Sonic Genetics
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Making medicines personal

# Personalise the prescribing of codeine

Bulletin for Prescribers | September 2019

## The challenge of codeine prescribing

Codeine-containing analgesics are often part of the management of acute and chronic pain. While effective, there is growing concern about the increasing use of prescription opioids in Australia and the increase in opioid-related harms. A recent article in the MJA[1] summarised various approaches to managing opioid use and emphasised the importance of reducing harms associated with use, whilst ensuring that patients who may clinically benefit, can continue to access opioid treatment.

There can be marked variability in how people respond to codeine. Some may be unresponsive on substantial doses, while others are susceptible to codeine toxicity on standard doses.

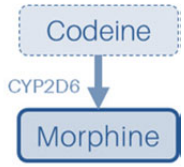
**A standard dose of codeine may not work for your patient, or may cause toxicity.**

A personalised approach to prescribing codeine-containing analgesics can help meet the needs of the individual patient effectively and responsibly.

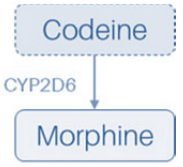
## The CYP2D6 gene and codeine metabolism

Codeine is a prodrug that requires bioactivation by a liver enzyme called CYP2D6 to form morphine.[2]

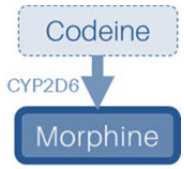
The amount of codeine converted into morphine by CYP2D6 varies from person to person. A patient's CYP2D6 'metaboliser status' can be predicted from genetic analysis of the CYP2D6 gene. This information can inform the prescribing of the most suitable analgesic for that patient.




Most patients have normal CYP2D6 genes and are 'extensive metabolisers', converting 5-15% of ingested codeine into morphine. The remaining codeine is excreted as inactive metabolites.




Some patients have low enzyme activity and are 'poor metabolisers' of codeine. They convert little of the ingested codeine into morphine and gain little analgesic benefit.




A few patients have high enzyme activity and are 'ultra-rapid metabolisers'. They produce excessive morphine at a standard codeine dose and are at increased risk of opioid toxicity e.g. sedation, severe nausea, constipation.

Some patients with near-normal enzyme activity are classified as 'intermediate metabolisers'.

## Genetic testing to inform analgesic prescribing

If a patient's CYP2D6 metaboliser status is known, there are international guidelines that can inform the choice and dose of analgesic for that patient to improve the effectiveness and safety. These guidelines are summarised overleaf.

CYP2D6 is a key enzyme in codeine metabolism. However, there are many other genes involved in the absorption, digestion, metabolism and excretion of analgesics.

**Sonic Genetics provides a comprehensive pharmacogenomic test, the Sonic PGx Panel, with a detailed report to inform the prescribing of analgesics and many other classes of medication.**



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## Prescribing advice for codeine and alternative analgesics based on CYP2D6 phenotype per Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines[2]

| Phenotype | Implications for codeine metabolism | Recommendations for codeine therapy | Evidence level for recommendation | Considerations for alternative analgesics |
|---|---|---|---|---|
| **Ultra-rapid metaboliser** (~1-2% of patients) | Increased formation of morphine following codeine administration, leading to higher risk of toxicity | **Avoid codeine use due to potential for toxicity** | Strong | Alternatives that are not affected by this CYP2D6 phenotype include non-opioid analgesics, hydromorphone, fentanyl, buprenorphine, tapentadol and morphine.[#] Tramadol and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity. |
| **Extensive metaboliser** (~77–92% of patients) | Normal morphine formation | Use label-recommended age or weight-specific dosing | Strong | - |
| **Intermediate metaboliser** (~2–11% of patients) | Reduced morphine formation | Use label-recommended age or weight-specific dosing, and if no response, consider alternative analgesics | Moderate | Tramadol and oxycodone are affected by this CYP2D6 phenotype to a lesser extent and may be used with extra monitoring for potential toxicities. Alternatives that are not affected by this CYP2D6 phenotype include non-opioid analgesics, hydromorphone, fentanyl, buprenorphine, tapentadol and morphine.[#] |
| **Poor metaboliser** (~5–10% of patients) | Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief | **Avoid codeine use due to lack of efficacy** | Strong | Alternatives that are not affected by this CYP2D6 phenotype include non-opioid analgesics, hydromorphone, fentanyl, buprenorphine, tapentadol and morphine.[#] Tramadol and oxycodone are not good alternatives because metabolism is also affected by CYP2D6 activity. |

[#]Standard considerations and PBS restrictions apply for the prescribing and monitoring of strong opioids.

## Patients likely to benefit from genetic testing to inform analgesic prescribing

**Patients who have yet to take codeine for chronic pain.** The test may predict the likely benefit and risks of codeine selection and inform dose selection.

**Patients who have yet to take codeine for acute pain.** There is growing international interest in pre-emptive testing, that is, testing a patient well in advance of any prescribing decisions being required. This may predict the likely benefit and risks of codeine selection to inform dose selection.

**Patients taking codeine with limited benefit.** The test may indicate whether an increased dose or selection of a different analgesic is likely to benefit the patient.

**Patients taking codeine with unwanted side-effects.** The test may indicate whether a reduction in codeine dose or selection of a different analgesic is warranted.

## Arranging a Sonic PGx Panel for your patient

The Sonic PGx Panel covers 10 genes involved in drug metabolism and the report provides detailed prescribing information for more than 90 different medications.

The test can be performed at any Sonic Healthcare pathology collection centre nationally. Complete a Pharmacogenomic (PGx) Panel Request Form or request the 'Sonic PGx Panel' using your local pathology request form. Please specify the patient's current and proposed medications, together with any adverse drug reactions or lack of efficacy.

A blood sample is the preferred method of DNA collection; buccal swabs can be used by prior arrangement.

Medicare does not cover the cost of the Sonic PGx Panel and your patient will receive an invoice.* Please refer to the Sonic Genetics website, www.sonicgenetics.com.au/pgx, for current pricing. The test turnaround time is 2 weeks.

For further information, contact your local Sonic Healthcare pathology practice, or Sonic Genetics on 1800 010 447 or info@sonicgenetics.com.au.


References

1. Campbell G, Lintzeris N, Gisev N, et al. Regulatory and other responses to the pharmaceutical opioid problem. *Med J Aust*. 2019; 210(1):6-8.e1
2. Crews K, Gaedigk A, Dunnenberger H, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther*. 2014; 95(4):376-382


*Correct at time of printing