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How to switch from morphine or oxycodone to methadone in cancer patients? A randomised clinical phase II trial

K. Moksnes [a,*], O. Dale [a,b], J.H. Rosland [c,d], Ø. Paulsen [a,e], P. Klepstad [a,b], S. Kaasa [a,f]

[a] Pain and Palliation Research Group, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), NO-7006 Trondheim, Norway
[b] Department of Anaesthesiology and Emergency Medicine, St. Olav's University Hospital, NO-7006 Trondheim, Norway
[c] Sunniva Clinic for Palliative Care, Haraldsplass Deaconess Hospital, NO-5009 Bergen, Norway
[d] Department of Surgical Sciences, Faculty of Medicine, University of Bergen, NO-5009 Bergen, Norway
[e] Department of Medicine, Palliative Medical Unit, Telemark Hospital, NO-3710 Skien, Norway
[f] Department of Oncology, St. Olav's University Hospital, NO-7006 Trondheim, Norway

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ABSTRACT

Aim: Opioid switching is a treatment strategy in cancer patients with unacceptable pain and/or adverse effects (AEs). We investigated whether patients switched to methadone by the stop and go (SAG) strategy have lower pain intensity (PI) than the patients switched over three days (3DS), and whether the SAG strategy is as safe as the 3DS strategy.
Methods: In this prospective, open, parallel-group, multicentre study, 42 cancer patients on morphine or oxycodone were randomised to the SAG or 3DS switching-strategy to methadone. The methadone dose was calculated using a dose-dependent ratio. PI, AEs and serious adverse events (SAEs) were recorded daily for 14 days. Primary outcome was average PI day 3. Secondary outcomes were PI now and AEs day 3 and 14 and number of SAEs.
Results: Twenty one patients were randomised to each group, 16 (SAG) and 19 (3DS) patients received methadone. The mean preswitch morphine doses were 900 mg/day in SAG and 1330 mg/day in 3DS. No differences between groups were found in mean average PI day 3 (mean difference 0.5 (CI −1.2–2.2); SAG 4.1 (CI 2.3–5.9) and 3DS 3.6 (CI 2.9–4.3) or in PI now. The SAG group had more dropouts and three SAEs (two deaths and one severe sedation). No SAEs were observed in the 3DS group.
Conclusion: The SAG patients reported a trend of more pain, had significantly more dropouts and three SAEs, which indicate that the SAG strategy should not replace the 3DS when switching from high doses of morphine or oxycodone to methadone.

1. Introduction

Pain is a prevalent symptom in cancer patients.[1,2] Opioids may provide pain control in 85–90% of these patients,[3] still a large number of cancer patients have unacceptable high pain intensity.[2,4] A change of route or a switch to another opioid have been recommended to improve pain and/or opioid related adverse effects (AEs).[5,6]

Despite the low level of evidence, opioid switching is recommended by experts,[5,7] as well as by major textbooks on cancer pain.[8,9] The rationale behind the opioid switch is not fully understood. However, pharmacogenetic variability,

* *Corresponding author:* Address: Pain and Palliation Research Group, Department of Circulation and Medical Imaging, St. Olav's University Hospital, Bevegelsessenteret 3 etg., NO-7006 Trondheim, Norway. Tel.: +47 99 22 66 74; fax: +47 72 82 60 28.
E-mail address: kristin.moksnes@ntnu.no (K. Moksnes).
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pharmacodynamic and pharmacokinetic factors such as incomplete cross-tolerance to the analgesic effect amongst opioid agonists or the metabolic clearance of the previous toxic opioid with AE resolution may contribute.[10–12] Whilst opioid switching is generally recognised, there are several unresolved questions; which opioid to use?, what is the optimal switching strategy? and which equianalgesic dosage should be applied?

Methadone is the most commonly applied secondary opioid.[13,14] It has no active metabolites, high oral bioavailability and its elimination is largely independent of renal function. Dosing may be challenging due to a long terminal half-life (13–50 h),[15,16] potential drug-drug interactions and the risk of arrhythmia.

The dominating switching strategies are the 'stop and go' (SAG) where the current opioid is immediately replaced by methadone[17–21] and the '3-days switch' (3DS) where the dose of the current opioid is reduced stepwise by 1/3 every day and substituted with 1/3 of the equianalgesic dose of methadone over three days.[22–24] The 3DS is the standard approach as it may avoid methadone accumulation and toxicity, especially in patients on high doses.[23,25] SAG has been proposed to be safe, and more effective than 3DS.[18] Advocates for SAG argue that a rapid switch gives faster onset of analgesia and reduction of AEs.[18]

Several equianalgesic conversion ratios for morphine and methadone have been proposed and found effective such as a fixed 5:1 ratio,[19,26] or dose-dependent ratios ranging from 1:1 to 20:1.[23,27,28] However, no randomised trials on opioid switching to methadone have been published[13,29]. The studies have primarily been done in patients receiving less than 350 mg morphine limiting their validity for advanced, frail cancer patients who are switched from 800 to 1500 mg morphine equivalence doses.

In order to evaluate the effect and safety of the SAG strategy compared to the standard 3DS when switching from morphine or oxycodone to methadone in cancer patients, a randomised study was conducted with the following hypotheses: Patients allocated to the SAG strategy have lower PI than the 3DS patient's day 3, and SAG is as safe as 3DS.

2. Patients and methods

2.1. Trial design, randomisation and masking

This was a prospective, open, parallel group, multicentre randomised controlled phase II trial. The randomisation (central telephone) was stratified by hospital (block size of two) and allocation was concealed until interventions were assigned. Observation time was 14 days. The Regional Committee for Medical Research Ethics approved the study and it was conducted according to the Helsinki declaration. Informed and written consent was obtained. This trial is registered in ClinicalTrials.gov id: NCT0014496.

2.2. Patients and setting

Cancer patients >18 years, treated with morphine or oxycodone (>1 week) and having increasing pain considered to be untreatable with further opioid titration and/or having opioid related adverse effects were eligible. In- and out-patients (if observed by next of kin) were recruited from four hospitals in Norway; Telemark Hospital, Haraldsplass Deaconess Hospital, Kristiansund Hospital and St. Olav's University Hospital.

2.3. Switching procedure

In SAG patients the current morning opioid dose was replaced by an estimated equianalgesic dose of methadone at day 1 (Fig. 1). In 3DS patients, the current opioid dose was reduced by 1/3 and substituted with 1/3 of an equianalgesic dose of methadone each day and then discontinued from day 3 (Fig. 1). Racemic methadone was administered every eight hours as capsules or mixture (10, 20, 50 and 100 mg produced by St. Olav's Hospital Pharmacy). No titration was recommended until day 5 (4 days after the switch). The rescue dose

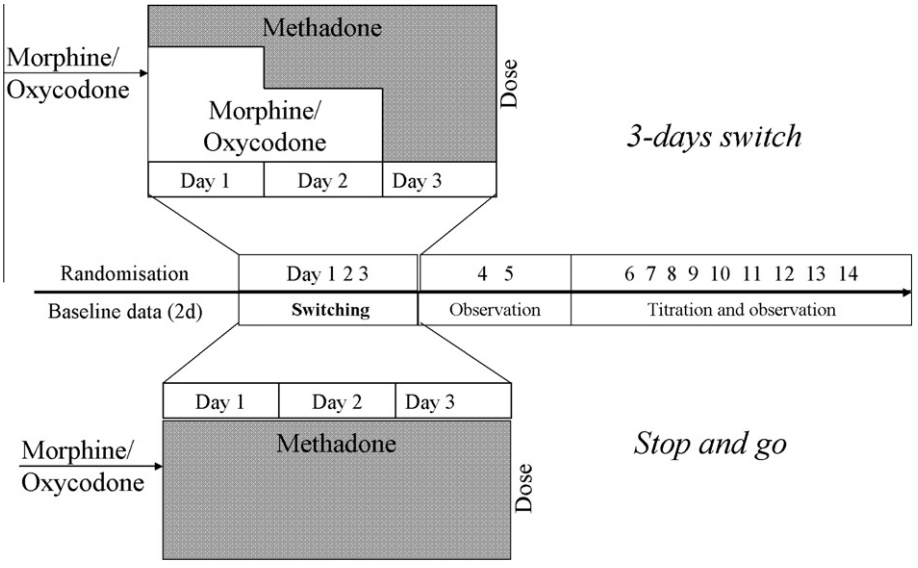

Fig. 1 – Study design. Note that day 1 is the day of the switch.

was 1/6 of the baseline opioid dose. Adjuvant non-opioid analgesics and anti-cancer treatment were maintained stabile.

The methadone dose was calculated from the oral morphine equivalent dose (last 24 h, including mean rescue dose last 48 h) using a dose-dependent conversion ratio (Table 1). (For conversion: parenteral morphine: oral morphine = 1:3 and oral oxycodone: oral morphine = 1:2).

2.4. Data collection

Patient demographics and clinical characteristics were recorded by the physician/investigator at baseline. Opioid dose changes and use of rescue were recorded daily.

Patients reported average pain intensity (PI) last 24 h and PI now before 12 am at baseline, day 3 and 14 on a numerical rating scale (NRS, 0 = no pain and 10 = worst pain imaginable) using the brief pain inventory (BPI).[30] AEs (nausea, drowsiness, loss of appetite and dry mouth) today were recorded daily (NRS 0–10) before 12 am using a Norwegian version of the Edmonton Symptom Assessment System (ESAS).[31]

The Mini Mental State Examination (MMSE) was used to assess cognitive function at baseline and day 3. Three electrocardiograms (ECG) were obtained to supervise QT-prolongation (baseline, between day 4–7 (same dose $\geqslant$2 days) and day 14). The preswitch rate-corrected QT_c-interval (Bazett formula) estimated by the physician had to be <480 ms for patients not at-risk and <460 ms for patients at-risk of arrhythmia before methadone was introduced. Patients with QT_c-intervals above these values at inclusion or who reached a QT_c-interval >500 ms after the switch were excluded.

2.5. Statistics and outcomes

The trial was initially designed to detect a difference of two days to achieve pain relief ($\leqslant$4 (NRS 0–10)), and sample size calculations were made accordingly. However, it was subsequently decided to make assessments only at baseline, day 3 and 14, with the primary outcome being average PI day 3 with pain now, drowsiness, nausea, loss of appetite and dry mouth day 3 and 14 as secondary outcomes. We placed emphasis on estimation of effects, with the uncertainty due to sample size being made explicit by wide confidence intervals, rather than *p*-values which could be misleading because of the possible type II errors.

All data are reported as means, 95% confidence intervals (CI), ranges, medians or frequencies (*N* (%)) as appropriate. Spearman's correlation (*r*) was used to compare the preswitch morphine: methadone doses and ratios with the final doses and ratios. Statistical software SPSS 17.0 was used in all analysis.

3. Results

3.1. Patients

Forty-two patients were randomised from June 2004 to March 2008, 21 to each group (CONSORT flowchart Fig. 2). The two study groups had similar patients' characteristics (Table 2) except time on WHO step 3 opioids (SAG mean 9.1 months and 3DS 23.6 months, mean difference 14.4 (CI −26.6 to −2.3)). Both groups had high mean preswitch equianalgesic morphine doses; SAG 900 mg/day (CI 650–1150) and 3DS 1330 mg/day (CI 820–1840).

More SAG patients dropped out of the study than 3DS patients (11 versus 3, respectively, RR = 3.3 (CI 1.1–8.5)). Three of the dropouts in SAG were SAEs (2 died and 1 severely sedated), none in the 3DS group. The number needed to harm (NNH) in the SAG group was seven; which means that every seventh patient will experience a SAE. Dropout reasons are shown in Table 3.

3.2. Pain and adverse effects

No differences were found between groups in means of average PI day 3 (mean difference 0.5, CI −1.2–2.2) as shown in Table 4. The 3DS reported a clinically significant lower average PI than SAG with mean difference of 2.1 (CI −0.8–5.0) at day 14 and the SAG group reported a trend of increasing pain during the 14 days.

The secondary outcomes; mean PI now and mean AEs day 3 and 14 showed no significant differences between group means (Table 4). All mean AE scores were below four from baseline through day 14 in both groups, and no group had a clinically significant reduction of AEs. The mean differences between groups day 3 were for drowsiness 0.0 (CI −1.3–1.6), for nausea 0.1 (CI −1.0–1.0), for loss of appetite 1.2 (CI −1.1–3.5) and for dry mouth 0.6 (CI −1.2–2.3) (Table 4).

3.3. The switching table

This study confirms that the stabilised dose of methadone (day 14) is highly correlated to the preswitch morphine dose ($r = 0.80$). The protocol ratios used at baseline and the final ratios (preswitch morphine dose: methadone dose at day 14) after titration were correlated ($r = 0.63$), however, the ratios

Table 1 – Dose dependent switching table and distribution of patients in each dose group, *n* = 35.

Baseline morphine dose (mg)	Protocol ratio Mo:Me[a]	Final ratio[b] Mo:Me Mean (min–max)	*N* Stop and go/3-days switch
30–90	4:1		0/0
91–300	6:1	4:1 (3.3–4.7)	1/1
301–600	8:1	7.5:1 (4.4–10)	4/4
601–1000	10:1	11.7:1 (7.1–17.3)	5/3
>1000	12:1	14.2:1 (8.6–26.7)	6/11

[a] Mo = morphine, Me = methadone.
[b] Baseline Mo:Me day 14.

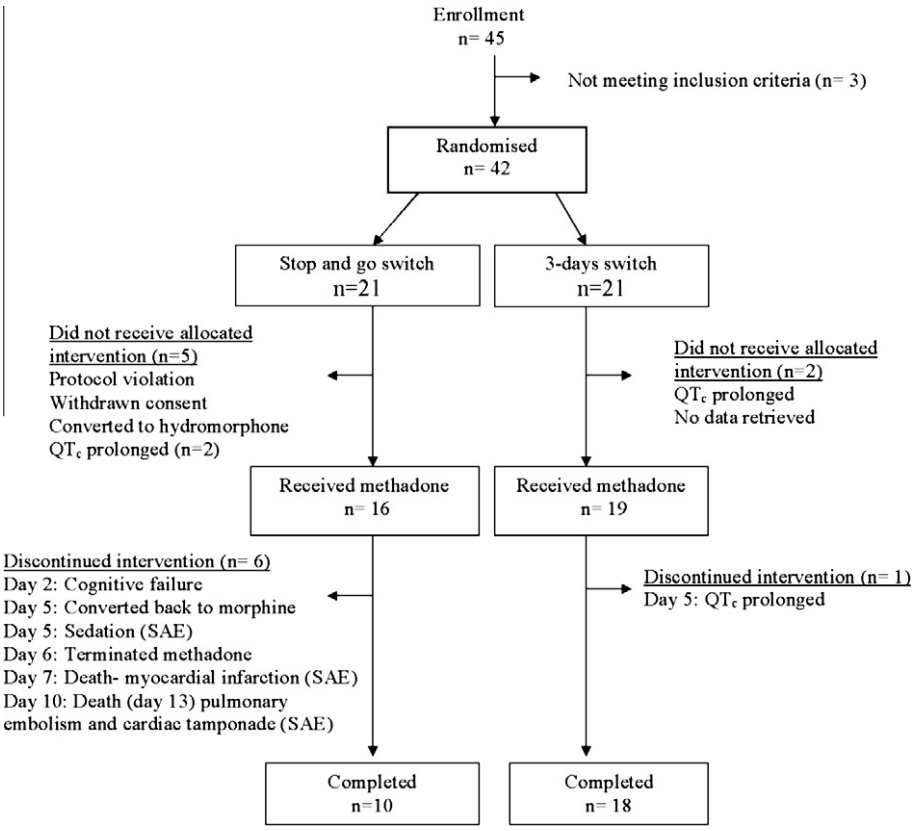

Fig. 2 – CONSORT flowchart.

varied substantially within each morphine dose equivalent, especially for the patients on high opioid doses where the ratios varied from 8.6:1 to 26.7:1 (Table 1). The final median methadone doses were lower than the estimated methadone doses preswitch; SAG from 80 to 65 mg and 3DS from 106 to 90 mg.

3.4. *Rescue*

The 3DS-patients reported two-fold more rescue episodes per day than the SAG-patients all 14 days. The mean difference in total number of rescue episodes the first 3 days was 4.0 episodes (CI −8.2–0.1).

3.5. *QT-interval*

The final (d14) average QT_c was 416 ms (CI 379–446) ($n = 6$) (15 ms increase from baseline) in SAG, whilst the average QT_c was 407 ms (CI 372–443) ($n = 9$) (5 ms decrease from baseline) in 3DS.

4. Discussion

The main finding in this randomised phase II trial was that the stop and go (SAG) approach when switching to methadone from morphine or oxycodone was associated with a trend of more pain, a higher number of dropouts and serious adverse events than with the 3-days switch (3DS) approach in cancer patients on high opioid doses. Since few patients ($n = 28$) completed the study – the confidence intervals are wide and consequently no firm conclusions can be made with regard to group differences or group similarity for the primary outcome, namely average PI day 3.

In a recent systematic review on opioid switching in cancer patients[29] no RCTs were found, and the evidence level was graded D (Grade's approach[32]). The experience from this study and the lack of randomised trials published on this topic reflect that conducting scientifically sound trials in this population is challenging and one need to sample according to a 50–75% attrition rate. Second, this cohort of patients are difficult to recruit in intervention studies due to the complexity of the disease with many symptoms, often short life-expectancy and health care providers that may act as gatekeepers. This raises a need for pragmatic trials recognising the possible methodological limitations met in the most severe sick patients compared with studies including more healthy patients. The relevant population for many interventions in cancer patients, exemplified by this study's research question, is the patients at the very end of life where scientific rigour is difficult. Studies in these patients, give clinically important information that cannot be achieved in other populations. Also, because the number of such cases successfully identified and recruited into studies are low, many centres need to take part in order to obtain a sufficient number of patients in due time (2–3 years).

In previous uncontrolled studies on the SAG strategy it has been argued that this approach will rapidly improve pain relief.[19,20,33,34] Mercadante et al. reported successful switches (PI $\leqslant$ 4 on NRS 0–10) in 80% of 52 patients within 3.65 days in one study[20] and after only 24 h in 46% of 24 patients in another study.[19] This observation was not confirmed in the

Table 2 – Patient demographics and clinical characteristics ($n = 41$)[a].

	Stop and go $n = 21$	3-days switch $n = 20$[a]
Gender F/M	9/12	10/10
Age (years, CI)	61 (58–65)	58 (54–63)
Ethnicity (*n*)		
Caucasian	20	20
Latin American	1	0
Baseline pain intensity		
Mean (CI)	5.4 (4.1–6.6)	5.5 (4.4–6.5)
Karnofsky performance status (%)		
Mean (CI)	59 (53–65)	60 (52–67)
Min–max	30–80	30–90
MMSE baseline		
Mean (CI)	28.3 (26.3–30.2)	28.3 (26.7–29.8)
Cancer diagnosis (*n*)		
Breast	2 (9.5%)	0
Prostate	4 (19%)	3 (15%)
GI	3 (14.3%)	6 (30%)
Lung	3 (14.3%)	4 (20%)
Gynaecologic	2 (9.5%)	1 (5%)
Other	7 (33.3%)	4 (20%)
Double diagnosis	0	2 (10%)
Metastatic (M1)	16 (76%)	19 (95%)
Concomitant disease (*n*)		
None	11 (52.3%)	13 (65%)
Cardiac	5 (23.8%)	4 (20%)
Anaemia	0	2 (10%)
Lung	2 (9.5%)	0
Rheumatism	1 (4.8%)	1 (5%)
Other	5 (23.8%)	4 (20%)
Cancer treatment last weak (*n*)		
None	11 (52.4%)	13 (65%)
Chemotherapy	0	2 (10%)
Radiation	2 (9.5%)	0
Surgery	0	0
Hormone	2 (9.5%)	2 (10%)
Combination	2 (9.5%)	3 (15%)
Missing	4 (19%)	1 (5%)
Concomitant medication ($n > 5$)		
Paracetamol	11 (52.4%)	18 (90%)
Steroids	7 (33.3%)	9 (45%)
Anticonvulsants	8 (38.1%)	11 (55%)
Laxatives	3 (14.3%)	5 (25%)
Benzodiazepines	3 (14.3%)	6 (30%)
Main indication for switch *n* (%)		
Pain	4 (19%)	8 (40%)
Adverse effects	2 (9.5%)	1 (5%)
High dosage	1 (4.8%)	0
Combination	12 (57%)	11(55%)
Current opioid (*n*)		
Morphine	13 (61.9%)	12 (60%)
Oxycodone	8 (38.1%)	7 (35%)
Fentanyl	0	1 (5%)
Preswitch equianalgesic morphine dose (mg)		
Mean (CI)	900 (650–1150)	1330 (820–1840)
Min–max	350–2000	90–3840
Median	690	1200

[a] Data on one patient in the 3-days switch group was not retrievable.

Table 3 – Patients that dropped out after the intervention ($n = 7$).

Switching strategy	Day of dropout	Reason	Gender age	Baseline opioid	Equianalgesic preswitch opioid dose (mg/day)
SAG	2	Cognitive failure	Female 60 y	Morphine	1200
SAG[a]	5	Sedation and respiratory arrest (reversed with Naloxone) (SAE[c])	Male 59 y	Morphine	1080
SAG	5	Switched back to morphine; pain and drowsiness	Female 68 y	Oxycodone	1580
SAG	6	Terminated all medications at home	Female 61 y	Oxycodone	640
SAG	7	Died from myocardial infarction (SAE)	Male 72 y	Morphine	510
SAG	10	Died from cardiac tamponade and pulmonary embolism (SAE)	Female 58 y	Morphine	640
3DS[b]	5	QT_c prolonged	Male 69 y	Oxycodone	1800

[a] SAG = stop and go.
[b] 3DS = 3-days switch.
[c] SAE = serious adverse event.

Table 4 – Average pain intensity (last 24 h), pain intensity now and adverse effects (last 24 h) at baseline, day 3 and 14 (11-point NRS) in the patients receiving methadone ($n = 35$), means (95% CIs).

	Baseline	Day 3	Day 14
Average pain intensity			
Stop and go	4.6 (3.5–5.7)	4.1 (2.3–5.9)	4.9 (2.1–7.7)
3-Days switch	4.7 (3.6–5.8)	3.6 (2.9–4.3)	2.8 (1.8–3.9)
Mean difference (CI)	−0.8 (−1.6–1.5)	0.5 (−1.2–2.2)	2.1[a] (−0.8–5.0)
Pain intensity now			
Stop and go	2.9 (1.9–4.0)	3.3 (1.6–5.0)	3.3 (1.9–4.7)
3-Days switch	4.2 (3.1–5.2)	2.8 (1.7–3.9)	2.6 (1.6–3.7)
Mean difference (CI)	−1.2 (−2.7–0.2)	0.5 (−1.4–2.3)	0.7 (−1.0–2.3)
Drowsiness			
Stop and go	3.5 (2.0–5.0)	2.7 (1.5–3.9)	2.9 (0.9–4.8)
3-Days switch	3.3 (2.0–4.5)	2.7 (1.7–3.6)	2.9 (1.8–4.0)
Mean difference (CI)	0.2 (1.7–2.1)	0.0 (−1.3–1.6)	0.0 (−2.0–1.9)
Nausea			
Stop and go	1.5 (0.5–2.6)	1.0 (0.3–1.7)	1.3 (0.8–3.3)
3-Days switch	1.6 (0.2–2.5)	0.9 (0.3–1.7)	0.7 (0.1–1.5)
Mean difference (CI)	0.2 (−1.4–1.8)	0.1 (−1.0–1.0)	0.6 (−1.1–2.1)
Loss of appetite			
Stop and go	3.9 (1.7–6.0)	3.9 (1.7–6.0)	2.9 (0.4–6.1)
3-Days switch	2.9 (1.9–3.9)	2.7 (1.7–3.7)	2.7 (1.4–4.1)
Mean difference (CI)	1.0 (−1.4–3.3)	1.2 (−1.1–3.5)	0.2 (−2.6–2.8)
Dry mouth			
Stop and go	2.7 (0.7–4.6)	3.0 (1.5–4.5)	1.6 (−0.2–3.3)
3-Days switch	3.1 (1.9–4.4)	2.4 (1.7–3.7)	2.0 (1.2–2.8)
Mean difference (CI)	−0.4 (−2.5–1.7)	0.6 (−1.2–2.3)	−0.4 (−1.9–1.1)

[a] Clinically significant difference between groups ($\geqslant 2$).

present study where the SAG approach was associated with a trend of more pain overall during the 14 day period.

The higher rate of dropouts after intervention in the SAG group (38%) and three SAEs raise the question whether SAG is less safe than 3DS (5% dropout and no SAEs) in this cohort. However, five patients in the SAG group did not receive the allocated treatment and two of the SAEs were disease related. This might not be related to the switching strategy alone, but rather a coincidence or a result of different groups. Still, the accumulation of dropouts and SAEs in one group raises concerns. The high number of SAEs in the SAG group is supported by the findings by Auret et al. who switched 15 patients from morphine to methadone using the SAG strategy (fixed methadone: morphine ratio 6:1). Five patients (33.3%) dropped out and one died.[26] Severe sedation was also reported in one patient (d5) with chronic non-malignant pain switched by the 3DS strategy.[35] Similar risk of SAEs has not been reported in other SAG studies.[18,19] Thus, the observation time of three to five days in some studies might be too short to observe accumulation of methadone or adverse effects. Also

some studies include patients on relatively low doses of opioids before the switch. Taken together, the safety of the SAG is questionable in patients with short life expectancy on high doses of opioids and it should not replace the 3DS in routine clinical practice. However, this study only addresses one SAG approach and other 'as needed' SAG approaches have been claimed effective,[36,37] but no randomised trials are performed.

The inability of this study to reproduce the findings from the above and previous studies[19,20] may be a cohort effect. In this study 33/35 patients used opioid doses >300 mg (49% > 1000 mg) and few exclusion criteria were employed. Only 3/52 used doses of morphine >300 mg in the study by Mercadante et al. and patients with anticancer treatment, poor liver/kidney function and brain metastases were excluded.[20] In contrast, the present study included very sick cancer pain patients which may have different outcomes than patients included earlier in the disease trajectory. These observations underline the importance of classifying the cancer cohorts in clinical cancer pain studies, and that a common system needs to be agreed upon.

The final ratios between the preswitch morphine doses and the final methadone doses in the present study support the conclusions of Bruera et al. and later Ripamonti et al. that the relative potency of methadone increases in patients on higher preswitch doses[24,25,27] and that there are strong indications that the differences in dose ratios are dose-dependent.[23] Both groups used rescue regularly during the trial indicating that a more aggressive titration of methadone might be more appropriate. It is important to acknowledge that the reported equianalgesic dose ratios are really ratios between an opioid dose, which provide unacceptable AEs in the presence of uncontrolled pain and the methadone dose which provided adequate pain control with an acceptable level of AEs.

5. Conclusion

The level of evidence remains low for the most treatment strategies during end of life care. The present study underlines the importance of conducting controlled studies before changes in treatment strategies are implemented into guidelines and/or clinical practice. The observations in this study including the severe SAE in the SAG group give no support for replacing the 3DS switch with the SAG approach in seriously ill patients using high doses of opioids.

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Conflict of interest statement

None declared.

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