CODEMISUSED is a European Union funded project looking into Use, Misuse and Abuse of Codeine. Research has been undertaking in the Republic of Ireland, the United Kingdom and the Republic of South Africa.

The misuse of opioid containing pharmaceuticals is of growing global concern. It is driven by a host of factors, including marketing strategies, inappropriate prescribing, public perceptions of safety, access to other illicit sources, self-medication of pain and recreational popularity. [1-6] Opioid use is commonly associated with lower educational attainment, unemployment, disability, comorbidity, history of problematic substance use and suicide. [7]

Codeine is a widely used opioid worldwide, with different countries regulating its supply to different extents. Some governments only permit its supply on prescription, whereas it is common to allow purchase from pharmacies in limited doses and quantities. The legislation has been tightened more recently in some areas as a response to the growing diversion of codeine containing pharmaceuticals for illicit purposes.

There is growing concern about risk/benefit ratio with questions whether it has any place remaining in therapy. [8] Codeine is a pro-drug that is metabolized by the enzyme CYP 2D6 in the liver to morphine. Codeine itself has very little intrinsic pain relieving activity. The metabolism rate varies in people according to their race or geographical location (see table 1). There is considerable concern about ultra-rapid metabolizers as it leads to sudden high levels of morphine in their blood, which can lead to respiratory depression and other adverse effects. Conversely slow metabolizers often do not obtain adequate pain relief as they only achieve sub therapeutic blood concentrations of morphine.

**Risk Factors for Misuse**
- History of Substance and Alcohol Abuse
- History of Chronic Pain
- Request for replacement prescriptions
- Multiple appointments with different GPs
- Purchasing of medicines from pharmacies to supplement prescription medication
- Using other peoples medication
Table 1 [9]

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Ultra-rapid metabolisers</th>
<th>Slow Metabolisers</th>
</tr>
</thead>
<tbody>
<tr>
<td>African</td>
<td>5-30%</td>
<td>0-20%</td>
</tr>
<tr>
<td>Asian</td>
<td>1.2% to 2%</td>
<td>No data found</td>
</tr>
<tr>
<td>Caucasian</td>
<td>3.6% to 6.5%</td>
<td>7-10%</td>
</tr>
</tbody>
</table>

There is no consensus in the literature about the definitions of misuse and abuse. We think the following will be helpful:

**Misuse**

‘*The problematic consumption of codeine where risks and adverse consequences outweigh the benefits, and which includes use of codeine with or without prescription, outside of acceptable medical practice or guidelines, for recreational reasons, when self-medicating, with higher doses and for longer than advisable*.’ [10]

**Abuse**

‘*A pattern of maladaptive substance use that is associated with recurrent and significant adverse consequences*.’ (American Psychiatric Association 2000)

Pharmaceutical forms of Codeine are increasingly being diverted for illicit use. There are different ways of obtaining Codeine such as:

- family sharing, when the drug is passed onto family members or friends
- doctor and pharmacy shopping, where different healthcare professionals are accessed to obtain excessive amounts
- and the black market.

‘*Tampering*’ with pharmaceutical forms of Codeine is increasingly common in order to extract Codeine or to produce other related substances of abuse, for example:

- **Cold Water Extraction**
  - Easy home-based method utilizing the different solubility of paracetamol and codeine in cold water. This allows the extraction of nearly pure codeine from co-codamol preparations.

- **Krokodil**
  - Home-made substance derived as a replacement for herion in Russia from readily available chemicals and pharmaceutical forms of codeine. A highly addictive substance containing Desomorphine and impurities which causes devastating health outcomes. [11] [12]

- **Purple Drank**
  - There are different home-made mixtures containing codeine cough syrups, alcohol, soft drink or energy drink and possibly other substances such as promethazine. [13]

- **Home bake**
  - Home-made form of heroin produced from pharmaceutical forms of codeine. Particularly seen in New Zealand. [14] [12]
Consequences of Misuse

Adverse Effects

Chronic use can cause dependency which leads to patients taking higher doses to achieve the same effects and avoid withdrawal symptoms such as sweats, runny nose, anxiety, muscle cramps, nervous tremor, diarrhoea.

Our search of the literature has revealed a number of further consequences of codeine use and misuse.

Normal Side Effects

In common with other opioids, codeine can cause a range of side effects with normal use. The most common are: drowsiness and cyclomotor impairment, nausea and vomiting, constipation, itching and rarely, breathing difficulties.

Impairment

There is weak evidence that suggest that codeine can lead to psychomotor impairment. [15] This has consequences for driving and performing other complicated tasks. One study compared the volume and weight of bilateral corpus striatum in codeine cough syrups addicts to healthy subjects and found reduced values. [16] Scans suggested alteration in a dopaminergic system responsible for cognitive and motor action. Another study found that driving test parameters and a psychomotor-vigilance test correlated with morphine and codeine blood concentrations. [17] Further research is required to confirm these findings.

Injury

Increase risk of injury as a result of using codeine medication was found in two papers, one in an older population and one in the normal population. [18] It is possible that comorbidities such as rheumatoid and osteoarthritis are confounding factors in these studies. Further research is required.

Adverse Health Effects

A number of case reports have reported adverse health effects which were considered to be chronic or life threatening. Two papers
reported adverse effects on neonate following administration of prescribed co-codamol to the mother post-partum. Both mother and infant are found to be fast metabolizers of codeine [19]. This added to reports of death of children in the USA post tonsillectomy. This led to medicines control agencies around the world issuing recent guidance on the use of codeine such as Medicines and Healthcare Product Regulatory Agency (MHRA) in the UK, found on page 4.

Those who use opiates often experience psychiatric disturbances. One paper found that a number of patients were admitted with psychiatric disorders including psychosis and affective episodes following abuse of codeine containing cough syrups. [20]

Rare reports of acute pancreatitis are in the literature following repeated high doses use of codeine. All patients recovered after the codeine was stopped. One case was readmitted after resumption of codeine taking.

There are reports of chronic headaches after prolonged misuse. Cellular changes were noted in one study. [21]

**Combined Preparations**

Codeine is frequently taken as a combination product with either paracetamol or ibuprofen. Its addictive potential means that patients can expose themselves to high doses and prolonged use of these other substances.

Hypokalemia and gastro-intestinal problems have been reported due to overuse of codeine/ibuprofen preparations. [22] [23, 24]

**Dependence**

Overall the number of studies examining dependence on codeine is small, the majority of the research identified looks specifically at opioids as a group of medication and it is often hard to ascertain the extent of the problem. Severe dependence on opioids appears to be part of a multiple substance misuse pattern and more research is required to evaluate the role of codeine in development of dependency.

**Latest MHRA Guidance**

- Codeine should only be used to relieve acute moderate pain in children older than 12 years and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen
- Codeine is contraindicated in all children (i.e., younger than 18 years) who undergo tonsillectomy or adenoidectomy (or both) for obstructive sleep apnoea
- Codeine is not recommended for use in children whose breathing might be compromised, including those with: neuromuscular disorders; severe cardiac or respiratory conditions; upper respiratory or lung infections; multiple trauma; or extensive surgical procedures. The symptoms of morphine toxicity may be increased in these settings
- In children age 12–18 years, the maximum daily dose should not exceed 240 mg. This may be taken in divided doses, up to four times a day at intervals of no less than 6 hours. It should be used at the lowest effective dose for the shortest period. Duration of treatment should be limited to 3 days and if no effective pain relief is achieved, treatment should be reviewed by a physician
- Information should be given to parents and caregivers on how to recognise the signs of morphine toxicity, and advice should be given to stop giving the child codeine and to seek medical attention immediately if their child is showing these signs or symptoms
- Symptoms of codeine toxicity include: reduced levels of consciousness; lack of appetite; somnolence; constipation; respiratory depression; ‘pin-point’ pupils; or nausea and vomiting
- Codeine is contraindicated in all patients of any age known to be CYP2D6 ultra-rapid metabolisers
- Codeine should not be used by breastfeeding mothers because it can pass to the baby through breast milk and potentially cause harm
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