health
Department:
Health
REPUBLIC OF SOUTH AFRICA

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

TITLE: Transdermal fentanyl for severe stable pain in patients with severe renal impairment and/or on dialysis where morphine dose titration has been unsuccessful and other opioids cannot be safely prescribed.

Date: October 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 with severe renal impairment and/or on dialysis who are unable to safely take morphine and other opioids.
Prevalence of condition: The patient population with chronic intractable pain for whom fentanyl transdermal patches are being requested are a very small subset of patients with chronic kidney disease with an eGFR of < 30mL/min/1.73m^2, where morphine is contraindicated due to severe renal impairment/failure.
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.[1] For patients with kidney failure, the choice of analgesics is adapted to exclude drugs unsafe in renal failure.
- Morphine metabolises to the inactive metabolite morphine-3-glucuronide (M3G), and small amounts of morphine-6-glyucuronide (M6G) an active metabolite more potent than morphine. Although M3G itself lacks analgesic effect, it may have neuroexcitatory effects that lead to adverse effects such as allodynia, myoclonus and seizures. Both M3G and M6G (excreted by the kidneys) accumulate in patients with advanced renal insufficiency.[2] Thus in patients with severe renal impairment, where the use of morphine is limited, a safer alternative opioid is needed.
- An initial search of literature yielded limited results thus the eligibility criteria were widened. Ten documents were ultimately included (2 systematic review, 2 guidelines and 6 professional information leaflets).
- A systematic review conducted by the European Palliative Care Research Collaborative opioid guidelines project recommended fentanyl, alfentanil and methadone as the medications least likely to cause harm in patients with renal impairment (King et al. 2011).[13]
- The European Society for Medical Oncology (ESMO)[18] recommends buprenorphine or fentanyl as the preferred opioid in cancer patients with moderate to severe pain, and moderate to severe renal dysfunction or on dialysis. The South African Renal Palliative and supportive care statement[17] also recommends transdermal fentanyl for severe stable pain in patients with severe renal impairment.
- Professional information leaflets generally advise caution and reduced dosing for use of morphine in patients with renal impairment. While caution and monitoring are also recommended with use of fentanyl in renal impairment, diminished renal function is not expected to affect fentanyl elimination to a clinically relevant extent.

- Transdermal fentanyl was recently approved for inclusion on the Tertiary EML for use in patients who are unable to take oral morphine preparations and do not have access to a syringe driver.
- This review is an extension of this indication to include patients with severe renal impairment where morphine cannot be used or safely titrated to appropriate effect.

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 suggested that transdermal fentanyl be considered for the management of severe stable pain in patients with severe renal impairment (GFR < 30ml/min/1.73m^2) or on dialysis where other opioids cannot be safely used. *Rationale: For the niche group of patients with renal impairment where morphine cannot be titrated appropriately to prevent toxicity, transdermal fentanyl is a potentially safer alternative with less concern around accumulation and subsequent toxicity.* **Level of Evidence: III** (Guidelines, Narrative Systematic Reviews, Pharmacokinetics) **Review indicator:** Price, signals of harm.					
NEMLC RECOMMENDATION: NEMLC recommended that transdermal fentanyl be included on the Tertiary Essential Medicines List for the management of severe stable pain in patients with severe renal impairment (GFR < 30ml/min/1.73m^2) or on dialysis where other opioids cannot be safely used.					
Monitoring and evaluation considerations: Periodic assessment to prevent irrational medicine use					
Research priorities: n/a					

1. **Name of author(s)/motivator(s)**
   - Zainab Mohamed (Head Clinical Unit Radiation Oncology, Groote Schuur Hospital, University of Cape Town).
   - Jane Riddin (Essential Drugs Programme, National Department of Health).

   Acknowledgements:
   - Kim MacQuilkan (EpiC-SCTA)
   - Derusha Frank (CHAI)
   - Marc Blockman (Department of Clinical Pharmacology, Groote Schuur Hospital, Cape Town, Western Cape, South Africa and the Department of Medicine, University of Cape Town, Cape Town, Western Cape, South Africa).
   - Roger Wiseman (Liberty Health (Pty) Ltd, South Africa)

2. **Author affiliation and conflict of interest details**
   - All reviewers had no conflicts of interest to declare.

3. Introduction/ Background

In June 2024, the National Essential Medicines List Committee (NEMLC) approved the use of transdermal fentanyl for severe stable pain in patients who are unable to take oral medication, and do not have access to subcutaneous opioids via a syringe driver (NEMLC Meeting 27 June 2024).[3] Subsequently, the population of patients with severe stable pain and severe renal impairment and/or on dialysis has been identified as a group where morphine use may be a concern.

Opioids should be used with caution in patients with eGFR < 30 ml/min.[4] Morphine metabolises to the inactive metabolite morphine-3-glucuronide(M3G), and small amounts of morphine-6-glyucuronide (M6G), an active metabolite more potent than morphine. Although M3G itself lacks analgesic effect, it may have neuroexcitatory effects that lead to adverse effects such as allodynia, myoclonus and seizures. Both M3G and M6G (excreted by the kidneys) accumulate in patients with advanced renal insufficiency.[5] It is generally recommended that morphine slow-release oral preparations should be avoided in renal impairment as they may prolong adverse effects.[6]

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.[7]

This review seeks to expand on the previous work undertaken on transdermal fentanyl and establish the safety and efficacy of transdermal fentanyl in the management of patients (2 years of age and older) with chronic stable pain and severe renal impairment and/or on dialysis where safe morphine dose titration has been unsuccessful and other opioids cannot safely be used.

4. Research Question

Can transdermal fentanyl be utilised as an alternative to morphine in the management of severe stable pain in patients with renal impairment?

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

Population:	Patients (children, adolescents, adults) with severe renal failure or on dialysis with severe stable pain where safe morphine dose titration has been unsuccessful and other opioids cannot safely be used.
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, randomized-controlled trials.

6. Methods:

A search was run on 28 June 2024, using both *PubMed and Cochrane Library* (See Appendix 2: Search strategy – A. Initial Search). Only one case series (2 patients on haemodialysis was identified).[8] Following discussion with the Tertiary Committee, the search was broadened to encompass:

- Systematic reviews evaluating fentanyl and morphine in patients with renal impairment or on dialysis;
- Clinical Practice Guidelines (CPGs) on management of pain in renal impairment, chronic kidney disease or dialysis; and
- Professional information (PI) leaflets for morphine and fentanyl.

The search was rerun on 23 July 2024 in Pubmed and Cochrane Library (See appendix 2: Search strategy - B. Follow-up Search). Additionally, a search for CPGs and PI leaflets was conducted in Google, Google Scholar and the South African Health Products Authority (SAHPRA) database.

The search and screening of studies was undertaken by two reviewers (JR and ZM) and presented to the ERC for discussion and final selection. Included systematic reviews (SRs) and CPGs were assessed in duplicate by two reviewers utilising AMSTAR II[9] and AGREE II[10] respectively (JR, DF, KM). Results were presented narratively.

7. Results:

The widened search resulted in the identification of 15 documents. Post screening of titles and abstracts, 12 documents underwent full text review after which two systematic reviews were excluded, see Table 1 below. Ultimately, 10 documents were included (2 systematic reviews, 2 clinical practice guidelines, 6 professional information leaflets) – See Figure 1: PRISMA diagram below.

Table 1: Excluded systematic reviews:

Author, date	***Type of study***	***Reason for exclusion***
Nagar VR et.al. 2017[11]	Systematic review	Not focused on medicine management, rather prevalence of chronic pain and opioid management among patients with CKD.
Wyne A et.al. 2011[12]	Systematic review	Not focused on medicine management, rather prevalence of chronic pain and opioid management among patients with end stage renal disease

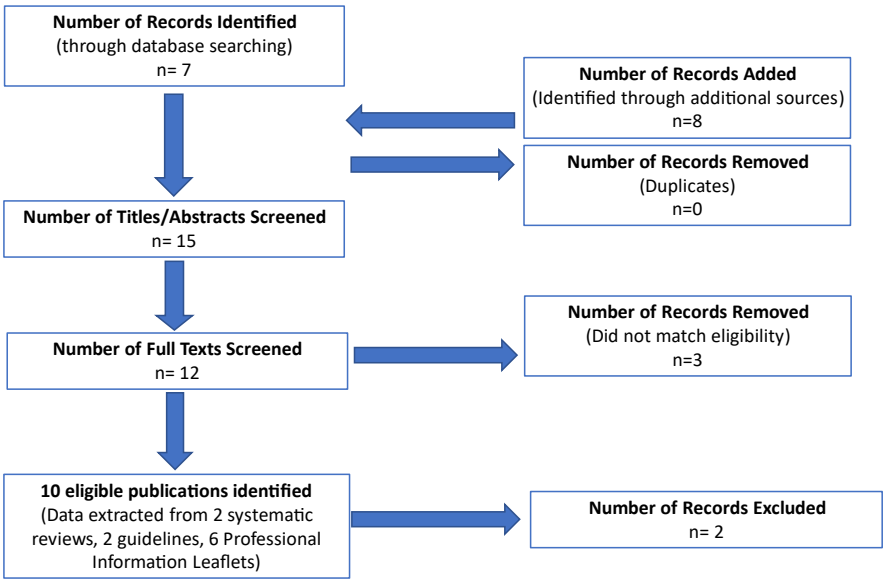

Figure 1: PRISMA Diagram

a. Description of included Documents

- Systematic Reviews:

Two systematic reviews, King.et.al. 2011[13] and Sande et.al. 2017[14] were included for evaluation (See Table 2 below for characteristics of included SRs).

Table 2: Characteristics of included SRs

Author	Study Type	Population	Intervention & comparators	Outcome
King et.al. 2011[13]	Systematic review including prospective observational studies and retrospective studies (no meta-analysis)	Adult patients with renal impairment and cancer-related pain	Opioids including morphine and fentanyl	Fentanyl indicated as one of agents least likely to cause harm. Morphine associated with toxicity in patients with renal impairment.
Sande et.al. 2017[14]	Systematic review (no meta-analysis)	Patients with renal impairment and cancer related pain, taking an opioid.	Opioids including morphine and fentanyl	No recommendation could be made on preferred opioid in patients with renal impairment. Morphine should be used with caution. Fentanyl one of recommended agents in renal impairment based on pharmacokinetics and clinical experience – but based on little published clinical evidence.

- Guidelines:
  Two CPGs were included for evaluation (one local and one international):
  - Guideline: Renal palliative and supportive care in South Africa – a consensus statement. 2020.[17]
  - ESMO Clinical Practice Guidelines. Management of cancer pain in adult patients. 2018.[18]

- Package inserts
  Six professional information leaflets morphine (oral and IV) and fentanyl (transdermal and iv) in South Africa were included (See Table 3). *(Note not all commercially available products included – just a range to understand key recommendations and contraindications)*

  Table 3: Professional information leaflets

Generic drug	Trade Name	Manufacturer
Transdermal fentanyl	Durogesic®	Janssen
Transdermal fentanyl	Fendermal®	Sandoz
Fentanyl injection	Pharma-Q Fentanyl®	Pharma-Q Holdings
Oral morphine drops	Oramorph®	Eurolab
Oral Morphine (prolonged release)	MST Continus®	Mundipharma
Morphine injection	Pharma-Q Morphine®	Pharma-Q Holdings

b. Evidence quality:

Evidence in this area is generally limited and of poor quality. King et. al. 2011[13] indicated that there was significant risk of bias within all the studies identified for the review, due to design methodologies used (uncontrolled prospective and retrospective studies only). Additionally, significant risk of publication bias was identified. This review GRADED certainty of evidence as generally very low quality.

Systematic Reviews

AMSTAR II assessments were conducted in duplicate (JR and KM) on the systematic reviews:

Systematic Review	AMSTAR II results
King et.al. 2011.[13]	Low quality: no meta-analysis, no heterogeneity interrogation, limited details of included studies, no detailed list of excluded studies.
Sande et.al.2017. [14]	Critically low quality: no meta-analysis, no risk of bias assessments, no heterogeneity interrogation, limited details of included studies, no detailed list of excluded studies.

Guidelines

AGREE II assessments were conducted for each guideline (single assessments done by JR and DF):

Guideline	AGREE II assessment
ESMO Clinical Practice Guidelines. Management of cancer pain in adult patients. 2018.[18]	**Overall assessment score:** 51%, 4 out of 7 **Score for rigour and methodology domain:** 58%
Guideline: Renal palliative and supportive care in South Africa – a consensus statement. 2020.[17]	*Note: This was a consensus statement – and thus scored very low – and did not follow the usual guideline principles.* **Overall assessment score:** 35%, 3 out of 7 **Score for rigour and methodology domain:** 15%

c. Efficacy and Safety

- **Systematic Reviews**

Both systematic reviews had very heterogenous data, and thus no meta-analysis could be done, and included study findings were discussed narratively.

Both King et.al.[13] and Sande et.al.[14] only included one study to support transdermal fentanyl; a study by Mazzocato et. al.[15] which retrospectively exclusively assessed aspects of fentanyl use in the palliative care setting assessing patients with renal impairment treated with subcutaneous fentanyl. Fifty-three records were evaluated, where all patients had renal impairment with GFR < 60 ml/min (not stratified). Pain control was complete in 31/53 (59%) of patients and partial in 14/53 (26%) of patients. In patients that had experienced neurotoxic symptoms thought to be opioid-related, the symptoms resolved completely in 8/26 (31%) and partly in 6/26 (26%) of patients. This study by Mazzocato et. al[15] is referenced as an abstract presented at the European Association of Palliative Care, 4th research forum, however a full publication cannot be identified.

Sande et.al.[14] discussed one other retrospective study that considered fentanyl, Kurita et.al 2015[16] which evaluated renal function and symptoms/adverse effects in opioid-treated patients with cancer, which showed that fentanyl appeared to be safe in routine cancer pain management in patients with renal impairment.

- **Guidelines**

There were no guidelines specifically evaluating the PICO developed, however the included guidelines did make general recommendations on management of pain in patients with severe renal impairment, and thus included. The South African document[17] included was a consensus statement, and thus assessment poorly on AGREE II as no formal methods recorded. The ESMO guidelines[18] which scored moderately on AGREE II, had limitations in the methodological rigour component; and scored poorly on applicability, purpose and stakeholder involvement. The recommendations of these guidelines are captured in table 4 below:

Table 4: Summary of Guidelines Recommendations

Guideline	Morphine	Fentanyl (transdermal)	Guideline Quality
Renal palliative and supportive care in South Africa – a consensus statement, 2020.[17]	Generally, not recommended as metabolites are renally excreted and in normal doses will cause toxicity If used should be with significant caution Start with 1 – 2.5 mg PO/SC as needed and titrate to effect If pain is stable, consider switching to transdermal fentanyl	Only use when pain is stable Fentanyl 12.5 or 25 mcg	*Consensus statement: assessed as very low quality on AGREE II, no formal methods recorded.*
ESMO Clinical Practice Guidelines. Management of cancer pain in adult patients. 2018. [18]	In general, adjustment of opioid doses is required in renal dysfunction. Accumulation of toxic metabolites can cause a variety of distressing and life-threatening symptoms, including confusion, drowsiness and hallucinations. Preferred opioids for patients with moderate to severe dysfunction or on dialysis are buprenorphine or fentanyl. Recommendation: Fentanyl and buprenorphine (transdermal or IV) are the safest opioids in patients with chronic kidney disease stages 4 or 5 (eGFR < 30mL/min/1.73m^2) [III, B]* ** III - Prospective cohort studies; B - Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.*		*Assessed as 4 out of 7 on AGREE II with limitations in methodology, purpose, stakeholder involvement and applicability.*

- **Professional Information Leaflet**

  Details from the six included PIs were extracted (See Table 5 below). This data was assessed to try to understand whether there were specific renal function thresholds for use of these agents. This however was not the case, with all products just recommending that caution be taken in renal impairment.

Table 5: Extractions from included Professional Information Leaflets

Generic drug	Trade Name	Manufacturer	Recommendations
Transdermal fentanyl	Durogesic®[7]	Janssen	Presently insufficient information exists to make recommendations regarding the use in patients with impaired renal or hepatic functions. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and limited renal excretion of fentanyl.
Transdermal fentanyl	Fendermal®[19]	Sandoz	Patients with hepatic or renal impairment should be observed carefully and the dose reduced if necessary. Even though impairment of renal function is not expected to affect fentanyl elimination to a clinically relevant extent, caution is advised because fentanyl pharmacokinetics has not been evaluated in this patient population.
Fentanyl injection	Pharma-Q Fentanyl®[20]	Pharma-Q Holdings	In patients with renal impairment reduced dosing of Pharma-Q Fentanyl Injection should be considered and these patients should be observed carefully for signs of fentanyl toxicity
Oral morphine drops	Oramorph®[21]	Eurolab	In patients with impaired liver or kidney function and in those with suspected delayed gastrointestinal passage Oramorph® Oral Drops 20mg/ml should be dosed with special caution.
Oral Morphine (prolonged release)	MST Continus®[22]	Mundipharma	In renal failure, the levels of morphine-6-glucuronide can accumulate. MST CONTINUS® must be given with caution, or in reduced doses, to patients with, impaired kidney function.
Morphine injection	Pharma-Q Morphine®[23]	Pharma-Q Holdings	Doses should generally be reduced in the elderly or debilitated patients or in patients with renal impairment.

8. Alternative agents:

Alternatives that could be used in this population:

- Transdermal buprenorphine - currently too expensive.
- Methadone – only approved for pilot use in drug withdrawal. Complex agent to use with difficulties in titration due to long half-life, and potential accumulation.

(these agents not considered in this review)

9. 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
	Morphine 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
	Morphine 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
	Morphine 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
	Morphine 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
	Morphine 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.

Budget impact

Patient numbers are unknown; however, this population is expected to be small.

10. Summary

Morphine's active metabolites can accumulate in patients with severe renal impairment, potentially leading to toxicity and adverse effects. Guidelines typically advise against the use of morphine in individuals with severe renal impairment, specifically those with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min. While data is limited and generally of low quality, alternative analgesics such as fentanyl, buprenorphine, methadone, and alfentanil are viewed as safer options for managing pain in this patient population, largely based on clinical experience and pharmacokinetics.

11. Conclusion

Use of morphine can pose significant risks in patients with severe renal impairment due to the potential for metabolite accumulation and toxicity. In this context, where morphine titrated dosing cannot be safely managed, the Tertiary/Quaternary Expert Review Committee suggests that transdermal fentanyl be used as an alternative in patients with severe stable chronic pain.

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 [X] 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	*Quality assessment of included SRs and CPGS* *SRs – very low (Sande 2017[14]) to low (King 2011[13]) based on AMSTAR II* *CPGs – very low (SA Renal consensus statement[17]) to low (ESMO guidelines[18])* *Quality of evidence included within SRs* *King et al. 2011 rated quality* of evidence with GRADE as very low* **Note utilising terminology from SR – referred to as quality not certainty).*
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [X] None [ ]	*Transdermal fentanyl has been shown to be an effective opioid, potentially safer than morphine in the cohort of severe renal impairment patients.*
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [X] 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	*Quality of evidence was generally low to critically low – see above*
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge [ ] Moderate [ ] Small [X] None [ ]	*Fentanyl generally seen as safer option in this cohort of patients*
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [X] Favours control [ ] Intervention = Control *or* Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X]	
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	*Already approved for the indication of severe stable pain where oral route cannot be used or where there is no access to a syringe driver.*

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain: [X]	**See costs above.** Similar to costs of sustained release morphine tablets.
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: [ ]	• Would allow a safer treatment access option to individuals

Appendix 2: Search strategy

A. Initial searches

PubMed – 28 June 2024

Search	Query	Search Details	Results
#2	Transdermal fentanyl and renal dialysis	"administration, cutaneous"[MeSH Terms] AND "fentanyl"[MeSH Terms] AND "renal dialysis"[MeSH Terms]	1
#1	Transdermal fentanyl and renal insufficiency	"administration, cutaneous"[MeSH Terms] AND "fentanyl"[MeSH Terms] AND "renal insufficiency"[MeSH Terms]	1

COCHRANE LIBRARY– SEARCH RUN 28 June 2024

search	**Query**	**Results**
#1	MeSH descriptor: [Administration, Cutaneousl] explode all trees	**4669**
#2	MeSH descriptor: [Fentanyl] explode all trees	**6778**
#3	MeSH descriptor: [Renal Insufficiency] explode all trees	**13227**
#4	MeSH descriptor: [Renal Dialysis] explode all trees	**7401**
#5	#1 AND #2 AND (#3 OR #4)	**0**

B. Follow up search (widened criteria)

PubMed – search rerun on 23 July 2024

Search	Query	Search Details	Results
#1	Fentanyl and renal insufficiency	("analgesics, opioid"[MeSH Terms] AND "renal insufficiency"[MeSH Terms]) AND (meta-analysis[Filter] OR systematicreview[Filter])	7

COCHRANE LIBRARY– SEARCH RERUN 23 July 2024

search	**Query**	**Results**
#1	MeSH descriptor: [Analgesics, Opioid] explode all trees	**10770**
#2	MeSH descriptor: [Renal Insufficiency] explode all trees	**13227**
#3	MeSH descriptor: [Renal Dialysis] explode all trees	**7401**
#4	#1 AND #2	**12**
#5	#1 AND #3	**4**
#6	#4 OR #5 in Cochrane Reviews	**0**

Search summary

Pubmed	7 citations
Cochrane	0 citations
Overlap	0 citation
Excluded	3 citations
Total for consideration	**4 citations**

References:

[1] Ventafridda V, Saita L Ripamonti C, De Conno FD. WHO guidelines for the use of analgesics in cancer pain. Int J Tissue React. 1985, 7(1): 93-96.

[2] Davidson SN. Clinical Pharmacology Considerations in Pain Management in Patients with Advanced Kidney Failure. CJASN. 2019, 14: 917-931. https://doi.org/10.2215/CJN.05180418.

[3] TQ ERC. 2024. Rapid review available from: https://knowledgehub.health.gov.za/system/files/elibdownloads/2024-07/Medicine_Review_Fentanyl_patches_N_June_24_final%5B1%5D.pdf

[4] Doncaster and Bassetlaw Teaching Hospitals. Analgesia in patients with impaired renal function – Formulary Guidance. NHS Foundation Trust. July 2022.

[5] Davidson SN. Clinical Pharmacology Considerations in Pain Management in Patients with Advanced Kidney Failure. CJASN. 2019, 14: 917-931. https://doi.org/10.2215/CJN.05180418.

[6] Greater Manchester Health and Social Care Partnership. Palliative Care Pain and Symptom Control Guidelines for Adults, 5th Edition. 2019. https://www.england.nhs.uk/north-west/wp-content/uploads/sites/48/2020/01/Palliative-Care-Pain-and-Symptom-Control-Guidelines.pdf

[7] Janssen Pharmaceutica (Pty) Ltd. Durogesic Professional Information https://www.sahpra.org.za/wp-content/uploads/2020/06/DUROGESIC_PI_Janssen-Pharmaceutica_MCC-Format28-May-2018.pdf

[8] Han J, Saraf SL, Gordeuk VR, Gowhari M. Safety of Chronic Transdermal Fentanyl Use in Patients on Hemodialysis. Am J Health Syst Pharm. 2016, 73(13): 947 -948.

[9] Shea B J, Reeves B C, Wells G, Thuku M, Hamel C, Moran J et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both BMJ 2017; 358:j4008 doi:10.1136/bmj.j4008

[10] Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, Graham ID, Grimshaw J, Hanna SE, Littlejohns P, Makarski J, Zitzelsberger L; AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010 Dec 14;182(18):E839-42. doi: 10.1503/cmaj.090449. Epub 2010 Jul 5. PMID: 20603348; PMCID: PMC3001530.

[11] Nagar VR, Birthi P, Salles S, Sloan PA. Opioid Use in Chronic Pain with Chronic Kidney Disease: A Systematic Review. Pain Medicine. 2017, 18: 1416 -1449.

[12] Wyne A, Rai R. Cuerden M Clark WF, Suri RS. Opioid and Benzodiazepine Use in End-Stage Renal Disease: A Systematic Review. Clin J Am Soc Nephrol. 2011, 6: 326 – 333.

[13] King S, Forbes L, Hanks GW, Ferro CJ, Chambers EJ. A Systematic Review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: A European Palliative Care Research Collaborative Opioid Guideline Project. Palliative Medicine. 2011, 25(5): 525-552.

[14] Sande TA, Laird BJA, Fallon MT. The use of opioids in cancer patients with renal impairment. Support Care Cancer. 2017, 25:661-675.

[15] Mazzocato C, Beauverd M, Anwar D (2006) Subcutaneous fentanyl in severely ill patients with renal failure (abstract from the 4th research forum of the EAPC). Palliat Med 20:301.

[16] Kurita GP, Lundstrom S, Sjogren P et al (2015) Renal function and symptoms/adverse effects in opioid-treated patients with cancer. Acta Anaesthesiol Scand 59:1049–1059

[17] Wearne N, Krause R, Davidson B, Brennan F, et.al. Guideline: Renal palliative and supportive care in South Africa – a consensus statement. African Journal of Nephrology. 2020. 23(1): 86-107.

[18] Fallon M, Giusti R, Aielli F, Hoskin P, Rolke R, Sharma M, Ripamoonti CI, et.al. European Society for Medical Oncology (ESMO) Clinical Practice Guidelines: Management of cancer pain in adult patients. Annals of Oncology. 2018, 29(S4): iv 166 – iv 191.

[19] Sandoz SA (Pty) Ltd. Fendermal Professional information. https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2024/07/pi-fendermal-clean-19032024.pdf

[20] Pharma Q Holdings (Pty) Ltd. Pharma-Q-Fentanyl Professional information. https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2024/05/Approved-PI-Pharma-Q-Fentanyl-100-%C2%B5g_2-ml-IInjection.pdf

[21] Eurolab (Pty)Ltd. Oramorph Professional Information. https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2023/01/Final_PI_ORAMORPH-Oral-Drops_Applicant.pdf

[22] Mundipharma (Pty) Ltd. MST Morphine Professional Information. https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2021/08/mst_approved_clean_pi_aug21-.pdf

[23] Pharma Q (Pty) Ltd. Pharma Q Morphine Professional Information. https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2024/05/Approved-PI-Pharma-Q-Morphine-inj.pdf