



CTD MODULE 2

2.5. CLINICAL OVERVIEW

PARACETAMOL/CODEINE 500/15 MG, 1000/30 MG TABLETS

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Document status: final, amended July 2019_v01

Date: 02 March 2015

Number of pages: 66



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ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Drug Reaction
AUC	Area Under the (plasma concentration vs. time) Curve
BCS	Biopharmaceutics Classification System
CI	Confidence Interval
C _{max}	peak plasma Concentration
CNS	Central Nervous System
COX	Cyclooxygenase
CSF	Cerebrospinal Fluid
CV	Coefficient of Variation
CYP	Cytochrome P450
EMA	European Medicines Agency
FDA	Food and Drug Administration
HPLC	High Performance Liquid Chromatography
ITT	Intention-To-Treat
MAO	Monoaminoxidase
NAC	N-acetylcysteine
NAPQI	N-Acetyl-p-aminobenzoquinoneimine
NNT	Number-Needed-to-Treat
NSAID	Nonsteroidal Antiinflammatory Drug
NO	Nitric Oxide
OA	Osteoarthritis
OR	Odds Ratio
OTC	Over-The-Counter
PGE ₂	Prostaglandin E ₂
PP	Per Protocol
RCT	Randomised Controlled Trial
SD	Standard Deviation
SE	Standard Error
t _{max}	time to C _{max}
t _{1/2}	elimination half life
VAS	Visual Analogue Scale
WHO	World Health Organization



2.5.1. Product Development Rationale

Paracetamol (acetaminophen), a nonopiate nonsalicylate analgesic, was first used in medicine by von Mering in 1983. However, it gained popularity only after 1949, after it was recognized as the major active metabolite of both acetanilide and phenacetin.

Codeine is the natural alkaloid and constituent of opium, together with morphine, papaverine and thebaine, all belonging to the class of opiates. Opium occurs in the poppy plant (*Papaver somniferum*). Codeine has been first isolated from opium in 1832, by the French chemist P.-J. Robiquet. It has been used as a narcotic analgesic and a pain reliever, but also as an antitussive and an antidiarrhoeal drug. Moreover, codeine is used in numerous preparations in combination with no narcotic analgesics, antihistamines, and other drugs.

Codeine has been found to add significantly to the analgesic effect of paracetamol. Both paracetamol and codeine have been in therapeutic use for several decades. The first clinical studies on the efficacy of paracetamol-codeine combination were published in the late sixties.

There are several brands of paracetamol/codeine, available as tablets, capsules or other formulations all over the world. They contain usually 500 mg of paracetamol and 8 – 30 mg codeine (most frequently as phosphate hemihydrate), or 1000 mg paracetamol and 30-60 mg codeine. Paracetamol plus codeine containing products in the EU are shown below (not all currently available):

Invented Name	Strength (paracetamol/codeine phosphate hemihydrate) mg	MAH	Member State in EU
Algocod	500/30	Laboratories SMB	Belgium
Dafalgan Codeine	500/30	Bristol-Meyers Squibb	Belgium
Dafalgan Codeine	500/30	Aktuapharma	Belgium
Panadol Codeine	500/30	GSK	Belgium
Paracetamol codeine teva	500/30	Teva	Belgium
Paracodmylan	500/30	Mylan	Belgium
Talvosilen	500/20	Multi-Pharm	Cyprus
Talvosilen Forte	1000/60	Multi-Pharm	Cyprus
Partcoten	500/10	Aegis	Cyprus
Korylan	325/28.73	Zentiva	Czech Republic
Talvosilen Forte	500/30	Bene	Czech Republic
Kodipar	500/30.6	Takeda	Denmark
Algocalm	500/30	Zentiva	Estonia
Paracetamol/Codeine Vitabalans	500/30	Vitabalans	Estonia
Co-codamol	500/8	Actavis	Estonia
Pamol Cod	500/30	Takeda	Finland
Panacod	500/30	Sanofi-Aventis	Finland
Paracetamol/Codein Bene	500/30	Bene	Finland
Paramax-Cod	500/30	Vitabalans	Finland
Paracetamol Codeine EG 500mg/30mg	500/30	EG Labo	France
Sedarene	300/10	Societe Cilfa	France
Codoliprane Adultes	400/20	Sanofi-Aventis	France
Codoliprane Enfants	400/20	Sanofi Aventis	France
Claradol Codeine	500/20	Bayer	France
Codoliprane 500mg/30mg	500/30	Sanofi-Aventis	France
Klupal Codeine 600mg/30mg	600/50	Pierre Fabre	France
Klupal Codeine 300mg/25mg	300/25	Pierre Fabre	France
Paracetamol Codeine Arrow	500/30	Arrow	France
Compralgyl	400/20	Gifrer Barbezat	France
Paracetamol Codeine TEVA	500/30	Teva	France

Paracetamol Codeine Sandoz	500/30	Sandoz	France
Paracetamol Codeine Biogaran	500/30	Biogaran	France
Paracetamol Codeine Mylan	500/30	Mylan	France
Dafalgan Codeine	500/30	Bristol Myers Squibb	France
Copralgir	400/20	Elapharm	France
Gaosedal Codeine	500/20	Merck	France
Algisedal	400/24	Meda	France
Paracetamol AL	500/30	ALIUD Pharma	Germany
Azur compositum SC	500/30	Aristo Pharma	Germany
Paracetamol/Codein 500mg/30mg	500/30	Bene	Germany
Talvosilen	500/20	Bene	Germany
Talvosilen Forte	500/20	Bene	Germany
Titretta	500/30	Berlin Chemie	Germany
Contraneural	500/30	Dr R Pflieger	Germany
Dolviran N	500/30	Meda	Germany
Gelonida	500/30	Pfizer	Germany
Paracetamol comp. STADA	500/30	Stadapharm	Germany
Lonalgal	500/30	Boehringer Ingelheim	Greece
Parcodin	500/30	Vitabalans	Hungary
Talvosilen Forte	500/30	Bene	Hungary
Pinex Comp Forte	500/30	Actavis	Iceland
Solpadol	500/30	Sanofi-Aventis	Ireland
Panadeine	500/8	GlaxoSmithKline	Ireland
Panadeine Extra	500/12.8	GlaxoSmithKline	Ireland
Migraleve Yellow	500/8	McNeill	Ireland
Tylex	500/30	UCB	Ireland
Kapake	500/15	Galen Ltd.	Ireland
Co Efferlgan	500/30	Bristol Myers Squibb	Italy
Codamol	500/30	Ablogon	Italy
Lonarid	400/10	Boehringer Ingelheim	Italy
Tachidol	500/30	Aziende Chimiche	Italy
Paracetamol e codeina Alter	500/30	Alter	Italy
Adorea	500/30	Abiogen Pharma	Italy
Azshara	500/30	Abiogen Pharma	Italy
Ultracod	500/30	Zentiva	Latvia
Co-codamol	500/8	Actavis	Latvia
Ultracod	500/30	Zentiva	Lithuania
Algisedal	400/25	Meda	Luxembourg
Algocod	500/30	SMB	Luxembourg
Dafalgan codéine	500/30	Bristol Myers Squibb	Luxembourg
Panadol codéine	500/30	GlaxoSmithKline	Luxembourg
Paracod Mylan	500/30	Mylan	Luxembourg
Talvosilen forte 500/30	500/30	Bene	Luxembourg
Talvosilen forte 1000/60	1000/60	Bene	Luxembourg
Migraleve Yellow	520/8	McNeill	Malta
Co-Codamol	500/8	M&APharmachem	Malta
Paramax	500/30	Vitabalans	Norway
Codaxol	500/30	Ratioharm	Norway
Pinex Forte	500/30	Actavis	Norway
Efferalgan Codeine	500/30	Bristol Myers Squibb	Poland
Talvosilen Forte	500/30	Bene	Poland
Talvosilen	500/20	Bene	Poland
Dafalgan codeine	500/30	Bristol Myers Squibb	Poland
Ultracod	500/30	Zentiva	Poland
Paramax-Cod	500/30	Vitabalans	Poland
Ultracod 500mg/30mg	500/30	Zentiva	Romania
Korylan	325/21.17	Zentiva	Slovak Republic
Paramax Cod	500/30	Vitabalans	Slovak Republic
Analgiplus	500/30	Faes Farma	Spain
Dolomedil	500/10	Kern Pharma	Spain
Dolocatil Codeina 325mg/15mg	325/15	Ferrer	Spain
Dolocatil Codeina 650mg/30mg	650/30	Ferrer	Spain
Dolocatil Codein 500mg/30mg	500/30	Ferrer	Spain
Cod-Efferalgan	500/30	Bristol Myers Squibb	Spain
Talgo Codeina	300/30	Laboratorios ERN	Spain
Paracetamol Codeina KERN 500mg/30mg	500/30	KERN	Spain

Fludeten	500/30	ALTER	Spain
Citodon minor	350/15	Biophausia	Sweden
Citodon forte	1000/60	Biophausia	Sweden
Citodon	500/30	Biophausia	Sweden
Codalvonil	500/30	Meda	Sweden
Panocod	500/30	Sanofi-Aventis	Sweden
Paracetamol Kodein Evolan	500/30	Evolan	Sweden
Paracetamol/Codeinfosfaat ratiopharm 50/20mg	500/20	Ratiopharm	The Netherlands
Paracetamol/Codeinfosfaat ratiopharm 500/10mg	500/10	Ratiopharm	The Netherlands
Paracetamol/Codeinfosfaat 500/20mg PCH	500/20	Pharmachemie	The Netherlands
Paracetamol/Codeinfosfaat 500/50mg PCH	500/50	Pharmachemie	The Netherlands
Paracetamol/Codeinfosfaat Apotex 500/10mg	500/10	Apotex	The Netherlands
Paracetamol/Codeinfosfaat Apotex 500/20mg	500/20	Apotex	The Netherlands
Paracodol	500/8	Bayer	UK
Bayer co-codamol	500/8	Bayer	UK
Paracetamol and codeine	500/8	Boots	UK
Tylen	500/8	UcB	UK
Medocodene	500/30	UCB	UK
Tylen 30/500	500/30	UCB	UK
Codis 500	500/8	Reckitt Benkiser	UK
Solpadeine max	500/12.8	Omega	UK
Cox codamol	500/8	Actavis	UK
Teva UK Co-codamol	500/8	Teva	UK
Pharmachem Co-codamol	500/8	Pharmachem	UK
M&A Pharmachem Co-codamol 30/500	500/30	Pharmachem	UK
M&A Pharmachem Co-codamol 60500	500/60	Pharmachem	UK
Sandoz Co-codamol	500/30	Sandoz	UK
Solpadol	500/30	Aventis	UK
Co-codamol 15mg/500mg	500/15	Galen	UK
Co-Codamol 15/500mg	500/15	Zentiva	UK
Co-codamol 15/500mg	500/15	Accord UK Ltd.	UK

Products containing other active constituents, e.g. caffeine, or containing only codeine are not included.

In many countries, codeine is regulated under various narcotic control laws. In some countries, however, it is available without a medical prescription in combination preparations from licensed pharmacists in doses up to 15 mg.

Paracetamol Codeine combination is indicated for the relief of severe pain. Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

This non-clinical overview is based on published scientific literature. Searches were carried out in bibliographic (EMBASE, MEDLINE), and factual (CCRIS) databases. Specific search criteria were used (e.g. for efficacy: *acetaminophen/paracetamol, codeine, combination, acute pain, chronic pain, clinical trial, meta-analysis*, etc; for safety: *safety, adverse, toxicity*, etc.), adjusted to the specific database terminology, scope and structure, covering all aspects required for this overview. Primarily English language literature was selected initially on the basis of search results including abstracts, and subsequently on the basis of original publications acquired. Where necessary, reference lists of original publications were searched manually for complementary publications. Websites of EMA and FDA were also searched for relevant data.



The proposed contraindications, precautions and warnings applied to this formulation of paracetamol and codeine are the same as those applied to all other preparations used in this indication on the market and are supported by the findings in the published literature.

This overview has been prepared as part of a marketing authorisation application to market a formulation of Paracetamol Codeine 500/15 mg and 1000/30 mg tablets.

2.5.2. Overview of Biopharmaceutics

Paracetamol Codeine 500/15 mg and 1000/30 mg tablet is an immediate-release tablet formulation containing paracetamol (acetaminophen) and codeine, both of well established use.

Literature data were reviewed on the properties of acetaminophen (paracetamol) related to the biopharmaceutics classification system (BCS) [REDACTED]. According to the current BCS criteria, acetaminophen is BCS Class III compound. Differences in composition seldom, if ever, have an effect on the extent of absorption. However, some studies show differences in rate of absorption between brands and formulations. In particular, sodium bicarbonate, present in some drug products, was reported to give an increase in the rate of absorption, probably caused by an effect on gastric emptying. In view of Marketing Authorizations (MAs) given in a number of countries to acetaminophen drug products with rapid onset of action, it is concluded that differences in rate of absorption were considered therapeutically not relevant by the Health Authorities. Moreover, in view of its therapeutic use, its wide therapeutic index and its uncomplicated pharmacokinetic properties, *in vitro* dissolution data collected according to the relevant Guidances can be safely used for declaring bioequivalence of two acetaminophen formulations. Therefore, accepting a biowaiver for immediate release (IR) acetaminophen solid oral drug products is considered scientifically justified, if the test product contains only those excipients reported in this paper in their usual amounts and the test product is rapidly dissolving, as well as the test product fulfils the criterion of similarity of dissolution profiles to the reference product.

A monograph reviewed the data relevant to applying the biowaiver procedure for the approval of immediate-release multisource solid dosage forms containing codeine phosphate [REDACTED]. Both biopharmaceutical and clinical data of codeine were assessed. Solubility studies revealed that codeine meets the "highly soluble" criteria according to World Health Organization (WHO), the European Medicines Agency (EMA), and the United States Food and Drug Administration (FDA). Codeine's fraction of dose absorbed in humans was reported to be high (>90%) based on cumulative urinary excretion of drug and drug-related material following oral administration. The permeability of codeine was also assessed to be high in both Caco-2 monolayers and rat intestinal perfusion studies. The main risks associated with codeine, that is, toxicity (attributed to CYP2D6 polymorphism) and its abuse potential, are present irrespective of the dosage form, and do not need to be taken into account for bioequivalence considerations. Taken together, codeine is a class I drug with manageable risk and is a good candidate for waiver of *in vivo* bioequivalence studies.

According to the "Guideline On The Investigation Of Bioequivalence" "where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation".

Dissolution tests have been performed for Paracetamol/Codeine 500 mg/15 mg tablets [REDACTED] and Paracetamol/Codeine 1000 mg/30 mg tablets [REDACTED]. In all tested buffers (0.1M HCl, pH 4.5, pH 6.8), more than 85% of paracetamol and codeine were released from the tablets within 15 min.



Based on the dissolution test results, both strengths of the product can be classified as “rapid dissolving tablets”. The drug substances are completely and fast dissolved independently of the applied medium. Thus, the use of these paracetamol/codeine products as painkiller can be considered as not compromising the safety, efficacy and tolerability of paracetamol/codeine treatment regimens.

2.5.3. Overview of Clinical Pharmacology

2.5.3.1. Pharmacokinetics

a) Paracetamol

Absorption

Paracetamol is well absorbed from the gastrointestinal tract in humans, and oral bioavailability has been estimated at 63-89% compared with the intravenous form. Speed of absorption appears independent of dose, and a plasma half-life of 2.7 minutes (SE 1.2 mins) and lag time of 4.2 minutes (SE 0.4 mins) has been reported in children. The formulation of the dose (i.e. soluble or plain) has little effect on speed of absorption, suggesting that paracetamol is absorbed beyond the stomach, and that gastric emptying occurs before significant absorption takes place. The ingestion of food along with paracetamol does not seem to affect its absorption. Paracetamol is not subject to a large degree of first-pass metabolism in the liver, and the hepatic extraction ratio is 0.11-0.37 in adults.

Distribution

Paracetamol is rapidly and relatively uniformly distributed in the tissues. The ratio of concentrations in red blood cells and plasma is about 1.2: 1 and binding to plasma proteins is insignificant. The apparent volume of distribution of paracetamol in man is about 0.9 L/kg. Protein binding is approximately 20%.

Metabolism

Paracetamol has a plasma half-life of around two hours. Metabolism of the drug is primarily in the liver, via conjugation with glucuronic (60%) and sulphuric (35%) acids, or cysteine (3%). A small amount of drug undergoes cytochrome P-450 mediated N-hydroxylation to form N-acetyl-p-aminobenzoquinoneimine (NAPQI). The most important isoform of cytochrome P-450 responsible for this oxidative pathway is CYP2E1, but forms CYP3A4 and CYP1A2 are also involved. Under normal circumstances, the NAPQI combines with sulphhydryl groups in hepatic glutathione, and is neutralised. Following the ingestion of large amounts of paracetamol, hepatic glutathione is depleted, and the NAPQI reacts instead with sulphhydryl groups on hepatic proteins. This can lead to subacute hepatic necrosis, and in severe cases to hepatic failure.

Elimination

Paracetamol has a plasma half-life of around two hours. After 24 hours, 90-100% of the drug is recoverable in the urine as conjugates. Paracetamol is dialyzable.

b) Codeine

Absorption

Four healthy male subjects received single oral doses of 15, 30 and 60 mg of codeine. Blood was sampled for 12 h after codeine administration. Plasma concentrations of free (unconjugated) and total (unconjugated plus conjugated) codeine and morphine were determined by radioimmunoassay and selected pharmacokinetic parameters were derived from these data. Pharmacokinetics of codeine were independent of dose. Codeine was absorbed rapidly, mean t_{max} was 0.6 – 1.1 hours (depending on dose). The pharmacokinetic parameters of codeine and morphine are shown in Table 1 and Table 2, respectively. Codeine kinetics were adequately described by a one-compartment open model with first-order absorption.

Table 1. Model-independent pharmacokinetic parameters for codeine after 60 mg oral codeine

Subject	Free			Total		
	C_{max} (ng ml ⁻¹)	t_{max} (h)	AUC* (ng ml ⁻¹ h)	C_{max} (ng ml ⁻¹)	t_{max} (h)	AUC* (ng ml ⁻¹ h)
1	135	1.5	793	908	1.3	6082
2	227	0.5	945	1034	1.0	5288
3	167	2.0	820	1198	2.0	6257
4	167	1.0	631	1742	1.5	5850
5	253	0.8	1017	1300	1.0	6500
6	238	0.5	1014	2116	0.8	6937
Mean	198	1.1	870	1383	1.3	6152
s.d.	48	0.6	151	459	0.5	564

*AUC 0–24 h

Table 2. Model-independent pharmacokinetic parameters for morphine after 60 mg oral codeine

Subject	Free			Total		
	C_{max} (ng ml ⁻¹)	t_{max} (h)	AUC* (ng ml ⁻¹ h)	C_{max} (ng ml ⁻¹)	t_{max} (h)	AUC* (ng ml ⁻¹ h)
1	2.0	1.0	14.5	40.5	1.5	356
2	6.0	0.5	26.1	95.7	2.0	564
3	6.5	1.5	43.5	96.4	2.0	648
4	0.0	0.0	0.0	4.6	1.5	24
5	6.4	0.25	24.9	74.4	1.25	426
6	0.5	0.5	1.7	5.4	1.25	32

*AUC 0–12 h

The pharmacokinetics of codeine, codeine glucuronide, morphine, and morphine glucuronide were assessed after single- (60 mg) and multiple-dose (60 mg every six hours for nine doses) oral administration of codeine sulphate to six normal volunteers. No significant alterations in codeine pharmacokinetics were noted after multiple-dose oral administration. However,

accumulation of morphine during multiple dosing was significant ($AUC_{24} = 102 \pm 33$ ng/mL/hr after single dose versus 212 ± 118 ng/mL/hr after the last multiple dose). Peak concentration and AUC_{24} data for morphine glucuronide indicated that significant accumulation of this compound occurs upon multiple-dose administration. These data indicate that morphine and morphine glucuronide serum concentrations are significantly increased during chronic oral codeine therapy and suggest that morphine, and perhaps morphine glucuronide, contribute significantly to the analgesic activity of chronic oral codeine therapy.

Distribution

The volume of distribution is approximately 3.6 l/kg. The total body clearance of codeine is approximately 0.85 l/min. Codeine enters the tissues rapidly and is concentrated in the kidney, lung, liver and spleen. The bulk of the total drug is in the skeletal muscle. The brain does not accumulate high levels of the opiate. Within the brain, 80% or more is associated with opiate receptors, which are especially concentrated in the caudate nucleus, amygdala, and periaqueductal grey matter of the hypothalamus, midbrain and medial thalamus. Codeine crosses the placenta and is present in the milk of lactating mothers.

Metabolism

Plasma concentrations of conjugated codeine were much greater than those of the unconjugated alkaloid. Biotransformation of codeine to morphine was evident in all subjects, although the extent of this metabolic conversion varied considerably between subjects [REDACTED]

Codeine is metabolized in the liver by O-demethylation to form morphine (codeine is in fact a pro-drug to morphine), N-demethylation to form *nor*codeine, and conjugation to form glucuronides and sulphates of both codeine and its metabolites. Of the excreted material in urine, 40-70% is free or conjugated codeine, 5-15% is free or conjugated morphine, 10-20% is free or conjugated *nor*codeine, and very small amounts may be free or conjugated *norm*morphine together with other trace metabolites. The analgesic effect of codeine is the result of its conversion to morphine by the genetically polymorphic CYP2D6 which is absent in 7-10% of the white population and present in the remainder. Poor metabolisers of debrisoquine may show absence of analgesia following codeine administration. To address this issue, the kinetics of codeine and seven of its metabolites codeine-6-glucuronide (C6G), *nor*codeine (NC), NC-glucuronide (NCG), morphine (M), M-3 glucuronides (M3G) and 6-glucuronides (M6G), and *norm*morphine (NM) were investigated after a single oral dose of 50 mg codeine phosphate in 14 healthy Caucasian subjects including eight extensive (EM) and six poor (PM) hydroxylators of debrisoquine. The plasma and urine concentrations of codeine and the metabolites were measured by HPLC. The mean area under the curve (AUC), half-life and total plasma clearance of codeine were 1020 ± 340 nmol/l h, 2.58 ± 0.57 h and 2.02 ± 0.73 L/h/kg, respectively. There were no significant differences between EM and PM in these aspects. PM had significantly lower AUC of M3G, the active metabolites M6G, NM and M ($P < 0.0001$), and lower partial metabolic clearance by O-demethylation ($P < 0.0001$). In contrast, the PM had higher AUC of NC ($P < 0.05$) than the EM. There was no difference between PM and EM in the AUC of C6G and NCG, nor in the partial clearances by N-demethylation and glucuronidation. Among EM, the AUC of C6G was 15 times higher than that of codeine, which in turn was 50 times higher than that of

M. The AUCs of M6G and NM were about 6 and 10 times higher than that of M, respectively. The partial clearance by glucuronidation was about 8 and 12 times higher than those by N- and O-demethylations, respectively. The clinically important findings were the negligible plasma concentration of the O-demethylated active metabolites M6G, NM and M in PM, and the relatively high concentrations of M6G and NM in EM. Considering the low plasma concentration of M as well as the potent analgesic effects of M6G and NM, the latter compounds might play an important role in the analgesic effect of codeine [REDACTED]

Codeine is acting on μ -opiate receptors predominantly via its metabolite morphine, which is formed almost exclusively by the genetically polymorphic enzyme CYP2D6. It is known that individuals lacking CYP2D6 activity (poor metabolizers, PM) suffer from poor analgesia from codeine, ultra-fast metabolizers (UM) due to the CYP2D6 gene duplication may experience exaggerated and even potentially dangerous opioidergic effects.

A single dose of 30 mg codeine was administered to 12 UM of CYP2D6 substrates carrying a CYP2D6 gene duplication, 11 extensive metabolizers (EM) and three PM [REDACTED]. Genotyping was performed using polymerase chain reaction-restriction fragment length polymorphism methods and a single-base primer extension method for characterization of the gene-duplication alleles. Pharmacokinetics was measured over 24 h after drug intake and codeine and its metabolites in plasma and urine were analyzed by liquid chromatography with tandem mass spectrometry. Significant differences between the EM and UM groups were detected in areas under the plasma concentration versus time curves (AUCs) of morphine with a median (range) AUC of 11 (5-17) $\mu\text{g h/L}$ in EMs and 16 (10-24) $\mu\text{g h/L}$ in UM ($P = 0.02$). In urine collected over 12 h, the metabolic ratios of the codeine+codeine-6-glucuronide divided by the sum of morphine + its glucuronides metabolites were 11 (6-17) in EMs and 9 (6-16) in UM ($P = 0.05$). Ten of the 11 CYP2D6 UMs felt sedation (91%) compared to six (50%) of the 12 EMs ($P = 0.03$). CYP2D6 genotypes predicting ultrarapid metabolism resulted in about 50% higher plasma concentrations of morphine and its glucuronides compared with the EM. No severe adverse effects were seen in the UMs in this study. Therefore, codeine is contraindicated in patients if it is known they are CYP2D6 ultra-rapid metabolizers.

Elimination

Codeine was eliminated relatively rapidly [elimination $t_{1/2} = 2.3 \pm 0.4$ h (mean $\pm$ SD) [REDACTED]]. After an oral dose, about 86% is excreted in the urine in 24 h as free drug and metabolites, mostly in the form of metabolites. Some of a dose of codeine is excreted in the bile and trace amounts are found in the faeces. Unchanged drug accounts for 6-8% of the dose in urine in 24 h, which may be increased to about 10% when the urinary pH is decreased.

Of the excreted material in urine, 40-70% is free or conjugated codeine, 5-15% is free or conjugated morphine, 10-20% is free or conjugated *nor*codeine, and very small amounts may be free or conjugated *norm*morphine together with other trace metabolites [REDACTED]

The renal clearance of codeine was 183 ± 59 ml/min in healthy volunteers after the oral administration of 30 mg codeine and was inversely correlated with urine pH ($r = 0.81$). These data suggest that codeine undergoes filtration at the

glomerulus, tubular secretion and passive reabsorption. The renal clearance of codeine-6-glucuronide (one of its major metabolites; see below) was 55 ± 21 ml/min, and was not correlated with urine pH. Its binding to human plasma was less than 10%. These data suggest that codeine-6-glucuronide undergoes filtration at the glomerulus and tubular reabsorption. This latter process is unlikely to be passive

c) Combination of Paracetamol and Codeine

This section presents pharmacokinetic data regarding combination therapy: in particular, how the pharmacokinetic properties of each agent are affected by co administration of the other.

In nine healthy volunteers, the clearance and metabolism of acetaminophen 1000 mg i.v. was evaluated with and without two concomitant oral doses of codeine in order to investigate a possible interaction. Plasma acetaminophen was followed for 720 min and urine was collected for 24 h after each dose for determination of metabolites. When codeine was coadministered, the average total clearance of acetaminophen and its clearance by glucuronidation, sulphation and mercapturate formation were 0.58 to 1.12-times the control values. It is concluded that therapeutic doses of codeine do not influence the clearance or metabolism of acetaminophen

Plasma and urine concentrations of codeine and its measurable metabolites were determined by HPLC in six healthy subjects after a single 30 mg oral dose of codeine either alone or after 7 doses of 1 g paracetamol 8 hourly. After codeine alone, the $t_{1/2}$ (h), AUC ($\mu\text{M}\cdot\text{L/h}$) and clearance (ml/min) for codeine were 2.2, 0.81, and 252 respectively. These were not significantly altered by paracetamol: 2.2, 0.84, and 291 respectively. For codeine-6-glucuronide the values were 2.4, 22.0, and 29.7 respectively. These were not significantly different from those after codeine plus paracetamol: 2.4, 21.9, and 39.6. There were no significant differences between the two treatments in the apparent partial clearances (ml/min) of codeine to morphine (88 codeine alone, 70 codeine plus paracetamol), to norcodeine (71 codeine alone, 88 codeine plus paracetamol), and to codeine-6-glucuronide (820 codeine alone, 1022 codeine plus paracetamol). The urinary excretion of codeine-6-glucuronide, morphine, norcodeine, and codeine were not significantly different between the two treatments.

2.5.3.1.1 Special Populations

Renal: The renal clearance of unchanged (but not conjugated) paracetamol was related to the urine flow rate. However, forced diuresis is of no practical value and is contraindicated on clinical grounds. There was no correlation between urine pH and clearance of unchanged or conjugated drug

The pharmacokinetics and pharmacodynamics of codeine and its metabolites codeine glucuronide, morphine, and morphine glucuronide were assessed after the administration of a single 60 mg oral dose of codeine sulfate and a single 60 mg intravenous dose of codeine phosphate in six healthy volunteers and six patients on chronic haemodialysis. Codeine elimination half-life and mean residence time were increased significantly in the haemodialysis group (18.69 ± 9.03 hours and 12.77 ± 7.09 hours, mean $\pm$ SD, respectively) compared with the

healthy volunteer group (4.04 ± 0.60 hours and 3.90 ± 0.52 hours, respectively). The total body clearance and volume of distribution of codeine were not significantly different between groups. Peak concentrations, times to peak concentrations, and AUCs for the three metabolites were also not significantly different between the groups, in part as a result of significant interpatient variability in the haemodialysis group. Examination of pupillometry and vital sign data did not reveal clinically significant differences in pharmacodynamics between the groups. Adjustment of dosage regimen may be required in some patients with uraemia receiving multiple-dose codeine therapy [REDACTED].

Hepatic: Paracetamol metabolism was impaired in the patients with liver damage. The plasma half-life of the unchanged drug was significantly prolonged, and the ratio of the plasma concentrations of unchanged to conjugated paracetamol was significantly higher than in the patients without liver damage [REDACTED].

Since the oxidative enzyme capacity of the liver has been shown to be impaired in patients with hepatic cirrhosis, it can be assumed that patients with cirrhosis will experience little or no analgesia from codeine. Even worse, the use of codeine in these patients might expose them to the adverse effects caused by codeine itself. Therefore, the use of codeine in severe liver disease should be avoided [REDACTED].

Children: Paracetamol absorption may occur at a somewhat greater rate in children if the syrup form is utilized. The overall plasma elimination of paracetamol is somewhat slow in the neonate, but is comparable to that of adults in both children and adolescents, as judged by half-life determinations. This would suggest that the frequency of paracetamol administration in children should be similar to the schedule recommended for adults and that a dosing interval of four hours should not result in drug accumulation. The question of a toxic quantity of paracetamol for young children must remain open until adequate metabolic or retrospective toxicologic data become known. Since the volumes of distribution (V_d) appear to be the same in both adults and children, the same dose should apply in both groups; currently, 10 mg/kg is considered to be both safe and effective for antipyresis [REDACTED].

The vast majority of pharmacokinetic data for codeine has been obtained from investigations in adults. Very little information is available from studies in children [REDACTED]. Codeine metabolism depends on genetic polymorphism of CYP2D6. CYP2D6 maturation is slow, and by the age of 5 years, levels may still be less than a quarter of equivalent adult values. Therefore, young children tend to be slower metabolisers but unpredictability remains. Following deaths in its use after adenotonsillectomy in patients with known sleep apnoea, the regulations for codeine use have been revised. Codeine should now not be used for children under the age of 12 years and only used in those above this age for acute mild-moderate pain if it cannot be relieved by other analgesics such as paracetamol or ibuprofen. It is now completely contraindicated in known ultra-rapid metabolisers [REDACTED].

Despite codeine being an 'old' drug, there are few clinical studies in children which relate blood levels of codeine or morphine to pain score. When pharmacokinetic studies are done, they rarely involve all paediatric groups. We

often depend on data from older patients to guide us in our dosing strategies

Dosing is based on experience. Usual dosage: 0.5 mg/kg of codeine phosphate orally 3 to 4 times a day; individually titrate to a dose that provides adequate analgesia while minimizing adverse reactions. Maximum dosage: 4000 mg of acetaminophen and 360 mg of codeine daily

Elderly: Thirty-two healthy men and women, 23 to 78 yr old, received single 650-mg intravenous doses of paracetamol and the drug's kinetics were determined from multiple plasma samples drawn over the next 8 to 12 hr. Paracetamol elimination half-life averaged 2.7 hr (range, 1.9 to 4.3 hr) and was not related to age or sex. Volume of distribution (V_d , corrected for weight) was larger in men than in women (0.99 and 0.86 l/kg) and declined with age in both sexes. This probably reflects increased fat per kilogram body weight in women and in the elderly, together with incomplete distribution of this nonlipophilic drug into body fat. Paracetamol clearance tended to decline with age in both sexes, but differences were of borderline significance. On the basis of kinetics data alone, adjustment of paracetamol dosage for the elderly is generally not necessary.

There are no data on codeine pharmacokinetics in the elderly. In general, pharmacokinetic changes include a reduction in renal and hepatic clearance and an increase in volume of distribution of lipid soluble drugs (hence prolongation of elimination half-life) whereas pharmacodynamic changes involve altered (usually increased) sensitivity to several classes of drugs. Therefore, elderly patients (aged 65 years or older) may have increased sensitivity to paracetamol/codeine. Caution should be exercised when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Pharmacokinetic Interactions

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paracetamol), to norcodeine (71 codeine alone, 88 codeine plus paracetamol), and to codeine-6-glucuronide (820 codeine alone, 1022 codeine plus paracetamol). The urinary excretion of codeine-6-glucuronide, morphine, norcodeine, and codeine were not significantly different between the two treatments.

Concomitant use of codeine with CYP3A4 substrates, e.g. ritonavir, etc., and inhibitors, e.g. erythromycin, has resulted in increased codeine and morphine concentrations. Concomitant use of codeine with CYP2D6 inhibitors, e.g. clobazam, may reduce plasma concentration of morphine [REDACTED]

Known inhibitors of UGT2B7 activity, e.g. ketoconazole, fluconazole, increase codeine plasma concentrations [REDACTED]

Pharmacokinetic drug-drug interactions with codeine are likely common. However, the ability to predict these interactions is difficult [REDACTED]. Inhibition, induction, or altered enzyme genotypes of CYP2D6 and UGT2B7 could alter codeine's effectiveness. More definitive studies are needed for codeine to sort these issues in order to make more definitive predictions about its potential as a prodrug and for drug-drug interactions.

Opioids reduce plasma concentration of ciprofloxacin.

Codeine may cause delayed absorption of mexiletine.

Cimetidine inhibits the metabolism of opioid analgesics causing increased plasma concentration of codeine.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs such as rifampin or isoniazid or drugs that induce liver microsomal enzymes. Isoniazid inhibits the metabolism of paracetamol [REDACTED]. The pharmacokinetic interaction of rifampicin with codeine is complex, but the coadministration of rifampicin with codeine leads to markedly decreased concentrations of both codeine and morphine and markedly decreased pharmacodynamic effects of codeine [REDACTED]. Alcohol may potentiate the hepatotoxicity of paracetamol [REDACTED]

Pretreatment with probenecid can decrease paracetamol clearance and increase its plasma half-life. Although urinary excretion of the sulphate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged [REDACTED]

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect [REDACTED]

The speed of absorption of paracetamol may be increased by drugs stimulating gastric emptying [REDACTED] such as metoclopramide or domperidone.

Cholestyramine and activated charcoal reduce the absorption of paracetamol [REDACTED]

Antiepileptics, such as carbamazepine, phenobarbital, phenytoin and primidone can reduce the effects of paracetamol and increase the risk of hepatotoxicity. However, these data are either old, or contradictory [REDACTED] [REDACTED]. A recent critical review of the literature has established that therapeutic doses of paracetamol either alone or in the presence of enzyme inducers do not produce hepatotoxicity [REDACTED].

Paracetamol may increase the elimination half-life of chloramphenicol [REDACTED]. However, [REDACTED] found no interaction between paracetamol and chloramphenicol.

Oral contraceptives induce glucuronidation and oxidative metabolism of paracetamol [REDACTED] [REDACTED].

CYP2D6 inhibitors (amiodarone, cimetidine, diphenhydramine, fluoxetine, paroxetine, quinidine, ritonavir) may increase plasma levels of codeine and reduce plasma concentrations of the active metabolite [REDACTED] [REDACTED]. In case of quinidine, codeine-O-demethylation was significantly reduced when codeine was coadministered with quinidine. The inhibition of codeine-O-demethylation was ethnically dependent [REDACTED] [REDACTED].

No study has been designed to evaluate the effects of opioid analgesics on the pharmacokinetics of mexiletine. However, it was reported that the mean concentrations measured 3 hours following the first mexiletine dose were significantly lower in patients taking morphine and diamorphine [REDACTED].

2.5.3.2. Pharmacodynamics

a) Paracetamol

Paracetamol is thought to have a central mode of action for both antipyresis and analgesia. Studies measuring plasma and cerebrospinal fluid (CSF) paracetamol concentrations have shown that maximal analgesic and antipyretic activity occur 1-2 hours after peak plasma levels. Initially, CSF levels of paracetamol lag behind those seen in plasma, with an equilibration half-time of 0.72 hours (CV 117%). In the later stages of the study, CSF paracetamol levels rose higher than those found in plasma. The CSF to plasma partition coefficient has been estimated at 1.18 (CV 8%), a figure in keeping with a drug known to be distributed in plasma water without binding to plasma proteins. Calculations based upon pharmacodynamic models of the plasma-CSF-effector site system suggest that concentrations found in the CSF do not directly reflect those found at the effector site, i.e. further period of time is required to allow the drug to reach its receptors. The antipyretic effects of paracetamol have been related to drug concentration using a sigmoidal E_{max} model with a low Hill coefficient. This model fits the observed pharmacodynamic data, and also predicts a maximum effect (E_{max}) which cannot be exceeded despite further increases in drug concentration. For antipyresis a paracetamol concentration of 10-20 µg/ml has been shown to be effective, and E_{max} is estimated as 3°C. The situation is more complex for analgesia, as pain is more difficult to quantify than temperature. A similar sigmoidal E_{max} model has been proposed, and a plasma paracetamol concentration of 10 µg/ml has been estimated to provide satisfactory analgesia for 50% of children undergoing tonsillectomy [REDACTED].

Despite the similarities to NSAIDs, the mode of action of paracetamol has been uncertain, but it is now generally accepted that it inhibits COX-1 and COX-2 through metabolism by the peroxidase function of these isoenzymes. This results in inhibition of phenoxyl radical formation from a critical tyrosine residue essential for the cyclooxygenase activity of COX-1 and COX-2 and prostaglandin (PG) synthesis. Paracetamol shows selectivity for inhibition of the synthesis of PGs and related factors when low levels of arachidonic acid and peroxides are available but conversely, it has little activity at substantial levels of arachidonic acid and peroxides. The result is that paracetamol does not suppress the severe inflammation of rheumatoid arthritis and acute gout but does inhibit the lesser inflammation resulting from extraction of teeth and is also active in a variety of inflammatory tests in experimental animals. Paracetamol often appears to have COX-2 selectivity

When concentrations of arachidonic acid are low, the COX-2 pathway is activated in preference to the COX-1 pathway and, therefore, paracetamol generally appears to be a selective COX-2 inhibitor *in vitro* with IC₅₀ values often below 10 µM, well within the therapeutic plasma concentration range [redacted]. This explains why paracetamol has anti-nociceptive or antipyretic actions involving COX-2 [redacted].

[redacted] investigated the effect of paracetamol and the analgesic adjuvant caffeine on the activity of NO synthase in mouse spinal cord and cerebellar slices *in vitro*, by measuring the conversion of [3H]arginine to [3H]citrulline. Paracetamol (100 µM) had no effect on NO synthase activity in cerebellum, but in the spinal cord both paracetamol (100 µM) and caffeine (30 µM) attenuated glutamate (5 mM)-induced [3H]citrulline production and in combination they abolished it. In conclusion paracetamol inhibits spinal cord NO synthesis and this may be related to its analgesic effects.

Experimental evidence suggests that inhibition of prostaglandin biosynthesis contributes to the pharmacological actions of paracetamol. Three cyclooxygenase (COX) isoenzymes are involved in prostaglandin biosynthesis, COX-1, COX-2 and a recently discovered splice-variant of COX-1, COX-3. [redacted] compared the antinociceptive action of paracetamol with the non-selective non-steroid anti-inflammatory drug, diclofenac and studied paracetamol antinociception in COX-1 and COX-2 knockout mice. Paracetamol (100–400 mg/kg) inhibited both acetic acid- and iloprost-induced writhing responses. In contrast, diclofenac (10–100 mg/kg) inhibited only acetic acid-induced writhing. Only diclofenac reduced peripheral prostaglandin biosynthesis whereas both drugs reduced central prostaglandin production. PGE₂ concentrations were reduced in different brain regions by administration of paracetamol. COX-1, COX-2 and COX-3 enzyme proteins were expressed in the same brain regions. The effects of paracetamol on writhing responses and on brain PGE₂ levels were reduced in COX-1, but not COX-2, knockout mice. The selective COX-3 inhibitors, aminopyrine and antipyrine also reduced writhing responses and brain PGE₂ biosynthesis. These results suggest that the antinociceptive action of paracetamol may be mediated by inhibition of COX-3.

b) Codeine

Codeine is an opiate agonist. It can, in similarity with morphine and some other opiates, activate opiate receptors in human brain, e.g. mu (µ) and delta (δ)

receptors. Mu receptors are most highly concentrated in areas of the brain involved in pain sensation. These receptors have a high affinity for the morphine-like agonist drugs and produce analgesia, respiratory depression, miosis and euphoria when stimulated with these drugs. The role of the delta receptor has not been fully understood. The stimulatory effects of opioids are the result of "disinhibition" as the release of inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA) and acetylcholine is blocked. The exact mechanism how opioid agonists can cause stimulatory effects is not well understood.

Effects on CNS: Similar to other opioids, codeine produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO₂ tension and to electrical stimulation. Codeine depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Codeine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of haemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of codeine overdose

Gastrointestinal Tract and Other Smooth Muscle: Codeine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase

Cardiovascular System: Codeine may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension

Endocrine System: Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes

Immune System: *In vitro* and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Single oral codeine doses (60 and 120 mg/70 kg) were administered to 19 volunteers. Plasma was analyzed for free codeine, norcodeine, morphine, and normorphine by solid-phase extraction combined with gas chromatography-mass spectrometry (SPE/GC-MS). Physiologic and subjective effects were examined. Mean (SE) peak codeine concentrations were 214.2 ± 27.6 and 474.3 ± 77.0 µg/L in plasma. The mean half-life (t_{1/2}) of codeine was 2.2 ± 0.10 h

in plasma. The effects of 60 and 120 mg/70 kg doses of oral codeine on physiologic measures are illustrated in Figure 1. Statistically significant dose-related miosis was observed at 4 h after 60 mg/70 kg and from 1 to 4 h after 120 mg/70 kg oral codeine ($P < 0.05$). Pulse, respiration, diastolic and systolic blood pressures, skin and core temperatures, and blood oxygenation were not significantly affected by single 60- or 120-mg doses of oral codeine. Mean responses on the PCAG (sedation) and LSD (psychotomimetic effect) scales of the ARCI were significantly increased compared with placebo ($P < 0.05$) after 120 mg of codeine for 1–2 h and 1–4 h, respectively. In addition, “feel drug”, “relaxed”, and “high” self-rating scales of the SDQ were significantly increased from placebo ($P \leq 0.05$) from 0.5 to 2 h after the high dose. No significant differences were found for the other ARCI, SDQ, or VAS measures at any time after single 60 or 120 mg/70 kg oral codeine doses.

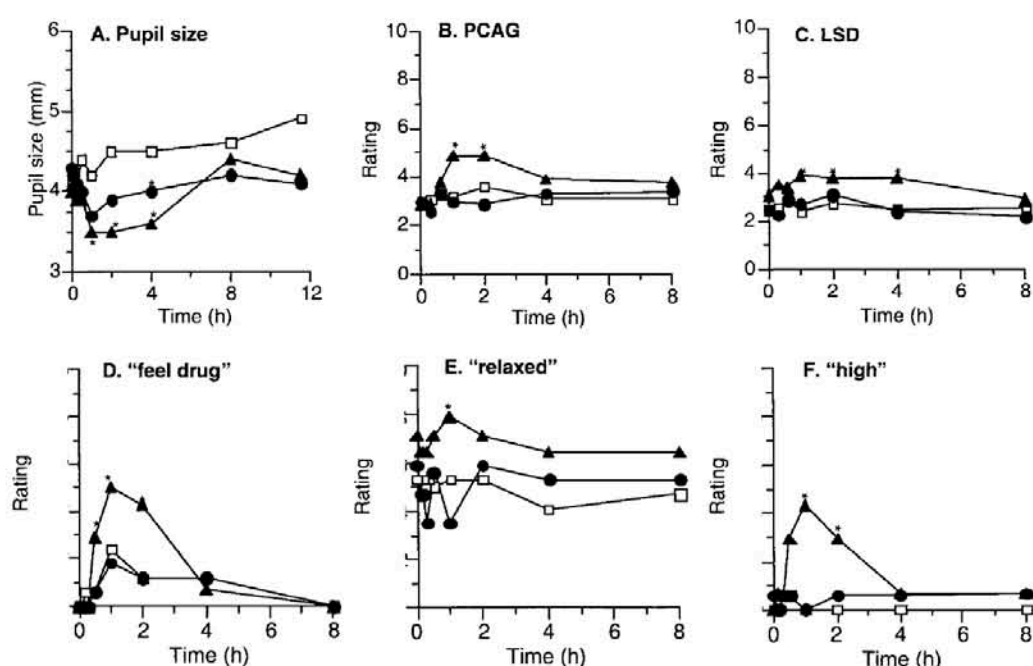


Fig. 1. Mean time course ($n = 19$) of effects after 60 mg/70 kg codeine (●), 120 mg/70 kg codeine (▲), and placebo (□). Effects: (A), pupil size; (B), PCAG group (ARCI), a measure of sedation; (C), LSD (ARCI), a measure of psychotomimetic effect; (D), “feel drug”; (E), “relaxed”; (F), “high”. D–F are included in the SDQ. Each point represents the mean rating across all participants

A study compared symptom relief obtained with buprenorphine patches plus oral paracetamol with that obtained with an oral codeine-paracetamol combination tablet (Co-codamol) in older adults with OA. Two hundred and twenty people (aged ≥ 60 years) with OA hip and/or knee pain were randomised to treatment with 7-day buprenorphine patches plus oral paracetamol (5–25 $\mu\text{g/h}$ buprenorphine patches plus 1000 mg oral paracetamol q.i.d. (4 times daily); $n = 110$) or Co-codamol tablets (two 8/500–two 30/500 mg tablets q.i.d.; $n = 110$). They entered a titration period of up to 10 weeks, during which their dose of study medication was adjusted until they reached optimum pain control. Patients who achieved optimum pain control entered a 12-week assessment period. The primary outcome was average daily pain scores recorded using the

box scale-11 (BS-11) pain scale. Both treatments significantly reduced patient pain scores. The estimated treatment difference [95% confidence interval (CI)] was -0.02 (-0.64, 0.60) for the per protocol (PP) population (Table 3).

Table 3. BS-11 pain scores at baseline, end of titration and during the assessment period

		BS-11 pain scores (boxes) mean (SD)			
		PP population		Full analysis population	
		7-day buprenorphine patch plus oral paracetamol (n = 61)	Co-codamol tablets (n = 56)*	7-day buprenorphine patch plus oral paracetamol (n = 107)	Co-codamol tablets (n = 102)
Baseline		7.0 (1.31)	7.0 (1.11)	7.0 (1.29)	7.0 (1.27)
End of titration		3.4 (1.44)	3.7 (1.66)	4.3 (1.94)	4.4 (2.12)
Assessment period	Weeks 1 and 2	2.9 (1.71)	3.2 (2.00)	4.0 (2.21)	4.1 (2.45)
	Weeks 3 and 4	3.0 (1.80)	3.0 (2.02)	4.0 (2.27)	4.0 (2.54)
	Weeks 5 and 6	2.9 (1.65)	2.9 (1.99)	4.0 (2.21)	4.0 (2.56)
	Weeks 7 and 8	2.9 (1.74)	2.9 (1.96)	4.0 (2.27)	4.0 (2.55)
	Weeks 9 and 10	2.8 (1.71)	3.0 (1.99)	4.0 (2.26)	4.1 (2.53)
	Weeks 11 and 12	3.0 (1.85)	3.0 (2.12)	4.0 (2.29)	4.2 (2.61)

* Except for Weeks 11 and 12 of the assessment period (n = 54).

Pharmacodynamic Interactions

A feature of the clinical use of paracetamol is its small number of interactions with other drugs although, not surprisingly, opioids and NSAIDs, potentiate the analgesic actions of paracetamol.

Apart from the mutual potentiation with other analgesics, paracetamol also can potentiate the anticoagulant effects of warfarin, and clotting tests should be conducted if paracetamol treatment is added or removed from the treatment of patients taking warfarin. Paracetamol does not have sufficient anti-platelet effect to potentiate the anticoagulant effect of warfarin and the interaction is due to paracetamol decreasing the synthesis of vitamin K-dependent clotting factors.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs such as rifampin or isoniazid or drugs that induce liver microsomal enzymes. Alcohol may potentiate the hepatotoxicity of paracetamol.

MAO inhibitors (e.g. linezolid, moclobemide, selegiline) may enhance CNS effects of codeine (excitation or depression). Concurrent use (or within 14 days) with MAO inhibitors is contraindicated. Sedative antihistamines, hyponotics, anxiolytics, general anaesthetics, antipsychotics and tricyclic antidepressants may enhance sedative and hypotensive effect and increase risk of respiratory depression.

Concomitant use of metoclopramide and a CNS depressant (e.g., sedatives, hypnotics, opiates, and anxiolytics) may result in an increased risk of CNS depression and should be avoided. If coadministration is necessary, monitor for adverse effects.

No interaction between domperidone and codeine has been reported, however, concomitant use of domperidone and methadone resulted in prolonged QT interval.

Since codeine significantly delays intestinal transit [REDACTED] [REDACTED] [REDACTED] coadministration with antidiarrhoeal drugs (e.g. loperamide, kaolin) may increase the risk of severe constipation.

Anticholinergics and morphine derivatives antagonise the effects of metoclopramide on the gastrointestinal motility [REDACTED]

Combination of CNS depressants, e.g. morphine derivatives with metoclopramide may result in potentiation of sedative effects [REDACTED]

Opioid antagonists e.g. buprenorphine, naltrexone, naloxone may precipitate withdrawal symptoms due to competitive binding at opioid receptors [REDACTED] [REDACTED]. Significant improvement after the additions of oral naltrexone to methadone occurred in a patient with painful peripheral neuropathy. Both medications were reduced by 50% a week before presentation due to concerns about medication-seeking behaviour. Over the next several months he underwent numerous dose adjustments but the pain would return. He also complained of nausea. Eight months after presentation, the patient was taking methadone 60 mg 4 times daily and methylphenidate 30 mg twice daily for opioid-induced sedation [REDACTED] [REDACTED]

Hypotension caused by opiate alkaloids is mainly as a result of vasodilatation and peripheral pooling of blood. Intravenous codeine may cause severe hypotension [REDACTED] [REDACTED]. Antihypertensive drugs may enhance hypotensive effect of codeine.

2.5.4. Overview of Efficacy

The combination of paracetamol/codeine (and other opiate agonists) has been evaluated in a number of placebo- or active-controlled clinical studies using (NSAIDs or other analgesics as comparators).

2.5.4.1 Acute Pain States

The combination was studied in acute pain states, such as dental pain, acute low-back pain postsurgical pain and tension headache. Only controlled studies are detailed.

A double-blind, multicentre analgesic trial was carried out in patients suffering from pain after removal of an impacted lower wisdom tooth. 266 patients were evaluated after random allocation to treatment with paracetamol 500 mg, paracetamol 500 mg plus codeine 20 mg, paracetamol 500 mg plus codeine 30 mg, or paracetamol 500 mg plus codeine 40 mg. On the day of surgery the patients assessed their own pain intensity hourly on a visual analogue scale. The analysis of the results was carried out according to the method which considered repeated dose intake. A statistically significant dose-response relationship was obtained between the supplementary doses of codeine and analgesic efficacy. In the comparison of side effects, their frequency increased with increasing amounts of codeine. In clinical practice codeine 30 mg appeared to be the optimal supplement for paracetamol 500 mg.

In a randomised, double-blind, double-dummy, multiple dose, crossover study in 30 patients compared an ibuprofen/codeine combination (400 mg ibuprofen/25.6 mg codeine phosphate) with a paracetamol/codeine/caffeine combination (1 g paracetamol/16 mg codeine phosphate/60 mg caffeine) for pain relief over 6 days after two-stage bilateral lower third molar removal. The ibuprofen combination produced significantly greater analgesia than the paracetamol combination, both on single-dose analysis of the first and second days and on multiple-dose measures for days 1, 2, 3 and 4. The mean incidence of adverse effects over the 6 days was 20% for both combinations.

A study determined the analgesic efficacy of a single oral dose of rofecoxib 50 mg compared with the combination of codeine 60 mg/acetaminophen 600 mg in a model of postsurgical dental pain. In this double-blind, placebo- and active comparator-controlled, parallel-group study, patients experiencing moderate or severe pain after the surgical extraction of > or = 2 third molars, at least 1 of which was a mandibular impaction, were randomized to receive placebo, rofecoxib 50 mg, or codeine 60 mg/acetaminophen 600 mg. Patient evaluations of pain intensity, pain relief, and global assessments were recorded throughout the 24-hour period after dosing. The 2-stopwatch method was used to determine time to confirmed perceptible pain relief. The primary end point assessing overall analgesic effect was total pain relief over 6 hours (TOPAR6). Secondary end points were patient global assessment of response to therapy (PGART) at 6 hours, onset of analgesia, peak analgesic effect, and duration of analgesia. A total of 393 patients were enrolled; 182 received rofecoxib, 180 received codeine/acetaminophen, and 31 received placebo. The overall analgesic effect of rofecoxib 50 mg was greater than that of codeine 60 mg/acetaminophen 600 mg for TOPAR6 (12.4 vs. 7.0; $P < 0.001$) and PGART at 6 hours ($P < 0.001$). The onset of analgesic effect was similar for rofecoxib and

codeine/acetaminophen. Peak analgesic effect as measured by peak pain relief scores during the first 6 hours was significantly greater in the rofecoxib group compared with the codeine/acetaminophen group ($P < 0.001$), as was the duration of analgesic effect measured by the time to rescue analgesia (9.6 hours vs. 2.3 hours, $P < 0.001$). Adverse events were reported in 33.0%, 46.1%, and 32.3% of patients treated with rofecoxib, codeine/acetaminophen, and placebo, respectively. The most common adverse events were nausea (6.0%, 25.0%, and 9.7%, respectively) and vomiting (3.8%, 18.3%, and 6.5%, respectively). Significantly more patients in the codeine/acetaminophen group than in the rofecoxib group experienced adverse events overall ($P < 0.050$) and nausea in particular ($P < 0.001$). In this study of moderate to severe postoperative dental pain, the analgesic efficacy of rofecoxib 50 mg was greater than that of codeine/acetaminophen, with a lower incidence of adverse events and nausea.

A randomized, single centre, double-blind prospective parallel group trial was performed to compare paracetamol 1000 mg with paracetamol 1000 mg with codeine 30 mg for the relief of pain following surgical removal of impacted third molars, and analysed on an intention-to-treat (ITT) basis [REDACTED] [REDACTED]. Eighty-two patients were assigned randomly to receive either drug for a maximum of three doses. Patients recorded their pain intensity one hour after surgery and hourly thereafter for 12 hours. The average increase in pain intensity over 12 hours was significantly less in patients receiving paracetamol plus codeine than in those receiving paracetamol alone ($p = 0.03$) -1.81 cm/h compared with 0.45 cm/h - a difference of 1.13 cm/h (95 per cent CI: 0.18 to 2.08). Of the patients who received the paracetamol codeine combination, 62 per cent used escape medication compared with 75 per cent of those on paracetamol alone ($p = 0.20$). There was no significant difference between the two groups in the proportion of patients experiencing adverse events ($p = 0.5$). In conclusion, a combination of 1000 mg paracetamol and 30 mg codeine was significantly more effective in controlling pain for 12 hours following third molar removal, with no significant difference of adverse effects during the 12 hour period studied.

[REDACTED] conducted a randomised double-blind placebo-controlled single-centre study to compare the effect of preoperative ibuprofen 600 mg, diclofenac 100 mg, paracetamol 1 g with codeine 60 mg or placebo (Vitamin C 50 mg) tablets for relief of postoperative pain in 119 patients who had day case operations under general anaesthesia for removal of impacted third molars. Patients were given the tablets 1 h before operation. Pain was assessed using visual analogue scales and verbal rating scales preoperatively at 15 and 30 min and 1 and 3 h postoperatively. After they had gone home, patients were contacted by telephone at 6 and 24 h postoperatively to find out whether they had any adverse effects from the analgesics. There was no significant difference in the extent of postoperative pain among the four groups, but the placebo group had significantly shorter times before their first request for postoperative analgesics (median 17 min, range 14-90) than the diclofenac group (median 32, range 15-150). Preoperative analgesics at the stated doses are effective in providing immediate postoperative pain control after operations on third molars. There were, however, some side-effects including nausea, vomiting, headaches, and gastrointestinal discomfort, but there were no significant differences among the active analgesic groups with respect to adverse events either shortly after operation or at 6 or 24 h.

██████████ compared the efficacy and safety profiles of aspirin, acetaminophen with codeine, and placebo in the treatment of post-operative dental pain. It was a randomized, double-blind, placebo-controlled, single-dose clinical trial that assigned participants (2:2:1) to receive either aspirin (1000 mg), acetaminophen (300 mg) with codeine (30 mg), or placebo. The primary efficacy end point was the sum of pain intensity differences from baseline (SPID) over 6 hours for the dental pain study. Other common analgesic measures, in addition to safety, were also evaluated. Aspirin provided statistically significant efficacy compared with acetaminophen with codeine for SPID(0-4) ($P = 0.028$). There were no significant differences between aspirin and acetaminophen with codeine at any evaluation of SPID ($P \geq 0.070$), complete relief ($P \geq 0.179$), or time to meaningful relief ($P \geq 0.245$). Regarding safety, there were no statistically significant differences between treatment groups in the incidence of adverse events in the dental pain. In conclusion, treatment with aspirin (1000 mg) provides statistically significant analgesic efficacy compared with placebo use and comparable efficacy with acetaminophen (300 mg) with codeine (30 mg) therapy after impacted third molar extraction.

██████████ investigated the efficacy of paracetamol/codeine in polytrauma patients. 60 polytrauma patients were enrolled for this study. 30 patients were treated with acetaminophen 1000 mg plus codeine 60 mg tid for 24 hours (Group A), while the remaining 30 with ketorolac 10 mg qid for 24 hours (Group B). Pain intensity has been evaluated using an analogical visual scale (VAS) ranging from 0 (no pain) to 10 (very severe pain). The level of pain was valuated at enrolment (T0) as well as after 2 (T2), 12 (T12) and 24 (T24) hours from the starting of the analgesic therapy. Results obtained by the group A were compared with those reported by the group B. T0: Group A mean score was 6.4 ± 1.5 compared with 6.6 ± 1.5 of Group B ($p = ns$); T2: Group A mean score was 3.4 ± 2.8 , compared with 3.5 ± 2.4 of group B ($p = ns$); T12: Group A mean score was 3.4 ± 3.4 , compared with 3.5 ± 3 of Group B ($p = ns$); T24: Group A mean score was 2.9 ± 1.5 , compared to 3.0 ± 1.6 of Group B ($p = ns$). All those drugs determined a significant reduction of pain intensity during the course of therapy. Acetaminophen plus codeine is effective in pain control in polytrauma patients at least in our series. It may represent a valid alternative to NSAIDs, especially in patients with a documented haemorrhage or with a high haemorrhagic risk.

In a cross-sectional, observational, prospective, cohort study, paracetamol-codeine was compared to ketorolac for pain control in the Emergency Department ██████████. Inclusion criteria were patients >18 year old presenting to the ED for localized traumatic or inflammatory pain involving only extremities. Numeric scale (NRS) was recorded thirty minutes and two hours after the administration of the analgesic therapy, consisting of 15 mg of ketorolac or 1000 mg/60 mg of paracetamol/ codeine, both orally. Two-hundred patients were consecutively enrolled; 87 were treated with paracetamol/codeine and 113 with ketorolac. The combination paracetamol/codeine resulted to be not inferior to ketorolac in non-traumatic pain group and trauma group ($p = 0.635$ and $p = 0.482$, respectively). Compared to ketorolac, the combination paracetamol/codeine exerted a significantly higher analgesic activity in patients with fractures and muscular pain ($p = 0.044$) and was more effective in acute pain ($p = 0.002$), with a significant effect two hours after the administration ($p = 0.029$). They concluded that paracetamol/codeine is equivalent to ketorolac in non-traumatic pain and post-traumatic pain, but is superior in acute pain and in patients with fractures and muscular pain. Those results play in favour of the use of the combination

paracetamol/codeine in patients accessing the ED for non-traumatic or traumatic pain of the extremities.

tested the hypothesis that oxycodone/acetaminophen provides analgesia superior to codeine/acetaminophen following emergency department (ED) discharge. It was a prospective, randomized, double-blind, trial in ED patients with acute extremity pain who were discharged home. Patients randomized to oxycodone/acetaminophen (5 mg/325 mg) or codeine/acetaminophen (30 mg/300 mg). The primary outcome, obtained via telephone one day after ED discharge, was the between-group difference in improvement in numerical rating scale (NRS) pain scores over a 2-hour period following the most recent ingestion of study drug. Secondary outcomes included proportion of patients with >50% pain reduction, side-effect profile, and patient satisfaction. Two hundred and forty patients were enrolled. Mean baseline NRS scores were 7.9 in both groups. Mean decrease over 2 hours was 4.5 NRS units in the oxycodone/acetaminophen group vs. 4.2 NRS units in the codeine/acetaminophen group, for a clinically and statistically nonsignificant difference of 0.2 NRS units (95% CI -0.4-0.9 NRS units). Similarly, 66% vs. 61% achieved >50% pain relief for a nonsignificant difference of 5% (95% CI -8% to 17%). Side-effect profile and patient satisfaction were similar. Their hypothesis that oxycodone/acetaminophen provides analgesia superior to codeine/acetaminophen was rejected. Although pain within each group was reduced by more than half, the between-group difference was not significant. Pending independent validation, these unexpected findings suggest that codeine/acetaminophen, a Schedule III agent, may be a clinically reasonable outpatient opioid alternative to oxycodone/acetaminophen, a more tightly restricted Schedule II agent thought to be more prone to misuse.

compared the efficacy of paracetamol-codeine phosphate and naproxen sodium-codeine phosphate on postoperative pain and tramadol consumption during the first 24 hours after a lumbar disk surgery. After Ethics Committee approval and informed consent had been obtained, 64 patients were allocated into three groups. Patients received oral paracetamol-codeine (300 mg + 30 mg; Group P), naproxen sodium-codeine (550 mg + 30 mg; Group N), or placebo tablets (Group C) 30 minutes prior to induction of anaesthesia. Patient-controlled analgesia was supplied postoperatively using tramadol. Pain intensity, tramadol consumption, and side effects were recorded every 1 hour, 2 hours, 6 hours, 12 hours, and 24 hours after surgery. Whole study period pain intensity (visual analogue scale scores) was lower in Group P ($p = 0.007$) and Group N ($p = 0.001$), compared with Group C, however, there was no statistically significant difference between Group P and Group N regarding pain intensity ($p > 0.05$). Tramadol consumption was lower in Group P and Group N, compared with Group C ($p < 0.001$), and in turn the lowest incidence of tramadol consumption was detected in Group P compared with Group N ($p < 0.001$) and Group C ($p < 0.001$). Side effects were similar between the groups. Preemptive administration of paracetamol-codeine and naproxen sodium-codeine combination significantly reduced tramadol consumption and provided more effective analgesia compared with placebo. The paracetamol-codeine combination was superior to naproxen sodium-codeine with regard to tramadol consumption.

A study determined the effectiveness of preoperative administration of single-dose of paracetamol-codeine, in the relieving of acute postoperative pain after the surgical removal of an impacted mandibular third molar. The

study cohort consisted of 32 Caucasian outpatients, giving a total of 64 bilateral symmetrical impacted mandibles. Patients were randomized in two experimental groups to receive a preoperative oral dose of paracetamol-codeine (analgesic group) or a placebo (placebo group) at the first and second surgeries. Study participants were asked to record pain intensity scores during the operation and the next 2 days, the time of the first request for rescue analgesic, and the total number of postoperative-supplement paracetamol-codeine tablets. The pain intensity score on the first day was significantly lower in the analgesic group than in the placebo group ($p < 0.001$). The time to using rescue therapy was significantly longer in the analgesic group than in the placebo group ($p = 0.004$). The number of paracetamol-codeine tablets used postoperatively did not differ between the analgesic and placebo groups ($p = 0.104$). In conclusion, preoperative paracetamol-codeine is effective in providing immediate postoperative pain control after third molar surgery and in delaying the initial onset of pain.

In a randomized, double-blind, placebo-controlled trial, [REDACTED] assessed the efficacy and safety of the combination of codeine plus acetaminophen (paracetamol) versus placebo as an add-on therapy for pain control after photorefractive keratectomy (PRK). One eye was randomly allocated to the intervention, whereas the fellow eye was treated with a placebo. Eyes were operated 2 weeks apart. The participants were adults older than 20 years with refractive stability for ≥ 1 year, who underwent PRK for correction of myopia or myopic astigmatism. Codeine (30 mg) plus acetaminophen (500 mg) was given orally 4 times per day for 4 days after PRK. The follow-up duration was 4 months. The study outcomes included pain scores at 1 to 72 hours, as measured by the visual analogue scale, McGill Pain Questionnaire, and Brief Pain Inventory, as well as adverse events and corneal wound healing. Of the initial 82 eyes, 80 completed the trial (40 intervention, 40 placebo). Median (interquartile range) pain scores as measured by the visual analogue scale were statistically and clinically lower during treatment with codeine/acetaminophen compared with the placebo: 1 hour: 4 (2-4) versus 6 (3-6), $P < 0.001$; 24 hours: 4 (3-6) versus 7 (6-9), $P < 0.001$; 48 hours: 1 (0-2) versus 3 (2-5), $P < 0.001$; and 72 hours: 0 (0-0) versus 0 (0-2), $P = 0.001$. Virtually identical results were obtained by the McGill Pain Questionnaire and Brief Pain Inventory scales. The most common adverse events with codeine/acetaminophen were drowsiness (42%), nausea (18%), and constipation (5%). No case of delayed epithelial healing was observed in both treatment arms. In conclusion, when added to the usual care therapy, the oral combination of codeine/acetaminophen was safe and significantly superior to the placebo for pain control after PRK.

2.5.4.2 Chronic Pain States

Osteoarthritis Pain

In a flare of osteoarthritis (OA) pain, increasing the dose of standard anti-inflammatory or routine analgesic drugs may not be practical because of an increased incidence of side effects. In patients achieving inadequate pain relief from traditional nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase (COX)-2-selective inhibitors, it may be appropriate to add an analgesic agent with a different mechanism of action, thereby targeting multiple components of the pain pathway.

A randomized, double-blind, multi-centre study was undertaken to evaluate the efficacy and safety of treatment for 4 weeks with codeine plus paracetamol versus paracetamol in relieving chronic pain due to OA of the hip [REDACTED]. A total of 158 outclinic patients entered the study. Eighty-three patients (mean age 66 years) were treated with codeine 60 mg plus paracetamol 1 g 3 times daily, and 75 patients (mean age 67 years) with paracetamol 1 g 3 times daily. Ibuprofen 400 mg was prescribed as rescue medication. Due to an unexpected high rate of adverse drug reactions, the study was closed before the planned 400 patients had entered. Over weeks 1-4, 87%, 64%, 61% and 52% of patients in the codeine plus paracetamol group, and 38%, 31%, 22% and 29% of patients in the paracetamol group had one or more adverse drug reactions. Significantly more patients in the codeine plus paracetamol group had adverse drug reactions in each of the 4 weeks. Nausea, dizziness, vomiting and constipation were predominant adverse reactions in the codeine plus paracetamol group. During the first week of treatment, 30 patients (36%) in the codeine plus paracetamol group and 9 (12%) in the paracetamol group dropped out. As evaluated from patients completing the first week of treatment, the pain intensity during that week compared to their baseline pain was significantly lower in the codeine plus paracetamol group than in the paracetamol group. Moreover, during the first week the paracetamol group received rescue medicine significantly more frequently. In conclusion, when evaluated after 7 days of treatment, the daily addition of codeine 180 mg to paracetamol 3 g significantly reduced the intensity of chronic pain due to osteoarthritis of the hip joint. However, several adverse drug reactions, mainly of the gastrointestinal tract, and the larger number of patients withdrawing from treatment means that the addition of such doses of codeine cannot be recommended for longer-term treatment of chronic pain in elderly patients.

Opioid/paracetamol combination analgesics are widely prescribed for the relief of moderate pain. The purpose of this study was to compare the efficacy and tolerability of tramadol/paracetamol tablets with codeine/paracetamol capsules [REDACTED]. This 4-week, randomized, double-blind, parallel-group, active-control, double-dummy, multicenter trial compared tramadol/paracetamol (37.5 mg/325 mg) with codeine/paracetamol (30 mg/300 mg) for the management of chronic nonmalignant low back pain, OA pain, or both in adults. Pain relief (scale, 0 = none to 4 = complete) and pain intensity (scale, 0 = none to 3 = severe) were measured 30 minutes and then hourly for 6 hours after the first daily dose each week. Patients and investigators assessed the efficacy (scale, 1 = poor to 5 = excellent) of each medication, and patients recorded daily doses of study and rescue medications. A total of 462 patients (mean age, 57.6 years) were randomly assigned to treatment, with 112 (24%) reporting chronic low back pain, 162 (35%) reporting OA pain, and 188 (41%) reporting both low back and OA pain; 309 patients (67%) received tramadol/paracetamol and 153 (33%) received codeine/paracetamol. Pain relief and changes in pain intensity were comparable from day 1, as early as 30 minutes after the first dose, and lasted for at least 6 hours. Total pain relief scores (11.9 for tramadol/paracetamol; 11.4 for codeine/paracetamol) and sum of pain intensity differences (3.8 for tramadol/paracetamol; 3.3 for codeine/paracetamol) were also comparable throughout. Overall assessments of efficacy by patients (mean score 2.9 in each treatment group) and investigators (mean score 3.0 for tramadol/paracetamol, 2.9 for codeine/paracetamol) were similar for the 2 treatment groups. Equivalent mean doses (3.5 tablets or capsules daily) and maximum daily doses (5.5 tablets or 5.7 capsules) were used in the 2 treatment groups. The overall incidence of adverse events was comparable, with a significantly higher proportion of patients in the

codeine/paracetamol group reporting somnolence (24% [37/153] vs. 17% [54/309], $P = 0.05$) or constipation (21% [32/153] vs. 11% [35/309], $P < 0.01$) and a larger proportion of patients in the tramadol/ paracetamol group reporting headache (11% [34/309] vs. 7% [11/153], $P = 0.08$). The authors conclude that tramadol/paracetamol tablets (37.5 mg/325 mg) are as effective as codeine/paracetamol capsules (30 mg/300 mg) in the treatment of chronic nonmalignant low back pain and OA pain and are better tolerated.

evaluated the efficacy and safety of oxycodone/acetaminophen (O/A) and codeine/acetaminophen (C/A) vs. conventional therapy (CT) without opioids in older women suffering from OA-related pain, sub-optimally responsive to prior conventional treatments. They performed a 6 week, randomized, single blind, controlled study in three nursing homes. They enrolled 154 women with painful OA. They were assigned to treatment with O/A ($n = 52$) and C/A ($n = 52$) vs. CT ($n = 50$). They evaluated at baseline and at week 6: average pain in the last week (mean pain, MeP), pain at rest (RP), pain in movement (MP) (numeric rating scale, NRS); depressive symptoms (Beck Depression Inventory-II, BDI-II); functional status (activities of daily living, ADL) and cognitive status (mini mental state evaluation, MMSE). They considered the adverse events (AEs) in the study period. At week 6, MeP, RP and MP were significantly reduced in all three groups ($p < 0.001$); compared to CT, O/A and C/A were associated with greater reductions in MeP ($p < 0.001$ and $p = 0.004$, respectively), in RP ($p = 0.028$ and $p = 0.032$, respectively) in MP ($p < 0.001$ and $p = 0.002$, respectively) and with significant improvement in BDI-II score ($p = 0.05$ and $p = 0.04$, respectively) and ADL value ($p = 0.04$ and $p = 0.05$, respectively). AE rates did not differ between groups.

A study compared symptom relief obtained with buprenorphine patches plus oral paracetamol with that obtained with an oral codeine-paracetamol combination tablet (Co-codamol) in older adults with OA. Two hundred and twenty people (aged ≥ 60 years) with OA hip and/or knee pain were randomised to treatment with 7-day buprenorphine patches plus oral paracetamol (5-25 $\mu\text{g/h}$ buprenorphine patches plus 1000 mg oral paracetamol q.i.d. (4 times daily); $n = 110$) or Co-codamol tablets (two 8/500-two 30/500 mg tablets q.i.d.; $n = 110$). They entered a titration period of up to 10 weeks, during which their dose of study medication was adjusted until they reached optimum pain control. Patients who achieved optimum pain control entered a 12-week assessment period. The primary outcome was average daily pain scores recorded using the box scale-11 (BS-11) pain scale. Both treatments significantly reduced patient pain scores. The estimated treatment difference [95% confidence interval (CI)] was -0.02 (-0.64, 0.60) for the per protocol (PP) population. The results were similar for the full analysis population. Patients receiving 7-day buprenorphine patches plus oral paracetamol needed significantly less escape medication (ibuprofen) than those receiving Co-codamol tablets ($P = 0.002$; PP population). Less than 10% of patients in the 7-day buprenorphine patches plus oral paracetamol group were receiving the highest dose level at the end of the study, compared with 34% in the Co-codamol group. Withdrawal rates were high in both groups. The incidence of adverse events (AEs) was comparable between the groups (86.4% of patients in the 7-day buprenorphine patches plus oral paracetamol group; 81.7% in the Co-codamol group). Six serious AEs were reported in three patients (2.7%) in the 7-day buprenorphine patches plus oral paracetamol group and one (0.9%) in the Co-codamol group. 7-day buprenorphine patches plus oral paracetamol were non-inferior to Co-codamol

tablets with respect to analgesic efficacy in older adults with OA pain in the hip/knee.

Cancer Pain

██████████ compared the effects of providing analgesia with either transdermal fentanyl (TTS-fentanyl) or paracetamol and codeine (P/C) in addition to radiotherapy in patients with metastatic bone pain. In a prospective study, 26 patients with radiologically confirmed bony metastases received radiotherapy (R/T). They were randomised to receive either 500 mg paracetamol and 30 mg codeine four times per day (P/C group), or transdermal fentanyl patches delivering 25 µg fentanyl/h (TTS-fentanyl group). Pain was assessed using visual analogue pain ratings (VAS) and the Greek Brief Pain Inventory (G-BPI) questionnaire administered before R/T and after 3 months. Data were available from 24 eligible patients. Use of TTS-fentanyl was associated with significantly superior pain relief. Mean VAS fell from 7.0 to 1.1 with TTS-fentanyl and from 8.3 to 4.3 with P/C, $p < 0.01$. The TTS-fentanyl group also showed significantly greater improvements of important G-BPI domains including global quality of life, pain, and physical, cognitive, and role functioning, than the P/C group ($p < 0.01$). Four patients receiving TTS-fentanyl and three receiving P/C reported severe nausea/vomiting. In conclusion, Transdermal fentanyl combined with R/T was more effective in reducing metastatic bone pain and resulted in greater improvements in quality of life than paracetamol and codeine.

A study compared the analgesic efficacy and tolerability of codeine phosphate versus hydrocodone bitartrate in combination with acetaminophen in the relief of cancer-related pain ██████████. This 23-day, prospective, double-blind, randomized, parallel-group study was conducted at 3 Colombian centres: University Libre, Social Security Institute, and General Hospital of Medellín, Cali, Colombia. Outpatients with cancer were eligible for the study if they were aged > 18 years and had chronic (duration, ≥ 3 months) moderate to severe cancer-related pain (score on 10-cm VAS, > 3 cm [moderate]; score on a 4-point verbal pain-intensity scale, > 1 [moderate]). Eligible patients were randomly assigned to receive 1 tablet of codeine/acetaminophen (C/A) 30/500 mg or hydrocodone/acetaminophen (H/A) 5/500 mg PO q4h (total daily doses, 150/2500 and 25/2500 mg, respectively) for 23 days. In both groups, if pain intensity was rated as > 3 on the VAS at week 1 or 2, the dosage was doubled. The primary end point was the proportion of patients who achieved pain relief (defined as a score of > 1 on a 5-point verbal rating scale [VRS] (0 = none; 1 = a little; 2 = some; 3 = a lot; and 4 = complete) on study days 1 and 2 and weeks 1, 2, and 3. The secondary end point was the proportion of patients in whom pain was decreased (VAS score, < 3 cm). AEs were self-reported on a 4-point VRS (0 = absent; 1 = mild; 2 = moderate; and 3 = severe). Of the 121 patients who participated, 59 received C/A and 62 received H/A. Of the total number of cases, 59% were aged 60 to 89 years, and 55% were men. At baseline, 88% of the patients described their pain intensity as moderate; 12%, severe. Of the patients who received C/A, 58% responded to the initial dosage of 150/2500 mg/d, and 8% of the patients responded to the double dosage; 34% did not experience pain relief. In patients with H/A, pain was reported as absent or mild in 56% of patients at the starting dosage of 25/2500 mg/d; an additional 15% of the patients responded to the double dosage; the remaining 29% of patients did not experience any pain relief. None of the between-group differences in response rates were significant. The most common AEs in the C/A and H/A groups were constipation (36% and 29%, respectively),

dizziness (24% and 19%), vomiting (24% and 16%), and dry mouth (15% and 18%), with no significant differences between groups. In this study, efficacy and tolerability were comparable between C/A and H/A over 23 days of treatment in these patients with moderate or severe, chronic, cancer-related pain.

Meta-analyses

A meta-analysis quantified the analgesic efficacy of paracetamol and its combination with codeine or caffeine through a systematic overview and meta-analysis of relevant randomized controlled trials (RCTs). Systematic retrieval of relevant clinical trials was carried out using computerized searches, historical searches and communication with manufacturers. The results of RCTs were pooled to estimate (i) the difference in percentage improvement of total pain relief (TOTPAR%) and the sum of pain intensity difference (SPID%); (ii) the proportions of patients obtaining moderate to excellent pain relief relative to placebo (ResRR) and (iii) the ratio of patients requiring analgesic re-medication (RemRR). Head-to-head comparisons were also undertaken for paracetamol versus its combination with codeine or caffeine. A total of 80 RCT reports describing 103 placebo comparisons and 26 head-to-head comparisons were identified. The characteristics of RCTs are shown in Table 4. The head-to-head comparisons are shown in Table 5.

Table 4. Summary of characteristics of RCTs of paracetamol

	Placebo-controlled trials			Head-to-head comparisons	
	P vs. pl	P+Cod vs. pl	P+Caf vs. pl	P+Cod vs. P	P+Caf vs. P
Total RCT reports obtained	62	33	3	19	2
No. of the reports eligible*	52	25	2	16	2
No. of comparisons included	64	29	10	16	10
No. of patients†	3313/2702	997/931	635/464	529/535	635/650
Types of pain					
Dental	32	22	1	12	0
Episiotomy	12	1	3	0	0
Postpartum uterine cramp	10	0	6	0	10
Others	10	5	0	4	0
Observation hours (Mean ± SD)	5.03 ± 1.12	5.48 ± 0.94	4 ± 0.00	5.19 ± 1.05	4 ± 0.00

*Excluding studies which were not eligible, e.g. non oral administration, extra strength formulation, abstract or short report and non double-blind studies.

†The number of patients on the left of the solidus received active treatment (or the combination), the number of patients on the right of the solidus received placebo (or paracetamol alone).

Abbreviations: P=paracetamol; pl=placebo; Cod=codeine; Caf=caffeine.

Table 5. Characteristics of randomized head-to-head comparison trials between paracetamol plus codeine and paracetamol

Trials	Reference	Types of pain	Combination (mg)	Paracetamol (mg)	Observation (h)	Mean age (range in years)	Mean weight (range in kg)	Mean %BPS	nc	np
Bentley (1987)	11	tooth removal	1000+60	1000	5	26	63.65	0.57	41	41
Cooper (1976)	15	tooth removal	600+60	600	3	23	66.50	0.72	40	40
Cooper (1981)	17	3rd molar removal	650+60	650	4	23	65.47	0.74	42	37
Cooper (1984)	18	tooth removal	600+60	600	4	25	65.17	—	41	44
Cooper (1988)	21	3rd molar removal	600+60	600	6	25	65.17	0.8	31	36
Cooper (1991)	23	tooth removal	650+60	650	6	23	64.34	0.87	39	37
Dionne (1994)	26	3rd molar removal	650+30	650	6	29	68.22	—	24	27
Forbes (1982)	28	3rd molar removal	600+60	600	4	—	—	—	31	34
Forbes (1983)	29	general, gynecological, orthopaedic surgeries	600+60	600	6	38 (18–56)	77.53	0.76	26	26
Forbes (1989)	32	3rd molar removal	600+60	600	6	22 (16–39)	62.99	0.79	17	22
Forbes (1990)	33	3rd molar removal	600+60	600	6	22 (16–46)	65.69	0.76	38	36
Gertzbein (1986)	70	surgeries	1000+60	1000	5	34	70.51	—	45	45
Honig (1984)	37	abdominal, orthopaedic, rectal surgeries	600+60	600	6	44 (19–87)	72.36 (46–104)	—	30	28
Quiding (1983)	48	meniscectomy	1000+60	1000	4	35	80.88	0.54	16	20
Skoglund (1991)	51	3rd molar removal	1000+60	1000	6	25	—	0.67	37	32
Sunshine (1986)	52	3rd molar removal	650+60	650	6	21	59.1	0.58	31	30

%BPS: the weighted ratio of baseline pain score to the maximum pain score of the scale used. %BPS=(BPS – minimum score on the scale)/(maximum score on the scale – minimum score on the scale). %BPS 0=no pain, %BPS 0.5=moderate pain, and %BPS 1=severe pain. nc: number of subjects in the combination group. np: number of subjects in the paracetamol group. The trials were all of a double-blind parallel design.

Table 6. Head-to-head comparisons of efficacy (difference in TOTPAR%) of the combination versus paracetamol

Comparisons	No. of trials	No. of patients [▲]	TOTPAR%						
			Combination	Paracetamol	dt	SE	Z	95% CI	χ^2_{heter} [‡]
Paracetamol + codeine vs. paracetamol									
600+60 vs. 600	7	214/226	42.89	31.61	11.28	3.09	3.65¶	5.22, 17.23	13.33§
650+60 vs. 650	3	112/104	41.48	39.84	1.64	3.17	0.52	- 4.56, 7.85	2.31
1000+60 vs. 1000	3	123/118	50.62	47.55	3.56	6.31	0.56	- 8.82, 15.93	6.98§
Total	13	449/448	44.34	37.09	7.39	2.43	3.04¶	2.62, 12.16	30.00¶

[▲]The number of patients shown to the left of the solidus received the combination; the number shown to the right of the solidus received paracetamol alone.

td is the difference in TOTPAR% between the combination and paracetamol.

‡χ²_{heter} is the chi-square statistic for heterogeneity. Where the results are heterogeneous, the random effects model was used to provide pooled interval estimates.

§P≤0.05; ¶P≤0.01.

Table 7. Head-to-head comparisons of efficacy (difference in SPID%) of the combination versus paracetamol

Comparisons	No. of trials	No. of patients [▲]	SPID%						
			Combination	Paracetamol	d†	SE	Z	95% CI	χ^2_{heter} [‡]
Paracetamol + codeine vs. paracetamol									
600+60 vs. 600	7	214/226	25.77	16.47	9.31	1.66	5.60§	6.05, 12.56	11.17
650+60 vs. 650	3	112/104	23.08	18.43	4.65	2.54	1.83	- 0.33, 9.62	2.35
1000+60 vs. 1000	3	123/118	17.36	11.76	3.34	1.96	1.70	- 0.51, 7.19	1.03
Total	13	449/448	23.32	16.30	6.38	1.13	5.63§	4.16, 8.61	20.53

[▲]The number of patients shown to the left of the solidus received the combination; the number shown to the right of the solidus received paracetamol alone.

†d is the difference in SPID% between the combination and paracetamol.

[‡] χ^2_{heter} is the chi-square statistic for heterogeneity. Where the results are heterogeneous, the random effects model was used to provide pooled interval estimates.

§P < 0.01

Table 8. Head-to-head comparisons of efficacy (response rate ratio ResRR and re-medication rate ratio RemRR) of the combination versus paracetamol alone

Comparisons	No. of trials	No. of patients (active/placebo)	lnRR	SE	Z	$\chi^2_{heter} \ddagger$	RR	95% CI
Paracetamol + codeine vs. paracetamol								
ResRR[▲]								
600+60 vs. 600	6	111/182	0.13	0.08	1.62	3.49	1.14	0.97, 1.34
650+60 vs. 650	2	44/81	0.19	0.16	1.16	1.33	1.21	0.88, 1.67
RemRR[†]								
600+60 vs. 600	6	173/182	-0.03	0.06	-0.55	5.40	0.97	0.87, 1.08
650+60 vs. 650	2	73/67	-0.28	0.31	-0.89	2.09	0.75	0.41, 1.40

[▲]ResRR is the response rate ratio for patients receiving the combination relative to paracetamol. Response rate is defined as the proportion of patients reporting moderate to excellent, or more than 50% pain relief, during the observation. lnRR is the loge of the rate ratio. SE is the standard error of lnRR. Z is corresponding standard statistics. 95% CI is the confidence interval of the rate ratio.

[†]RemRR is the re-medication rate ratio for patients receiving the combination relative to paracetamol. Re-medication rate is defined as the proportion of patients requiring rescue analgesics during the observation hours.

[‡] χ^2_{heter} is the chi-square statistic for heterogeneity. Where the results are heterogeneous, the random effects model was used to provide pooled interval estimates.

The total pain relief score in the single dose studies increased by 38 percentage points for paracetamol and by 24 points for placebo. The difference (d) in TOTPAR% between the two was highly significant (d = 14, 95% CI: 12, 16). For the difference in SPID%, d = 12, 95% CI: 11, 13. Patients were more than twice as likely to obtain moderate to excellent pain relief on paracetamol than on placebo (ResRR = 2.39, 95% CI: 1.89, 3.02), and less likely to require re-medication (RemRR = 0.78, 95% CI: 0.69, 0.88). There was no significant (P > 0.05) dose-response relationship. The analgesic efficacy of paracetamol 600 mg was enhanced with the addition of codeine 60 mg (using TOTPAR% as outcome) in both indirect and head-to-head comparisons (Table 6). SPID%, but not ResRR and RemRR, data supported this conclusion (Table 7, Table 8). Much weaker effects were observed with the caffeine combination. Adverse effects were mild. Surprisingly, drowsiness was seen more often with paracetamol and paracetamol-

codeine combinations than with placebo. The relative risks (95% CI) were 1.83 (1.29, 2.59) and 2.39 (1.58, 3.57), respectively. In conclusion paracetamol is an effective analgesic for post-surgical pain. There is some evidence that codeine 60 mg adds to the analgesic effects of paracetamol 600 mg, using pain relief or pain intensity scores as outcomes, but this is not necessarily translated into an increase in number of patients who obtain moderate to excellent pain relief.

assessed whether adding codeine to paracetamol has an additive analgesic effect and assessed the safety of paracetamol-codeine combinations versus paracetamol alone. It was a systematic literature review with meta-analysis, methodological quality of published trials being scored by means of 13 predefined criteria. 24 of 29 trials that met the inclusion criteria. Models studied in the trials were postsurgical pain (21), postpartum pain (one), osteoarthritic pain (one), and experimentally induced pain (one). Dosages ranged from 400 to 1000 mg paracetamol and 10 to 60 mg codeine. Main outcome measures were: the sum pain intensity difference (efficacy analysis) and the proportion of patients reporting a side effect (safety analysis). Most trials were considered of good to very good quality. Only the single dose studies could be combined for analysis of analgesic efficacy. Pooled efficacy results indicated that codeine added to paracetamol provided a 5% increase in analgesia on the sum pain intensity difference. This effect was comparable to the difference in analgesic effect between codeine and placebo. The cumulative incidence of side effects with each treatment was comparable in the single dose trials. In the multidose studies a significantly higher proportion of side effects occurred with paracetamol-codeine preparations. In conclusion, the difference in analgesic effect between paracetamol-codeine combinations and paracetamol alone was small but statistically significant. In the multidose studies the proportion of patients reporting a side effect was significantly higher with paracetamol-codeine combinations. For occasional pain relief a paracetamol-codeine combination might be appropriate but repeated use increases the occurrence of side effects.

In order to assess the analgesia obtained from single oral doses of paracetamol alone and in combination with codeine in postoperative pain, conducted a systematic review of randomised controlled trials. They found 31 trials of paracetamol against placebo with 2515 patients, 19 trials of paracetamol plus codeine against placebo with 1204 patients and 13 trials of paracetamol plus codeine against the same dose of paracetamol with 874 patients. Fourteen trials were in oral surgery and five in postsurgical pain. Doses were paracetamol 300 mg plus codeine 30 mg in five trials, paracetamol 600 plus codeine 60 mg in eight, paracetamol 650 mg plus codeine 60 mg in five, and paracetamol 1000 mg plus codeine 60 mg in one (Fig 2).

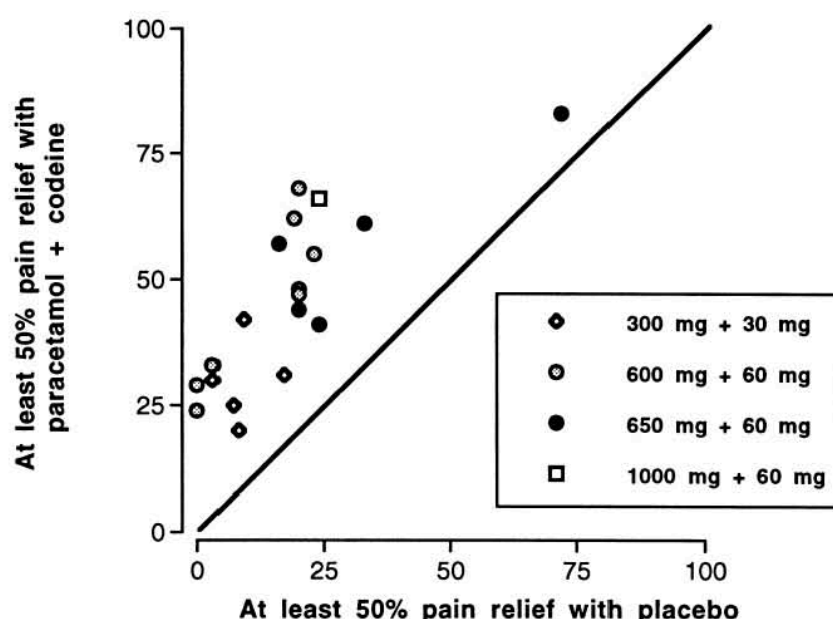


Figure 2. Plot of single dose studies of paracetamol plus codeine against placebo in postoperative pain. Each point represents one of the included trials

Pain relief information was extracted, and converted into dichotomous information (number of patients with at least 50% pain relief). Wide variations in responses to placebo (0-72%) and active drug (3-89%) were observed. In postoperative pain states paracetamol 1000 mg alone against placebo had an number-needed-to-treat (NNT) of 3.6 (3.0-4.4) and paracetamol 600/650 mg alone an NNT of 5.0 (4.1-6.9). Paracetamol 600/650 mg plus codeine 60 mg against placebo had a better NNT of 3.1 (2.6-3.8), with no overlap of 95% confidence intervals with paracetamol 600/650 mg alone. In direct comparisons of paracetamol plus codeine with paracetamol alone the additional analgesic effect of 60 mg of codeine added to paracetamol was 12 extra patients in every 100 achieving at least 50% pain relief. In indirect comparisons of each with placebo it was 14 extra patients per 100. This was an NNT for adding codeine 60 mg of 9.1 (5.8-24). The results confirm that paracetamol is an effective analgesic, and that codeine 60 mg added to paracetamol produces worthwhile additional pain relief even in single oral doses.

A systematic review compared the analgesic effect and safety profile of acetaminophen/codeine (A + C) with NSAIDs in the management of pain after laparotomy. A systematic search was performed by using MEDLINE, EMBASE, CINAHL, and Cochrane Library databases to identify randomized controlled trials comparing A + C to NSAIDs for postlaparotomy pain. Selected articles were critically appraised by using the CONSORT method and Jadad score. Nine relevant articles were identified. All 9 studies used a visual analogue scale for pain intensity and reported the incidence of adverse effects as an outcome. None of the studies showed lower pain intensity scores after treatment with A + C compared with different NSAIDs. In 3 studies, the number of patients with adverse effects was significantly lower in the NSAID group compared with the A + C-group. In 1 other study, the rate of constipation was significantly lower in the NSAID group when compared with the A + C-group. The

other 5 studies did not report any significant differences in the rates of adverse effects between the 2 groups. In conclusion, none of the studies found A + C to be superior to NSAIDs in controlling postlaparotomy pain. NSAIDs appear to be an equipotent alternative in the treatment of postlaparotomy pain. Four of the 9 studies reported less adverse effects in the NSAID group. There appears to be an overall better risk/benefit ratio for the use of NSAIDs for postpartum pain.

An updated review sought to evaluate efficacy and safety of paracetamol plus codeine using current data, and compare findings with other analgesics evaluated similarly [REDACTED]. The objective of this review was to assess efficacy of single dose oral paracetamol plus codeine in acute postoperative pain, increase in efficacy due to the codeine component, and associated adverse events. They searched CENTRAL, MEDLINE, EMBASE, the Oxford Pain Relief Database in October 2008 for this update. Randomised, double-blind, placebo-controlled trials of paracetamol plus codeine, compared with placebo or the same dose of paracetamol alone, for relief of acute postoperative pain in adults were selected. Two authors assessed trial quality and extracted data. The area under the "pain relief versus time" curve was used to derive proportion of participants with paracetamol plus codeine and placebo or paracetamol alone experiencing least 50% pain relief over four-to-six hours, using validated equations. NNT was calculated using 95% confidence intervals (CIs). Proportion of participants using rescue analgesia over a specified time period, and time to use of rescue analgesia, were sought as additional measures of efficacy. Information on adverse events and withdrawals were collected. Twenty-six studies, with 2295 participants, were included comparing paracetamol plus codeine with placebo. Significant dose response was seen for the outcome of at least 50% pain relief over four-to-six hours, with NNTs of 2.2 (95% CI 1.8 to 2.9) for 800 to 1000 mg paracetamol plus 60 mg codeine, 3.9 (2.9 to 4.5) for 600 to 650 mg paracetamol plus 60 mg codeine, and 6.9 (4.8 to 12) for 300 mg paracetamol plus 30 mg codeine. Time to use of rescue medication was over four hours with paracetamol plus codeine and two hours with placebo. The NNT to prevent remedication was 5.6 (4.0 to 9.0) for 600 mg paracetamol plus 60 mg codeine over four to six hours. Adverse events increased of mainly mild to moderate severity with paracetamol plus codeine than placebo. Fourteen studies, with 926 participants, were included in the comparison of paracetamol plus codeine with the same dose of paracetamol alone. Addition of codeine increased proportion of participants achieving at least 50% pain relief over four-to-six hours by 10 to 15%, increased time to use of rescue medication by about one hour, and reduced proportion of participants needing rescue medication by about 15% (NNT to prevent remedication 6.9 (4.2 to 19).

Table 9 Forest plot of comparison: Paracetamol 800 to 1000 mg plus codeine 60 mg versus paracetamol 1000 mg, outcome: participants with at least 50% pain relief over 4 to 6 hours [REDACTED]



Table 10. Forest plot of comparison: Paracetamol 600 to 650 mg plus codeine 60 mg versus paracetamol 600 to 650 mg, outcome: participants with at least 50% pain relief over 4 to 6 hours

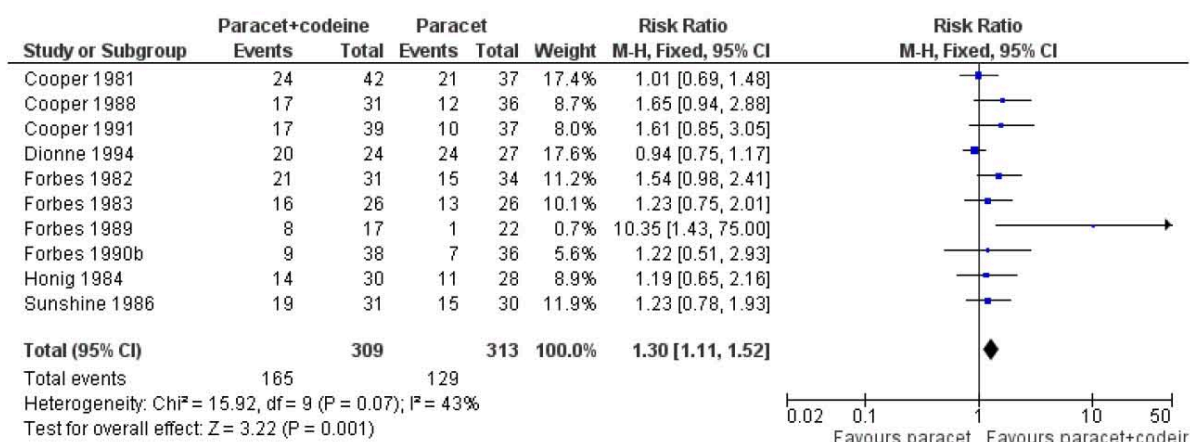


Table 11. Participants achieving at least 50% pain relief over 4 to 6 hours: paracetamol plus codeine versus the same dose of paracetamol alone

Dose (mg)	Studies	Participants	Paracetamol + codeine (%)	Paracetamol (%)	NNT (95%CI) ≥50% PR
800-1000/60	4	304	59	42	6.1 (3.6 to 19)
1000/60	3	217	68	48	5.1 (3.1 to 15)
600-650/60	10	622	53	41	8.2 (5.0 to 23)

Adverse events were mainly mild to moderate in severity and incidence did not differ between groups. The authors conclude that this update (this is an updated version of the Cochrane review published in Issue 4, 1998) confirms previous findings that combining paracetamol with codeine provided clinically useful levels of pain relief in about 50% of patients with moderate to severe postoperative pain, compared with under 20% with placebo. New information for remedication shows that the combination extended the duration of analgesia by about one hour compared to treatment with the same dose of paracetamol alone. At higher doses, more participants experienced adequate pain relief, but the amount of information available for the 1000 mg paracetamol plus 60 mg codeine dose was small, and based on limited information.

The combination acetaminophen/codeine represents the standard medication in the second step of the WHO analgesic scale and codeine is one of the most commonly used opioid analgesic for a variety of pain conditions. However, many aspects related to safety and efficacy are still undefined. A recent meta-analysis summarized and reviewed the results of the most relevant studies on the efficacy and safety profile of acetaminophen/codeine combination in the treatment of pain of different origin. They performed a literature search to identify and evaluate all relevant English-language randomized controlled trials (RCTs), meta-analyses and reviews about the codeine plus paracetamol

combination in the treatment of pain from any source. Acetaminophen/codeine combination is effective in the treatment of moderate to severe pain in all setting analyzed in this study, which include headache, postoperative, osteoarticular and post-traumatic. The best results in terms of safety and efficacy have been obtained in postoperative pain. Efficacy of acetaminophen/codeine combination is not inferior to NSAIDs. Acetaminophen/codeine combination is effective in the treatment of pain, through a synergistic action of the two molecules, and is not inferior to NSAIDs. Side effects of acetaminophen/codeine are usually minor, differently from NSAIDs, which may induce some potentially life threatening conditions.

A review determined the efficacy and safety of codeine used alone or in combination with paracetamol for relieving cancer pain [REDACTED]. They searched the Cochrane Central Register of Controlled Trials ([REDACTED]), MEDLINE and EMBASE from inception to 5 March 2014, supplemented by searches of clinical trial registries and screening of the reference lists of the identified studies and reviews in the field. They sought randomised, double-blind, controlled trials using single or multiple doses of codeine, with or without paracetamol, for the treatment of cancer pain. Trials could have either parallel or cross-over design, with at least 10 participants per treatment group. Studies in children or adults reporting on any type, grade, and stage of cancer were eligible. They accepted any formulation, dosage regimen, and route of administration of codeine, and both placebo and active controls. Two review authors independently read the titles and abstracts of all studies identified by the searches and excluded those that clearly did not meet the inclusion criteria. For the remaining studies, two authors read the full manuscripts and assessed them for inclusion. They resolved discrepancies between review authors by discussion. Included studies were described qualitatively, since no meta-analysis was possible because of the small amount of data identified, and clinical and methodological between-study heterogeneity. They included 15 studies including 721 participants with cancer pain due to diverse types of malignancy. All studies were performed on adults; there were no studies on children. The included studies were of adequate methodological quality, but all except for one were judged to be at a high risk of bias because of small study size, and six because of methods used to deal with missing data or high withdrawal rates. Three studies used a parallel group design; the remainder were cross-over trials in which there was an adequate washout period, but only one reported results for treatment periods separately. Twelve studies used codeine as a single agent and three combined it with paracetamol. Ten studies included a placebo arm, and 14 included one or more of 16 different active drug comparators or compared different routes of administration. Most studies investigated the effect of a single dose of medication, while five used treatment periods of one, seven or 21 days. Most studies used codeine at doses of 30 mg to 120 mg. There were insufficient data for any pooled analysis. Only two studies reported these preferred responder outcome of 'participants with at least 50% reduction in pain' and two reported 'participants with no worse than mild pain'. Eleven studies reported treatment group mean measures of pain intensity or pain relief; overall for these outcome measures, codeine or codeine plus paracetamol was numerically superior to placebo and equivalent to the active comparators. Adverse event reporting was poor: only two studies reported the number of participants with any adverse event specified by treatment group and only one reported the number of participants with any serious adverse event. In multiple-dose studies nausea, vomiting and constipation were common, with somnolence and dizziness frequent in the 21-day study. Withdrawal from the studies, where reported, was less than 10% except in

two studies. There were three deaths, in all cases due to the underlying cancer. In conclusion, they identified only a small amount of data in studies that were both randomised and double-blind. Studies were small, of short duration, and most had significant shortcomings in reporting. The available evidence indicates that codeine is more effective against cancer pain than placebo, but with increased risk of nausea, vomiting, and constipation. Uncertainty remains as to the magnitude and time-course of the analgesic effect and the safety and tolerability in longer-term use. There were no data for children.

A meta-analysis assessed the analgesic efficacy and adverse events of paracetamol with or without codeine or dihydrocodeine for chronic neuropathic pain in adults [REDACTED]. They searched the Cochrane Central Register of Controlled Trials (REDACTED), MEDLINE, and Embase from inception to July 2016, together with reference lists of retrieved papers and reviews, and two online study registries. They included randomised, double-blind studies of two weeks' duration or longer, comparing paracetamol, alone or in combination with codeine or dihydrocodeine, with placebo or another active treatment in chronic neuropathic pain. Two review authors independently searched for studies, extracted efficacy and adverse event data, and examined issues of study quality and potential bias. They did not carry out any pooled analyses. They assessed the quality of the evidence using GRADE. No study satisfied the inclusion criteria. Effects of interventions were not assessed as there were no included studies. They have only very low quality evidence and have no reliable indication of the likely effect. In conclusion, there is insufficient evidence to support or refute the suggestion that paracetamol alone, or in combination with codeine or dihydrocodeine, works in any neuropathic pain condition.

2.5.4.3 Efficacy in Children and Adolescents

In a prospective, randomized, double-blind study, [REDACTED] compared the effectiveness of acetaminophen versus acetaminophen with codeine after pediatric tonsillectomy and adenoidectomy. Fifty-one children ages 3 to 12 years scheduled for outpatient tonsillectomy and adenoidectomy were studied. Patients were randomly assigned to receive acetaminophen or acetaminophen with codeine in unlabeled bottles for postoperative pain control. The Wong-Baker FACES pain rating scale was used to help children quantify their level of pain after surgery. The level of pain, quantity of pain medication required, presence of side effects, and the percentage of a normal diet consumed was recorded for 10 postoperative days. There was no difference ($P > 0.05$, all time points) in the level of postoperative pain reported by the parents and children in the two groups. The acetaminophen with codeine group tended to have increased problems with nausea, emesis, and constipation, but these differences did not reach statistical significance. Children in the acetaminophen group consumed a significantly higher percentage of a normal diet on the first 6 postoperative days ($P < 0.05$, all time points). There was no difference in the level of pain control provided by acetaminophen and acetaminophen with codeine as measured by the Wong-Baker FACES pain rating scale. Postoperative oral intake was significantly higher in children treated with acetaminophen alone.

[REDACTED] compared the analgesic effectiveness of acetaminophen-codeine with that of ibuprofen for children with acute traumatic extremity pain, with the hypothesis that the two medications would demonstrate equivalent reduction in pain scores in an emergency department (ED) setting. This was a randomized,

double-blinded equivalence trial. Paediatric ED patients 5 to 17 years of age with acute traumatic extremity pain received acetaminophen-codeine (1 mg/kg as codeine, maximum 60 mg) or ibuprofen (10 mg/kg, maximum 400 mg). The patients provided Colour Analogue Scale (CAS) pain scores at baseline and at 20, 40, and 60 minutes after medication administration. The primary outcome measured was the difference in changes in pain score at 40 minutes, compared to a previously described minimal clinically significant change in pain score of 2 cm. The difference was defined as (change in ibuprofen CAS score from baseline) - (change in acetaminophen-codeine CAS score from baseline); negative values thus favour the ibuprofen group. Additional outcomes included need for rescue medication and adverse effects. The 32 acetaminophen-codeine and the 34 ibuprofen recipients in our convenience sample had indistinguishable pain scores at baseline. The intergroup differences in pain score change at 20 minutes (-0.6, 95% confidence interval [CI] = -1.5 to 0.3), 40 minutes (-0.4, 95% CI = -1.4 to 0.6), and 60 minutes (0.2, 95% CI = -0.8 to 1.2) were all less than 2 cm. Adverse effects were minimal: vomiting (one patient after acetaminophen-codeine), nausea (one patient after ibuprofen), and pruritus (one after acetaminophen-codeine). The three patients in each group who received rescue medications all had radiographically demonstrated fractures or dislocations. This study found similar performance of acetaminophen-codeine and ibuprofen in analgesic effectiveness among ED patients aged 5-17 years with acute traumatic extremity pain. Both drugs provided measurable analgesia. Patients tolerated them well, with few treatment failures and minimal adverse effects.

compared the treatment of pain in children with arm fractures by ibuprofen 10 mg/kg versus acetaminophen with codeine 1 mg/kg/dose (codeine component). This was a randomized, double-blind, clinical trial of children during the first 3 days after discharge from the emergency department (ED). The primary outcome was failure of the oral study medication, defined as use of the rescue medication. Pain medication use, pain scores, functional outcomes, adverse effects, and satisfaction were also assessed. Three hundred thirty-six children were randomized to treatment, 169 to ibuprofen and 167 to acetaminophen with codeine; 244 patients were analyzed. Both groups used a median of 4 doses (interquartile range 2, 6.5). The proportion of treatment failures for ibuprofen (20.3%) was lower than for acetaminophen with codeine (31.0%), though not statistically significant (difference=10.7%; 95% confidence interval -0.2 to 21.6). The proportion of children who had any function (play, sleep, eating, school) affected by pain when pain was analyzed by day after injury was significantly lower for the ibuprofen group. Significantly more children receiving acetaminophen with codeine reported adverse effects and did not want to use it for future fractures. In conclusion, ibuprofen was at least as effective as acetaminophen with codeine for outpatient analgesia for children with arm fractures. There was no significant difference in analgesic failure or pain scores, but children receiving ibuprofen had better functional outcomes. Children receiving ibuprofen had significantly fewer adverse effects, and both children and parents were more satisfied with ibuprofen. Ibuprofen is preferable to acetaminophen with codeine for outpatient treatment of children with uncomplicated arm fractures.

2.5.4.4 Dosing

In adults and adolescents over 50 kg the usual dose of paracetamol is 650-1000 mg orally 4-6 hours, as needed. The maximum daily dose is 3250-4000 mg.

In adolescents and children under 60 kg, 10-15 mg/kg 4-6 hours as needed, The maximum daily dose is 100 mg/kg.

A longer dosing interval and a reduced total daily dose of paracetamol may be warranted in cases of severe renal impairment (GFR 30 mL/min or less). It has been recommended to increase the dosing interval to every 8 hours in paediatric patients with severe renal failure (GFR less than 10 mL/min). No dose adjustments are required for paediatric patients with GFR 10 mL/min or greater

Reduction of the total daily dose of paracetamol may be warranted when hepatic function is impaired. Paracetamol is contraindicated in patients with severe hepatic impairment or severe active liver disease.

It must be realized that the half-life is based on the sulfate and glucuronide conjugates, which account for 92% of its metabolism. The toxic metabolite accounting for 4% of the metabolism may not be reflected in the half-life

In adults the initial dosage of codeine is 15 to 60 mg orally every 4 hours as needed; individually titrate to a dose that provides adequate analgesia while minimizing adverse reactions. The maximum daily dose is 360 mg
In clinical trials of acute pain in children codeine was administered in 1-1.5 mg/kg/dose

In clinical studies paracetamol/codeine combination was administered in various doses (from 300/30 mg to 1000 mg). In acute pain states dose ranged from 300/30 mg through 500/30 mg and 600/60 mg to 1000/30 mg and 1000/60 mg

In chronic pain states doses ranged from 300/30 mg or 500/30 mg to 1000/60 mg Daily doses ranged from 1500/90 mg to 4000/240 mg.

In children and adolescents, paracetamol/codeine was dosed according to the codeine content of 1 mg/kg

2.5.4.5 Summary of Efficacy

Earlier studies indicated that there is some evidence that codeine adds to the analgesic effects of paracetamol, using pain relief or pain intensity scores as outcomes.

A Cochrane review confirms previous findings that combining paracetamol with codeine provided clinically useful levels of pain relief in about 50% of patients with moderate to severe postoperative pain, compared with under 20% with placebo. New information for remedication shows that the combination extended the duration of analgesia by about one hour compared to treatment with the same dose of paracetamol alone. At higher doses, more participants experienced



adequate pain relief, but the amount of information available for higher doses was small, and based on limited information.

Acetaminophen/codeine combination is effective in the treatment of pain, through a synergistic action of the two molecules, and is not inferior to NSAIDs. Side effects of acetaminophen/codeine are usually minor, differently from NSAIDs, which may induce some potentially life threatening conditions.

2.5.5. Overview of Safety

a) Paracetamol

Due to its widespread use, the clinical experience with paracetamol is even broader. The safety and tolerability of paracetamol has been reviewed [REDACTED]

Adverse effects of paracetamol are rare and usually mild, although haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Skin rashes and other hypersensitivity reactions occur occasionally. Hypotension has been reported rarely with parenteral use. Overdosage with paracetamol can result in severe liver damage and sometimes acute renal tubular necrosis.

Allergic reactions to paracetamol have been reported, ranging from rashes [REDACTED] to bronchospasm and anaphylactic shock.

Frequent use of paracetamol may contribute to asthma morbidity and (allergic) rhinitis in adults [REDACTED]

b) Codeine

Similar to other opioids, adverse effects of codeine are usually dose related. They affect mainly the gastrointestinal tract (nausea, vomiting and constipation), the central nervous system (sedation, dizziness, cognitive impairment, respiratory depression and myoclonus), the skin (pruritus) and the urinary tract (possible urinary retention). Except for constipation, tolerance to these effects usually develops rapidly. Patients who develop nausea and vomiting may be prescribed antiemetics, e.g. low doses of haloperidol or metoclopramide.

While patients taking codeine-containing medication are advised not to operate machinery if affected by dizziness or sedation, a study did not reveal any significant impairment in performance due to the three therapeutic doses of codeine/paracetamol (20/400, 40/800, 60/1200 mg) used in healthy young volunteers [REDACTED]. However, the relationships between drug blood concentration and behavioural measures suggest that an inter-subject variability in blood concentration may influence the power of the observed drug effect.

Although opioids offer potent analgesia for severe acute and chronic noncancer pain, adverse gastrointestinal effects potentially undermine their clinical utility. In particular, between 40% and 95% of patients develop opioid-induced constipation (OIC). Therefore, there is a consensus that patients should commence laxatives at the start of opioid therapy and continue throughout treatment. Nevertheless, laxatives are not routinely coprescribed with opioids. Even when concurrent laxatives are prescribed, approximately half the patients treated for OIC do not achieve the desired improvement. Moreover, laxatives do not target the underlying cause of OIC (opioid binding to the μ -receptors in the enteric system) and as such are not very effective at managing OIC. [REDACTED]

c) Paracetamol Codeine Combination

In the studies analysed by a meta-analysis, relative risk estimates were calculated for addition of codeine 60 mg to paracetamol 600/650 mg for the most commonly reported adverse effects ('drowsiness'/somnolence', 331 patients; 'dizziness', 290 patients; and nausea/vomiting, 342 patients). The pooled data showed no significant difference between paracetamol plus 60 mg codeine and the same dose of paracetamol alone for any adverse effect. No additional safety data were reported in the update of this meta-analysis.

In another systematic literature review with meta-analysis of this fixed combination, of the 24 trials eligible for the safety analysis, six were excluded because they did not provide safety data or safety data were not categorised per treatment group. Pooled analyses of the occurrence of adverse effects did not reject the assumption of homogeneity across single dose and multidose studies. Table 12 shows the pooled safety results for single dose and multidose studies. No serious or unexpected adverse event was noted.

Table 12. Frequency of adverse effects in studies of paracetamol-codeine combinations versus paracetamol alone

Source	Paracetamol-codeine combination	Paracetamol	Pooled rate ratio (95% confidence interval)
Single dose studies (n = 15)			
No of patients reporting ≥1 event	484	488	1.1 (0.8 to 1.5)
No with adverse reaction	116	100	
No of events:			
Dizziness	14	11	
Drowsiness	39	35	
Nausea	18	17	
Vomiting	6	7	
Other	43	41	
Multidose studies (n = 3)			
No of patients reporting ≥1 event	307	164	2.5 (1.5 to 4.2)
No with adverse reaction	122	37	
No of events:			
Dizziness	42	2	
Drowsiness	12	2	
Nausea	69	9	
Vomiting	19	3	
Constipation	17	7	
Other	90	38	

Concerns about the cerebrovascular and cardiovascular safety of acetaminophen have recently been raised. In a nested-case-control study, it was determined whether acetaminophen or an acetaminophen-codeine combination is associated with an increased risk of acute cerebrovascular and cardiovascular events (ACCEs) in patients with osteoarthritis. The source was: Health Search IMS Health Longitudinal Patient Database. A total of 36,754 adults with a diagnosis of osteoarthritis and an incident (first-time) prescription of NSAIDs between January 2002 and June 2012 were identified; of these patients, cases were defined as those who had a diagnosis of an ACCE during the follow-up.

period (index date was the date of ACCE diagnosis; 2182 cases). For each case, up to five controls were randomly selected who were matched based on age, sex, month and year of cohort entry, and duration of follow-up (10,301 controls). Matched controls were assigned the same index date as their respective cases. For each case and matched controls, all prescriptions of acetaminophen-containing medicines filled during follow-up were identified. The risk of ACCEs was investigated with respect to the recency of use of acetaminophen and/or an acetaminophen-codeine combination. Patients were classified as current (0-90 days preceding index date), recent (91-180 days), or past (181-365 days) acetaminophen users, or nonusers (longer than 365 days), with nonusers representing the reference category. Conditional logistic regression was estimated to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Of the 36,754 patients with osteoarthritis and newly prescribed NSAIDs, the incidence rate of ACCEs was 117.6 per 10,000 person-years. No significant association between exposure to acetaminophen-containing medications and ACCEs was observed in current (OR 1.22, 95% CI 0.96-1.55), recent (OR 1.12, 95% CI 0.80-1.55), or past users (OR 1.13, 95% CI 0.86-1.48). A secondary analysis evaluating exposure to acetaminophen monotherapy or acetaminophen-codeine combination therapy showed similar results for current users. Their findings indicate that no association can be made between the use of acetaminophen and/or an acetaminophen-codeine combination and the occurrence of ACCEs. This information contributes to support clinicians in the choice of acetaminophen therapy for osteoarthritis-related pain, especially in those patients presenting with cerebrovascular and cardiovascular morbidities or related risk factors.

Pharmacovigilance

Three 'weak' opioid analgesics in association with paracetamol are marketed in France as step 2 analgesics: dextropropoxyphene, tramadol and codeine. These combinations are involved in several adverse drug reactions (ADRs), but no data are available about their comparative reporting rate. [REDACTED] compared the reporting rate of ADRs between tramadol/paracetamol (TRM+P), codeine/paracetamol (COD+P) and dextropropoxyphene/paracetamol (DXP+P). All spontaneous reports submitted to the French Pharmacovigilance Database from 1 January 1987 to 31 December 2006 suspected to be induced by one of the three step 2 analgesic combinations (DXP+P, TRM+P, COD+P) were extracted. Their consumption for the same period was obtained from the French Drug Agency. The number of ADRs, serious ADRs and different organ classes of ADRs were compared according to their consumption. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each variable using DXP+P as reference. The reporting rate of ADRs was calculated as 24.9/100 000 person-years for DXP+P, 44.5/100 000 person-years for TRM+P and 12.5/100 000 person-years for COD+P. The reporting rate (OR 0.56, 95% CI 0.50, 0.63) and 'seriousness>>' (OR 0.65, 95% CI 0.53, 0.80) of ADRs were significantly higher with TRM+P than with DXP+P. However, hepatobiliary ADRs were significantly more frequent with the DXP+P combination (OR 2.62, 95% CI 1.59, 4.37). In contrast, the reporting rate (OR 1.99, 95% CI 1.82, 2.18) and 'seriousness' (OR 2.64, 95% CI 2.24, 3.11) of ADRs were significantly higher with DXP+P than with COD+P. Among the three step 2 analgesic combinations, reporting rate and 'seriousness' of ADRs are the highest with TRM+P and the lowest with COD+P.

A more recent pharmacovigilance study [REDACTED] [REDACTED] analysed the ADRs of analgesic medicines in Romania. The frequency of ADRs of paracetamol-codeine combinations (9.1%) was lower than other opioids or paracetamol alone (26.1%) =Table 13).

Table 13. Most frequently suspected medicines for each analgesic class* [REDACTED]

Analgesics-antipyretics (n = 23)	%	Opioids (n = 22)	%	NSAIDs (n = 18)	%	Anticonvulsants (n = 11)	%
Metamizole	47.8	Pethidine	40.9	Ibuprofen	44.4	Pregabalin	63.6
Paracetamol	26.1	Fentanyl	13.6	Ketoprofen	22.2	Carbamazepine	18.2
Aspirin	13.0	Tramadol	13.6	Diclofenac	16.6	Gabapentin	18.2
Aspirin, paracetamol and caffeine	8.7	Morphine	9.1	Aceclofenac	5.6		
Paracetamol, propyphenazone and caffeine	4.4	Codeine and paracetamol	9.1	Etoricoxib	5.6		
		Tramadol and paracetamol	9.1	Lornoxicam	5.6		
		Oxycodone	4.6				

*For antidepressants and triptans, one case reported for each class (duloxetine and sumatriptan, respectively).

Adverse reactions according to MedDRA convention:

The frequency of undesirable effects is classified as follows: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data) [REDACTED] [REDACTED]

Blood and lymphatic system disorders

Rare: Thrombocytopenia, haemolytic anaemia, agranulocytosis, leukopenia.

Very rare: Pancytopenia.

Immune system disorders

Rare: Allergic reactions.

Psychiatric disorders

Rare: Sleep disturbances.

Nervous system disorders

Common: Drowsiness, headache.

Uncommon: Dizziness.

Eye disorders

Uncommon: Disturbances of vision.

Vascular disorders

Common: Bouts of perspiration.

Respiratory, thoracic and mediastinal disorders

Rare: Breathlessness.

Gastrointestinal disorders

Common: Nausea, constipation, vomiting.

Uncommon: Dryness of the mouth.

Hepatobiliary disorders

Rare: Hepatotoxicity, liver damage which may lead to liver failure.

Very rare: Acute pancreatitis.

Skin and subcutaneous tissue disorders

Rare: Rash, urticaria erythema.

Renal and urinary disorders

Very rare: Renal damage (may occur in long-term therapy.)

General disorders and administration site conditions

Common: Fatigue.

Very rare cases of serious skin reactions have been reported.

Table 14. Frequency of adverse effects in studies of paracetamol-codeine combinations versus paracetamol alone [REDACTED] [REDACTED]

Special Patient Groups

Children and Adolescents

[REDACTED] compared the treatment of pain in children with arm fractures by ibuprofen 10 mg/kg versus acetaminophen with codeine 1 mg/kg/dose (codeine component). This was a randomized, double-blind, clinical trial of children during the first 3 days after discharge from the emergency department (ED). The primary outcome was failure of the oral study medication, defined as use of the rescue medication. Pain medication use, pain scores, functional outcomes, adverse effects, and satisfaction were also assessed. Three hundred thirty-six children were randomized to treatment, 169 to ibuprofen and 167 to acetaminophen with codeine; 244 patients were analyzed. Both groups used a median of 4 doses (interquartile range 2, 6.5). The proportion of treatment failures for ibuprofen (20.3%) was lower than for acetaminophen with codeine (31.0%), though not statistically significant (difference=10.7%; 95% confidence interval -0.2 to 21.6). The proportion of children who had any function (play, sleep, eating, school) affected by pain when pain was analyzed by day after injury was significantly lower for the ibuprofen group. Significantly more children receiving acetaminophen with codeine reported adverse effects and did not want to use it for future fractures. In conclusion, ibuprofen was at least as effective as acetaminophen with codeine for outpatient analgesia for children with arm fractures. There was no significant difference in analgesic failure or pain scores, but children receiving ibuprofen had better functional outcomes. Children receiving ibuprofen had significantly fewer adverse effects, and both children and parents were more satisfied with ibuprofen. Ibuprofen is preferable to acetaminophen with codeine for outpatient treatment of children with uncomplicated arm fractures.

Table 15. Adverse events

Adverse Effect	Acetaminophen With Codeine, Ibuprofen,		Difference, % (95% CI)
	%	%	
Any effect (n=234)	50.9	29.5	21.4 (9.1 to 33.7)
Nausea (n=231)	18.0	5.0	13 (4.8 to 21.1)
Vomiting (n=230)	11.0	2.4	8 (2.0-15.0)
Drowsy (n=231)	30.6	20.8	9.8 (-1.4 to 21)
Dizzy (n=231)	5.4	2.5	2.9 (-2.1 to 8.0)
Constipation (n=233)	1.7	2.5	-0.7 (-4.3 to 3.0)
Other (n=232)	10.8	6.6	4.1 (-3.1 to 11.4)

CMDh endorsed PRAC recommendation on restrictions on use of codeine for pain relief in children. Codeine is now only indicated in patients older than 12 years of age for the treatment of acute moderate pain that cannot be relieved by other analgesics such as paracetamol or ibuprofen (alone).

- Codeine should be used at the lowest effective dose for the shortest period of time.
- Codeine is now contraindicated: in all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome and in patients of any age who are known to be CYP2D6 ultra-rapid metabolisers (up to approximately 10% of Caucasians are CYP2D6 ultra-rapid metabolisers, but prevalence differs according to racial and ethnic group), due to an increased risk of developing serious and life-threatening adverse reactions; and in women who are breastfeeding.
- Codeine is not recommended for use in children in whom respiratory function might be compromised as this may worsen the symptoms of morphine toxicity

Elderly

The frequency of adverse effects of paracetamol-codeine combination in the elderly patients did not differ from that of younger population. The most common AEs (in%) in 219 patients with OA were constipation (32%), nausea (25%), vomiting (8%) and dizziness (6%)

In elderly women with OA, experienced a relatively high rate (27.9%) of discontinuation due to AEs, typical to opiate therapy: nausea, vomiting and drowsiness. They stress the careful up-titration of drug doses, and comprehensive patient treatment, in particular routine management with appropriate laxative therapy.

Special Warnings and Precautions for Use

There are conditions where codeine, similar to other opioids, are contraindicated:

- Acute asthma and respiratory depression – Morphine is a primary and continuous depressant of respiration. Morphine has the potential to precipitate or exacerbate asthmatic attacks and should be avoided in patients with a history of asthma.

- Acute alcohol intoxication (alcoholism) – Alcohol may potentiate the hepatotoxicity of paracetamol. Alcohol may enhance sedative and hypotensive effect and increase risk of respiratory depression.
- Head injury and raised intracranial pressure – The respiratory depressant effects of opioids and the related capacity to elevate intracranial pressure must be considered in the presence of head injury or an already elevated intracranial pressure. While head injury per se does not constitute an absolute contraindication to the use of opioids, the possibility of exaggerated depression of respiration and the potential need to control ventilation of the patient must be considered.
- Hepatocellular insufficiency – All opioid analgesics are metabolized by the liver and should be used with caution in patients with hepatic disease because increased bioavailability after oral administration or cumulative effects may occur.
- Biliary tract surgery – Morphine and related opioids produce increased pressure in the biliary tract.
- MAO inhibitors may enhance CNS effects of codeine (excitation or depression) (see PD Interactions).
- Children below 12 years of age – Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine.
- Paediatric patients who undergo tonsillectomy/adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life threatening adverse reactions.
- During breast-feeding.
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers. Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

Care should be observed in administering the product to any patient, whose condition may be exacerbated by opioids, including

- the elderly, who may be sensitive to their central and gastro-intestinal effects;
- those on concurrent CNS depressant drugs for enhanced sedative effects;
- those with prostatic hypertrophy and those with inflammatory or obstructive bowel disorders, since morphine, exerting antimuscarinic effects, may enhance the symptoms;
- Addison's disease – since opiates may block ACTH response;
- myasthenia gravis – due to higher of respiratory depression;
- hypothyroidism – Severely hypothyroid patients have impaired ventilatory drive and respiratory muscle weakness, which renders them more sensitive to the effects of sedatives, opioids, and neuromuscular blocking agents.

Codeine is not recommended for use in children and adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks [REDACTED]. Risk factors include conditions associated with hypoventilation, such as neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity, in particular respiratory depression [REDACTED].

Pregnancy and Breast-feeding

There is inadequate evidence of the safety of codeine in human pregnancy, but there is epidemiological evidence for the safety of paracetamol. Animal studies with paracetamol and with codeine do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Co-codamol during pregnancy. Codeine should not be used during breastfeeding. At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

Paracetamol remains the first line for the treatment of pain and fever in pregnancy. Recently published epidemiological studies suggested a possible association between paracetamol exposure in utero and attention-deficit-hyperactivity disorder/hyperkinetic disorder (ADHD/HKD) or adverse development issues in children. However, the effects observed are in the weak to moderate range, and limitations in the studies' design prevent inference on a causal association with ADHD/HKD or child neurological development. In parallel, recent animal data showed that cognition and behaviour may be altered following exposure to therapeutic doses of paracetamol during early development. These effects may be mediated by interference of paracetamol with brain-derived neurotrophic factor, neurotransmitter systems (including serotonergic, dopaminergic, adrenergic, as well as the endogenous endocannabinoid systems), or cyclooxygenase-2. However, no firm conclusion can be made on the relevance of these observations to humans. [REDACTED] conclude that additional well-designed cohort studies are necessary to confirm or disprove the association. In the context of current knowledge, paracetamol is still to be considered safe in pregnancy and should remain the first-line treatment for pain and fever.

[REDACTED] analysed the effect of codeine on pregnancy outcome. Pregnancy outcomes of 2,666 women who used codeine during pregnancy were compared with 65,316 women who used no opioids during pregnancy. Information on maternal sociodemographic and medical characteristics, potential confounders, and pregnancy outcome was obtained from The Norwegian Mother and Child Cohort Study [den norske Mor & barnundersøkelsen (MoBa)] data set and the Medical Birth Registry of Norway (MBRN) data set. The data sets were linked via the maternal personal identification number. Associations between codeine therapy and pregnancy outcomes were identified using logistic regression analyses. No significant differences were found in the survival rate [adjusted odds ratio (OR) 0.9, 95% CI 0.6-1.5] or the congenital malformation rate (adjusted OR 0.9, 95% CI 0.8-1.1).

between codeine-exposed and unexposed infants. Codeine use anytime during pregnancy was associated with planned Caesarean delivery (adjusted OR 1.4, 95% CI 1.2-1.7; $P < 0.0001$). Third-trimester use was associated with acute Caesarean delivery (adjusted OR 1.5, 95% CI 1.3-1.8; $P < 0.0001$) and postpartum haemorrhage (adjusted OR 1.3, 95% CI 1.1-1.5; $P < 0.0001$). No significant associations with other adverse pregnancy outcomes were found. No effects of maternal codeine intake during pregnancy were observed on infant survival or congenital malformation rate. These findings are reassuring; however, the association with acute Caesarean delivery and postpartum haemorrhage may justify a certain level of caution when administering codeine toward the end of pregnancy.

reported on a breastfed infant who succumbed to opioid toxicity following exposure to morphine, the active metabolite of codeine, which was prescribed to his mother who was a CYP2D6 ultrarapid metaboliser. They conducted a systematic review of the medical literature using several databases. The Naranjo Adverse Drug Reaction Probability Scale (NADRPS) was used to examine causality. In addition to their case report, three abstracts and two full-length studies reported adverse drug reactions (ADRs) in infants exposed to codeine in breast milk. In total, 35 infants were identified. Specifically, ADRs were described as unexplained episodes of drowsiness, apnoea, bradycardia, and cyanosis in suckling infants. Using the NADRPS, codeine was found to be a definite cause of CNS depression in breastfed infants. The authors conclude that the use of codeine by breastfeeding mothers can cause adverse CNS events in breastfed infants. Physicians should recognize codeine use during breastfeeding as a cause of CNS depression in infants, and breastfeeding mothers should be educated on these adverse events before receiving codeine.

Abuse, Addiction

Although codeine is often described as a weak opioid analgesic, codeine dependence is a well recognised complication of long-term use. Substance-dependent individuals who escalate their dose of medication above recommended amounts are at risk of harm from the accompanying simple analgesic, including toxicity from non-steroidal anti-inflammatory drugs, such as ibuprofen or paracetamol. investigated morbidity related to misuse of over-the-counter (OTC) codeine-ibuprofen analgesics. It was a prospective case series collected from Victorian hospital-based addiction medicine specialists between May 2005 and December 2008. Twenty-seven patients with serious morbidity were included, mainly with gastrointestinal haemorrhage and opioid dependence. The patients were taking mean daily doses of 435–602 mg of codeine phosphate and 6800–9400 mg ibuprofen. Most patients had no previous history of substance use disorder. The main treatment was opioid substitution treatment with buprenorphine-naloxone or methadone. The authors conclude that although codeine can be considered a relatively weak opioid analgesic, it is nevertheless addictive, and the significant morbidity and specific patient characteristics associated with overuse of codeine combination.

Misuse of opioid analgesics is an emergent global public health concern. Codeine has an identified abuse liability, given its effect and development of tolerance within a short timeframe on regular or excessive use. Misuse of products containing codeine can occur following initial legitimate therapeutic use of the

drug for the treatment of pain and also from initial non-therapeutic use, where the drug is consumed to produce intoxication [REDACTED]

Overdosage

In case of overdose, the symptoms may include the signs and symptoms of toxicity of codeine or paracetamol or of both these active ingredients.

Codeine containing analgesics are commonly taken in overdose, but the frequency of respiratory depression is unknown. [REDACTED] investigated whether paracetamol-codeine combination overdoses caused respiratory depression more than paracetamol alone. They reviewed deliberate self-poisoning admissions with paracetamol (>2 g) and paracetamol-codeine combinations presenting to a tertiary toxicology unit (1987-2013). Demographic information, clinical effects, treatment (naloxone, length of stay [LOS], mechanical ventilation) were extracted from a prospective database. Primary outcome was naloxone requirement or ventilation for respiratory depression. From 4488 presentations, 1376 admissions were included with paracetamol alone (929), paracetamol-codeine combinations (346) or paracetamol-codeine-doxyamine combinations (101) without co-ingestants. Median age was 23 years (12-89 years); 1002 (73%) were female. Median dose was 12 g (interquartile range [IQR]: 7.5-20 g). Median LOS was 16 h (IQR: 6.5-27 h) and 564 (41%) were given acetylcysteine. Significantly larger paracetamol doses were ingested and more acetylcysteine given in paracetamol alone versus paracetamol combination overdoses. Seven out of 1376 patients were intubated or received naloxone (0.5%; 95% CI: 0.2-1.1%), three intubated, three given naloxone and one both. Three out of 929 patients ingesting paracetamol alone (0.3%; 95% CI: 0.1-1%) required intubation or naloxone, compared to two out of 346 ingesting paracetamol-codeine combinations (0.6%; 95% CI: 0.1-2.3%; absolute difference, 0.26%; 95% CI: -0.7-1.2%; P = 0.62). Two out of 101 patients ingesting paracetamol-codeine-doxyamine combinations (2%; 95% CI: 0.3-8%) required intubation or naloxone. Four patients were intubated for reasons other than respiratory depression: hepatotoxicity (2), retrieval (1), no data (1). Two out of 929 (0.2%) paracetamol alone overdoses had a Glasgow coma score < 9 compared to three out of 346 (0.9%) in the paracetamol-codeine group. The authors conclude that paracetamol-codeine combination overdoses are rarely associated with severe respiratory depression, with only two given naloxone and none intubated for respiratory depression.

An overdose is of particular concern in young children. Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported. Liver damage is possible in adults who have taken 7.5-10 g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Nausea and vomiting are prominent symptoms of codeine toxicity and if there is evidence of circulatory and respiratory depression, suggested treatment is gastric



lavage and catharsis. If CNS depression is severe, assisted ventilation, oxygen and parenteral naloxone may be needed.

Patients in whom oxidative liver enzymes have been induced, including alcoholics and those receiving barbiturates and patients who are chronically malnourished, may be particularly sensitive to the toxic effects of paracetamol in overdose.

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention and any adult or adolescent who had ingested around 7.5 g or more of paracetamol in the preceding 4 hours or any child who has ingested 150 mg/kg of paracetamol in the preceding 4 hours should undergo gastric lavage. Paracetamol concentrations in blood should be measured later than 4 hours after overdose in order to be able to assess the risk of developing liver damage (via the paracetamol overdose nomogram). Administration of oral methionine or intravenous N-acetylcysteine (NAC) which may have a beneficial effect up to at least 48 hours after the overdose, may be required. Administration of intravenous NAC is most beneficial when initiated within 8 hours of overdose ingestion. However, NAC should still be given if the time to presentation is greater than 8 hours after overdose and continued for a full course of therapy. NAC treatment should be started immediately when massive overdose is suspected. General supportive measures must be available. Irrespective of the reported quantity of paracetamol ingested, the antidote for paracetamol, NAC, should be administered orally or intravenously, as quickly as possible, if possible, within 8 hours following the overdose.



2.5.6. Benefits and Risks Conclusions

Management of acute and chronic pain is important, not only for the patient's well-being, but also to prevent long-term complications and morbidity. The response to nociceptor sensory input is a multifactorial process, with both central and peripheral mechanisms involved. Several neurotransmitters and receptors participate in the transmission and modulation of this multifaceted process and thus, it is often difficult to achieve complete pain control using a single pharmacological agent without significant adverse events. Hence, combining, two analgesic agents with complementary mechanisms of action may enhance analgesia and at the same time reduce the risk of adverse events. Furthermore, the ease of taking two analgesic agents as a fixed tablet may improve compliance.

Combining drugs from different classes with different modes of action may offer opportunity to optimise efficacy and tolerability, using lower doses of each drug to achieve the same degree of pain relief.

The mode of action of paracetamol has been uncertain, but it is now generally accepted that it inhibits COX-1 and COX-2 through metabolism by the peroxidase function of these isoenzymes. This results in inhibition of phenoxyl radical formation from a critical tyrosine residue essential for the cyclooxygenase activity of COX-1 and COX-2 and prostaglandin (PG) synthesis. Although it is a prostaglandin synthetase inhibitor, the synthetase system in the CNS rather than the periphery appears to be more sensitive to it. This may explain paracetamol's lack of appreciable anti-inflammatory activity. Paracetamol also exhibits antipyretic activity. Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

Following oral administration paracetamol and codeine phosphate is absorbed rapidly, the mean time to maximum plasma concentrations is ~1 hour. The bioavailabilities of paracetamol and codeine when given as the combination are similar to those when they are given separately. The relative bioavailability ranges from 38-76% in rats, 85% to 98% in humans. Paracetamol appears to be widely distributed throughout most body fluids except fat. The apparent volume of distribution of paracetamol is 0.95 L/kg. A relatively small proportion (10% to 25%) of paracetamol is bound to plasma proteins and binding is only slightly increased in plasma concentrations associated with overdose. The sulphate and glucuronide metabolites do not bind to plasma proteins even at relatively high concentrations. Low protein binding and low molecular weight allow paracetamol to pass through the blood-brain barrier. Paracetamol is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: a) conjugation with glucuronide; b) conjugation with sulphate; c) oxidation via the cytochrome, P450-dependent, mixed-function oxidative enzyme pathway. The biologic half-life of paracetamol is approximately 2 to 3 hours in the usual dosage range. Paracetamol is eliminated from the body primarily by formation of glucuronide and sulphate conjugates in a dose-dependent manner. Codeine is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by the liver, spleen, and kidneys, the volume of distribution is: 3.5 L/kg. Plasma protein binding is 7-25%. Plasma half-life is 2.5-3.0 hours. Codeine is mainly

metabolized by glucuronidation to codeine-6-glucuronide. Minor routes of metabolism include O- demethylation leading to morphine, N-demethylation to norcodeine and after both O- and N-demethylation formation of normorphine. Morphine and norcodeine are further transformed in glucuroconjugates. Unchanged codeine and its metabolites are mainly excreted by urinary route within 48h ($84.4 \pm 15.9\%$). The O-demethylation of codeine to morphine is catalyzed by CYP2D6 which shows genetic polymorphism that may affect the efficacy and toxicity of codeine. Genetic polymorphism in CYP2D6 leads to ultra-rapid, extensive and poor metaboliser phenotypes.

The orally administered fixed combination tablet of paracetamol plus codeine provides effective analgesia in patients with moderate to severe acute pain and those with chronic painful conditions. The efficacy and safety of this combination has been extensively studied in randomized controlled trials in acute (e.g. dental, postoperative) pain and chronic pain states, such as osteoarthritis and other rheumatologic conditions.

Paracetamol/codeine combination is effective in the treatment of pain, through a synergistic action of the two molecules, and is not inferior to NSAIDs. Adverse effects of paracetamol/codeine are usually minor, differently from NSAIDs, which may induce some potentially life threatening conditions.

The most commonly reported adverse effects during the clinical trials performed with the paracetamol/codeine combination were nausea, dizziness and somnolence, observed in more than 10 % of the patients.

Paracetamol/codeine combination is indicated for the relief of severe pain. Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

The dose for adults is 1000 mg/30 mg to be taken every four hours as required, up to a maximum of 4000 mg/120 mg in any 24-hour period. In children (12-15 years of age) 500 mg/15 mg every four hours as required, up to a maximum of 2000 mg/60 mg in any 24-hour period. In elderly patients the usual dosages may be used, however the careful up-titration of drug doses, and comprehensive patient treatment, in particular routine management with appropriate laxative therapy are advised.

For adults and adolescents under 50 kg, the daily dose is determined by body weight; the maximum daily dose of paracetamol of 60 mg/kg/24 hours not be exceeded. For children and adolescents aged 12 to 18 and body weight between 33 and 50 kg, the amount per dose is weight dependent, specifically codeine 0.5-1 mg/kg and paracetamol 15 mg/kg per dose. The recommended dose for children over 12 years old should be 1 tablet (500 mg/30 mg) depending on the severity of the pain and the patient's response, up to 4 times daily if necessary. A period of 6 hours must be respected between the doses. The maximum daily dose of paracetamol of 60 mg/kg and codeine of 240 mg should not be exceeded.

Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine.



Patients should be advised not to operate machinery if affected by dizziness or sedation.

The therapy is contraindicated in case of hypersensitivity to codeine, paracetamol (or to any of the excipients); in conditions where morphine and opioids are contraindicated e.g., acute asthma, respiratory depression, acute alcoholism, head injuries, raised intra-cranial pressure, hepatocellular insufficiency and following biliary tract surgery; monoamine oxidase inhibitor therapy, concurrent or within 14 days; during breastfeeding; in patients for whom it is known they are CYP2D6 ultra-rapid metaboliser.

Care should be observed in administering the product to any patient, whose condition may be exacerbated by opioids, including the elderly, who may be sensitive to their central and gastro-intestinal effects, those on concurrent CNS depressant drugs, those with prostatic hypertrophy and those with inflammatory or obstructive bowel disorders, Addison's disease or myasthenia gravis. Care should also be observed if prolonged therapy is contemplated.

This combination is also contraindicated in all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions.

Due to interactions, concomitant use is not recommended with CNS depressants (including other opioid analgesics, tranquilisers, sedative hypnotics and alcohol), MAO inhibitors or tricyclic antidepressants and anticholinergics. Isoniazid may increase the risk of hepatotoxicity of paracetamol. Antiepileptics, such as carbamazepine, phenobarbital, phenytoin and primidone can reduce the effects of paracetamol and increase the risk of hepatotoxicity. Paracetamol may increase the elimination half-life of chloramphenicol. Oral contraceptives may increase its rate of clearance. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

There is inadequate evidence of the safety of codeine in human pregnancy, but there is epidemiological evidence for the safety of paracetamol. Animal studies with paracetamol and with codeine do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Co-codamol during pregnancy. Codeine should not be used during breastfeeding. At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

Misuse of opioid analgesics is an emergent global public health concern. Codeine has an identified abuse liability, given its effect and development of tolerance within a short timeframe on regular or excessive use. Misuse and abuse have been reported with codeine-containing combinations. Therefore, higher doses and longer treatment than advised should be avoided.



In conclusion, paracetamol codeine combination is a safe and effective in relieving moderate to severe pain if used appropriately (according to the SPC). Since the 500/15 mg and 1000/30 mg strength combinations are positioned between the highest, i.e. 60 mg and the lowest, i.e. 8 mg codeine-containing strengths approved in the EU market, their efficacy and safety is expected to be secured and justified.

Practical experience of codeine, paracetamol, and their combinations on the market in a large number of patients has also confirmed its safety and efficacy. These facts provide sufficient support for its further use.



2.5.7. Literature References

