Review of the Efficacy and Safety of Propoxyphene

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VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary

This review of the efficacy and safety of propoxyphene incorporates information published since our initial review (August 2001). This report update evaluates the evidence addressing the following clinical questions:

1. In VA patients with acute or chronic pain, does the potential analgesic efficacy of DPP alone or in combination with co-analgesics exceed the potential risks of its adverse effects?
2. How does DPP compare with other opioids in cost-effectiveness?
3. Which agents may be used as therapeutic alternatives to DPP?

The objectives of this updated review are to examine any new evidence on the comparative efficacy, effectiveness, safety, tolerability, and cost-effectiveness of DPP; revisit its place in therapy; and recommend possible alternatives to DPP therapy.

Methods. A computerized literature search using search terms for propoxyphene was performed on the PubMed/ Medline (August 2000 to March 2006) and the Cochrane Central Registry of Controlled Trials (to March 2006) databases. Reports of any design were retrieved and evaluated for relevance. In addition, information was obtained from the VAMedWatch database of propoxyphene and other opioid–related adverse drug experiences (ADEs) reported by VA centers as part of the Food and Drug Administration (FDA) MedWatch program from FY2004 to FY2005.

Pharmacologic and pharmacokinetic considerations. The absorption of DPP from the gastrointestinal tract is rapid. The fast rate of absorption is believed to contribute to the rapid deterioration seen in DPP overdoses. DPP undergoes extensive dose-dependent first-pass metabolism and is quickly converted to an active metabolite, norpropoxyphene (NPP), which has very weak analgesic properties. After single doses of DPP, both DPP and NPP may have long elimination half-lives, about 12 and 36 hours, respectively. In elderly (65- to 90-year old) hospitalized patients, the mean half-lives have been reported to be even longer, 35.7 and 53.3 hours, respectively. The recommended dosing interval, however, is every 4 hours. Because of the long biologic half-lives, accumulation of DPP and NPP may occur when the drug is dosed at the recommended dosing interval. Marked interindividual variation in plasma concentrations of DPP have been observed after standard doses due to differences in absorption and biotransformation.

Animal studies have demonstrated that NPP has less neurotoxic effects than DPP but greater cardiotoxic effects due to membrane-stabilizing properties. The local anesthetic properties of DPP and NPP are similar to those of tricyclic antidepressants and Type I antiarrhythmics. *In vivo* data showed that, at high concentrations of drug similar to those observed in fatal DPP overdoses, DPP and NPP block HERG (human ether-a-go-go-related gene) potassium channels, which have been implicated in the mechanism of the long QT syndrome.

Efficacy. In patients with acute pain, *single*-dose DPP ± APAP is not better than NSAIDs and APAP, but combinations of codeine, oxycodone, or tramadol plus APAP are also not better than APAP alone.[53] [QE: I] Meta-analyses suggest that DPP 65 mg + APAP 650 mg is inferior to codeine 60 mg + APAP 1000 mg and similar in efficacy to combinations of codeine 30 to 60 mg plus smaller doses of APAP (300 to 650 mg). Combination oxycodone (5 to 10 mg) + APAP (325, 650, 1000 mg) is similar

to DPP 65 mg + APAP 650 mg; there was insufficient evidence to make a definite conclusion for oxycodone 5 mg + APAP 500 mg.[53] [QE: I] The same dose of combination DPP + APAP is more efficacious than codeine 60 mg or tramadol 50 mg without APAP.[53] [QE: I]

The analgesic efficacy of *multiple* doses of DPP alone or in combination with APAP is inferior to [4 QE: I] or not statistically different from [9 I, 1 II-1] that of NSAIDs or high-dose APAP (3900 to 4000 mg/day) in the treatment of acute pain. Results varied depending on the type of NSAID used.[1][QE: I]

Six RCTs comparing DPP(N) ± APAP to opioids found DPP(N) ± APAP to be similar to [56,62] [55,61] [4 QE: I], [63][1 QE: II-1] or less effective than [60][QE: I] the opioid preparation in the treatment of acute pain.

Well-designed RCTs evaluating the efficacy of DPP in the treatment of chronic pain or under steady-state conditions are lacking. Limited data suggest that the analgesic efficacy of DPP(N) ± APAP in patients with chronic pain is similar to that observed in the treatment of acute pain: DPP(N) ± APAP is no better than NSAIDs or other opioids.[68-70][3 QE: I], [87] [QE: II-1] The analgesic efficacy of titrated DPP (mean dose: 60 ± 22.5 mg/day) was not statistically different from low-dose morphine SR (20.1 ± 6.0 mg/day) in the first 10 days' treatment of cancer pain in opioid-naïve patients. [87] [QE: II-1] However, DPP may be better tolerated than low-dose morphine and may provide adequate pain relief in some opioid-naïve individuals. In addition, contrary to single-dose, acute pain trial results, further benefit was gained from the addition of DPP to an NSAID (diclofenac) in this patient population. These results need to be confirmed in additional chronic pain trials.

There was no evidence to justify the practices of prescribing DPP ± APAP in addition to Step 3 analgesics or as an analgesic placebo.

Safety. Based on published study results, standard therapeutic doses of DPP are generally well tolerated and seem to be associated with few SAEs [47-49][3 QE: I], [26 RCTs, QE: 23 I, 3 II-1]. Based on limited data, DPP may be less tolerated than NSAIDs or APAP [1][I], and more tolerated than codeine + APAP [56][QE: I]. As a WHO Step 2 agent in the treatment of opioid-naïve cancer patients, DPP may be better tolerated than low-dose morphine in some patients [71][QE: II-1]. There was no convincing evidence suggesting that single or multiple doses of DPP ± APAP was associated with a higher frequency of NSAEs than codeine ± APAP. Single doses of DPP + APAP cause dizziness less often than tramadol 100 mg [47][QE: I].

Elderly patients (aged 65 years or older) treated with DPP may be at higher risk of developing hip fractures [90][QE: II-2]. A similar increase in risk was also associated with codeine [91][QE: II-2]. The results of these two studies contradict those of a more recent systematic review and meta-analysis (which did not include the two former studies) that found no increased risk of falls in older patients (> 60 years old) in association with narcotic analgesics [89][QE: I]. The differences in results may be due to differences in inclusion criteria and targeted outcomes (hip fractures versus falls).

More recent information from two retrospective studies that evaluated adverse outcomes or diagnoses associated with the use of DPP in elderly nursing home residents were inconsistent. While one study showed that there was a 2.4-fold greater likelihood of adverse health outcomes in DPP-treated residents relative to those not treated with potentially inappropriate medications (Beers criteria), the other study showed no adverse events (diagnoses) associated with DPP despite use of this agent by more than one-half of the opioid-treated residents.

There is no convincing data that DPP is more addicting than other opioids. However, the available evidence on the comparative risks of dependency, misuse, or abuse as serious adverse events with DPP relative to other opioids is limited. The problem of DPP misuse that may be considered to be a form of addictive behavior among patients with acute or chronic pain has not been well reported, and

recent U.S. studies comparing DPP with other opioids are lacking. Furthermore, data on the frequency of opioid addiction in veterans is limited.

Serious toxicity, including coma, respiratory depression, pulmonary edema, seizures, cardiac arrhythmias, and death, primarily occurred in patients with certain characteristics associated with intentional or unintentional overdose. The complications often occurred in patients who had a history of misuse (overuse) of DPP or other prescription drugs, who had psychiatric or emotional problems, and who co-ingested alcohol or other CNS depressants with moderate (6 to 20 capsules or tablets) or larger (suicidal) overdoses of DPP(N) ± APAP. The danger of the additive or potentiating effects on the toxicity of the combination of CNS depressants and DPP cannot be overemphasized. In an isolated case, co-ingestion of a sub-lethal quantity of alcohol with just 2 capsules of DPP resulted in death.[88][QE: III] In a few cases, postmortem drug concentrations < 1 µg/ml suggested that deaths could have occurred after ingestion of therapeutic doses of propoxyphene alone, without co-ingestion of other CNS depressants or alcohol. [42][QE: III] Because post-mortem DPP concentrations are highly variable, no conclusions can be made merely because therapeutic DPP concentrations are found in post-mortem blood. The development of SAEs is probably partly dependent on the individual's level of opioid tolerance.[43][QE: III]

In the case of poisonings, there is fairly consistent indirect evidence showing that DPP ± APAP is one of the most toxic products relative to nonopioids and other opioids in intentional overdoses (due to suicide attempt, misuse, or abuse) and unintentional therapeutic errors or misuse.

In U.S. veterans, VAMedWatch data do not support that the use of DPP ± APAP is associated with more adverse drug experiences relative to other opioids.

Potential alternatives to propoxyphene. A recent observational study showed that replacement of DPP, meperidine, or high-dose APAP (approaching 4 g/day) with tramadol in selected elderly residents of a long-term care facility improved pain scores, use of adjunctive medications, and other clinical outcomes. Usage patterns of DPP and other opioids among veterans suggest that hydrocodone and tramadol products are being used as alternatives to DPP, codeine, and oxycodone.

Cost-effectiveness. No pharmacoeconomic studies were found by the literature search. If single-dose efficacy is assumed to predict relative multiple-dose efficacy of the analgesics in acute pain (5-day) treatment, then codeine 60 mg + APAP 1000 (950) mg (as separate components) and oxycodone 5 to 10 mg + APAP 325 to 1000 mg would have comparable or better cost-effectiveness than DPPN 100 (or DPP 65 mg) plus APAP 650 mg or DPP(N) alone. Combination hydrocodone plus APAP has the lowest unit drug cost of the five opioid preparations compared. All preparations of tramadol are less cost-effective than DPP(N) + APAP.

Conclusion. Although new data became available on the single-dose efficacy of propoxyphene and on safety concerns associated with propoxyphene abuse and accidental fatal overdoses, we found no substantive evidence to alter our previous conclusions about the efficacy and safety of propoxyphene relative to other opioids. Our recommendations on the use of propoxyphene in the Veterans Health Administration remain essentially the same as in the previous review.

In the majority of VA patients with mild to moderate acute pain and who do not have certain characteristics associated with intentional or unintentional overdose, single-dose or short-term therapy with DPP ± APAP probably provides adequate analgesia with an acceptable safety profile. The efficacy and safety of long-term therapy with DPP ± APAP for treatment of chronic pain has not been adequately studied.

In patients with certain characteristics associated with intentional or unintentional overdose, the potential for DPP toxicity probably outweighs the drug's potential analgesic benefit. Important safety issues that remain unclear are what is the frequency and risk of serious DPP toxicity among veterans with risk factors, and how does that risk compare with the risk associated with other opioids. Until

these questions are answered, it seems prudent to restrict the use of DPP ± APAP to those veterans who do not have the particular characteristics associated with intentional or unintentional overdose and in whom NSAIDs, extra-strength or high-dose APAP, and other opioids are inadequate, intolerable, or contraindicated.

Based on single doses with similar analgesic efficacy in the treatment of postoperative pain, codeine or oxycodone, and probably hydrocodone, in combination with APAP are just as or more cost-effective than DPP ± APAP and are probably acceptable alternatives for DPP ± APAP. These alternative opioids seem to be slightly safer than DPP ± APAP in intentional or unintentional overdoses. Tramadol products may also be considered alternatives but are the least cost-effective and have been associated with substantial toxicities in veterans.

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Abbreviations

AAPCC	American Association of Poison Control Centers
ADDIS	Alkohol Drog Diagnos InStrument (Swe.)
ADE	Adverse drug event or experience (term used in MedWatch program)
ADR	Adverse [drug] reaction (term used in AAPCC TESS data)
AE	Adverse event
APAP	Acetaminophen
ASA	Aspirin
CI	Confidence interval
CNS	Central nervous system
DAWN	Drug Abuse Warning Network
DPP	*d*-propoxyphene
DPP + APAP	*d*-propoxyphene in combination with acetaminophen
DPP ± APAP	*d*-propoxyphene alone or in combination with acetaminophen
DPP HCl	*d*-propoxyphene hydrochloride
DPPN	*d*-propoxyphene napsylate
DSM	Diagnostic and Statistical Manual of Mental Disorders
ED	Emergency department
FDA	Food and Drug Administration
%maxTOTPAR	percentage of the maximum possible for the area under the curve of pain relief (categorical scale) against time; also percentage of maximal total pain relief
ME	Medical examiner
NMDA	N-methyl-D-aspartate
NNH	Number-needed-to-harm
NNT	Number-needed-to-treat
NPDB	National Pain Data Bank
NPP	Norpropoxyphene
NSAE	Nonserious adverse event
NSAID	Nonsteroidal anti-inflammatory drug
PBM-MAP	Pharmacy Benefits Management-Medical Advisory Panel
RCT	Randomized controlled trial
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation

SUDDS	Substance Use Disorder Diagnostic Schedule
TESS	Toxic Exposure Surveillance System
VAMC	Veterans Affairs Medical Center
VAS	Visual analogue scale
VISN	Veterans Integrated Service Network
WHO	World Health Organization

1 Introduction

The opioid analgesic *d*-propoxyphene (DPP) has remained a contentious drug, identified as an agent with a low benefit-to-risk ratio[2,3] yet prescribed to a relatively large extent, particularly in the elderly.[4-15] The Beers criteria, created by expert panel consensus, consider DPP a potentially inappropriate medication (with a low severity rating) for older adults aged 65 years and older because it is no better than acetaminophen (APAP) yet has the adverse effects of other narcotics.[2] Yet experts disagree on the appropriateness of using DPP, and the Beers criteria have been criticized for listing DPP as a potentially inappropriate medication for older adults in the absence of clinical evidence.[16]

Several events have prompted us to update our review of the efficacy and safety of DPP. In late January 2005, the Committee on Safety of Medicines advised the gradual withdrawal of the combination DPP-APAP product from the U.K. market because of low efficacy and potential for fatal intentional or unintentional overdoses. In early 2006, the Public Citizen group petitioned the Food and Drug Administration (FDA) to phase out DPP from the U.S. market because it was an addictive agent with safer alternatives and had been associated with more than 2000 accidental deaths. Within the VHA, pharmacy benefit administrators are once again asking whether DPP should remain nonformulary and made available to veterans.

2 Clinical questions and objectives

This report update evaluates the evidence addressing the following clinical questions:

1. In VA patients with acute or chronic pain, does the potential analgesic efficacy of DPP alone or in combination with co-analgesics exceed the potential risks of its adverse effects?
2. How does DPP compare with other opioids in cost-effectiveness?
3. Which agents may be used as therapeutic alternatives to DPP?

The objectives of this review update are to examine any new evidence on the comparative efficacy, effectiveness, safety, tolerability, and cost value of DPP; revisit its place in therapy; and recommend possible alternatives to DPP therapy.

3 Methods

A computerized literature search using the search terms *propoxyphene*, *Darvon*, *Darvocet*, and *co-proxamol* was performed on the PubMed/Medline (August 2000 to March 2006, limited to adults and English language) and the Cochrane Central Registry of Controlled Trials (to March 2006) databases. Reports of any design were retrieved and evaluated for relevance. Search methods used in the original report (August 2001) are presented in Appendix 1.

In addition, information was obtained from the VAMedWatch database of propoxyphene and other opioid–related adverse drug events or experiences (ADEs) reported by VA centers as part of the Food and Drug Administration (FDA) MedWatch program from FY2004 to FY2005. It should be noted that the purposes of the FDA MedWatch program are to perform post-marketing safety surveillance and to identify signals of potential drug problems. The frequency of ADEs cannot be determined from MedWatch data because of the voluntary nature of the reporting system and the lack of a valid denominator. Serious adverse drug experiences (ones which result in death, hospitalization, disability, congenital anomaly/teratogenicity, are life threatening or require intervention), ADEs for new drugs, and unlabeled reactions for older drugs are required to be reported to the FDA according to VA policy.

New studies were added to the previous report (dated August 2001) and any information no longer relevant to this report update was removed.

This report starts with a review of the pharmacologic and pharmacokinetic properties of DPP, as they are central to understanding the safety concerns with DPP. An exhaustive literature review assesses the safety and efficacy of DPP after single and multiple doses and in various clinical situations (therapeutic, overdose, and drug abuse or addiction). Potential alternatives to DPP were assessed based on literature and recent opioid utilization patterns in VA.

For this report, 65 mg of DPP hydrochloride (HCl) was considered to be equivalent to 100 mg of DPP napsylate (DPPN).[17] Unless otherwise specified, the term DPP 65 mg in this report refers to DPP HCl 65 mg or its equivalent as DPPN 100 mg.

4 Pharmacologic and Pharmacokinetic Considerations

DPP, the α*d*-isomer of propoxyphene, is a synthetic, diphenylheptane-derivative opiate agonist with moderate analgesic effects. DPP shares structural similarities with methadone, the isomers of which have been suggested to have at least weak N-methyl-D-aspartate (NMDA) antagonist activity in vivo.[18,19] A recent study suggests that in addition to activity at opiate receptors, DPP also exhibits antagonist activity at the NMDA receptor.[20] DPP may have a theoretical beneficial effect in the treatment of hyperalgesia of chronic pain associated with nerve or soft tissue injury,[21-24] and in the development of opioid tolerance,[21,25] both of which have been shown in animal experiments to be related to stimulation of the NMDA receptor.

A summary of the pharmacokinetic and pharmacologic properties of DPP is shown in Table 1. Other selected opioids are also shown for reference.

Table 1 Pharmacokinetic and pharmacologic properties of selected oral opioids

	***D*-propoxyphene**	**Codeine**	**Hydrocodone**	**Oxycodone**[†]	**Tramadol**
Onset (min)	30 to 60	15 to 30	< 30	10 to 30	60
T_{max} (h)	2 to 2.5	0.5 to 1	1.3	1	2
Duration (h)	4 to 6	4 to 6	4 to 6	3 to 6	3 to 6
$t_{1/2}$ of parent drug [active metabolite] (h)	6 to 12 [30 to 36]	3 [1.5 to 2]	3.3 to 4.5 [1.5 to 2]	3.2 [1.5 to 2]	5.5 | [6.7]
Active metabolite	Norpropoxyphene	Morphine	Hydromorphone	Oxymorphone	M1
Elimination	Hepatic / Renal	Hepatic / Renal	Hepatic / Renal	Hepatic / Renal	Hepatic / Renal
Dosage reduction in elderly	Yes	Yes	Yes	Yes	Yes (max. dose 300 mg for age > 75 y)
Dosage reduction in renal failure	Yes	Yes	Yes	Yes	Yes (CrCl < 30 ml/min)
Dosage reduction in hepatic failure	Yes	Yes	Yes	Yes	Yes
Equivalent oral dose (mg, q 4 h)[‡]	65[§]	22.5	3.75	2.5[‖]	ND[††]
Recommended dose	65 mg q 4 h[§]	30 mg q 4 h	5 to 10 mg q 4 to 6 h	5 mg q 6 h[‖]	50 to 100 mg q 4 to 6 h
Maximum dose (mg/d)	390	[Limited by APAP content][‡‡]	[Limited by APAP content] [‡‡]	[Limited by APAP content] [‡‡]	400

Sources: [26]; [27]; [28]; [29]

† Oxycodone immediate release

‡ Based on Opioid Converter[26] Equivalent oral doses for conversion are shown WITH 30% reduction for incomplete cross-tolerance. Equivalent oral doses refer to 1 tablet of *d*-propoxyphene HCl 65 mg ± acetaminophen 650 mg; 1.5 tablets of codeine 15 mg ± acetaminophen 300 mg; 1.5 tablets of hydrocodone 2.5 mg + acetaminophen 500 mg; and 0.5 tablet of oxycodone 5 mg + acetaminophen 500 mg.

§ Doses of *d*-propoxyphene expressed as HCl salt; 65 mg of HCl is equivalent to 100 mg of napsylate salt.

‖ Dose of oxycodone expressed as HCl salt; 5 mg HCl is equivalent to 4.88 mg combination HCl / terephthalate salts

†† ND = No data[26]

‡‡ Maximum dose of APAP (acetaminophen): 4 g/d

The absorption of DPP from the gastrointestinal tract is rapid. The fast rate of absorption is believed to contribute to the rapid deterioration seen in DPP overdoses where collapse and death of the subject often occur within 1 hour, and in some cases in 15 minutes (see Section 6.1.1.5).

DPP undergoes extensive dose-dependent first-pass metabolism and is quickly converted to an active metabolite, norpropoxyphene (NPP), which has very weak analgesic properties. Blood concentrations of NPP resemble those of DPP with a dramatic increase of the metabolite concentrations to the maximum at 2 to 4 hours.

After single doses of DPP, both DPP and NPP may have long elimination half-lives, about 12 and 36 hours, respectively (N = 4).[30] There seems to be considerable interpatient variability, however, as Inturrisi, *et al.* observed much shorter half-lives of about 3 and 10 hours, respectively, after single doses (N = 6).[31] The pharmacokinetic study by Inturrisi, *et al.* suggested that DPP and NPP inhibit the hepatic metabolism of DPP. After single doses, 50% to 80% of DPP in the hepatoportal system was converted to NPP but only 5% was biotransformed after multiple doses. In elderly (65- to 90-year old) hospitalized patients, the mean half-lives have been reported to be even longer, 35.7 and 53.3 hours, respectively.[32]

Because of the self-inhibition of metabolism, plasma concentrations of DPP and NPP after multiple doses were 3 to 5 times higher and 7 times higher, respectively, than after single doses.[31] Likewise, half-lives of DPP and NPP increased 4- to 6-fold to 11.8 and 39.2 hours, respectively, with repeated dosing. In the same study, plasma concentrations of NPP increased to 13 times the plasma

concentration of DPP in tolerant patients taking large doses (900 to 1200 mg) of DPP on a long-term basis (4 to 16 weeks) for heroin withdrawal (DPP maintenance).[31]

The recommended dosing interval for DPP, however, is every 4 hours. Because of the long biologic half-lives, accumulation of DPP and NPP may occur when the drug is dosed at the recommended dosing interval. The majority of RCTs that involved multiple doses of DPP for the treatment of acute or chronic pain and that were reviewed for this report, however, used longer dosing intervals of every 6 to 8 hours or 3 to 4 daily doses (see Section 5.1.2). The literature search found no trials that documented the duration of analgesia resulting from DPP therapy under steady-state conditions.

Marked interindividual variation in plasma concentrations of DPP have been observed after standard doses due to differences in absorption and biotransformation.[31 33] Results of studies evaluating the relationship between dosage size (or plasma DPP concentration) and number of AEs have been variable with studies finding no relationship[33,34] or a linear relationship.[35]

The absorption of the napsylate salt tends to be delayed (time to peak, 2 h) in comparison with the HCl salt (1 to 2 h) at equivalent doses.[33] Toxicologic studies in animals have demonstrated less or delayed toxicity with the napsylate salt due to decreased or delayed absorption.[36] However, in humans the extent of absorption for the two salts at supratherapeutic doses (equivalent to 130 to 195 mg of the HCl salt) has been shown to be similar.[33] A toxicologic advantage with the napsylate salt has not been confirmed in man.

Animal studies have demonstrated that NPP has less neurotoxic effects than DPP but greater cardiotoxic effects due to membrane-stabilizing properties.[37] The local anesthetic properties of DPP and NPP are similar to those of tricyclic antidepressants such as amitriptyline and Type I antiarrhythmics such as lidocaine and quinidine.[27,37-39] Recent in vivo data showed that, at high concentrations of drug similar to those observed in fatal DPP overdoses, DPP and NPP block HERG (human ether-a-go-go-related gene) potassium channels, which have been found to be the main mechanism of the long QT syndrome associated with nonsedating antihistamines, haloperidol, and thioridazine.[40] Ulens, *et al.* suggested that the cardiotoxic effects of DPP and NPP may be partly due to their interaction with HERG cardiac potassium channels.

As with other opioids, tolerance to the analgesic and adverse effects of DPP may develop. Plasma concentrations of DPP associated with therapeutic use[31,41] may be similar to those seen in acute fatal overdoses[42] but without manifestations of toxicity, even with high doses such as those used for maintenance treatment of heroin addiction.[31,43]

About 15% of acute overdose cases have had blood concentrations (0.1 to 1.0 µg/ml) that overlap with the range of concentrations (0.2 to 0.3 µg/ml)[30] achieved from single therapeutic doses or those (0.13 to 0.15 µg/ml)[41] from multiple therapeutic doses of DPP (also see Section 6.1.1.5).[42] Inturrisi, *et al.* proposed that ingestion of a single, larger than usual dose may saturate first-pass metabolic processes, causing a higher systemic concentration of DPP and a lower NPP to DPP ratio than those observed with therapeutic use of DPP.[31]

In healthy volunteers, alcohol has been shown to have no pharmacokinetic interaction or to increase the bioavailability of DPP by 25% to 31%, probably by decreasing its first-pass hepatic metabolism.[44,45] Although the combination of DPP and alcohol has not been shown to potentiate the psychomotor depressant effects of either agent alone,[44] reductions in ventilatory function have been noted.[46]

5 Efficacy

5.1 Results of Published Randomized Trials

5.1.1 Single-dose trials

Three systematic reviews or meta-analyses, in which a total of 7087 patients were randomized to DPP (alone or in combination with APAP) or to placebo, tramadol, or APAP in single doses, were identified by the literature search.[47-49] In addition, the Oxford League Table of Analgesic Efficacy was located on the Web. This table is based on ongoing systematic reviews of randomized, double-blind, single-dose studies of analgesics in patients with postoperative pain.[50]

DPP alone was shown to have a weak analgesic effect in a systematic review of RCTs comparing single doses of DPP 65 mg alone to placebo (6 trials, 440 patients) and DPP 65 mg + APAP 650 mg to placebo (5 trials, 963 patients) for moderate to severe post-operative pain .[47] The number-needed-to-treat (NNT) for one more patient to achieve at least 50% pain relief was found to be 7.7 (95% CI: 4.6 to 22) when compared with placebo over 4 to 6 hours (Table 2).

Table 2 Number-needed-to-treat to achieve 50% pain relief over 4 to 6 hours with single-dose DPP alone and with APAP for post-operative pain in comparison with placebo

Active Treatment	N	Control Event Rate	Treatment Event Rate	Relative Benefit (95% CI)	NNT (95% CI)
Current systematic review					
DPP 65 mg	440	85/214	60/226	1.5 (1.2 to 1.9)	7.7 (4.6 to 22)
DPP 130 mg	50	10/25	1/25	10.0 (1.4 to 72)	2.8 (1.8 to 6.5)
DPP + APAP 65 + 650 mg	963	184/478	74/485	2.5 (2.0 to 3.2)	4.4 (3.5 to 5.6)
Previous systematic review					
Ibuprofen 400 mg	NR	NR	NR	NR	2.7 (2.5 to 3.0) *
Codeine+APAP 60 +650 mg	NR	NR	NR	NR	3.6 (2.9 to 4.5) **
Tramadol 100 mg	NR	NR	NR	NR	4.8 (3.8 to 6.1)

From Collins, *et al.* 2000[47]. Previous, equivalent systematic review by Collins, *et al.* 1998[51]

NNT = Number-needed-to-treat in order to achieve at least 50% pain relief (as measured by 50% maximum total pain relief, 50%maxTOTPAR) over 4 to 6 hours in one more patient relative to placebo for post-operative pain of moderate to severe intensity.

Includes DPP HCl 65 mg or napsylate 100 mg

* Ibuprofen was the only analgesic previously evaluated in an equivalent systematic review[51] whose 95% CI for NNT did not overlap that of DPP + APAP; the 95% CI also does not overlap with that of DPP 65 mg.

** 95% CI does not overlap with that of DPP 65 mg

The combination of DPP and APAP was more effective than DPP alone (NNT; 95% CI: 4.4; 3.5 to 5.6) and was found to be similar in efficacy to codeine 60 mg + APAP 650 mg or tramadol 100 mg based on data from a previous, equivalent systematic review. In these indirect comparisons, ibuprofen 400 mg seemed to be more effective (lower NNT of 2.7; 95% CI: 2.5 to 3.0) than both the DPP 65 mg + APAP 650 mg combination and tramadol 100 mg, and was the only agent of a wide range of analgesics tested in postoperative pain whose 95% CI did not overlap the CI of DPP + APAP. Although a higher dose (130 mg) of DPP seemed to be more effective (lower NNT) than the 65 mg dose, the small sample size and overlapping confidence intervals prevent a definite conclusion.

A single-patient data meta-analysis in 3453 patients with moderate or severe pain after surgery or dental extraction support the results of the indirect comparison between combination DPP + APAP and tramadol.[48] The meta-analysis found similar efficacy (i.e., 95% CIs overlap) between a combination of DPP 100 mg (salt form unspecified; probably napsylate salt based on dose) and APAP 650 mg (NNT compared with placebo; 95% CI: 4.0; 3.0 to 5.7) and tramadol 50 mg (7.1; 4.6 to 18), 100 mg (4.8; 3.4 to 8.2), or 150 mg (2.4; 2.0 to 3.1) for post-operative pain (Table 3).

Table 3 Number-needed-to-treat for at least 50% pain relief over 8 hours with single doses of analgesics in dental and post-surgical pain in comparison with placebo control

Active Treatment	Control Event Rate	Treatment Event Rate	Relative benefit (95% CI)	NNT (95% CI)
Post-surgical pain				
Codeine 60 mg	35/283	63/275	1.9 (1.3 to 2.7)	9.1 (6 to 23.4)
Tramadol 50 mg	13/136	38/163	2.4 (1.4 to 4.4)	7.1 (4.6 to 17.9)
Tramadol 75 mg	31/187	74/186	2.4 (1.7 to 3.5)	4.4 (3.1 to 7.0)
Tramadol 100 mg	13/136	51/168	3.2 (1.8 to 5.6)	4.8 (3.4 to 8.2)
Tramadol 150 mg	31/187	106/184	3.5 (2.5 to 4.9)	2.4 (2.0 to 3.1) *
DPP[N] 100 mg + APAP 650 mg	34/227	91/225	2.7 (1.9 to 3.8)	4.0 (3.0 to 5.7)
Codeine 60 mg + ASA 650 mg	4/68	24/70	5.8 (2.1 to 15.9)	3.6 (2.5 to 6.3)
Dental pain				
Codeine 60 mg	28/373	36/374	1.3 (0.8 to 2.1)	50 (16.3 to ∞)
Tramadol 50 mg	13/225	41/246	2.9 (1.6 to 5.2)	9.1 (6.1 to 18.8)
Tramadol 75 mg	6/95	16/95	2.7 (1.1 to 6.5)	9.1 (5.1 to 64.5)
Tramadol 100 mg	22/278	89/300	3.8 (2.4 to 5.8)	4.6 (3.6 to 6.4) **
Tramadol 150 mg	6/95	29/95	4.8 (2.1 to 11.1)	4.2 (2.9 to 7.3) **
DPP[N] 100 mg +APAP 650 mg	6/95	23/91	4.0 (1.7 to 9.4)	5.3 (3.4 to 11.4) **
Codeine 60 mg + ASA 650 mg	13/225	52/235	3.8 (2.2 to 6.8)	6.3 (4.5 to 9.8) **

From Moore, *et al.*[48]

At least 50% pain relief was measured as >50% of %maxTOTPAR (50%maxTOTPAR), %maxTOTPAR is percentage of the maximum possible for the area under the curve of pain relief (categorical scale) against time.

NNT = Number-needed-to-treat (for 8 hours) in order to achieve at least 50% pain relief in one more patient.

NR = Not reported.

* NNT 95% CI does not overlap with that of tramadol 100 mg, and just overlaps with that of tramadol 75 mg for post-surgical pain.

** NNT 95% CI does not overlap with that of codeine 60 mg for dental pain.

There was a similar pattern for DPP + APAP treatment comparisons but with slightly higher NNT values for dental pain. This meta-analysis also found comparable analgesic efficacy between DPP + APAP and codeine 60 mg + aspirin 650 mg for both post-operative pain (NNT; 95% CI: 4.0; 3.0 to 5.7 vs. 3.6; 2.5 to 6.3, respectively) and dental pain (5.3; 3.4 to 11.4 vs. 6.3; 4.5 to 9.8, respectively). DPP + APAP was more efficacious than codeine 60 mg for both post-operative pain (NNT, 95% CI for codeine: 9.1; 6 to 23.4) and dental extraction pain (50; 16.3 to ∞). Of note, the NNTs were lower for post-surgical pain than dental pain, indicating that the analgesics were more efficacious in post-surgical pain than in dental pain despite significantly more patients having severe pain intensity at baseline in post-surgical pain; however, the NNT 95% CIs associated with each agent for post-surgical and dental pain overlapped.

While there is a widely held view that the combination of DPP and APAP has additive effects, a systematic review of 24 single-dose RCTs involving 2231 patients found that the combination was no more effective than APAP alone in the treatment of dental, postpartum, post-operative, arthritis, and musculoskeletal pain.[49] The difference in pain intensity between DPP HCl 65 mg + APAP 650 mg and APAP 650 mg alone was 7.3% (95% CI: -0.2 to 14.9). In direct comparisons, the difference in response rate ratio was 1.05 (95% CI: 0.8 to 1.3) for the combination therapy and APAP monotherapy, where response was defined as moderate to excellent pain relief.

The Oxford League Table of Analgesic Efficacy presents a summary of the analgesic efficacy of single doses of analgesics in patients with moderate to severe acute postoperative pain (Table 4).[50] Analgesic efficacy (NNT) was based on the proportion of patients achieving at least 50% pain relief over 4 to 6 hours compared with placebo in randomized, double-blind trials.

Table 4 Efficacy of single-doses of selected oral analgesics in patients with moderate to severe acute postoperative pain in increasing order of NNT

Drug (doses in mg)	N (active drug)	Percent (%) with ≥ 50% pain relief	NNT	95% CI
Valdecoxib 40	473	73	1.6	1.4 to 1.8
Diclofenac 100	411	67	1.9	1.6 to 2.2
Codeine 60 + APAP 1000	197[†]	57	2.2	1.7 to 2.9
Oxycodone 5 + APAP 500	150[†]	60	2.2	1.7 to 3.2
Diclofenac 50	738	63	2.3	2.0 to 2.7
Naproxen 440	257	50	2.3	2.0 to 2.9
Oxycodone IR 15	60[†]	73	2.3	1.5 to 4.9
Ibuprofen 400	4703	56	2.4	2.3 to 2.6
Aspirin 1200	279	61	2.4	1.9 to 3.2
Oxycodone 10 + APAP 650	315	66	2.6	2.0 to 3.5
Ketorolac 10	790	50	2.6	2.3 to 3.1
Ibuprofen 200	1414	45	2.7	2.5 to 3.1
Oxycodone 10 + APAP 1000	83[†]	67	2.7	1.7 to 5.6
Piroxicam 20	280	63	2.7	2.1 to 3.8
DPP 130	**50**[†]	**40**	**2.8**	**1.8 to 6.5**
Tramadol 150	561	48	2.9	2.4 to 3.6
Tramadol 75 + APAP 650	1376	NR	3.0	2.5 to 4.0
APAP 500	561	61	3.5	2.2 to 13.3
APAP 1000	2759	46	3.8	3.4 to 4.4
Oxycodone 5 + APAP 1000	78[†]	55	3.8	2.1 to 20.0
Codeine 60 + APAP 600 / 650	1123	42	4.2	3.4 to 5.3
Ibuprofen 100	396	31	4.3	3.2 to 6.3
DPP 65 + APAP 650	**963**	**38**	**4.4**	**3.5 to 5.6**
Aspirin 600 / 650	5061	38	4.4	4.0 to 4.9
APAP 600 / 650	1886	38	4.6	3.9 to 5.5
Ibuprofen 50	316	31	4.7	3.3 to 7.9
Tramadol 100	882	30	4.8	3.8 to 6.1
Tramadol 75	563	32	5.3	3.9 to 8.2
Codeine 60 + ASA 650	598	25	5.3	4.1 to 7.4
Oxycodone 5 + APAP 325	149[†]	24	5.5	3.4 to 14.0
Codeine 30 + APAP 300	379	26	5.7	4.0 to 9.8
DPP 65	**440**	**40**	**7.7**	**4.6 to ∞**
Tramadol 50	770	19	8.3	6.0 to 13.0
Codeine 60	1305	15	16.7	11.0 to 48.0

Adapted from the Bandolier Oxford League Table of Analgesic Efficacy (2006).[53] Tramadol + APAP values are from a separate meta-analysis.[54] DPP 65 mg was no longer shown in the 2006 Oxford League Table of Analgesic Efficacy; values shown are from the 1999 version.[50] Oral non-opioid agents with N ≥ 250 and opioid agents (with N of any number) marketed in the U.S. were selected for this table.

For reference, morphine 10 mg i.m. has an analgesic efficacy rate of 50% and an NNT of 2.9 (95% CI: 2.6 to 3.6; N = 946); meperidine 100 mg i.m., 54% and NNT 2.9 (2.3 to 3.9; N = 364); ketorolac 30 mg i.m., 53%, NNT 3.4 (2.5 to 4.9; N = 359)

DPP = Propoxyphene hydrochloride or equivalent dose of napsylate salt (65 mg hydrochloride ≅ 100 mg napsylate).

IR = Immediate-release.

NNT = Number needed to treat for one more patient with moderate or severe pain to achieve at least 50% pain relief compared with placebo over a treatment period of 4 to 6 hours. NR = Not reported. 95% CI = 95% Confidence interval.

[†] A data set consisting of less than about 250 patients is considered to be probably inadequate for accurate estimation of the magnitude of the analgesic effect. NNT point estimates and 95% CIs based on data sets smaller than 250 patients should be interpreted with caution.

Table 5 summarizes the relative analgesic efficacy of DPP preparations in comparison with NSAIDS, APAP, or other opioids based on the information in Table 4.

Table 5 Relative analgesic efficacy of DPP preparations based on 95% CIs of NNTs for at least 50% pain relief within 4 to 6 hours following a single dose of analgesic

DPP formulation	Superior to	Similar to	Inferior to
DPP 130[†]	Opioids Codeine 60	Opioids Codeine 30–60 + APAP 300–1000 Codeine 60 + ASA 650 DPP 65 ± APAP 650 Oxycodone IR 15[†] Oxycodone 10 + APAP 650 Oxycodone + APAP 5/325–500, 5/1000, 10/1000[†] Tramadol 50–150 Tramadol 75 + APAP 650 NSAIDs / APAP APAP 500–1000 Ketorolac 10 ASA 600–1200 Naproxen 440 Diclofenac 50–100 Piroxicam 20 Ibuprofen 50–400 Valdecoxib 40	—
DPP 65 + APAP 650	Opioids Tramadol 50 Codeine 60	Opioids Codeine 30–60 + APAP 300–650 Codeine 60 + ASA 650 DPP 130[†]/65 Oxycodone IR 15[†] Oxycodone 10 + APAP 650 Oxycodone + APAP 5/325[†], 5–10/1000[†] Tramadol 75–150 Tramadol 75 + APAP 650 NSAIDs / APAP APAP 500–1000 Ibuprofen 50–100 ASA 600–1000 Piroxicam 20	Opioids Codeine 60 + APAP 1000[†] Oxycodone 5 + APAP 500[†] NSAIDs / APAP ASA 1200 Diclofenac 50–100 Ibuprofen 200–400 Ketorolac 10 Naproxen 440 Valdecoxib 40
DPP 65	—	Opioids Codeine 60 Codeine 30–60 + APAP 300–650 Codeine 60 + ASA 650 DPP 130[†] DPP 65 + APAP 650 Oxycodone IR 15[†] Oxycodone + APAP 5/325[†], 5–10/1000[†] Tramadol 50–100 NSAIDs / APAP APAP 500–1000 ASAP 600–650 Ibuprofen 50–100	Opioids Codeine 60 + APAP 1000[†] Oxyocodone + APAP 10/650, 5/500[†] Tramadol 150 NSAIDs / APAP APAP 1000 Diclofenac 50–100 Naproxen 440 Ketorolac 10 Piroxicam 20 Ibuprofen 200–400 ASA 1200 Valdecoxib 40

Sources: Table 4, based on the Oxford League Table of Analgesic Efficacy[53] and separate meta-analysis for tramadol + APAP.[54] All doses shown in mg.

APAP = Acetaminophen; ASA = Aspirin; DPP = Dextropropoxyphene; IR = Immediate-release; NSAID = Nonsteroidal anti-inflammatory drug

[†] Interpret with caution because of small (N < 250) data sets.

DPP 130 mg appears to have greater efficacy than DPP 65 mg + APAP 650 mg, followed by DPP 65 mg; however, the 95% CIs overlap and the data set for DPP 130 mg is small (N < 250). DPP 130 mg and DPP 65 mg + APAP 650 mg seem to be no better than NSAIDs and at least extra-strength doses of APAP (500 to 1000 mg). Like DPP, oxycodone immediate-release (IR) 15 mg and codeine 60 mg as well as oxycodone or codeine in combination with APAP are, with few exceptions, generally also no better than NSAIDs and APAP (500 to 1000 mg). Of opioids in combination with APAP 600/650 that have larger data sets (N > 250), DPP 65, codeine 60, oxycodone 10, and tramadol 75 all seem to be no better than APAP 600/650.

Comparisons between opioids and NSAIDs or APAP may bear less relevance when one considers that opioids are generally used after unsuccessful trials of APAP or NSAIDs. To determine potential alternatives for DPP, a more relevant comparison would be between DPP and other opioids. Codeine 60 mg in combination with high-dose (1000 mg) APAP and oxycodone 5 mg + APAP 500 mg may be more effective than DPP 65 mg + APAP 650 mg. Oxycodone 10 mg + APAP 650 mg, the 95% CI of which slightly overlaps with that of DPP 65 mg + APAP 650 mg, appears to be at least as effective as as the DPP–APAP combination, and similar in analgesic effect to DPP 130 mg. Caution should be used in interpreting the NNTs, however, as the data sets for codeine 60 mg + APAP 1000 mg, oxycodone 5 mg + APAP 500 mg, and DPP 130 mg are small (N < 250). Tramadol 150 mg is better than DPP 65 mg and tramadol doses of 75 to 150 mg are similar to DPP 130 mg and DPP 65 mg + APAP 650 mg.

A meta-analysis of single-dose, placebo-controlled trials involving patients with postoperative dental pain (N = 1376) showed that the combination of tramadol (75 mg) and APAP (650 mg) (NNT for 50% pain relief, 3; estimated 95% CI: 2.5 to 4) improved analgesic efficacy over tramadol (NNT 12; 7 to 30) or APAP (NNT 6; 4 to 8) alone.[54] Based on the 95% CIs, combination tramadol+APAP appears to be similar in single-dose analgesic efficacy to DPP 130 mg and DPP 65 mg + APAP 650 mg.

Codeine alone (60 mg) performs the worst of the opioid agents evaluated. Adding extra-strength APAP to either DPP or codeine improves their analgesic efficacy, whereas this effect is less apparent with oxycodone.

Although the use of 50%maxTOTPAR is useful for comparison of analgesics across different trials, this measurement should not be over-interpreted. It is possible for patients with less than 50%maxTOTPAR to obtain useful pain relief. Conversely, it is also possible for patients with at least 50%maxTOTPAR to obtain near maximal pain relief.

5.1.2 Multiple-dose trials

The usual practice in pain management is to prescribe multiple doses of analgesics. Young, *et al.* found that a statistically significantly smaller proportion of patients obtained at least 50% maximal pain relief following a single dose as compared with two doses of either DPPN 100 mg (7 of 30 patients, 23%, vs. 21 of 30 patients, 70.0%; p = 0.001) or codeine 60 mg (7 of 31 patients, 22.5%, vs. 23 of 30 patients, 76.7%; p < 0.001) given 4 hours apart.[55] Therefore, the results of single-dose trials may not be applicable to repeated doses of analgesics.

5.1.2.1 Acute pain

For the purposes of this report, acute pain was defined as pain of less than 3 months' duration, pain immediately following tissue injury, or pain of undisclosed duration but that was described as acute by the author. One trial involving acute exacerbation of chronic pain was considered under acute pain.[56] One trial included patients with acute exacerbation of low back pain of undisclosed duration.[1] A summary of the multiple dose, acute pain trials is presented in Appendix 3, Appendix Table 2 and Appendix Table 3.

A total of 19 efficacy-safety RCTs were included in the multiple-dose efficacy evaluation of this report. In these trials, 1395 patients with acute pain were included in the analgesic efficacy analyses. An accurate account of the number of randomized patients was not possible because of incomplete information (1406 patients were recruited, randomized, or analyzed). The acute pain trials differed in study design, patient characteristics, pain severity, type of pain, sample size, and treatment regimens. For an overview of the study designs of these trials, see Appendix 3.

5.1.2.1.1 Trials comparing DPP with NSAIDs or APAP

Thirteen RCTs, in which 698 analyzed patients had been randomized to DPP(N) (alone or in combination with APAP) or to NSAIDs or APAP (alone or in combination with non-analgesics), examined the efficacy of DPP in comparison with non-opioid agents (see Appendix 3, Appendix Table 2). Three trials found DPP + APAP less efficacious ($p < 0.05$) than NSAIDs in relieving pain[1,57,58] and one trial found DPP to be less efficacious ($p < 0.05$) than a combination APAP product (Percogesic).[59] The results of 10 trials showed no difference in analgesic efficacy between DPP products and either NSAIDs or APAP.[1, 53-63] None of these 10 trials performed a priori power calculations or presented results using 95% confidence intervals (which reflect sample size). Therefore, the results of these 10 trials may be inconclusive because of Type II error (no significant difference was found when a true difference existed).

The results of the trial by Evans, *et al.* demonstrated that differences in analgesic efficacy between DPP + APAP and NSAIDs may depend on the type of NSAID.[1] DPP + APAP was compared with four NSAIDs and APAP alone in this single-blind, three-period crossover study involving 60 patients (aged 47.0 ± 9.2 years; 20 men, 40 women) suffering from acute exacerbations of low back pain primarily of moderate intensity. The treatment regimens were DPP + APAP (Distalgesic, 65/650 mg QID), aspirin (900 mg QID), indomethacin (Indocid, 50 mg TID), mefenamic acid (Ponstan, 500 mg TID), phenylbutazone (Butazolidin, 100 mg TID), and APAP (1000 mg QID). Each treatment was given for 1 week. There was no statistically significant difference in spinal anterior flexion between treatment groups. A statistically significant difference was found between mefenamic acid (mean ± standard error, SE: 1.38 ± 0.09) and APAP (1.66 ± 0.09) or DPP + APAP (1.71 ± 0.09) (in favor of mefenamic acid), and between ASA (1.42 ± 0.09) and DPP + APAP (in favor of ASA) in terms of the daily pain index as measured by a 4-point pain intensity scale (0 = nil, 1 = mid, 2 = moderate, and 3 = severe). Notably, there was no statistically significant difference between DPP + APAP and either APAP, indomethacin, or phenylbutazone in terms of pain intensity. The percentage of the recommended dose taken by patients was lowest with DPP + APAP (71.7%), and treatment differences in this regard were significant between DPP + APAP and phenylbutazone (96.5%; $p < 0.01$), mefenamic acid (91.8%; $p < 0.01$), and APAP (89.8%; $p < 0.05$) (also see Section 0). Patient's preference, ranked on a scale of 1 (best) to 3 (worst), favored phenylbutazone (mean rank: 1.68) and mefenamic acid (1.75). Significant differences ($p < 0.05$) were found between each of these two agents and aspirin (2.37). DPP + APAP was rated fourth (mean rank: 2.07) among the six agents.

5.1.2.1.2 Trials comparing DPP with opioids

A total of 697 analyzed patients had been randomized in six trials to DPP(N) ± APAP or opioids ± APAP for the treatment of acute pain (see Appendix 3, Appendix Table 3). Codeine-containing combination analgesics or tramadol were shown to have greater analgesic efficacy than DPP + APAP in one study[60] and to produce analgesia that was not statistically different from either DPP alone [55] or DPP(N) + APAP[56,61-63] in five trials.

Of the five trials that found no statistically significant difference in pain intensity between DPP(N)+A and another opioid agent, two showed adequate power (at least 0.80) to detect a statistically significant difference if a true difference existed based on a priori [61] or post hoc[56] power calculations. The results

of the remaining three trials were not presented using 95% confidence intervals (which reflect sample size) and, therefore, were inconclusive.[55,62,63]

One RCT also evaluated treatment based on a measure of clinical outcome.[64] Beveridge, *et al.* found that football players with soft tissue injuries treated with naproxen returned to training about 1 day sooner than those treated with DPP (mean: 7.0 vs. 7.8 days; no statistical analysis reported). The numbers of days for patients to be available for selection were also lower for naproxen than DPP patients (8.3 vs. 9.6 days; no statistical analysis reported). However, a greater proportion of patients randomized to naproxen had been prescribed rehabilitation exercises.

5.1.2.1.3 Validity of acute pain trial results

The major and minor validity criteria are described in Appendix 2. The results of all the RCTs were considered to be of doubtful validity because of one or more of the major, minor, or other validity issues outlined in Appendix 3.

In total, eight trials [1,55,56,58,59,61,65,66] met major validity criteria and six trials [48, 50, 53, 56, 57, 65] met minor validity criteria. Only the trials by Buck, *et al.* (preliminary results) and Young, *et al.* met both major and minor (excluding other) validity criteria.

5.1.2.2 Chronic pain

For the purposes of this report, chronic pain was considered to be pain of 3 months' duration or longer, persistent pain related to an incurable disease (e.g., cancer), or pain described by the author as being associated with deterioration in quality of life (a characteristic more typical of chronic pain than acute pain).[67] Four RCTs involved patients with chronic pain as defined for this report (see Appendix 3, Appendix Table 4).

Two of the four RCTs compared DPP ± APAP to NSAIDs[68,69] and two compared DPP to opioids (either dihydrocodeine[70] or morphine[71]). A total of 864 patients were included in the analgesic efficacy analyses. One trial found DPP to be inferior to diclofenac sustained release,[68] and the remaining three trials found no difference between DPP ± APAP and either indomethacin[69] or opioids (dihydrocodeine or morphine sustained release).[70,71]

As with the acute pain, multiple-dose RCTs, the chronic pain trials varied in study design, patient populations, pain characteristics, and treatment regimens. For an overview of the study designs of the chronic pain trials, see Appendix 3.

One of the three studies that found no statistically significant difference between DPP + APAP and comparator agents performed an a priori power calculation.[70] The other trials did not perform power calculations or did not present results using 95% confidence intervals (which reflects sample size) and, therefore, their results are inconclusive.

The study by Mercadante, *et al.* was an open-label RCT that assessed the long-term use of DPP for the treatment of pain in terminally ill patients with cancer.[71] Daily doses of DPP 120 to 240 mg (N=16) were compared with low-dose morphine SR 20 mg (N=16) in opioid-naive cancer patients with moderate pain. This study was unique in that it was the only study that compared DPP as a WHO step 2 with a step 3 opioid analgesic. The objective of the study was not to compare equianalgesic doses of the two drugs, but to compare the analgesia and adverse effects of DPP with morphine SR as the second step in the WHO analgesic ladder (i.e., a step 2 opioid vs. a step 3 opioid, skipping a step 2 agent). The step 1 agents (mainly diclofenac 100 mg orally or 75 mg intramuscularly twice daily) were continued upon addition of opioid treatment.

The overall mean duration of therapy was 46 days for DPP and 68 days for morphine. In the first 10 days of therapy, the mean equianalgesic dose of DPP (mean in morphine equivalents: 14 ± 5.2 mg;

calculated as being equivalent to greater than 91 ± 33.8 mg of DPP) was statistically significantly lower than those of morphine (20.1 ± 6 mg; $p < 0.01$)[a] without a difference in pain intensity (median and range VAS score: 3 cm and 2 to 5 cm, respectively, in both treatment groups). Three patients maintained DPP therapy until death (mean: 38 days' therapy; range: 25 to 131 days). Three of the 16 morphine patients had to switch to DPP 5 to 7 days after starting treatment because of intolerable side effects (vomiting, drowsiness) and continued DPP with adequate pain relief until death.

A total of 13 patients were switched to morphine after reaching the ceiling dose (240 mg) of DPP. Two of these patients were able to continue DPP with adequate relief until 1 to 2 days before death when they became unable to swallow and were switched to subcutaneous morphine. Nausea, vomiting, drowsiness, and dry mouth were significantly more frequent and severe in the morphine group than the DPP group ($p < 0.01$); however, the differences in each case were relatively small (median and mean symptom intensity: 0 and 0.5 to 0.6 for DPP; 1 and 1.2 for morphine, where 0 was not at all, 1 was slight, 2 a lot, and 3 awful).

The study did not exclude the possibility that lower doses of morphine could have had fewer adverse effects. The results suggested that DPP produced a more favorable balance between analgesia and adverse effects than when a low dose of morphine was used to skip step 2 of the WHO analgesic ladder in opioid-naïve patients.

The authors concluded that the results stressed the role of "weak" opioids during initiation of opioid therapy in opioid-naive cancer patients. In addition, the results of this long-term study demonstrated that some patients experience an improvement in analgesia when DPP is added to nonopioid analgesics.

5.1.2.2.1 Validity of chronic pain trial results

The validity of results in all chronic pain trials was considered to be doubtful because of the major and minor validity issues outlined in Appendix 3 (for validity criteria, see Appendix 2).

None of the chronic pain trials met major validity criteria.

5.1.2.3 Patient Characteristics: Applicability of published results to VA patients

The 2298 patients recruited, randomized, or analyzed in the published RCTs consisted of mostly females (60%, 1372) with no or few co-morbid conditions. Patients were generally young with a mean or median age ranging from 19.2 to 55 years among 1613 patients (12 trials)[64 1,55,58,60,61,63,66,68,72-74] and from 66 to 81 years among 299 patients (4 trials) [56,70,71,75]. Age range was < 16 to 67 years in 4 trials reporting only age range (n = 281).[50, 55, 57, 68] Age was not stated in two trials (n = 272)[65,76].

The VA patient population is composed of mostly elderly men (95.2% men; age, mean ± SD: 59.9 ± 15.1 years) with co-morbidities.[77] A substantial proportion of the veteran population suffer from painful medical conditions (weighted percentages): 21.6% have osteoarthritis, 16.5% low back pain, and 10.7% cancer.

Because of these differences in characteristics between RCT and VA patients, the patients included in the RCTs were considered to have sociodemographic features or pathobiologic characteristics that may be sufficiently different from VA patients that the results were not completely applicable to the veteran population. Efficacy results should be particularized to veteran patients with caution, since sex differences in pain perception have been reported (with women more sensitive to pain than men).[78-83]

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[a] An equianalgesic ratio of 65 mg DPP (and APAP 650 mg [*sic*]) to < 10 mg morphine orally was suggested in the reference cited by the trial report.[52]]

Older persons may require lower opioid doses.[84-86] Furthermore, differences in analgesic (and toxic) effects might exist between young and elderly patients due to differences in renal function and blood concentrations of DPP or NPP.

6 Safety

6.1 Published trials

Safety data included frequencies of serious adverse events (SAEs), risks of drug dependency and abuse as an SAE, risks associated with dependency and abuse, non-serious adverse events (NSAEs), and tolerability. To address the safety concerns regarding DPP use in veterans, the discussion here focuses on SAEs. NSAE and other safety data from published trials are summarized in Appendix 3.

Clinical safety data was obtained from the results of 3 meta-analyses or systematic reviews, 23 efficacy/safety RCTs, 4 safety RCTs, 1 follow-up study, 1 retrospective cohort, 2 retrospective case-control studies, 6 large retrospective reporting programs, 17 retrospective surveys or case reviews, 3 large case series, and 4 small case series or case reports.

A total of 25 efficacy-safety or safety RCTs evaluated the safety of standard therapeutic doses of DPP(N) ± APAP in comparison with NSAIDs or opioids (codeine ± APAP, tramadol, or morphine). The numbers of patients with known exposures to the different treatments were 1160 for DPP-containing products, 701 for NSAIDs, 355 for codeine ± APAP or dihydrocodeine, 26 for morphine, and 21 for tramadol (total for opioids: 406; the treatment assignments of 3 patients who were withdrawn were not reported in one study and are therefore unaccounted for in the overall patient population exposed to treatment[63]). Based on reported information, a total of 2306 patients were evaluated for safety in the RCTs reviewed in this report.

6.1.1 Serious adverse events

Serious adverse events in this report were defined according to the FDA regulations on postmarketing reporting of adverse events (or experiences) (21 CFR 314.80). These regulations define a serious adverse event as any adverse event occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- congenital anomaly or birth defect
- important medical events that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., seizures that do not result in inpatient hospitalization, development of drug dependency or abuse).

6.1.1.1 SAEs observed at standard therapeutic doses

6.1.1.1.1 Deaths

No deaths were reported in meta-analyses and systematic analyses of RCTs evaluating single doses of DPP alone or in combination with APAP.[47-49]

A death due to the ingestion of large quantities of alcohol after taking therapeutic doses of DPP has been reported in a retrospective review of DPP-related deaths.[88] In this "well documented" case, a subject lost consciousness 4 hours after taking only two Distalgesic tablets (equivalent to 65 mg of

DPP and 650 mg of APAP; blood DPP concentration: 0.2 µg/ml) in combination with half a bottle each of champagne and martini (blood alcohol concentration, BAC: 168 mg%).

6.1.1.1.2 Other SAEs

No SAEs were reported in meta-analyses and systematic analyses of RCTs evaluating single doses of DPP alone or in combination with APAP.

No SAEs were reported among the 1160 patients exposed to DPP ± APAP in the RCTs reviewed in this report. Two SAEs associated with codeine preparations were observed among 163 patients exposed to codeine + APAP and 62 patients exposed to codeine + APAP + caffeine (Solpadeine). The first SAE was acute pulmonary edema possibly related to codeine + APAP treatment; the patient was also taking a beta-blocker.[56] The second SAE, postoperative hemorrhage, was reported in a patient who received codeine + APAP + caffeine (Solpadeine) after tonsillectomy.[63]

No seizures, cardiac arrhythmias, or pulmonary edema related to standard doses of DPP alone or in combination with APAP were reported in controlled clinical trials.

Furthermore, the literature search did not identify any case reports of such SAEs in association with therapeutic doses of DPP-containing products in the absence of other CNS depressants (cases were found when DPP-containing products were misused, abused, or overdosed with or without other CNS depressants; see Section 6.1.1.5).

6.1.1.1.3 SAEs in older patients

No relationship between the use of opioid analgesic (mainly DPP, codeine, and oxycodone) and increased **risk of falls** in older patients (> 60 years old) was found in a systematic review and meta-analysis of 29 nonrandomized, cohort (with at least 6 months' follow-up), case-control, or cross-sectional studies.[89] Based on the results of 13 studies involving 4537 patients (of whom 442 were taking drug), the pooled odds ratio (OR) for associations between use of opioid analgesics and occurrence of one or more falls was 0.97 (95% CI: 0.78 to 1.20).

In a follow-up study conducted in Sweden, Guo *et al.* assessed the effects of cognitive function and drug use on the incidence of **hip fracture** in a community-based population of 1,608 patients aged 75 years or older.[90] A total of 134 first hip fractures were identified during the 7,124 person-year follow-up. Of 109 patients using opioid analgesics, 106 (97%) took DPP. Opioid analgesic use was associated with an 80% increased risk of developing hip fracture (relative risk [RR] of 2.01 [95% CI: 1.19 to 3.40]). The major limitation of this study was that drug use was not monitored after the initial baseline assessment and, therefore, the temporal relationship between DPP use and the occurrence of hip fracture is uncertain.

The results of this study support those of a previous retrospective case-control study that also found an increased risk of **hip fracture** among elderly patients (aged 65 years or older) who were current users of DPP (RR 1.6; 95% CI: 1.2 to 2.2) or codeine (1.6; 1.3 to 1.9) in comparison to nonusers.[91] There was no difference in the relative risks of developing hip fracture between the two opioid analgesics (95% CIs overlap).

Neither of the latter two studies were reviewed in the meta-analysis by Leipzig, *et al.* which focused on associations between the use of opioid analgesics and falls as opposed to hip fractures.

A retrospective study evaluated data from the Systematic Assessment of Geriatric Drug Use via Epidemiology database to characterize analgesic drug use in the management of 10,372 elderly (≥ 65 years old) nursing home residents with persistent pain. DPP was the most commonly used short-acting opioid (2046/4002 residents, 51.1%) and second most common agent of all analgesics (18.2%), behind APAP (37.2%).[10] **No adverse diagnoses** (constipation, dysphagia, unsteady gait/falls,

delirium, depression) were observed with DPP, probably because relatively low doses were used in more than 90% of the residents (overall daily *opioid* dose averaged 19.7 mg morphine equivalents, or about 130 mg DPP[a]). Hydrocodone was the second most commonly used opioid (760/4002 residents, 19.0%), followed by tramadol (606/4002 residents, 15.1%). No adverse diagnoses were also observed with tramadol. The authors did not report whether adverse diagnoses were reported with hydrocodone. Notably, relative to no analgesic use, opioid use was not associated with a higher rate of unsteady gait / falls, delirium, severe constipation, or depression.

The relationship between prescribing of a potentially inappropriate medication (Beers criteria) and adverse clinical outcomes was evaluated in a retrospective cohort study of 1117 elderly residents of 15 nursing homes in Georgia.[92] Of these patients, 519 (46.5%) received at least one inappropriate medication and 143 (12.8%) experienced at least one adverse health outcome (hospitalizations, emergency department visits, or deaths, as identified from Medicaid claims data). The top five potentially inappropriate medications or drug classes prescribed to residents were propoxyphene, promethazine, hydroxyzine, digoxin, and iron supplements. Patients who received inappropriate medication(s) were more than twice as likely to experience at least one adverse health outcome (OR 2.34, 95% CI: 1.61 to 3.40). Of the top five potentially inappropriate medications, only the use of DPP significantly increased the likelihood of an adverse health outcome (OR 2.39, 95% CI: 1.54 to 3.71). The authors concluded that the use of inappropriate medications, particularly DPP, increases the risk of adverse health outcomes in the elderly. The study results were limited by the retrospective design, lack of control of confounding factors, lack of comparisons with specific "appropriate" medications, and inability to establish a cause-effect relationship. The internal validity of the results are questionable because, counterintuitively, chronic disease diagnoses such as cancer, diabetes, stroke, heart disease, and hypertension were not significantly associated with adverse health outcomes.

6.1.1.2 SAEs observed at high doses in the treatment of heroin maintenance

In a double-blind RCT in which 125 patients with heroin addiction took high doses (mean, 1000 mg/d) of DPPN (equivalent to 650 mg/d of the HCl salt), two SAEs were reported.[43] In the first case, a 52 year old man with diabetes developed a transient cerebral ischemic attack and required hospitalization. In the second case, the patient, who had a history of alcohol, sedative, benzodiazepine, and narcotic abuse, became obtunded apparently because of concomitant ingestion of DPPN 300 mg b.i.d. and other sedatives (two 30-mg flurazepam capsules and five "pills" of unknown content). None of the patients developed cardiac arrhythmias or seizures. The total daily doses taken for treatment of heroin dependence in this study are within the range of single doses taken in fatal acute overdoses. The relative lack of significant respiratory or CNS depressant effects in this population of narcotic addicts was believed to be due to tolerance to the opiate agonist effects.

6.1.1.3 Risks of dependency, misuse, or abuse as SAEs

Although DPP was first marketed in the U.S. in 1957 with initial claims that it lacked risk of dependency, its liability for dependence, addiction, and abuse typical of opioid narcotics was recognized by the late 1960s. DPP's abuse potential was considered to be relatively low based on several observations: (1) its transient opioid effects (in daily doses of 390 to 1625 mg) as a substitute for heroin or morphine among narcotic abusers; (2) its weaker abstinence-suppressing effects in comparison with codeine in patients physically dependent on morphine; and (3) its reportedly low use as a drug of primary abuse among abusers seeking euphoric effects.[93] The low abuse liability of DPP has also been reviewed by Miller, *et al.*[94]

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[a] Calculated using equianalgesic doses suggested by Hanks (1992): 65 mg DPP (and APAP 650 mg [*sic*]) to < 10 mg morphine orally.[52]

Among US Army soldiers stationed in West Germany between 1969 and 1971, however, the nonmedical use of DPP reached epidemic proportions.[95] In 1974 the U.S. DAWN found DPP to rank eighth among the most abused drugs. It was suggested that DPP was a likely target for abuse and addiction because of its relative ease of availability by prescription and lower cost compared with illicit opiates.[96] Despite the reports of DPP abuse, in discussion comments to Lader's review on the abuse of weak opioid analgesics, Finkle noted that information that had been presented at hearings in the U.S. and supported by the Law Enforcement Agency, the National Institute on Drug Abuse, and the Drug Early Warning Network, showed that the overall rate of DPP abuse during the 1960s and 1970s was very low.[93]

In a review of DPP as a drug of medical misuse, Lader cited many published cases of high-dose dependence on the drug, both psychological and physical.[93]

Although the likelihood of developing dependency on DPP is rated to be less than that with morphine, hydromorphone, oxycodone, and oxymorphone,[27] there has been a paucity of controlled trials comparing DPP with other opioids in terms of addiction liability. A recent double-blind, placebo-controlled trial involving non-drug–abusing individuals showed that single oral doses of morphine (40 mg) and lorazepam (2 mg) produced subjective effects, whereas DPP (50, 100, and 200 mg) produced no statistically significant subjective effects, although about 30% to 50% of the volunteers who took DPP appeared to experience subjective effects.[97] Lorazepam, but not DPP, produced psychomotor or cognitive impairment. Both DPP and morphine induced miosis. The findings were consistent with the existence of variability among individuals in their sensitivity to opioid effects.

The year-end 1999 emergency department (ED) data from the Drug Abuse Warning Network (DAWN) provided information on the frequency of DPP abuse-related visits among the participating EDs.[98] DPP was mentioned as a licit drug whose non-medical use resulted in or was related to an ED visit in 6252 (1%) of 554,932 episodes (DAWN estimate of total ED visits: 91.1 million).[a] Among the narcotic analgesics, hydrocodone was mentioned most often (3%, 14,639), and the frequency of mentions of oxycodone (1%, 6429) and codeine + APAP (1%, 3721) were similar to that of DPP (codeine alone was not one of the selected drugs reported).

The estimated rate of drug mentions per 100,000 population was highest for hydrocodone (6.0), followed by DPP and oxycodone (each with 2.6), and then codeine + APAP (1.5). In comparison, the rates for cocaine and heroin/morphine were 80.7 and 34.7. (Note: These estimates were based on a representative sample of non-Federal, short-stay hospitals with 24-hour EDs in the coterminous U.S.)

The problem of DPP misuse that may be considered to be a form of addictive behavior among patients treated with opioids for acute or chronic pain has not been well studied. In one study of 144 consecutive patients referred to a treatment program for chronic nonmalignant pain, 35 (24%) were found to be drug-dependent, 59 (41%) drug abusers, and 50 (35%) nonabusers.[99] The definitions of drug abuse and drug dependence were based on modified criteria of the WHO, Feighner and associates', and DSM III. DPP was misused in 8 (14%) of 59 drug abusers and 6 (17%) of 35 drug-dependent patients. Codeine (23, 39% and 15, 43%, respectively) and oxycodone (12, 20% and 11,

[a] The annual survey of hospital emergency departments participating in the Drug Abuse Warning Network (DAWN) was conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA). Eligible hospitals were non-Federal, short-stay facilities located in the coterminous U.S. and that had emergency departments (EDs) open 24 hours a day. The survey did not measure prevalence of drug use in the population, but was intended to collect data on ED episodes that are induced by or related to the use of an illegal drug or the nonmedical use of a legal drug. Drug Abuse was defined as the nonmedical use of a drug for any of the following reasons: psychic effect, dependence, or suicide attempt/gesture. A Drug-Related Episode, or drug episode, is an ED visit that was induced by or related to the use of an illegal drug(s) or the nonmedical use of a legal drug for patients age 6 years and older. A Drug Mention referred to a substance that was mentioned during a drug-related ED episode (up to 4 drugs could be reported for each drug abuse episode).

31%, respectively) were most frequently misused. The findings are outdated, however, and may not necessarily reflect current opioid prescribing or usage patterns.

The prevalence of DPP and codeine use disorders was assessed in a single retrospective survey involving patients with orthopedic and chronic pain who were admitted to a Swedish hospital orthopedic ward for rehabilitation.[100] [QE = III] All 265 patients referred to the ward were interviewed using ADDIS (Alkohol Drog Diagnos InStrument) (Swe.), a Swedish version of SUDDS (Substance Use Disorder Diagnostic Schedule). The ADDIS/SUDDS instrument allowed the diagnosis of substance use disorders based on DSM-III-R criteria. ADDIS assessments were recoded into DSM-IV criteria (7 criteria of dependence) for comparisons with DSM-III-R (9 criteria of dependence). Of 243 patients who completed the survey, a total of 58 patients (22%) met DSM-III-R criteria for analgesic use disorders, and 49 patients (18.5%) met DSM-IV criteria. DPP was the most frequently prescribed analgesic in the study population (32% of 243) and was taken by 25 of 54 (47%) of the patients who met DSM-III-R criteria for analgesic use disorders as compared with 49 of 189 (26%) of patients with no analgesic use disorder ($p = 0.003$ for the difference, Chi-square). The corresponding figures for codeine were 10 (18%) and 17 (9%) ($p = 0.06$ for the difference, Chi-square).

A study evaluating the effectiveness of opioids for the treatment of chronic back pain in veterans found that 3 (2.5%) of 122 opioid-treated patients who were interviewed showed drug abuse behaviors involving oxycodone, tramadol, or both.[101] Of the 230 patients screened, most were treated with codeine (79%), followed by oxycodone (32%), propoxyphene (18%), and tramadol (12%). Propoxyphene was not reported to be involved in abuse behaviors in the patient cohort.

The interpretation of results on DPP abuse, dependency, and misuse are hampered by varying definitions for each of the drug use disorders among the studies.

6.1.1.4 SAEs associated with DPP dependency, misuse, or abuse

In 1997, among four Nordic countries (Denmark, Finland, Norway, and Sweden), the rates of drug addict deaths relative to the total numbers of fatal intoxications among drug addicts (N = 52 to 216 per country) for DPP (0.5% to 20%) seem to be comparable to those of codeine (0% to 27%) and methadone (0% to 21%), and apparently lower than those for heroin/morphine (38% to 93%).

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Toxicologic and drug abuse data have identified a number of notable adverse reactions associated with DPP misuse. A random questionnaire survey of 5300 soldiers revealed that about 15% to 20% of the 180,000 American soldiers stationed in West Germany in the fall of 1970 (prior to instituting restrictions on DPP use as a narcotic in that country) used DPP orally, subcutaneously, or intravenously at least once for nonmedical reasons.[95] There were 13 reported deaths, each of which was preceded by seizures and occurred within 30 to 45 minutes after oral ingestion of DPP HCl in doses ranging from 1300 to 1950 mg (24 to 32 mg/kg of body weight). Other important medical complications were seizures, respiratory depression or arrest, phlebitis (with intravenous use), and withdrawal symptoms. Psychiatric complications, including disorientation, delusions, hallucinations, and extreme confusion were also noted. Further information on DPP misuse and abuse in the context of overdose and poisoning can be found in Section 6.1.1.5.

The frequency of seizures associated with DPP abuse can be high. In a retrospective, noncontrolled review of the records of patients admitted to the Detoxification Unit in the Mental Health Institute in Mexicali, Mexico from March to December 1988, 53% of 73 patients (median age: 26 years, 97% males) had confirmed, generalized seizures while intoxicated from oral DPP abuse.[102] All except one of these patients had no history of seizures prior to DPP abuse. The average daily dose of DPP was 1365 mg (range: 195 to 3575 mg) and most patients had abused DPP for at least 4 continuous years. All patients had a diagnosis of DPP dependence according to DSM-III-R criteria. Note that the lower end of the dosage range among the abusers was only slightly greater than a standard therapeutic dose of DPP (195 mg, equivalent to three 65-mg capsules). The dosage range of DPP among the patients

who developed seizures was not reported and, therefore, it is not known whether the 195-mg dose was associated with seizures. A similar, high frequency of seizures among DPP abusers has not been reported elsewhere.

6.1.1.5 Overdose and Poisoning

DPP has been recently reported to be one of the major drugs involved in fatal poisonings in Nordic countries[103,104] and the U.K.[105,106] In one U.K. study, 23 (18.5%) of 123 subjects who died from suicidal overdoses consumed DPP+APAP prescribed for someone else; therefore, the high risk of death from DPP poisoning extended beyond the person for whom the drug was intended.[107]

The symptoms characteristic of overdoses involving DPP, alone or in combination with alcohol or other central nervous system (CNS) depressants, are similar to those of other opioids. They include respiratory depression, central nervous system depression, and miosis, all of which are reversible by naloxone. Psychotic reactions have also been reported.[95] The symptomatology and time course of codeine, hydrocodone, and oxycodone overdoses have not been documented as extensively as they have been for DPP.

In addition to the typical signs of opioid toxicity, however, DPP may cause seizures, wide QRS complexes, bradycardia, and cardiac arrhythmias.[42,95,108,109] These complications are probably at least partly due to the neurotoxic effects of DPP and the membrane-stabilizing, quinidine-like [37-39] or possibly nonsedating histamine-like [40] cardiotoxic effects of DPP and NPP. The cardiotoxic effects are not reversible with naloxone.

Pulmonary edema has been reported to occur after DPP overdose.[110-114] However, this effect is not specific to DPP; other opioids have also been associated with pulmonary edema following overdose, including codeine[115], morphine[116], heroin[114,117-121], fentanyl[122], oxycodone[123], and methadone[124-131]. The mechanism of pulmonary edema is unclear. On autopsy, pulmonary edema is a frequent and nonspecific finding attributed to terminal hypoxia following overdose.[42,95,113,114] The literature search did not identify any reports of pulmonary edema occurring with therapeutic use of DPP.

DPP overdoses are remarkable for the rapidity with which cardiopulmonary arrest, seizures, coma, or death can occur. Prolongation of the QRS interval without increase in heart rate has been prospectively observed to occur within 4 hours after overdose of DPP+APAP (mean [95% CI] 99.36 [96.19 to 102.53] msec), relative to other combination opioid-APAP products (82.84 [80.81 to 84.88] msec), and persist for 24 hours.[132] Victims have collapsed within an hour, sometimes in as little as 15 minutes, after ingestion.[95] Therefore, profound pharmacologic effects occur during the absorption and distribution phases for the drug. In a U.K. study of deaths due to DPP over a 3-year period, 31 (91%) of 35 victims died before effective medical care could be given.[88] The co-ingestion of alcohol or other CNS depressants seems to be associated with rapid onset of DPP poisoning and death.[133]

Also remarkable is the observation that relatively small overdoses (6 to 20 tablets) may be lethal especially in combination with other CNS depressants.[88,107,109,134] Even a therapeutic dose (2 tablets) combined with alcohol has been fatal (also see Section 6.1.1.1.1).[88]

Finkle, *et al.*[42] noted there was an overlap between postmortem DPP blood concentrations (ranging from less than 0.1 to greater than 20 µg/ml; median: 3 to 4 µg/ml; mode: 1 to 2 µg/ml)[a] and plasma concentrations obtained by therapeutic doses (0.2 to 0.3 µg/ml) or doses only moderately above the usual recommended dose in healthy volunteers. Blood DPP concentrations have been reported to be 0.13 to 0.21 µg/ml after single doses of DPP 130 mg or 195 mg of the HCl salt (n = 8); and 0.8 µg/ml

[a] Postmortem blood concentrations of DPP were measured by gas chromatography (GC) and/or ultraviolet (UV) analysis with almost twice as many cases using GC as UV. The GC analysis detected DPP only (sensitivity, 0.1 µg/ml) The UV analyses measured both DPP and NPP concentrations (sensitivity, 0.5 to 1.0 µg/ml).

after 13 consecutive doses of DPP 130 mg every 8 hours (n = 1).[31,33] The postmortem DPP concentrations also overlap with steady-state blood concentrations that have been observed in tolerant patients (0.42 to 0.57 µg/ml after ingestion of 900 to 1200 mg/d for 4 to 16 weeks [n = 3],[31] and 2 µg/ml after ingestion of 1200 mg daily for two weeks[42]. It has been suggested that tolerance to DPP may be overcome when DPP is ingested in large, single doses, resulting in toxicity or death.

Of 143 cases found to have postmortem DPP concentrations < 1 µg/ml, 14 (9.8%) were categorized as ingestions of DPP alone and 129 (90.2%) as ingestions of DPP plus another drug or alcohol. None of the cases categorized as ingestions of DPP alone had concentrations less than 0.2 µg/ml, and 3 cases (2%) had concentrations of 0.2 to 0.3 µg/ml, which overlap with blood drug concentrations observed after therapeutic doses of DPP. The number of cases involving DPP alone was too small to draw firm conclusions. The subpopulation of cases with low DPP concentrations (< 1 µg/ml) was considered to probably represent multiple-drug ingestions.

Fatal poisoning cases involving "low" concentrations of DPP resulting from ingestion of a DPP + APAP combination product in the U.K. were examined in more detail because of anecdotal reports that even small quantities of DPP may be fatal.[133] Nine of 1456 cases (0.6%) involved DPP concentrations < 1.0 µg/ml and no alcohol or other drugs. Results were inconclusive. Wide variability between DPP concentrations for particular APAP levels was noted.

The CNS and respiratory depressant effects of DPP are increased by alcohol and other CNS depressants.[88,135,136] Postmortem DPP blood concentrations have been found to be statistically significantly lower when alcohol was co-ingested with DPP + APAP (mean DPP concentration: 1.7 µg/ml; range: 0.2 to 8.5 µg/ml; n = 27) than in cases where DPP + APAP only were detected (mean: 6.2 µg/ml; range: 0.2 to 77 µg/ml; n = 48; $p < 0.01$, Mann-Whitney *U* test).[88] Finkle, *et al.* found that co-ingestion of alcohol or other drugs occurred in 90.2% of 143 cases in which fatal DPP blood concentrations were very low (1 µg/ml or less), and 50% of these cases involved BACs greater than 0.22% (mean: 0.20%).[42]

A Finnish study of the interaction between alcohol and drugs in fatal intoxications showed that postmortem blood alcohol concentrations are also lower when DPP was present, and the difference in median postmortem blood alcohol concentrations were similar between cases involving alcohol only and alcohol (≥ 0.5%) with DPP, amitriptyline, doxepin, or promazine.[137] The fatal toxicity index, calculated from the annual number of deaths and sales expressed in terms of defined daily doses per 1000 inhabitants per day, for DPP (32.0; 95% CI: 23.3 to 40.7) was lower than that for promazine (120.8; 97.7 to 143.9); similar to that of doxepin (20.9; 15.0 to 28.8); and higher than that for amitriptyline (12.2; 9.3 to 15.2), citalopram (1.4; 1.1 to 1.7), diltiazem (1.4; 1.1 to 1.7), zopiclone (0.9; 0.7 to 1.2), and temazepam (0.9; 0.7 to 1.1).

A recent U.K. study found that individuals who drank alcohol at the time of fatal DPP+APAP overdoses took an average of 25 fewer tablets (95% CI 0 to 49) than those who did not ingest alcohol ($p = 0.048$).[107] In addition to additive or potentiated pharmacologic effects of DPP and alcohol, alcohol may increase DPP blood concentrations via a pharmacokinetic interaction (see Section 4, Pharmacologic and Pharmacokinetic Considerations).

Notably, DPP abuse (16 of 1022 cases, 1.6%) was rarely seen among the patients who died from DPP overdose in the U.S between 1972 and 1975.[42] On the contrary, there were "definite tendencies" to overuse DPP. Abuse or misuse of alcohol or drugs, alone or in combination, was common, occurring in 350 (34.2%) of the cases; a history of drug misuse was present in 175 cases (17.1%). The majority (82%) of the deceased had psychiatric or "emotional problems." The manner of death was categorized as suicide in 468 cases (45.8%), but a substantial number (267 cases, 26.1%) was categorized as accidental. Additional information on this study is summarized in Appendix 4. These findings were confirmed in subsequent surveys covering the periods 1976 to 1978 and 1969 to mid-1983.[138,139]

The characteristics of the deceased and method of overdose with DPP poisoning have been noted to differ from those of codeine poisoning, in which drug addiction, street drug abuse, and accidental deaths were more common among the deceased.[140]

Early animal studies comparing the two salts of DPP found DPP napsylate to be markedly less toxic than the HCl salt.[36] These interesting results have not been confirmed in humans, and DPP-related fatalities have involved both salt types.

6.1.1.5.1 Mortality rates in DPP overdoses

There is limited published information on the mortality rate associated with DPP overdoses relative to other opioids as well as other analgesics. One study in New Zealand estimated the risk of mortality from coroner-reported opioid poisonings recorded in the surveillance database of fatal opioid poisonings of the Institute of Environmental Science and Research, and prescription records for morphine, methadone, and DPP identified from the PharmHouse database.[141] Morphine detected in the coroner's toxicology report may have been derived from morphine, heroin, or codeine. The time period covered in both databases was January 2001 to December 2002. The rate of deaths (95% CI) per 100,000 prescriptions was 5.94 for morphine (4.09 to 8.34), 2.5 (1.45 to 4.12) for DPP, and 1.34 for methadone (0.91 to 1.91). Expressed per 1,000,000 defined daily doses (100 mg for morphine, 25 mg for methadone, 200 mg for DPP HCl, and 300 mg for DPPN), the rate of deaths was highest for morphine at 0.94 (0.65 to 1.32), followed by methadone at 0.40 (0.27 to 0.56), and lowest for DPP at 0.14 (0.08 to 0.22). The authors recommended that the availability of DPP should be restricted, and the monitoring of methadone prescribing and dispensing should be increased to decrease deaths due to opioids in New Zealand. Since the prescribing practices and illicit availability of opioids probably differ between the U.S. and New Zealand, the results of this study may have limited applicability to the U.S. veteran population.

A study examined national mortality data on 15,299 deaths recorded as suicides or open verdicts in England and Wales,[105] where—at the time of the study—DPP was the second most common prescription drug used to commit suicide. Of these deaths, 4192 (27%) were drug related. During the 3-year study period (1997 to 1999), the number of deaths per year (95% CI) due to poisoning were 309 (289 to 330) for tricyclic antidepressants alone, followed by 255 (238 to 274) for DPP+APAP alone, and 123 (110 to 136) for APAP alone. Deaths due to tricyclic antidepressants alone comprised 22% of all drug-related suicides, significantly higher than the rate of 18% for DPP+APAP alone ($p < 0.001$) and 9% for APAP alone. However, ratios of fatal to nonfatal poisonings suggested that the odds of death due to DPP overdose were 2.3 (2.1 to 2.5) times higher than that for tricyclic antidepressants and 28.1 (24.9 to 32.9) times higher than that for APAP. These findings from a U.K. study may have limited applicability to the U.S. and veteran populations.

In a study of fatal poisonings in Sweden (1992 to 2002), DPP had a fatality ratio (number of fatal intoxications with toxic postmortem drug concentrations relative to defined daily doses) of 10.8, the highest ratio among 7 drugs.[104] The fatality ratio for dihydropropiomazine was 4.2; for 7-amino-nitrazepam, 4.2; 7-amino-flunitrazepam, 3.2; APAP 2.3; zopiclone, 1.7; and citalopram, 1.0.

Additional comparative data on mortality comes from a retrospective, Danish study published more than a decade ago. This study included 1423 consecutive patients admitted to an intensive care unit on 1558 occasions between 1975 and 1980 because of severe self-poisonings.[142] The main drug classes (and corresponding number of patients) were barbiturates (438), tricyclic antidepressants (302), DPP (212), tranquilizers (127), neuroleptics (116), salicylate (82), other hypnotics (61), strong analgesics (58), and others (162). The highest rates of death due to the acute self-poisoning were seen with salicylates (11%), DPP (9%), and strong analgesics (9%). These deaths reflect those of severe self-poisonings admitted to an intensive care unit and do not apply to all cases of self-poisoning for any

individual agent, particularly given that many DPP-related fatalities occur prior to hospital admission.[42,88]

6.1.1.5.1.1 AAPCC TESS data on moderate, major, and fatal outcomes

Limited data on the relative toxicity of opioids may be obtained from a surveillance program coordinated by the American Association of Poison Control Centers (AAPCC). The 2004 Toxic Exposure Surveillance System (TESS) data compiled by the AAPCC reflects over 2.4 million human exposure cases reported by 62 participating poison centers.[143] Of the 835,832 (34.3%) exposures in adults aged 20 to 99 years or of unknown adult age, more than half occurred in women (58.6%). Overall, most of the reported exposures were due to unintentional (84.1%)or intentional (12.4%) overdose; a relatively small proportion (2.5%) was due to adverse reactions. From 2003 to 2004, there were marked increases in the number of deaths primarily attributed to methadone (from 38 to 76 cases) and oxycodone (from 22 to 31 cases). In 2004, there were 33 deaths attributed to long-acting or transdermal opioids. A relatively large number of such deaths were also seen in 2003. A summary of the moderate, major, and fatal medical outcomes from exposures to selected opioid and non-opioid analgesics is presented in Table 6.

Medical outcome categories were defined as follows: *Moderate effect*—The patient exhibited signs or symptoms a a result of the exposure that were more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement (e.g., disorientation, hypotension that is rapidly responsive to treatment, and isolated brief seizures that respond readily to treatment). *Major effect*—The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement (e.g., repeated seizures, status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest). *Death*—The patient died as a result of the exposure or as a direct complication of the exposure. Only those deaths that were probably or undoubtedly related to the exposure were coded.

Table 6 Moderate, major, and fatal medical outcomes associated with selected analgesic exposures by drug class in decreasing order of moderate outcome frequency (%): 2004 AAPCC TESS data

		% of all analgesic	Outcome					
	No. of	exposures	Moderate		Major		Death	
Agent implicated in exposure	Exposures	(N = 279,955)	No.	%	No.	%	No.	%
Opioids								
Methadone	3965	1.4%	967	24.4%	425	10.7%	96	2.4%
***D*-propoxyphene**	417	0.1%	92	22.1%	31	7.4%	8	1.9%
Morphine	3097	1.1%	572	18.5%	173	5.6%	18	0.6%
Meperidine	444	0.2%	75	16.9%	17	3.8%	5	1.1%
Tramadol	3769	1.3%	629	16.7%	161	4.3%	6	0.2%
Oxycodone	5510	2.0%	853	15.5%	313	5.7%	43	0.8%
Pentazocine	175	0.1%	21	12.0%	1	0.6%	0	0.0%
Codeine	1281	0.5%	87	6.8%	11	0.9%	4	0.3%
Other/unknown	6974	2.5%	1312	18.8%	534	7.7%	43	0.6%
Acetaminophen + opioid combinations								
Acetaminophen + ***d*-propoxyphene**	6089	2.2%	792	13.0%	198	3.3%	32	0.5%
Acetaminophen + Hydrocodone	22594	8.1%	2868	12.7%	751	3.3%	86	0.4%
Acetaminophen + Oxycodone	6949	2.5%	833	12.0%	228	3.3%	16	0.2%
Acetaminophen + Codeine	5496	2.0%	559	10.2%	111	2.0%	12	0.2%
Acetaminophen + Other opioid	456	0.2%	64	14.0%	14	3.1%	0	0.0%
Aspirin + opioid combinations								
Aspirin + Codeine	243	0.1%	45	18.5%	11	4.5%	1	0.4%
Aspirin + Oxycodone	144	0.1%	23	16.0%	5	3.5%	2	1.4%
Aspirin + ***d*-propoxyphene**	39	0.0%	3	7.7%	3	7.7%	0	0.0%
Aspirin + Other opioids	73	0.0%	8	11.0%	4	5.5%	0	0.0%
Ibuprofen + opioid combinations								
Ibuprofen + Hydrocodone	60	0.0%	5	8.3%	0	0.0%	0	0.0%
NSAIDs / Acetaminophen								
Aspirin alone, adult formulations	7031	2.5%	926	13.2%	88	1.3%	17	0.2%
Indomethacin	709	0.3%	58	8.2%	11	1.6%	3	0.4%
Acetaminophen alone, adult formulations	32395	11.6%	2559	7.9%	624	1.9%	70	0.2%
COX-2 inhibitor	5834	2.1%	436	7.5%	83	1.4%	6	0.1%
Naproxen	14273	5.1%	890	6.2%	137	1.0%	10	0.1%
Ibuprofen	70916	25.3%	2216	3.1%	292	0.4%	13	0.0%
Other NSAID	5133	1.8%	371	7.2%	85	1.7%	8	0.2%
Acetaminophen alone, unknown formulations	8609	3.1%	1132	13.1%	382	4.4%	78	0.9%
Aspirin alone, unknown formulations	10111	3.6%	1850	18.3%	310	3.1%	37	0.4%
Combined totals								
All DPP-containing agents	6545	2.3%	887	13.6%	232	3.5%	40	0.6%
All oxycodone-containing agents	12603	4.5%	1709	13.6%	546	4.3%	61	0.5%
All hydrocodone-containing agents	22654	8.1%	2873	12.7%	751	3.3%	86	0.4%
All codeine-containing agents	7020	2.5%	691	9.8%	133	1.9%	17	0.2%

Adapted from Watson, *et al.*[143]
AAPCC TESS = American Association of Poison Control Centers Toxic Exposure Surveillance System

During 2004, exposures to DPP alone were associated with the second highest rates of moderate (92/417, 22.1%), major (31/417, 7.4%), and fatal (8/417, 1.9%) medical outcomes among 29 selected opioid and non-opioid analgesic drug or drug class exposures reported by the 62 participating poison

control centers (Table 6). These figures were similar to those in the 1999 and 1998 TESS data presented in the previous DPP review. In both years, DPP alone had the second highest rate of major medical outcomes and the highest rate of death among the opioid exposures. The rates of moderate, major, and fatal outcomes for DPP, a so-called "weak" opioid analgesic, approximate those of "strong" opioids such as methadone and morphine.

Of specified APAP-opioid combinations, those containing DPP had similar or slightly higher rates of moderate (13.0%) and fatal (0.5%) effects relative to APAP combinations with hydrocodone (12.7% and 0.4%), oxycodone (12.0% and 0.2%), and codeine (10.2% and 0.2%). The combinations of APAP and DPP, hydrocodone, or oxycodone were each associated with a 3.3% rate of major effects, whereas major effects accounted for 2% of combination APAP and codeine exposures.

Overall, exposures to all DPP-containing agents comprised a small proportion of the total analgesic exposures reported (6545 of 279,955 exposures, 2.3%). This rate was somewhat similar to that of all codeine-containing agents (7020, 2.5%) and lower than all oxycodone-containing agents (12,603, 4.5%) and all hydrocodone-containing agents (22,654, 8.1%). In comparison, 25.3% of all analgesic exposures involved ibuprofen and 11.6% involved adult formulations of acetaminophen alone.

Of 6545 exposures to all DPP-containing agents, the reason for exposure was most often considered to be intentional (suicidal, misuse, abuse, or unknown motive (3769, 57.5%) or unintentional (2365, 36.1%). *Intentional* reasons referred to the intentional improper or incorrect use of a substance for reasons other than to experience psychotropic effects (*intentional misuse)* and where the victim was likely to be pursuing euphoric or psychotropic effects (*intentional abuse)*. *Unintentional* reasons included unintentional (unplanned or unforeseen) *therapeutic error* (improper or incorrect use of a medication) and *misuse* (improper or incorrect use of a nonpharmaceutical substance).

The 2004 AAPCC TESS data suggests that exposures to DPP-containing agents is less common than exposures to ibuprofen or adult formulations of APAP alone. Most exposures to DPP-containing agents were intentional, due to suicide attempt, misuse, or abuse, and a substantial percentage of exposures were due to unintentional therapeutic errors or misuse. Poisoning exposures to DPP-containing agents seem to be similar or slightly more toxic than those for hydrocodone-, oxycodone-, and codeine-containing agents in terms of moderate, major, and fatal outcomes, but DPP alone seems to be more toxic than most of the other opioids reported.

These results were based on selective cases reported to participating poison control centers and are difficult to apply to the veteran population in the U.S. because of possible differences in patient age, and possibly other, unreported patient characteristics, prescribing patterns, and socioeconomic conditions.

6.1.1.5.1.2 DAWN data

The most extensive information on deaths related to recent drug use comes from annual DAWN surveys, which were redesigned in 2003 to cover any drug-related deaths reported by medical examiners and coroners, rather than focusing on drug abuse–related deaths as in previous reports.

According to the most recent report (*DAWN 2003: Area Profiles of Drug-related Mortality*),[144] drug misuse deaths involved an opioid, and often multiple opioids, more often than any other drug in 29 of the 32 participating metropolitan areas and in all 6 participating states. Reported in more than one-quarter of deaths involving opioids were methadone (in 12 metropolitan areas and 3 states), hydrocodone (4 metropolitan areas), and oxycodone (4 metropolitan areas). Opioids were also the most common drugs reported in drug-related suicide deaths. Morphine (which may be a pharmaceutical or a metabolite of heroin) was reported in at least one-quarter of suicides involving opioids in 9 metropolitan areas. Methadone (4 metropolitan areas, 2 states), hydrocodone (15 metropolitan areas, 2 states), and oxycodone (14 metropolitan areas, 4 states) were also reported in

more than one-quarter of suicide deaths involving opioids. The most common single agents implicated in opioid-related suicide deaths were hydrocodone, oxycodone, and propoxyphene.

6.1.1.6 AAPCC TESS adverse drug reaction data

The 2004 AAPCC TESS data included adverse [drug] reactions (ADRs) that had been reported to participating poison centers. An ADR was an adverse event that occurred with normal, prescribed, labeled, or recommended use of the product, as opposed to overdose, misuse, or abuse, and included unwanted effects due to an allergic, hypersensitive, or idiosyncratic response to the active ingredients, inactive ingredients, or excipients (excluding concomitant use of a contraindicated medication or food). The ADRs were not classified by seriousness and are presented in this report under SAEs because they resulted in a call to a poison center.

Interestingly, DPP alone or in combination with APAP had the sixth lowest rate of reported ADRs among the 8 opioids (excluding other/unknown opioid*)* and the lowest rate among APAP + opioid combinations (excluding APAP plus other opioid; Table 7). Furthermore, all DPP-containing agents had the lowest rate of reported ADRs (4.7%) in comparison with all codeine (7.8%), all oxycodone (7.0%), and all hydrocodone agents (5.9%).

In contrast to the AAPCC TESS data on poison exposures to DPP-containing agents (which showed DPP to have a similar or slightly greater percentage of ADR cases in comparison with hydrocodone-, oxycodone-, and codeine-containing agents and similar percentages of moderate, major, and fatal outcomes to the stronger opioids, methadone and morphine [see Section 6.1.1.5.1.1]), the therapeutic use of DPP-containing agents seems to be associated with somewhat lower percentages of ADRs reported by poison centers in comparison with the other opioids except methadone and oxycodone, and in comparison with all hydrocodone, all oxycodone, or all codeine agents.

Table 7 Number of adverse drug reactions reported by poison centers by analgesic class in decreasing order of frequency (%): 2004 AAPCC TESS data

Substance implicated in exposure	No. of Exposures	No. of ADRs	%
Opioids			
Meperidine	444	58	13.1%
Morphine	3097	288	9.3%
Pentazocine	175	16	9.1%
Tramadol	3769	324	8.6%
Codeine	1281	98	7.7%
***D*-propoxyphene**	417	27	6.5%
Methadone	3965	244	6.2%
Oxycodone	5510	327	5.9%
Other/unknown opioid	6974	897	12.9%
Acetaminophen + opioid combinations			
Acetaminophen + codeine	5496	443	8.1%
Acetaminophen + oxycodone	6949	539	7.8%
Acetaminophen + hydrocodone	22594	1330	5.9%
Acetaminophen + ***d*-propoxyphene**	6089	278	4.6%
Acetaminophen + other opioid	456	19	4.2%
Aspirin + opioid combinations			
Aspirin + ***d*-propoxyphene**	39	5	12.8%
Aspirin + oxycodone	144	12	8.3%
Aspirin + codeine	243	10	4.1%
Aspirin + other opioid	73	12	16.4%
Ibuprofen + opioid combination			
Ibuprofen + hydrocodone	60	6	10.0%
NSAIDS / Acetaminophen			
Indomethacin	709	87	12.3%
Aspirin only (adult formulations)	7031	175	2.5%
Ibuprofen	70916	1219	1.7%
Acetaminophen only (adult formulations)	32395	409	1.3%
Acetaminophen only, unknown formulations	8609	103	1.2%
Other NSAIDs	5133	297	5.8%
Combined totals			
All codeine	7020	551	7.8%
All oxycodone	12603	878	7.0%
All hydrocodone	22654	1336	5.9%
All *d*-propoxyphene	6545	310	4.7%

Source: Watson (2005)[143]

An adverse [drug] reaction (ADR) was an adverse event that occurred with normal, prescribed, labeled, or recommended use of the product, as opposed to overdose, misuse, or abuse, and included unwanted effects due to an allergic, hypersensitive, or idiosyncratic response to the active ingredients, inactive ingredients, or excipients (excluding concomitant use of a contraindicated medication or food).

6.1.2 Tolerability

In the acute pain, multiple-dose trial comparing DPP + APAP with NSAIDs or APAP by Evans, *et al.*, DPP + APAP was associated with the highest number of defaults (total of 17), where a default from the full regimen occurred if the patient took fewer than the prescribed number of tablets on any of the 6 non-clinic days for which that treatment was prescribed.[1] The second and third highest numbers of defaults were seen with indomethacin with 14 defaults and aspirin with 10 defaults. Most of the defaults with the three agents occurred because of adverse effects (13 of 17 with DPP + APAP; 14 of 14 with indomethacin; and 10 of 13 with aspirin). Phenylbutazone had the fewest defaults followed by mefenamic acid then APAP (6, 8, and 9 defaults, respectively).

Dropouts due to adverse events were three times higher with codeine + APAP (27 of 68 patients [39.7%]) than with DPP + APAP (9 of 68 patients [13.2%]; $p < 0.001$) in the RCT by Boissier, *et al.* [56]

6.2 Unpublished safety findings from VA data

6.2.1 VAMedWatch adverse drug experience data

The number of opioid-related adverse drug experiences (ADEs) voluntarily reported in 2004 and 2005 to the VAMedWatch system as part of the FDA MedWatch program are shown in Table 8. The rates of ADEs are expressed in terms of the number of unique patients prescribed any products containing the respective opioids. Since the opioids shown are not new drugs, the ADEs are likely to be serious adverse events (SAEs).

Table 8 Number and rate of opioid-related adverse drug experiences reported to VAMedWatch

Drug as Reported	ADE count 2004	ADE count 2005	Total uniques FY04	Total uniques FY05	ADE count / unique (x 1000) 2004	ADE count / unique (x 1000) 2005
Fentanyl	113	94	25,243	24,829	4.5	3.8
Morphine	247	270	64,717	71,380	3.8	3.8
Methadone	82	63	27,100[†]	32,981[†]	3.0	1.9
Oxycodone/Acetaminophen	74	95	179,999	177,096	0.4	0.5
Oxycodone	103	76	235,852	238,095	0.4	0.3
Tramadol	37	49	164,636	209,504	0.2	0.2
Hydrocodone/Acetaminophen[‡]	74	89	356,154	418,927	0.2	0.2
Propoxyphene/Acetaminophen	33	13	102,214	99,499	0.3	0.1
Codeine	37	18	204,536	199,380	0.2	0.1
Propoxyphene	4	8	126,105	120,111	0.0	0.1

[†] Rx Uniques may not include methadone dispensed from OAT clinics
[‡] Includes one ADE in 2004 for hydrocodone/carbinoxamine/pseudoephedrine

Propoxyphene/acetaminophen and propoxyphene had ADE rates similar to those for oxycodone-, tramadol-, hydrocodone-, and codeine-containing products. In 2005, they were the lowest of the opioids evaluated. Fentanyl, morphine, and methadone had higher ADE rates.

The top three types of ADEs reported in 2005 are shown by drug in Table 9. The most common ADE reported for DPP + APAP was hypoglycemia; remarkably, ADEs typical of opioids did not constitute the most common ADEs for DPP. The top three ADEs for the other opioids were generally consistent with the known adverse event profiles for those agents. Tramadol was notable for having six types of most common ADEs, including seizures, serotonin syndrome, and shock.

Table 9 Top Three ADEs by Drug (2005)

Drug as Reported	ADE	Count	Total Uniques[†]	Count / Unique (x 1000)
Morphine	Mental status changes	18	71,380	0.25
	Nausea	10	71,380	0.14
	Confusional state	9	71,380	0.13
	Overdose	9	71,380	0.13
	Reversal of opiate activity	9	71,380	0.13
	Vomiting	9	71,380	0.13
Fentanyl	Nausea	5	24,829	0.20
	Hypotension	4	24,829	0.16
	Mental status changes	4	24,829	0.16
	Vomiting	4	24,829	0.16
Methadone	Edema	4	32,981	0.12
	Anxiety	3	32,981	0.09
	Dyspnea	3	32,981	0.09
	Nausea	3	32,981	0.09
Hydrocodone/acetaminophen	Confusion	10	418,927	0.02
	Constipation	6	418,927	0.01
	Delirium	5	418,927	0.01
Oxycodone	Mental status changes	5	238,095	0.02
	Hypotension	4	238,095	0.02
Oxycodone/acetaminophen	Confusional state	4	177,096	0.02
	Nausea	4	177,096	0.02
Propoxyphene/acetaminophen	Hypoglycemia	2	99,499	0.02
Tramadol	Seizure	4	209,504	0.02
	Rash	2	209,504	0.01
	Serotonin syndrome	2	209,504	0.01
	Mental status changes	2	209,504	0.01
	Shock	2	209,504	0.01
	Dizziness	2	209,504	0.01
Codeine	Vomiting	2	199,380	0.01
	Nausea	2	199,380	0.01
	Hives	2	199,380	0.01

[†] From national prescription database, FY05

The data did not suggest that there is a greater safety problem with DPP than other opioid use in veterans. However, this type of data is subject to a number of limitations. The MedWatch program was intended to identify unexpected problems with a drug, and not to register all adverse events related to drug products. It is estimated that only about 1% of all SAEs are reported to the FDA.[145] The number of ADEs reported to MedWatch are probably underestimated because of under-reporting by health professionals, and are subject to reporting bias.

7 Potential alternatives to propoxyphene

7.1 Studies evaluating potential alternatives to propoxyphene

A poor-quality, noncontrolled observational study was designed to determine whether **tramadol** could meet the standards of pain management under the new JCAHO (Joint Commission on Accreditation of Healthcare Organizations) pain guidelines and Tennessee Medicaid (TennCare) reimbursement schedule.[146] Subjects included 14 elderly residents (mean age 85 years; 1 male, 13 females) of a long-term care facility who met the following inclusion criteria: pain intensity scores > 4 on a modified Wong Baker Pain Scale; prescription orders for DPP, meperidine, and / or high dosages of APAP (approaching 4 g/day); suspected neuropathic or mixed nociceptive/neuropathic pain; and / or a diagnosis of diabetes, osteoarthritis, or degenerative joint disease. Patients who had a history of seizures or opioid or alcohol abuse or who had hypersensitivity to tramadol or opioids were excluded. All as-needed medications were discontinued except those used for breakthrough pain. After 4 to 6 weeks on a stable dose of tramadol (titrated from 25 to 300 mg/d over 16 days), the patients' pain scores, use of adjunctive medications, and other clinical outcomes improved (Table 10).

Table 10 Results before and after conversion to tramadol

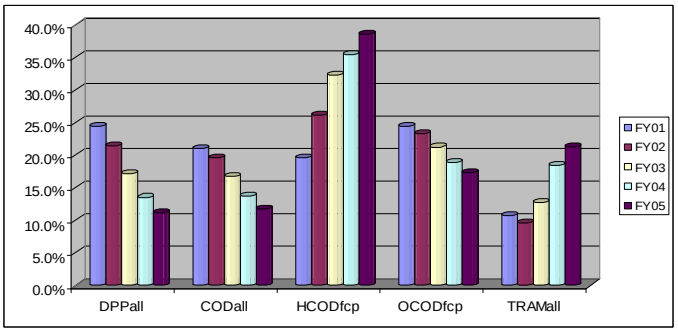
Outcome Measures	Before tramadol (N = 14)	After tramadol
Pain Scores (mWBPS, 0 to 10)	6	2
Taking DPP (% of patients)	50%	14%
Taking high doses of APAP products (% of patients)	43%	14%
Falls (% of patients)	28%	14%
Weight loss (% of patients)	28%	14%
Inappropriate behavioral symptoms (% of patients)	50%	28%
Showing signs of depression (% of patients)	57%	25%
Taking psychotropic drugs (% of patients)	71%	50%
Improvement in ADLs (% of patients)	—	25%

ADL, Activity of Daily Living; APAP, Acetaminophen; DPP, Propoxyphene; mWBPS, Modified Wang Baker Pain Scale

7.2 Current usage patterns of propoxyphene and alternative opioids

From FY01 to FY05, reductions were seen in the percentages of DPP, codeine, and combination oxycodone products dispensed of the total quantity of the five opioid products dispensed (DPP, codeine, hydrocodone, oxycodone, and tramadol). In contrast, the percentages for hydrocodone and tramadol products increased over the 5-year period (Figure 1). This utilization pattern suggests that hydrocodone and tramadol products are being used as alternatives to DPP, codeine, and oxycodone.

Figure 1 Quantity of opioid dispensed as percentage of total quantity of all selected opioids dispensed (FY01 to FY05)



DPPall = All *D*-propoxyphene or *d*-propoxyphene-containing products; CODall = All Codeine or codeine-containing products; HCODfcp = Hydrocodone-containing fixed combination products; OCODfcp = Oxycodone-containing fixed combination products ; TRAMall = All Tramadol-containing products

In FY05, the cost per 30-day equivalent prescription was, in increasing order, $3.42 for hydrocodone-containing products, $5.18 for tramadol-containing products, $5.46 for oxycodone fixed combination products, $5.73 for codeine-containing products, and $6.26 for DPP-containing products. Utilization of the two least costly agents (hydrocodone and tramadol) was higher than that of the three more costly agents (oxycodone, codeine, and DPP).

8 Cost-effectiveness

No pharmacoeconomic study of DPP was found by the literature search.

The FSS drug costs of selected analgesics are shown in Table 11.

Table 11 Lowest FSS costs for single doses of selected opioids

Agent (doses in mg)	Separate components used	FSS Cost Per Dose[†]	NNT	Cost x NNT
Codeine 60 + APAP 1000 (950)	Codeine 60 + APAP 300 and APAP 325 (x 2)	$0.094	2.2[‡]	$0.21
Codeine 30 + APAP 300	No	$0.047	5.7	$0.27
Codeine 60 + APAP 600/650	Codeine 60 + APAP 300 and APAP 325	$0.090	4.2	$0.38
Codeine 60 + ASA 650	Codeine 60 + ASA 325 and ASA 325	$0.122	5.3	$0.65
Codeine 60 and APAP 1000 (975)	Codeine 60 and APAP 325 (x 3)	$0.507	2.2[‡]	$1.12
Hydrocodone 5 mg + APAP 500	No	$0.022	NR	—
Hydrocodone 7.5 mg + APAP 750	No	$0.029	NR	—
Hydrocodone 7.5 mg + APAP 500	No	$0.030	NR	—
Hydrocodone 7.5 mg + APAP 650	No	$0.034	NR	—
Oxycodone 5 mg + APAP 500	No	$0.063	2.2[‡]	$0.14
Oxycodone 10 mg + APAP 650	No	$0.071	2.6	$0.18
Oxycodone 10 + APAP 1000 (975)	Oxycodone 10 + APAP 650 and APAP 325	$0.075	2.7[‡]	$0.20
Oxycodone 5 + APAP 325	No	$0.036	5.5[‡]	$0.20
Oxycodone 5 + APAP 1000	Oxycodone 5 + APAP 500 and APAP 500	$0.070	3.8[‡]	$0.27
Oxycodone 10 + APAP 1000	Oxycodone 5 + APAP 500 (x 2)	$0.126	2.7[‡]	$0.34
Propoxyphene N 100 + APAP 650	No	$0.031	4.4	$0.14
Propoxyphene HCl 65 + APAP 650	No	$0.058	4.4	$0.26
Propoxyphene HCl 130	Propoxyphene HCl 65 (x 2)	$0.294	2.8[‡]	$0.82
Propoxyphene HCl 65	No	$0.147	7.7	$1.13
Propoxyphene N 100	No	$0.653	7.7	$5.03
Tramadol 75	Tramadol 50 (x 1.5)	$0.052	5.3	$0.28
Tramadol HCl 50	No	$0.035	8.3	$0.29
Tramadol 150	Tramadol 50 (x 3)	$0.105	2.9	$0.30
Tramadol 100	No	$0.070	4.8	$0.34
Tramadol 75 + APAP 650	Tramadol 37.5 + APAP 325 (x 2)	$0.764	3.0	$2.29

APAP = Acetaminophen; ASA = Aspirin; EC = Enteric coated; FSS = Federal supply schedule; N = Napsylate

[†] Lowest FSS price (as of 29 March 2006) was used when more than one product was available; non-unit dose formulations.

[‡] Interpret with caution because NNT is based on small data set (N < 250)

If single-dose efficacy is assumed to predict relative multiple-dose efficacy of the analgesics in acute pain (5-day) treatment, the following generalizations can be made about the cost-effectiveness of the opioid analgesics (also refer to Table 4 and Table 5).

At recent VA drug costs (March 2006), it may be less costly to use separate components rather than a fixed combination of codeine 60 mg + APAP 1000 (950) mg. Codeine 60 mg + APAP 1000 (950) mg, using separate components, and oxycodone 5 to 10 mg + APAP 325 to 1000 mg would have comparable or better cost-effectiveness relative to DPPN 100 (or DPP 65 mg) plus APAP 650 mg. Although NNTs have not been reported for combination hydrocodone plus APAP, it has the lowest unit drug cost of the five opioid preparations compared. All preparations of tramadol are less cost-effective than DPP(N) + APAP.

Preparations of DPP(N) alone are less cost-effective than most of the other opioid preparations.

Therefore, switching from a DPP(N) + APAP product to either APAP combinations of codeine, oxycodone, or possibly hydrocodone, could be slightly more cost-effective.

9 Discussion

DPP ± APAP remains a relatively popular analgesic among non-veteran and veteran patients suffering from painful disorders despite more than a 30-year controversy about its therapeutic value. This report assessed the efficacy and safety of DPP in different clinical situations—therapeutic use, drug abuse, and overdose, and for acute and chronic pain—as well as in single and multiple doses to attempt to clarify the conditions which might affect the benefit-to-risk ratio and to shed perspective on the relative efficacy and safety of DPP compared with other opioids. At least part of the reason for the ongoing controversy about the value of DPP as an analgesic may be due to differences among clinical trials in formulation; duration of therapy; pain intensity; cause or type of pain; trial design; method of pain assessment, and prescribed versus actual dosing regimens (compliant versus under- or over-compliant). Another issue to add to the controversy is that the results of the majority of the published RCTs were of doubtful validity and may not be completely applicable to the VA patient population because of differences in patient characteristics (see Section 5.1.2.3).

The generalizability of efficacy results is limited because the majority of trials investigating the efficacy of DPP have involved single doses of drug. Single-dose trials are designed to demonstrate analgesic efficacy, but may not necessarily indicate how multiple doses of a drug will perform in terms of both efficacy and safety or tolerability. A similar disparity between single and repeated doses has been previously observed with oral morphine.[147] The pharmacokinetics of DPP (accumulation of DPP with multiple dosing due to its long half-life) may provide some rationale for claims of improved efficacy of multidose DPP in comparison with single-dose DPP.

The findings of this critical review of the published literature on DPP were generally supportive of the statement that DPP ± APAP was no better than NSAIDs or extra-strength APAP. The best evidence addressing this issue was available from meta-analyses and systematic reviews of RCTs involving single-dose treatment with analgesics. While the analgesic efficacy of DPP is often stated to be similar to that of extra-strength ASA or APAP, DPP differs from NSAIDs or APAP in pharmacologic and safety profiles. Depending on the patient's medical conditions and risk factors, these agents may not always be interchangeable.

Comparisons between DPP ± APAP and other so-called weak opioid analgesics are probably more appropriate. With few exceptions, the evidence generally does not support that there is a significant difference in efficacy between DPP ± APAP and other opioids, such as oxycodone, codeine, and tramadol (alone or in combination with APAP or an NSAID, see Table 4, Section 5.1.1). There was less efficacy and safety data comparing DPP ± APAP with hydrocodone + APAP; however, the pharmacologic and analgesic[148,149] similarities of hydrocodone and oxycodone indirectly suggest that hydrocodone would also have similar efficacy to DPP. Some evidence also suggests that therapeutic doses of DPP tend to be better tolerated and have fewer adverse events than other opioids. At standard therapeutic doses *in the majority of patients without certain characteristics associated with intentional or unintentional overdose*, DPP ± APAP seems to have an acceptable safety profile and has been seldom reported to be associated with SAEs.

The more serious manifestations of DPP toxicity, including coma, respiratory depression, pulmonary edema, seizures, cardiac arrhythmias, and death, have been reported to occur primarily after accidental or suicidal overdoses or in patients with certain characteristics. These characteristics are co-ingestion of alcohol or other CNS depressants, in particular benzodiazepines, tranquilizers, and other sedatives; DPP or other prescription drug misuse (overuse); alcohol or drug abuse or both; emotional problems; and self-destructive behavior (e.g., suicide attempts). It is unknown whether the use of another opioid

agent in patients with these characteristics would be any safer than the use of DPP; however, DPP ± APAP appears to be one of the most toxic agents in intentional and unintentional overdoses.

DPP toxicity is increased with the concomitant ingestion of alcohol or other CNS depressants, and even therapeutic misuse of DPP can be potentially fatal. Although these risk factors may also apply to other weak opioids, only DPP carries a black box warning that advises prescribers to avoid prescribing DPP for patients who are suicidal or addiction prone, taking tranquilizers or antidepressant drugs, and using alcohol excessively, and to educate patients not to exceed their recommended dose and to limit alcohol intake.

Elderly patients (≥ 65 years old) treated with DPP may be at higher risk of hip fractures; however, the risk was no different from that seen with codeine. There was no convincing evidence that the use of other opioids would be safer than DPP in this patient population. There have been no systematic studies evaluating the risk of developing serious complications from DPP in veterans. VAMedWatch data do not suggest that DPP ± APAP poses a greater safety problem than other opioids in veterans. The frequency of DPP dependency, misuse, or addiction among patients with chronic pain requires further study, particularly in veterans.

10 Conclusion

Although new data became available on the single-dose efficacy of propoxyphene and on safety concerns associated with propoxyphene abuse and accidental fatal overdoses, we found no substantive evidence to alter our previous conclusions about the efficacy and safety of propoxyphene relative to other opioids. Our recommendations on the use of propoxyphene in the Veterans Health Administration remain essentially the same as in the previous review.

In the majority of VA patients with mild to moderate acute pain and who do not have certain characteristics associated with intentional or unintentional overdose, single-dose or short-term therapy with DPP ± APAP probably provides adequate analgesia with an acceptable safety profile. The efficacy and safety of long-term therapy with DPP ± APAP for treatment of chronic pain has not been adequately studied.

In patients with certain characteristics associated with intentional or unintentional overdose, the potential for DPP toxicity probably outweighs the drug's potential analgesic benefit. Important safety issues that remain unclear are what is the frequency and risk of serious DPP toxicity among veterans with risk factors, and how does that risk compare with the risk associated with other opioids. Until these questions are answered, it seems prudent to restrict the use of DPP ± APAP to those veterans who do not have the particular characteristics associated with intentional or unintentional overdose and in whom NSAIDs, extra-strength or high-dose APAP, and other opioids are inadequate, intolerable, or contraindicated.

Based on single doses with similar analgesic efficacy in the treatment of postoperative pain, codeine or oxycodone, and probably hydrocodone, in combination with APAP are just as or more cost-effective than DPP ± APAP and are probably acceptable alternatives for DPP ± APAP. These alternative opioids seems to be slightly safer than DPP ± APAP in intentional or unintentional overdoses. Tramadol products may also be considered alternatives but are the least cost-effective and have been associated with substantial toxicities in veterans.

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Appendices

Appendix 1 Methods for Original Report (August 2001)

Published reports of systematic reviews, meta-analyses, reviews, and randomized controlled trials on the efficacy and safety of propoxyphene were retrieved by a computerized literature search of the Medline (1966 to 2000) database. The search terms were *propoxyphene/*therapeutic use* and *propoxyphene/*administration and dosage.* These Medline articles were limited to English language, human subjects, meta-analyses, randomized controlled trials, and clinical trials.

The safety of propoxyphene was also searched on Medline (1966–2000) in all report types using the search terms *propoxyphene/*adverse effects; propoxyphene; substance-related disorders; substance abuse, intravenous; substance abuse detection ; drug and narcotic control; substance withdrawal syndrome, drug interactions*, and *Drug Abuse Warning Network (DAWN)*, and the limiters English language and human subjects. For studies of prognosis, the search terms included *cohort studies*, *mortality*, *follow-up studies, prognosis*, *predict*, and *course.*[150] All subfiles on the Toxline database (1985–present) were searched using the search terms *propoxyphene* and *human* and excluded overlapping Medline articles. A search of the abstracts of the Cochrane Database of Systematic Reviews relating to propoxyphene was also performed. Additional articles were found from the reference list of articles found by the literature search.

Studies with active controls were preferred over those with only placebo controls. In order to make clinically feasible recommendations about possible alternative analgesic treatments, this evaluation included trials that compared propoxyphene to U.S. drug products. Reports that compared propoxyphene to only agents unavailable in the U.S. were excluded from this evaluation; however, articles involving foreign brand products that contained drug entities available in the U.S. were included.

In this report, the primary efficacy variable and primary efficacy evaluation were based on the efficacy variable used for a priori or retrospective power calculations or the first statistically analyzed evaluation of the patient's (not clinician's) assessment of analgesic efficacy that was presented in the results section.

For supplemental information, the Web sites of the Agency for Healthcare Research and Quality (AHRQ), National Institute for Clinical Excellence (NICE), Food and Drug Administration (FDA), European Medicines Evaluation Agency (EMEA), DAWN, and World Health Organization (WHO) were also checked for pertinent reports, pharmacovigilance documents, or clinical guidelines regarding the use of DPP.

Inclusion and exclusion criteria

Reports fulfilling the following criteria were **included**:

- Article published in a journal in hard copy or electronically in English language.
- Treatments consisted of drugs available in the U.S.
- For efficacy evaluations, randomized trials or meta-analyses and systematic reviews of randomized trials involving an active comparator treatment group. (Note: RCTs were included based on the best available evidence; i.e., for a given topic, individual RCTs were excluded if meta-analyses or systematic reviews were available). A randomized trial was considered to be one that was reported to be randomized by the author(s) even if the randomization technique was not specified.
- For safety evaluations, any reports providing safety data were included based on the best available evidence.

Reports fulfilling the following criteria were **excluded**:

- A non-random method was definitely used for treatment allocation. (No trials involving U.S. drugs met this exclusion criterion.)
- All comparator treatments consisted of drugs not available in the U.S. regardless of dosage formulation.
- Trial included children or teenagers (age less than 18 years).
- None of the treatment differences for analgesic efficacy were statistically analyzed.

Appendix 2 Validity criteria and evidence rating scale

The validity of the results of the RCTs reviewed in this report were assessed using major and minor criteria as suggested by Sacket, *et al.*[151] Major criteria for validity were (1) randomization (and concealment) of treatment assignment; (2) complete and sufficient follow-up of patients; and (3) intent-to-treat (ITT) analysis (all patients were analyzed in the groups to which they were randomized). Minor validity criteria were (4) blinding to treatment; (5) equally treated groups (except in regards to experimental therapy); and (6) similar treatment groups at the start of the trial.

The quality of evidence and strength of recommendations were assessed using a rating scale based on the evidence rating system used by the U.S. Preventative Services Task Force[a] and adapted from the Canadian Task Force on the Periodic Health Examination (see Appendix Table 1).

Appendix Table 1 Evidence Rating Scale

Quality of Evidence	
I	Evidence obtained from at least one properly designed, randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series studies with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.
Strength of Recommendation	
A	There is good evidence to support that the intervention be adopted.
B	There is fair evidence to support that the intervention be adopted.
C	There is insufficient evidence to recommend for or against the intervention, but recommendations may be made on other grounds.
D	There is fair evidence to support that the intervention be excluded.
E	There is good evidence to support that the intervention be excluded.

[a] (http://text.nlm.nih.gov/cps/www/cps.3.html)

Appendix 3 Summary of trials

Overviews of study designs for both acute pain and chronic pain trials as well as nonserious adverse events are provided in this section. Summaries of the multiple-dose, acute pain trials evaluated in this review are presented in Appendix Table 2 and Appendix Table 3. A summary of the multiple-dose, chronic pain trials is provided in Appendix Table 4.

Overview of study designs: RCTs evaluating multiple-dose DPP ± APAP in acute pain

The acute pain trials differed in study design, patient characteristics, pain severity, type of pain, sample size, and treatment regimens. Fourteen of the multiple-dose, acute pain trials evaluated DPP HCl in combination with APAP (DPP + APAP),[1, 49-51, 53-61, 64] and two trials used DPPN+A.[63,73] Three trials used either DPP[59] or DPPN alone.[55,64] There was one open-label trial[66]; all others were single- or double-blinded investigations. Two trials used placebo controls in addition to active comparators.[55,65]

Of the 19 RCTs, 14 used two treatment arms,[49, 51, 52, 55-65] 3 trials had 3 treatment arms,[57,61,65] 1 trial had 5 treatment arms,[55] and 1 study had 6 treatment arms[1]. Results for the six-arm trial are presented by the comparative efficacy of the NSAID relative to DPP (superior or no difference) and, therefore, the Evans, *et al.* reference appears twice in Appendix Table 2.

Patient populations consisted of only women in five trials,[57,58,61,65,66] only men in one trial,[64] and elderly patients (aged 70 to 93 years) in one trial[75]; the remaining 10 trials included men and women.

The DPP dosing interval was longer than the recommended interval of every 4 hours in 14 of the multiple-dose trials. Drug was dosed every 6 hours [63,72,74] or 4 times daily[1,62,64,75] in seven trials; and every 8 hours[57] or 3 times daily[49, 51, 53, 57, 60, 61] in seven trials. Four of the multiple-dose trials dosed DPP every 4 hours[55,59,73] or every 4 to 6 hours.[61]

Two of the trials specified the primary efficacy variable used to determine analgesic efficacy.[56,60] The majority of the trials did not declare the primary efficacy variable. As noted in Appendix 1, for these trials, the assumption about the primary efficacy variable was based on the first statistically analyzed evaluation of the patient's assessment of analgesic efficacy that was presented in the results section.

All except two of the trials used pain intensity, assessed by pain intensity rating scales, visual analogue scales (VASs), or categorical, non-numerical verbal pain scales, as the primary analgesic efficacy variable. The exceptions were one trial that rated treatment based on pain relief[59] and another trial that evaluated analgesia by a dichotomous (most/least effective), subjective general assessment of efficacy by the patient.[57]. Although most of the trials used pain intensity as the primary efficacy variable, the methods and frequencies of assessing pain intensity differed. Eleven trials used either 4-point,[1, 53, 57, 60, 62] 5-point,[55,58,66,72,75] or 11-point[73] pain intensity or verbal pain scales. Four trials used the more sensitive tests, visual analogue scales (VASs),[60,62,63,74] and two trials used visual analogue and verbal pain scales[56, 61]. Frequencies of assessments varied between trials from one final assessment[57] to hourly assessments for 12 hours.[66]

Validity of acute pain trial results

The major and minor validity criteria are described in Appendix 2. The results of all the RCTs were considered to be of doubtful validity because of one or more of the following major, minor, or other validity issues:

Major validity issues

- Properly performed but ineffective randomization resulted in mismatched treatment groups, and the discrepancy between groups may have affected the results. Baseline characteristics of treatment groups differed in age ($p < 0.05$)[63] or proportion of patients prescribed rehabilitation exercises.[64] For these reasons, the quality of evidence (QE) for these trials was rated

category II-1. The QE for each of the remaining trials was rated category I (based on proper randomization). (Also see Appendix 1 for assumptions about randomization technique.)

- High rate of patients lost to follow-up (23.2%, 13 of 56 enrolled patients). [57]
- An intent-to-treat analysis was not used (i.e., such analysis was not described in the methods, or treated patients who were excluded or withdrawn were clearly or apparently not analyzed in the group to which they were randomized).[55-60, 63-65]

Minor validity issues

- The assessor of analgesia was not blinded to treatment (in all[1,58,62,64,66,75] except one[63] of the single-blinded trials).
- Treatment regimens were designed to be dissimilar between groups and the difference may have affected efficacy results, such as different doses of APAP[56]; different dosing frequencies[58]; or use of a loading dose in only one of the treatment groups.[73]
- Dosage regimens within treatment groups may have been different because variable (as-needed) dosing of study analgesics was allowed[59-61,73,74,76] (furthermore, since the use of an as-needed dosing schedule has been reported to be inadequate at least 34% of the time[67] it may have affected the trial results).

Other validity issues

- The actual duration of treatment was too short (less than 7.5 days or five times 36 hours, the maximum half-life of NPP[17]) to allow development of steady-state blood concentrations of DPP and NPP and, therefore, the results may not have reflected the full analgesic effects of DPP and NPP (only two trials evaluated drugs at steady-state[64,73]).
- Results were inconclusive because of possible Type II error (a statistically significant difference was not found when a true difference existed).[1,55,62-64,66,72,74-76]
- Results were based on preliminary data.[53, 57]
- General assessment of treatment efficacy at the final visit relied on patient recall, which may have influenced the patient's interpretation of pain intensity or relief.[57]

In total, eight trials met major[1,55,56,58,59,61,65,66] and six trials met minor[48, 50, 53, 56, 57, 65] validity criteria. Only the trials by Buck, *et al.* (preliminary results) and Young, *et al.* met both major and minor (excluding other) validity criteria.

Overview of study designs: RCTs evaluating multiple-dose DPP ± APAP in chronic pain

As with the acute pain, multiple-dose RCTs, the chronic pain trials varied in study design, patient populations, pain characteristics, and treatment regimens (see Appendix Table 4). One of the trials focused on the psychomotor effects of the analgesics.[69] Another trial evaluated treatments based on health status as a clinical outcome measure.[68]

The dosing interval of DPP was longer than the recommended interval of every 4 hours in three of the chronic pain trials (3 times daily[68,69]; or 3 to 4 times daily[70]). In one trial, the dosing interval was not stated.[71]

Validity of chronic pain trial results

The validity of results in all chronic pain trials was considered to be doubtful because of the following major and minor validity issues (for validity criteria, see Appendix 2):

Major validity issues

- Bias in pain assessment due to open-label treatment.[71]
- Lack of intent-to-treat analysis.[68-70]

Minor validity issue

- Unequal treatments due to the use of different dosing methods (titrated DPP vs. fixed dose morphine).[71]

None of the chronic pain trials met major validity criteria.

Nonserious adverse events

Nonserious adverse events included here were those specified as nonserious, those described as minimal, minor, or in other similar terms, or those not reported by the author as being serious.

Acute pain, single-dose trials (meta-analyses and systematic reviews)

No statistically significant difference in the relative risk of reported nonserious AEs (NSAEs) (headache, nausea, dizziness, or drowsiness) was found between DPP + APAP (65 mg + 650 mg) and APAP (650 mg) when given in single doses for various types of pain [49].

In the systematic analyses including data on single-dose DPP + APAP for post-operative pain by Collins, *et al.*[47] and Moore, *et al*,[48] the main AEs evaluated were dizziness, drowsiness / somnolence, headache, nausea, and vomiting. The frequencies of dizziness and drowsiness / somnolence were lower for DPP + APAP (65 mg + 650 mg) than for codeine + APAP (60 mg + 650 mg); however, the 95% CIs for number-needed-to-harm (NNH) overlapped. The NNH was 50 (24 to ∞) and 14 (9.1 to 30) for the two AEs, respectively, for DPP + APAP, and 25 (7.7 to 257) and 10 (4.6 to 31), respectively, for codeine + APAP.[47] The same dose of combination DPP + APAP had a similar frequency (NNH 95% CIs overlap) of drowsiness / somnolence in comparison with tramadol 100 mg (NNH, 95% CI: 13, 9 to 20). Dizziness was the only AE that showed a statistically significant difference between treatments with the frequency lower for DPP + APAP than for tramadol 100 mg (9, 6 to 13). [47]

The frequencies of nausea and dizziness were lower with DPP + APAP (~5% and ~1%, respectively) than with tramadol 150 mg (~24% and ~25%) in the treatment of dental pain (no statistical data).[48]

The results of studies investigating the cognitive and psychomotor effects of single-dose DPP are conflicting. Impairment in critical flicker fusion threshold (CFFT) was noted in healthy volunteers,[152] while no significant impairment was found in CFFT and other measures in other studies.[44,153] The impairment in cognitive or psychomotor function associated with DPP seems to be less pronounced than that of either alcohol[44] or lorazepam.[152]

Acute pain, multiple-dose RCTs

Only a few trials performed statistical analyses on safety evaluations. Boissier, *et al.* observed more NSAEs with codeine + APAP than with DPP + APAP on both an open questionnaire (51 of 71, 71.8% and 38 of 70, 54.3%, respectively; p=0.019), and on a closed questionnaire (60 of 71, 84.5% and 50 of 70, 71.4%, respectively; p=0.029). Significantly more gastrointestinal (p=0.010) and neurologic (p=0.048) intolerance was noted with codeine + APAP.

In the study of Evans, *et al.*, there were no statistically significant differences between DPP + APAP and NSAIDs or APAP in terms of adverse events. The results of the trial by Sleet, *et al.* showed that a substantially greater proportion of patients on DPP + APAP (21 of 46, 45.6%) than on mefenamic acid (6 of 41, 14.6%) developed NSAEs. A higher frequency of nausea or vomiting was seen with DPP + APAP than mefenamic acid (7 of 46 patients [15.2%] vs. none of 41 patients, respectively;

$p < 0.05$). These results differ from those of Evans, *et al.*, who found no difference between DPP + APAP and mefenamic acid.

A low frequency of AEs was seen in all treatment groups in each of the remaining acute pain, multiple-dose RCTs. No remarkable differences in AE rates were noted between treatment groups (no statistical analyses).

Chronic pain, multiple-dose trials

Parr, *et al.* found more patients on DPP + APAP than diclofenac SR experienced tiredness/sleep disturbance (50 vs. 21 patients [13.1% vs. 5.6%]; $p < 0.01$) and dizziness/lightheadedness (30 vs. 14 patients [7.8% vs. 3.8%]; $p < 0.05$), while fewer DPP + APAP patients than diclofenac SR patients suffered abdominal/epigastric pain or indigestion (18 vs. 40 [4.7% vs. 10.7%]; $p < 0.01$) and diarrhea (2 vs. 14 [0.5% vs. 3.8%]; $p < 0.01$).

When DPP was compared as a WHO Step 2 agent with morphine as a Step 3 agent in the treatment of opioid-naive patients with cancer pain, 3 (18.7%) of the 16 morphine patients had to switch to DPP because of intolerable side effects.[71] Nausea and vomiting, drowsiness, and dry mouth were statistically significantly more severe in the group taking morphine SR 20 mg daily than the group taking DPP 120 to 240 mg daily ($p < 0.01$); however, clinical differences were small (i.e., none vs. slight symptom intensity).

Saarialho-Kere, *et al.* observed that DPP (65 mg t.i.d. × 2 d then 130 mg × 1 dose) impaired body balance and critical flicker discrimination while not affecting coordination or reactive skills.[69] DPP in combination with amitriptyline (DPP 65 mg b.i.d. + amitriptyline 25 mg × 2 d then single dose of DPP 65 mg + amitriptyline 25 mg) also decreased critical flicker discrimination and body balance, as well as medial attention and symbol copying. In comparison, indomethacin (25 mg t.i.d. × 2 d then 50 mg × 1 dose) transiently affected flicker recognition and slightly improved lateral attention. Overall, all treatments caused mild alterations in psychomotor performance that corresponded with peak plasma concentrations of drug.

Safety trials

Two additional RCTs evaluated the psychomotor effects of DPP.[152 154] For details, see Appendix 3, Appendix Table 5.

Maintenance treatment trials

In the study by Woody, *et al.*, only 12% of the 227 opioid-tolerant heroin addicts who took high doses (400 to 1000 mg/d) of DPPN for more than 4 weeks developed NSAEs. The symptoms were consistent with CNS irritability (increased anxiety, restlessness, or confusion).[43] The AEs resolved after discontinuation of DPPN.

Appendix Table 2 RCTs comparing multiple doses of DPP ± APAP with NSAIDs or APAP in acute pain

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP ± APAP preparation and dosage regimen[‡]	Comparator(s) and dose(s)	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				**(years)**	**[HCl equivalent (mg/day)]**	**[mg/day]**	**(days)**	**(n, unless otherwise stated)**	**(n, unless otherwise stated)**
DPP ± APAP inferior to NSAID or APAP combination in terms of analgesic efficacy (p < 0.05)									
Anderson (1978)[57] [I, B]	DBCO (SGA)	Primary dysmenorrhea (NR)	30 [0 M / 30 F]	(<16 to 34)	DPP+APAP 65 + 650 mg q8h [195 + 1950]	Mefenamic acid (MA) 500 mg q8h until symptoms gone or menses ended [1500][§]	3.5[‖††]	Lost to follow-up: 13 of 56 enrolled patients (23.2%) General assessment by patient at the final visit: More patients chose MA as the most effective treatment vs. DPP+APAP (12 vs. 3) and fewer patients chose MA as the least effective treatment (2 vs. 15). MA > DPP+APAP* for general patient preference using +1, 0, and –1 scores for best, second best, and worst treatments, respectively (total scores 10.5 vs. –12.5; p < 0.001) MA > DPP+APAP* for total symptom score with 3 indicating greatest severity for any symptom, 315 vs. 440 (p < 0.01) MA = DPP+APAP for absence from work or school (10.5 d vs. 15.25 d; p > 0.05) MA = DPP+APAP for number of capsules taken (548 vs. 633; p > 0.05) Fewer doses of additional analgesics taken in MA vs. DPP+APAP group (mean for 3 cycles, 2.6 vs. 6.8; p < 0.01)	AEs, seriousness / intensity not reported: 2 MA (1 DVT, 3 wk after taking MA; 1 extremely dizzy and nauseated); 1 DPP+APAP (extremely dizzy and nauseated; completed trial) WDAE: 2 MA (1 headaches, 2 DVT)

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP ± APAP preparation and dosage regimen[‡]	Comparator(s) and dose(s)	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent (mg/day)]	[mg/day]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Evans (1980)[1] [I, B]	SBCO (4PIRS)	Low back pain (Moderate)	60 (30 per treatment group) [20 M / 40 F]	47.0 ± 9.2	DPP+APAP 65 + 650 mg q.i.d. [260 + 2600]	Mefenamic acid (MA) 500 mg t.i.d. [1500] Aspirin (ASA) 900 mg q.i.d. [3600]	7	Spinal anterior flexion: MA = DPP+APAP (mean, 5.7 vs. 5.6 cm; p > 0.05). ASA = DPP+APAP (mean, 5.7 vs. 5.6; p > 0.05). Mean daily pain index with 0–nil, 3–severe: MA > DPP+APAP* (1.4 vs. 1.7; p < 0.05). ASA > DPP+APAP* for mean daily pain index with 0–nil, 3–severe (1.4 vs. 1.7; p < 0.05). MA > DPP+APAP* for radiating pain not brought on by sneezing (p < 0.05). Higher percentage of recommended dose taken in MA vs. DPP+APAP group (91.8% vs. 71.7%; p < 0.01). Fewer defaults from full regimen in MA vs. DPP+APAP group (8 vs. 17, out of 30 possible). MA = DPP+APAP: patients' preference with 1–best, 3–worst (mean ranks, 1.75 vs. 2.07; p > 0.05).	Intensity of AEs not recorded. Fewer defaults from full regimen due to AE in MA vs. DPP+APAP group (2 vs. 13; p < 0.001). Larger proportion of MA patients with no AEs but treatment difference not statistically significant (60% vs. 37%, p > 0.05). Smaller proportion of MA patients with neurologic AEs but treatment difference not statistically significant (8 vs. 15; p > 0.05). Number of patients with any AE: 12 MA vs. 19 DPP+APAP.

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP ± APAP preparation and dosage regimen[‡]	Comparator(s) and dose(s)	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent (mg/day)]	[mg/day]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Langrick (1982)[58] [I, B]	SBPG (5PIRS)	Primary dysmenorrhea (Mild to severe)	39 [0 M / 39 F]	[21] (16 to 34)	DPPN+APAP 100 + 650 mg at onset of pain then t.i.d. [195 + 1950]	Naproxen (NAP) 275 mg at onset of pain then q.i.d. [1100]	3[ǁ]	Lost to follow-up: 3 (2 NAP, 1 DPPN+APAP) 9 of 12 hourly mean pain scores on day 2 were lower on NAP vs. DPPN+APAP (p < 0.05) Patients' daily assessments of pain severity was lower on NAP vs. DPPN+APAP on day 2 (1.7 vs. 2.1; p < 0.05) and day 3 (0.4 vs. 0.8; p < 0.05) with 0–none, 4–very severe. Symptom control higher on NAP vs. DPPN+APAP on day 1 (3.9 vs. 3.4; p < 0.05) and day 2 (4.3 vs. 3.7; p < 0.01) on scale of excellent to worse (values not specified). Lower degree of disturbance of concentration or ability to go about normal routine on NAP vs. DPPN+APAP based on 4-point rating scale for Episode 1 (0.67 vs 1.37; p < 0.05), Episode 2 (0.62 vs. 1.33; p < 0.05), and Episode 3 (0.50 vs. 1.43; p < 0.01)	WDAE: 1 NAP (nausea) AE, seriousness not reported: 6 NAP, 9 DPPN+APAP
Cantor (1968)[59] [I, B]	DBPG (4PRS)	Gingivectomy (NR)	100 [26 M / 74 F]	(19 to 56)	DPP 64 mg q4h or prn [384 or prn]	Percogesic (PERC) 2 cap q4h or prn [APAP 3900, phenyltoxamine 360, homatropine methybromide 30, caffeine 360 or prn]	1 to 2	PERC > DPP* using ridit analysis for time of onset (0.58; p < 0.05) and degree of pain relief (0.60; p < 0.05)[ǁǁ] PERC = DPP, ridit analysis: duration of pain relief (0.47; p > 0.05)[ǁǁ] PERC = DPP, for onset (1.50 vs. 1.32), duration (0.66 vs. 0.62), and pain relief (2.14 vs. 1.86) (p > 0.05 for each analysis) by distribution analysis (using 3-point scoring system where the number of points assigned were 3 for excellent pain relief; 2 for onset < 30 min, duration 4 to 6 h, or good pain relief; 1 for onset 30 to 60 min, duration 2 to 4 h, or poor pain relief; and no points for others)	AEs minimal in both groups. 11 cases PERC (4 nausea, 5 drowsiness, 2 heartburn) 4 cases DPP (3 drowsiness, 1 nausea)

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP ± APAP preparation and dosage regimen[‡]	Comparator(s) and dose(s)	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent (mg/day)]	[mg/day]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
No difference between DPP+ APAP and NSAID in terms of analgesic efficacy (p > 0.05)									
Giles (1981)[72] [I, B]	DBPG (5PIRS)	Dental extraction (NR)	38 [16 M / 23 F]	25 ± NR	DPP+APAP up to 65 + 650 mg q6h [260 + 2600]	Ibuprofen (IBU) 400 mg q6h [1600 (max)]	7	Withdrawal due to lack of efficacy: 2 DPP+APAP IBU = DPP+APAP for degree of pain at day 3 (mean score with 0–none, 4–very severe: 1.8 vs. 2.1; p > 0.10) and day 7 (1.0 vs. 0.9; p > 0.10). IBU = DPP+APAP for degree of pain relief at day 3 (mean score with 0–no relief, 4–complete: 3.0 vs. 3.0; p > 0.10) and day 7 (3.3 vs. 3.3; p > 0.10). Less trismus on IBU with mean mouth opening greater on POD 3 (83.5% vs. 73.8%; p < 0.025) but no difference on POD 7 (91.8% vs. 91.9%; p > 0.10).	WDAE, severe: 5 DPP+APAP (excluded from efficacy analyses). AEs, seriousness not reported: 3 infected sockets (1 IBU, 2 DPP+APAP). Number of reports by severity (IBU vs. DPP+APAP; severity scores of 1 to 3 were not defined): 1 12 vs. 17 2 6 vs. 8 3 4 vs. 15 Number of reports by organ system (IBU vs. DPP+APAP): GI 1 vs. 10 CNS 21 vs. 30 Total 22 vs. 40 Fewer patients on IBU reported AEs during early post-op period (no data; p < 0.05)
Buck (1978)[65] [I, C]	DBPG DD Preliminary (4PIRS)	Episiotomy (NR)	57 [0 M / 57 F]	NR	DPP+APAP 65 + 650 mg t.i.d. [195 + 1950]	Diflunisal (DIF) 500 mg b.i.d. [1000] Placebo (PL) control	2	All 3 treatments produced the same effect in relieving pain at night. DIF = DPP+APAP = PL for spontaneous pain at 2, 4, 6, and 8 h after start of therapy (no data; p-value NR) All 3 treatments equally beneficial in patients' opinion (no data). DIF better than DPP+APAP, and both better than PL according to investigator's opinion of response (no data).	AEs: 1 DIF (tiredness) 4 DPP+APAP (tiredness and dizziness) 2 PL (tiredness)

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP ± APAP preparation and dosage regimen[‡]	Comparator(s) and dose(s)	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent (mg/day)]	[mg/day]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Jaffé (1978)[57] [I, B]	DBPG DD Ongoing (4PIRS)	Sprains and strains (Moderate)	51 [29 M / 20 F]	(16 to 62)	DPP+APAP 65 + 650 mg t.i.d. [195 + 1950]	Diflunisal (DIF) 500 mg b.i.d. [1000]	3	DIF = DPP+APAP for patients' assessment of relief of spontaneous pain (complete, partial, no relief, and no answer) on day 1 (2, 6, 17, 1 vs. 1, 13, 11, 0) and day 3 (8, 11, 7, 0 vs. 8, 14, 2, 1) (p-values NR). DIF = DPP+APAP for pain on movement on day 1 (1, 14, 10, 1 vs. 0, 12, 13, 0) and day 3 (2, 18, 6, 0 vs. 1, 18, 5, 1) (p-values NR). DIF = DPP+APAP for patients' and physicians' overall evaluations of treatment (p-values NR).	3 DPP+APAP complained of the quantity of tablets and found them difficult to take (1 withdrew, omitted from analysis; 1 withdrew after 24 h, results from first 24 h included; 1 completed trial). 1 DIF (headache, considered by clinician to be causally related) 1 DPP+APAP (nausea on 2 occasions, considered by clinician to be causally related).

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP ± APAP preparation and dosage regimen[‡]	Comparator(s) and dose(s)	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent (mg/day)]	[mg/day]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Rao (1982)[75] [I, B]	SBPG (5PIRS)	Traumatic injury (Moderate)	40 [7 M / 33 F]	80 to 81 (70 to 93)	DPP+APAP 65 + 650 mg q.i.d. [260 + 2600]	Diflunisal (DIF) 500 mg b.i.d. [1000]	5	Lost to follow-up: 1 1 DPP+APAP obtained no relief after 4 d and did not return on day 5. DIF = DPP+APAP for spontaneous pain in terms of ratio of number of patients who were much better (M) or better (B) to same (S) or worse (W). M/B:S/W for DIF vs. DPP+APAP, results for day 5 only shown here, 15:1 vs. 15:1. DIF = DPP+APAP for night pain; results for day 5 only shown here, 17:1 vs. 11:2. DIF > DPP+APAP* for pain on passive movement on day 3, 13:2 vs. 4:8 (p < 0.007); day 4, 13:2 vs. 6:6 (p < 0.049); and day 5, 14:1 vs. 6:5 (p < 0.032). DIF > DPP+APAP* for tenderness on day 2, 16:4 vs. 8:11 (p = 0.01); and day 3, 17:1 vs. 12:7 (p = 0.05). DIF = DPP+APAP for patient's evaluation of overall response based on success:failure ratio (success–excellent and good; failure–fair, poor, and none), results for day 5 only shown here, 13:7 (65%) vs. 8:11 (40%) (p-value NR). DIF = DPP+APAP for clinician's assessment of overall response, 14:6 (70%) vs. 11:9 (56%) (p-value NR).	NSAEs: 1 DIF (nausea and vomiting of moderate intensity thought to be probably related to DIF). 1 DPP+APAP (nausea of moderate intensity thought to be possibly related to DPP+APAP).

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP ± APAP preparation and dosage regimen[‡]	Comparator(s) and dose(s)	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent (mg/day)]	[mg/day]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Jokl (1989)[73] [I, B]	OLPG (11PIRS)	Arthroscopic knee surgery (Mild to moderate)	26 [20 M, 6 F]	36.5 ± 11.0 Diflunisal 35.1 ± 10.0 DPPN+APAP	DPPN+APAP 100 + 650 mg q4h prn [600 + 3900 prn]	Diflunisal (DIF) 500 mg q12h prn [1000 prn] (following 1000 mg loading dose)	15 (max.)	DIF = DPPN+APAP for mean self-rating pain scores (0–no pain, 1 to 3–mild pain, 4 to 7–moderate pain, 8 to 10–severe pain) during 8 to 16 h, 17 to 24 h, 25 to 48 h, and 8 to 48 h (overall rating) (p-values ≥ 0.32). Overall rating only shown here, 4.1 vs. 4.6 (p = 0.59). DIF = DPPN+APAP for patients' global assessment of efficacy; 9 of 12 (75%) vs. 10 of 14 (71%) patients rated treatment good or excellent (p = 0.84); and 4 (33%) vs. 3 (21%) rated treatment excellent (p = 0.50).	No patients reported AEs.
Sleet (1980)[74] [I, B]	DBPG DD (100VAS)	Traumatic injury or soft tissue infection (NR)	87 [50 M / 37 F]	37.0 ± 17.1 (15 to 80)	DPP+APAP (32.5 + 325 mg/cap) 2 cap to total of 3 doses in first 24 h, followed by 1 or 2 cap q6h prn [130 to 260 + 1300 to 2600 prn]	Mefenamic acid (MA) (250 mg/cap) same dosing regimen as DPP+APAP [1000 to 2000 prn]	5	MA =/> DPP+APAP* for mean pain relief on retiring adjusted for regression on initial pain (calculated pain scores from 0.00 to 1.57 corresponding to original analgesic VAS from 0 to 100); no treatment differences except on day 3 (0.25 vs. 0.02, p < 0.05 for the difference). MA = DPP+APAP for mean number of capsules / dummy placebo tablets taken per day, adjusted for regression on initial pain score, on days 1 to 5; results for day 5 only shown here, 6.3 vs. 7.3 (p > 0.05 for each analysis). MA = DPP+APAP for pain, if disturbing sleep, adjusted for regression on pain before retiring on days 1 to 5; results for day 5 only shown here, 0.43 vs. 0.40 (p > 0.05 for each analysis).	1 Severe AE: DPP+APAP (nausea) 4 WDAEs: 0 MA, 4 DPP+APAP (1 severe nausea, 1 headache, 1 rash/fever/backache, 1 nausea) 27 AEs: 6 MA, 21 DPP+APAP (no statistics reported). Vomiting and nausea associated with DPP+APAP (0 vs. 7; p < 0.05).

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP ± APAP preparation and dosage regimen[‡]	Comparator(s) and dose(s)	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent (mg/day)]	[mg/day]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Stableforth (1977)[76] [I, B]	DBPG (4PIRS)	Soft tissue injury (NR)	48 34 M / 14 F]	NR	DPP+APAP 65 + 650 mg up to t.i.d. prn [195 + 1950 prn (max)]	Mefenamic acid (MA) 500 mg up to t.i.d. prn [1500 prn (max)]	3	MA = DPP+APAP for all the following assessments (p > 0.05 for each) (0–no change, 3–good improvement), day 7 values only shown here: –Pain 2.21 vs. 1.87 –Swelling 1.79 vs. 1.93 –Tenderness 2.00 vs. 1.80 –Joint mobility 1.67 vs. 1.72 –Overall assessment 1.67 vs. 1.65 2 Study treatment ineffective: 1 MA and 1 DPP+APAP; both took alternative or additional analgesic.	4 WDAE: 2 MA, 2 DPP+APAP (all GI intolerance) 8 AE, no further details: 4 MA, 4 DPP+APAP
Williams (1982)[66] [I, B]	OLPG (5PIRS)	Primary dysmenorrhea (NR)	59 [0 M / 59 F]	19.2 to 20.3 (15 to 36)	DPP+APAP 65 + 650 mg t.i.d. [195 + 1950]	Naproxen (NAP) 275 mg q.i.d. [1100]	3[ll]	Lost to follow-up: 9 (15%), 7 NAP and 2 DPP+APAP Hourly scores of pain showed similar changes in the two treatment groups (no statistics). NAP = DPP+APAP for pain severity (0–none, 4–very severe) on day 1 (1.52 vs. 1.65), day 2 (1.25 vs. 1.72), and day 3 (0.67 vs. 0.81) (p > 0.05 for each analysis). NAP > DPP+APAP* for symptom control (1–worse, 2–no change, 3–mild, 4–moderate, 5–excellent) on day 2 (4.04 vs. 3.58) and day 3 (4.43 vs. 4.06) (p < 0.05 for both analyses).	6 Severe AEs (all DPP+APAP, no details). 2 WDAEs (both DPP+APAP, CNS AEs) Smaller proportion of patients reported AEs with NAP (6 of 24, 25%) than with DPP+APAP (14 of 24, 58%) (p = 0.03). Most frequently reported AEs for NAP vs. DPP+APAP were nausea (2 vs. 6), dizzy/giddy (1 vs. 6), and sleepy/drowsy (2 vs. 6), and these AEs were more frequent in the DPP+APAP group. 2 NAP reported gastric upset.

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP ± APAP preparation and dosage regimen[‡]	Comparator(s) and dose(s)	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent (mg/day)]	[mg/day]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Beveridge (1985)[64] [II-1, B]	SBPG (4PIRS)	Soft-tissue injury (Moderate)	63 [68 M, 0 F]	21.5 ± 4.2	DPPN 100 mg initially, then q.i.d. [260]	Naproxen (NAP) 550 mg initially, then 275 mg q.i.d. [2200]	5 to 14[§§]	Lost to follow-up: 1 A greater proportion of patients were instructed to perform rehabilitation exercises in the NAP group (10 of 31, 32%) than in the DPPN group (3 of 32, 9%). Cumulative total number of patients requiring no further treatment was greater with NAP than with DPPN on day 8 (~11 vs. 5), day 9 (~13 vs. ~6), and day 10 (~17 vs. 9) (p < 0.05 for each analysis). NAP >/= DPPN* for mean number of days for patients to return to training: 7.0 vs. 7.8 d; to be available for selection: 8.3 vs. 9.6 d (no statistics). NAP = DPPN for mean daily symptom scores (4–none, 1–severe) for pain on passive movement (2.00 vs. 2.03) and tenderness (1.77 vs. 1.75) (p > 0.05 for each analysis). NAP >/= DPPN* for swelling on days 2 to 6 (~3.5 to 3.8 vs. ~3.5 to 3.6) (p < 0.05). 1 Study treatment ineffective: (DPPN, withdrew from trial)	1 WDAE (NAP, epigastric pain and heartburn).

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP ± APAP preparation and dosage regimen[‡]	Comparator(s) and dose(s)	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent (mg/day)]	[mg/day]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Evans (1980)[1] [I, B]	SBCO (4PIRS)	Low back pain (Moderate)	60 (30 per treatment group) [20 M / 40 F]	47.0 ± 9.2	DPP+APAP 65 + 650 mg q.i.d. [260 + 2600]	Indomethacin (INDO) 50 mg t.i.d. [150] Phenylbutazone (PBZ) 100 mg t.i.d. [300] APAP 1000 mg q.i.d. [4000]	7	INDO = PBZ = APAP = DPP+APAP for spinal anterior flexion. INDO = PBZ = APAP = DPP+APAP for mean daily pain index with 0–nil, 3–severe (1.5 vs. 1.4 vs. 1.7 vs. 1.7; p > 0.05 for all analyses). PBZ > DPP+APAP* for percentage of recommended dose taken (96.5% vs. 71.7%; p < 0.01). APAP > DPP+APAP* for percentage of recommended dose taken (89.8% vs. 71.7%; p < 0.05). Fewer defaults from full regimen in INDO, PBZ, and APAP groups (14, 6, and 9, respectively) vs. DPP+APAP (17, out of 30 possible). INDO = PBZ = APAP = DPP+APAP for patients' preference with 1–best, 3–worst (mean ranks, 1.98 vs. 1.68 vs. 2.15 vs. 2.07; p > 0.05 for all analyses).	Fewer defaults from full regimen due to AE on PBZ and on APAP vs. DPP+APAP (1 and 4 vs. 13; p < 0.001). A larger proportion of PBZ and APAP patients had no AEs but the treatment differences were not statistically significant (37%, 53% and 57% vs. 37%; p > 0.05). A smaller proportion of PBZ and APAP patients (27% and 27%) than DPP+APAP and INDO patients (50% and 53%) had neurologic AEs but treatment differences were not statistically significant (p > 0.05). Number of patients with any AE: 4 PBZ, 13 APAP, 19 INDO, 19 DPP+APAP.

Results presented for agents available in the U.S. (See [§] below.)

AE = Adverse event; APAP = Acetaminophen; DPP = *d*-Propoxyphene; F = Females; M = Males; NR = Not reported; POD = Post-operative day; Prn = Pro re nata (as needed); QE = Quality of evidence; RRA = Recruited, randomized, or analyzed (patient sex was reported for different study populations among the various trials); SoR = Strength of recommendation regarding treatment comparisons for analgesic efficacy; WDAE = Withdrawal from study or discontinuation of medication due to adverse event. Abbreviations for drugs are shown under the columns for either age or dosage regimens in the relevant table row.

[†] Study design: DBPG = Double-blind, parallel group; DD = Double-dummy; OLPG = Open-label parallel group; SBCO = Single-blind, crossover; SBPG = Single-blind, parallel group.
PEV (Primary efficacy variable); PAM (Pain assessment method): 4PIRS = 4-point Pain intensity scale; 5PIRS = 5-point Pain intensity scale; 4PRS = 4-point pain relief scale; SGA = Subjective general assessment (most/least effective); 100VAS = 100-mm Visual analog scale.

[‡] DPP + APAP = *D*-propoxyphene + acetaminophen. Daily DPP doses (shown in brackets) are expressed in terms of DPP HCl equivalent (100 mg DPP napsylate equivalent to 65 mg DPP HCl).

[§] Flufenamic acid not included (not available in U.S.); flufenamic acid was statistically significantly superior to DPP in terms of the patient's subjective general assessment of symptom relief.

[‖] Number of days for each of 3 consecutive menstrual cycles

[††] Duration of DPP + APAP therapy; value was estimated by calculating the number of days of treatment per patient per month based on a total of 633 DPP + APAP capsules taken.

[§§] About 21 (66%) of 32 DPP patients and about 14 (45%) of 31 naproxen patients required more than 10 days' treatment (values obtained from graphical presentation of results).

[‖‖] Comparisons were based on mean ridit score for PERC with DPP as the reference population. The ridit analysis is a "distribution free" method and allows a scoring system to be determined by the distribution of the reference population.

Appendix Table 3 RCTs comparing multiple doses of DPP ± APAP with opioids in treatment of acute pain

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)[‡]	DPP(N) ± APAP preparation and dosage regimen	Comparator(s) and dose(s)[‡]	Treat-ment duration	Efficacy results (For treatment comparisons: > means superior to; < means inferior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent[‡] (mg/day)]	(mg/day)	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Opioid superior to DPP + APAP in terms of analgesic efficacy (p < 0.05)									
Sagne (1987)[60] [I, B]	DBPG (100VAS) The evaluation of analgesic efficacy was based on the extent of pain reduction and pain reduction index (PRIX) after dose 1, and doses 1 and 2.	Dental extraction (mean, 64 mm DPP+APAP, 65 mm Codeine+APAP)	180 [93 M / 87 F]	28.4 to 30.8	DPP+APAP 65 + 650 mg at least 2 h apart prn, up to 3 doses [65 to 195 + 650 to 1950 prn]	Codeine+APAP (COD+APAP) 60 + 1000 mg at least 2 h apart prn, up to 3 doses [60 to 180 + 1000 to 3000 prn]	0.4	COD+APAP > DPP+APAP* for duration of effect after first dose (6.6 h vs. 5.7 h; p < 0.05). Fewer doses taken in COD+APAP than DPP+APAP group in terms of proportion of patients who took 1 dose (~30% vs. ~25%), 2 doses (~50% vs. ~45%), or 3 doses (~25% vs. ~35%) but not statistically significant; (p > 0.05 for each analysis). COD+APAP > DPP+APAP* for mean percentage pain reduction after dose 1 for men (65.8% vs. 50.1%) and whole group (63.8% vs. 53.3%;); and after doses 1 and 2 for whole group (67.3% vs. 59.4%) (0.01 < p < 0.05 for each analysis). COD+APAP > DPP+APAP* for mean PRIX after dose 1 for males (476.9 vs. 317.0; 0.01 < p < 0.05) and for whole group (442.3 vs. 330.5; 0.001 < p < 0.01); and after doses 1 and 2 for males (480.1 vs. 367.0) and for whole group (461.5 vs. 376.9) (0.01 < p < 0.05 for both analyses). No significant differences for females in percentage pain reduction or PRIX.	Dizziness, tiredness and nausea were most frequent AEs. A greater proportion of females experienced AEs on COD+APAP (55%) than on DPP+APAP (31%; p < 0.05); no significant difference for males (18% vs. 23%).

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)[‡]	DPP(N) ± APAP preparation and dosage regimen	Comparator(s) and dose(s)[‡]	Treat-ment duration	Efficacy results (For treatment comparisons: > means superior to; < means inferior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				**(years)**	**[HCl equivalent[‡] (mg/day)]**	**(mg/day)**	**(days)**	**(n, unless otherwise stated)**	**(n, unless otherwise stated)**
No difference between opioid and DPP + APAP in terms of analgesic efficacy (p > 0.05)									
Boissier (1992)[56] [I, B]	DBPG DD (VAS/4VPS[§]) A priori estimate of sample size Principal trial criterion (success–failure) was defined from overall assessment of acceptability by patient classified into the following 4 categories: treatment very poorly and poorly tolerated (failure); treatment well and very well tolerated (success). WDAEs were also classified as failures.	Osteoarthritis (NR)	141 [38 M / 103 F]	66 ± NR	DPP+APAP (DI-Antalvic) 60 + 800 mg t.i.d. [180 + 2400]	Codeine+APAP (COD+APAP, Efferalgan-Codeine) 60 + 1000 mg t.i.d. [180 + 3000]	5	COD+APAP = DPP+APAP for visual pain scale (3.7 cm vs. 3.3 cm); verbal pain scale (pain severity nil : moderate : severe or very severe, 7 : 40 : 14 vs. 7 : 48 : 13); overall efficacy assessment by physician (no change or worse : improved : greatly improved, 19 : 30 : 11 vs. 12 : 45 : 11) and by patient (16 : 32 : 12 vs. 14 : 38 : 15) (p > 0.05 for each analysis).	1 SAE: Codeine+APAP (acute pulmonary edema; association confounded by beta-blocker treatment). Failure rate was higher with COD+APAP (36 of 68, 53%) than with DPP+APAP (20 of 68, 29%; p = 0.005). No significant difference in success rate (32, 47% vs. 48, 71%). COD+APAP < DPP+APAP* for overall acceptability assessment by patient in terms of treatment well tolerated (success) (17 vs. 25; p = 0.013). WDAEs were three times more frequent with COD+APAP (27) than with DPP+APAP (9; p = 0.001). Reasons were GI, neurologic, or other types of intolerance ($p \leq 0.03$ for each analysis). None of these AEs were serious enough to require hospitalization.

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)[‡]	DPP(N) ± APAP preparation and dosage regimen	Comparator(s) and dose(s)[‡]	Treat-ment duration	Efficacy results (For treatment comparisons: > means superior to; < means inferior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent[‡] (mg/day)]	(mg/day)	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Edmondson (1983)[62] [I, B]	SBPG (VAS)	Dental extraction (NR)	83 [32 M / 51 F]	NR (17 to 49)	DPPN+APAP 100+650 mg q.i.d. [260 + 2600]	Codeine+APAP+Caffeine (Solpadeine effervescent, SOL)[‖] 16 + 1000 + 60 mg q.i.d. [64 + 4000 + 240]	3	SOL = DPP+APAP for pain intensity (no data), mean interval between doses (6.91 vs. 7.53 h), or overall pain relief (very good or good, 63.4% vs. 50%) (p > 0.05 for each analysis). SOL > DPP+APAP* for medication easier to take (90.5% vs. 65%; p < 0.01). A smaller proportion of SOL than DPP+APAP patients described their medication as having an unpleasant taste (14% vs. 39%; p < 0.025); and a smaller proportion of SOL patients commented that their tablets didn't dissolve well (7.1% vs. 26.8%). At 1-wk follow-up visit, more DPP+APAP (13 of 41, 32%) than SOL (2 of 42, 5%) patients described their pain as sharp. More SOL (32, 76%) than DPP+APAP (24, 58%) patients described their pain as dull.	No SAEs. NSAEs: 11 (26.2%) SOL vs. 12 (29.3%) DPP+APAP. More patients on SOL (n = 8) than DPPN+APAP (n = 3) reported nausea.

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)[‡]	DPP(N) ± APAP preparation and dosage regimen	Comparator(s) and dose(s)[‡]	Treat-ment duration	Efficacy results (For treatment comparisons: > means superior to; < means inferior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent[‡] (mg/day)]	(mg/day)	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
MacKay (1982)[63] [II-1, B]	SBPG (VAS)	Tonsillectomy (NR)	74 [21 M / 53 F]	25.7 DPPN+APAP; 23.9 Solpadeine (SOL)	DPPN+APAP 100 + 650 mg q6h [260 + 2600]	Codeine+APAP+CAF (SOL)[‖] 16+1000+60 mg q6h [32 + 2000 + 120]	3	Female DPPN+APAP patients older than SOL patients (mean age, 26.0 vs. 22.2 yr; p < 0.05). SOL = DPPN+APAP for clinician's assessment of pain relief (1–poor, 4–excellent); mean score 2.8 vs. 2.6 (p > 0.05). A greater proportion of SOL patients (8, 20%) than DPPN+APAP (3, 8.8%) had excellent pain relief (no statistics). SOL = DPPN+APAP for patient's assessment of pain severity on day 1, number of times awoken during night, severity of pain on eating, severity of pain on waking, daytime pain relief, and severity of pain on retiring (p > 0.05 for each analysis).	1 SAE: SOL (post-operative hemorrhage; code broken). 3 WDAEs: 2 SOL, 1 DPPN+APAP (all 3 because of upset stomach). AEs, seriousness or intensity not reported: 1 SOL (nausea, vomiting), 2 DPPN+APAP (1 pins and needles in the jaw; 1 nausea, dizziness, and extreme drowsiness).

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)[‡]	DPP(N) ± APAP preparation and dosage regimen	Comparator(s) and dose(s)[‡]	Treat-ment duration	Efficacy results (For treatment comparisons: > means superior to; < means inferior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent[‡] (mg/day)]	(mg/day)	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Young (1978)[55] [I, A]	DBPG (5PIRS)	Major surgery (Mild to moderate)	151 [68 M / 83 F]	47.5 M; 44.6 F (18 to 88)	DPPN 100 mg at 0 and 4 h (DPPN2) DPPN 100 mg at 0 h (DPPN1) [130 and 65]	Codeine 60 mg at 0 and 4 h (COD2) Codeine 60 mg at 0 h (COD1) [120 and 60] Placebo at 4 h	< 1	Single-dose regimen of either drug did not produce satisfactory 8-h analgesia (did not exceed 50% of maximum) in the majority of patients (COD 24 of 31, 77% and DPPN 23 of 30, 77%). Proportion of patients who obtained satisfactory analgesia scores (> 50% of maximum): DPPN2 > DPPN1*: 70% vs. 23% (p = 0.001). COD2 > COD1*: 77% vs. 23% (p < 0.001). COD2 = DPPN2: 74% vs. 70% (p > 0.50).	No SAEs. No severe AEs. NSAEs: 4 reports among 60 DPPN patients (3 nausea, 1 itching) vs. 7 reports among 61 COD patients (5 nausea, 1 weakness, 1 abdominal pain). All slight or moderate in intensity.

Ref.	Study design (PEV PAM)[†]	Type of pain (Baseline pain intensity)	N, Efficacy analysis [Sex, RRA patients]	Age, mean ± SD [median], (range)[‡]	DPP(N) ± APAP preparation and dosage regimen	Comparator(s) and dose(s)[‡]	Treat-ment duration	Efficacy results (For treatment comparisons: > means superior to; < means inferior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE, SoR]				(years)	[HCl equivalent[‡] (mg/day)]	(mg/day)	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Crighton (1997)[61] [I, B]	DBPG (4VPS/VAS) A priori estimation of sample size.	Laparoscopic sterilization (Mild)	68 [0 M / 75 F]	(33.1 to 34)	DPP+APAP 65 + 650 mg after emergence from anesthesia, then 32.5 to 65 mg + 325 to 650 mg q 4 to 6 h prn, up to 260 + 2600 mg/24 h [114 + 1140] (mean; doses given prn)	Tramadol (TRAM) 100 mg after emergence from anesthesia, then 50 to 100 mg q 4 to 6 h prn, up to 400 mg/24 h [400 (max)] Codeine+APAP (COD+APAP) 60 + 1000 mg after emergence from anesthesia, then 30 to 60 mg + 500 to 1000 mg q 4 to 6 h prn, up to 240 + 4000 mg/24 h [240 + 4000 (max)]	1	TRAM = COD+APAP = DPP+APAP for pain intensity for average pain and worst pain, sleep disturbed by pain, mobility, pain relief, satisfaction, and number of tablets taken (p > 0.05 for each analysis).	No differences between TRAM, COD+APAP, and DPP+APAP in proportion of patients who experienced at least one AE (57% vs. 78% vs. 61%; p = 0.37), nausea and/or vomiting (39% vs. 44% vs. 38%; p = 0.93), or CNS AEs (drowsiness, dizziness, headache) (72% vs. 39% vs. 52%; p = 0.11). Proportion of patients who experienced itching were similar (6% vs. 4% vs. 5%; no p-value reported). Proportion of patients experiencing CNS AEs was lower with COD+APAP than with TRAM, 39% vs. 72% (p = 0.035).

NSAE = Nonserious adverse event; SAE = Serious adverse event; WDAE = Withdrawal from study or discontinuation of medication due to adverse event

† Study design: DBPG = Double-blind, parallel group; DD = Double-dummy; MC = Multicenter; 5PIRS = 5-point Pain intensity rating scale; RRA = Recruited, randomized, or analyzed (patient sex was reported for different study populations among the various trials); SBPG = Single-blind, parallel group; WDAE = Withdrawal from study or discontinuation of medication due to adverse event.
PEV (Primary efficacy variable) PAM (Pain assessment method): 100VAS = 100 mm (10 cm) Visual analog scale; VAS = Visual analog scale (parameters not stated); 4VPS = 4-item verbal pain scale (categorical, non-numerical)

‡ DPP + APAP = *D*-propoxyphene hydrochloride in combination with acetaminophen; DPPN+A = *D*-propoxyphene napsylate in combination with acetaminophen; F = Females M = Males; NR = Not reported; QE = Quality of evidence; SoR = Strength of recommendation regarding treatment comparisons for analgesic efficacy; Tx = Treatment (group).

§ Secondary efficacy variable

‖ Combination product not available in U.S.

Appendix Table 4 RCTs comparing multiple doses of DPP with NSAIDs or opioids in treatment of chronic pain

Ref.	Study design (PEV PAM)†	Type of pain (Baseline pain intensity)	N (Efficacy) [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP preparation and dosage regimen	Comparator(s) and dosage regimen	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE]				(years)	[HCl equivalent (mg/day) ‡	[mg/day)]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
DPP inferior to NSAID in terms of analgesic efficacy (p < 0.05)									
Parr (1989)[68] [I, B]	DBPG DD, QoL (100VAS)	Arthralgia (NR)	752 [355 M, 400 F]	55.0 Diclofenac SR (DSR) 54.6 DPP+APAP	DPP+APAP 60 + 650 mg t.i.d. (and dummy placebo diclofenac 1 tablet qam) [180 + 1950]	DSR 100 mg qam (and dummy placebo DPP+APAP 2 tablets t.i.d.) [100]	28	DSR > DPP+APAP* for pain relief as measured by reduction on VAS; p < 0.05). DSR resulted in 8% greater relative (%) pain reduction from baseline in terms of VAS scores relative to DPP+APAP and a 13% greater relative (%) improvement in physical mobility (p < 0.05 for both analyses). The difference between mean absolute changes, however, was small (–4.3 mm on 100-mm VAS; 95% CI for the difference between changes for diclofenac and DPP-A: –7.7 to –0.9 mm DSR = DPP+APAP for pain relief as measured by Nottingham Health Profile (NHP) (p = 0.13). DSR > DPP+APAP* for limitation on movement. The numbers of patients whose mobility improved, did not change, and deteriorated were better on DSR (120, 222, and 7, respectively) than on DPP+APAP (86, 258, and 8; p < 0.05). DSR > DPP+APAP* for Improvement (change) in mobility as measured by NHP; p < 0.01). Certain health related problems were less frequent on DSR; developed problems with work (1% of 373 vs. 5% of 382; p < 0.05); time lost from work (1% and 6%; p < 0.05). 13 Withdrawals due to inefficacy: 5 DSR, 8 DPP+APAP.	1 Death (DSR, myocardial infarction). 81 WDAEs: 39 of 373 (10%) DSR, 42 of 382 (11%) DPP+APAP (mostly GI and CNS AEs in both groups). CNS AEs more common on DPP+APAP (24.3%) than on DSR (12.8%; p < 0.01). CNS AEs that were more common on DPP+APAP than DSR were dizziness / lightheadedness (7.8% vs. 3.8%; p < 0.05) and tiredness / sleep disturbance (13.1% vs. 5.6%; p < 0.01). GI AEs that were more common on DSR than DPP+APAP were abdominal/epigastric pain or indigestion (10.7% vs. 4.7%; p < 0.01) and diarrhea (3.8% vs. 0.5^; p < 0.01).

Ref.	Study design (PEV PAM)†	Type of pain (Baseline pain intensity)	N (Efficacy) [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP preparation and dosage regimen	Comparator(s) and dosage regimen	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE]				(years)	[HCl equivalent (mg/day) ‡	[mg/day)]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
No difference between DPP and NSAID in terms of analgesic efficacy (p > 0.05)									
Saarialho-Kere (1988)[69] [I, B]	DBCO (100VAS)	Rheumatoid arthritis (mean, 42.3 mm)	15 [2 M / 14 F]	(21 to 67)	Days 1 to 3: (Tx 3 and 4) APAP 500 mg b.i.d. Days 4 to 5: (Tx 3) DPP 65 mg t.i.d. (Tx 4) DPP 65 mg b.i.d. + amitriptyline (AMI) 25 mg qhs Day 6: (Tx 3) DPP 130 mg (Tx 4) DPP 65 mg + AMI 25 mg [Tx 3: DPP 130 to 195] [Tx 4: DPP 65 to 130 + AMI 25]‡	Days 1 to 3: (Tx 1 and 2) APAP 500 mg b.i.d. Days 4 to 5: (Tx 1) Placebo (PL) (Tx 2) Indomethacin (INDO) 25 mg t.i.d. Day 6: (Tx 1) Placebo (Tx 2) INDO 50 mg [Tx 2: INDO 50 to 75]	3	INDO = DPP for pain intensity (0–no pain, 100 mm–very severe pain), at 2 h (42 mm vs. 36 mm) and 4 h (36 mm vs. 34 mm) (p > 0.05). DPP > DPP+AMI* for pain intensity at 4 h, 34 vs. 44 mm. INDO and DPP > PL*: Pain intensity at 2 h (p < 0.05) but not at 4 h. INDO and DPP > baseline* for pain intensity at 4 h.	1 Severe AE: INDO (nausea and dizziness). DPP tended to cause vertigo and DPP+AMI tended to cause dry mouth. No statistically significant differences in AEs between treatment groups because of small number of subjects and high frequency of AEs on PL. All treatments caused relatively mild alterations in psychomotor skills that coincided with peak drug concentrations.

Ref.	Study design (PEV PAM)†	Type of pain (Baseline pain intensity)	N (Efficacy) [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP preparation and dosage regimen	Comparator(s) and dosage regimen	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE]				(years)	[HCl equivalent (mg/day) ‡	[mg/day)]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
No difference between DPP and opioid agent in terms of analgesic efficacy (p > 0.05)									
Lloyd (1992)[70] [I, B]	DBPG (100-mm VAS) A priori power calculation.	Osteoarthritis (NR)	65 [28 M, 58 F]	66 (33 to 85)	DPP + APAP 65 + 650 mg t.i.d. to q.i.d. Lower dose was given to dihydrocodeine (DHC)-naïve patients or patients who had been on ≤ 6 tab of DPP+APAP (32.5 + 325 mg/tab). Higher dose was given to patients who had been on DHC at any dose ≤ 240 mg/d or DPP+APAP > 6 tab/d. [97.5 to 130 + 975 to 1300]	DHC CR 60 mg to 120 mg b.i.d. Determination of dosage regimen as described under DPP+APAP dosage regimen. [120 to 240]	14	Lost to follow-up: 5 of 86 (5.8%). DHC = DPP+APAP for maximum average daily VAS pain scores for week 1 (58.3 mm vs. 48.6 mm) or week 2 (49.8 mm vs. 49.2 mm) (p > 0.05 for both analyses). DHC = DPP+APAP for mean average daily VAS pain scores for week 1 (50.1 mm vs. 38.2 mm) and week 2 (39.2 mm vs. 39.8 mm) (p > 0.05 for both analyses). DHC = DPP+APAP for number of waking nights due to pain (p > 0.05). DHC > DPP+APAP* for pain on passive movement at visit 3; number of patients with no, mild, moderate, or severe pain, 2, 15, 7, 0 for DHC vs. 1, 15, 15, 5 for DPP+APAP (p = 0.02). However, there was no data for 19 (44%) DHC patients and 7 (16%) DPP+APAP patients. 3 Withdrawals due to inefficacy: 1 DHC, 2 DPP.	21 WDAEs: 17 of 43 (39.5%) DHC, 4 of 43 (9.3%) DPP+APA (no statistics). No difference between lower and higher dosage regimens. Severity of nausea and of vomiting was significantly greater on DHC than DPP+APAP at visit 2 but not at visit 3. Number of patients with none, mild, moderate, or severe nausea at visit 2: 21, 6, 3, 9 on DHC vs. 31, 6, 2, 2 on DPP+APAP (p = 0.02). For vomiting, 29, 2, 3, 5 vs. 38, 1, 2, 0 (p = 0.02). Missing data 19 (44%) for DHC and 7 (16%) for DPP+APAP for both AEs. No significant treatment differences in severity of constipation, and drowsiness, difficulty in concentrating (p > 0.05 for each analysis). No significant differences between treatment groups and between lower and higher dosage groups in other AEs.

Ref.	Study design (PEV PAM)†	Type of pain (Baseline pain intensity)	N (Efficacy) [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP preparation and dosage regimen	Comparator(s) and dosage regimen	Treatment duration	Efficacy results (For treatment comparisons: > means superior to; = means not different from [p > 0.05]) * indicates statistically significant (p < 0.05)	Safety results
[QE]				(years)	[HCl equivalent (mg/day) ‡	[mg/day)]	(days)	(n, unless otherwise stated)	(n, unless otherwise stated)
Mercadante (1998)[71] [II-1, B]	OLPG (100 VAS)	Cancer (Moderate)	32 [16 M, 16 F]	69.0 DPP 67.7 Morphine SR (MSR) (47 to 87)	DPP dose adjusted according to clinical situation; 120 to 240 mg/d. [60 ±22.5 (mean ± SD)]	MSR 10 mg b.i.d. [20.1 ± 6.0 (mean ± SD)] Step 1 agents (mainly diclofenac 100 mg orally or 75 mg intramuscularly twice daily) were continued upon addition of opioid treatment.	10 (46 DPP; 68 Morphine SR) §	The overall mean duration of therapy was 46 days for DPP and 68 days for morphine. Days on MSR were longer in MSR group (68 d) than in DPP group (29 d; p < 0.01). Median daily doses of morphine equivalents in the last 4 weeks were higher in MSR group (42 mg) than DPP group (30 mg; p < 0.01). In the DPP group, 3 of 16 (19%) patients maintained DPP until death (range, 25 to 131 d) and 13 (81%) were switched to MSR. Reasons for switching to MSR were the need to increase analgesia in 11 patients and inability to swallow in 2 patients. Mean equianalgesic doses in the first 10 d of therapy were lower with DPP (14 mg) than MSR (20.1 mg; p < 0.01) without difference in pain relief. MSR = DPP for pain intensity (10-cm VAS) in first 10 d, assessed by patient when possible or by home physician; median (range), 3 cm (2 to 5 cm) vs. 3 cm (2 to 5 cm) (p > 0.05).	There were statistically significant differences in the intensity of drowsiness, nausea / vomiting, xerostomia, and symptom distress score (sum of the symptom intensity) between treatment groups (worse with MSR; p < 0.01 for each analysis); however, clinical differences were slight (scores were 0 with DPP and 1 with MSR, where 0 was not at all, 1 was slight, 2 was a lot, and 3 was awful). 3 MSR patients switched to DPP after 5 to 7 d because of intolerable AEs, principally vomiting and drowsiness. These patients continued DPP until death with adequate pain relief.

CR = Controlled release; DPP = *D*-propoxyphene HCl (or unspecified salt); DPP + APAP = *D*-propoxyphene HCl (or unspecified salt) in combination with acetaminophen; F = Females M = Males; NR = Not reported; Prn = Pro re nata (as needed); QE = Quality of evidence; RRA = Recruited, randomized, or analyzed (patient sex was reported for different study populations among the various trials); SoR = Strength of recommendation (in regards to comparative analgesic efficacies of treatments); SR = Slow- or sustained release;

‡ Pain scores were statistically significantly lower (less pain) on DPP alone than on DPP + amitriptyline (p < 0.05)

§ Assessments of pain intensity reported for the first 10 days of treatment at the doses shown; mean total duration of treatment was 46 days for DPP (120 to 240 mg/day, titrated) and 68 days for morphine (20 mg/day). DPP patients were switched to morphine sulfate sustained release when pain was no longer controlled at daily DPP doses of 240 mg. For further explanation, see text.

Appendix Table 5 Summary of safety RCTs

Ref.	Study design	Type of subjects	N (Safety) [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP preparation and dosage regimen	Comparator(s) and dose(s)	Treatment duration	Safety results
[QE, SoR]				(years)	[HCl equivalent (mg/day) ‡	[mg/day)]	(days)	(n, unless otherwise stated)
O'Neill (1995)[152] [I, A]	DBCO	Healthy	12 [3 M, 9 F]	36 (30 to 50)	(Tx 1) DPPN 100 mg [65] (Tx 2) DPPN 200 mg [130]	(Tx 3) Lorazepam (LOR) (Tx 4) Placebo (PL)	Single dose treatments separated by 1 wk	DPPN did not produce significant impairment of cognitive and psychomotor function. A dose related effect in critical flicker fusion threshold (CFFT) was detected with DPPN 200 mg ($p < .05$). DPPN 200 mg significantly increased word recognition sensitivity at 4 h ($p < 0.05$). in contrast, LOR produced marked slowing on simple reaction time task and choice reaction time task, caused disruption of word recall, word recognition task, and picture recognition tasks, and decreased CFFT in comparison with PL ($p < 0.05$ for each analysis). LOR significantly decreased subjective alertness compared with PL ($p < 0.05$); no differences were seen in any subjective assessments (alertness, contentment, calmness) with DPPN.
O'Neill (2000)[154] [I, A]	DBCO	Healthy	10 [4 M, 6 F]	31 (25 to 40)	(Tx 1) DPPN 100 mg q4h × 4 doses [260]	(Tx 2) Morphine sulfate (MS) 10 mg q4h × 4 doses [40] (Tx 3) Lorazepam (LOR) 0.5 mg q4h × 4 doses [2] (Tx 4) Placebo (PL)	1	DPPN impaired choice reaction time and picture recognition at some time points ($p < 0.05$). MS increased accuracy of responding on choice reaction time task at every assessment ($p < 0.05$), had sporadic effects on other tests, and increased subjective calmness. LOR impaired the speed of responding on all tasks in which speed was recorded ($p < 0.05$) except digit vigilance, and increased subjective calmness. 2 Non-minor AEs: Both DPPN (severe nausea / vomiting and troublesome headache). No remarkable differences in frequency of any AEs between treatment groups.

Ref.	Study design	Type of subjects	N (Safety) [Sex, RRA patients]	Age, mean ± SD [median], (range)	DPP preparation and dosage regimen	Comparator(s) and dose(s)	Treatment duration	Safety results
[QE, SoR]				(years)	[HCl equivalent (mg/day) ‡	[mg/day)]	(days)	(n, unless otherwise stated)
Woody (1980)[43] [I, A]	DB, 2-center	Heroin addicts	227 [NR]	NR	DPPN 200 to 400 mg b.i.d. initially, then increasing by as much as 200 mg/d until a maximum of 500 mg b.i.d. [650, max]	Methadone (METH) 12 to 24 mg/d initially, then increasing to 32 mg/d	Up to 180	At one center, of 79 patients who began DPPN, 57 dropped out before 1 mo and were excluded from analyses, leaving 22 patients who received 2 mo of treatment. Of these, 17 received 4 mo of treatment, and 14 completed 6 mo of treatment. At the other center, 36 remained in treatment for a month. 2 SAEs on DPPN: 1 TIA in 52 yr old male with mild diabetes. 1 obtundation in patient with history of alcohol, sedative, benzodiazepine, and narcotic abuse; SAE occurred on third day of treatment apparently due to ingestion of DPPN 300 mg b.i.d. with sedative drugs (two 30-mg flurazepam capsules and five "pills" of unknown content). CNS irritability (anxiety, restlessness, or confusion) seen in 12% of patients who took DPPN for more than 1 mo. Otherwise no symptoms resembling those seen in DPP(N) overdoses. No significant changes in mean values of laboratory tests for DPPN or METH. Among DPPN patients, the frequency of abnormal values for SGOT and total bilirubin decreased over 6 mo ($p < 0.05$). ECGs of DPPN patients were normal or were initially slightly abnormal then became normal during the study. No seizure activity was noted clinically or on EEG in any DPPN patients.

Appendix 4 Summary of a national assessment of propoxyphene in postmortem medicolegal investigation (1972–1975)

In 1976 the main manufacturer of DPP, Lilly Research Laboratories, sponsored an extensive survey of 1022 DPP-related deaths that occurred in the U.S. and Toronto and the Province of Ontario, Canada between 1972 and 1975.[42] The results of this survey formed the foundation for what is currently known about DPP-related deaths and supports the black-box warnings for DPP.

Terminal signs and symptoms

Terminal signs and symptoms were clearly described by a witness and officially documented in the case report in 180 cases (17.6% of total). Respiratory depression (~ 50%) was the most common final event, followed by cardiac arrest (~ 40%), coma (~ 40%), seizures (~ 20%), intoxication (~ 18%), and syncope (~ 10%). Seizures were slightly more frequent among cases involving only DPP (about 12%) than among those involving DPP and other drugs (about 10%). The typical findings on autopsy consisted of pulmonary and cerebral edema and visceral congestion. It is noteworthy that signs of intoxication (ataxia, disorientation, or slurred speech) apparently did not always precede the subject's collapse.

Characteristics of fatal cases

Finkle, *et al.* identified the following characteristics of the deceased or the nature of DPP exposure that are now considered to be reasons for avoiding DPP use:

- History of prescription drug misuse, such as excessive self-medication (17.1%), alcohol abuse (17.0%), or either alcohol or drug abuse, or both (34.3%). A minority of the deceased had a history of heroin abuse (3.3%) or DPP abuse (1.6%).
- Emotional problems (82%).
- Self-destructive behavior (death classified as suicide or documented history of suicide attempts; 50.7%).
- Co-ingestion of alcohol (42.0% of total cases, 40.8% of suicides, 42.7% of accidental deaths, and 43.2% of undetermined cases).
- Involvement of another drug (76.1%), excluding aspirin, phenacetin, and caffeine. Diazepam was the most frequently mentioned agent (44%), and about three fourths of all the cases involved psychotropic/tranquilizer agents (40.1%), sedative/hypnotics (21.2%), or analgesics (12.1%).

The manner of death was most frequently classified as suicide (468 cases, 45.8%). Death was accidental in 267 cases (26.1%), and undetermined in 213 cases (20.8%). A small number of cases listed natural causes, homicide, and unknown manner of death.

Death was rapid with 20% of 769 cases having a survival time (interval from the time the deceased was last seen alive until death) of less than 1 hour. More than half (52%) of the victims died in 5 hours or less, and 81% died within 10 hours. There was a small group (n = 52) who had sudden unexplained deaths (survival times less than 15 minutes), of which 84.6% were preceded by respiratory arrest, 30.8% by cardiac arrest, and 30.8% by syncope.