Original Article

Opioid Rotation in Cancer Pain Treatment

A Systematic Review

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Summary

Background: Rotating several different WHO level III opioid drugs is a therapeutic option for patients with chronic cancer-related pain who suffer from inadequate analgesia and/or intolerable side effects. The evidence favoring opioid rotation is controversial, and the current guidelines in Germany and other countries contain only weak recommendations for it.

Methods: This review is based on pertinent publications retrieved by a systematic review of the literature on opioid rotation for adult patients with chronic cancer-related pain who are regularly taking WHO level III opioids by the oral or transdermal route.

Results: 9 individual studies involving a total of 725 patients were included in the analysis, and 3 previous systematic reviews of studies involving a total of 2296 patients were also analyzed. Morphine, oxycodone, fentanyl, hydromorphone, and buprenorphine were used as first-line opioid drugs, and hydromorphone, buprenorphine, tapentadol, fentanyl, morphine, oxymorphone, and methadone were used as second-line opioid drugs. In all of the studies, pain control was achieved for 14 days after each rotation. In most of them, the dose of the new drug introduced in each rotation needed to be increased above the dose initially calculated from a rotation ratio, with the exception of rotations to methadone. The frequency of side effects was only rarely lessened, but patients largely considered the result of opioid rotation to be positive. No particular opioid drug was found to be best.

Conclusion: Opioid rotation can improve analgesia and patient satisfaction. The success of opioid rotation appears to depend on the magnitude of the initial dose, among other factors. Tables of equianalgesic doses should be considered no more than a rough guide for determining the dose of the new drug. Rotations to methadone should be carried out under clinical supervision in experienced hands.

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Pain is experienced by 50 to 90% of cancer patients (1). It is estimated that adequate pain relief can be achieved in 71 to 100% of cases if the "WHO analgesic ladder" for cancer pain is used (2). Nevertheless, around 30% of patients treated with powerful opioids still have pain, opioid-associated adverse drug reactions, or both (3). The term opioid rotation describes the change from one drug ("first-line opioid") to another ("second-line opioid") owing to intolerable adverse events accompanying adequate analgesia or to increasing side effects when the opioid dose is increased because of inadequate pain relief (4, 5). There are limited opportunities for dose escalation, because the risk of opioid-associated mortality increases sharply at morphine equivalent daily doses over 100 mg (6).

The terms opioid rotation and opioid switch are largely used synonymously in the literature. It should be noted that authors do not always distinguish rotation for the reasons outlined above from rotation on grounds of "convenience." The latter is more correctly referred to as opioid conversion and may take place, for example, because the patient prefers a particular preparation although stable analgesia without side effects has already been achieved.

In principle opioid rotation can also be used to alleviate non-cancer pain, but in practice it plays a much smaller part, particularly since the publication of the LONTS guideline in Germany (7). According to the literature opioid rotation is necessary in 20 to 44% of cancer pain patients and can lead to clinical improvement in 40 to 80% of cases (8, e1).

Following a Cochrane review in 2004, only two further systematic reviews of the efficacy of opioid rotation specifically in cancer pain patients appeared up to 2010 (9, 10). The authors of all three publications came to the conclusion that although opioid rotation is widely practiced, robust evidence is lacking due to the mainly methodological limitations of the studies concerned. The dose equivalents listed in *Table 1* are commonly used in clinical practice and form the basis of various guideline recommendations.

The mostly cautious nature of the recommendations in guidelines *(Box)* makes it clear that considerable uncertainty prevails in the practice of opioid rotation for the management of cancer pain.

The aim of this review is therefore to provide an update on opioid rotation in cancer-related chronic pain by means of a systematic survey of publications with a high level of evidence.

TABLE 1

Recommendations on equianalgesic dose ratios[*1] (guidelines and aggregated evidence)

Active substances	Relative analgesic ratios	Evidence level
Morphine p.o. – oxycodone p.o.	1.5 : 1	Strong
Oxycodone p.o. – hydromorphone p.o.	4 : 1	Strong
Morphine p.o. – hydromorphone p.o.	5 : 1	Weak
Morphine p.o. – methadone p.o.	5 : 1 – 12 : 1[*2]	None[*2]
Morphine p.o. – buprenorphine t.d.	75 : 1	Weak
Morphine p.o. – fentanyl t.d.	100 : 1	Strong

[*1] Current recommendations on equianalgesic dose ratios based on (9) and on the recommendations of the EAPC (European Association for Palliative Care) [e1] or the S3 guideline on palliative medicine [e2].
[*2] The authors (EAPC und S3) make no recommendations for methadone; according to Mercadante et al., depending on the initial opioid dose the ratio can be higher than 12:1.
p.o. = per os, t.d. = transdermal

Method

Literature search

The systematic literature search was oriented on the recommendations of the PRISMA Statement (11) and the rules of the Association of Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*, AWMF) for the formulation of guidelines (e6).

A Cochrane review by Quigley (8), published in 2004, systematically examined the primary literature on opioid rotation for treatment of pain from 1960 to January 2003. We carried out a systematic search for aggregated evidence published thereafter (January 2003 to January 2017) in DARE (Database of Abstracts of Reviews of Effects) and MEDLINE (PubMed). Inspection and evaluation of the aggregated evidence revealed one high-quality systematic review published by Dale et al. in 2011 (10) (search period for primary literature 2003 to 2010). Based on the search strategy in that review, we defined a sensitive strategy for searching the databases MEDLINE (via PubMed) and CENTRAL (Central Register of Controlled Trials). Furthermore, we carried out a hand search of the major German and international journals. The detailed search strategy for all databases is presented in *eTable 1*.

Title/abstract screening

Abstracts of the publications found in all sources were initially screened for relevant content. The research question was formulated in PICO format *(Table 2)*.

BOX

Current international guideline recommendations for opioid rotation

- **EAPC (European Association of Palliative Care) (2012) (e1)**
  - Together with morphine, oxycodone and hydromorphone p.o. are recommended as equivalent first-line opioids for the treatment of cancer pain. The data show no relevant differences among these substances. Explicitly no conversion ratio is recommended for methadone, the use of which is restricted to experienced physicians.
  - With satisfactory analgesia the conversion should follow the conversion ratios listed in *Table 1*.
  - With inadequate analgesia and/or severe side effects the dose of the second-line opioid should be lower than the calculated dose, followed by titration depending on the clinical effect.
- **AWMF-S3 Guideline for Palliative Medicine (2015) (e2)**
  - Together with morphine, oxycodone and hydromorphone p.o. are recommended as equivalent first-line opioids for the treatment of cancer pain. Levomethadone is recommended for use only by treating physicians with the necessary extensive experience.
  - Opioid switch is viewed as a "can" recommendation in the event of inadequate analgesia or intolerable side effects and conversion according to *Table 1* is recommended together with dose reduction and subsequent retitration.
- **NHS (National Health Service) (2014) (e3)**
  - Opioid rotation should be selected in the presence of intolerable side effects despite good analgesia with combined opioids and adjuvant analgesics, moderate to severe impairment of liver function, and low compliance with oral medication.
  - The dose of the new opioid should be reduced by 30% and retitrated if the patient reacts with "opioid toxicity" on grounds of age or multimorbidity.
- **NICE (National Institute for Health and Care Excellence) (2016) (e4)**
  - Opioid rotation is classed as a treatment alternative but with no recommendation on how it should be implemented.
- **NCCN (National Comprehensive Cancer Network) (2016) (e5)**
  - Opioid rotation should be considered if despite opioid titration the patient experiences pain scoring >4 on an 11-point numeric rating scale and adverse drug reactions occur, namely nausea for >1 week or sedation for more than 2 to 3 days. If refractory obstipation occurs, rotation to fentanyl or methadone is explicitly recommended.

p.o. = per os

TABLE 2

Criteria for abstract screening in PICO format

Population/patients	Adult patients (≥ 18 years of age) with chronic cancer-related pain (with or without accompanying neuropathic pain) and regular oral or transdermal administration of WHO level III opioids
Intervention	Opioid rotation between WHO level III opioids owing to insufficient analgesia and/or intolerable adverse drug reactions with details of dosing regimen and at least 14 days observation of progress
Outcomes/endpoints	**Primary endpoint:** Pain intensity (measured on a visual analog scale or a verbal rating scale) **Secondary endpoints:** Occurrence of adverse drug reactions (adverse events), additional analgesics required for breakthrough pain, patient preference/satisfaction, quality of life, rotation ratio of dosages (conversion ratio), efficacy of rotation

Study selection: inclusion/exclusion criteria

Two reviewers (MS and FH) read the full text of all articles identified as potentially relevant on abstract screening for a priori defined inclusion and exclusion criteria regarding content and methods *(eTable 2)*. With regard to study design, we included systematic reviews (SRs) with or without meta-analysis, randomized controlled trials (RCTs), and prospective observational studies (with or without a control group). Narrative/non-systematic reviews, retrospective observational studies, case series, and individual case reports were excluded.

Data extraction and evaluation

The central clinical and methodological data of all included studies are reported in evidence tables stratified by study design (SRs: *eTable 3,* RCTs and prospective observational studies: *eTable 5*).

Quality assessment of the included systematic reviews and studies

The SRs were evaluated by means of the validated AMSTAR assessment tool (A measurement tool to assess the methodological quality of systematic reviews) (12, 13).

The risk of bias (RoB) in the included RCTs was assessed by two independent reviewers using the validated Cochrane Risk of Bias Tool (14).

The study quality of the prospective observational studies was judged with the aid of the validated MINORS assessment instrument (Methodological Index for Non-randomized Studies) (15).

Classification of the evidence

In addition to quality assessment of the included publications, the SRs and individual studies were classified according to the Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence LoE 1a to LoE 5 (16).

Results

Altogether, the database survey and hand search identified 502 publications, 12 of which satisfied our inclusion criteria: three SRs (9, 10, 17), four RCTs (18–21), and five prospective observational studies without a control group (22–26). For the sake of completeness, the results of two SRs identified during the search for aggregated evidence in the years 2003 to 2010 were tabulated (8, 27). None of the reviews had performed a meta-analysis of the individual studies' results. Three of the five identified SRs had explicitly followed the PRISMA Statement. On the basis of the AMSTAR criteria, the methods of all reviews except one were classed as high quality and together with the primary literature represent evidence level 3a.

Results of the systematic reviews

The 2011 review by Dale (10), conceived as a follow-up to Quigley's Cochrane review (8), included 11 uncontrolled prospective studies (n = 280) of various opioids with low numbers of cases (n = 10 to 32). With regard to pain, seven studies reported a reduction of >3/10 points on the numeric rating scale (NRS). Three studies expressed the amelioration of pain as a success rate of 50 to 80%; however, the measurement criteria were inconsistent. No advantage could be discerned for any individual substance, but the success of rotation was associated with the dose intensity of the first-line opioid. The authors concluded that higher dosage tended to lead to lower success of rotation. Most studies did not report whether there had been adequate titration of the primary opioid or whether the follow-up period after rotation had been sufficiently long. The authors reasoned that observation for at least 14 days after rotation is necessary to obtain meaningful data.

The SR of 10 prospective studies (including one RCT, n = 42) and 15 retrospective studies (n = 1229) by McLean (17) examined rotation to methadone and took a look at various rotation regimens *(Table 4)*. However, only in 17 of these studies were the endpoints ascertained by means of validated instruments; in the remaining eight studies they were established by clinical assessment alone. While pointing out methodological limitations, the authors stated that the result of rotation was rated positive in almost all studies. Both the ad libitum approach and the 3-day switch method were judged successful in over 90% of patients, but this was the case for only 78% of patients in whom the rapid conversion technique was used.

Mercadante and Caraceni (9) conducted an SR of 5 RCTs and 26 prospective case series (n = 1887) with

TABLE 3

Dose escalation following opioid rotation

Study	Second-line opioid	Mean MEDD of first-line opioid	To achieve final MEDD, adjusted by factor:	Indication for rotation
Imanaka, et al. (18)	Tapentadol	<40 mg	1.18	C
Slatkin, et al. (21)	Oxymorphone	92 mg	1.4	C
Minami, et al. (25)	Fentanyl	33 mg	1.13	C
Moksnes, et al. (19)	Methadone	900 mg (SAG group)	0.81 (SAG group)	P/AE
		1330 mg (3DS group)	0.87 (3DS group)	P/AE
Poulain, et al. (20)	Methadone	n.d.	Same	P/AE
Lundorff, et al. (23)	Buprenorphine	>150 mg	n.d.; escalation ensued in 9/13 patients	AE
Mercadante, et al. (24)	Tapentadol	112 mg	1.25	P/AE/C
Porta-Sales, et al. (26)	Methadone	194 mg	n.d.	P/AE
Lee, et al. (22)	Hydromorphone	124 mg	1.47	P

AE = adverse events (intolerable side effects), C = convenience,
MEDD = morphine equivalent daily dose, n.d. = no data, P = pain, SAG = stop and go, 3DS = 3-day switch

the aim of verifying the evidence level of equianalgesic dose recommendations. This SR formed the basis for the recommendations in *Table 1*, but also found clear-cut dependence on the dose intensity of the first-line opioid: the higher the dose, the less likely was successful rotation without dose adjustment, while the data in *Table 1* for oxycodone, hydromorphone, fentanyl, and buprenorphine in lower dosage proved reliable. The authors did not specify a cut-off value for a first-line opioid dose below which the recommendations in the table should be followed. They explicitly gave no equianalgesic recommendation for rotation to methadone due to the large variance of results.

Results of the individual studies

In six of the nine individual studies included (total n = 725), opioid rotation had been carried out because of pain or intolerable side effects, while in the other three studies analgesia was stable and the reason for rotation was purely for convenience *(eTable 5)*.

With regard to the primary endpoint, all of the studies showed amelioration of pain (if that was the reason for rotation) or continuation of stable pain relief (if the intervention was performed on grounds of convenience).

All of the studies featured dose titration phases to achieve stable analgesia, and in all of them one or more dose adjustments were made in the follow-up period to attain the endpoint. The first-line opioid dose differed considerably between studies with patients who were switching for convenience (MEDD 33 to 92 mg) and those in which the patients had inadequate analgesia and/or intolerable side effects (MEDD 124 to 1330 mg). In the majority of studies the dose of the second-line opioid was increased in the course of the follow-up period after rotation *(Table 3)*. Only Moksnes (19), who rotated to methadone using the stop-and-go method (SAG) or the 3-day switch (3DS), found a reduction in the equivalent dose of methadone at the end of the 14-day observation phase. In the study by Poulain (20) the methadone dose remained stable with no great variation during the observation period.

Opioid-related side effects were described in all studies, although the criteria and the instruments used for measurement were heterogeneous. The stated proportions of patients with adverse effects varied from 25% and 33% for Poulain (20) to >90% in the studies by Slatkin (21), Imanaka (18), and Lee (22). Two studies found no difference in the rate of side effects before and after rotation (20, 24). In their convenience study, Imanaka et al. (18) described superiority of tapentadol over morphine (38 % versus 54 %) with regard to the occurrence of gastrointestinal adverse effects. The remaining side effects were comparable in the two groups. In another convenience population, Minami et al. (25) found an amelioration of oxycodone-associated fatigue after rotation to fentanyl while other adverse effects were comparable. None of the studies of patients with pain or intolerable side effects revealed any advantage for a specific substance.

Three studies investigated the patients' subjective satisfaction. The highest rate (96%) was reported by Slatkin; at the same time, 93% of the patients stated they had experienced at least one new undesired effect following rotation (21). In two other studies (22, 25) with rotation from oxycodone to hydromorphone (n = 114, rotation due to pain) and from oxycodone to fentanyl (n = 49, rotation for convenience), around 60% of patients were satisfied with the results 14 days after rotation.

TABLE 4

Methods for rotation from WHO level III opioids to methadone*

Stop and go (SAG) or rapid conversion (RC) (Ripamonti et al., 1998) (31), (Mercadante, 2012) (33)	MEDD (mg/d)	30–90	91–300	301–600	601–1000	>1000	
	MED : methadone ratio	4 : 1	6 : 1	8 : 1	10 : 1	12 : 1	
	Abrupt discontinuation of first-line opioid. Administration of calculated methadone dosage in three identical doses at 8-h intervals.						
Progressive method (Poulain et al., 2016) (20)	Conversion as for SAG/RC; first-line opioid given at 50% of previous dose on 1st day of rotation and 25% on second day in addition to methadone, not left out altogether until 3rd day of rotation.						
Three-day switch (3DS) or Edmonton method (Gagnon et al., 1999) (29), (Moksnes et al. 2011) (19)	Starting from a MED : methadone ratio of 10 : 1 (with MEDD up to 300 mg) or 12 : 1 (with MEDD >300 mg), the first-line opioid is reduced daily by 1/3 and replaced with 1/3 of the equivalent dose of methadone. The calculated dosage of methadone is administered in three identical doses.						
German model (Ostgathe et al., 2011) (30)	The first-line opioid is abruptly discontinued and initially replaced with a dose of 5 to 10 mg L-methadone every 4 h. The dosage is adjusted as required and after 72 h the interval between doses is increased to 8 h; the amount given each time remains unchanged.						
Ayonrinde method (Ayonrinde & Bridge, 2000) (32)	MEDD (mg/d)	<100	100–300	300–600	600–800	800–1000	>1000
	MED : methadone ratio	3 : 1	5 : 1	10 : 1	12 : 1	15 : 1	20 : 1
	Abrupt discontinuation of first-line opioid. Administration of calculated methadone dosage in three identical doses at 8-h intervals.						
Friedman method (Friedman, 2004) (34)	MEDD (mg/d)			<1000	<1000	1000–2000	>2000
	Age (years)			<65	>65	any	any
	Methadone proportion of MEDD in%			10%*	5%*	5%*	3%*
	*The proportion of the MEDD is divided over several doses of methadone.						
Ad libitum method or Morley–Makin method (Morley & Makin, 1998) (35)	MEDD (mg/d)	up to 300			>300		
	Methadone dose	Each dose of methadone = 1/10 MEDD			Each dose of methadone = 30 mg		
	The first-line opioid is abruptly discontinued and replaced by 1/10 of the equivalent dose of methadone to a maximum of 30 mg. The interval between doses is no less than 3 h, depending on pain. On day 6 the dose to be given every 6h or every 12 h is calculated from the total consumption over the previous 2 days.						
Outpatient titration (Hagen & Wasylenko, 1999) (36)	The first-line opioid continues to be taken as before with the addition of a 5-mg dose of methadone every 4 h. The methadone is increased by 5 mg per dose every 3 days until adequate analgesia is achieved. Only then is the first-line opioid reduced by 1/3 and the amount of methadone increased as and when necessary. Further reduction of the first-line opioid and subsequent titration of the methadone dosage ensue over a variable period of time.						
Methadone product information sheet (ROXANE LABORATORIES, 2006) [e7]	MEDD (mg/d)	<100	100–300	300–600	600–1000	>1000	
	Methadone proportion of MEDD in%	20–30 %	10–20 %	8–12 %	5–10 %	>5 %	

* Various methods described in the literature for the rotation from WHO level III opioids to methadone.
In all methods with stated conversion ratios the first-line opioid is abruptly discontinued and replaced with the corresponding equivalent dose of methadone.
MED = morphine equivalent dose, MEDD = morphine equivalent daily dose

Discussion

Applicability of equianalgesic conversion charts

Once the decision to switch opioids has been made, the dose of the second-line opioid must be selected for safety as well as efficacy. If the change is being made because of insufficient analgesia, intolerable side effects, or both, guidelines recommend that the new dose should be lower than calculated at first, then titrated upward after rotation (8). In the studies investigated here, however—with the exception of those on methadone—the initially calculated dose of opioid had to be increased to achieve adequate analgesia, regardless of the indication for rotation *(Table 3)*. In this regard, McLean et al. (17) point out that precisely in patients who are clinically unstable or experiencing exacerbated pain, one should consider giving a higher dosage of the second-line opioid from the very beginning, to avoid the risk of persisting undertreatment. High dosage of the first-line opioid may reflect a complex pain situation and have an important effect on the success of rotation (24).

Special features of the clinical deployment of methadone

A variety of methods are used for rotation to methadone *(Table 4)*. The 3-day switch and ad libitum methods seem effective, despite weak evidence, while models that attempt swift rotation (stop and go, rapid conversion) appear to yield no advantage (17). Owing to the long half-life, the time required to achieve dose stability varies from 35 to 325 h (13.5 days). The higher the dosage of the first-line opioid, the greater is the effect of the methadone. Therefore, a comparably low dosage of methadone is used in rotations from high-dose first-line opioids *(Table 4)*. Moreover, high initial doses (≥ 40 mg/day) and rapid increases (>25 mg/day) are classed as risky (28). Therefore, regardless of the method selected one should follow the EAPC guideline recommendation (e1) and monitor the patient during the opioid rotation.

Opioid-associated adverse drug reactions

Gastrointestinal side effects are among the most frequently occurring adverse drug reactions associated with opioid intake. In particular, obstipation affects 41 to 73% of cancer patients treated with opioids (37). In cases of refractory obstipation, guidelines (16) recommend, among other options, rotation to fentanyl or methadone. Combination of opioids with naloxone is also thought to be beneficial by decreasing the effect on μ-receptors (38), and studies of patients with non-cancer pain have shown that administration of tapentadol is helpful in the presence of gastrointestinal side effects (39, 40). This was confirmed in a comparative study in which 100 patients rotated to either tapentadol or morphine (18): the rate of gastrointestinal adverse effects was much lower in the tapentadol group than in those who switched to morphine.

Limitations

The systematic reviews included in this study displayed considerable heterogeneity with regard to their methods, the nature of the studies they covered, their choice of endpoints, and their assessment of the individual studies analyzed. Despite a sensitive, systematic search for primary literature we identified only a small number of randomized controlled trials. One general problem in the conduct of clinical studies on patients with pain is that for ethical reasons it is difficult or impossible to include those suffering from uncontrolled pain or adverse drug reactions in studies of that nature (27), and this restricts the data available. Furthermore, our hand search and database survey principally brought up studies that demonstrated the efficacy of opioid rotation while simultaneously having high drop-out rates. Publication bias is likely.

A further limitation of the individual studies included in our analysis is the high potential for bias in documentation of the endpoints. Although pain and side effects are often measured with standardized instruments (numerical/verbal rating scales), they are reported by the patients and are thus subjective endpoints vulnerable to bias. Just as vulnerable are the treating physicians' estimations of the endpoints in the absence of blinding. There was particularly pronounced variation in the interpretations placed on the commonly used terms "effective" and "successful." The real "success" of opioid rotation is therefore difficult to assess, very hard to compare, and above all should not be evaluated too early. According to Dale (10) the observation period should not be less than 14 days.

Conclusion

The conversion ratios for the attainment of effective analgesia described in the publications investigated here differ, in some cases considerably, from the prevailing recommendations and in all studies—with the exception of rotation to methadone—they were higher than the calculated equianalgesic doses. In this light it seems advisable to ascertain whether the current guidelines, which recommend initial dose reduction on opioid rotation precisely in patients with insufficient analgesia, should be reevaluated to avoid long-term analgesic undertreatment.

From the methodological viewpoint, further high-quality RCTs with low risk of bias are required to increase the strength of evidence for the guideline recommendations, which at the moment are based largely on consensus. Overall, opioid rotation should not be withheld from properly selected patients with cancer pain, as amelioration of analgesia, reduction of side effects, and improvement in quality of life can be achieved.

Conflict of interest statement
Dr. Laufenberg-Feldmann has received lecture fees from Grünenthal.
The remaining authors declare that no conflict of interest exists.

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Key messages

- Opioid rotation between various WHO level III opioids can be used as an alternative treatment in the case of insufficient relief of chronic tumor-related pain and/or intolerable side effects and is rated positively by most patients.
- In the majority of the studies investigated, dose escalation after rotation was necessary to achieve effective analgesia. Rotation to methadone formed an exception.
- The equianalgesic ratio of two opioids seems to depend on the dose of the first-line opioid. A higher first-line dose may reflect a complex pain situation and have a negative impact on the success of rotation.
- There are a variety of established regimens for rotation to methadone. Regardless of the method chosen, rotation to methadone should be reserved for experienced users and carried out under clinical monitoring.
- Equianalgesic tables should serve solely to guide the determination of conversion doses.

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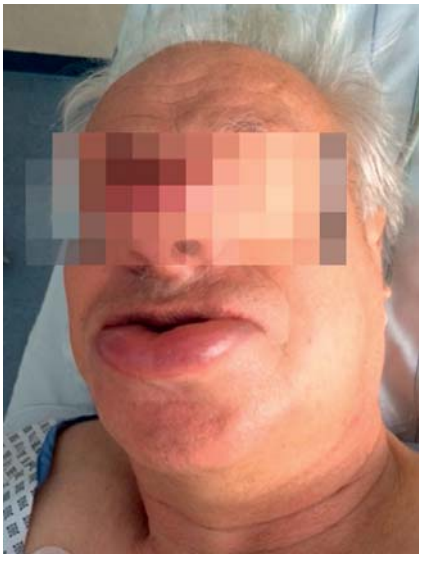
► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref0918

eTables, eFigure
www.aerzteblatt-international.de/18m0135

CLINICAL SNAPSHOT



Angioedema Two Weeks After the Initial Administration of an ACE Inhibitor

We report the case of a 76-year-old man with newly diagnosed congestive heart failure who was treated with an angiotensin-converting enzyme (ACE) inhibitor (ramipril 5 mg po bid) in accordance with existing guidelines. Two weeks after the drug was started, he was admitted to the intensive care unit with angioedema of the lower lip. Intrapharyngeal mucosal edema and glottal edema were ruled out. The ACE inhibitor was discontinued, a 250 mg bolus of prednisolone was given, and the swelling of the lower lip resolved. Angioedema induced by ACE inhibitors comes about through a bradykinin-dependent mechanism. A further therapeutic option is the administration of icatibant, a selective bradykinin B2-receptor antagonist. Our patient remained in stable condition and was not given this drug. Angioedema is an occasional side effect of ACE inhibitors and angiotensin II receptor blockers, along with irritative cough and hypokalemia. It can cause asphyxiation and death within hours. Patients should be informed of this possible side effect and should be told to telephone the emergency medical services immediately in case it arises. Angioedema can appear acutely, but it can also appear years after the drug is initially given. It arises in 0.1% to 0.7% of patients treated with ACE inhibitors.

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Supplementary material to:

Opioid Rotation in Cancer Pain Treatment

A Systematic Review

by Michael Schuster, Oliver Bayer, Florian Heid, and Rita Laufenberg-Feldmann

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eTABLE 1

Detailed search strategies

No.	Search term	n
a) MEDLINE via PubMed		
#1	Analgesics, opioid[pharmacological action] OR "analgesics, opioid"[MeSH] OR morphin*[tw] OR buprenorphin*[tw] OR fentanyl[tw] OR hydrocodon*[tw] OR hydromorphon*[tw] OR methadon*[tw] OR levomethadon*[tw] OR oxycodon*[tw] OR oxymorphon*[tw] OR tapentadol*[tw] OR opioid*[tw] OR opiat*[tw]	170 813
#2	switch*[tw] OR substitut*[tw] OR conversion*[tw] OR rotation*[tw]	723 248
#3	(chronic*[tw] OR noncancer*[tw] OR cancer*[tw]) AND pain*[tw]) OR "pain management"[MeSH]	146 355
#4	#1 AND #2 AND #3	864
#5	(#1 AND #2 AND #3) NOT (animals[MeSH] NOT humans[MeSH]) (humans only studies – Cochrane standard)	830
#6	"2010/01/01"[PDat]: "2017/01/31"[PDat]	406
b) Cochrane Library		
#1	MeSH descriptor: [analgesics, opioid] explode all trees	6076
#2	morphin* or buprenorphin* or fentanyl or hydrocodon* or hydromorphon* or methadon* or levomethadon* or oxycodon* or oxymorphon* or tapentadol* or opioid* or opiat*:ti,ab,kw (word variations were searched)	28 547
#3	switch* or substitut* or conversion* or rotation*:ti,ab,kw (word variations were searched)	24 942
#4	MeSH descriptor: [pain management] explode all trees	2458
#5	(chronic* or noncancer* or cancer*) and pain*:ti,ab,kw (word variations were searched)	19 869
#6	#1 or #2	28 547
#7	#4 or #5	21 581
#8	#6 and #3 and #7 publication year from 2010 to 2017	93
c) Hand search according to the inclusion criteria		
#1	*Pain*, *Journal of Pain*, *European Journal of Pain*, *Journal of Pain and Symptom Management*, *Clinical Journal of Pain*, *Cancer*, *Journal of Palliative Medicine*, *Palliative Medicine*, and *Der Schmerz*.	3
#2	Survey period 2010 to 2017	

eTABLE 2

Inclusion and exclusion criteria for study selection (full texts)

Inclusion criteria	
I1: Publication type	Systematic reviews; meta-analyses, randomized controlled trials, prospective observational studies
I2: Search period	1 January 2010 to 1 February 2017 (consecutive search)
I3: Language	English, German, Dutch, French, Italian, Spanish, Russian
I4: Patients	Adults ≥ 18 years
I5: Type of pain	Cancer pain with or without neuropathic pain
I6: Treatment	Regular oral or transdermal intake/application of WHO level opioids because of pain and/or opioid-associated undesired effects
Exclusion criteria	
E1	Studies on patients with chronic non-cancer pain, neuropathic pain without accompanying cancer pain, acute pain, postoperative pain; studies exclusively on treatment of breakthrough pain
E2	Studies on mixed populations with chronic cancer or non-cancer pain WITHOUT separate presentation of the findings in the group of cancer pain patients
E3	No rotation performed, or opioid-naive patients, or switch from WHO level I/II to WHO level III opioids, or change to different route of administration with same opioid
E4	Minors (<18 years), studies with healthy probands, studies on experimental pain, studies on toxicity without investigation of pain or adverse events
E5	Studies on opioid abuse or substitution therapy in opioid-dependent persons
E6	Administration other than oral or transdermal (e.g., intrathecal, neuraxial, subcutaneous, intravenous)
E7	Editorial, commentary, case report, correspondence, non-systematic/narrative review, case series n <10, retrospective analyses of databases or patients' records
E8	Other languages (not I3), e.g., Polish, Japanese, Chinese, Turkish
E9	No full text available
E10	Duplicate publication, or more recent publication available, or publication withdrawn, or date of publication outside survey period
E11	Content obsolete
E12	Observation period <14 days

eTABLE 3

Systematic reviews on opioid rotation (evidence table)

Reference	Studies and population	Intervention	Endpoints	Principal results	Study design and assessment of study quality according to AMSTAR1	Evidence level (Oxford)
Quigley (2004) Opioid switching to improve pain relief and drug tolerability (8)	**Survey period:** Up to and including January 2003 **Databases:** Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 to January 2003), EMBASE (1980 to January 2003) **Studies included:** n = 52 studies (cancer pain n = 50, non-cancer pain n = 2), including n = 14 prospective uncontrolled studies, n = 15 retrospective studies, n = 23 case reports (no. of cases 1 to 6, median 2) **Inclusion criteria (studies):** RCT (published and unpublished) **Inclusion criteria (study participants):** – Adults and children with acute or chronic pain including post-operative pain and cancer pain **Exclusion criteria (study participants):** – Studies with healthy volunteers and/or opioid treatment for experimental pain	Rotation from one opioid to another because of inadequate analgesia and or intolerable side effects, independent of treatment duration or form of administration	– **Pain and undesired effects** (measured using visual analog scales or verbal rating scales) – **Additional requirement for analgesics to cope with break-through pain** – **Patient preference** – **Quality of life** – **Global improvement**	– The majority of studies used morphine as first-line opioid; the most frequently used second-line opioid was methadone. – All studies except one concluded that opioid rotation is a clinically useful means of improving pain control and/or reducing opioid-related side effects. **Authors' conclusions:** For patients with inadequate pain control and intolerable opioid related side effects, rotation to an alternative opioid may be the only way to control the symptoms. The evidence for this is, however, largely anecdotal, based on observational and uncontrolled studies.	Systematic review of observational studies (without meta-analysis), narrative presentation of findings **9/10 AMSTAR criteria fulfilled (item 9—method of summarizing the studies—does not apply)** **The following criteria were not fulfilled:** – Study selection not definitely carried out by two independent researchers – (Data were not pooled, therefore item 9 was not assessed) **Funding:** n.s.	Level of evidence (LoE) 3a

Reference	Studies and population	Intervention	Endpoints	Principal results	Study design and assessment of study quality according to AMSTAR1	Evidence level (Oxford)
Mercadante & Bruera (2006) Opioid switching: A systematic and critical review (27)	**Survey period:** n.s. **Databases:** MEDLINE, PubMed, Cancerlit, EMBASE **Studies included:** n = 31 **Inclusion criteria (studies):** – Retrospective and prospective studies – Case series and case reports with n ≥ 10 patients **Exclusion criteria (studies):** – Letters – Case reports with n <10 patients – Comparative studies in various study arms **Inclusion/exclusion criteria (study participants):** – Adult patients with chronic cancer pain	Opioid rotation because of pain or opioid treatment-associated undesired effects	– **Success rate of rotation** – **Time to dose stabilization**	**Success rate of rotation:** Opioid rotation in patients with chronic pain and insufficient analgesia with the first-line opioid led to clinically relevant improvement in over 50% of cases. **Time to dose stabilization:** The time to dose stabilization was stated for n = 21 studies; it varied from 1 to 15 days (median 3). **Authors' conclusions:** – Opioid rotation is common practice, although the data on how it is performed are sparse. – Data on the long-term outcome of opioid rotation are lacking. – The reason for opioid rotation may influence the chosen dose of opioid. – Dose finding should not rely on a mathematical calculation but be adjusted to the individual clinical situation.	Systematic review of observational studies (without meta-analysis), narrative presentation of findings **1/10 AMSTAR criteria fulfilled (item 9 does not apply)** **The following criteria were not fulfilled:** – No reference to an a priori study protocol – Studies not selected by more than one person – No detailed depiction of search strategy: only individual search terms reported – No data on relevance of publication status for inclusion of studies – Only included studies listed (no details of excluded studies given) – Scientific quality of included studies not assessed and documented – Quality of included studies not adequately covered in Discussion – (Data were not pooled, therefore item 9 was not assessed) – Possible publication bias not explored – Potential conflicts of interest for the individual studies not presented **Funding**: n.s.	LoE 3a

Reference	Studies and population	Intervention	Endpoints	Principal results	Study design and assessment of study quality according to AMSTAR1	Evidence level (Oxford)
Dale et al. (2011) European Palliative Care Research Collaborative Pain Guidelines: opioid switching to improve analgesia or reduce side effects. A systematic review (10)	**Survey period:** 1 January 2003 to January 2010 **Databases:** PubMed (including MEDLINE), EMBASE via OvidSP, Cochrane Central Register of Controlled Trials (CENTRAL) **Studies included:** n = 11 uncontrolled prospective studies (including 2 multicenter, 9 single-center studies), no RCT **Inclusion criteria (studies):** – Prospective studies published in English **Exclusion criteria (studies):** – Case reports and retrospective studies **Inclusion/exclusion criteria (study participants):** n.s.	Opioid rotation because of imbalance between pain and/or undesired effects during treatment with WHO level III opioids	– **Pain intensity** (measured using visual or verbal analog scales) – **Undesired effects** – **Success rate of rotation** – **Time to dose stabilization**	The studies' observation periods varied from 4 d to 4 w (28 d). n = 10 studies stated the morphine equivalent dose before rotation (including n = 3 studies with MEDD <100 mg/d; in no study was the initial MEDD >485 mg/d). **Pain intensity** (stated in n = 11 studies): Inconsistent measurement instrument; n = 7 studies stated pain reduction of >3 points on an 11-point scale. **Undesired effects** (stated in n = 11 studies): Inconsistent statement of the nature, frequency, and measurement of side effects during and after rotation and among the studies; the most commonly occurring side effects were sedation, nausea, vomiting, and obstipation. **Success rate of rotation** (stated in n = 3 studies): Inconsistent criteria used; success rates varying between 50 and 80% reported. **Time to dose stabilization** (stated in n = 3 studies): Varying between 2 and 5 days. **Authors' conclusions:** – Opioid rotation may be helpful for some patients, but robust evidence is lacking. – It is unclear (because not investigated) whether increasing the dose of the first-line opioid would have been an appropriate alternative to rotation in the studies concerned. – The success rates of rotation may depend on the dose of the first-line opioid. – The duration of the observation period should be at least 14 d.	Systematic review of observational studies (without meta-analysis), narrative presentation of findings **6/10 AMSTAR criteria fulfilled (item 9 does not apply)** **The following criteria were not fulfilled:** – No reference to an a priori study protocol – No data on relevance of publication status for inclusion of studies – Only included studies listed (reasons for exclusion are reported in detail, but the excluded studies are not listed) – (Data were not pooled, therefore item 9 was not assessed) – Potential conflicts of interest for the individual studies not presented **Strengths:** – GRADE method used to evaluate the studies **Funding:** Partly supported by the European Palliative Care Research Collaboration (EPCRC) in the context of the 6th Framework Programme of the EU Commission (contract no. LSHC-CT-2006-037777)	LoE 3a

Reference	Studies and population	Intervention	Endpoints	Principal results	Study design and assessment of study quality according to AMSTAR1	Evidence level (Oxford)
Mercadante & Caraceni (2011) Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review (9)	**Survey period:** Up to 31 December 2009 **Databases:** MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) **Studies included:** n = 31 **Inclusion criteria (studies):** – prospective studies published in English – Statement of conversion ratio **Exclusion criteria (studies):** – Case series with n < 10 patients – Comparative parallel group trials **Inclusion criteria (study participants):** – Adults with chronic cancer pain **Exclusion criteria (study participants):** n.s.	Opioid rotation between oral or transdermal WHO level III opioid on grounds of (a) convenience, i.e., with pain already controlled by existing opioid treatment, or (b) uncontrolled pain or undesired effects on current opioid treatment	– **Initial and final conversion ratio** – **Initial and final morphine equivalent dose**	**Initial and final conversion ratio:** From and to buprenorphine: – Covered in 2 studies (n = 33) TDfe : TDbu 1 : 1.3 initial and final; in 1 study (n = 32), dependence on direction of rotation mentioned: TDfe > TDbu 1 : 0.7, TDbu:TDfe 2.8:1 – Covered in 1 study (n = 11) ORmo : TDbu 75 : 1 initial and final From and to hydromorphone: – Most often mentioned ORmo : ORhm 5 : 1 (4 : 1 to 8 : 1) – 1 study (n=85) described dose increase in 27% of cases at 5 : 1; 1 study (n = 239) described dose increase in 54% at 8 : 1 From and to fentanyl TD: – Most frequently ORmo: TDfe 100 : 1 – In 1 study (n = 38) dose escalation was described in 58%, final ratio 70 : 1; in another study (n = 312) dose escalation in the 1st week after rotation, no final ratio stated From and to oxycodone: – Most often mentioned: initial ORmo : ORox 1.5 : 1 (1.8 to 1.3 : 1) – Final ratio 1 : 1 to 1.5 : 1 From and to methadone: – Initial ratio MED:ORme between 4 : 1 and 12 : 1 (the higher the initial MED, the greater the ratio) – Final ratio 2 : 1 to 15 : 1 **Authors' conclusions:** – The reason for rotation, whether for convenience or due to an uncontrolled situation, has a major impact on the conversion ratio – Rotation to methadone requires great caution – On the basis of the existing prospective studies, it seems that the conversion ratios for hydromorphone, morphine, oxycodone, buprenorphine TD and fentanyl TD can be predicted accurately if the dose of the first-line opioid is low	Systematic review of observational studies (without meta-analysis), narrative presentation of findings **4/10 AMSTAR criteria fulfilled (item 9 does not apply)** **The following criteria were not fulfilled:** – No reference to an a priori study protocol – Study selection not definitely carried out by more than one person – No data on relevance of publication status for inclusion of studies – Only included studies listed (reasons for exclusion are reported in detail, but the excluded studies are not listed) – Possible publication bias not explored – (Data were not pooled, therefore item 9 was not assessed) – Potential conflicts of interest for the individual studies not presented **Strengths**: – GRADE method used to evaluate the studies **Funding:** Partly supported by the European Palliative Care Research Collaboration (EPCRC) in the context of the 6th Framework Programme of the EU Commission (contract no. LSHC-CT-2006-037777)	LoE 3a

Reference	Studies and population	Intervention	Endpoints	Principal results	Study design and assessment of study quality according to AMSTAR1	Evidence level (Oxford)
McLean et al. (2015) Methods of rotation from another strong opioid to methadone for the management of cancer pain: a systematic review of the available evidence (17)	**Survey period:** MEDLINE to week 12/2012, EMBASE/PsycINFO/CINAHL to week 31/2014 **Databases:** MEDLINE, EMBASE, PsycINFO, CINAHL **Studies included:** n = 25 **Inclusion criteria (studies):** – RCT, cohort studies, case series, case reports published in English – Clear description of method of opioid rotation and clinical outcome after rotation **Exclusion criteria (studies):** – Abstracts without full text, review articles – Rotation FROM methadone TO other opioids – Studies with establishment of equianalgesic ratio as primary endpoint **Inclusion criteria (study participants):** – Adults with chronic cancer pain **Exclusion criteria (study participants):** n.s.	Opioid rotation from WHO level III opioids to methadone because of suboptimal pain control or AE in adult patients with chronic cancer pain during oral or transdermal treatment with WHO level III opioids	– **Pain intensity** (VAS/NRS) – **Success of rotation** (clinical or statistical amelioration of pain intensity, side effects, or both)	**Three-day switch method (3DS):** 1 RCT, 1 prospective study, 1 case report (total n = 80; 4 dropouts): rotation described as successful in 55/80 cases; AE (mild sedation) in n = 37 **Rapid conversion method (RC):** 1 RCT, 10 case series (7 prospective, 3 retrospective) (total n = 782; 219 dropouts): rotation successful in 561/782 cases (71.2%), ADR in n = 58 (33 sedation, 3 respiratory depression, 19 unspecified) **Ad libitum method (AL):** 1 prospective study, 8 retrospective case series or case reports (total n = 264; 22 dropouts): rotation successful in 245/264 cases (92.8%) **German method:** 1 case series, 1 case report (total n = 53; 8 dropouts): rotation successful in 45/53 cases **Outpatient method:** 1 retrospective case series (n = 29; 11 dropouts): ADR in 20/29 cases **Authors' conclusions:** 3DS and AL seem effective despite the low level of evidence. The RC method appears to offer no advantage over 3DS and AL and may lead to more ADR. Because of the generally high risk of ADR in the context of rotation, whatever method is used the patients should be monitored closely during the first few days of rotation.	Systematic review of observational studies (without meta-analysis), narrative presentation of findings **8/10 AMSTAR criteria fulfilled (item 9 does not apply)** **The following criteria were not fulfilled:** – Only included studies listed (reasons for exclusion are reported in detail, but the excluded studies are not listed) – (Data were not pooled, therefore item 9 was not assessed) – Potential conflicts of interest for the individual studies not presented **Strengths:** – Quality assessment by means of the Edwards Methods Score **Funding:** MSc Programme in Palliative Care, King's College London (supported by the Irish Hospice Foundation and the Ciaran Maree Scholarship Fund); according to the authors, no conflicts of interest	LoE 3a

ADR = Adverse drug reactions, AE = adverse events, AMSTAR = A MeaSurement Tool to Assess systematic Reviews, bu = buprenorphine, d = day, fe = fentanyl, hm = hydromorphone, LoE = level of evidence, me = methadone, NRS = numeric rating scale, OR = oral, ox = oxycodone, RCT = randomized controlled trials, TD = transdermal, VAS = visual analogue scale, VRS = verbal rating scale, w = weeks

eTABLE 4

Overview of the excluded publications

Study	Exclusion criterion	Reason for exclusion
Afsharimani et al., 2015 [e8]	A7	Non-systematic/narrative review
Agbalaka et al., 2012 [e9]	E3	Mostly WHO level II opioids included, no separate presentation of results for WHO level III opioids
Argoff et al., 2015 [e10]	E1	Non-cancer pain
Baron et al., 2016 [e11]	E7	Non-systematic/narrative review
Berland et al., 2013 [e12]	E1	Non-cancer pain
		Retrospective analysis
Bradley et al., 2013 [e13]	E7	Non-systematic/narrative review
Broglio et al., 2016 [e14]	E1	Non-cancer pain
Bruera & Paice, 2015 [e15]	E7	Non-systematic/narrative review
Coluzzi & Mattia, 2010 [e16]	E7	Non-systematic/narrative review
Gatti et al., 2010 [e17]	E2	Mixed patient population with no separate presentation of results for cancer pain patients
Gonzalez-Barboteo et al., 2010 [e18]	E7	Non-systematic/narrative review
Gonzalez-Barboteo et al., 2014 [e19]	E12	Observation period <14 days
Hanaoka et al., 2011 [e20]	E8	Article in Japanese
Ikeda et al., 2012 [e21]	E8	Article in Japanese
Kanbayashi et al., 2011 [e22]	E7	Retrospective analysis
Kern et al., 2014 [e23]	E2	Mixed patient population with no separate presentation of results for cancer pain patients
Khojasteh et al., 2012 [e24]	E10	Date of publication outside survey period
Kim et al., 2015 [e25]	E12	Observation period <14 days
Lawlor et al., 2012 [e26]	E9	No full text available
Leppert, 2010 [e27]	E7	Non-systematic/narrative review
McNamara, 2012 [e28]	E10	Date of publication outside survey period
Mercadante, 2013 [e29]	E7	Non-systematic/narrative review
Mercadante, 2013 [e30]	E12	Observation period <14 days
Mercadante et al., 2012 [e31]	E6	Administration other than oral or transdermal
Mücke et al., 2016 [e32]	E2	Mixed patient population with no separate presentation of results for cancer pain patients
Ravera et al., 2011 [e33]	E2	Mixed patient population with no separate presentation of results for cancer pain patients
Rhondali et al., 2013 [e34]	E7	Retrospective analysis
Riley et al., 2015 [e35]	E3	No rotation according to inclusion criteria
Roberto et al., 2017 [e36]	E3	No rotation according to inclusion criteria
Roland et al., 2011 [e37]	E1	Non-cancer pain
Schwittay et al., 2012 [e38]	E2	Mixed patient population with no separate presentation of results for cancer pain patients
Schwittay et al., 2013 [e39]	E2	Mixed patient population with no separate presentation of results for cancer pain patients
Sittl, 2017 [e40]	E10	Date of publication outside survey period
Trescot, 2010 [e41]	E7	Non-systematic/narrative review
Vissers et al., 2010 [e42]	E7	Non-systematic/narrative review
Wahle et al., 2013 [e43]	E1	Non-cancer pain
Wallace et al., 2012 [e44]	E10	Date of publication outside survey period
Webster et al., 2011 [e45]	E1	Non-cancer pain
Webster et al., 2016 [e46]	E1	Non-cancer pain

eTABLE 5a

Randomized controlled clinical trials on opioid rotation (evidence table)

Study (author, year of publication)	Population	Intervention			Endpoints	Follow-up	Principal results	Study design and assessment according to Cochrane Risk of Bias Tool (RoB)*[1]	Level of evidence
		First-line opioid	Second-line opioid	Indication for rotation					
Imanaka et al., 2014 (18)	n = 100	Morphine, oxycodone, fentanyl	Tapentadol, morphine	C	– Efficacy = after 7 days, increase in pain by max. ≥ 1.5 points (on 11-point NRS) and max. two rescue doses/d for BTP episodes – Occurrence of AE (clinical assessment) – PGIC score (7-point VRS for evaluation of pain reduction)	8 w	**Pain:** Baseline pain (NRS): tapentadol group 1.5/10 (SD 1.11); morphine group 1.8/10 (SD 1.14); mean daily breakthrough pain always stayed ≤ 2/10; pain control: 42/50 patients in the tapentadol group achieved pain control after 7 days. **Opioid dosage:** In the tapentadol group, the dose was increased in n = 14/50 (28%) in week 1 and in n = 29/50 (58%) by week 8 (mean tapentadol DD in week 1: 147.6 mg (SD 91.06); mean DD over the 8-week period: 173.5 mg (SD 101.5). **Adverse events:** n = 45/50 (tapentadol) and n = 47/50 (morphine) reported at least 1 AE within the 8-week period. Gastrointestinal side effects occurred less often in the tapentadol group (38% vs. 54% for morphine) **Loss to follow-up:** 43/100 (43%)	Single center (phase III, open label) **High risk of bias:** Blinding of study participants and personnel; blinding for endpoint documentation; incomplete data on endpoints; selective reporting of endpoints **Low risk:** Generation of randomization sequence **Unclear risk:** Concealed group allocation; other sources of bias	LoE 2b
Moksnes et al., 2011 (19)*[2]	n = 42 (outpatients and inpatients)	Morphine, oxycodone	Methadone	P, AE	– Pain intensity (11-point NRS) – Interference (BPI) – Cognitive impairment (MMSE) – Severity of AE (ESAS) – QTc time (ECG)	14 d	**Pain:** Mean daily pain (NRS) SAG vs. 3DS: day 0: 4.6/10 vs. 4.7/10; day 3: 4.1/10 vs. 3.6/10; day 14: 4.9/10 vs. 2.8/10 ≥ patients of the 3DS group had less pain **Opioid dosage:** The final methadone DD was estimated as lower than pre-switch (SAG: 65 vs. 80 mg; 3DS: 90 vs. 106 mg); patients with <600 mg MEDD tended to need less methadone than estimated, patients with >600 mg MEDD more than estimated. The methadone dose on day 14 was closely correlated with the pre-switch morphine dose **Adverse events:** No significant difference with regard to frequency or reduction **Loss to follow-up:** 14/42 (33%)	Multicenter (phase II, open label) **High risk of bias:** Blinding of study participants and personnel; blinding for endpoint documentation; incomplete data on endpoints **Low risk:** Generation of randomization sequence; concealed group allocation **Unclear risk:** Selective reporting of endpoints; other sources of bias	LoE 2b

Study (author, year of publication)	Population	Intervention			Endpoints	Follow-up	Principal results	Study design and assessment according to Cochrane Risk of Bias Tool (RoB)*1	Level of evidence
		First-line opioid	Second-line opioid	Indication for rotation					
Poulain et al., 2016 (20)	n = 146 (inpatients)	Oxycodone, fentanyl, morphine, hydro-morphone	Methadone	P, AE	– Rotation success = pain reduction on day 4 of at least 2 points (NRS) **and** <5/10 (NRS) – BTP frequency – Overdosing (bradypnea <8/min, Rudkin scale ≥ 3) – Severity of AE (3-point VRS) – Withdrawal symptoms (Handelsman score) – QTc time (ECG)	2 m	A = SAG, B = progressive **Rotation success:** 44% (A); 37.5% (B) **Pain:** Median pain (NRS) in group A 5.6/10, B 6.2/10. Subjectively adequate analgesia in 45% overall (median after 3 days), 40.8% in group A, and 49.3% in group B; time to attain adequate analgesia 4.6 days (A) vs. 3.4 days (B); BTP episodes dropped from 4 to 2 per day on day 3 and remained stable until day 56. **Opioid dosage:** the median single dose was almost identical in groups A and B and remained nearly constant from day 0 to day 56: group A 19.7 mg (4–98), group B 18.3 mg (4–67). The median total dose was higher in group A (1400 mg) than in group B (1100 mg). **Adverse events:** Similar incidence in the two group: 25.4% (A) vs. 32.9% (B) **Loss to follow-up:** 71/144 (49%)	Multicentric (phase IIb, open label) **High risk of bias:** Blinding of study participants and personnel; blinding for endpoint documentation; incomplete data on endpoints **Low risk:** Selective reporting of endpoints **Unclear risk:** Generation of randomization sequence; concealed group allocation; other sources of bias	LoE 2b
Slatkin et al., 2010 (21)	n = 80 (follow-up studies)	Morphine, oxycodone	Oxymorphone	C	– Pain intensity (11-point VAS) – Analgesic efficacy (BPI-SF) – Patient satisfaction (5-point VRS) – Severity of AE (3-point VRS)	52 w	**Pain:** Average pain (NRS) remained stable: initial 3.05/10 (SD 1.96), final 3.59/10 (SD 2.11) **Opioid dosage:** To attain adequate analgesia it was necessary to increase the dosage over the observation period: initial MEDD 91.9 mg (SD 9.8), final MEDD 129.2 mg (SD 18.2) **Adverse events:** n = 74 (92.5%) experienced at least one treatment-associated AE **Loss to follow-up:** 54/80 (68%)	Pooled long-term follow-up of two randomized crossover studies, multicentric No assessment with RoB tool possible	LoE 2b

*1 The Cochrane Risk of Bias Tool comprises seven domains, for each of which the risk of bias is estimated as high, low, or unclear.
*2 The study by Moksnes et al., 2011 is included in the review by McLean et al., 2015 (23).
AE = adverse events, BPI/BPI-SF= Brief Pain Inventory (SF=short form), BTP= break-through pain, C = convenience, CTCAE = Common Terminology Criteria for Adverse Events version 3.0, d = day(s), DD = daily dose, ER = extended release, ESAS = Edmonton Symptom Assessment System, ESS = Epworth Sleepiness Scale, IR = immediate release, LoE = level of evidence (Oxford System), m = months, MEDD = morphine-equivalent daily dose, MMSE = Mini-Mental-State Examination, NRS = numeric rating scale, OPI = overall pain interference, OTS = overall toxicity score , P = pain, PGIC = patient global impression of change, SAG = stop and go, VAS = visual analog scale, VRS = verbal rating scale, w = weeks, 3DS = 3-day switch

eTABLE 5b

Prospective observational studies on opioid rotation (evidence table)

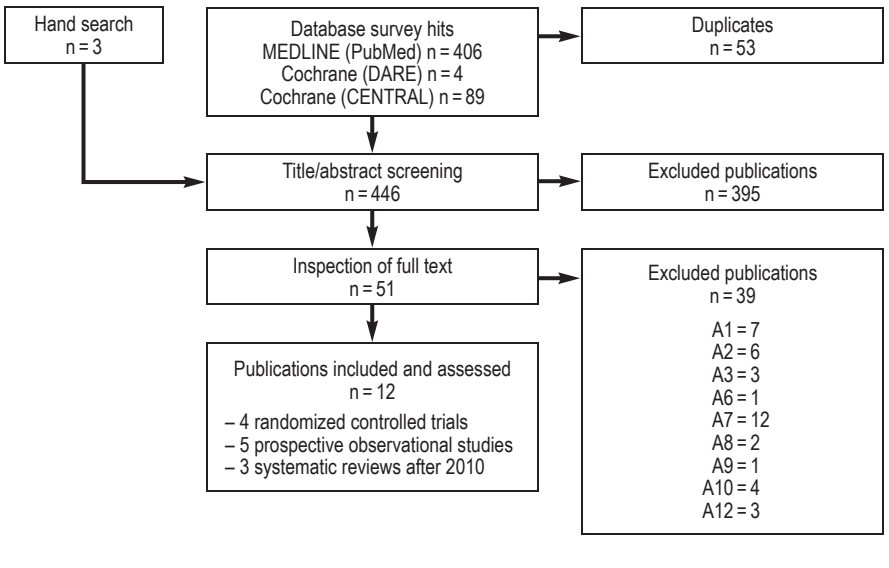
Study (author, year of publication)	Population	Intervention			Endpoints	Follow-up	Principal results	Study design and assessment according to Cochrane Risk of Bias Tool (RoB)*[1]	Evidence level
		First-line opioid	Second-line opioid	Indication for rotation					
Lee et al., 2012 (22)	n = 114	Oxycodone	Hydromorphone	P	– Efficacy = decrease in frequency of BTP requiring rescue medication between day 0 and day 14 – Subjective efficacy (5-point VRS) – Pain intensity (11-point NRS) – Interference, quality of life (BPI, EORTC QLQ-C30) – Pain reduction (percentage) – Occurrence of AE	14 d	**Pain:** Efficacy: BTP frequency decreased from 3.67/day (day 0) to 2.44/day (day 14); BTP medication decreased from 2.93 ×/day (day 0) to 2.00 ×/day (day 14); average daily pain (NRS): 11% decrease (from 3.6/10 to 3.0/10); 15.3% of the patients showed >50% pain reduction on day 14 vs. day 0. Satisfaction after rotation: 60% **Opioid dosage:** Increase from 27.9 mg (day 0) to 41.1 mg (day 14) **Adverse events:** Found in 93% of the patients (confusion, somnolence, obstipation) **Loss to follow-up:** 16/114 (14%)	Prospective cohort study (phase IV, open label) Multicentric No control group **MINORS score: 14/16**	LoE 4
Lundorff et al., 2013 (23)	n = 18 (inpatients)	Unspecified WHO level III opioids	Buprenorphine	AE	– Pain intensity (11-point NRS) – Pain reduction (5-point VRS) – Pain-related sleep disturbance (11-point NRS) – Interference, quality of life (BPI, EORTC QLQ-C30) – Occurrence of AE (clinical symptoms)	26 +/- 2 d	**Pain:** Median pain (NRS) 3/10 (day 0) vs. 2/10 (day 26+/-2) **Opioid dosage:** Increase in 9/13 patients **Adverse events:** No differences before/after rotation **Other:** No differences regarding sleep, interference, quality of life **Loss to follow-up:** 5/18 (28%)	Prospective cohort study Multicentric No control group **MINORS score: 11/16**	LoE 4
Mercadante et al., 2014 (24)	n = 30 (outpatients and inpatients)	Morphine, hydromorphone, fentanyl	Tapentadol	P, AE, C	– Pain intensity (11-point NRS) – Severity of AE (4-point NRS, distress score) – Tapentadol escalation index (TP maximal dose – TP starting dose/day)	4 w	**Pain:** Average daily pain (NRS):decrease from 5/10 (day 0) to 2.6/10 (week 4) **Opioid dosage:** Pre-switch MEDD 112.2 mg (+/-57.4), initial tapentadol DD 343.3 mg (+/-150.1); final tapentadol DD 427 mg (+/-178) (= increase by factor of 1,25 from initial dose). **Loss to follow-up:** 10/30 (33%)	Prospective cohort study Single center No control group **MINORS score: 11/16**	LoE 4

Study (author, year of publication)	Population	Intervention			Endpoints	Follow-up	Principal results	Study design and assessment according to Cochrane Risk of Bias Tool (RoB)*1	Evidence level
		First-line opioid	Second-line opioid	Indication for rotation					
Minami et al., 2014 (25)	n = 50 (inpatients)	Oxycodone	Fentanyl	C	– Pain intensity (11-point NRS) – Frequency of BTP requiring rescue medication – Severity of AE (4-point NRS, ESS, defecation frequency) – Global satisfaction (5-point VRS)	15 d	**Pain:** No difference before/after rotation; NRS >3 in 6/8/6 patients (day 0/7/15) **Opioid dosage:** On average the fentanyl dose had to be increased only slightly after rotation (from 13.7+/-4.8 µg/h to 15.5+/-6.0 µg/h [day 15]); **Adverse events:** Fatigue significantly reduced, remaining AE comparable **Other:** Satisfaction improved: 43% (day 0), 63% (day 7), 61% (day 15) **Loss to follow-up:** 1/50 (2%)	Prospective cohort study Two centers No control group **MINORS score: 14/16**	LoE 4
Porta-Sales et al., 2016 (26)	n=145 (outpatients)	Fentanyl, morphine, oxycodone, buprenorphine (+ n=2 others)	Methadone	P, AE	– Efficacy = decrease of median strongest pain – Pain intensity (11-point VRS) – Interference (BPI, OPI) – Occurrence of (CTCAE, 11-point OTS) – Frequency of BTP requiring rescue medication	28 d	**Pain:** Efficacy: Median strongest pain (VRS) decreased from 9 (8–10) to 6 (3–8) between day 0 and day 28. Median average pain (VRS) decreased from 6 (5–7) to 4 (2–5) between day 0 and day 28; 56% of the patients reported a 30% reduction in pain on day 28, 41% a reduction of over 50-%. **Opioid dosage:** Mean MEDD before rotation 193.7 mg (SD 127.4); mean methadone DD after rotation 24.2 mg (SD 9.5), mean final conversion ratio 8:1 **Loss to follow-up:** 90/145 (62%)	Prospective cohort study Multicentric No control group **MINORS score: 12/16**	LoE 4

*1 The Cochrane Risk of Bias Tool comprises seven domains, for each of which the risk of bias is estimated as high, low, or unclear.

AE = adverse events, BPI/BPI-SF= Brief Pain Inventory (SF=short form), BTP= break-through pain, C = convenience, CTCAE = Common Terminology Criteria for Adverse Events version 3.0, d = day(s), DD = daily dose, ER = extended release, ESAS = Edmonton Symptom Assessment System, ESS = Epworth Sleepiness Scale, IR = immediate release, LoE = level of evidence (Oxford System), MEDD = morphine-equivalent daily dose, MMSE = Mini-Mental-State Examination, NRS = numeric rating scale, OPI = overall pain interference, OTS = overall toxicity score , P = pain, PGIC = patient global impression of change, SAG = stop and go, VAS = visual analog scale, VRS = verbal rating scale, w = weeks, 3DS = 3-day switch

eFIGURE



Flow chart of literature survey