European Palliative Care Research Collaborative pain guidelines: Opioid switching to improve analgesia or reduce side effects. A systematic review

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European Palliative Care Research Collaborative pain guidelines: Opioid switching to improve analgesia or reduce side effects. A systematic review

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Abstract
According to a Cochrane review on opioid switching, sound evidence on the practice of substituting one strong opioid with another to improve pain control and reduce adverse effects was lacking in 2004. A systematic search strategy was developed to include studies after 2004, with adult cancer patients switching between strong opioids and reporting estimates of effect on pain and adverse effects. The search retrieved 288 publications (71 duplicates); 187 abstracts and 19 full papers were excluded. Eleven papers met the inclusion criteria; none were randomized controlled trials/meta-analyses. Studies comprised 280 patients (group size 10–32). A variety of opioids and switching strategies were studied. Pain intensity was significantly reduced in the majority of studies. Serious adverse effects were improved. Due to serious design limitations, the level of evidence was low (D). Randomized trials, with standardization of cohort classification, use of outcomes and analysis are warranted to establish the practice of opioid switching.

Keywords
Neoplasm, pain, opioids, switch/rotation

Introduction
Opioid switching is the term given to the clinical practice of substituting one strong opioid with another when a satisfactory balance between pain relief and adverse effects is not achieved with the first opioid. The biological mechanisms for the empirical observed effect of switching from one µ-opioid receptor agonist to another is not fully understood. However, the overall principle is a variation in each individual in their sensitivity to each of the opioids. The factors involved are probably inter-individual variability related to pharmacokinetics and pharmacodynamics of opioids and the variety of sites where they may exert their actions. The opioids have different physiochemical properties resulting in different pharmacokinetics, such as speed in crossing biological barriers, both by passive diffusion and active processes like the P-glycoprotein, which is subject to genetic polymorphism. Moreover, the opioids are eliminated by different pathways and some have active metabolites, again subject to genetic
polymorphism for some opioids. The μ-opioid receptor system is not static, but may respond to drugs with increased tolerance or increased sensitivity. Moreover, they are subject to genetic polymorphism and variable gene expression. Finally, other pathways, such as the adrenergic system, may interact with the actions of the opioids; these may also be subject to genetic polymorphism.\(^1\)\(^-\)\(^5\)

An Expert Working Group of the European Association of Palliative Care (EAPC) (2001) recommended morphine as the standard step 3 opioid analgesic in cancer pain.\(^6\) A switch of route or opioid should be considered as an approach when patients develop intolerable side effects before achieving adequate pain relief. In a systematic Cochrane review on opioid switching published in 2004\(^7\) no randomized controlled trials (RCTs), but 52 uncontrolled studies were found, of which 14 were prospective. Consequently, no data were available for analysis. It was stated that reporting bias was highly probable, as only one study reported potential problems with switching.\(^8\) However, it was also concluded that opioid switching appeared to be effective, both in terms of improving pain control and reducing opioid-related adverse effects, unfortunately without robust evidence. Better controlled studies were therefore called for.

The European Palliative Care Research Collaborative (http://www.epcrc.org/) is an EU-funded research project. One of its aims in collaboration with the EAPC Research Network (EAPC-RN; http://www.eapcnet.org/researchNetwork/research.html), is to bring forward the scientific basis for revising the European guidelines for approximately 20 items. This required systematic reviews for all these items, with opioid switching being one of these. A separate conference, the fifth Bristol opioid conference (http://www.eapcnet.org/download/forDiary/5thBristolOpioidConference.pdf), was organized to discuss these reviews. The aim is to provide new guidelines on opioid treatment in cancer patients.

The research question of the present study was therefore: what is the evidence (after 2004) of opioid switching resulting in improved analgesia or reduced adverse effects in adult patients suffering from cancer pain?

**Methods**

A systematic search in the databases PubMed (i.e. including MEDLINE), EMBASE through OvidSP, and CENTRAL – Cochrane Central Register of Controlled Trials through Wiley Interscience (Cochrane Library) was the basis for this study. A search strategy comprising free text and indexing terms was set up for each of these databases. Indexing terms were selected from MeSH vocabulary in PubMed and from Emtree vocabulary in EMBASE. Search details Pubmed:


**Final combination**

#1 AND #2 AND #3 AND #4 limits Entrez Date from 2003/01/01, humans, subset ‘cancer’

The searches covered the period 1 January 2003–January 2010 as the Cochrane report by Quigley 2004 was considered state-of-art evidence up until then. The reference lists of the retrieved articles were also searched. It should be noted that papers published in 2002 may be registered in PubMed in 2003, and hence be included in this study.

**Inclusion criteria.** Only studies written in English with adult cancer pain patients switching from one strong opioid (World Health Organization (WHO) ladder, step 3) to another were included. Moreover, the studies had to include estimates of effect on pain and/or adverse effects. Case reports and retrospective studies were excluded. Other study design limitations were not enforced. If eligibility could not be determined from the abstract, the full paper was retrieved.

A data extraction form was constructed in which the following was summarized: publication details, study design and limitations, patient population details, setting, interventions, methods for assessing outcomes, such as efficacy and adverse effects, results and narrative summary of the main findings. Each study was reviewed and rated independently by two assessors. The data were analysed in accordance with the Grade approach,\(^9\) which includes reporting of an evidence profile for each outcome. This profile included number and type of eligible studies, number of participants, study limitations, consistency, directness, precision, publication bias and factors that might increase quality of evidence. On this basis a recommendation was given. Finally, the process will be reported in...
accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) requirements (http://www.prisma-statement.org/).

**Results**

Figure 1 shows the inclusion process for the studies that were included in the analysis (period 1 January 2003–August 2009). The search retrieved 288 publications, among them 71 duplicates. Based on the abstracts, 187 did not meet inclusion criteria. The full papers of 30 studies (including seven review articles) were reviewed; a hand search of the reference list of these papers did not provide any more eligible studies. Eleven papers remained for the final analysis. The reasons for the 19 exclusions are listed in the lower, right box in Figure 1. A new search in January 2010 retrieved another 18 studies that did not meet the inclusion criteria.

Neither RCTs, systemic reviews nor meta analyses were found after Quigley published her systematic review in 2004. Therefore, only a narrative description of the 11 studies meeting the inclusion criteria is given:

The most important data for all included studies are summarized in Table 1, which should be consulted for details. The 11 studies were all uncontrolled, prospective studies that included a total of 280 evaluable patients. Only two of the studies reported sample-size estimations. Two of the studies were multicentre studies (among them one sponsored by a pharmaceutical company); the remaining were single-centre studies. Centres were located in Europe, Japan and North America.

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**Figure 1.** PRISMA flowchart.


<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td><strong>Aurilio et al., 2009</strong></td>
<td>Outpatient 1 centre</td>
<td>16: TDB→TDF, 16:TDF→TDB. SG.</td>
<td>Pain: Mean weekly pain VAS 0–100. Present pain intensity (PPI), VRS 0–5 Pain rating index (PRI) (McGill Pain Questionnaire 0–3) AE: Nausea/vomiting, constipation, dysphoria (yes/no). Sedation: (VRS 0–3) Weekly assessments</td>
<td>Pain: TDF: mean (SD) VAS: 67 (14)→21 (12) (p &lt; 0.0001), PPI: 3.5 (0.8)→0.9 (0.7) (p &lt; 0.0001), PRI: 32 (2)→12 (1.6) (p &gt; 0.0001), TDB: p &lt; 0.0001 all weeks for VAS, PPI and PRI. AE: Number of patients with: Nausea: 7 → 3, TDB 9 → 2, constipation: TDF 10 → 5, TDB 11 → 4, dyspnoea: TDF 0 → 0, TDB 2 → 0.</td>
</tr>
<tr>
<td></td>
<td>40 screened</td>
<td>POD: TDB: 7.0 μg/h, TDF: 75 μg/h.</td>
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<td></td>
<td>32 included (age 62 (42–78)).</td>
<td>Switched to 50% of equianalgesic dose. No titration after switch.</td>
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<td>32 completed</td>
<td>4 weeks observation.</td>
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<tr>
<td><strong>Benitez-Rosario et al., 2004</strong></td>
<td>Inpatients 1 centre</td>
<td>All TDF→ME</td>
<td>Pain: PI VRS 1–4 Number of rescue doses daily. Effective pain control: pain control complete (no pain and 0–1 rescue doses in 24 hours) or recovery from AEs AE: Attention test, MMSE Somnolence/sedation: VRS 0–4 Delirium reversed when MMSE ≥24 and normal psychomotoric activity</td>
<td>Pain: Somatic pain: effective 12/15 patients, partially effective 3/15. Neuropathic pain: non-effective 2/2 No need for rescue after day 4 AE: Delirium: effective 4/5, non-effective 1/5 Final TDF:ME ratio: 1 : 17</td>
</tr>
<tr>
<td></td>
<td>1) Uncontrolled cancer pain with high dose (TDF ≥ 300 μg/h) or ≥ 3 escalating doses reaching at least 125 μg/h in last 10 days, 2) developed AEs to MO and then fentanyl and 3) cancer pain with uncontrolled pain and dose-limiting effects. Karnofsky &gt;40% 560 admitted in study period (1.5 y) 17 required switch (age 63 (range 43–89), M/F 8/9, Karnofsky 50 (40–70), somatic pain: 13, somatic/neuropathic: 2 17 completed</td>
<td>POD: TDF: 150 (100–275) μg/h (median (range)). Stop and titration. Ratio: TDF/MO = 1 : 100. MO: ME = 5 : 1 (10 : 1 if &gt;400 μg/hour/delirium). ME initiated 8–24 hours after the patch removal. 30–50% dose titration every 3 d. Rescue dose: 10% 7 days observation</td>
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<tr>
<td><strong>McNamara, 2002</strong></td>
<td>In and outpatients 1 centre</td>
<td>MO→TDF. POD not given. SG.</td>
<td>Pain: PI VAS 0–100. AE: Patients global assessment of well being (VAS), Daytime sleepiness/ drowsiness (VAS). Cognitive function (Cognitive Drug Research microcomputerized assessment system). Hallucinatory behaviour, delirium (diagnostic and statistical manual IV), vomiting present/absent. Hospital Anxiety Depression scale (HAD). Myoclonus, dizziness, nausea, bowel function (4-point scale). Assessment at each visit (days 1,2,3,5,7,9,11,14)</td>
<td>Pain: VAS: 37.5 (CI 27.3–47.8)→30.3 (CI 20.9–39.8) (p = 0.2773) AE: Global assessment VAS: (Mean (95% CI) 36.3 (25.6–6.9)→54.8 (42.3–67.3) (p = 0.0031), sleepiness: 9.4 (8–10.7)→7.3 (5.7–8.9) (p = 0.0012), drowsiness: 67.8 (53.9–81.8)→48.6 (32.9–64.4) (p = 0.0171). Cognitive function: (2/3 variables sign better). Dizziness sign improved (p = 0.0156). No sign decrease in no of patients with myoclonus. No change in level of anxiety/depression. One severe treatment related respiratory depression 53% continued with TDF after study was completed.</td>
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<td>Malignancy related pain needing continuous strong opioids (morphine ≥ 60 mg/day), a poor sense of well being and to be distressed as the result of opioid toxicity. Inclusion over 2 years 19 included, (mean age 66 (range 42–86), M/F 12/7 9 completed</td>
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<td>In and outpatients 1 centre</td>
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<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Mercadante et al., 2003</td>
<td>Inpatients 1 centre</td>
<td>MO→ME</td>
<td>Pain: PI or pain relief NRS 0–10</td>
<td>Pain: Pain intensity (mean 95% CI) 6.9 (5.4–8.4)→2.9 (1.3–4.4) (p &lt; 0.05)</td>
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<td>POD: MO 317 mg (95% CI 22–612), SG. Fixed MO:ME = 5:1 rescue 1/5 ME 4 days observation</td>
<td>AE: Confusion, myoclonus, drowsiness (VRS 0–4)</td>
<td>AE: Not reported separately</td>
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<tr>
<td>Mercadante et al., 2005</td>
<td>Inpatients 1 centre</td>
<td>7 ME→TDF, 24 TDF→ME, POD: ME: 30.8 mg·d = MO 154 mg·d TDF 4.2 mg·d = MO 420 mg·d, SG. Ratio: Fixed TDF:ME of 1:20 (1/6 rescue), ME:TDF = 20/1 Oral MO 100 = iv MO 33 = TDF 1 = iv F 1 = oral ME 20 = iv ME 16</td>
<td>Pain: PI (or pain relief) NRS 0–10</td>
<td>Data for successful switches:</td>
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<td></td>
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<td>AE: DS (distress score (sum of symptom intensity). Nausea/vomiting, drowsiness, confusion, constipation, dry mouth (VRS 0–3))</td>
<td>Pain: ME→TDF 7/7, TDF→ME 18/24.</td>
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<td></td>
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<td>Successful switch: PI and DS decreased at least 33% of basal value within 4–7 d.</td>
<td>ME→TDF 5.8 (4.1–7.6)→2.6 (1.5–3.6) (p &lt; 0.05) from day 1.</td>
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<td>Dose stabilization: Two consecutive days with same dose and no more than 2 rescue doses . the dose on the first of the two days = time of stabilization</td>
<td>TDF→ME: mean (95% CI) 5.9 (5–6.9)→1.8 (1.2–2.5) (p &lt; 0.05) from day 1.</td>
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<td>AE: ME→TDF: Drowsiness 1.7 (1–2.2)→1.1 (0.8–1.5) (p &lt; 0.05), confusion 1.4 (0.9–1.9)→0.1 (0–0.5) (p &lt; 0.05), DS 10.7 (7.4–14)→6.1 (3.1–9.1) (p &lt; 0.5).</td>
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<td>Nausea (NS) 1.8 (0.7–2.9)→1.6 (0.2–2.9), constipation (NS) 1.7 (0–3.4)→0.9 (–0.3–1.9), dry mouth 2.2 (1.1–3.2)→2.1 (1.1–3.1)</td>
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<td>TDF→ME: Nausea 0.9 (0.3–1.5)→0.3 (0.0–0.5) (p &lt; 0.05), drowsiness 1.6 (1.2–1.9)→0.8 (CI 0.5–1.1) (p &lt; 0.05), DS 6.5 (5.3–7.7)→3.3 (2.2–4.3) (p &lt; 0.05), Confusion (NS) 0.5 (0.1–0.9)→0.3 (–0.1–0.6), constipation (NS) 2.0 (1.1–2.8)→1.1 (0.5–1.7), dry mouth (NS) 1.2 (0.7–1.6)→0.8 (0.4–1.1).</td>
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<td></td>
<td>Dose stabilization: ME→TDF 2 d, TDF→ME 3.8 d</td>
</tr>
<tr>
<td>Mercadante et al., 2007</td>
<td>Inpatients 1 centre</td>
<td>Advanced cancer; admitted because of pain and adverse effects and requiring an opioid switch, or patient with poor analgesic response after double dose last week. No anti-cancer therapy during study.</td>
<td>Pain: PI NRS 0–10</td>
<td>Data for successful switches:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 switched, data available for 16: mean age 54 (SD 10.8), M/F 12/4 7 analysed (successful switch)</td>
<td>AE: Confusion, myoclonus, drowsiness, confusion, constipation and dry mouth VRS 0–3. DS: Sum of symptom intensity</td>
<td>Pain: ME→TDF 7/7, TDF→ME 18/24.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Successful switch: PI and DS decreased at least 33% of basal value within 4–7 d.</td>
<td>ME→TDF 5.8 (4.1–7.6)→2.6 (1.5–3.6) (p &lt; 0.05) from day 1.</td>
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<td></td>
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<td>Dose stabilization: Planned daily dose requiring no more than two extra doses as needed</td>
<td>TDF→ME 4.3 d</td>
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<td>AE: Nausea: 1.3 (0–2.6)→0.6 (CI 0–1.5), DS: 7 (CI 5.1–8.9)→4.3 (CI 2.4–6.1).</td>
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<td></td>
<td>Dose stabilization: 3.8 days (2.4–5.2) Successful 7/16 or 18%, Ineffective 9/16</td>
</tr>
</tbody>
</table>
Unacceptable AEs despite good pain control (at least one relevant symptom (drowsiness, confusion, myoclonus >2 (scale 0–3)) or severe constipation or dry mouth. Poor analgesic response despite doubling of dose last week. Both lack of pain control and AEs. Switched for convenience or preference (dysphagia limiting oral route or other).

Pain: PI NRS 0–10
AE: Nausea/vomiting, drowsiness, confusion, constipation, dry mouth, myoclonus and sweating (VRS 0–3)

MO: 2.4 mg/d
POD: MO 100 = iv MO 33 = TDF

TDF → ME: 6.2 (5.2–7.2) → 2.0

MO: 6.9 (6.1–7.6) → 3.9
(MO → ME: 6.9 (5.8–7.2) → 3.5 (3–4.6)
ME: 2.7 (2.0–3.2) → 2.5

AE: DS mean (95% CI)
TDF: 1.9 (2.1–2.9)
MO: 2.5 (0.8–6.3)

TDF: 2.0 (1.4–2.6)

Pain: mean (95% CI)
TDF: 4.9 (4.3–5.6) → 2.3

AE: DS mean (95% CI)
1.6 (1.7–2.8)

MO: 4.9 (4.3–5.6) → 2.3

AE: DS mean (95% CI)
1.0 (0.83) day 7 (< 0.001)

Moryl et al., 2005

Agitated delirium: uncontrolled severe pain (NRS ≥5) and delirium (MDAS rating above 10). After enrolment: all patients with pain and delirium who did not improve for 24 h or longer after starting neuroleptic medication. English understanding.

Dose stabilization: First of two consecutive days requiring no more than two rescue doses

Sedation: haloperidol or risperidone 7 d observation

Dose stabilization: 3.2 d (2.7–3.6)

Delirium: Mean MDAS from 14 → 3.6
(p < 0.001)

Pain: VRS mean (SD) 2.2 (0.77) → 1.1

(0.76) day 7 (p = 0.001), STAS 2.6
(0.83) → 1.3 (0.79) day 7 (p = 0.001).

AE: Dry mouth: 0.75 (SD) 0.91 → 0.25

(0.72) day 7 (p = 0.001), nausea 1.2
(1.4) → 0.1 (0.45) day 7 (p = 0.001),

vomiting 0.85 (1.4) → 0 day 7
(p < 0.001), performance status 3.3
(0.64) → 2.9 (0.81) day 7 (p < 0.001).

Constipation, diarrhoea and sweating NS, myoclonus (n): 4 → 1.


Pain: Mean 8.2 → 2.5

27 eligible
20 included, age 47–77. M/F 10/10

Dole et al.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Narabayashi et al., 2008&lt;sup&gt;19&lt;/sup&gt;</td>
<td>≥20 years expected to be able to take oral medication for at least two weeks from entry and able to keep a diary. Moderate or severe pain (2, 3, 4-point scale); moderate or severe pain, intolerable side effects resulted at previous dose increase (during 7 d prior to enrolment); or slight pain, but at previous dose reduction to alleviate intolerable side effects, which increased pain intensity to moderate or severe.</td>
<td>MO→OX&lt;br&gt;POD: MO 44.4 mg/d (SD 33.8), MO:OX = 3:2, Titrated with 5 and 20 mg OX/24 h, Rescue: 1/6 of daily OX</td>
<td>Pain: Mean PI last 24 h, VRS 0–3, VAS 0–100.&lt;br&gt;Adequate pain control: Oxycodone dose unchanged in 48h, PI slight (0–1), ≤2 rescue/24h, side effects tolerable, analgesics/adjuvant analgesic unchanged.&lt;br&gt;Successful switch: adequate pain control within 10 days.&lt;br&gt;AE: Nausea, drowsiness, vomiting, constipation VRS 0–3</td>
<td>Pain: mean VRS 1.9→1 (p = 0.0001). VAS 53.5→27.6 (p = &lt; 0.0001).&lt;br&gt;AE: Nausea 2.3→0.4 (p = 0.0005), drowsiness 2.1→0.9 (p = 0.0313).&lt;br&gt;Vomiting and constipation not improved. Intolerable side effects: Nausea 13→0 (p = 0.0003), vomiting 5→0 (p = 0.0253), Constipation 5→1 (p = 0.1797), drowsiness 7→0 (p = 0.0082).&lt;br&gt;&lt;strong&gt;Successful switch : 21/25 in 2.3 days (mean)&lt;/strong&gt;</td>
</tr>
<tr>
<td>Tani et al., 2008&lt;sup&gt;20&lt;/sup&gt;</td>
<td>PI VAS ≥ 4 during treatment with a low dose of oral MO</td>
<td>MO→TDF&lt;br&gt;POD: 20–30 mg/day, TDF 2.5 mg/3d, titration possible. Rescue: MO or NSAID&lt;br&gt;28 d observation</td>
<td>Pain: Pain VAS (0–10). Responder ≤4&lt;br&gt;AE: Interview. Graded by the National Cancer Institute Common Toxicity Criteria, (NCI-CTC version 2.0)</td>
<td>Pain: Mean (SD) VAS 5.67 (2.4) O→2.6 (2.8). 18 patients were responders.&lt;br&gt;AE: Number of patients (%) with: nausea 7 (29.2%)→1 (4.2%) (p &lt; 0.05), no changes in vomiting, constipation or tiredness.</td>
</tr>
</tbody>
</table>
Four of the studies, representing 120 patients, came from one centre in Italy. Seven studies included inpatients, two outpatients and one both in and outpatients, and not stated in one. Only one study reported the Karnofsky performance status of their patients. The average ages reported varied from 54 to 67 years and more men than women were included (Table 1). The evaluable sample sizes varied from 10 to 32 patients. Observation periods varied greatly, from four days to four weeks. Most of the studies aimed at treating an imbalance between pain and adverse effects, but two addressed delirium as the primary inclusion criterion.

A variety of opioids, switching strategies and ratios were studied. Of the 10 studies reporting a preswitch opioid dose, three studies included patients with doses equivalent to morphine <100 mg/d. None was above 485 mg/d (transdermal (TD) fentanyl 1:oral morphine 100). Thus no cohort included patients with very high doses of opioids. Four studies reported switches from different opioids using the stop-and-go procedure. Three studies reported a switch from one opioid to methadone (two used a stop-and-go procedure), while three studies switched from morphine to TD fentanyl (which was also a switch of route), with one of these using both TD and parenteral fentanyl, and finally one study switched to oxycodone with a titration strategy.

Pain intensity was recorded by either visual analog scale (VAS, n = 3), numerical rating scale (NRS, n = 4), verbal rating scale (VRS, n = 3) or numerical analog scale (NAS, n = 1), most often as estimates of the mean before and after the switch. Seven of the studies reported a reduction in pain intensity of more than three on 11-point scales.

The reporting of adverse effects during and after the switch was inconsistent. The side effects (and the measurements) selected for reporting varied greatly from study to study, in one paper adverse effects were not reported separately. The most common side effects reported were sedation, nausea, vomiting and constipation. Most of the side effects were reported as means before and after the switch, but in three studies the change (reduction) in the number of patients with specified adverse effects was reported. Regardless, patients with severe adverse effects frequently reported significant relief. The two studies aiming at management of delirium used the same instrument (memorial delirium assessment scale) for grading the outcome and both reported significant improvement after the switch.

Success rates (inconsistent criteria employed) were reported in three studies only (among them one on delirium), varying from about 50–80%. Moreover, time-to-dose stabilization was given in three studies, varying from two to five days.

The evidence profiles for the two efficacy outcomes of pain intensity and side effects were similar and both started the grading procedure from evidence level C, based on a design with serious limitations (open, uncontrolled). However, the data was considered imprecise with a high probability of reporting bias. On the other hand, the effects reported were of significant magnitude. It was concluded that the evidence level was very low (D).

Discussion

The major finding of this review is that the firm evidence for opioid switching is still missing, despite the fact that a number of studies have been conducted since Quigley published her systematic review. We concur with Quigley that we still do not know whether the switch is a true drug effect, and that the uncontrolled confounders, such as the placebo effect, reduce the possibility of interpreting the data. Finally, reporting bias is imminent, as virtually no new studies since Moryl et al. have been critical to opioid switching.

The evidence level was graded D according to the Grade approach. The study’s open and uncontrolled design is subject to significant bias, not least the placebo effect. The magnitude of the placebo effect may be as large as 21%, or a change of three on a NRS scale of 0–10. However, seven of the 11 studies reported effects on pain that were >3 on the 0–10-point scale. This observation would increase the level of evidence from a C (starting point for open, uncontrolled studies); however, the imminent possibility of reporting bias and the data imprecision reduced the evidence level by two points, ending at level D. However, due to rather consistent reporting of positive effects, and success rates that were all >50%, opioid switching may still be considered a useful clinical manoeuvre in some patients.

The process of systematically tabulating the core content of the studies (see Table 1) revealed that a number of areas related to opioid-switch research can be improved. First, randomized controlled studies are required. Since these patients are difficult to recruit, multicentre studies are probably necessary to obtain an adequate sample within a reasonable time point. Although in N = 1 studies, a cross-over design, which is switching patients to another opioid and then back again, may provide strong evidence, this type of study may be challenging to perform in very sick patients as it require longer study periods than parallel group studies. Therefore, ordinary randomized parallel group studies, even without blinding, may be a good choice for gaining more evidence on the efficacy of opioid switching.

Second, the entry criteria for patients to opioid-switch studies should be more standardized. Neither the functional status nor pain characteristics are
systematically reported, factors that are important for the understanding of the patient population included. Moreover, reporting of cancer duration, occurrence of metastasis and time since start of opioid may also be warranted. In the future one may recommend using one of the emerging cancer pain classification systems for population description.\textsuperscript{23,24}

The large variation and dominance of a rather low preswitch dose of morphine equivalents among the studies, combined with a low intensity of adverse effects in some studies, raise the question of whether an increase of the dose of the primary opioid would have been an appropriate alternative to switching. The problem with different entry doses can be illuminated by Moryl et al.,\textsuperscript{8} who have delivered the only real critical paper to opioid switching. Indeed, only one of the 13 patients switched from (second- or third-line) methadone to another opioid were successfully maintained on the second opioid. The mean pre-opioid-switch dose in this study was 515 mg/d, in contrast to 31 mg/d in seven patients switched from methadone to TD fentanyl in the report of Mercadante et al.\textsuperscript{14} While Moryl et al.’s switches were overall unsuccessful, Mercadante et al.’s were all successes. This may certainly indicate that low-dose switches represent a different population than high-dose switches and one may even speculate whether there is any indication for switching in this and similar patient cohorts. These observations draw attention to the importance of a clear and clinical sound description of the populations entered into clinical studies. Such a description is necessary in order to apply the findings in daily clinical practice.

More evidence would probably have been available if we had concentrated on fewer drugs and compared fewer procedures. Moreover, outcome measures should be standardized, both for pain intensity and adverse effects. This also includes standardizing the time points for the observations. Moreover, the observation period should be a minimum of 14 days, and that measures should be taken to determine the survival time of the patients.

In conclusion, firm evidence for the efficacy of opioid switching is lacking; however, opioid switching may well be a useful clinical manoeuvre in some patients. One may also question whether increasing the dose would have been more appropriate than switching the opioid in most patients on low opioid doses. RCTs based on more standardized inclusion criteria, switch procedures and reporting, may improve the evidence level.

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Conflict of interest statement

None declared.

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