Drug Use Research & Management Program
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Month/Year of Review: July 2013 **Date of Last Review:** March 2010
PDL Classes: Short Acting Opioids (SAO) **Source Document:** Provider Synergies

Current Status of PDL Class:

- **Preferred Agents:** CODEINE SULFATE TABLET AND SOLUTION, HYDROCODONE/ACETAMINOPHEN TABLETS (10MG/325MG, 10MG/500MG, 10MG/650MG, 10MG/660MG, 10MG/750MG, 2.5MG/500MG, 5MG/325MG, 7.5MG/325MG, 7.5MG/500MG, 7.5MG/650MG, 7.5MG/750MG STRENGTHS), HYDROMORPHONE HCL TABLET, MORPHINE SULFATE TABLET AND SOLUTION, OXYCODONE HCL TABLET AND SOLUTION, OXYCODONE HCL/ACETAMINOPHEN CAPSULES, OXYCODONE/ACETAMINOPHEN TABLETS (10MG/325MG, 10MG/650MG, 2.5MG/325MG, 5MG/325MG, 7.5MG/325MG, 7.5MG/500MG STRENGTHS) TRAMADOL HCL
- **Non-Preferred Agents:** CODEINE/CARISOPRODOL/ASPIRIN, DIHYDROCODEINE/ACETAMINOPHEN/CAFFEINE, DIHYDROCODINE/ASPIRIN/CAFFEINE (SYNALGOS-DC®), FENTANYL CITRATE SPRAY (LAZANDA®), FENTANYL CITRATE FILM (ONSOLIS®), FENTANYL CITRATE LOZENGE, FENTANYL CITRATE SUBLINGUAL (ABSTRAL®), FENTANYL CITRATE EFFORVESCENT (FENTORA®), HYDROCODONE/ACETAMINOPHEN CAPSULE (STAGESIC®), HYDROCODONE/ACETAMINOPHEN SOLUTION, HYDROCODONE-ACETAMINOPHEN TABLETS (10MG/300MG, 10MG/400MG, 5MG/300MG, 5MG-400MG, 7.5MG/300MG, 7.5-400MG STRENGTHS), HYDROMORPHONE LIQUID, MEPERIDINE HCL SOLUTION AND TABLET, OXYCODONE CAPSULE AND ORAL CONENTRATE, OXYCODONE TABLET ORL (OXECTA®), OXYCODONE/ACETAMINOPHEN SOLUTION (ROXICET®), OXYCODONE/ACETAMINOPHEN TABLET (PRIMLEV®, MAGNACET®), OXYCODONE/ASPIRIN, PENTAZOCINE/ACETAMINOPHEN, PENTAZOCINE/NALOXONE, TAPENTADOL (NUCYNTA®), TRAMDOL TAB RAPDIS (RYBIX ODT®), TRAMADOL/ACETAMINOPHEN, BUTORPHANOL TARTRATE SPRAY, FENTANYL SPRAY (SUBSYS®)

Previous Recommendations:
- Fentanyl products only be used in opioid tolerant patients
- Should have long acting analgesic therapy instituted
- Consider quantity limits
- Consider edit based on acetaminophen dosage

Current PA Criteria: Prior authorization is in place for fentanyl transmucosal and buccal (Appendix 1) to ensure that Actiq/Fentora/Onsoils is appropriately prescribed in accordance to FDA black box warnings.

Methods:
A Medline OVID search was conducted with the following search terms: codeine, hydrocodone, oxycodone, hydromorphone, morphine, oxymorphone, fentanyl, buprenorphine, tramadol, tapentadol, acetaminophen, opioids, opioid analgesics, short-acting opioids, pain, pain relief, and treatment. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to June week two 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Trials (Appendix 1):
A total of 624 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Ashburn[1] et al assessed the efficacy of buccal fentanyl compared with oral oxycodone in decreasing pain intensity of breakthrough pain in opioid-tolerant patients. This was a double-blind multi-center crossover study with multiple phases that lasted up to a total of eight weeks. Subjects (n=323) with chronic pain were randomized to titrate up to a successful dose of fentanyl or oxycodone; this was followed by a washout then titration period for the other study medication. After the titrations, subjects were re-randomized to take either buccal fentanyl and an oral placebo or buccal placebo and oral oxycodone to use for ten breakthrough pain incidents. This was followed by a crossover treatment period where subjects now received the other active medication plus placebo for another ten breakthrough pain incidents. The primary endpoint was improvement in pain intensity fifteen minutes after taking the medication as measured by an 11 point scale. Fentanyl significantly decreased pain intensity compared with oxycodone after 15 minutes (mean difference 0.82 vs. 0.6, 95% CI 0.18 to 0.29). Fentanyl maintained a significant difference over oxycodone at all other time points (5, 30, 45, and 60 minutes) measured as secondary efficacy endpoints. This was a fair quality study with good descriptions of patient baseline characteristics, inclusion and exclusion criteria. Allocation concealment, randomization and blinding procedures were not explicitly described.

Davies[2] et al compared intranasal fentanyl spray with immediate release oral morphine for relief from breakthrough pain in cancer patients. This double-blind multi-center randomized crossover trial was conducted in phases up to seven weeks duration. After completing an open label titration phase, patients (n=110) were randomly assigned to five treatments with either fentanyl spray and oral placebo or morphine tablet and placebo nasal spray (10 treatments total). The primary endpoint was improvement in pain intensity measured by an 11 point scale. Measurements were taken at 5, 10, 15, 30, 45, and 60 minute intervals. Intranasal fentanyl improved pain intensity by statically significant difference at the 10 minute (reduction in pain intensity: 52.4 versus 45.4, $p<0.05$) and the 15 minute (75.5 vs. 69.3, $p<0.05$) measurements. By 30 minutes there was no statistical difference between the two medications. This was a poor quality study. Although allocation concealment was discussed, blinding and randomization methods were not and there appeared to be multiple opportunities for bias (i.e. leading questions for patient satisfaction).

New drugs:
None

New Formulations/Indications:
Several new formulations have been approved since the last review. Two new combination hydrocodone solutions are now available.

Two new oxycodone products were approved in an effort to decrease misuse. OxyContin[5] (controlled release oxycodone) was relaunched in April 2010 as a new chemical entity with additional non-active ingredients to help prevent breakability and discourage crushing. OxyContin is indicated for the management of moderate to severe pain when a continuous opioid analgesic is needed for extended period of time. Oxecta[6] (oxycodone) approved in June 2011 also contains additional non-active ingredients to prevent dissolution and crushing. Oxecta is indicated for the management of acute and chronic moderate to severe pain.

Two new extended release opioids were recently approved. Exalgo[7] (hydromorphone) extended release tablets were approved in March 2010 for the indication of moderate to severe pain in opioid tolerant patients needing chronic continuous analgesia. Opana ER[8], an extended release oxymorphone oral tablet, was approved in December 2011 to treat chronic moderate to severe pain in patients requiring continuous pain coverage.
Three new formulations of fentanyl are now available.

In January 2011, Abstral[9] (fentanyl citrate) a sublingual tablet was approved. Lazanda[10] a fentanyl nasal spray was approved in June 2011. In January 2012, the fentanyl sublingual spray Subsys[11] was approved. Abstral, Lazanda and Subsys are all indicated for the management of breakthrough pain in adult opioid-tolerant cancer patients on concurrent continuous opioids. All patients must be enrolled in the TIRF REMS Access program to receive these medications.

Finally, a new extended release tapentadol oral tablet was approved in August 2011. Nucynta ER[12] is indicated for the management of chronic moderate to severe pain or neuropathic pain associated with diabetic peripheral neuropathy in adults who need continuous analgesia. In addition, a new oral solution of immediate release Nucynta[13] was approved in October 2012 for treatment of moderate to severe pain in adults.

New FDA safety alerts:

In February 2013, the FDA issued a Drug Safety Communication for codeine[14]. A Black Box Warning was added to codeine to restrict use in children for post-operative pain. Deaths have occurred post-operatively in children with obstructive sleep apnea who received codeine following a tonsillectomy and/or adenoidectomy. These children had evidence of being ultra-rapid metabolizers of codeine causing fatal amounts of morphine in the body. The Contraindication, Warnings/Precautions, Pediatric Use, and Patient Counseling Information sections of the drug label were also updated with this information.

In October 2012, the FDA issued a Safety Communication detailing an increased risk of developing thrombotic thrombocytopenic purpura (TTP) with Opana ER misuse.[15] This blood disorder has been seen in people crushing and intravenously injecting the medication. The FDA cautions that TTP has not been found in patients correctly using the oral medication.

In July 2012, the FDA approved a risk evaluation and mitigation strategy (REMS) for extended-release and long-acting opioids.[16] The REMS introduces safety measures designed to reduce risks and improve the safe use of these opioid formulations, while continuing to ensure access to patients in pain.

In April 2012, the FDA released a Safety Communication reminding patients, caregivers, and healthcare professionals of the importance of careful handling, storage and disposal of fentanyl patches.[16] Accidental exposure to fentanyl can cause hospitalization and even death. Children were singled out as the population at greatest risk of exposure.

In January 2011, the FDA issued a Safety Alert to recommend manufacturers limit the amount of acetaminophen to 325 mg or less for individual dosages.[17] In addition, a Black Box Warning was added to all prescription acetaminophen formulation label information highlighting the risk of severe liver injury with over use. This labeling change will affect all opioid acetaminophen combination products.

Lastly, the FDA requested propoxyphene products be removed from the market in November 2010. In a Safety Communication, the FDA detailed the reasons for the recommendation; most significantly new data had shown propoxyphene can cause severe cardiac toxicity even at therapeutic doses.[18]

New Systematic Reviews: (Appendix 2)

Two new systematic reviews were identified. Please see Appendix 2 for the full abstracts.

Vissers[19] et al compared the efficacy of immediate release fentanyl products and oral morphine in reducing pain intensity of breakthrough cancer pain. This systematic review included six randomized control trials with a total of 594 patients. Trial quality was not assessed. Five trials used a placebo comparator with intranasal fentanyl spray, transmucosal fentanyl or buccal fentanyl; one trial compared oral morphine with transmucosal fentanyl; and one trial compared transmucosal and intranasal fentanyl. The meta analysis endpoint was pain intensity difference (PID) reported on a 0 to 10 scale at 15 minute intervals up to 60 minutes after intake. The results of all trials were analyzed with a mixed comparison technique and reported with 95% credible interval (CrI). Intranasal fentanyl showed the greatest reduction in pain relative to placebo: PID 1.7 points (95% CrI: 1.4; 1.9) at 15 minutes. PID for transmucosal and buccal fentanyl relative to placebo were 0.4 (95% CrI: 0.0; 0.8) and 0.5 (95% CrI: 0.3; 0.7) at 15 minutes. All fentanyl treatments provided a reduction in pain superior to placebo at other time points. Oral morphine was not significantly different from placebo at 15 or 30 minutes, but achieved significance at 45 and 60 minutes: PID at 45 minutes 0.8 (95% CrI: 0.1 to 1.5) and 1.0 (95% CrI: 0.2 to 1.8). In head to head comparisons, intranasal fentanyl provided a greater reduction in PID at 15 minutes than morphine, transmucosal and buccal fentanyl. Differences in PID favoring intranasal fentanyl were 1.2 points (95% CrI: 0.8; 1.5) relative to buccal fentanyl, 1.3 (95% CrI: 0.9 to 1.6) points relative to transmucosal fentanyl and 1.7 (95% CrI: 1.1 to 2.3) points relative to oral morphine.

Reimsma[20] et al performed a systematic review to compare tapentadol with other schedule II opioids for the treatment of severe chronic pain. Two different analyses were conducted: one for trials with subjects in serious pain and another for trials which included subjects with either moderate or severe pain. The primary endpoint of the meta analysis was decrease in pain intensity measured by a standardized 0 to 100 point scale. Twelve

trials were included to compare patients in severe pain. Of these four were combined to show tapentadol as superior to oxycodone with respect to difference in pain intensity (mean difference -2.64 [95% CI: -4.84 to -0.44]). Tapentadol was also compared with placebo in five pooled trials and found to have a statistically significant difference in pain intensity (mean difference -6.33 [95% CI: -8.55 to -4.11]). Forty-two trials were included to compare patients in moderate to severe pain. Of these trials, seven were pooled to show tapentadol as statistically superior to oxycodone in decreasing pain intensity (mean difference -2.45 [95% CI: -4.04 to -0.86]). There were statistically significant differences in pain relief of 30% and of 50% at the end of treatment in favor of tapentadol, in comparison with oxycodone based on four trials (RR 0.72; 95% CI 0.59 to 0.88 and RR 0.74, 95% CI 0.59 to 0.94, respectively). For this population, tapentadol was compared with placebo in six trials. Overall, the pooled mean difference showed a statistically significant difference in pain intensity in favor of tapentadol (mean difference -6.91, 95% CI:-9.80 to -4.02). Indirect comparisons were made by network analysis between tapentadol and morphine (mean difference -3.93, 95% CI:-6.86 to -1.00), and between tapentadol and hydromorphone (mean difference -8.00, 95% CI: -11.59 to -4.41) for pain intensity. All other comparisons (buprenorphine, fentanyl, and oxymorphone) showed non-significant differences in pain intensity. In terms of 30% pain relief tapentadol was superior to oxycodone (OR 0.58, 95% CI: 0.49 to 0.69), hydromorphone (OR 0.59, 95% CI: 0.37 to 0.95), and placebo (OR 0.74, 95% CI: 0.64 to 0.86). These figures were similar for 50% pain relief. Trial quality varied widely, with the authors' acknowledgment that more than half of the included trials were of low quality. Data from this review is difficult to interpret as the included trials were of various lengths; with many types of chronic pain (nociceptive or neuropathic, malignant or nonmalignant, etc.); and utilizing all formulations of study medications (immediate versus extended release). Inclusion criteria for meta analysis was not transparent (i.e. twelve trials were included for review but four were pooled). For the network analyses, the population designations of severe and moderate to severe were abandoned. Overall, the quality of the review was poor.

Guidelines:

The updated opioid prescribing guidelines from the American Society of Interventional Pain Physicians[21] were reviewed. As was the joint guideline for the treatment of diabetic neuropathy from the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine and the American Academy of Physical Medicine and Rehabilitation[22]. The National Institute for Health Care Excellence clinical guideline for Opioid use in Palliative Care[23] from the UK was also reviewed. Finally, the updated VA/DoD guideline for the Management of Opioid Therapy for Chronic Pain[24] was evaluated. No changes regarding the use of medications were found.

Recommendations:

- No further research or review needed at this time.
- There is no clinical evidence necessitating changes to current PDL status. Evaluate comparative costs in executive session.
- Update PA criteria to include new spray formulations of fentanyl to current PA criteria.

References:

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2. Davies A, Sitte T, Elsner F, et al. Consistency of Efficacy, Patient Acceptability, and Nasal Tolerability of Fentanyl Pectin Nasal Spray Compared with Immediate-Release Morphine Sulfate in Breakthrough Cancer Pain. *Journal of Pain and Symptom Management*. 2011;41(2):358–366. doi:10.1016/j.jpainsymman.2010.11.004.

3. Vituz (hydrocodone bitartate and chlorpheniramine maleate) Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204307s000lbl.pdf. Accessed June 23, 2013.

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10. Lazanda (fentanyl) Nasal Spray Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022569s007lbl.pdf. Accessed June 24, 2013.

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12. Nucynta ER (tapentadol) Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/200533s001lbl.pdf. Accessed June 24, 2013.

13. Nucynta (tapentadol) Oral Solution Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203794s000lbl.pdf. Accessed June 24, 2013.

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15. Drug Safety and Availability > FDA warns about serious blood disorder resulting from misuse of Opana ER. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm322432.htm. Accessed June 24, 2013.

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Appendix 1: Prior Authorization Criteria

Fentanyl Transmucosal and Buccal

The purpose of this prior authorization policy is to ensure that Actiq/Fentora/Onsolis is appropriately prescribed in accordance to FDA black box warning:

- *"Actiq/Fentora/Onsolis is indicated only for the management of breakthrough cancer pain in clients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.*
- *Clients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.*
- *Because life-threatening hypoventilation could occur at any dose in clients not taking chronic opiates, Actiq/Fentora/Onsolis is contraindicated in the management of acute or postoperative pain.*
- *This product must not be used in opioid non-tolerant clients. Actiq/Fentora/Onsolis is intended to be used only in the care of cancer clients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.*
- *When prescribing do not convert patients from other fentanyl products on a mcg per mcg basis. Pharmacokinetic differences between products could cause fatal over dose.*
- *Caution should be used when combining Actiq/Fentora/Onsolis with CYP3A4 inhibitors. Increases in fentanyl concentrations could cause fatal respiratory depression.*
- *Patients and their caregivers must be instructed that Actiq/Fentora/Onsolis contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly."*

Initiative: MAP: Actiq/Fentora

Length of Authorization: Up to 6 months (w/qty limit)

Covered Alternatives: Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

The following requires PA: Non-preferred drugs

GSN	GENERIC	BRAND
022358, 022360, 041339, 041340, 041341, 041342	Fentanyl Citrate	Actiq
061492, 061493, 063177, 061495, 061496, 061497	Fentanyl Citrate	Fentora
65552, 65553, 65554, 65555, 65556	Fentanyl Citrate	Onsolis

Approval Criteria		
1. What is the diagnosis for which Actiq/Fentora/Onsolis is being requested?		Record ICD9 code and reject/internal error code
2. Is the pain diagnosis above the line or below the line? *(for DMAP, Actiq/Fentora/Onsolis is not limited to cancer pain but must be severe chronic pain)*	**Above the line:** go to #3.	**Below the line:** No, Pass to RPH; Deny, (Not Covered by the OHP).
3. Is the prescriber an oncologist or pain specialist?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny, (Medical Appropriateness*), with message*: "*The described use is not consistent with the FDA labeling which Actiq/Fentora/Onsolis be used only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain."*
4. Is client tolerant to opioids **(Check profile),** defined as chronic long-acting opioid dose of: • Morphine greater than 60 mg per day? **OR** • Transdermal fentanyl 50 mcg per hour? **OR** • Equianalgesic dose of another opioid for at least one week?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny, (Medical Appropriateness*), with message*: *"Your request was reviewed and denied because it is not consistent with the FDA labeling. A trial of immediate release morphine or oxycodone is recommended prior to use of Actiq/Fentora/Onsolis."*
5. Has the client tried and failed immediate release morphine or oxycodone? OR is the client allergic, unable to swallow or intolerant to morphine and oxycodone?	**Yes:** Go to #6.	**No:** Pass to RPH; Deny, (Medical Appropriateness*), with message*: *"Your request was reviewed and denied based on the following: A trial of immediate release morphine or oxycodone is recommended prior to use of Actiq/Fentora/Onsolis."*
6. Is the quantity >4 doses per day?	**Yes:** Pass to RPH; Deny, (Medical Appropriateness*),* with message: *"Your request for a quantity greater than 4 has been denied because it exceeds limits."*	**No:** Approve for up to 6 months with quantity limit of 4 lollipops/tablets per day (i.e. 120/30 days).

DUR Board Action: *3/18/10 (DO); 12-3-09 (KS), 9-15-05, 5-12-05*
Revision(s): *4/26/10 (DO); 4/1/08, 6/1/08, 1/1/10*
Initiated: *9-1-06*

Appendix 1

Randomized Control Trials

Ashburn MA, Slevin KA, Messina J, Xie F. The Efficacy and Safety of Fentanyl Buccal Tablet Compared with Immediate-Release Oxycodone for the Management of Breakthrough Pain in Opioid-Tolerant Patients with Chronic Pain. *Anesthesia & Analgesia*. 2011;112(3):693–702. doi:10.1213/ANE.0b013e318209d320.

Context. We recently reported that fentanyl pectin nasal spray (FPNS) provides superior pain relief from breakthrough cancer pain (BTCP) compared with immediate-release morphine sulfate (IRMS), with significant effects by five minutes and clinically meaningful pain relief from 10 minutes postdose.

Objectives. To report the consistency of efficacy, tolerability, and patient acceptability of FPNS vs. IRMS.

Methods. Patients (n ¼ 110) experiencing one to four BTCP episodes/day while taking $60 mg/day oral morphine (or equivalent) for background pain entered a double-blind, double-dummy (DB/DD), multiple-crossover study. Those who completed an open-label titration phase (n ¼ 84) continued to a DB/DD phase; 10 episodes were randomly treated with FPNS and overencapsulated placebo or IRMS and nasal spray placebo (five episodes each). Pain intensity (PI) and pain relief scores were assessed. Patient acceptability scores were assessed at 30 and 60 minutes. Safety and tolerability were assessed by adverse events (AEs) and nasal assessments.

Results. Per-episode analysis revealed that FPNS consistently provided relief from pain more rapidly than IRMS; by 10 minutes, there were significant differences in PI difference scores and in the percentages of episodes showing clinically meaningful pain relief ($P < 0.05$). Overall acceptability scores were significantly greater for FPNS than for IRMS at 30 ($P < 0.01$) and 60 ($P < 0.05$) minutes. Patients were ''satisfied/very satisfied'' with the convenience (79.8%)

Davies A, Sitte T, Elsner F, et al. Consistency of Efficacy, Patient Acceptability, and Nasal Tolerability of Fentanyl Pectin Nasal Spray Compared with Immediate-Release Morphine Sulfate in Breakthrough Cancer Pain. *Journal of Pain and Symptom Management*. 2011;41(2):358–366. doi:10.1016/j.jpainsymman.2010.11.004.

BACKGROUND: Current clinical guidelines have identified the need for studies comparing the effect of different short-acting or rapid-onset opioids for the treatment of breakthrough pain (BTP). In this study we evaluated the efficacy and safety of treatment with fentanyl buccal tablet (FBT) in comparison with immediate-release oxycodone in alleviating BTP in opioid-tolerant patients with chronic pain.

METHODS: In this cross-over design study, opioid-tolerant patients were randomized to open-label titration with FBT (200, 400, 600, 800 mcg) followed by oxycodone (15, 30, 45, 60 mg) or vice versa for the management of BTP. After titration to a successful dose of both study drugs, patients were rerandomized to double-blind treatment for 10 BTP episodes with 1 of the already identified successful doses of study drug followed by cross-over to double-blind treatment for 10 BTP episodes with the other study drug. The primary efficacy measure was the difference in pain intensity (based on an 11-point numerical scale) 15 minutes after administration of study drug (PID15). Other efficacy measures included PID at other time points postdose (5 through 60 minutes), the sum of pain intensity differences (SPID) at 30 and 60 minutes postdose, pain relief (5 through 60 minutes), proportion of BTP episodes for which patients experienced meaningful reduction in pain intensity, and patient preference for BTP medication. Adverse events were also recorded.

RESULTS: Of the 323 patients enrolled, 203 achieved a successful dose of both study drugs, 191 completed the titration phase, and 180 completed the double-blind phase. PID15 was significantly greater after FBT versus oxycodone (mean [SD], 0.82 [1.12] vs. 0.60 [0.88]; 95% confidence interval [CI] _ 0.18, 0.29; *P* _ 0.0001). Secondary efficacy measures favored FBT and showed differences versus oxycodone from 5 minutes postdose for PID and 10 minutes postdose for pain relief. SPID30 and SPID60 were greater with FBT than with oxycodone (*P* _ 0.0001 for both measures). A _33% improvement in pain intensity occurred in a larger proportion of FBT-treated episodes versus oxycodone beginning 15 through 45 minutes postdose (*P* _ 0.05). FBT was preferred by 52% of patients, oxycodone by 33%. Adverse events with both study drugs were generally typical of opioids, and the majority occurred during titration. Two serious adverse events (pneumonia) were reported in 1 patient; both occurrences were considered unrelated to study drug.

CONCLUSION: FBT resulted in more rapid onset of analgesia and was generally well tolerated in comparison with oxycodone for the treatment of BTP in opioid-tolerant patients.

Appendix II

Systematic Reviews

Vissers D, Stam W, Nolte T, Lenre M, Jansen J. Efficacy of intranasal fentanyl spray versus other opioids for breakthrough pain in cancer. *Current Medical Research and Opinion*. 2010;26(5):1037–1045. doi:10.1185/03007991003694340.

Objective: To compare the efficacy of intranasal fentanyl spray (INFS), oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablet (FBT) and oral morphine (OM) for the treatment of breakthrough cancer pain (BTCP).

Methods: A systematic literature review (Medline, EMBASE, BIOSIS; 1996–2007) identified six randomised controlled trials (RCTs) investigating the effects of INFS, OTFC, FBT and OM for the treatment of BTCP. The endpoint of interest was pain intensity difference (PID, reported on a 0–10 numeric rating scale [NRS]) up to 60 minutes after intake. Results of all trials were analysed simultaneously with a mixed treatment comparison (extended meta-analysis). MTC can be considered a valid method when included studies are comparable regarding effect modifying baseline patient and study characteristics.

Results: INFS provided the greatest reduction in pain relative to placebo: PID 1.7 points (95% CrI: 1.4; 1.9) at 15 minutes, 2.0 (1.6; 2.3) at 30 minutes, 2.0 (1.5; 2.4) at 45 minutes and 1.9 (1.5; 2.4) at 60 minutes. PID for OTFC and FBT relative to placebo were 0.4 (0.0; 0.8) and 0.5 (0.3; 0.7) at 15 minutes. Both treatments provided a reduction in pain superior to placebo at other time points. INFS displayed a more than 99% probability of providing the greatest pain reduction out of all interventions compared at 15 minutes after intake. This was maintained for any measured time point before 45 minutes when compared to FBT and for any measured time point before 60 minutes when compared to OTFC. Only from 45 minutes onwards did OM show a greater pain reduction than placebo.

Conclusion: Based on currently available evidence, INFS is expected to provide the greatest improvement in the treatment of BTCP. Due to its slow onset to effect OM cannot be considered an efficacious treatment for BTCP.

Riemsma R, Forbes C, Harker J, et al. Systematic review of tapentadol in chronic severe pain. *Current Medical Research and Opinion*. 2011;27(10):1907–1930. doi:10.1185/03007995.2011.611494.

Aim: A systematic review of chronic pain treatment with strong opioids (step 3 WHO pain ladder) and a comparison to a new drug recently approved for the treatment of severe chronic pain in Europe, tapentadol (Palexia, Nucynta*), were performed.

Methods: Thirteen electronic databases were searched as well as a number of other sources from 1980 up to November 2010 for relevant randomized controlled clinical trials in chronic moderate and severe pain investigating at least one step 3 opioid. Chronic pain could be nociceptive or neuropathic, malignant or nonmalignant, all systemic administrations were considered as well as trials of different lengths. Two separate analyses were performed, one only for trials which reported (at least as sub-groups) the outcome in patients with severe pain, the other including both moderate and severe pain conditions. With the exception of the direct comparison between tapentadol, oxycodone and placebo, indirect comparisons were performed based on a network analysis. Trials with an enriched or an

enriched withdrawal design were excluded. Primary (pain intensity) and a number of secondary endpoints were evaluated, including pain relief (30% and 50%), patient global impression of change, quality of life, quality of sleep, discontinuations, as well as serious adverse events and selected adverse events.
Results: Only 10 trials were eligible for analysis of patients with severe pain (eight investigating tapentadol and two trials comparing buprenorphine patch vs placebo). For moderate and severe pain, 42 relevant trials were identified and indirect comparisons with transdermal buprenorphine, transdermal fentanyl, hydromorphone, morphine, and oxymorphone were performed. This report focuses on the network analysis. Tapentadol showed statistically favourable results over oxycodone for pain intensity, 30% and 50% pain relief, patient global impression of change (PGIC), and quality of life. Furthermore, some of the most important adverse events of chronic opioid treatment were significantly less frequent with tapentadol as compared to oxycodone, i.e. constipation, nausea, and vomiting; discontinuations due to these adverse events were found significantly reduced with tapentadol. Similar results were obtained for the network analysis, i.e. tapentadol was superior for the primary outcome (pain intensity) to hydromorphone and morphine, whereas fentanyl and oxymorphone showed trends in favour of these treatments. Significantly less frequent gastrointestinal adverse events of tapentadol were observed in comparison with fentanyl, hydromorphone, morphine, and oxymorphone, apparently leading to significantly reduced treatment discontinuations (for any reason).
Conclusions: Taken together, the benefit–risk ratio of tapentadol appears to be improved compared to step 3 opioids.

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