CLINICAL PRACTICE GUIDELINE: *CYP2D6* GENOTYPING FOR SAFE AND EFFICACIOUS CODEINE THERAPY

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ABSTRACT

This guideline is intended to provide a basis for informed decision-making regarding genetic testing to identify those individuals who will not benefit from codeine therapy, as well as those who are at an increased risk for codeine-induced toxicity. This guideline addresses the following key questions: 1) Should genetic testing for *CYP2D6* be performed in patients prior to the initiation of codeine therapy? 2) How should patients with an indication for codeine therapy be managed based on their genotyping results for *CYP2D6*?

Key Words: *Codeine, morphine, pharmacogenetics, CYP2D6, guidelines*

This guideline is intended to provide a basis for informed decision-making regarding genetic testing to identify those individuals who will not benefit from codeine therapy as well as those who are at an increased risk for codeine-induced toxicity. This guideline addresses the following key questions:

1) Should genetic testing for *CYP2D6* be performed in patients prior to the initiation of codeine therapy? 2) How should patients with an

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indication for codeine therapy be managed based on their genotyping results for *CYP2D6*?

While recommendations have been provided on the management of patients in the context of codeine therapy and *CYP2D6* genotype results, there is a staggering breadth of diversity in both patient populations that receive codeine and clinical settings in which codeine is prescribed. As such, the recommendations provided in this guideline should never be regarded as imperative. Instead, they should be interpreted individually in the context of the unique clinical circumstances for each patient. Importantly, an evaluation of cost-effectiveness of genetic testing was not within the scope of this guideline.

Target audience

The principal target audience of this guideline is primary care physicians and specialists managing patients with an indication for codeine. However, it also includes other health care providers and health care policy makers, as well as genetic counselors and molecular or clinical diagnostic laboratory personnel. This guideline is not intended for patients to determine how to alter their prescribed therapy based on genetic test results without consulting their treating health care provider and should not be viewed as a substitute for medical advice.

Glossary

ADR: adverse drug reaction
CNS: central nervous system
Genotype: an individual's genetic (hereditary) information; for example, the molecular blueprint which determines the nature and function of protein expression
Deletion: the complete absence of a sequence of DNA
Null mutation: a genetic mutation or deletion which results in a completely non-functional or absent protein
Phenotype: an individual's expressed properties; for example, actual CYP2D6 protein expression
Extensive metabolizer: a CYP2D6 phenotype classification associated with two functional copies of CYP2D6 protein
Intermediate metabolizer: a CYP2D6 phenotype classification associated with limited/partially functional CYP2D6 protein
Poor metabolizer: a CYP2D6 phenotype classification associated with completely non-functional or absent CYP2D6 protein
Ultrarapid metabolizer: a CYP2D6 phenotype classification associated with greater than two functional copies of CYP2D6 protein
CYP2D6 inhibitor: a compound/medication, which decreases the activity of CYP2D6. All CYP2D6 substrates are potential inhibitors. As such, when two CYP2D6 substrates are co-administered, there is competition between them and one of the two substrates may act as an inhibitor of the second substrate's metabolism. However, there are also compounds that inhibit CYP2D6 but are not substrates. These so-called 'true inhibitors' prevent or delay the metabolism of CYP2D6 substrates by binding or obstructing the CYP2D6 substrate binding site. Unlike substrates, true inhibitors are themselves not metabolized by CYP2D6 (definition adapted from[1]).

Target drug, relevant clinical outcomes, mechanism of gene-drug interaction

Codeine is a commonly used opioid analgesic and is indicated for the treatment of mild to moderate pain. However, it is not codeine, but its pharmacologically active metabolite morphine (produced in the body as a consequence of hepatic metabolism), that is primarily responsible for both analgesia and adverse effects associated with codeine. Morphine is a potent opioid with an affinity over 600 times greater than codeine for the μ opioid receptor.[2]

There is wide inter-individual variability in the amount of morphine that the body produces from codeine, ranging anywhere from 0% to upwards of 75%[3] of the total codeine dose. This variability arises in part from the polymorphic cytochrome P450 2D6 (CYP2D6) enzyme, which mediates codeine biotransformation into morphine. To date, there have been over 80 genetic polymorphisms described in the *CYP2D6* gene. Combinations of different *CYP2D6* alleles result in a range of CYP2D6 activity. Individuals are commonly grouped in 4 different activity ranges, referred to as phenotype (*Table 1, Figure 1*).

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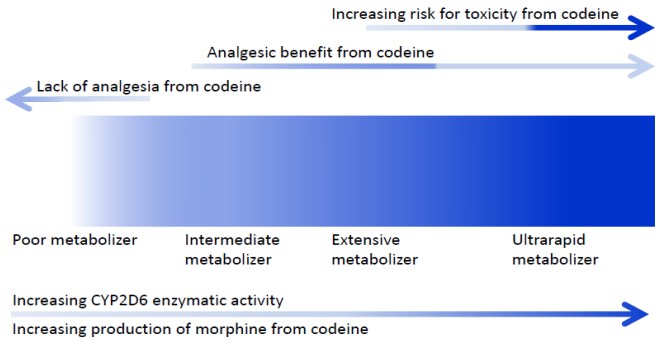
TABLE 1 Phenotypes associated with CYP2D6 alleles.[5]

Phenotype	Genetic Variants		
Ultrarapid Metabolizer (UM)	More than 2 functional alleles.		
Extensive Metabolizer (EM)	2 normally functioning alleles	1 normally functioning allele and 2 reduced function alleles	2 normally functioning alleles and 1 reduced function allele
Intermediate Metabolizer (IM)	1 normally functioning allele and 1 reduced function allele	1 normally functioning allele and 1 null allele	
Poor Metabolizer (PM)	2 null alleles	1 null allele and 1 reduced function allele	

Poor metabolism is the phenotype associated with completely non-functional or absent CYP2D6 protein. *Intermediate metabolism* is a phenotype classification associated with limited/partially functional CYP2D6 protein. *Extensive metabolism* is a phenotype classification associated with fully active enzyme function because of two functional copies of CYP2D6 protein. Finally *ultrarapid metabolizer* is a CYP2D6 phenotype classification associated with elevated CYP2D6 activity due to highly increased amount of CYP2D6 protein as a result of an increased number of functional gene copies (i.e., greater than two functional copies of CYP2D6) (*Table 1*). Up to 13 copies of the *CYP2D6* gene have been reported, although duplications (2 copies) are most typical. Table A5 in Appendix presents estimates of CYP2D6 phenotype frequencies in different geographical regions of the world.[4]

Although most individuals will receive pain relief from codeine, a sub-fraction of the population carries *CYP2D6* variants that do not produce an active enzyme (due to deletions/null mutations in the *CYP2D6* gene; i.e. poor metabolizers) and will not have any pain relief as a result of negligible morphine production. On the other hand, amongst those who are able to produce morphine from codeine, a proportion of individuals are at risk of morphine-induced central nervous system (CNS) depression (*Figure 1*). While there are several important non-genetic risk factors that contribute to codeine-related CNS depression, functional duplications in the *CYP2D6* gene (resulting in increased enzyme activity, and consequently increased morphine production; i.e. ultrarapid metabolism) have been associated with life-threatening opioid toxicity in vulnerable individuals.

FIG. 1 A gradient of CYP2D6 enzymatic activity mediates a range of clinical responses with codeine analgesia.



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Candidate populations for pharmacogenetic testing

Codeine is a controversial analgesic[3], but nonetheless, remains to be commonly prescribed in children and adults in numerous clinical settings. There are many products containing codeine in various dosages either alone or in combination with other active ingredients (i.e. Tylenol No.1, Tylenol No.2, Tylenol No.3, Tylenol No. 4, Emtec, Robaxisal-C, Fiorinal-C, Tylenol/Codeine Elixir, Codeine Contin, Ratio-Lenoltec No.1, Ratio-Lenoltec No.2, Ratio-Lenoltec No.3, Ratio-Lenoltec No.4). Most, but not all, of these products require a prescription, and depending on jurisdiction may belong to the triplicate prescription program.

Given that up to 10% of individuals may not receive analgesic benefit from codeine due to genetic polymorphisms in *CYP2D6*, these individuals may benefit from pre-emptive *CYP2D6* screening prior to the initiation of codeine therapy. In this way, individuals identified as codeine non-responders can receive other analgesics that do not require activation by CYP2D6 for analgesic effect. In addition, individuals currently on high doses of codeine who continue to have severe and debilitating pain may also benefit from *CYP2D6* testing. There have been several cases in the literature exemplifying the continued clinical benefit of *CYP2D6* screening in identifying non-responders AFTER codeine has been initiated.[6-9] In the latter case of non-response, genetic testing should be performed after a complete review of the patient's drug chart to ensure that no drug-drug interactions are present that would explain the observed situation (*see section Caveats and clinical considerations with CYP2D6 genetic testing and Table A6*).

CYP2D6 testing may also identify individuals who are susceptible to codeine-induced respiratory depression as a result of an increased number of functional CYP2D6 gene copies and increased morphine production from codeine. There have been numerous cases of serious adverse events in both children and adults prescribed codeine; most, but not all, of these individuals carried functional duplications of the *CYP2D6* gene. It has emerged that certain populations are especially susceptible to codeine-induced respiratory depression as a result of gene duplication; these are breastfed infants of codeine-prescribed mothers, and children with underlying respiratory illness (e.g. sleep apnea) receiving codeine. However, within these groups, factors such as codeine dose, duration, neonatal morphine clearance capacity[10], and drug interactions may either modulate or provide a protective effect against the presence of high morphine concentrations due to functional *CYP2D6* gene duplication.

SUPPORTING EVIDENCE SUMMARY

TABLE 2 Grading scheme used for critical appraisal of evidence. Refer to "Methods" page *e381* for more details on summary and guideline development process.

Grade	Results	Description
++++	Consistent, generalizable	Strong **general conclusions** can be drawn that are **unlikely to change** based on further research
+++	Consistent, but limited quantity, quality or generalizability	Evidence allows **general conclusions**, but with **reduced confidence**; further research is likely to have an important impact on confidence in conclusions
++	Inconsistent or insufficient quantity/quality, encouraging	No general conclusions can be drawn or conclusions are **likely to change** based on further research, but current evidence is **encouraging**
+	Inconsistent or insufficient quantity/quality, discouraging	No conclusions can be drawn or conclusions are **likely to change** based on future studies, and current evidence is **discouraging**

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CLINICAL PRACTICE RECOMMENDATIONS

TABLE 3 Grading scheme used for grading of clinical practice recommendations. Refer to "Methods" page *e381* for more details on summary and guideline development process.

Grade	Strength	Evidence basis
A	Strong	Based on **strong** scientific evidence; benefits clearly outweigh risks
B	Moderate	Based on **reduced confidence** scientific evidence and expert opinion; benefits likely to outweigh risks
C	Optional	Based mainly on **expert opinion**, for use with **evidence development** in a research context

SUMMARY OF RECOMMENDATIONS

1. Who should be tested and when?

- Young children about to receive codeine for pain management and women about to receive codeine for postpartum pain while breastfeeding should be tested for CYP2D6 (Grade A – strong recommendation).
- Children and adults who continue to have pain despite high doses of codeine should be tested for *CYP2D6* (Grade B – moderate recommendation).
- Genetic testing for CYP2D6 should be considered before administering codeine for the first time in all children and adults in order to rule out non-responders and to identify individuals who may be susceptible to adverse effects from codeine (Grade C – optional recommendation).

2. What gene variants should be tested?

Given the numerous polymorphisms in *CYP2D6* and the diversity of the Canadian population, a full-scale analysis of both common and rare CYP2D6 variants is advised (Grade B- moderate recommendation)

- *CYP2D6* alleles with decreased or no function: *CYP2D6 *3 - 12, 14-15, 17, 19-20, 29, 40-42, 44, 49, 50, 54-56, 59; *4XN, *10XN*
- CYP2D6 alleles with normal or increased function: *CYP2D6 *2* (normal), **1XN* (increased), **2XN* (increased), **17XN, *35XN* (increased), **41XN*, in addition to CYP2D6 copy number determination.

Recommendations: Genotype-Specific Treatment Options

- Poor metabolizers of CYP2D6 should not receive codeine for pain relief (Grade A- strong recommendation).
- Ultrarapid metabolizers of CYP2D6 should avoid codeine for pain relief and receive alternative analgesics that do not have potent CYP2D6 metabolites (Grade B- moderate recommendation).
- Certain populations, especially opioid naïve breastfed neonates of mothers with functional *CYP2D6* gene duplications taking codeine and young children may be particularly susceptible to codeine-induced central nervous system depression. Breastfeeding mothers and young children who are ultrarapid metabolizers of CYP2D6 should avoid codeine (Grade A – strong recommendation).
- In individuals with IM or EM *CYP2D6* genotypes, codeine can be used as per standard of care. Existing evidence suggests that caution is still warranted in CYP2D6 EMs receiving codeine if they are receiving maximal therapeutic doses of codeine and have additional risk factors for toxicity.

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Who should be tested and when?

Young children about to receive codeine for pain management and women about to receive codeine for postpartum pain while breastfeeding should be tested for *CYP2D6* (Grade A - strong recommendation). Children and adults who continue to have pain despite high doses of codeine should be tested for *CYP2D6* (Grade B - moderate recommendation). Genetic testing for *CYP2D6* should be considered before administering codeine for the first time in all children and adults to rule out non-responders and to identify individuals who may be susceptible to adverse effects from codeine (Grade C - optional recommendation).

Rationale

CYP2D6 genetic testing can detect individuals who are non-responders to codeine (++++, strong evidence). *CYP2D6* genetic testing can detect individuals who are at increased risk of morphine-induced respiratory depression from codeine (+++, moderate evidence). In spite of the reduced strength of evidence for codeine-related respiratory depression due to the limited number of studies available, the severity of the associated outcome (lethal intoxications) warrants a strong recommendation (Grade A - benefits clearly outweigh risks) for genetic testing in susceptible populations, particularly young children and breastfeeding mothers.

Clinical Considerations

While an acute, low dose of codeine may protect a CYP2D6 UM from morphine-induced respiratory depression, non-fatal but nonetheless severe ADRs have been reported with only 60mg of codeine.[11] To date, there have been two case reports of opioid toxicity from codeine in adults, who were CYP2D6 Ums.[3,11] The safe, tolerable dose of codeine in a CYP2D6 UM has not been studied. Genetic testing is advisable in all individuals where it can be carried out prior to codeine administration to rule out both CYP2D6 PM and CYP2D6 UM status. In pediatric populations and in neonates whose breastfeeding mothers are receiving codeine, genetic testing is strongly recommended to rule out CYP2D6 UM status.

The time period with the greatest risk for opioid toxicity from codeine is upon initiation/exposure to codeine and its morphine metabolite. The risk of toxicity may be inherently higher in opioid-naïve individuals. On the other hand, in patients who are chronically managed with codeine and are experiencing pain relief with no adverse effects, genetic testing is of little benefit, unless they are unresponsive (and poor metabolism is suspected). Thus, the *CYP2D6* test is particularly useful if the results can be obtained before codeine is administered. In some clinical scenarios, *CYP2D6* genetic testing prior to codeine administration may not be feasible at this time. With the advent of rapid point-of-care genotyping technology, this possibility may arise in the future.

Drug interactions can result in inhibition of the CYP2D6 enzyme and block the metabolism of codeine into morphine. In codeine non-responders, a complete review of a patient's drug chart should be performed to rule out whether drug-interactions can explain the observed situation (*see Table A6*). It should also be noted that codeine is often prescribed as a combination product with acetaminophen. Acetaminophen may be wholly responsible for the pain-relieving effects of a codeine-acetaminophen formulation[13] in individuals who are CYP2D6 poor metabolizers and thereby unable to transform codeine into morphine.

What gene variants should be tested?

The following variants should be tested:

- ***CYP2D6* alleles with decreased or no function: *CYP2D6 *3 - 12, 14-15, 17, 19-20, 29, 40-42, 44, 49, 50, 54-56, 59; *4XN, *10XN***
- ***CYP2D6* alleles with normal or increased function: *CYP2D6 *2* (normal), **1XN* (increased), **2XN* (increased), **17XN, *35XN* (increased), **41XN*, in addition to *CYP2D6* copy number determination.**

Rationale

Given the numerous polymorphisms in *CYP2D6* and the diversity of the Canadian population, a full-scale analysis of both common and rare *CYP2D6* variants is advised (Grade B- moderate

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recommendation for full-scale analysis of all *CYP2D6* alleles listed in *Table A4*). From a practical perspective, many commercially available CYP2D6 panels are optimized to test for only a handful of common CYP2D6 variants based on European populations. Users must be aware of the limitations of phenotype classification based on genotype when a less comprehensive CYP2D6 assay is utilized, particularly in multi-ethnic populations. *See Table 1* to understand how different combinations of *CYP2D6* alleles are converted into CYP2D6 phenotype classifications. Refer to *Table A4* in the Appendix for a list of genetic variants, their type of mutation, level of activity and potential implications for codeine analgesia. In addition to considering the comprehensive nature of the CYP2D6 panel as part of genotype analysis, an additional analytical step of determining the number of duplicated *CYP2D6* copies is extremely important and can have implications for CYP2D6 UM classification in the presence of partially active *CYP2D6* variants.

Clinical Considerations

CYP2D6 genotype analysis can be performed on DNA obtained from biological samples; most commonly blood, saliva, or buccal samples. Currently, CYP2D6 genotype analysis is not routinely available in community hospitals across Canada but is available in several specialized/academic tertiary care settings within the country. The CEPMED website (accessed via http://www.cepmed.com/personalized-medicine-testing), can be referred to for a list of both public and private pharmacogenetic test providers in Canada. Co-administration of a CYP2D6 inhibitor together with codeine may result in a "poor metabolizer" phenotype regardless of the genotype status of the individual. Regardless of genotype, all neonates less than 2 weeks of age are phenotypically "poor metabolizers" due to low levels of CYP2D6 expression. As codeine is not indicated for children less than 2 weeks of age, neonates are more commonly exposed to codeine via maternal breast milk. Pregnancy may induce CYP2D6 enzymatic activity in women with functional *CYP2D6* genotypes.[14] Many commercial CYP2D6 panels are not comprehensive in the coverage of all CYP2D6 alleles listed in Table A4; this limitation should be noted when genotype results are interpreted.

GENOTYPE-SPECIFIC TREATMENT OPTIONS

Poor metabolizers of CYP2D6 should not receive codeine for pain relief (Grade A- strong recommendation).

Clinical Considerations

Analgesics that do not require activation by CYP2D6, such as morphine, are suitable alternatives. Some evidence suggests that non-opioid analgesics, such as ibuprofen, have performed at least as well as opioids in terms of pain relief.[15] Caution should always be utilized when patients are switched from one opioid to another. Dosing conversion charts between opioids are based on morphine equivalents and do not consider inter-individual variability between patients. In particular, these conversions may not be suitable for CYP2D6 PM patients who are receiving codeine (given their inability to produce morphine from codeine).

Ultrarapid metabolizers of CYP2D6 should avoid codeine for pain relief and receive alternative analgesics that do not have potent CYP2D6 metabolites (Grade B - moderate recommendation).

Clinical Considerations

Oxycodone, hydrocodone, and tramadol are all metabolized by the CYP2D6 enzyme into the more potent oxymorphone, hydromorphone, and M1 metabolites respectively. While oxycodone and hydrocodone may be suitable alternatives for poor CYP2D6 metabolizers, they are not (together with tramadol) recommended alternatives for CYP2D6 ultrarapid metabolizers. Opioid-related adverse events have been reported in ultrarapid metabolizers administered oxycodone[16] and tramadol.[17] Alternatively, a reduced codeine dose could be considered in patients with ultrarapid metabolizer phenotype. However, severe ADRs have been reported with only 60mg of codeine in an UM patient[11], or in children with sleep apnea

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who received therapeutic doses of codeine.[18] How to adjust doses in an ultra rapid metabolizer needs further study. In one trial (unpublished), breastfeeding mothers, some of whom were retrospectively determined to be ultrarapid metabolizers, were instructed to use codeine for no more than four days after Caesarian surgery. No adverse events were reported in breastfed infants of codeine-using mothers who were CYP2D6 ultrarapid metabolizers in this study. These findings are also supported by a modeling study which illustrated that the combination of maternal codeine dose, duration, metabolic capacity and neonatal morphine clearance capacity are co-dependent risk factors towards predicting toxicity in breastfed infants.[19]

Overall, given that no evidence is available on how to prospectively reduce the starting codeine dose in a known CYP2D6 ultrarapid metabolizer at this time, the use of an alternative medication, if available, is considered the safest option.

Certain populations, especially opioid naïve breastfed neonates of mothers with functional *CYP2D6* gene duplications taking codeine and young children may be particularly susceptible to codeine-induced central nervous system depression. Breastfeeding mothers and young children who are ultrarapid metabolizers of CYP2D6 should avoid codeine (Grade A - strong recommendation).

Clinical Considerations

Compromised respiratory function (i.e. obstructive sleep apnea) or impaired drug clearance due to a patient's age or disease status may increase the risk of serious central nervous system depression in susceptible patients.

In individuals with IM or EM *CYP2D6* genotypes (the majority of the population), codeine can be used as per standard of care. Existing evidence suggests that caution is still warranted in CYP2D6 EMs receiving codeine if they are receiving maximal therapeutic doses of codeine and have additional risk factors for toxicity.

Clinical Considerations

Adverse events have been reported in extensive CYP2D6 metabolizers, who received maximal therapeutic doses of codeine over a number of days.[18,20-23] Therefore, patients with extensive metabolizer phenotype may also be at increased risk of central nervous system depression if administered high doses of codeine, particularly when additional risk factors (e.g. young child, compromised respiratory function) are present.

Benefits/potential harms of implementing recommendations

Determination of *CYP2D6* genotype will benefit individuals by helping determine whether codeine is a safe and effective analgesic drug for them. In addition, many other medications are substrates of CYP2D6. Therefore, knowledge of *CYP2D6* genotype may have implications for other drugs such as tamoxifen. However, the potential harm exists in the reality that extrapolation and interpretation of *CYP2D6* genotype for the majority of other CYP2D6 substrates is not well-studied or known. There is also a possibility that individuals may develop adverse reactions to drugs used as alternatives to codeine in poor and ultrarapid CYP2D6 metabolizers. Many alternative medications will likely to have their own pharmacogenetic interactions (e.g. drugs metabolized through CYP3A4/3A5, which are also mediated by polymorphic genes).

KEY MESSAGES

- Careful consideration should be given to classifying an individual with the ultrarapid metabolizer phenotype as some gene duplications do not produce a functional gene copy and therefore do not always translate into ultrarapid metabolism.
- An individual's CYP2D6 phenotype can change throughout their lifetime as drug interactions, diet, and pregnancy can affect CYP2D6 enzymatic activity. *See Appendix, Table A6 for a list of CYP2D6 inhibitors.*
- Developmental changes in drug metabolizing enzymes should be considered when interpreting CYP2D6 genetic results in newborns and young children.

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Caveats and clinical considerations with *CYP2D6* genetic testing

In addition to its highly polymorphic nature, *CYP2D6* variation is characterized by gene duplication events resulting in as many as 13 *CYP2D6* copy number variants. Careful consideration should be given to classifying an individual with the ultrarapid metabolizer phenotype, keeping in mind that gene duplication by itself does not always translate into ultra rapid metabolism. Many duplications can result in enzymes of reduced or no function. In addition, the functionality of the second other (non-duplicated) allele needs to be considered (*Table 1*). The current technology used to determine *CYP2D6* copy number is not robust and copy number determination is not available on most commercial platforms. Thus, a tendency for over-reliance on test results based on the current status of the testing should be avoided, as genetic technology and interpretation will change over time.

An individual's CYP2D6 phenotype will change throughout their lifetime. Non-genetic factors, including drug interactions, diet, and pregnancy can affect CYP2D6 enzymatic activity in an individual. CYP2D6 is subject to inhibition by a broad range of medications. It has been shown that co-administration of a strong CYP2D6 inhibitor together with codeine may result in a "poor metabolizer" phenotype even when an individual has a functional *CYP2D6* genotype status (i.e. is an extensive metabolizer).[24] A list of CYP2D6 substrates/inhibitors, along with their relevant potency, is provided in Appendix, Table A6.

During pregnancy, CYP2D6 enzymatic levels may increase, as pregnancy is the only time that CYP2D6 is known to be induced.[25] Inductive mechanisms appear to be specific to a sub-categorization of women with functional CYP2D6 genotypes, while an apparent competitive inhibition mechanism with endogenous substrate appears to further inhibit the metabolism of CYP2D6 compounds in individuals with a genetic predisposition to low levels of CYP2D6 expression.[14] This might have implication in interpretation of maternal genotype to phenotype in the context of breastfeeding.[14]

CYP2D6 diversity is by far greater between individuals than it is between populations.[4] However, more work needs to be done in understanding the relationship between *CYP2D6* genotype and phenotype in diverse populations. Lower average CYP2D6 metabolic rates have been observed between populations with the same *CYP2D6* genotype scores.[26] These differences may be due to yet unidentified sequence variations altering CYP2D6 activity, variations within other genes impacting CYP2D6 activity and/or non-genetic factors such as diet.

The ontogeny of drug metabolizing enzymes in newborns and young children should also be considered when interpreting *CYP2D6* genetic results in these populations.[27] At birth, neonates less than 2 weeks of age are functionally characterized, regardless of genotype, as "poor metabolizers" due to low levels of CYP2D6 expression.[28] As codeine is not indicated for children less than 2 weeks of age, neonates are more commonly exposed to codeine via maternal breast milk. Young children also have limited glucuronidation capacity, resulting in a compromised capability to clear codeine and morphine from the body.[29]

The availability of diagnostic genetic tests varies locally and was not exhaustively assessed in this guideline. For enquiries regarding local availability and cost of genetic tests, local diagnostic laboratories (e.g. hospital-based molecular diagnostic laboratories) should be contacted.

Possible implications of genetic test results in the context of diseases or the response to medications other than those included in the guideline recommendations were not systematically addressed by this guideline. Other therapies should therefore not be changed based on genetic test results and this guideline. As more evidence on the impact of genetic variation on drug response and diseases becomes available, the understanding of such genetic effects may evolve and change. Therefore, other therapies should only be changed based on evidence-based clinical practice guidelines systematically addressing the respective diseases or medications in the context of genetic information

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SUPPORTING EVIDENCE

CYP2D6

The pharmacokinetic relationship between CYP2D6 enzymatic heterogeneity and serum morphine concentrations following codeine administration has been well studied. From these investigations (which include four randomized, double-blind, controlled trials)[24,30-32], it has clearly and unanimously emerged that individuals who are unable to produce morphine (as a result of genetically-mediated deficiencies in CYP2D6 enzymatic expression *or* due to drug-related inhibition of the CYP2D6 enzyme) are unable to achieve analgesic benefit from codeine (*Table A1, Appendix*). Collectively, these studies constitute approximately 200 individuals who were phenotypically and/or genotypically assessed as poor metabolizers of CYP2D6.[6-9,12,24,30-40] Most studies could not detect morphine in the plasma or the urine of CYP2D6 poor metabolizers administered codeine. In fact, no more than 1% of the total codeine dose was ever recovered as morphine in these research participants. In addition to negligible morphine production, these poor metabolizers did not have significant analgesia based on subjective and objective pain thresholds[7,8,30,31,34], and had significantly more hospital admissions due to persistent pain following codeine use.[6,37] The studies were conducted in both children and adults. Although African-American[6,37] populations were studied, the overall cohort was predominately Caucasian.

However, the sensitivity and specificity of pre-emptive *CYP2D6* genetic screening to identify codeine non-responders has not been well studied. In a nested cohort study, seven out of eight (87.5%) participants in the lowest 15% quartile of morphine formation following codeine administration were correctly identified by either genotyping or phenotyping for CYP2D6 activity.[35] Yet the extrapolation of CYP2D6 enzymatic activity to analgesic effect may be more complex than *CYP2D6* genotype alone. In the context of acute post-operative pain, systematic literature reviews have estimated that the number needed to treat for one patient to experience at least 50% pain relief over four to six hours following administration of 60 mg codeine is 12 (range 8-18) as compared to placebo.[41] The NNT falls to 2.2 when 60 mg codeine is prescribed in combination with 1000 mg acetaminophen.[13] These figures suggest that *CYP2D6* genetic variation may only partially account for codeine-ineffectiveness. In additional to the complexity of pain perception and pharmacodynamic factors associated with pain response, drug-drug interactions *(see Caveats and clinical considerations with CYP2D6 genetic testing and Appendix, Table A6 for a list of drug interactions*) are an important non-genetic clinical factor to consider in the context of codeine efficacy and effectiveness.

It has also been well established that individuals with genotypes associated with functional CYP2D6 activity are able to produce morphine. Moreover, there is a gene dose effect so that as the number of functional *CYP2D6* gene copies increases, the amount of morphine produced from codeine also increases (*Table A2, Appendix*). These studies collectively total over 255 individuals who were phenotypically and/or genotypically assessed as extensive metabolizers of codeine.[3,9,11,12,18,20-24,30,31,33,34,36,38-40,42-45]

However, within this group of extensive *CYP2D6* metabolizers, there is large variation in analgesic response to codeine. It follows that, two individuals with the same functional *CYP2D6* genotype may not necessarily produce the same amount of morphine from codeine due to environmental factors resulting in basal differences in enzymatic activity. Moreover, ultrarapid *CYP2D6* genotype is rarely a sole cause of serious and life-threatening codeine-related toxicity. In most cases, there is interplay with a myriad of pharmacodynamic factors; such as opioid naivety, age-related ontogeny, co-administration of drugs that inhibit opioid metabolic pathways or synergize with opioid sedative effects, and underlying disease such as airway complications and compromised renal function (*Table A3, Appendix*).[3,11,18,20-23,42-44]

There are uncertainties regarding the sensitivity and specificity of CYP2D6 genetic testing to identify patients at risk of morphine-related toxicity as a result of codeine administration. What has emerged from a systematic review of the literature is that young children are disproportionately affected by codeine-induced

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respiratory depression. While there have been numerous reports of toxicity in children who have received codeine, genotype information has not been available for most cases.[27] Of those individuals who have been genotyped, four codeine-related deaths have been reported; three deaths in toddlers (2 ultrarapid metabolizers; 1 extensive metabolizers)[18,20,42], and one death in a breastfed neonate whose mother was a CYP2D6 ultrarapid metabolizer (*Table A3, Appendix*).[43,44,46] These cases were often compounded by indications that on their own can compromise respiration, such as post-tonsillectomy pain relief, and treatment of cough/cold symptoms. Therefore, special consideration should be given to the pediatric population, and *CYP2D6* genotype interpretation should be considered within the context in which codeine is prescribed.

Renal failure has been shown to significantly impair morphine clearance following codeine administration in extensive CYP2D6 metabolizers (EMs).[36] A modeling study has shown that reduced renal function leads to a significant increase in plasma exposure to the active morphine 6-glucuronide M6G metabolite after codeine administration. Specifically, a CYP2D6 IM with severe renal impairment may exhibit plasma exposure of M6G comparable to that of a CYP2D6 UM with normal renal function.[47] It follows that poor renal function was associated with life-threatening respiratory depression in a codeine-prescribed adult male who was a CYP2D6 UM and concomitantly received medications that inhibited other codeine metabolic pathways.

KEY MESSAGES

- Glucuronidation is the major metabolic pathway of codeine
- UGT2B7 metabolizes codeine and morphine into codeine 6-glucuronide and morphine 3-glucuronide (inactive metabolite) /morphine 6-glucuronide (major active metabolite)
- Inhibition of UGTs may lead to increased morphine exposure in individuals with functional CYP2D6 activity
- The functional effect of UGT2B7 genetic polymorphisms in the context of codeine and/or morphine administration is not clear
- Further studies that are coupled with a pharmacokinetic evaluation of codeine and morphine glucuronides are needed to understand the clinical significance of the *UGT2B7*2* genetic variant

Other variants involved in codeine metabolism and response

UDP glucuronosyltransferase 2 family, polypeptide B7 (UGT2B7)

Codeine and morphine are both glucuronidated, in part by the enzyme UGT2B7, into codeine 6-glucuronide and morphine 3-glucuronide/morphine 6-glucuronide, respectively. Morphine 6-glucuronide is a major active metabolite, whereas morphine 3-glucuronide is considered an inactive metabolite. Moreover, codeine 6-glucuronide is considered to be the primary and most abundant codeine metabolite.

There have been several polymorphisms identified in the *UGT2B7* gene[48]; the *UGT2B7*2* variant in particular has been the most studied in the context of morphine metabolism and response with equivocal results. More recently, haplotype 4 of the *UGT2B7* gene has been associated with significant increases in enzymatic activity and subsequent formation of the morphine 3-glucuronide variant.[48] The functional significance of *UGT2B7* polymorphisms in the context of codeine metabolism and response has not been comprehensively studied. In an extreme case of infant fatality, the codeine-prescribed breastfeeding mother was a CYP2D6 UM in addition to being a homozygous carrier of the *UGT2B7*2* variant.[44] Morphine 3 - and 6-glucuronide levels were not available for assessment in this case.[44] Yet in larger studies of codeine-prescribed breastfeeding mothers conducted by the same group, the *UGT2B7*2* variant was not significantly associated with

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neonatal CNS depression.[21,22] This latter finding was supported by a modeling study, which illustrated that increased UGT2B7 activity may be associated with a *decrease* in active opioid exposure.[47] The authors of this study suggested that high UGT2B7 activity may shift the codeine mass balance towards a higher production of the inactive codeine 6-glucuronide metabolite, which will decrease the risk of adverse events due to higher morphine 6-glucuronide levels.[47] Conversely in individuals with *decreased* UGT activity (i.e. due to drug-drug interactions), the risk of toxicity may be increased because of the greater contribution of the CYP2D6 pathway.

Thus the balance of evidence to date suggests that inhibition of UGT enzymes may be a more relevant clinical consideration than the effect of *UGT2B7*2* polymorphism as it pertains to codeine-related toxicity. Pharmacogenetic studies that are coupled with a pharmacokinetic evaluation of codeine and morphine glucuronides in patients may shed more light on the contribution of the *UGT2B7*2* variant as it pertains to codeine therapy.

Cytochrome P450 3A4 (CYP3A4)

Cytochrome P450 3A4 is the enzyme responsible for the conversion of codeine into the inactive norcodeine metabolite.[33,49] CYP3As are major enzymes involved in the metabolism of hydrocodone and oxycodone, but they play a minor role in codeine metabolism as compared to glucuronidation, which accounts for at least 70% of codeine metabolism.[33,45] In the case of hydrocodone[10,19] and oxycodone[16] which are predominantly metabolized by CYP3A as well as CYP2D6, numerous studies illustrate that the inhibition of CYP3A results in an increase of CYP2D6 metabolites as more of the parent opioid is shunted down the CYP2D6 pathway.

It appears that this shunting is not similarly significant for codeine, given the major role glucuronidation plays in codeine metabolism. A modeling study suggests that inhibition of CYP3A4 (via co-administration of a CYP3A4 inhibitor) results in increases of approximately 10% in morphine exposure and 15% in morphine 6-glucuronide exposure and this value remains similar for various CYP2D6 phenotypes.[47] Therefore, based on this theoretical model, concomitant administration of codeine and a CYP3A4 inhibitor may not result in a clinically significant interaction[47].

Although the compensatory mechanism does not appear to be significant in a theoretical model, it is conceivable to assume that CYP3A4 inhibition can further increase morphine exposure and synergize with other factors, particularly in individuals with co-morbid conditions. One case report highlights the culmination of CYP3A inhibition, UGT inhibition and CYP2D6 ultrarapid metabolism resulting in an ADR in an adult male with poor renal function who was administered codeine.[3] However, the full extent of the interplay of CYP3A inhibition with CYP2D6 genotype remains unclear at this time and requires further research.

ATP-binding cassette, sub-family B (MDR), member 1 (*ABCB1*)

A recent study has investigated genetic markers involved in codeine response.[22] In particular, single nucleotide polymorphisms previously associated with decreased expression of *ABCB1*, a gene encoding for the morphine transporter P-glycoprotein (P-gp), were investigated for the first time in the context of codeine toxicity. The study, which assessed 111 mother-infant breastfeeding pairs exposed to codeine, determined that a combination of both *CYP2D6* and *ABCB1* variation was significantly associated with the adverse outcome in infants (OR 2.68; 95%CI 1.61-4.48; p_{trend}=0.0002) and mothers (OR 2.74; 95%CI 1.55-4.84; p_{trend}=0.0005). Together with clinical factors, this genetic model predicted 87% of the infant and maternal CNS depression cases with a sensitivity of 80% and a specificity of 87%. This finding holds the promise of better optimizing the genetic prediction of codeine toxicity and needs to be replicated in other settings and studies.[22]

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FUTURE DIRECTIONS

Further studies are needed to investigate:

- Other genetic and clinical markers that mediate codeine and morphine analgesia and toxicity
- The contribution of other codeine metabolites besides morphine that affect codeine efficacy
- The incidence of morphine-related toxicity in a *prospective* study
- The sensitivity, specificity, positive and negative predictive values for *CYP2D6* testing
- The mechanisms of increased sensitivity in neonates and young children
- The duration of maternal CYP2D6 induction postpartum
- Technical advancement for improved determination of CYP2D6 ultrarapid metabolizer phenotype
- The contribution of *CYP2D6* variants in populations of non-European ancestry
- The impact of compromised renal function in CYP2D6 genotyped-adults receiving codeine
- The influence of CYP3A and/or UGT inhibitors on codeine metabolism and response

Further work is needed to elucidate the genetic and clinical markers that mediate codeine and morphine analgesia and toxicity. Given that within a group of extensive CYP2D6 metabolizers, there is a wide variation in analgesic response to codeine, a close investigation of novel pharmacodynamic targets is necessary. Along this line, independent studies are needed to replicate and validate the novel association of *ABCB1* as a marker of codeine-induced toxicity.[22] There are also some lingering questions on the contribution of other codeine metabolites besides morphine in relation to codeine efficacy[50] and toxicity[30] that should be further studied. For example, one modeling study suggests that the codeine 6-glucuronide metabolite may be contributing to codeine-related analgesia[51], despite the low binding affinity of codeine 6-glucuronide[50] at the mu opioid receptor.

Importantly, the actual incidence of morphine-related toxicity as a result of codeine administration should be *prospectively* elucidated. The sensitivity, specificity, positive and negative predictive values for *CYP2D6* genetic testing in regards to codeine therapy (both efficacy and toxicity) must also be determined. Further research to understand the mechanisms that contribute to the increased sensitivity of neonates and young children to the CNS-depressant effects of opioids, including codeine would be beneficial. Studies evaluating the duration of maternal CYP2D6 induction postpartum would also help elucidate genotype to phenotype correlations in breastfeeding mothers using opioid analgesics.[14]

Additional studies are also warranted in order to better understand how renal dysfunction, CYP3A and UGT inhibitors, and reduced respiratory function in adults may contribute to adverse events in the context of *CYP2D6* genotype. Additional clinical guidelines on how to select suitable opioid analgesics for patients based on their genotype also need to be developed.

Technical advancements in the determination of *CYP2D6* copy number variation are needed to aid in more robust and sensitive characterization of the CYP2D6 ultrarapid metabolizer phenotype in patients. Additionally, the specific contribution of the majority of *CYP2D6* variants has not been directly studied. Most studies investigating the relationship between *CYP2D6* and codeine pharmacokinetics have been performed in populations of European ancestry. Only the most commonly occurring *CYP2D6* variants in the European population have been studied in relation to codeine.

METHODS

Guideline development group

The guideline development group included scientists and practicing physicians with different backgrounds such as clinical pharmacologists, clinical pharmacists, geneticists, pharmaceutical medicine physicians, and family practitioners.

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Process

A standard guideline development process was followed, in accordance with the quality criteria suggested by the Appraisal of Guidelines Research and Evaluation Enterprise (AGREE), an international endeavor aimed at improving the quality of practice guidelines.[52] This process involved a systematic literature search, followed by critical appraisal of the retrieved evidence. Clinical practice recommendations were developed during a workshop meeting of guideline development group members. Draft guideline documents were submitted to a tiered review process, which included internal review by the guideline development group members, followed by external review both by content experts and by members of the intended target audience.

Identification and critical appraisal of evidence

A comprehensive systematic search of the relevant English-language, published, peer-reviewed literature was performed to identify available evidence on genetic testing for *CYP2D6*, *UGT2B7*, *ABCB1*, and any other pharmacogenomic variants in the context of codeine therapy. Embase from the period of 1980 to July 2011 (using the OVID interface) and MEDLINE from the period of 1948 to July 2011 (using the OVID interface) were searched. The complete search strategy, including search keywords used and numbers of articles retrieved and reviewed is provided in the Appendix. Titles and abstracts of all records retrieved were scanned for relevance to the guideline key questions. English language original studies relevant to the guideline questions were selected for full-text review. Editorials, notes, short surveys, and review articles were not included in the full-text review. Conference abstracts were only included if they were published in or after 2009. After the initial search in July 2011, monthly updates of the systematic literature search were performed. The last update of the literature search was performed in February 2012.

Strength of scientific evidence was graded using an approach similar to scheme suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[53] (*Table 4*) Strength of evidence was evaluated based on the consistency of results, magnitude of the effect, as well as the number and quality of studies conducted. Study quality assessment included the evaluation of limitations in the study design, imprecision of effect estimates, and indirectness of evidence, as well as the possibility of publication bias.

TABLE 4 Grading scheme used for critical appraisal of evidence.

Grade	Results	Description
++++	Consistent, generalizable	Strong **general conclusions** can be drawn that are **unlikely to change** based on further research
+++	Consistent, but limited quantity, quality or generalizability	Evidence allows **general conclusions**, but with **reduced confidence**; further research is likely to have an important impact on confidence in conclusions
++	Inconsistent or insufficient quantity/quality, encouraging	No general conclusions can be drawn or conclusions are **likely to change** based on further research, but current evidence is **encouraging**
+	Inconsistent or insufficient quantity/quality, discouraging	No conclusions can be drawn or conclusions are **likely to change** based on future studies, and current evidence is **discouraging**

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Development of clinical practice recommendations

Clinical practice recommendations were developed during a two-day workshop with participation of all guideline development group members using an informal consensus process. Supporting evidence and draft recommendations were presented by one member to the group, followed by discussion and revision of recommendations according to group consensus.

Each clinical practice recommendation was assigned to one of three categories of strength, based on the strength of available evidence, on which the recommendation was formulated, the balance between benefits and risks of genetic testing and genotype-guided treatment, as well as the likelihood of variability in the individual values and preferences of patients (*Table 5*). A strong recommendation (Grade A) was considered a therapeutic option that is expected to be chosen by a majority of informed health care providers and patients, whereas a moderate grading (B) was given for a recommendation that is expected to require individualized informed decision making by patients and health care providers, taking into account the individual needs, values and preferences of each patient. A recommendation of grade C is considered an optional recommendation, e.g. for use of a genetic test in a research context.

TABLE 5 Grading scheme used for grading of clinical practice recommendations.

Grade	Strength	Evidence basis
A	Strong	Based on **strong** scientific evidence; benefits clearly outweigh risks
B	Moderate	Based on **reduced confidence** scientific evidence and expert opinion; benefits likely to outweigh risks
C	Optional	Based mainly on **expert opinion**, for use with **evidence development** in a research context

Review

As a first step, the draft guideline document was reviewed internally by all guideline development group members. Secondly, the draft guideline was reviewed externally by two independent content experts. Finally, a third review was performed by a group of members of the target audience of the guideline. This third review step was aimed to ensure the clarity of the presented context, as well as the ease of use of the guideline and its applicability in clinical practice.

Acknowledgements

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APPENDIX
Systematic Literature Search Strategy

<table>
<tr><th colspan="2">Database: Embase <1980 to 2011 Nov 2>, Ovid MEDLINE(R) 1948 to Present with Daily Update</th></tr>
<tr><td colspan="2">1 codeine.ab,ti. (7430)
2 (cyp2d6 or "cytochrome p450 2d6" or ugt2b7 or abcb1 or ultra-rapid metaboli* or ultrarapid).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, an, ui] (17189)
3 (pharmacogen* or genetic* or genom* or gene varia* or genotype* or polymorphism*).mp. (3159399)</td></tr>
<tr><td>4 (toxicit* or intoxicat* or central nervous system or cns or depression or adverse event or adverse effect or adverse reaction or breast or milk or infant or morphine).mp. (4214979)
5 1 and 2 and 3 and 4 (163)
6 remove duplicates from 5 (107)
7 limit 6 to (letter or note or "review" or short survey) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update; records were retained] (40)
8 6 not 7 (67)</td><td>4 (pain or poor metaboli* or PM).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, an, ui] (1037077)
5 1 and 2 and 3 and 4 (113)
6 (toxicit* or intoxicat* or central nervous system or cns or depression or adverse event or adverse effect or adverse reaction or breast or milk or infant).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, an, ui] (4118352)
7 1 and 2 and 3 and 6 (82)
8 5 not 7 (67)
9 remove duplicates from 8 (41)
10 limit 9 to (editorial or letter or note or "review" or short survey) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update; records were retained] (15)
11 9 not 10 (26)</td></tr>
<tr><td>19 articles included</td><td>8 articles included</td></tr>
<tr><td colspan="2">Additional articles provided by guideline authors: 5</td></tr>
<tr><td colspan="2">Total number of articles: 32</td></tr>
<tr><td colspan="2">Removed:
• Irrelevant articles (articles that did not study the correlation between genotypes and variability of codeine effect)
• Non-original studies, including editorials, notes, short surveys, conference abstracts prior to 2009 and reviews</td></tr>
</table>

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EVIDENCE SUMMARY TABLES

TABLE A1: Evidence summary: Individuals with genetically-mediated deficiencies in CYP2D6 enzymatic expression *or* who receive drugs that inhibit the CYP2D6 enzyme are unable to produce morphine from codeine and/or do not receive analgesic benefit from codeine.

Year, Study Design	Methods to determine CYP2D6 activity	# of poor metabolizers (PM)	Evidence summary	Ref
1996, Randomized, doubled blind	- debrisoquine phenotyping - quinidine (strong CYP2D6 inhibitor) co-administration	- 6 adult PM males -10 adult EM males who received quinidine	- after codeine administration: morphine and its metabolites were not detected in plasma of 6 PMs but were detected in 10 EMs - after quinidine & codeine administration: morphine and its metabolites were not detected in any subjects	[24]
2007, Prospective	- *CYP2D6 *2-6, *9-10, *35, 41* and gene duplication; codeine pharmacokinetics over 24 hours after a single 30mg dose	3 adult PM males	- median morphine plasma concentrations were 0.5 mcghr/l for PMs (vs. 11 and 16 mcg/hr for EM and UM respectively)	[12]
1991, Prospective	- debrisoquine phenotyping; codeine pharmacokinetics over 24 hours after a single 50 mg oral codeine dose	6 adult PMs	- negligible plasma concentrations of morphine and its metabolites (5 out of 6 undetectable, 1 very low)	[39]
1989 and 1997, Prospective	- debrisoquine phenotyping; codeine pharmacokinetics over 8 hours after a single 25 mg codeine dose	18 adult PMs	- morphine and subsequent metabolites accounted for <0.4% of the total codeine urine recovery in PMs	[38,40]
2009, Prospective	- codeine phenotyping; *CYP2D6 *17,*29, *4* analysis; codeine pharmacokinetics over 6 hours after a single 30 mg codeine dose	24 adults with no measurable morphine following codeine dose	- more hospital admissions in patients with no measurable morphine levels; these individuals were not more likely to possess **17*, **29*, or **41* reduced functional variants	[37]
2002, Randomized, double blind	- *CYP2D6 *1-5, 9-10, 1*; codeine pharmacokinetics after 1.5 mg/kg codeine dose or 0.15 mg/kg morphine dose	46 children with genotypes associated with reduced enzyme activity (PM or IM)	- significant relationship between genotype and phenotype (plasma morphine concentrations); morphine was not detected in PM patients	[32]
1991, Prospective	- dextromethorphan phenotyping; codeine pharmacokinetics after a single 30mg dose and after 7 doses (30 mg every 8 hours)	- 1 adult PM	- 0.5% of total dose was recovered as morphine after single or chronic administration of codeine (14 times lower than EMs)	[33]

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2010, Prospective	- *CYP2D6 *3, 4, 6;* codeine pharmacokinetics following a single 50 mg oral codeine dose over 28 hours	- 2 adult PMs with end-stage renal disease	- [M6G metabolite] was below the limit of quantification in PMs only (< 1nM); 2 hours after codeine intake, mean concentration of M3G was 3.5nM in PMs (vs. 210nM in EMs)	[36]
1991, Prospective	- sparteine phenotyping	- 1 adult PM	- no significant analgesia in PM based on subjective and objective pain thresholds; negligible morphine concentration as compared to EMs following codeine administration	[34]
1996, Randomized, double blind	- sparteine phenotyping; single 75mg or 100mg codeine dose versus 20 or 30 mg morphine dose versus placebo	- 14 adult PMs	- morphine & metabolites could be detected in 13 of 14 PMs; codeine did not reduce pain in PMs; no difference in incidence of adverse effects between codeine & placebo in PMs	[31]
1998, Randomized placebo-controlled double-blind	- *CYP2D6 *3, 4*; single 170 mg codeine dose versus 20 mg morphine versus placebo	- 9 adult PMs	- analgesia as measured by cold pressor test was observed in EMs but not PMs; only traces of morphine was detected in PMs; there was a similar incidence in adverse events between PMs and EMs	[30]
2011, Retrospective	- *CYP2D6 *2-10, 12, 14, 17, 29, 41* and **XN (*gene duplication)	- 2 adult PMs	- one PM took 13 doses of codeine without pain relief; the other PM switched medications after 2 doses due to persistent pain	[9]
2008, Retrospective	- genotyping for *CYP2D6 *4, 5, 6, 10, 17, 40* as well as gene duplications	42 children with genotypes associated with reduced CYP2D6 activity	- children with reduced functional *CYP2D6* alleles (and decreased analgesic response to codeine) were more likely to be taking hydroxyurea for severe pain	[6]
2006, Case report	- *CYP2D6* genotyping (alleles not listed)	1 female PM (*CYP2D6*4/*6)*	- long standing intolerance to codeine	[8]
2007, Case report	- genotyping for *CYP2D6* using Amplichip™ P450 Test	1 female PM	- poor tolerance and limited response to opioid analgesics and other CYP2D6 substrates	[7]
2009, Randomized cross-over design	- dextromethorphan phenotyping, single 50 mg codeine dose; *CYP2D6*3-8, *41*	8 adult PMs from a cohort of 515 Caucasians	- seven out of eight (87.5%) of participants at the lowest 15% quartile of morphine formation were correctly identified equally well with CYP2D6 phenotyping and *CYP2D6* genotyping	[35]

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TABLE A2: Evidence that *CYP2D6* extensive and/or ultrarapid metabolizers are able to produce morphine from codeine and/or are subject to morphine-related central nervous system depression from codeine.

Year, Study Design	Methods to determine CYP2D6 activity	# of extensive and/or ultrarapid metabolizers (EM and/or UM)	Evidence summary	Ref
1996, Randomized, doubled blind	- debrisoquine phenotyping - quinidine (strong CYP2D6 inhibitor) co-administration	- 10 male EMs	- morphine and its metabolites were detectable in EMs; respiratory, psychomotor and papillary effects of codeine were greater in EMs versus PMs ($p<0.01$);diminished production of morphine in EMs was associated with significantly reduced respiratory, psychomotor and papillary effects ($p<0.01$)	[24]
2007, Prospective	- *CYP2D6 *2-6, *9-10, *35, 41* and gene duplication; codeine pharmacokinetics over 24 hours after a single 30mg dose	- 11 male UMs carrying functional gene duplication, 12 male EMs	- median morphine plasma concentrations were 11 mcghr/l in EMs and 16 mcg/hr in UMs; 11/12 UMs felt sedation compared to 6/12 EMs	[12]
1991, Prospective	- debrisoquine phenotyping; codeine pharmacokinetics over 24 hours after a single 50 mg oral codeine dose	8 male EMs	- EM morphine concentrations from codeine were significantly higher in EMs as compared to PMs; relatively high concentration of morphine 6-glucuronide and normorphine detected	[39]
1991, Prospective	- debrisoquine phenotyping; codeine pharmacokinetics over 48 hours after a single 50 mg oral codeine dose	8 male EMs	- comparable formation of morphine from codeine between Chinese and Caucasian extensive *CYP2D6* metabolizers	[45]
1997, Prospective	- debrisoquine phenotyping; codeine pharmacokinetics over 8 hours after a single 25 mg oral codeine dose	14 EMs and 24 UMs as determined by phenotyping	- morphine accounted for 1.7-8.7% of total codeine recovery in EMs versus average of 15.3% in UMs; 45-fold difference in morphine recovery between ultrarapid and poor metabolizers	[38]
1989, Prospective	- debrisoquine phenotyping; codeine pharmacokinetics over 8 hours after a single 25 mg oral codeine dose	- 114 EMs	- > 5% of codeine dose was recovered as morphine in extensive metabolizers, as compared to less than 0.4% in poor metabolizers	[40]
1991, Prospective	- dextromethorphan phenotyping; codeine pharmacokinetics after a	- 7 EMs	- the recovery of total morphine in urine was 7.1 $\pm$ 1.1% of a single codeine dose; this recovery was not significantly	[33]

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	single 30mg dose and after 7 doses (30 mg every 8 hours)		different after chronic administration in healthy adult volunteers	
2010, Prospective	- *CYP2D6*3,4,6;* codeine pharmacokinetics after a 50 mg oral dose over 28 hours	- 9 EMs with end-stage renal disease	- morphine and metabolites remained unchanged or increased in EMs over 24 hours until the start of hemodialysis	[36]
1991, Prospective	- sparteine phenotyping	7 Ems	- EMs had significantly increased subjective and objective pain thresholds; 30 times higher morphine concentrations in EMs versus PMs following codeine administration	[34]
1998, Randomized double-blind	- *CYP2D6 *1, 2, 5, 10;* single 170 mg codeine dose versus 20 mg morphine versus placebo	- 9 EMs	- analgesia as measured by cold pressor test was observed in EMs only; 3.9% of total codeine dose was converted into morphine and its metabolites in EMs; there was a similar incidence in adverse events between PMs and EMs administered codeine	[30]
1997, Case Report	- *CYP2D6*XN (*gene duplication); debrisoquine phenotyping	- 1 female UM	-severe epigastric pain 30 minutes after a therapeutic codeine dose;*CYP2D6* genetic duplication corroborated by a very extensive CYP2D6 metabolic capacity using debrisoquine probe	[11]
2004, Case Report	- *CYP2D6*XN (*gene duplication); dextromethorphan phenotyping	- 1 male UM with reduced renal function receiving CYP3A inhibitor	-life-threatening respiratory depression reversed by administration of the opioid antagonist naloxone; total morphine and metabolites was 75% of the total amount of codeine present in body	[3]
1996, Randomized, double blind	- sparteine phenotyping; single 75mg or 100mg codeine dose versus 20mg or 30 mg morphine dose versus placebo	14 EMs	- morphine detected in 13/14 EMs; morphine 6-glucuronide was detectable in all EM subjects; codeine reduced pain measures significantly in EMs	[31]
2007, Case report	- CYP2D6 genotyping using Amplichip™ P450 Test	1 male toddler EM	- apnea resulting in brain injury following a codeine-acetaminophen dose after an uneventful tonsillectomy	[23]
2011, Retrospective	- *CYP2D6 *2-10, 12, 14, 17, 29, 41* and **XN (*gene duplication)	3 female UMs	- 2 of 3 UMs experienced immediate pain relief but stopped medication due to dizziness & constipation following codeine use	[9]
2009, Case Report	- *CYP2D6*4, 5, 9, 10, 41* and **XN* (gene duplication)	1 male toddler UM	- fatal respiratory depression as a result of repeated dosing of codeine,CYP2D6 UM status, potential for unresolved apnea following tonsillectomy, and bronchopneumonia	[42]
2012,	- *CYP2D6 *2-10, 12, 14, 17, 29,*	1 toddler UM, 1 toddler EM	- fatality following therapeutic doses of codeine	[18]

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Case Series	*41* and **XN (*gene duplication)		administered to a UM toddler; loss of consciousness following therapeutic doses of codeine in an EM toddler (successful resuscitation with mechanical ventilation and naloxone)	
2005, 2007, Case study	- *CYP2D6*2-11, 17, 29, 41, *1XN, *2xN, *4xN*	1 male breastfed neonate EM; 1 female breastfeeding mother UM	- fatal respiratory depression in breastfed infant of codeine prescribed mother who was a CYP2D6 UM - postmortem morphine blood concentration in infant was 70 ng/ml; breast milk morphine concentration was 87 ng/ml	[43,44]
2009, 2012, Retrospective case-control	- *CYP2D6*2-10, 12, 14, 17, 29, 41* and **XN (*gene duplication); mothers using codeine and breastfeeding	5 breastfeeding UM mothers; 94 breastfeeding EM mothers	- mothers of sedated infants were more likely UMs and carriers of *ABCB1 2677 T/T* variant; maternal codeine dose was a significant predictors of neonatal central nervous system depression	[21,22]
2009, Case Series	- genotyping for *CYP2D6 *3-6*	2 toddler male EMs	- inadvertent overdose of codeine-containing cough medication administered by drops to two EM infants resulting in one fatality	[20]
2009, Randomized cross-over design	- dextromethorphan phenotyping, single 50 mg codeine dose; CYP2D6*3-8, *41, gene duplication	8 adult UMs from a cohort of 515 Caucasians	- amongst 8 subjects at the upper 15% of morphine formation, 4/8 were correctly identified by *CYP2D6* gene duplications, 5/8 were correctly identified by phenotyping, and 7/8 were correctly identified by a joint genotyping and phenotyping strategy	[35]

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TABLE A3: Risk factors related to codeine-induced opioid toxicity.

Risk Factor	Case descriptions	Outcome	Ref
CYP2D6 ultrarapid metabolism **(functional *CYP2D6* gene duplications resulting in greater than two *CYP2D6* gene copies)**	11 healthy adult males received a single 30mg codeine dose	10 of 11 UMs were sedated	12
	1 healthy adult female receiving 60 mg of codeine for dental pain	Severe epigastric pain and dizziness	11
	2 breastfeeding mothers receiving codeine in the postpartum period	Dizziness and constipation	9
	1 Caucasian adult male with transient renal function, receiving clarithromycin (CYP3A4 inhibitor) and valproic acid (UGT inhibitor)	Loss of consciousness after 75 mg codeine/d for 3 days; naloxone resulted in dramatic improvement in level of consciousness	3
	1 four year old child who received codeine following tonsillectomy	Death	18
	3 breastfeeding mothers receiving codeine in the postpartum period	Sedation, lethargy, constipation	21,22
	1 two year old child with underlying respiratory disease who received codeine post- tonsillectomy	Death	42
Children Post-tonsillectomy	29 month old child received codeine following adenotonsillectomy	Apnea resulting in brain injury; the child was genotyped as an EM	23
	1 UM toddler and 1 EM toddler who received codeine following adenotonsillectomy	Death (UM), loss of consciousness and reversal with naloxone (EM)	18
	1 two year old child with underlying respiratory disease who received codeine post- tonsillectomy	Death (UM)	42
Breastfed Neonates	13 day old breastfed infant, codeine-prescribed mother was an UM	Lethargy and constipation (CYP2D6 UM mother); Death (breastfed infant)	43,44
	7 day old infant whose codeine-prescribed mother was an UM	Sedation, nausea, dizziness and weakness (CYP2D6 UM mother); lethargy and sedation in baby	21,22
Children (Other)	2 three year old toddlers who received inadvertent overdose of codeine cough drops	Death (1), CYP2D6 EM Loss of consciousness resulting in coma (1); CYP2D6 EM	20

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Relevant Genes/Genetic Variant

Table A4 lists the functional effect of *CYP2D6* allelic variants as it pertains to codeine metabolism and response. It should be noted that not all of these variants have been assessed in patients administered codeine; in some cases the potential contribution of the variant to codeine efficacy or toxicity has been inferred based on the known effect of the polymorphism on CYP2D6 protein activity.

TABLE A4: Description of CYP2D6 allele discrimination and their potential implications for codeine analgesia.[24]

Variant	Mutation	Activity	Potential Implications for Codeine Analgesia
CYP2D6*1xN	Gene duplication	Increased	Life threatening CNS depressive adverse effects
CYP2D6*2xN	Gene duplication (+2850C>T)	Increased	Life threatening CNS depressive adverse effects
CYP2D6*2	2850C>T	Normal	Therapeutically effective
CYP2D6*9	2615-17delAAG	Decreased	Reduced effect
CYP2D6*10	100C>T	Decreased	Reduced effect
CYP2D6*10XN	Gene duplication 100C>T	Normal*	Therapeutically effective*
CYP2D6*11	883G>C	Decreased	Reduced effect
CYP2D6*17	1023C>T	Decreased	Reduced effect
CYP2D6*17XN	Gene duplication 1023C>T	Normal*	Therapeutically effective*
CYP2D6*29	1659G>A	Decreased	Reduced effect
CYP2D6*35XN		Increased	Life threatening CNS depressive adverse effects
CYP2D6*41	2988G>A	Decreased	Reduced effect
CYP2D6*41XN	Gene duplication 2988G>A	Normal*	Therapeutically effective*
CYP2D6*12	124G>A	None	Severely impaired, poor analgesia
CYP2D6*14	1758G>A	None	Severely impaired, poor analgesia
CYP2D6*15	7_138insT	None	Severely impaired, poor analgesia
CYP2D6*19	2539_2542delAACT	None	Severely impaired, poor analgesia
CYP2D6*20	1973_1974insG	None	Severely impaired, poor analgesia
CYP2D6*29		Decreased	Reduced effect
CYP2D6*40	1863_1864ins(TTT CGC CCC)2	None	Severely impaired, poor analgesia
CYP2D6*42	3259_3260insGT	None	Severely impaired, poor analgesia
CYP2D6*44	2950G>C	None	Severely impaired, poor analgesia
CYP2D6*50	1720A>C	Decreased	Reduced effect
CYP2D6*54		Decreased	Reduced effect
CYP2D6*55		Decreased	Reduced effect
CYP2D6*56	3201C>T	None	Severely impaired, poor analgesia
CYP2D6*59	2291G>A	Decreased	Reduced effect
CYP2D6*3	2549delA	None	Severely impaired, poor analgesia
CYP2D6*4	1846G>A	None	Severely impaired, poor analgesia
CYP2D6*5	Gene deletion	None	Severely impaired, poor analgesia
CYP2D6*6	1707delT	None	Severely impaired, poor analgesia
CYP2D6*7	2935A>C	None	Severely impaired, poor analgesia
CYP2D6*8	1758G>T	None	Severely impaired, poor analgesia
CYP2D6*4xN	Gene duplication (+1846G>A)	None	Severely impaired, poor analgesia

*The CYP2D6*10, CYP2D6*17, and CYP2D6*41 variants are all associated with partial (decreased) CYP2D6 activity. Based on theoretical extrapolation, it is expected that multiple copies of such partially functional variants (in the case of gene duplication) will culminate into a phenotype consistent with normal enzyme activity.

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SUPPLEMENTAL TABLES

TABLE A5: A crude average estimate of regional CYP2D6 phenotype distribution predicted from a haplotypic assessment of 12 *CYP2D6* polymorphisms, whole-gene deletion, and gene duplication in 52 widely distributed geographic populations.[4]

Region	Poor Metabolism (%)	Intermediate Metabolism (%)	Extensive Metabolism (%)	Ultrarapid Metabolism (%)
Subsaharan Africa	~3	~16	~77	~6
North Africa	-	~9	~50	~40
Middle East	~2	~10	~76	~15
Europe	~8	~6	~85	~4
Central/South Asia	~2	~7	~90	~3
East Asia	-	~30	~70	~2
Oceania	-	-	~75	~25
The Americas (Aboriginal populations)[1]	-	-	~91	~8

[1]Pima from Mexico (n=25). Maya from Mexico (n=25), Piapoco and Curripaco from Colombia (n=13), Karitiana from Brazil (n=24), Surui from Brazil (n=21)

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TABLE A6: Pure inhibitors of CYP2D6 as well as weak, moderate, and strong CYP2D6 substrates with potential inhibitory effects.[1]

Pure Inhibitor	Strong Substrate	Moderate Substrate	Weak Substrate
Amiodarone	Flecainide	Carvedilol	Amitriptyline
*Bupropion (FDA list)	Fluoxetine	Chlorpromazine	Amphetamine
Chloroquine	Paroxetine	Clemastine	Atomoxetine
Cinacalet	Propafenone	Diphenhydramine	*Celecoxib (FDA list)
Imatinib	Thioridazine	Doxepin	*Cimitedine (FDA list)
Methotrimeprazine		Duloxetine	Citalopram
Orphenadrine		Fluphenazine	Clomipramine
Propoxyphene		Haloperidol	**CODEINE**
Quinidine		Maprotiline	Desipramine
Terbinafine		Metoclopramide	*Desvenlafaxine (FDA list)
		Metoprolol	Dextroamphetamine
		Mexiletine	Dextromethorphan
		Propranolol	*Diltiazem (FDA list)
		Risperidone	Dimenhydrinate
		Tamoxifen	Dolasetron
			Donepezil
			*Echinacea (FDA)
			Escitalopram
			*Febuxostat (FDA)
			Flunarizine
			Galantamine
			*Hydralazine (FDA)
			Hydrocodone
			*Hydroxychloroquine (FDA)
			Idarubicin
			Imipramine
			*Methadone (FDA)
			Mirtazapine
			Nortriptyline
			Ondasteron
			*Oral Contraceptives (FDA)
			Oxycodone
			Procainamide
			*Ranitidine (FDA)
			*Ritonavir (FDA)
			*Sertaline (FDA)
			*Telithromycin (FDA)
			Tetrabenazine
			Timolol
			Tolterodine
			Tramadol
			Trimipramine
			Venlafaxine
			*Verapamil (FDA)
			Zuclopenthixol

*This list is compiled from[1] (accessed November 15, 2012) except for medications indicated by asterisks. These drugs were additionally listed by the FDA as inhibitors of CYP2D6.[55]

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