South African National Essential Medicine List
Tertiary and Quaternary Medication Review Process
Component: Pain

TITLE: Transdermal fentanyl for severe stable pain in patient who are unable to take oral medication and do not have access to subcutaneous opioids via a syringe driver.

Date: June 2024

Executive Summary

Medicine (INN): transdermal fentanyl
Medicine (ATC): N02AB03
Indication (ICD10 code): R52.1 – Chronic intractable pain
Patient population: patients with severe stable chronic pain who are unable to take oral medication and do not have access to subcutaneous opioids via a syringe driver.
Prevalence of condition: A study by Goldman et al. 2006[1] noted that pain was a common symptom (70.6%) experienced by children and adolescents with advanced cancer referred for palliative care, and with a subsequent increase in prevalence closer to death (91.5%). However, the patient population for whom fentanyl transdermal patches are being requested is a small subset of this total population.
Level of Care: Tertiary
Prescriber Level: Specialist

Key findings

- The World Health Organization (WHO) recommends that opioid therapy be added to analgesic regimens for moderate to severe pain.[2] Opioid therapy can be delivered through various routes including oral, intravenous, intramuscular and transdermal.
- Currently there are no transdermal opioid options available in the public sector for patients with severe stable pain, but who are unable to swallow, or do not have access to subcutaneous opioids via a syringe driver.
- We conducted a literature review to explore the efficacy and safety of transdermal fentanyl for severe stable pain. No appropriate data could be found where transdermal fentanyl compared to oral morphine was evaluated for the setting where oral opioids could not be taken.
- Two systematic reviews were selected for data extraction, one evaluating both efficacy and safety (cancer patients with moderate to severe pain) and one evaluating safety (both cancer and non-cancer patients with moderate to severe pain).
- **Comparison: Transdermal fentanyl vs oral opioids**
  - Pain control
    - *Pain no worse than mild pain:* There was insuffiicient comparable data for meta-analysis to be undertaken or to produce numbers needed to treat (NNT) for the analgesic effect. Seven studies (n = 461) however reported pain intensity results after approximately 2 weeks, and the median or mean pain scores were on the borderline of mild and moderate pain, with most participants having no worse than mild pain when treated with transdermal fentanyl. One other study reported a 77% successful outcome with transdermal fentanyl, however the measure of successful outcome was not defined.

- Adverse events
  - *Constipation:* Kelly et.al. found that fewer participants experienced constipation with transdermal fentanyl (28%) than with oral sustained-release morphine (46%), giving a risk ratio of 0.61 (95% CI 0.47 to 0.78); the NNTp was 5.5 (3.8 to 10).
  - *Other adverse effects:* Transdermal fentanyl was found also have a significant benefit over slow-release morphine in terms of urinary retention (OR = 0.56, p = 0.015), laxative use (OR = 0.56, p <0.01), and patient preference (OR = 0.32, p < 0.001). (Tassinari et.al. 2009). Slow-release oral morphine was found to have a favourable benefit over transdermal fentanyl in terms of nausea (OR = 1.26, p =0.048), diarrhoea (OR = 1.87, p=0.0001) and sweating (OR = 1.91, p < 0.001). (Tassinari et.al. 2009).

➡ Current single exit pricing of transdermal fentanyl is similar to single exit pricing of sustained release oral morphine.

➡ The use of transdermal fentanyl patches in this population is expected to be small, as it would only be in the setting where oral opioids cannot be used and syringe drivers for parenteral opioids are not available.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation				**X**	

Recommendation: It is recommended that transdermal fentanyl be considered for the management of severe stable pain in patients who are unable to take oral medication and do not have access to subcutaneous opioids via a syringe driver.

Rationale: When compared with oral morphine, transdermal fentanyl has been shown to relieve pain in patients with chronic stable pain and is associated with a lower incidence of constipation. In patients unable to receive oral opioids and who do not have access to a syringe driver, transdermal fentanyl is an alternative pain management option.

Level of Evidence: Systematic Reviews (moderate to critically low quality).
Review indicator: Price, signals of harm, evidence of superiority.

NEMLC RECOMMENDATION:

NEMLC recommended that transdermal fentanyl be considered for the management of severe stable pain in patients who are unable to take oral medication and do not have access to subcutaneous opioids via a syringe driver.

Monitoring and evaluation considerations:

Research priorities:

1. **Name of author(s)/motivator(s)**
   - Zainab Mohamed (Head Clinical Unit Radiation Oncology, Groote Schuur Hospital, University of Cape Town).
   - Laura Stopforth (Head of Oncology, Greys Hospital, Pietermaritzburg).
   - Rene Krause (Division of Interdisciplinary Palliative Care Medicine, University of Cape Town).
   - Daleen van Jaarsveld (Palliative Care Physician, Bloemfontein).
   - Liezl Du Plessis (Paediatric Oncologist, Robert Mangaliso Sobukwe Hospital, Kimberley).
   - Jane Riddin (Essential Drugs Programme, National Department of Health).

2. Author affiliation and conflict of interest details

- All reviewers had no conflicts of interest to declare.

3. Introduction/ Background

The World Health Organization (WHO) recommends that opioid therapy be added to analgesic regimens for moderate to severe pain.[2] Opioid therapy can be delivered through various routes including oral, intravenous, intramuscular and transdermal.

Patients suffering severe pain due to advanced malignancies or other conditions have the right to receive effective palliative care to relieve suffering and maintain dignity and quality of life. The Stepwise Healthcare Interventions for Pain (SHIP) model was developed in South Africa and offers a holistic approach to pain assessment and intervention guided by the WHO analgesic ladder. Appropriate analgesics (by the ladder) should be taken regularly (by the clock) with the oral route being preferred (by mouth).

Not all patients are able to take pain medication orally, including those with obstructive cancers of the aerodigestive tract; cancers affecting the gastrointestinal system causing intractable vomiting and the inability to absorb analgesics; patients with neurological conditions affecting swallowing; young children unable to take tablets by mouth; those receiving chemotherapy and/or radiotherapy with severe mucositis and patients at end of life, who are unable to take oral opioids due to frailty or depressed level of consciousness. Analgesia may be administered parenterally to these patients, most commonly subcutaneous via a syringe driver or pump. In the state sector, this is only possible whilst patients are admitted to tertiary or secondary hospitals, or if they are being cared for by a hospice or palliative care provider with access to syringe drivers. In the absence of a non-oral opioid alternative, this cohort of patients are sent home without adequate analgesia.

Transdermal fentanyl is registered in South Africa for the management of chronic intractable pain that requires opioid analgesia which cannot be managed by lesser means such as paracetamol-opioid combinations, non-steroidal analgesics or as-required-dosing with short-acting opioids. Most commercially available products recommend use in patients 2 years of age and older, however caution should be taken in the elderly, where increased monitoring may be needed.[3]

This review seeks to establish the safety and efficacy of transdermal fentanyl in the management of patients (2 years of age and older) with chronic stable pain and to motivate for its inclusion on the Tertiary/Quaternary Essential Medicines List for patients unable to take oral medication and who do not have access to subcutaneous opioids via a syringe driver.

4. Purpose/Objective i.e. PICO question:

Population:	Patients (children, adolescents, adults) with severe stable pain who are unable to take pain medication orally and have no access to subcutaneous opioids via a syringe driver.
Intervention:	Transdermal Fentanyl patch 12, 25, 50, 75, 100mcg/hour strength
Comparators:	Oral morphine syrup, morphine slow-release tablets
Outcomes:	• Effective pain control: measured by validated assessment tool. • Adverse effects.
Study designs:	Systematic reviews, meta-analyses

5. Methods:

a. Data sources A search was run on 26 March 2024, using both *Pubmed and Cochrane Library.*

b. Search strategy *See appendix 2 for full search strategy. The table below outlines the search findings:*

Pubmed	23 citations
Cochrane	7 citations
Overlap	7 citation
Excluded	14 citations
Total for consideration	**9 citations**

The search and screening of studies was undertaken by two reviewers (JR and ZM) and presented to the ERC for discussion and final selection. Nine reviews were identified for full text review. Of these seven were excluded, see excluded studies list below. Two systematic reviews were selected for inclusion: Hadley et.al. 2013 and Tassinari et.al. 2009.

c. Excluded studies:

Author, date	***Type of study***	***Reason for exclusion***
Wang 2018	*Systematic review*	Includes Chinese studies that cannot be sourced
Tassinari et.al. 2008	*Systematic review*	Evaluation includes both buprenorphine and fentanyl vs oral morphine - 2009 below more specific to fentanyl patches.
Yang 2010	*Systematic review*	Includes Chinese studies that cannot be sourced
Clark 2004	*Systematic review*	Included uncontrolled trials, open label trial and RCTs
Quigley 2008	*Systematic review*	Included observational and RCTs
Wiffen 2017, Cochrane	*Systematic review*	Includes all opiates – Hadley more specific
Zernikow 2007[4]	*Narrative review*	Includes a narrative discussion on Children

d. Evidence synthesis

Data was extracted by one reviewer (JR), checked by another reviewer (ZM) and presented to the TQ ERC for final consensus.

Author, date	***Type of study***	**n**	**Population**	**Comparators**	**Primary outcome**	**Effect sizes**	**Comments**
Hadley 2013 (Cochrane)[5]	Systematic Review	9 Randomised controlled trials (6 RCTs of fentanyl vs oral morphine)	Inpatients or outpatients with chronic pain of moderate to severe intensity due to malignant disease (no age limit). (n=758 for fentanyl vs oral	Transdermal fentanyl Versus Oral Morphine OR paracetamol/ codeine OR Placebo	• Number of participants with pain reduction of ≥ 30% from baseline. • Number of participants with pain reduction of ≥50% from baseline. • Number of participants with pain no worse than mild.	Insufficient comparable data for meta-analysis for analgesic effect. Outcome: no worse than mild pain based on VAS pain intensity of 30 mm or less on a 100mm scale or equivalent pain scale.	Transdermal fentanyl – 461/479 (96%); no GRADE assessment given. There were major sources of potential bias, including lack of blinding, small size, high levels of attrition, and

			morphine studies)		• Number of participants with patient global impression of change (PGIC) of much improved or very much improved (or equivalent wording). Secondary outcomes: • Quality of life measures • Use of rescue medication • Patient satisfaction/ preference • Adverse events. • Attrition	• 5 studies where transdermal fentanyl compared to oral morphine reported an outcome of achievement of pain relief (no worse than mild) • 1 study reported that 94 /122 participants on transdermal fentanyl had a successful outcome (but not clearly defined). Adverse events Constipation In four studies it was possible to compare impact of constipation, fewer participants experienced constipation with transdermal fentanyl (28%) versus oral SRM (46%), RR 0.61 (95% CI 0.47 to 0.78), NNT = 5.5 (3.8 to 10)	inconsistent reporting.
Tassinari et.al. 2009	Systematic review	5 randomised clinical trials (n = 1309 patients)	Cancer and non-cancer patients with moderate to severe pain	Transdermal fentanyl Versus oral slow-release morphine	Difference in side effect ratio	A significant advantage of transdermal fentanyl was documented for constipation, urinary retention, laxative use, and patient preference. A significant advantage of	Critically low AMSTAR assessment.

						slow-release oral morphine was documented for nausea, diarrhea, and sweating.	

e. Evidence quality:

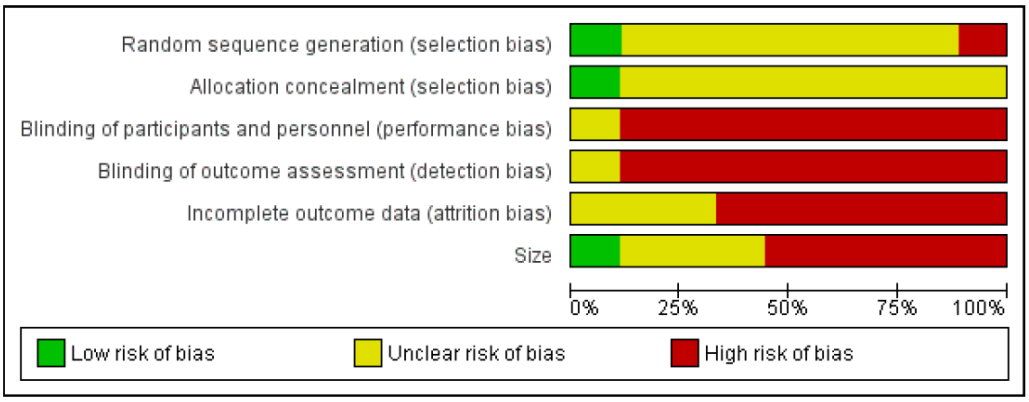
AMSTAR

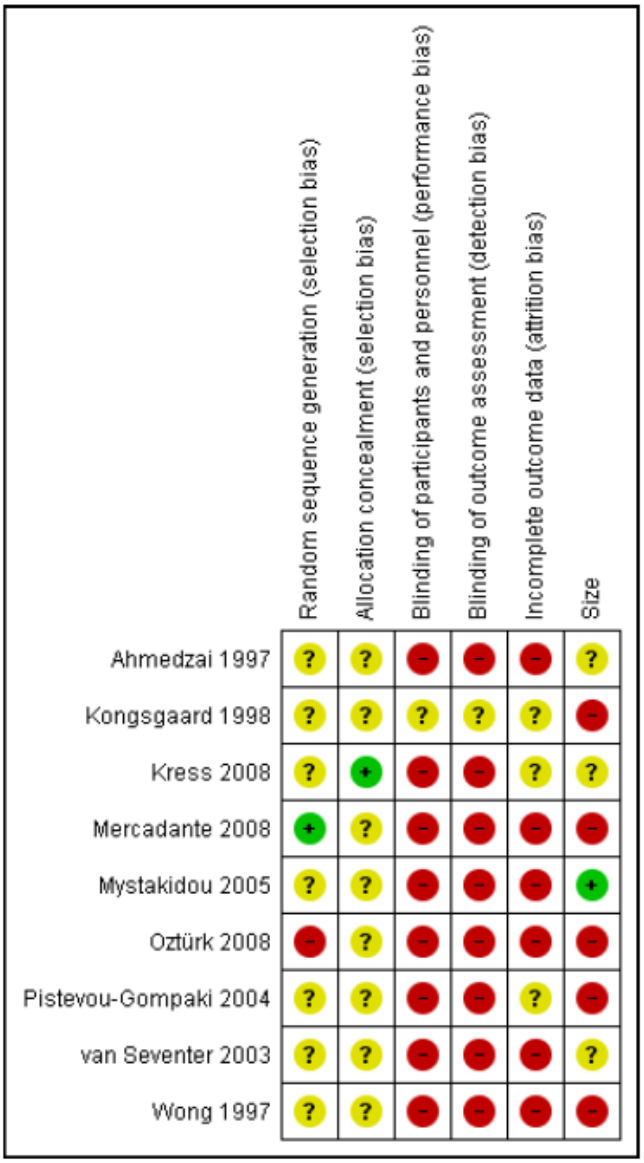
AMSTAR 2 assessments were performed in duplicate (JR and DF)

Study	AMSTAR 2 assessment	Notes
Hadley 2018	Moderate quality	No meta-analysis undertaken, no publication bias assessment, no funding of studies described.
Tassinari 2009	Critically low quality	No data extraction in duplicate, included studies not described adequately, no risk of bias assessment (only Jadad), no funding of studies described, no publication bias assessment, no declaration of conflicts of interest of authors.

Risk of Bias

Hadley 2018





Tassinari 2009

Jadad Quality score undertaken: three studies scored 3, and two studies scored 2 (scores under 3 indicate low quality).

Effects of interventions

Pain control

No worse than mild pain

There was insufficient comparable data for meta-analysis to be undertaken or to produce numbers needed to treat (NNT) for the analgesic effect.

Six studies compared transdermal fentanyl to oral morphine:

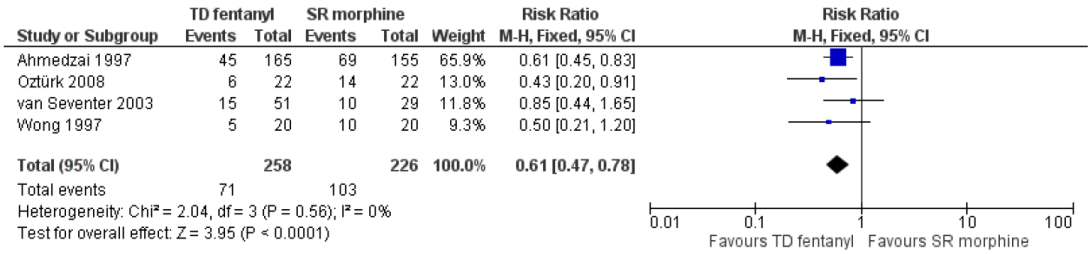
	Studies	Pain intensity for transdermal fentanyl
1	Ahmedzai 1997	94 out of 122 participants on transdermal fentanyl had successful outcomes (however this not clearly defined)
2	Kress 2008	Mean pain intensity result 31% +/- 2% after 30 days; n = 117
3	Mercadante 2008	Mean pain intensity result 3 out of 10 (range: 2 to 3.6) after 2 weeks; n = 36
4	Ozturk 2008	Mean pain intensity result 3 out of 10 (range: 0 to 3) after 2 weeks; n = 22
5	Van Seventer 2003	Mean pain intensity result approximately 3 out of 10 after 2 weeks; n = 45
6	Wong 1997	Mean pain intensity result 0.9 +/- 0.1 out of 4 after 2 weeks; n = 40

Adverse events

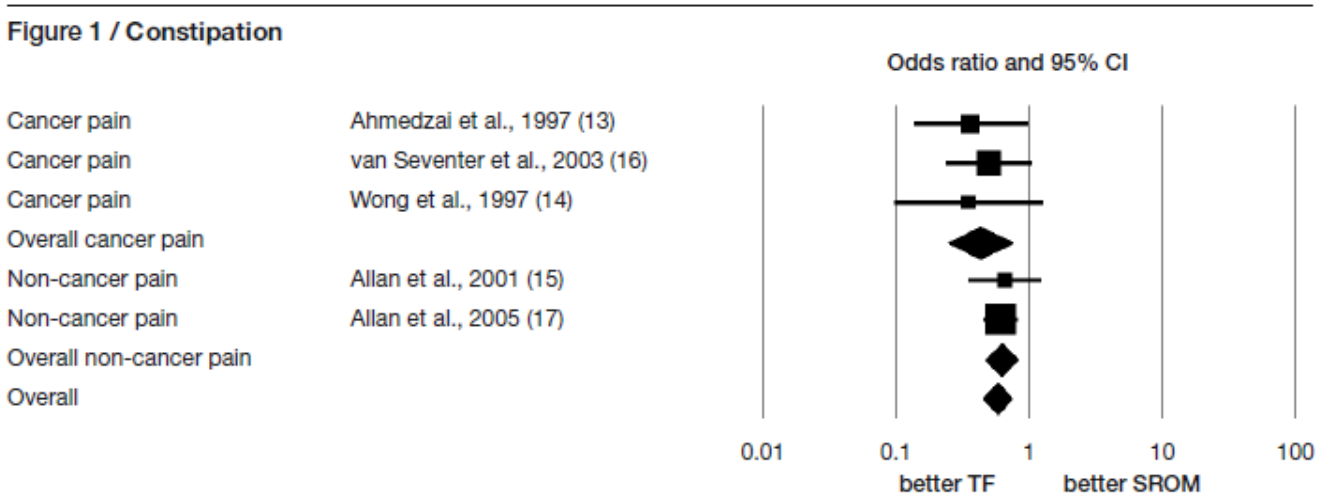
Constipation

Kelly et.al. found that fewer participants experienced constipation with transdermal fentanyl (28%) than with oral sustained-release morphine (46%), giving a risk ratio of 0.61 (95% CI 0.47 to 0.78); the NNTp was 5.5 (3.8 to 10).

Figure 3. Forest plot of comparison: 1 Fentanyl versus sustained release morphine, outcome: 1.1 Constipation.



Tassinari et.al. also found that transdermal fentanyl had a significant advantage over oral morphine, odds ratio = 0.56, p<0.001.



Other adverse effects

Transdermal fentanyl was also found to have a significant benefit over slow-release morphine in terms of urinary retention (OR = 0.56, p = 0.015), laxative use (OR = 0.56, p <0.01), and patient preference (OR = 0.32, p < 0.001). (Tassinari et.al. 2009)

Slow-release oral morphine was found to have a favourable benefit over transdermal fentanyl in terms of nausea (OR = 1.26, p =0.048), diarrhoea (OR = 1.87, p=0.0001) and sweating (OR = 1.91, p < 0.001). (Tassinari et.al. 2009)

6. Alternative agents: *None for patients where oral morphine cannot be used and syringe drivers are not available.*

7. Costs

Cost comparison to oral morphine preparations

	Product	Comparative dosing	Unit	Price	Cost per day
Comparative to 12mcg patch	Fentanyl Patch 12 mcg/hour	12	mcg (72 hours)	R71.76	R23.92
	Morphing extemporaneous solution	30	mg/day	R2.53	R2.53
	Morphine commercial solution	30	mg/day	R423.69	R31.77
	Morphine sustained release tablet	30	mg/day	R16.40	R16.40
Comparative to 25 mcg patch	Fentanyl Patch	25	mcg (72 hours)	R97.50	R32.50
	Morphing extemporaneous solution	60	mg/day	R5.05	R5.05
	Morphine commercial solution	60	mg/day	R423.69	R63.54
	Morphine sustained release tablet	60	mg/day	R26.45	R26.45
Comparative to 50 mcg patch	Fentanyl Patch	50	mcg (72 hours)	R161.40	R53.80
	Morphing extemporaneous solution	120	mg/day	R9.15	R9.15
	Morphine commercial solution	120	mg/day	R423.69	R127.08
	Morphine sustained release tablet	120	mg/day	R52.90	R52.90
Comparative to 75 mcg patch	Fentanyl Patch	75	mcg (72 hours)	R222.33	R74.11
	Morphing extemporaneous solution	180	mg/day	R13.72	R13.72
	Morphine commercial solution	180	mg/day	R423.69	R190.62
	Morphine sustained release tablet	180	mg/day	R79.35	R79.35
Comparative to 100 mcg patch	Fentanyl Patch	100	mcg (72 hours)	R284.61	R94.87
	Morphing extemporaneous solution	240	mg/day	R18.30	R18.30
	Morphine commercial solution	240	mg/day	R423.69	R254.16
	Morphine sustained release tablet	240	mg/day	R105.80	R105.80

Price references:

Fentanyl patches, Commercial morphine solution, Morphine sustained release tablets – Single Exit Prices (SEP) – April 2024.
Morphine extemporaneous solution – Contract pricing May 2024.
SEP prices based on most affordable generic product.

Utilisation data – Western Cape
April 2023 to March 2024 (12 months)

	Price per patch	Annual patches use	Annual expenditure	% discount from lowest SEP	Estimated patient days treated
Fentanyl 12mcg patch	R55.86	120	R6,703.20	22.16%	360
Fentanyl 25 mcg patch	R69.19	250	R17,297.52	29.04%	750
Fentanyl 50 mcg patch	R69.12	130	R8,985.30	57.18%	390

Total expenditure in Western Cape for 1 year: R32 986.02 *(approved indication wider than just where oral cannot be used)*

Budget impact
Assuming similar utilization in other provinces, an estimated annual national budget impact can be calculated as: R296 874.18.

This, however, is likely an overestimate for the niche population where approval is being sought. Additionally, no analysis has been undertaken to cost the alternative of hospitalisation for parenteral opioid therapy, which is expected to be a far more costly intervention.

8. Conclusion

Although the evidence is not robust, the efficacy of transdermal fentanyl is non-inferior to oral morphine in controlling moderate to severe cancer pain. Additionally, it has a better side effect profile with less constipation and urinary retention and carries less risk of toxicity than morphine in patients with renal failure. The transdermal route is a safe and efficient route of opioid delivery in patients 2 years and older with chronic stable pain.

In patients who are unable to take oral medication or use parenteral opioids, transdermal fentanyl is an alternative pain management option. An educational guideline has been prepared to assist doctors in safe prescribing and how to counsel patients being initiated on transdermal fentanyl.

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [ ] Very low [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [X] Small [ ] None [ ]	*Evidence shows achievement of 'no worse than mild pain' with use of transdermal fentanyl.*
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [X] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge [X] Moderate [ ] Small [ ] None [ ]	*Statistically significant benefit for constipation with transdermal fentanyl.*
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [ ] Intervention = Control *or* Uncertain [X]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X]	
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [X]	**See costs above.** Likely less intensive in certain cases where patients would have to remain admitted for parenteral opioid therapy.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	
EQUITY	**Would there be an impact on health inequity?** Yes [X] No [ ] Uncertain [ ]	Positive impact on health inequity • Patients unable to take oral opiates can experience the same measure of pain control as those able to take oral opiates. • Patients living in remote areas and areas not serviced by hospice or home-based palliative care services who would otherwise suffer severe pain have a good analgesic option. • Patients who would have to treated for severe pain in hospital during the last weeks to days of their lives can be comfortably managed at home.

Appendix 2: Search strategy

PubMed – 26 March 2024

Search	Query	Search Details	Results
#4		("dysphagia"[Title/Abstract] OR "odynophagia"[Title/Abstract]) AND "pain"[Title/Abstract] AND "transdermal"[Title/Abstract]	20
#3		"chronic pain"[MeSH Terms] AND "deglutition disorders"[MeSH Terms]	21
#2	Transdermal fentanyl AND systematic review/meta-analysis	(("administration, cutaneous"[MeSH Terms] OR ("administration"[All Fields] AND "cutaneous"[All Fields]) OR "cutaneous administration"[All Fields] OR "transdermal"[All Fields] OR "transdermally"[All Fields] OR "transdermals"[All Fields] OR "transdermic"[All Fields] OR "transdermically"[All Fields]) AND "fentanyl"[MeSH Terms]) AND (meta-analysis[Filter] OR systematic review[Filter])	23
#1	Transdermal fentanyl	("administration, cutaneous"[MeSH Terms] OR ("administration"[All Fields] AND "cutaneous"[All Fields]) OR "cutaneous administration"[All Fields] OR "transdermal"[All Fields] OR "transdermally"[All Fields] OR "transdermals"[All Fields] OR "transdermic"[All Fields] OR "transdermically"[All Fields]) AND "fentanyl"[MeSH Terms]	1091

COCHRANE LIBRARY– SEARCH RERUN 9 FEBRUARY 2024

search	Query	Results
#1	MeSH descriptor: [Fentanyl] explode all trees	**6714**
#2	Transdermal	**6719**
#3	#1 AND #2	**217**
#4	#3 in Cochrane Reviews	**7**

search	Query	Results
#1	MeSH descriptor: [Deglutition Disorders] explode all trees	**4079**
#2	MeSH descriptor: [Fentanyl] explode all trees	**6728**
#3	MeSH descriptor: [Transdermal Patch] explode all trees	**353**
#4	#1 AND #2 AND #3	**0**
#5	#4 in Cochrane Reviews	**0**

Search summary

Pubmed	23 citations
Cochrane	7 citations
Overlap	7 citation
Excluded	21 citations
Total for consideration	**2 citations**

Appendix 3: List of excluded studies

	Study Citation	Reason for exclusion
1	Efficacy and Safety of **Transdermal** Buprenorphine for Acute Postoperative Pain: A Systematic Review and Meta-analysis. Aguilar B, Penm J, Liu S, Patanwala AE.J Pain. 2023 Nov;24(11):1905-1914. doi: 10.1016/j.jpain.2023.07.001. Epub 2023 Jul 11.PMID: 37442403 Review.	Does not meet PICO – wrong intervention
2	**Transdermal** fentanyl for cancer pain: Trial sequential analysis of 3406 patients from 35 randomized controlled trials. Wang DD, Ma TT, Zhu HD, Peng CB.J Cancer Res Ther. 2018;14(Supplement):S14-S21. doi: 10.4103/0973-1482.171368.PMID: 29578144 **Free article.** Review	Excluded – could not identify included studies
3	Meta-Analysis of the Ease of Care From the Nurses' Perspective Comparing Fentanyl Iontophoretic **Transdermal** System (ITS) Vs Morphine Intravenous Patient-Controlled Analgesia (IV PCA) in Postoperative Pain Management. Pestano CR, Lindley P, Ding L, Danesi H, Jones JB.J Perianesth Nurs. 2017 Aug;32(4):329-340. doi: 10.1016/j.jopan.2015.11.012. Epub 2016 Nov 2.PMID: 28739065 **Free article.**	Does not meet PICO – wrong comparator and outcome
4	Meta-Analysis of the Ease of Care From a Patients' Perspective Comparing Fentanyl Iontophoretic **Transdermal** System Versus Morphine Intravenous Patient-Controlled Analgesia in Postoperative Pain Management. Lindley P, Ding L, Danesi H, Jones JB.J Perianesth Nurs. 2017 Aug;32(4):320-328. doi: 10.1016/j.jopan.2015.11.013. Epub 2016 Nov 2.PMID: 28739064 **Free article.**	Does not meet PICO – wrong comparator and outcome
5	Opioids for cancer pain - an overview of Cochrane reviews. Wiffen PJ, Wee B, Derry S, Bell RF, Moore RA.Cochrane Database Syst Rev. 2017 Jul 6;7(7):CD012592. doi: 10.1002/14651858.CD012592.pub2.PMID: 28683172 **Free PMC article.** Review.	Too broad – included specific Cochrane review
6	Sublingual, **transdermal** and intravenous patient-controlled analgesia for acute post-operative pain: systematic literature review and mixed treatment comparison. Katz P, Takyar S, Palmer P, Liedgens H.Curr Med Res Opin. 2017 May;33(5):899-910. doi: 10.1080/03007995.2017.1294559. Epub 2017 Mar 20.PMID: 28318323 Review.	Does not meet PICO – wrong comparator
7	Patient-Controlled Fentanyl Iontophoretic **Transdermal** System Improved Postoperative Mobility Compared to Intravenous Patient-Controlled Analgesia Morphine: A Pooled Analysis of Randomized, Controlled Trials. Oliashirazi A, Wilson-Byrne T, Shuler FD, Parvizi J.Pain Pract. 2017 Feb;17(2):197-207. doi: 10.1111/papr.12432. Epub 2016 May 21.PMID: 27206564 Review.	Does not meet PICO – wrong comparator
8	The Efficacy and Safety of the Fentanyl Iontophoretic **Transdermal** System (IONSYS()) in the Geriatric Population: Results of a Meta-Analysis of Phase III and IIIb Trials. Viscusi ER, Ding L, Itri LM.Drugs Aging. 2016 Dec;33(12):901-912. doi: 10.1007/s40266-016-0409-7.PMID: 27785733 **Free PMC article.**	Does not meet PICO – no comparator

9	Ease-of-care from the physical therapists' perspective comparing fentanyl iontophoretic **transdermal** system versus morphine intravenous patient-controlled analgesia in postoperative pain management. Hartrick CT, Abraham J, Ding L.J Comp Eff Res. 2016 Nov;5(6):529-537. doi: 10.2217/cer-2016-0038. Epub 2016 Jul 21.PMID: 27442803 **Free article.**	Does not meet PICO – wrong comparator
10	Fentanyl for neuropathic pain in adults. Derry S, Stannard C, Cole P, Wiffen PJ, Knaggs R, Aldington D, Moore RA.Cochrane Database Syst Rev. 2016 Oct 11;10(10):CD011605. doi: 10.1002/14651858.CD011605.pub2.PMID: 27727431 **Free PMC article.** Review.	Does not meet PICO – wrong indication
11	Fentanyl Iontophoretic **Transdermal** System: A Review in Acute Postoperative Pain. Scott LJ.Clin Drug Investig. 2016 Apr;36(4):321-30. doi: 10.1007/s40261-016-0387-x.PMID: 26968174 Review.	Does not meet PICO – wrong population
12	Meta-analysis of the efficacy of the fentanyl iontophoretic **transdermal** system versus intravenous patient-controlled analgesia in postoperative pain management. Sinatra RS, Viscusi ER, Ding L, Danesi H, Jones JB, Grond S.Expert Opin Pharmacother. 2015;16(11):1607-13. doi: 10.1517/14656566.2015.1054279. Epub 2015 Jun 8.PMID: 26050870	Does not meet PICO – wrong intervention
13		
14	Opioids for acute pancreatitis pain. Basurto Ona X, Rigau Comas D, Urrútia G.Cochrane Database Syst Rev. 2013 Jul 26;(7):CD009179. doi: 10.1002/14651858.CD009179.pub2.PMID: 23888429 Review.	Does not meet PICO – wrong population
15	Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain. Wolff RF, Aune D, Truyers C, Hernandez AV, Misso K, Riemsma R, Kleijnen J.Curr Med Res Opin. 2012 May;28(5):833-45. doi: 10.1185/03007995.2012.678938. Epub 2012 Apr 25.PMID: 22443154 Review.	Does not meet PICO – wrong comparator
16	Efficacy and adverse effects of **transdermal** fentanyl and sustained-release oral morphine in treating moderate-severe cancer pain in Chinese population: a systematic review and meta-analysis. Yang Q, Xie DR, Jiang ZM, Ma W, Zhang YD, Bi ZF, Chen DL.J Exp Clin Cancer Res. 2010 Jun 9;29(1):67. doi: 10.1186/1756-9966-29-67.PMID: 20529380 **Free PMC article.**	Excluded – could not identify included studies
17	**Transdermal** fentanyl as a front-line approach to moderate-severe pain: a meta-analysis of randomized clinical trials. Tassinari D, Sartori S, Tamburini E, Scarpi E, Tombesi P, Santelmo C, Maltoni M.J Palliat Care. 2009 Autumn;25(3):172-80.PMID: 19824278	Does not meet PICO – wrong population
18	Opioids in people with cancer-related pain. Quigley C.BMJ Clin Evid. 2008 Jul 31;2008:2408.PMID: 19445735 **Free PMC article.** Review.	Included observational and RCTs
19	Adverse effects of **transdermal** opiates treating moderate-severe cancer pain in comparison to long-acting morphine: a meta-analysis and systematic review of the literature. Tassinari D, Sartori S, Tamburini E, Scarpi E, Raffaeli W, Tombesi P, Maltoni M.J Palliat Med. 2008 Apr;11(3):492-501. doi: 10.1089/jpm.2007.0200.PMID: 18363493 Review.	Evaluation includes both buprenorphine and fentanyl vs oral morphine - 2009 below more specific to fentanyl patches.
20	System-related events and analgesic gaps during postoperative pain management with the fentanyl iontophoretic **transdermal** system and morphine intravenous patient-controlled analgesia. Panchal SJ, Damaraju CV, Nelson WW, Hewitt DJ, Schein JR.Anesth Analg. 2007 Nov;105(5):1437-41, table of contents. doi: 10.1213/01.ane.0000281442.36582.81.PMID: 17959979	Does not meet PICO – wrong comparator and population
21	The safety and efficacy of fentanyl iontophoretic **transdermal** system compared with morphine intravenous patient-controlled analgesia for postoperative pain management: an analysis of pooled data from three randomized, active-controlled clinical studies. Viscusi ER, Siccardi M, Damaraju CV, Hewitt DJ, Kershaw P.Anesth Analg. 2007 Nov;105(5):1428-36, table of contents. doi: 10.1213/01.ane.0000281913.28623.fd.PMID: 17959978	Does not meet PICO – wrong comparator
22	**Transdermal** fentanyl in childhood and adolescence: a comprehensive literature review. Zernikow B, Michel E, Anderson B.J Pain. 2007 Mar;8(3):187-207. doi: 10.1016/j.jpain.2006.11.008.PMID: 17350554 **Free article.** Review.	Narrative review – only included to narratively discuss the paediatric group
23	Efficacy and safety of **transdermal** fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. Clark AJ, Ahmedzai SH, Allan LG, Camacho F, Horbay GL, Richarz U, Simpson K.Curr Med Res Opin. 2004 Sep;20(9):1419-28. doi: 10.1185/030079904X2114.PMID: 15383190	Included uncontrolled trials, open label trial and RCTs

Version	Date	Reviewer(s)	Recommendation and Rationale

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[3] Janssen Pharmaceutica (Pty) Ltd. Durogesic Package Insert.

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