merck, Saintbois, Codethyline (Erfa) / Dionina (Merck) / Lepheton (Meda)

Nicodicon
Lyopect, Nicotinoylcodeine, Tusscodin, Tusscodin retard

Nicodideine
Not known to be available as a medicine

Norcodeine
Metabolite of codeine: not available as a medicine

Pholcodeine
Benylin, Galenphol, Covonia, Children’s dry coughs, Evaphol, Famel linctus, Pholcomed, Pervorial, Phol Tussil, Phol Tux Expectorans, Rectoceptal, Tixilix daytime, Pavacol-D
E. Street Names

The street cocktail “purple drank” may take several forms but seems to involve some type of cough syrup containing codeine and promethazine hydrochloride, an antihistamine with sedative properties. The cough syrup typically mixed with a soft drink and candy, with some variants including alcohol is popular with professional American athletes and southern rap music. Other names include “lean”, “drank”, “barre”, “purple stuff”, “syrup”, and “sizzurp” [2].

Street names for codeine alone include captain cody, cody, little c, and school boy. For Tylenol with codeine, street names include T1, T2, T3, T4, and dors and fours. Dihydrocodeine is sold as DFs or Diffs on the street. Triple C, Robitussin or CCC are also names for cough syrups containing codeine or pholcodine.

Street names for acetyldihydrocodeine, ethylmorphine, pholcodine, nicocodeine and nicodicidodine were not found.

F. Physical Appearance

Codeine, pholcodine and ethylmorphine appear as colourless crystals or white crystalline powders: light affects codeine, which effervesces in dry air, and has a bitter taste. Dihydrocodeine is a white to yellowish crystalline powder. The physical appearance of acetyldihydrocodeine, nicocodeine, nicodicidodine and norcodeine were not ascertained.

G. WHO Review History

A review of the analgesic and antitussive effects of codeine, dihydrocodeine, ethylmorphine, pholcodine, nicocodeine, and nicodicidodine was published in the Bulletin of the World Health Organization in five instalments between 1968 and 1969 in 5 instalments. The first, second, and third instalments dealt, with the analgesic action of codeine; its alternates for pain relief; and the antitussive action of codeine. The fourth instalment and fifth an assessment of potential alternates with antitussive action [3-7].

Preparations of codeine have not previously been reviewed by the WHO ECDD.

2. Chemistry

A. Chemical Name (IUPAC Name: CA Index Name)

**Acetyldihydrocodeine**

\[(4R,4aR,7S,7aR,12bS)-9\text{-methoxy}-3\text{-methyl}-2,4,4a,5,6,7,7a,13\text{-octahydro-1H-methanobenzofuro[3,2-e]isoquinolin-7-yl}]\text{ acetate}

**Codeine**

\{(4R,4aR,7S,7aR,12bS)-9\text{-methoxy}-3\text{-methyl}-2,4,4a,7,7a,13\text{-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-ol}\}
**B. Chemical Structure**

The molecular formula and weight of the preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs can be found in Table 1. Chemical structures are detailed below:

Chemical structure acetyldihydrocodeine
Chemical structure codeine

Chemical structure dihydrocodeine
(http://www.chemspider.com/Chemical-Structure.4447600.html)

Chemical structure ethylmorphine
Chemical structure nicodicodine

Chemical Structure nicocodine
Chemical structure norcodeine
(http://www.chemspider.com/Chemical-Structure.8101508.html?Rid=74ad9a70-48a5-4fee-9e5c-123fcbddd8ef)

Chemical structure pholcodine
(http://www.chemspider.com/Chemical-Structure.4470854.html?rid=de0a8e6f-0d7f-48a4-ac23-b252fe4beb44)

C. Stereoisomers

Details about the stereoisomerism of acetyldihydrocodeine was not established. The Drugbank
(https://www.drugbank.ca/drugs/DB01538) describes the compound as polycyclic with a four-ring skeleton with three condensed six-member rings forming a partially hydrogenated phenanthrene moiety, one of which is aromatic while the two others are alicyclic.

Opiates however, are known for their stereospecificity and codeine is no exception. In early pre-clinical work, l-codeine was active in the mouse tail-flick test as well as in the hot plate test whether given orally or subcutaneously. The d-isomer of codeine was inactive in both tests up to 100 mg/kg but caused hyperexcitability, convulsions and ultimately death. Although l-codeine was more potent
than d-codeine inhibiting the cough reflex in the anesthetized cat, the d-compound did have good activity. In these animals, l-codeine did not significantly affect the cardiovascular parameters at the doses tested, whereas d-codeine caused a significant but transient decrease in the blood pressure and heart rate [8].

The production of (−)-dihydrocodeine has been described [9], whereas, details of any stereoisomeric form for ethylmorphine, nicocodine, nicodicodine, norcodeine and pholcodine were not found.

D. Methods and Ease of Illicit Manufacturing

Many of the opioid preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs are older drugs developed in the early 1900s such as nicocodine and nicodicodine (nicocodeine) in 1904. Nicocodine production involves treating anhydrous codeine base with nicotinic anhydride at 130 °C (Pongratz and Zirm in Monatshefte für Chemie in 1957). Acetyldihydrocodeine was discovered in Germany in 1914.

Codeine, a natural product of the poppy plant paver somniferum var. album can be extracted from opium. The synthetic production of codeine is possible by the methylation of morphine. ‘Krokodil’ (also known as crocodile, croc, krok, and poor man’s heroin), a homemade injectable drug that has been used as a cheap heroin substitute in Russia, Europe, the UK and North America has codeine as its starting point [10, 11].

A. Chemical Properties

Chemical Properties of preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs include a variety of compounds: acetyldihydrocodeine, codeine, dihydrocodeine, ethylmorphine, nicocodine (nicocodeine), nicodicodine (nicodicodine), norcodeine and pholcodine (www.ChemSpider.com/; https://www.chemicalbook.com/; US Environmental Protection Agency’s EPISuite™ (Table 1)

Home manufacture using over-the-counter codeine or illicitly sourced pharmaceuticals has also been reported among injecting and recreational drug users [12]. The illicit manufacture of acetyldihydrocodeine, ethylmorphine, nicocodine, nicodicodine, norcodeine and pholcodine has not been described in the peer-reviewed literature.
### Table 1: Chemical properties of preparations listed in Schedule III

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acetyl Dihydrocodeine</th>
<th>Codeine</th>
<th>Dihydrocodeine</th>
<th>Ethlymorphine</th>
<th>Nicocodeine</th>
<th>Nicodicodine</th>
<th>Norcodeine</th>
<th>Pholcodine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>( \text{C}<em>{20}\text{H}</em>{23}\text{NO}_4 )</td>
<td>( \text{C}<em>{18}\text{H}</em>{21}\text{NO}_3 )</td>
<td>( \text{C}<em>{18}\text{H}</em>{23}\text{NO}_3 )</td>
<td>( \text{C}<em>{19}\text{H}</em>{23}\text{NO}_3 )</td>
<td>( \text{C}<em>{24}\text{H}</em>{26}\text{N}_2\text{O}_4 )</td>
<td>( \text{C}<em>{24}\text{H}</em>{26}\text{N}_2\text{O}_4 )</td>
<td>( \text{C}<em>{17}\text{H}</em>{19}\text{NO}_3 )</td>
<td>( \text{C}<em>{23}\text{H}</em>{30}\text{N}_2\text{O}_4 )</td>
</tr>
<tr>
<td>Molecular Weight (g/mol)</td>
<td>341.4</td>
<td>299.36</td>
<td>301.38</td>
<td>313.39</td>
<td>404.5</td>
<td>406.47</td>
<td>285.34</td>
<td>398.55</td>
</tr>
<tr>
<td>Melting point (°C)</td>
<td>172.37</td>
<td>154</td>
<td>192-193</td>
<td>123</td>
<td>209.51</td>
<td>208.80</td>
<td>309</td>
<td>91</td>
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<tr>
<td>Boiling Point (°C)</td>
<td>465.4 ± 45.0</td>
<td>440.69°C</td>
<td>462.0 ± 45.0</td>
<td>472.2 ± 45.0</td>
<td>549.7 ± 50.0</td>
<td>553.3 ± 50.0</td>
<td>467.7 ± 45</td>
<td>521.67°C</td>
</tr>
<tr>
<td>Density (g/cm³)</td>
<td>1.300</td>
<td>1.3200</td>
<td>1.3 ± 0.1</td>
<td>1.30</td>
<td>1.40</td>
<td>1.300</td>
<td>1.4±0.1</td>
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<td>Index of Refraction:</td>
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<td>1.643</td>
<td>1.654</td>
<td>1.668</td>
<td>1.650</td>
<td>1.675</td>
<td>1.659</td>
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<tr>
<td>Solubility (in water)</td>
<td>1 in 120</td>
<td>1 in 4.5</td>
<td>1 in 10</td>
<td>In ethanol</td>
<td>1 in 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissociation Constant: pKa</td>
<td>9.02</td>
<td>8.2 (20°)</td>
<td>8.8 (25°)</td>
<td>8.2 (20°)</td>
<td>9.23 (25°)</td>
<td>9.2 (25°)</td>
<td>8.0, 9.3 (37°)</td>
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<tr>
<td>Log partition coefficient: Log P (octanol-water)</td>
<td>2.26</td>
<td>0.6</td>
<td>1.5</td>
<td>1.8</td>
<td>2.80</td>
<td>2.96</td>
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<tr>
<td>Ultraviolet Spectrum (nm)</td>
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<td>283</td>
<td>284</td>
<td>284</td>
<td>284</td>
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### B. Identification and Analysis

#### Chemical spot tests [13]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Liebermann’s Test</th>
<th>Mandelin’s Test</th>
<th>Marquis Test</th>
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<tbody>
<tr>
<td>Acetyldihydrocodeine</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>Black</td>
<td>Green</td>
<td>Violet</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>Grey, Green</td>
<td></td>
<td>Violet</td>
</tr>
<tr>
<td>Ethylmorphine</td>
<td>Marquis Test</td>
<td>Yellow, Violet,</td>
<td>Black</td>
</tr>
<tr>
<td>Nicocodine</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norcodeine</td>
<td>Marquis Test</td>
<td>Blue, Yellow,</td>
<td>Violet</td>
</tr>
<tr>
<td>Nicodicodine</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norcodeine</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pholcodine</td>
<td>Liebermann’s Test</td>
<td>Black</td>
<td>Violet</td>
</tr>
</tbody>
</table>

To analyse the preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs a variety of different chromatographic tests are available.

For instance:

- an ultra-performance liquid chromatographic-tandem mass spectrometric method was developed and fully validated for the simultaneous determination of pholcodine, morphine, hydromorphone, oxymorphone, norcodeine, codeine, dihydrocodeine, oxycodone, 6-Monoacetylmorphine (6-MAM), hydrocodone, ethylmorphine, tramadol, 2-ethylidine-1,5-dimethyl-3,3-diphenyl pyrrolidine (EDDP), buprenorphine, propoxyphene, and methadone in blood. The limit of quantification ranged from 0.5 to 2.5 ng/mL depending on the compound and the therapeutic concentration [14].

- Sixteen different opioids including codeine, dihydrocodeine, ethylmorphine, fentanyl, hydrocodone, hydromorphone, morphine, norbuprenorphine, norcodeine, norfentanyl, oxycodone, oxymorphone, pholcodine have been detected using a triple-quadrupole and a quadrupole time-of-flight mass analyzer to quantify 16 opioids in human plasma [15].

- The quantitative detection of ethylmorphine has been determined in human hair using UHPLC high-resolution mass spectrometry [16].

- A chemiluminescence (CL) method has been described for pholcodine in human plasma and syrup based on the fact that pholcodine can greatly enhance the weak CL emission of reaction between tris(1,10 phenanthroline)ruthenium(II), Ru(phen)$_3^{2+}$, and acidic Ce(IV). The limit of detection (LOD) (S/N = 3) was 2.5 ng/mL [17].
3.  **Ease of Convertibility Into Controlled Substances**

Some preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs can be converted into a controlled substance. For instance, the treatment of codeine in chloroform with boron tribromide has consistently given morphine in 90-91% yield after a simple isolation procedure [18].

In the early 1980s a large number of small-scale illicit laboratories were reported to be producing morphine and heroin from commercially available, codeine-based pharmaceutical products in New Zealand. The codeine demethylation procedure was based on the use of pyridine hydrochloride. Only very simple laboratory equipment and reagents were required and production was achieved easily with little or no chemical background, by following a recipe. The process yielded a product known as 'homebake' [19]. See also section D above.

Codeine is also used to manufacture dihydrocodeine and acetyldihydrocodeine, and may also be used to manufacture the drugs usually manufactured by conversion of thebaine [UNODC, 2019]. (https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1953-01-01_3_page005.html/).

Information about the ease of convertibility of acetyldihydrocodeine, ethylmorphine, nicocodine, nicododeine, norcodeine and pholcodine into controlled substances has not been reported in the scientific literature

4.  **General Pharmacology**

   **A. Routes of administration and dosage**

In the main, preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs where they are clinically available as medicines as shown in section D above (acetyldihydrocodeine, codeine, dihydrocodeine, ethylmorphine, nicocodine (nicocodeine), and pholcodine are administered orally.

The drug bank (https://www.drugbank.ca/drugs/DB01538) suggests that details of the pharmacology of acetyldihydrocodeine and nicododeine (nicocodeine), are currently unavailable.

Nicocodeine cough medicines are available as syrups, extended-release syrups, and sublingual drops. Analgesic preparations are also available in the form of sublingual drops and tablets for oral administration (https://www.revolvy.com/page/Nicocodeine).

Dihydrocodeine products can be purchased over the counter in many European and Pacific Rim countries and generally contain from 2 to 20 mg of dihydrocodeine per dosing unit combined with one or more other active ingredients such as paracetamol (acetaminophen), aspirin, ibuprofen, antihistamines, decongestants, vitamins, medicinal herb preparations, and other such ingredients. In some countries 30 mg tablets and 60 mg controlled-release tablets are available over the counter and 90 and 120 mg strengths may be dispensed for specific indications (https://www.dralways.com/product/416).
In the United States, dihydrocodeine is dispensed in 16 and 32 mg formulations and many include acetaminophen and caffeine. In the UK and other countries, 30 mg tablets containing only dihydrocodeine as the active ingredient are available. In the UK, a 40 mg Dihydrocodeine tablet is available as DF-118 Forte and can be prescribed for palliative care. (https://bnf.nice.org.uk=dihydrocodeine).

Ethylmorphine considered to be less potent than morphine but more potent than codeine [20], is available in oral dosages ranging from 5 to 30 or 50 mg. Like codeine and close chemical relatives, ethylmorphine is not advocated for intravenous administration as the sudden histamine release can have dangerous impacts (https://infogalactic.com/info/Ethylmorphine). Psychonaut reports Tussipax tablets available as over-the-counter medication in France contain 10 mg of ethylmorphine and 10 mg of codeines; in Norway Cosylan and Solviect comp. cough syrups contain 1.7 mg/mL and 2.5 mg/mL ethylmorphine hydrochloride respectively; in Sweden the prescription medication Cocillana-Etyfin cough syrup contains 2.5mg/mL ethylmorphine. Lepheton, a combination containing 0.82 mg/mL ethylmorphine hydrochloride and 2.05 mg/mL ephedrine is also available. In the UK and USA there are no legal preparations of ethylmorphine and it is not available for medical purposes (https://psychonautwiki.org/wiki/Ethylmorphine). Ethylmorphine was used in ophthalmic preparations as Dionine to treat inflammations of the eye in 1904, but this preparation does not seem to have survived today [21].

Pholcodine classified as an antitussive (opioid cough suppressant) has a mild sedative effect with little or no analgesic effects. According to the electronic medicines compendium (https://www.medicines.org.uk/emc/product/4598/smpc), Pholcodine syrup is a clear orange viscous syrup containing 5mg/5 mL pholcodine and may be taken (up to 10 mL), 6 times a day. Pholcodine is not prescribed in the United States or Canada where it is classified as a Schedule I drug. The British National Formulary (bnf.nice.org.uk/drug/pholcodine.html) states when prepared extemporaneously, Pholcodine Linctus, BP should consist of pholcodine 5 mg/5 mL in a flavoured vehicle, containing citric acid monohydrate 1% and Pholcodine Linctus, Strong, BP consists of pholcodine 10 mg/5 mL in a suitable flavoured vehicle, containing citric acid monohydrate 2%

C. Pharmacokinetics

Acetyldihydrocodeine

For some of the preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs the pharmacokinetics are poorly described, such as acetyldihydrocodeine, which is a 6-acetyl derivative of dihydrocodeine and is metabolised in the liver by demethylation and deacetylation to produce dihydromorphine. However, it has been shown that phenanthrenic opioids, including codeine, can modulate morphine glucuronidation in preclinical studies. Dihydrocodeine and acetyldihydrocodeine were ineffective in primary cultures of rat hepatocytes previously incubated for 72 h with either codeine or its derivatives [22]. Little else has been reported about the pharmacokinetics of acetyldihydrocodeine in man or animals.

Nicodidone
Pharmacokinetic data has not been reported in the scientific literature as far as it has been possible to ascertain for nicodicodine.

**Nicocodine**

*The US National Formulary of Medicine, National Centre for Biotechnology Information (NCBI)* describes nicocodine is an ester of codeine closely related to dihydrocodeine and the codeine analogue of nicomorphine and is metabolised in the liver by demethylation to produce nicomorphine (6-nicotinoylmorphine). Nicodicodine is metabolised in the liver by demethylation to produce 6-nicotinoyldihydromorphine, and also subsequently further metabolised to dihydromorphine (https://pubchem.ncbi.nlm.nih.gov/compound/Nicocodeine).

**Codeine and Norcodeine**

Much more is known about codeine than the other preparations. Oral absorption of codeine from the gastrointestinal tract is almost complete (94% ± 4%) and the onset of action occurs 30–45 minutes after administration, when given orally. Volume of distribution was reported to be 3.6 L/kg, indicating extensive distribution of the drug into tissues and plasma protein binding was low at 7%–25%. Renal excretion has been reported to account for the major elimination pathway: major metabolites appear in the urine within 6 hours, and 40%–60% of the codeine is excreted free or conjugated, approximately 5%–15% as free and conjugated morphine and 10%–20% as free and conjugated norcodeine. Codeine has a plasma half-life that ranges from 2.2 h [23] to 3.2 h [24-26].

![Figure 1: Metabolism of codeine showing three major pathways](https://pubchem.ncbi.nlm.nih.gov/compound/Codine)
Metabolism of codeine follows three major pathways: conjugation to codeine-6-glucuronide, N-demethylation to norcodeine, and O-demethylation to morphine (Figure 1). The conjugation pathway is quantitatively the most important, with codeine-6-glucuronide recovered in urine accounting for 70% of an oral dose of codeine. The corresponding values for N-demethylation and O-demethylation are probably 7% and 5%, respectively; approximately 4% is excreted unchanged [27, 28].

In a study to compare codeine and pholcodine codeine was absorbed and eliminated relatively rapidly (half-life 2.3 ± 0.4 h) and kinetics were adequately described by a one-compartment open model with first-order absorption. A two-compartment model was required to describe pholcodine elimination from plasma (half-life, 37.0 ± 4.2 h). Plasma concentrations of conjugated codeine were much greater than the unconjugated alkaloid. By contrast, pholcodine appeared to undergo little conjugation. Biotransformation of codeine to morphine was evident in all subjects, although the extent of this metabolic conversion varied considerably between subjects. Morphine was not detectable in the plasma of any subject after pholcodine administration [29].

**Dihydrocodeine**

The pharmacokinetics of dihydrocodeine have been determined in seven human volunteers who received the drug orally (30 mg and 60 mg) and intravenously (30 mg) on separate occasions, and in twenty-four patients receiving 25 mg or 50 mg of the drug intravenously. Dihydrocodeine follows a two-compartment distribution model. After oral administration, absorption was relatively quick with mean peak concentrations at 1.6 h-1.8 h. The mean bioavailability was 21% (range 12-34%). The mean half-lives varied between 3.3 h-4.5 h depending upon dose. Peak concentrations of metabolites occurred between 1.8 h-2.0 h after oral administration and 2.2 h-2.5 h after intravenous administration suggesting substantial first-pass metabolism [30].

**Ethylmorphine**

The pharmacokinetics of ethylmorphine after administration of a single dose of the cough mixture Cosylan were investigated in 10 healthy subjects and the half-life of the drug was reported to be 2 h. Ethylmorphine-6-glucuronide was found to be the major metabolite. Serum and urine samples taken more than 8 and 24 h after administration of ethyl-morphine respectively, contained morphine and morphine-glucuronides, but no ethylmorphine, ethylmorphine-6-glucuronide or (serum only) norethylmorphine. Norethylmorphine was detected after hydrolysis of urine samples in all subjects [31]. Intra- and interindividual differences in morphine formation after single-dose intake of ethylmorphine at 25 and 50 mg has been explored in in 10 healthy volunteers. The decline in urinary ethylmorphine was more rapid than for morphine, which leads to an increasing morphine/Ethylmorphine ratio in urine over time. Morphine was formed from ethylmorphine at a high and variable rate and may be present in urine in concentrations greater than those of ethylmorphine even shortly after drug intake [32].

**Pholcodine**

In early work on the pharmacokinetics of pholcodine following two single doses (20 and 60 mg) with an interval of 3 weeks between the two treatments. Subsequently, the same subjects received 20 mg pholcodine 8 hourly orally for 10 days. After the single doses, pholcodine was absorbed rapidly and slowly eliminated with a mean half-life of 50.1 ± 4.1 h. The renal clearance of pholcodine was 137 +/- 34 ml min-1 and was inversely correlated with urine pH (r = 0.60). The protein binding of pholcodine is of approximately of 21-23% and it tends to have a slight variation depending if the
administration is chronic. The concentration of pholcodine in oral fluid was 3.6 times higher than in plasma. After chronic administration, the pharmacokinetics of pholcodine were not statistically different from the single dose parameters. The plasma protein binding was 23.5%. Morphine, in unconjugated or conjugated form, was not detected in the urine of any subject after pholcodine administration [25]. After oral administration of 60 mg of pholcodine, the Tmax and Cmax were reported to be 1.3 hours and 26.3 ng/ml. The absorption of pholcodine was reported to represent approximately 88% of the administered dose [25]. The volume of distribution differs according to the pharmacokinetic model applied: being 265L based on a one-compartment model to 3207L in a two-compartment model [29].

D. Pharmacodynamics

Acetyldihydrocodeine

Acetyldihydrocodeine has reportedly higher lipophilicity than codeine and is converted into dihydromorphine rather than morphine, and has been postulated to be more potent and longer-lasting. It also has a higher bioavailability than codeine.

Codeine

Codeine is a pro-drug with a weaker affinity for μ-opioid receptors than morphine (200-fold less). Glucuronidation inactivates up to 80% of the administered drug to codeine-6-glucuronide by uridine 5’-diphosphate glucuronosyltransferase-2B7 (UGT2B7) and N-demethylation to norcodeine by CYP3A4, 5-10% of codeine undergoes O-demethylation to morphine, its active form via CYP2D6 [33]. Without O-demethylation, codeine may confer only a small fraction of the analgesic potency of morphine: much of its analgesic effect coming from codeine 6-glucuronide [34]. Earlier work has shown analgesic and antitussive properties in experimental animal species [35]. An effective review of the receptor pharmacology of codeine as well as its binding affinity to µ- and δ-opioid receptors has been carried out by Trescot et al, (2008) [36].

Nevertheless the conversion of codeine to morphine have been investigated because this metabolic route is via CYP2D6, and patients with genetic variations in this enzyme may find codeine to be less effective as an analgesic. It has been widely reported that the genetic polymorphism of CYP2D6 is at least partly responsible for the variable response to medication. Individuals with the poor metaboliser CYP2D6 phenotype may not achieve adequate analgesia with codeine. There are inter-ethnic differences in frequency of these phenotypes; while 10% of Caucasians and 30% of Hong Kong Chinese are PM [37], 1% in Denmark and Finland, 10% in Greece and Portugal and 29% in Ethiopia [38] are UM. Hence, while codeine (single oral dose of codeine, 75 or 100 mg against morphine, 20 or 30 mg) may be less effective as an analgesic in about 2-10% of ethnic groups [39], it could be a dangerous analgesic in the latter populations, as excessive doses of morphine may be rapidly produced [37].

The INGENIOUS clinical trial in Indiana, USA, examined implementing pharmacogenomics into clinical practice (INdiana GENomics Implementation: an Opportunity for the Under Served INGENIOUS trial, NCT02297126). It was found that within 60 days of receiving codeine, clinicians more frequently prescribed an alternative opioid in ultra-rapid and poor metabolizers (odds ratio: 19.0; 95% CI: 2.8-160.4) as compared with normal or indeterminate metabolizers (p = 0.01). After
adjusting the CYP2D6 activity score for drug-drug interactions, uncontrolled pain was reported more frequently in individuals with reduced CYP2D6 activity (odds ratio: 0.50; 95% CI: 0.25-0.94) [40].

**Ethylmorphine**

Ethylmorphine is metabolised by N-demethylation to norethylmorphine and by O-deethylation to morphine, the latter step being due to CYP2D6. This was initially shown in human liver microsomes and is consistent with previous findings in healthy volunteers [41]. Studies also have found wide variation in the recovery of morphine and morphine-glucuronides after oral administration of ethylmorphine that could not be explained simply by a difference in CYP2D6 genotype. It was felt that constitutional variation in other enzymatic pathways involved in ethylmorphine metabolism was also likely and concluded that ratios of morphine to parent drug cannot be used to distinguish the source of morphine after administration of ethylmorphine. [31].

**Dihydrocodeine**

In early work, Kirkwood et al (1997) showed in human liver microsomes that CYP2D6 was the major O-demethylating enzyme involved in the biotransformation of dihydrocodeine to dihydromorphine, whereas CYP3A was the enzyme involved in the production of nordihydrocodeine [42]. The analgesic activity of dihydrocodeine has often been attributed to the dihydromorphine metabolite based on dihydromorphine having a binding affinity to µ receptors similar to that of morphine and possessing approximately 100 times the activity of the parent drug. However, CYP2D6 enzyme, mediates the conversion of dihydrocodeine to dihydromorphine. Inter-ethnic differences (greater than 10% of Asians lack the functional activity of CYP2D6) suggest that the analgesic effects of dihydrocodeine might be diminished in those races with high prevalence of the poor metaboliser phenotype of CYP2D6 [43].

However, more recently, Webb et al (2001) observed the analgesic effect following dihydrocodeine ingestion was mainly attributed to the parent drug rather than its dihydromorphine metabolite. This contradicts the view that polymorphic differences in dihydrocodeine metabolism to dihydromorphine have little or no effect on the analgesic affect [44]. Others have confirmed the work of Webb: Schmidt et al (2003) found that CYP2D6 phenotype has no major impact on opioid receptor-mediated effects of a single 60 mg dihydrocodeine dose, despite the essential role of CYP2D6 in the formation of highly active metabolites [45]. Further work is needed in this area.

**Pholcodine**

In very early work cough of any origin (upper respiratory tract, larynx, pleuro-pulmonary diseases etc) was always soothed by a single dose of pholcodine between 10 mg and 80 mg. The average daily doses were of the order of 40-120 mg orally or by subcutaneous injection [46]. The antitussive action of pholcodine was assessed to be similar to codeine but as a centrally sedative product it was seen as superior to codeine. Pholcodine depresses the respiration less than morphine and a little more than codeine and has low addiction liability [46]. Pholcodine is an anti-convulsant, unlike morphine, codeine and morphine derivatives, which are all convulsants (https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1961-01-01_2_page004.html).
5. Toxicology

Little recent data is available for the preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs (acetyldihydrocodeine, dihydrocodeine, ethlymorphine, nicocodine (nicocodeine), nicodicodine (nicodicodine), norcodeine and pholcodine). The material available stems from the 1950s and 1960s [3-7, 46].

Calen (1961) concluded that the toxicity of pholcodine was low in animals (mice, rabbits and dogs), (https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1961-01-01_2 page004.html). Others at the time concurred with these findings. The general sedative action of pholcodine was superior to that of codeine. In rabbits pholcodine depressed the respiratory rate and volume less than morphine and somewhat more than codeine [46]. Animal studies do not reveal a carcinogenic effect of codeine [47]. Mutagenicity studies do not show evidence of a genotoxic risk to man [48].

A. Clinical

One of the main Antitussives such as the preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs include a variety of compounds though elicit their clinical affect by directly inhibiting the medullary cough centre of the brain [49]. Various models suggest that cough suppression occurs via agonism of the μ2 or κ opioid receptors, or antagonism of the δ opioid receptor and the σ or N-methyl-d-aspartate (NMDA) receptors are likely also involved [27].

B. Respiratory depression

Opioid drugs reduce the sensitivity of the respiratory centre to carbon dioxide, which may result in decreased tidal volume and decreased respiratory rate. The triad of coma, pinpoint pupils, and respiratory depression is strongly suggestive of opioid poisoning. In severe overdose, particularly by the intravenous route, apnoea, circulatory collapse, cardiac arrest, and death may occur. Promethazine may add to the depressant effects of codeine. Children can be particularly susceptible to the toxicological effects of some of the preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs. A 10 month of child was given ethylmorphine in the evening (five milliliters of Cosylan® or Solvipect®, the two available antitussive preparations containing ethylmorphine, would amount to 8.5 or 12.5 mg of ethylmorphine, respectively. and was found dead the next morning. The autopsy report concluded a combination of opiate-induced sedation and weakening of respiratory drive, a respiratory infection, and a sleeping position that could have impeded breathing caused death [50].

The therapeutic doses of pholcodine do not cause depression of respiration, CNS excitation or other side effects associated with narcotics: the impact of pholcodine is selective on the cough centre without affecting the respiratory centre [46].

C. Seizures

Seizures are not common in opioid preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs such as codeine, dihydrcodeine, ethlymorphine, nicocodine and pholcodine. However, codeine phosphate-induced seizures following intravenous administration when patients are in need of acute pain control requiring intravenous narcotics [51].
D. Fatalities
In a study in Sweden twenty years ago, 14 fatal poisonings attributed to drug abuse were studies. The cause of death was specified as fatal ethylmorphine poisoning in two cases. Among the unspecified medicinal drug poisonings there were five cases with very high blood levels of ethylmorphine, indicating that this drug played an important contribution to the cause of death. The results indicate that deaths due to ethylmorphine in antitussive medicines may occur among drug addicts and alcoholics taking it in overdose [52].

E. Cardiovascular
Cardiac arrest leading to death was reported in a 52-year-old man, who ingested 750mg of pholcodine syrup. This was determined to be the result of hypoxia due to respiratory arrest connected to the opioid nature of pholcodine. Toxicological analysis showed a pholcodine blood level of 2500 ng mL (a lethal dose is >1000 ng mL, extrapolated from animal studies) [53].

Dihydrocodeine in overdose significantly reduces peripheral and aortic systolic, mean, end systolic pressures, and decreased peripheral pulse pressure. In a prospective study of patients who overdosed on dihydrocodeine reduced systemic and aortic diastolic blood pressure were observed. Augmentation index and heart rate, however, did not change but decreased arterial oxygen saturation occurred. Dihydrocodeine therefore has a notable effect on central and peripheral hemodynamics, which could reduce cardiac afterload, providing a pharmacological explanation for the apparent benefit of opioids in cardiovascular diseases [54].

6. Adverse Reactions in Humans
A. Acute
Acute side effects have been widely reported for opioids including codeine, dihydrocodeine and pholcodine and itching, nausea and respiratory depression. During higher doses especially during higher steady state doses headache, nausea, vomiting, dizziness, constipation, and a dry mouth [55].

Nausea, vomiting, headache, dizziness, drowsiness and confusion were the most commonly reported adverse effects with a single dose of oral dihydrocodeine 30 mg compared with placebo. These problems tend to occur in more than one patient out of 100 treated with DHC [56].

B. Chronic
There is a dearth of evidence on the chronic use of weak opioids. In practice, with opioid therapy, there is no evidence that codeine and dihydrocodeine are less risky than morphine at its lowest effective dose. Compared to morphine, the efficacy of these drugs varies more from one patient to another, and their multiple pharmacokinetic interactions can be difficult to manage. There is also a sometimes unpredictable risk of serious over-dose [57].

Natural alkaloids extracted from Papaver somniferum have long been known to cause allergic contact dermatitis, but the number of reported cases remains small. Affected workers have included nurses or other health personnel who handle the drugs, or factory employees engaged in their preparation. Most of these workers have been exposed to the drugs in powder form, and have
developed an airborne pattern of contact dermatitis particularly codeine (3-methylmorphine) [58-60] but there are also case reports for dihydrocodeine [61] but not ethylmorphine [62].

7. Dependence Potential

A. Animal Studies

Previous studies have demonstrated that codeine produces anti-nociceptive effects in mice, rats, and guinea pigs using a variety of tests [63] and antitussive effects in cats, guinea pigs and mice using variety of approaches to stimulate cough reflex (for example [64]). The peak effect of codeine, as a short acting drug, occurs within 1–2 hours, and the duration of antitussive action is 4–6 hours.

B. Human Studies

Codeine misuse and dependence has been described in in the UK and Ireland with both prescribed and OTC codeine. Codeine dependence was associated with daily use of codeine, faking or exaggerating symptoms to get a prescription for codeine and 'pharmacy shopping'. A higher number of respondents had sought advice on the Internet (12%) rather than from their general medical practitioner (GP) (5.4%) to control their codeine use [65]. In 1978, Marks et al, reported that dependence following prescription of dihydrocodeine occurs, with severe physical and psychological traits and abrupt withdrawal upon cessation. Five cases were used to illustrate the risk of physical dependence of this drug [66].

8. Abuse Potential

A. Animal Studies

The administration of codeine to 60 male Long-Evans rats (Charles River Laboratories Japan, Inc., Kanagawa, Japan) by the intraperitoneal route (codeine at 20 mg/kg generalized to the morphine-training dose) found 14 of the 15 animals displaying 80% or more morphine-lever responses within the range of 3 to 20 mg/kg. In the administration of codeine by the oral route (codeine at 60 mg/kg generalized to the morphine-training dose), 14 of the 15 animals showed 80% or more morphine-lever responses within the range of 10 to 60 mg/kg. Thus, the discriminative stimulus properties of morphine and codeine were comparable when using different administration routes to those at discrimination training [67].

When nicocodine was self-administered to the rhesus monkey in cross self-administration experiments the minimum reinforcing dose was found to be 10 times higher than that of codeine and 100 times higher than that of heroin. At reinforcing doses the rate of self-administered infusions of nicocodine were comparable with those of codeine. It was concluded that nicocodine was an opium-like reinforcing compound [68].
B. Human Studies

The opioid preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs (acetyldihydrocodeine, codeine, dihydrocodeine, ethylmorphine, nicocodine (nicocodeine), nicodicodine (nicodicodine), norcodeine and pholcodine) have not received much attention, often based on the belief that they are weaker opioids and less likely to cause dependence and fatal overdose than morphine.

Ethylmorphine is the 3-ethoxy congener of morphine, used mainly as an antitussive and has some potential for abuse. It is thought likely that the abuse liability of ethylmorphine might be linked to its metabolism to morphine. In turn, morphine may also mediate its effects through formation of active metabolites including the 6-glucuronide [5-7]. https://www.drugbank.ca/drugs/DB01466

The abuse potential of pholcodine is reported to be low whereas early work has suggested acetyldihydrocodeine, nicocodine and nicodicodine may have some abuse liability [3-7].

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Most codeine preparations classified under Schedule III are pharmacy controlled with a medical prescription required however, there is no requirement to keep controlled registers so that the extent of use is difficult to gauge.

Codeine is marketed as both a single-ingredient drug and in combination preparations with paracetamol (as co-codamol), and the Tylenol-with-codeine series, with aspirin (co-codaprin) or with ibuprofen (Nurofen Plus). These combinations are reported to provide greater analgesia than either compound alone [69]. Codeine in the form of cough syrups, alone or with other active ingredients, and as a linctus (e.g., Paveral) for all the indications of codeine are available. In some countries codeine-only products with a prescription as a time-release tablet or as suppositories are produced. Injectable codeine is also available for subcutaneous or intramuscular injection only; intravenous injection is contra-indicated, as this can result in nonimmune mast-cell degranulation and an anaphylactic reaction. Codeine is commonly used in the management of mild to moderate pain in adults (often dental or post-partum) and under strict monitoring in children [70].

Globally, the demand for codeine remains high and has risen by approximately 27% over the last decade with figures estimating that global purchasing reached an all-time high at 269 tonnes in 2011 compared to 164 tonnes in 1992 (INCB 2012). In some countries, codeine preparations are available without prescription in combination preparations (paracetamol, ibuprofen or aspirin) from licensed pharmacies and in retail outlets. Since the regulation and control of codeine dispensing varies between countries with some restricting the visual display and advertisement of over the counter codeine preparations to the consumer. The amount of over the counter sales of codeine containing medications is not easy to determine due to trade exemptions and because disclosure of information might prejudice the commercial interests of any person or public authority, but there is little doubt that it forms a substantial proportion of pharmacy sales [71]. In 2013, the global legal production of the three most common opiates in descending order were morphine 523 tonnes, codeine 361 tonnes and oxycodone 261 tonnes [72].
More codeine was consumed in the United Kingdom, Canada and Australia than any other opioid in 2012 [73]. Codeine is also one of the most accessible opioids, available without prescription (over-the-counter) in the UK, Canada, France, New Zealand and Australia [74]. In Australia, the overall rate of codeine–related deaths increased from 3.5/million in 2000 to 8.7/million in 2009. Deaths attributed to accidental overdoses were more common (48.8%) than intentional deaths (34.7%). Recorded deaths had high rates of prior comorbid mental health (53.6%), substance use (36.1%) and chronic pain (35.8%) problems [75].

In children aged 0-17 years codeine use has remained largely unchanged from 1996 to 2013 (1.08 vs. 1.03 million children, respectively) in the United States. Odds of codeine use was higher in ages 12–17 (OR, 1.40; [1.21–1.61]), outside of the Northeast US, and among those with poor physical health status (OR, 3.29 [1.79–6.03]). Codeine use was lower in children whose ethnicity was not white and those uninsured (OR, 0.47 [0.34–0.63]). Emergency doctors (18%) and dentists (14%) prescribed codeine to children the most for trauma-related pain [76].

Meta-analysis that investigated low dose codeine 15 to 30mg and found ten randomised controlled trials were eligible. They found low-quality evidence (n=211 participants) that a single dose of a combination analgesic product (with an nonsteroidal anti-inflammatory) containing low-dose codeine (15 to 30mg) provides small pain relief for acute dental pain. In addition, moderate-quality evidence (n=93) was determined for pain relief for post-episiotomy pain and orthopedic surgery pain. There was also low-quality evidence (n=80) that a multiple-dose regimen provides small pain relief for acute pain following photorefractive keratectomy and moderate-quality evidence of moderate pain relief for certain chronic pain conditions such as hip osteoarthritis and temporomandibular joint pain. Thus combination analgesic products containing low-dose codeine provide small to moderate pain relief for acute and chronic pain conditions in the immediate short term with limited trial data on use beyond 24 hours [77].

Dihydrocodeine is available in Japan as tablets which contain 2.5 mg of dihydrocodeine phosphate and caffeine, the decongestant d,l-methylephedrine HCl, and the antihistamine chlorpheniramine, and packets of granules which effervesce like Alka-Seltzer with 10 mg of dihydrocodeine with lysozyme and chlorpheniramine, marketed for OTC sale as New Bron Solution-ACE.

For a single dose of oral dihydrocodeine tartrate 30 mg compared with placebo the Number Needed to Treat (NNT) was 8.1 (4.1 to 540) for at least 50% pain relief over four to six hours in postoperative pain of moderate to severe intensity. Thus one in every eight participants with moderate to severe postoperative pain experienced at least 50% pain relief with dihydrocodeine 30 mg who would not have done with placebo. However, Ibuprofen 400 mg was significantly more effective than dihydrocodeine 30 mg or dihydrocodeine 60 mg for at least 50% pain relief over a period of four to six hours in postoperative pain of moderate to severe intensity [78].

### 10. **Listing on the WHO Model List of Essential Medicines**

The World Health Organization’s (WHO) model list of essential medicines (http://www.who.int/selection_medicines/list/en/) presents those medicines deemed necessary to meet priority health needs. The local implementation of essential medicines policies is associated with improved quality use of medicines [79, 80].
The World Health Organisation has placed codeine on ‘step 2’ of its pain ladder. Codeine is a weak opioid that was endorsed by the World Health Organization as the second step on the analgesic ladder for cancer pain and has been used routinely for postoperative and for breakthrough pain in chronic sufferers. Dihydrocodeine similarly is on step two of the analgesic ladder for example for musculoskeletal pain ([https://bpac.org.nz/BPJ/2008/December/docs/bpj18_who_ladder_pages_20-23.pdf](https://bpac.org.nz/BPJ/2008/December/docs/bpj18_who_ladder_pages_20-23.pdf)).

11. **Marketing Authorizations (as a Medicinal Product)**

Many companies hold marketing authorisations for codeine as a medicine. Some examples include, Actacode (Sigma), Bisoltus (Boehringer Ingelheim), Bromophar (Qualiphar), Bronchicum (Sanofi-Aventis), Bronchodine (Pharmacobel), Codant (Antigen), Codedrill (Pierre Fabre), Codein (Cristália), Codeisan (Belmac), Coderpina (Frycia Centro América), Codicalm (Welti), Codicept, Codinel (Pinewood), Coulcept, Cougel (Hwang’s), Coutan (Mey See), Dinco (Center), Farmacod (Farmacom), Galcodine (Thornton & Ross), Pectoral (Siphat) and Tussoret (MaxMedic).

In Ireland codeine medicines are currently authorised for the relief of pain in such conditions as rheumatic and muscular pain, migraine, headache, menstrual pain, toothache, backache and for symptoms of the common cold and influenza and the majority are available as non-prescription medicines, from retail pharmacy businesses only [81].

12. **Industrial Use**

Industrial use of preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs include is not reported.

13. **Non-Medical Use, Abuse and Dependence**

It is difficult to estimate the prevalence of non-medical use of the preparations listed in Schedule III of the 1961 Single Convention on Narcotic Drugs. However, it is known that the abuse of over the counter (OTC) antitussive preparations is a continuing problem in the United States and throughout the world [27]. Thought to be due to the increasing availability, social acceptance and the perception, especially among the young that pharmaceutical drugs are safe. With legislative activity, educational, and economic initiatives there may have been a shift to abuse of other more readily available, and easily attainable cough and cold preparations, such as those containing codeine. There seems to be a particular problem with codeine-promethazine hydrochloride cough syrup (CPHCS), which is a growing public health problem [82].

In a study in the UK 16 adults (13 women and 3 men) who had used codeine in the last 12 months other than as directed or as indicated were interviewed. Environments capable of producing harm included: unsupervised and long-term codeine prescribing, poor access to non-pharmacological pain treatments, barriers to provision of risk education of codeine related harm and breakdown in structures to reduce the use of over the counter codeine other than as indicated [83].
Nonmedical use of cough syrup (NUCS) has become an issue in some areas despite the well-documented dangers of cough syrup abuse: Hou et al (2011) associated chronic codeine cough syrup abuse to alterations in the dopaminergic system and the striatal dopamine transporter (DAT). Striatal DAT, responsible for the active dopamine reuptake into the presynaptic neuron and the regulation of striatal synaptic dopamine levels was significantly reduced in codeine syrup dependent compared to healthy volunteers [49]. Codeine is often misused through oral administration of combination tablets and tampering procedures which separate codeine from the accompanying analgesics appears to be a gaining popularity amongst certain codeine taking populations. Often referred to as ‘cold water extraction’, the aim is to keep as much codeine as possible in the extracted tampering products, while at the same time reducing the amount of non-opioid analgesics to non-toxic levels [84].

In Europe, the misuse of codeine-containing medicines in combination with new psychoactive substances (NPS) has been noted. Consuming codeine extracted from combination tablets (OR = 16.79, 95% CI [8.67, 32.51]); obtaining codeine from friends, family, and acquaintances (OR = 3.98, 95% CI [1.82, 8.7]); use of illicit controlled drugs (OR = 34.99, 95% CI [8.39, 145.94]) and; use of codeine to experience euphoria (OR = 6.41, 95% CI [3.42, 12.04]) [85] were all significantly more likely to predict NPS use. Tampering of codeine appeals to recreational users consuming high amounts of codeine to induce opioid euphoria, to codeine dependent concerned with the toxicity of non-opioid analgesics, and to those unable to obtain potent prescription opioids who may turn to codeine to prevent withdrawal and cravings [84].


The rapid rise of prescription opioid misuse has been identified as a key public health problem in the United States. Representations of codeine misuse through analysis of public posts on Instagram to identify text phrases related to misuse found that codeine misuse images were being glamorised through co-ingestion with soda (street name: lean) and alcohol, and popular culture imagery. There was concern that such activity holds the potential to normalise, increase codeine misuse, and overdose. This has led to calls for more Public health efforts to better understand the relationship between the potential normalisation, ritualisation, and commercialisation of codeine misuse [86].

The harmful effects of codeine misuse and dependence have long since been recognised by the medical community [87]. Misuse of codeine can occur in pill or syrup form has been well documented previously in the USA [88] India [89], Hong Kong [90] and elsewhere mixed with caffeine amongst other ingredients [64, 91]. Further detail can be found in a comprehensive review by Van Hout (2014) [91].

15. Licit Production, Consumption and International Trade

Most of the codeine currently manufactured globally comes from morphine through a semisynthetic process. There has been an increase in the cultivation of the opium poppy variety that is rich in codeine and in the manufacture of poppy straw concentrate rich in codeine, used for the extraction of codeine. Due to uncertain social, political, and climatic conditions in some producing regions, high-yielding methods for the chemical synthesis of opium alkaloids remain popular [9]. In searching
for high-yielding methods Geffe et al, (2014) reported on a short and high-yielding enantioselective synthesis of the –dihydrocodeine through the α-benzylation of a deprotonated bicyclic α-aminonitrile, followed by Noyori’s asymmetric transfer hydrogenation combined with the Grewe cyclization onto a symmetrical A-ring precursor [9].

The demand for codeine remains high and continues to rise (INCB, 2012). Both exports and manufacture of codeine have also seen a rising trend [71]. Codeine is used mainly for the manufacture of preparations in Schedule III of the 1961 Convention, while a smaller quantity is used for the manufacture of other narcotic drugs, such as dihydrocodeine and hydrocodone [92]. In 2011, figures show that the UK was the highest codeine manufacturer globally representing 22%, followed by France (21%), US (17%) and Australia (8%). Over-the-counter sales of codeine containing medications are not easy to determine despite supervision by a pharmacist being generally required (European Medicines Agency, 2013) [71]

16. Illicit Manufacture and Traffic and Related Information
In the 1980s, a large number of small-scale illicit laboratories producing morphine and heroin from commercially available, codeine-based pharmaceutical products were reported in New Zealand. The codeine demethylation procedure was based on the use of pyridine hydrochloride and was synthesised by people with little or no chemical background, following a recipe-like procedure known as 'homebake' [19].

A short and high-yielding enantioselective synthesis of (-)-dihydrocodeine has been published involving the α-benzylation of a deprotonated bicyclic α-aminonitrile, followed by Noyori's asymmetric transfer hydrogenation combined with the Grewe cyclization onto a symmetrical A-ring precursor. This compound can be converted to (-)-thebaine in high yield by known transformations, while (-)-codeine and (-)-morphine are available from an advanced intermediate [9].

17. Current International Controls and Their Impact
Preparations of codeine are listed in Schedule III of the 1961 Single Convention on Narcotic Drugs

18. Current and Past National Controls
The legal status of codeine differs internationally. In Australia, Canada, New Zealand, Sweden, the United Kingdom, the United States and many other countries, codeine is regulated under various narcotic control laws2. In some countries, codeine is available without a medical prescription and in combination preparations from licensed pharmacists in doses up to 20 mg, or 30 mg when sold combined with 500 mg paracetamol [93]. A brief summary follows:

Australia: Since February 1, 2018, preparations containing codeine have not been available without a prescription. Preparations containing pure codeine (e.g., codeine phosphate tablets or codeine

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phosphate linctus) are available on prescription and are considered S8 (Schedule 8, or "Controlled Drug Possession without authority illegal").

**Canada:** Tablets containing 8 mg of codeine combined with 15 mg of caffeine and 300 mg of acetaminophen are sold as T1s (Tylenol Number 1) without a prescription.

**Denmark:** Codeine is sold over the counter in dosages up to 9.6 mg (with aspirin, brand name Kodimagyn); anything stronger requires a prescription.

**France:** In 2017, the law was changed in France making mandatory a prescription for all codeine products along with ethylmorphine.

**Germany, Switzerland, and Austria.** Dispensing of products containing codeine and similar drugs (dihydrocodeine nicocodeine and ethylmorphine) generally requires a prescription or is at the discretion of the pharmacist.

**Greece:** Codeine is an illegal drug in Greece, although it is available by prescription (Lonarid-N, Lonagal).

**Hong Kong:** Codeine is regulated under Laws of Hong Kong, Dangerous Drugs Ordinance, Chapter 134, Schedule 1. But is available under a prescription.

**India:** Codeine preparations require a prescription. Codeine containing cough medicine has been banned in India since 2016.

**Iran:** Preparations of codeine in Iran are usually over-the-counter in combination with paracetamol or guaifenesin. Codeine phosphate (30 mg tablets) can be purchased with a special permit.

**Ireland:** Codeine remains a semi non-prescriptive, over-the-counter drug up to a limit of 12.8 mg per tablet, but these products "are not accessible to the public for self-selection". For medicines with more than 12.8 mg codeine a prescription is required [94].

**Italy:** Codeine tablets or preparations require a prescription in Italy (Co-Efferailgen and Tachidol).

**Japan:** Low dose codeine is available over the counter at pharmacies.

**Romania:** Codeine (Farmacod) requires a medical prescription. Doses do not exceed 15 mg.

**South Africa:** Codeine is freely available OTC and there is a low annual prevalence rate of opiate use at 0.3% [94].
Sri Lanka: Codeine preparations are available as OTC pharmacy medicines. The most common preparation is Panadeine, which contains 500 mg of Paracetamol and 8 mg of Codeine. Cough syrup containing codeine and promethazine is not permitted.

United Arab Emirates: Medicines containing codeine are banned without a doctor's prescription including visitors to the country.

United Kingdom: Codeine is a controlled substance or a Class A drug when prepared for injection. Codeine use without a prescription is permitted with at least one other active or inactive ingredient and that the dosage of each tablet, capsule, etc. does not exceed 100 mg or 2.5% concentration in the case of liquid preparations.

United States: Codeine is a Schedule II controlled substance when used in products for pain-relief (alone or more than 80 mg per dosage unit). Cough syrups are classed as Schedule III, IV or V, depending on formulation.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None
References


42nd ECDD (2019): Preparations of codeine

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Refer to separate Annex 1: Report on WHO questionnaire for review of psychoactive substances