

# Short-Acting Narcotic Analgesics Review

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### **FDA-Approved Indications**

<b>Drug</b>	<b>Federal Schedule</b>	<b>Manufacturer</b>	<b>Indication(s)</b>
acetaminophen/caffeine/ dihydrocodeine bitartrate (Panlor <sup>®</sup> SS; Panlor <sup>®</sup> DC) <sup>1</sup>	CIII	generic, Pan American Labs	Moderate to moderately severe pain
fentanyl oral transmucosal (Actiq <sup>®</sup> ) <sup>2</sup>	CII	generic	Breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain
fentanyl buccal (Fentora <sup>®</sup> ) <sup>3</sup>	CII	Cephalon	
fentanyl buccal (Onsolis <sup>™</sup> ) <sup>4</sup>	CII	Meda	
hydrocodone/ acetaminophen (Hycet <sup>®</sup> ) <sup>5</sup>	CIII	Xanodyne	Moderate to moderately severe pain
hydrocodone/ acetaminophen (Xodol <sup>®</sup> ) <sup>6</sup>	CIII	Victory	
hydrocodone/ acetaminophen (Zamicet <sup>™</sup> ) <sup>7</sup>	CIII	Hawthorn	
hydrocodone/ acetaminophen (Zydone <sup>®</sup> ) <sup>8</sup>	CIII	Endo	
hydrocodone/ibuprofen (Ibudone <sup>™</sup> ) <sup>9</sup>	CIII	Poly Pharmaceuticals	Short-term management of acute pain
hydrocodone/ibuprofen (Reprexain <sup>™</sup> ) <sup>10</sup>	CIII	Hawthorn	
hydromorphone liquid (Dilaudid <sup>®</sup> ) <sup>11</sup>	CII	Purdue	Management of pain in patients where an opioid analgesic is appropriate
oxycodone/ibuprofen (Combunox <sup>®</sup> ) <sup>12</sup>	CII	generic	Short term (seven days or less) treatment of acute, moderate to severe pain
oxymorphone IR (Opana <sup>®</sup> ) <sup>13</sup>	CII	Endo	Moderate to severe acute pain
propoxyphene napsylate (Darvon-N <sup>®</sup> ) <sup>14</sup>	CIV	Xanodyne	Mild to moderate pain
tapentadol (Nucynta <sup>™</sup> ) <sup>15</sup>	CII	OMJPI	Relief of moderate to severe acute pain
tramadol (Ultram <sup>®</sup> ) <sup>16</sup>	Not scheduled	generic	Management of moderate to moderately severe pain in adults
tramadol/acetaminophen (Ultracet <sup>®</sup> ) <sup>17</sup>	Not scheduled	generic	Short term (five days or less) treatment of acute pain

## **Overview**

Pain is often undertreated, and pain management greatly misunderstood. Seventy-three percent of hospitalized medical patients receiving opiates were found in severe or moderate distress despite their analgesic regimen.<sup>18</sup> Caregivers' misconceptions regarding opiate doses, duration of analgesic effect, and fear of addiction were partly responsible for this under treatment. Similar problems have been reported in ambulatory patients.<sup>19</sup> Different management techniques are utilized for acute and chronic pain.

Guidelines for pain management recommend a stepped approach with consideration for the type of pain and response to therapy.<sup>20,21</sup> Initial therapy should include nonopioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs). For mild to moderate pain, oral combinations of acetaminophen and NSAIDs with opioids are recommended. For moderate to severe pain, opioid analgesics are the mainstay. Titration of dose and frequency should be individualized to the patient's response and experience of side effects.

Although there are many products in this class available as generics, this review will focus on the most recent unique entries to the market.

## **Pharmacology**

Opioid agonists act primarily through interaction with opioid mu-receptors located in the brain, spinal cord, and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS). Opioid agonists produce respiratory depression by direct action on the brain stem respiratory center. The effectiveness of tapentadol (Nucynta) may also involve norepinephrine reuptake inhibition.

Tramadol is a centrally acting analgesic with dual opioid and nonopioid mechanisms. In addition to activity at opioid receptors, tramadol weakly inhibits norepinephrine and serotonin reuptake.

NSAIDs work by blocking cyclooxygenase (COX)-1 and COX-2, which prevent the synthesis of various prostaglandins. These prostaglandins are partially responsible for the development of pain and inflammation.

The exact mechanism of action for acetaminophen is unknown, but it mediates its actions centrally. Acetaminophen is thought to act primarily in the CNS and increase the pain threshold by inhibiting COX-1 and COX-2. Unlike NSAIDs, acetaminophen does not inhibit cyclooxygenase in peripheral tissues. Acetaminophen may also decrease sensitization of pain receptors to mechanical or chemical stimulation.

**Pharmacokinetics**

Drug	Half-Life (hr)	Tmax (hr)	Excretion
dihydrocodeine (component of Panlor) <sup>22</sup>	No data available	No data available	metabolized to active dihydromorphine
fentanyl oral transmucosal (Actiq) <sup>23</sup>	3.2-6.4	0.33-0.67	>90% metabolized and renally eliminated
fentanyl buccal (Fentora) <sup>24</sup>	2.63 – 11.7	0.5 – 0.75	>90% metabolized and renally eliminated
fentanyl buccal (Onsolis) <sup>25</sup>	14	1	>90% metabolized and renally eliminated
hydrocodone (component of Hycet, Xodol, Zamicet, Zydone) <sup>26,27,28, 29</sup>	3.8	1.3 - 3	hydrocodone and metabolites renally eliminated
hydrocodone/ibuprofen (Ibudone) <sup>30</sup>	2.2-4.5	1.7-1.8	hydrocodone and metabolites and ibuprofen renally eliminated
hydrocodone/ibuprofen (Reprexain) <sup>31</sup>	2.2-4.5	1.7-1.8	hydrocodone and metabolites and ibuprofen renally eliminated
hydromorphone liquid (Dilaudid) <sup>32</sup>	2.6 – 2.8	0.5 – 1	highly metabolized
oxycodone/ibuprofen (Combunox) <sup>33</sup>	oxycodone 3.1-3.7 ibuprofen 1.8-2.6	oxycodone 1.3-2.1 ibuprofen 1.6-3.1	oxycodone primarily metabolized and renally eliminated; ibuprofen renally
oxymorphone IR (Opana) <sup>34</sup>	7.3-9.4	No data available	highly metabolized; eliminated in urine and feces
propoxyphene napsylate (Darvon-N) <sup>35</sup>	6-12	2-2.5	metabolized to norpropoxyphene
tapentadol (Nucynta) <sup>36</sup>	4	1.25	highly metabolized eliminated in urine
tramadol (Ultram) <sup>37</sup>	6-7	2.3-2.4	tramadol 60 percent metabolized to active metabolites
tramadol/acetaminophen (Ultracet) <sup>38</sup>	tramadol 4.7-5.1 metabolites 6.2-7.8 acetaminophen 2.5	tramadol 1.8 metabolites 2.1-2.2 acetaminophen 0.9	tramadol 60 percent metabolized to active metabolites; acetaminophen primarily metabolized

**Contraindications/Warnings**

Fentanyl transmucosal (Actiq) and buccal (Fentora, Onsolis) products are contraindicated in the management of acute or post-operative pain. Additionally, they should not be used in opioid non-tolerant patients.<sup>39,40,41</sup> Fentanyl transmucosal and fentanyl buccal products carry black box warnings that instruct prescribers to use only for the management of breakthrough cancer pain in patients who are already receiving and are tolerant to opioid analgesics for the treatment of underlying, persistent pain. Fentanyl transmucosal and fentanyl buccal products carry a caution

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for caregivers to keep these medications out of the reach of children as they contain a dose that may be fatal. Fentanyl buccal also has a black box warning against substituting fentanyl products (transmucosal, buccal, transdermal) for another.

Oxymorphone (Opana) is contraindicated in patients with respiratory depression who are not being actively monitored for their condition.<sup>42</sup> Patients with known or suspected paralytic ileus or moderate or severe hepatic impairment should also avoid oxymorphone use.

Hydromorphone (Dilaudid liquid) is contraindicated in patients with respiratory depression or status asthmaticus, as well as for use in patients for obstetrical analgesia.<sup>43</sup> The liquid formulation contains sodium metabisulfite which may cause allergic-type reactions in susceptible patients.

Tapentadol (Nucynta) is contraindicated in patients with impaired pulmonary function due to the incidence of respiratory depression with opioid use.<sup>44</sup> Tapentadol is also contraindicated in patients with paralytic ileus or patients taking MAO inhibitors presently or in the past 14 days.

Propoxyphene (Darvon-N) prescribing information includes a black box warning guarding against prescribing the product for patients who are prone to suicide or addiction.<sup>45</sup> Caution should be used in prescribing this product for patients who are also on antidepressants, tranquilizers, or who ingest large amounts of alcohol. The recommended dose should not be exceeded. A FDA Advisory Committee in 2009 recommended that all propoxyphene-containing products be removed from the market based on their low benefit-to-risk ratio.<sup>46</sup>

Oxycodone/ibuprofen (Combunox) and hydrocodone/ibuprofen (Ibudone, Reprexain) are contraindicated in the treatment of peri-operative pain in the coronary artery bypass graft (CABG) setting.<sup>47,48,49</sup> The black box warnings for NSAID-containing products cite the increased risk for adverse events seen with NSAID use such as serious cardiovascular thrombotic events, myocardial infarction, stroke, and gastrointestinal adverse events, all of which can be fatal.

Tramadol and tramadol/acetaminophen (Ultracet) are contraindicated in any situation where opioids are contraindicated including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs.<sup>50,51</sup> Tramadol may worsen central nervous system and respiratory depression in these patients. Concomitant use of tramadol with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome. Withdrawal symptoms may occur if tramadol is discontinued abruptly. Clinical experience suggests that withdrawal symptoms may be avoided by tapering tramadol at the time of discontinuation.

Acetaminophen/caffeine/dihydrocodeine (Panlor SS, DC) is contraindicated in patients with hypersensitivity to any of the components or in situations where opioids are contraindicated. These include significant respiratory depression, particularly in unmonitored settings or in the absence of resuscitation equipment, acute or severe bronchial asthma, hypercapnia, or paralytic ileus.

All products in this class should be used with caution in patients who may be susceptible to intracranial effects of carbon dioxide retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be employed only if clinically warranted.

Opioids produce peripheral vasodilation which may result in orthostatic hypotension for some patients. Additionally, gastrointestinal opioid-induced effects may include a reduction in gastric, biliary, and pancreatic secretions.

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Other warnings instruct prescribers to be aware of the abuse potential of these products, the possibility of hypoventilation, the dangers to pediatric patients if used, and the increased risk of respiratory depression when used with CYP450 3A4 inhibitors. Impairment of physical and/or mental abilities, increased seizure risk, use of caution when performing hazardous tasks, respiratory depression, abuse potential, and increased sedation when used with other central nervous system depressants are also associated with opioid use.

Serotonin syndrome may occur with concomitant use of tapentadol and other drugs that impair the metabolism of serotonin, such as various antidepressants.

### **Drug Interactions**<sup>52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68</sup>

All agents should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, muscle relaxants, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Monoamine oxidase inhibitors (MAOI) may intensify the actions of other opioids. Fentanyl transmucosal (Actiq) and buccal (Fentora, Onsolis), hydrocodone/acetaminophen (Hycet, Xodol, Zamicet, Zydone), hydrocodone/ibuprofen (Ibudone, Reprexain), and tapentadol (Nucynta) are not recommended for use within 14 days of a MAOI due to severe and unpredictable potentiation. Tramadol should not be used with selective serotonin reuptake inhibitors (SSRIs) due to the risk of adverse effects including seizure and serotonin syndrome.

Fentanyl and tramadol are mainly metabolized by the CYP450 enzyme pathway, so coadministration of these agents with CYP450 enzyme inducers or inhibitors may adversely affect their metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol; concurrent administration of carbamazepine and tramadol is not recommended due to the increased tramadol metabolism by carbamazepine and because of the seizure risk associated with tramadol.

Due to the ibuprofen component, hydrocodone/ibuprofen is associated with interactions with ACE inhibitors, methotrexate, and warfarin that are more frequently seen with NSAID coadministration.

**Adverse Effects**

<b>Drug</b>	<b>Asthenia</b>	<b>Constipation</b>	<b>Dizziness</b>	<b>Dyspnea</b>	<b>Headache</b>	<b>Nausea</b>	<b>Rash</b>	<b>Somnolence</b>	<b>Vomiting</b>
acetaminophen/ caffeine/ dihydrocodeine bitartrate (Panlor) <sup>69,70</sup>	nr	reported	reported	nr	nr	reported	nr	reported	reported
fentanyl (Actiq) <sup>71</sup>	38	20	16	22	20	45	8	15	31
fentanyl (Fentora) <sup>72</sup>	16	26	26	8	11	36	11	17	27
fentanyl (Onsolis) <sup>73</sup>	13	11	11	12	9	26	reported	7	21
hydrocodone/ acetaminophen (Hycet, Xodol, Zamicet, Zydone) <sup>74,75,76,77</sup>	nr	reported	reported	reported	nr	reported	reported	reported	reported
hydrocodone/ ibuprofen (Ibudone) <sup>78</sup>	3-9	22	14	<3	27	21	<1	22	3-9
hydrocodone/ ibuprofen (Reprexain) <sup>79</sup>	3-9	22	14	<3	27	21	<1	22	3-9
hydromorphone liquid (Dilaudid) <sup>80</sup>	reported	reported	reported	reported	reported	reported	reported	reported	reported
oxycodone/ibuprofen (Combunox) <sup>81</sup>	<1	<1	5.1	<1	>1	8.8	<1	7.3	5.3
oxymorphone IR (Opana) <sup>82</sup>	<1	4.1	6.5	<1	6.8	19.0	<1	9.3	9.0
propoxyphene napsylate (Darvon N) <sup>83</sup>	nr	reported	reported	nr	reported	reported	reported	reported	reported
tapentadol (Nucynta) <sup>84</sup>	nr	8	24	<1	nr	30	1	15	18
tramadol (Ultram) <sup>85</sup>	6-12	24-46	26-33	<1	18-32	24-40	1-<5	16-25	9-17
tramadol/ acetaminophen (Ultracet) <sup>86</sup>	>1	6	3	<1	>1	3	>1	6	>1

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

The American Geriatric Society (AGS) guideline, "The Management of Persistent Pain in Older Persons" addresses "opioids of particular concern" in the geriatric population. Among these agents are propoxyphene and tramadol.<sup>87</sup> According to these guidelines, propoxyphene was shown to be no more effective than aspirin or acetaminophen but is more toxic. Tramadol has opioid activity with apparently low abuse potential and is reportedly about as effective and safe as codeine or hydrocodone. However, tramadol has the additional low risk of inducing seizures.

***Special Populations***<sup>88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104</sup>

*Pediatrics*

Fentanyl buccal (Fentora, Onsolis) and tapentadol (Nucynta) are indicated for patients 18 years old or older; fentanyl transmucosal (Actiq) is approved for patients 16 years old or older. Oxycodone/ibuprofen (Combunox) is safe and effective in patients 14 years and older. The safety and efficacy of tramadol in children under 16 years of age has not been studied and is not recommended. Hydrocodone/ibuprofen (Ibudone, Reprexain) has no established safety and efficacy in patients less than 16 years of age. Products containing propoxyphene have not been studied in children under the age of 12 years, and their use is not recommended. Hydrocodone/acetaminophen (Hycet, Zamicet) has not been studied in patients younger than two years old. Hydrocodone/acetaminophen (Xodol, Zydone) has not been adequately studied in pediatric patients. Hydromorphone liquid (Dilaudid) has not been studied in children. Many generically available products have been shown to be safe and effective in pediatric patients although the safety and effectiveness of the dihydrocodeine/acetaminophen/caffeine products have not been established.

*Pregnancy*

All products listed in this review are Pregnancy Category C.

*Geriatrics*

All products should be used with caution in elderly patients due to greater sensitivity of primary effects and adverse effects. Doses should be titrated to provide adequate efficacy while minimizing risk.

Plasma levels of oxymorphone may be seen up to 40 percent higher in elderly patients over age 65 years than seen in younger patients. For elderly patients over 75 years old, total tramadol dose should not exceed 300 mg/day.

*Hepatic and Renal Impairment*

Dihydrocodeine/acetaminophen/caffeine products should be used with caution and in reduced dosage in these patients as dihydrocodeine is metabolized in the liver, and acetaminophen potentially causes liver toxicity. The same guidance should be used for hydromorphone- and hydrocodone-containing products.

Fentanyl transmucosal and buccal should be used with caution in these patients due to hepatic metabolism of fentanyl and its renal excretion.

Oxymorphone immediate release should be used with caution in patients with mild impairment and titrated slowly. Oxymorphone is contraindicated in patients with moderate to severe hepatic impairment.

Tapentadol should be used with caution in patients with moderate hepatic impairment. Patients with severe renal or hepatic impairment should not use tapentadol.

Tramadol should be given every 12 hours for patients with CrCl < 30mL/minute with a maximum dose of 200 mg per day. Patients with cirrhosis should receive tramadol 50 mg every 12 hours.



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### Cardiac Disease

Fentanyl transmucosal and buccal should be used with caution in patients with bradyarrhythmias.

**Dosages**<sup>105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121</sup>

Drug	Starting Dose	Dosing Instructions	Available Strengths
acetaminophen / caffeine / dihydrocodeine (Panlor)	Panlor SS: One tablet every four hours	Dosage should be adjusted to the severity of the pain and patient response. Dosage should not exceed one tablet in a four hour period or five doses in a twenty-four hour period.	Panlor SS tablets: acetaminophen 712.8mg / caffeine 60 mg / dihydrocodeine 32 mg
	Panlor DC: One to two capsules every four to six hours		Panlor DC capsules: acetaminophen 356.4mg / caffeine 30 mg / dihydrocodeine 16 mg
fentanyl oral transmucosal units (Actiq)	200 mcg as needed	Until the appropriate dose is reached, patients may find it necessary to use an additional unit during a single episode. If treatment of several consecutive breakthrough cancer pain episodes requires more than one unit per episode, an increase in dose to the next higher available strength should be considered.	200 mcg 400 mcg 600 mcg 800 mcg 1,200 mcg 1,600 mcg
fentanyl buccal tablets (Fentora)	100 mcg as needed	Until the appropriate dose is reached, patients may find it necessary to use an additional unit during a single episode. If treatment of several consecutive breakthrough cancer pain episodes requires more than one unit per episode, an increase in dose to the next higher available strength should be considered.	100 mcg 200 mcg 300 mcg 400 mcg 600 mcg 800 mcg
fentanyl buccal soluble films (Onsolis)	200 mcg as needed	Titrate using 200 mcg increments (maximum of four 200 mcg films or a single 1,200 mcg film) to adequate analgesia without undue side effects. Not to exceed four doses per day, separated by at least two hours.	200 mcg 400 mcg 600 mcg 800 mcg 1,200 mcg
hydrocodone / acetaminophen (Hycet)	15 mL every four to six hours	Not to exceed 90 mL in 24 hours. See dosing chart in prescribing information for initial doses for children.	hydrocodone 7.5 mg/acetaminophen 325 mg per 15 mL
hydrocodone / acetaminophen (Xodol)	One to two tablets every four to six hours	Not to exceed six tablets in 24 hours.	hydrocodone 5, 7.5, 10 mg/acetaminophen 300 mg tablets
hydrocodone / acetaminophen solution (Zamicet)	15 mL every four to six hours	Not to exceed 90 mL in 24 hours. See dosing chart in prescribing information for initial doses for children.	hydrocodone 10 mg/acetaminophen 325 mg per 15 mL
hydrocodone / acetaminophen (Zydone)	One to two tablets every four to six hours	Not to exceed six to eight tablets in 24 hours	hydrocodone 5, 7.5, 10 mg/acetaminophen 400 mg tablets
hydrocodone / ibuprofen tablets (Ibudone)	One tablet every four to six hours	Not to exceed a maximum of five tablets in 24 hours	hydrocodone 5, 10 mg/ibuprofen 200 mg
hydrocodone / ibuprofen tablets (Reprexain)	One tablet every four to six hours	Not to exceed a maximum of five tablets in 24 hours	hydrocodone 2.5, 5, 7.5, 10 mg/ibuprofen 200 mg
hydromorphone liquid (Dilaudid)	2.5 – 10 mg every three to six hours	Dose should be adjusted so that at least three to four hours of pain relief may be achieved. Dose should be increased as needed according to patient's response.	5 mg/5 mL
oxycodone/ibuprofen tablets (Combunox)	One tablet per dose	Not to exceed a maximum of four tablets in 24 hours	oxycodone 5 mg/ ibuprofen 400 mg

**Dosages (continued)**

Drug	Starting Dose	Dosing Instructions	Available Strengths
oxymorphone IR tablets (Opana)	10-20 mg every four to six hours on an empty stomach	Dose adjusted based on patient pain intensity and adverse drug reactions to an acceptable level of analgesia.	5 mg 10 mg
propoxyphene napsylate tablets (Darvon-N)	One tablet every four hours	Not to exceed a maximum of six tablets in 24 hours	100 mg
tapentadol (Nucynta)	One tablet every four to six hours	Doses greater than 700 mg on the first day and doses of greater than 600 mg on subsequent days are not recommended	50, 75, 100 mg tablets
tramadol (Ultram)	25 mg every morning	Titrate in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times daily). Then the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times daily). After titration, tramadol 50-100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg per day.	50 mg tablet
tramadol / acetaminophen tablets (Ultracet)	Two tablets every four to six hours	Not to exceed a maximum of eight tablets in 24 hours; the elimination half-life of tramadol is increased in patients with severe renal impairment (CLcr <30 mL/min), cirrhosis of the liver, or over 75 years, so the dosing interval should be increased.	37.5 mg tramadol / 325 mg acetaminophen

Oxymorphone IR (Opana) should be given on an empty stomach; maximum concentration and area under the curve were increased 38 percent when given with a high-fat meal.<sup>122</sup> Bioavailability of oxymorphone may also be increased in patients with hepatic or renal insufficiency. Formal studies have not yet been done.

**Clinical Trials**

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

fentanyl oral transmucosal (Actiq) and morphine IR

In a randomized, double-blind, cross-over trial with 134 adult ambulatory cancer patients, fentanyl oral transmucosal and morphine sulfate immediate release (MSIR) were compared for the management of breakthrough pain.<sup>123</sup> Enrolled patients were stabilized on a fixed schedule

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opioid regimen of either morphine sulfate or transdermal fentanyl and an effective MSIR dose of 15 to 60 mg up to four times daily for breakthrough pain. In an open-label fashion, fentanyl oral transmucosal was administered to establish the effective dose for breakthrough pain for 69 percent of patients. Double-blind randomization occurred and then a set of capsules and oral transmucosal delivery systems (one placebo unit per set being either capsule or transmucosal unit) were administered for each breakthrough pain dosing. During the blinded study, fentanyl oral transmucosal was significantly better than MSIR for pain intensity reduction, pain relief, and pain intensity differences. Patients favored the fentanyl oral transmucosal for breakthrough pain based on global performance.

### fentanyl buccal (Fentora)

A double-blind, randomized, placebo-controlled study evaluated the efficacy, safety, and tolerability of fentanyl buccal tablets in opioid-treated patients (n=123) with cancer-related breakthrough pain.<sup>124</sup> After an open-label titration to identify an effective fentanyl dose to treat breakthrough pain episodes, fentanyl patients were randomly assigned to a pre-specified dose sequence of 10 tablets (seven fentanyl, three placebo). Sixty-five percent of patients were titrated to an effective dose. Measures of pain relief and patient ratings of global performance of medication significantly favored fentanyl over placebo at 30 minutes.

### oxymorphone IR (Opana) and oxycodone IR

In a double-blind, parallel-group study, oxymorphone IR was compared with placebo for efficacy and with oxycodone IR and placebo for safety in patients with acute moderate to severe postsurgical pain.<sup>125</sup> Three hundred patients received oxymorphone IR 10, 20, or 30 mg; oxycodone IR 10 mg; or placebo. All oxymorphone IR doses were superior to placebo for providing pain relief for eight hours ( $p<0.05$ ), each with a significant analgesic dose response compared to placebo ( $p<0.001$ ). All oxymorphone IR groups maintained analgesia for 48 hours. The median dosing interval was over 9.5 hours for oxymorphone IR 30 mg. Opioid-related adverse events, similar among groups, were generally mild or moderate; the overall safety profile was comparable to that of oxycodone IR.

### oxycodone/ibuprofen (Combunox) versus oxycodone/acetaminophen (Percocet) versus hydrocodone/acetaminophen (Vicodin ES)

In a multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group, single-dose study, patients experiencing moderate to severe pain after surgical removal of two or more ipsilateral impacted third molars were randomly assigned to receive oxycodone 5 mg/ibuprofen 400 mg, oxycodone 5 mg/acetaminophen 325 mg, hydrocodone 7.5 mg/acetaminophen 500 mg, or placebo.<sup>126</sup> The primary outcome measures were total pain relief through six hours after dosing, sum of pain intensity differences through six hours (SPID6), and adverse events. Oxycodone 5 mg/ibuprofen 400 mg provided significantly greater analgesia compared with oxycodone 5 mg/acetaminophen 325 mg, hydrocodone 7.5 mg/acetaminophen 500 mg, and placebo ( $p<0.001$ , oxycodone 5 mg/ibuprofen 400 mg versus all other treatments) six hours after dosing. SPID6 values also differed significantly for oxycodone 5 mg/ibuprofen 400 mg compared with all other treatments ( $p<0.001$ ). Oxycodone 5 mg/ibuprofen 400 mg was significantly more effective compared with the other treatments on all secondary end points ( $p<0.001$ ), with the exception of the time to onset of analgesia. The lowest frequency of nausea and vomiting occurred in the groups that received oxycodone 5 mg/ibuprofen 400 mg (6.5 and 3.2 percent, respectively) and placebo (3.2 and 1.6 percent).

oxycodone/ibuprofen (Combunox) versus oxycodone (Roxicodone) versus ibuprofen (Motrin)

In a multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group trial, women experiencing moderate to severe pain between 14 and 48 hours after surgery were randomized to receive a single dose of oxycodone/ibuprofen, ibuprofen, oxycodone, and placebo.<sup>127</sup> Four hundred fifty-six women participated in the study. Combination treatment was associated with significantly better scores for total pain relief six hours after dosing and sum of pain intensity differences six hours after dosing compared with ibuprofen alone ( $p < 0.02$  and  $p < 0.015$ , respectively), oxycodone alone ( $p < 0.009$  and  $p < 0.001$ ), or placebo (both  $p < 0.001$ ). Fewer patients receiving combination treatment required rescue medication, and the time to use of rescue medication was significantly longer in the combination treatment group compared with the other groups ( $p < 0.05$ ). The onset of pain relief occurred within 15 minutes of dosing with all regimens. Nausea was the most frequently reported adverse event in all groups, highest with placebo and followed by oxycodone, ibuprofen, and combination treatment.

In the multicenter, double-blind, double-dummy, parallel-group investigation, 498 patients with moderate to severe pain within five hours after extraction of two or more impacted third molars were randomized to single doses of oxycodone 5 mg/ibuprofen 400 mg, ibuprofen 400 mg, oxycodone 5 mg, or placebo.<sup>128</sup> Combination therapy was associated with greater analgesia than ibuprofen alone, oxycodone alone, or placebo, as measured by the sum of pain intensity difference over six hours ( $p < 0.001$  versus oxycodone or placebo,  $p = 0.002$  versus ibuprofen) and total pain relief through six hours ( $p < 0.001$  versus oxycodone or placebo,  $p = 0.012$  versus ibuprofen). Combination therapy was well tolerated, and pharmacokinetic evaluation implied no interaction between oxycodone and ibuprofen.

oxymorphone (Opana) versus oxycodone IR versus placebo

A multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group study was conducted in men and women aged 18 years and older undergoing abdominal surgery.<sup>129</sup> Patients were randomized to receive oxymorphone 10 or 20 mg, oxycodone 15 mg, or placebo every four to six hours. The study included single-dose and 48-hour efficacy assessments. The primary efficacy endpoint was the median time to study discontinuation for all causes. Three hundred thirty-one patients were included in the study. The median time to study discontinuation was significantly longer for all active treatments compared with placebo (oxymorphone 10 mg, 17.9 hours; oxymorphone 20 mg, 20.3 hours; oxycodone 15 mg, 24.1 hours; placebo, 4.8 hours;  $p < 0.006$ ). Oxymorphone 20 mg was significantly more effective than placebo over the six-hour single-dose evaluation ( $p < 0.05$ ). With multiple dosing, all active-treatment groups had significantly lower least squares mean current and average pain intensities compared with placebo ( $p < 0.004$  and  $p < 0.005$ , respectively). Discontinuations due to treatment-emergent adverse events did not differ significantly among the groups.

tapentadol (Nucynta) versus morphine IR

Patients ( $n = 400$ ) undergoing molar extraction were randomized to receive single doses of tapentadol 25, 50, 75, 100, or 200 mg, morphine sulfate 60 mg, ibuprofen 400 mg, or placebo.<sup>130</sup> Mean total pain relief over eight hours (TOTPAR-8) was the primary endpoint. Secondary endpoints included mean total pain relief over 4 hours (TOTPAR-4) and onset of analgesia. Of all measured endpoints, only mean TOTPAR-4 was higher (and onset of action appeared more rapid) for tapentadol 200 mg than morphine sulfate 60 mg. Pain relief scores with morphine sulfate 60 mg were between those of tapentadol 100 and 200 mg. The incidence of nausea and vomiting appeared to be lower with all doses of tapentadol compared with morphine sulfate 60 mg but was not statistically significant.

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tramadol/acetaminophen (Ultracet) versus codeine/acetaminophen

A randomized, double-blind, parallel-group, active-control, double-dummy trial compared the efficacy and tolerability of tramadol/acetaminophen (37.5 mg/325 mg) tablets with codeine/acetaminophen capsules (30 mg/300 mg) in 462 patients with chronic nonmalignant low back pain, osteoarthritis, or both.<sup>131</sup> Pain intensity was assessed hourly for six hours each week over a four-week period. Pain relief and changes in pain intensity were comparable in both groups throughout the study. Equivalent mean doses and maximum daily doses used in each group were similar. The overall incidence of adverse events was comparable, with more patients in the codeine/acetaminophen group reporting somnolence (24 versus 17 percent,  $p=0.05$ ) and constipation (21 versus 11 percent,  $p<0.01$ ) than the tramadol/acetaminophen group.

A multicenter, randomized, double-blind, active- and placebo-controlled trial evaluated tramadol plus acetaminophen for orthopedic and abdominal postsurgical pain.<sup>132</sup> Patients with moderate pain or greater were randomized to an initial two tablets of 37.5 mg tramadol plus 325 mg acetaminophen ( $n=98$ ), codeine 30 mg plus acetaminophen 300 mg ( $n=109$ ), or placebo ( $n=98$ ). Thereafter, they received one to two tablets every four to six hours as needed for pain for six days. Tramadol plus acetaminophen was superior to placebo for total pain relief, sum of pain intensity differences, and sum of pain relief and pain intensity differences ( $p\leq 0.015$ ). For average daily pain relief, average daily pain intensity, and overall medication assessment, tramadol plus acetaminophen was superior to placebo ( $p\leq 0.038$ ); codeine plus acetaminophen did not separate from tramadol plus acetaminophen in any criteria. Discontinuation because of adverse events occurred in 8.2 percent of tramadol plus acetaminophen, 10.1 percent of codeine plus acetaminophen, and three percent of placebo patients. Except for constipation and vomiting being more prevalent in codeine plus acetaminophen patients, adverse events were similar for active treatments.

A four-week, randomized, double-blind, parallel-group, multicenter trial compared tramadol/acetaminophen 37.5 mg/325 mg with codeine/acetaminophen 30 mg/300 mg for the management of chronic nonmalignant low back pain, osteoarthritis pain, or both in 462 adults.<sup>133</sup> Pain relief (scale, 0 = none to 4 = complete) and pain intensity (scale, 0 = none to 3 = severe) were measured after 30 minutes and then hourly for six hours after the first daily dose each week. Pain relief and changes in pain intensity were comparable from Day 1 and lasted for at least six hours. Total pain relief scores and sum of pain intensity differences were also comparable throughout. Overall assessments of safety and efficacy by patients and investigators were similar for the two treatment groups.

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tramadol/acetaminophen (Ultracet) versus hydrocodone/acetaminophen (Vicodin)

In a single-center, double-blind, parallel-group, placebo- and active-controlled study in adults with at least moderate pain after extraction of two or more impacted third molars, patients were randomized to receive one to two tramadol/acetaminophen 37.5 mg/325 mg tablets, one hydrocodone/acetaminophen 10 mg/650 mg tablet, or placebo.<sup>134</sup> Two hundred adults took part in the study. The median time to onset of pain relief was approximately 34 minutes with tramadol/acetaminophen tablets and 25.4 minutes with hydrocodone/acetaminophen. Although the median time to onset of pain relief was shorter with hydrocodone/acetaminophen, two tramadol/acetaminophen tablets had comparable efficacy to hydrocodone/acetaminophen. The median time to remedication with a supplemental analgesic agent was 169 minutes in the tramadol/acetaminophen group and 204 minutes in the hydrocodone/acetaminophen group; however, the duration of pain relief was not significantly different between the groups. The

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overall incidence of adverse events was lower with tramadol/acetaminophen (zero percent) than with hydrocodone/acetaminophen (four percent) or placebo (ten percent).

### tramadol/acetaminophen (Ultracet) versus tramadol (Ultram)

A total of 456 patients with moderate to severe pain within five hours of extraction of two or more third molars were randomized to receive two identical encapsulated tablets containing tramadol/acetaminophen 37.5 mg/325 mg, tramadol 50 mg, or placebo.<sup>135</sup> Tramadol/acetaminophen was superior to tramadol ( $p < 0.001$ ) or placebo ( $p < 0.001$ ) on all efficacy measures, including total pain relief over six hours, sum of pain intensity differences, and sum of both. The most common adverse events with active treatment were nausea, dizziness, and vomiting, which occurred more frequently in the tramadol group than in the tramadol/acetaminophen group.

### **Summary**

Pain management must be individualized for each patient. There are many opioid analgesic products available, differing in specific opioid (and coanalgesics), dosage form, and duration of action. Many are available in clinically effective generic forms, including combinations of non-narcotic acetaminophen or ibuprofen with the opioids hydrocodone or oxycodone. Although some manufacturers market unique strengths of these combination agents, the minor changes in the doses of acetaminophen, ibuprofen, and/or opioid in these products have not been shown to offer any advantage over similar generic combinations. Similarly, there are no data to suggest that a particular formulation of fentanyl (Actiq, Fentora, Onsolis) is safer or more effective for breakthrough cancer pain.

Dihydrocodeine/caffeine/acetaminophen (Panlor SS, DC), tapentadol (Nucynta), tramadol/acetaminophen (Ultracet), and oxymorphone (Opana) have not shown increased efficacy when compared to other opioids.

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