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ORIGINAL RESEARCH

Inhaled Methoxyflurane versus Intravenous Morphine for Severe Trauma Pain in the Emergency Setting: Subgroup Analysis of MEDITA, a Multicenter, Randomized, Controlled, Open-Label Trial

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Purpose: Opioid analgesics remain the cornerstone of treatment for severe trauma pain in the emergency setting, but there are barriers to their use. This post hoc analysis of a previously reported trial (MEDITA) investigated the efficacy and safety of low-dose methoxyflurane versus intravenous (IV) morphine for severe trauma pain.

Patients and Methods: MEDITA was a Phase IIIb, randomized, active-controlled, parallel-group, open-label study in Italian pre-hospital units and emergency departments (EudraCT: 2017-001565-25; NCT03585374). Adult patients (N=272) with moderate-to-severe trauma pain (score ≥4 on the Numerical Rating Scale [NRS]) were randomized 1:1 to inhaled methoxyflurane (3 mL) or standard analgesic treatment (SAT; IV paracetamol 1g or ketoprofen 100mg for moderate pain [NRS 4–6] and IV morphine 0.1mg/kg for severe pain [NRS ≥7]). Analyses were performed for the severe pain subgroup. The primary efficacy variable was the overall change from baseline in visual analog scale (VAS) pain intensity at 3, 5 and 10min post-randomization. Non-inferiority of methoxyflurane versus morphine was concluded if the upper 95% confidence interval (CI) for the treatment difference was <1; superiority was concluded if the upper 95% CI was <0.

Results: Ninety-three patients (methoxyflurane: 49; SAT: 44) were included in the severe pain intention-to-treat population. The reduction in VAS pain intensity over the first 10min was superior for methoxyflurane versus morphine (adjusted mean treatment difference: −5.54mm; 95% CI: −10.49, −0.59mm; p=0.029). Median time to onset of pain relief was 9min for methoxyflurane and 15min for morphine. Patients rated treatment efficacy and physicians rated treatment practicality "Excellent" or "Very good" for more methoxyflurane-treated patients (42.8% and 67.3%) than morphine-treated patients (18.1% and 22.8%). Adverse events, all non-serious, were reported in 20.4% of methoxyflurane-treated patients and in 4.8% of morphine-treated patients.

Conclusion: Methoxyflurane provided superior short-term pain relief to IV morphine in patients with severe trauma pain and offers an effective non-narcotic treatment option.

Keywords: acute pain, analgesic, emergency department, methoxyflurane, morphine, prehospital

Introduction

Management of acute pain is a fundamental part of patient care in the emergency setting, with pain prevalence estimates in patients attending the emergency department (ED) ranging from 61% to 91%.[1–3] High prevalence of pain is also reported in

the prehospital emergency setting.[4] The World Health Organization (WHO) three-step analgesic ladder[5] recommends use of non-opioid analgesics for mild pain and opioid analgesics for moderate-to-severe pain; however, this reference was developed for cancer-related pain and does not consider medications that have become available in the past 30 years. A lack of harmonized pain protocols means there is widespread variation in the approaches taken to assess and treat trauma pain at the national, local and individual level,[6,7] and suboptimal analgesic treatment is widely reported.[2–4,8] Intravenous (IV) opioid analgesics remain the cornerstone of treatment for acute severe trauma pain, but there are barriers to their use that may contribute to undertreatment of pain in the emergency setting. Obtaining IV access can be distressing for the patient, difficult in emergency rescue situations, and delay initiation of pain relief. Patients administered opioids require safety monitoring due to the risk of side-effects such as respiratory depression, cardiovascular events, nausea and vomiting, which together with initial placement of an IV catheter, incurs considerable time and resource costs.[9] Opioid analgesics are controlled medications and there may be reluctance among health-care professionals and patients to use opioids due to regulatory barriers in prescription and concerns about misuse and abuse.[7] Intranasal opioid analgesia is less invasive but is not suitable for patients with facial trauma.[10] There is a clear need for alternatives to opioid analgesics for patients with severe trauma pain.

Low-dose inhaled methoxyflurane (Penthrox®, 3 mL dose, Medical Developments International, Scoresby, Australia), a non-opioid, volatile fluorinated hydrocarbon, has been extensively used for short-term pain relief in the emergency setting and as procedural analgesia in Australia and New Zealand since 1975.[11–13] Methoxyflurane is self-administered by the patient by inhaling from the Penthrox inhaler, a lightweight, disposable device that provides ~25-60 min of analgesia depending on the frequency of inhalation.[14,15] Methoxyflurane has rapid onset and offset of action, thus it is also suitable for use as bridging analgesia. In 2015, methoxyflurane was approved in Europe for the emergency relief of moderate-to-severe pain in conscious adults with trauma and associated pain,[16] based on clinical evidence from a randomized, placebo-controlled trial (STOP!) in UK EDs.[17] The STOP! study demonstrated a mean reduction in VAS pain intensity of 35 mm in the methoxyflurane group, with onset of analgesia within 4 min or 6–10 inhalations on average and >80% of patients and health-care professionals (HCPs) rating methoxyflurane treatment as excellent, very good or good.[17] Reported adverse events (AEs) were mainly mild and transient dizziness and/or headache. Low-dose methoxyflurane analgesia has also been approved in Canada, Eastern Europe, Latin America, South Africa and the Gulf area.[18,19]

Recently completed[20,21] and ongoing studies[22,23] have investigated the effectiveness of methoxyflurane analgesia versus currently used analgesic treatments in the emergency setting. The InMEDIATE trial in Spanish EDs compared methoxyflurane with standard analgesic treatment (SAT, administered according to local practice) and reported a significantly greater decrease in pain intensity (on the Numerical Rating Scale [$NRS_{0\text{-}10}$] over 20 min; 2.47 vs 1.39), faster onset of pain relief (3 vs 10 min) and better patient and HCP ratings of pain control and comfort of treatment with methoxyflurane treatment.[20] Similarly, the MEDITA trial demonstrated superiority of methoxyflurane versus SAT in Italy (SAT comprising IV paracetamol/ketoprofen for moderate pain and IV morphine for severe pain[24]) in terms of the decrease in visual analog scale ($VAS_{0\text{-}100mm}$) pain intensity over the first 10-min post-baseline.[21] Furthermore, exploratory analysis of MEDITA data by pain subgroup (moderate, severe) showed that methoxyflurane was more effective than SAT for both subgroups.[21] Since the opioid-sparing potential of methoxyflurane is of particular interest, further exploratory subgroup analyses were performed in patients with severe pain, ie, comparing the efficacy and safety of methoxyflurane with IV morphine, and are the focus of this report.

Patients and Methods

Study Design

MEDITA (Methoxyflurane in Emergency Department in ITAly) was a Phase IIIb, randomized, active-controlled, parallel-group, open-label study (EudraCT number: 2017-001565-25; Clinicaltrials.gov identifier NCT03585374). The study was undertaken between 08 February 2018 and 22 February 2019 at 16 emergency medical centers (mainly EDs of hospitals or university hospitals, plus two ambulance rescue units [Sistema 118]) in Italy. Adult patients presenting at the hospital for triage or rescued in the prehospital environment through the Italian emergency medical service with moderate-to-severe pain due to limb trauma were randomized in a 1:1 ratio to receive treatment with

methoxyflurane or SAT. Study treatment was administered and all assessments were performed on the day of randomization, with a safety follow-up telephone call 14±2 days after discharge. The full methodology[25] and results for the full study population[21] have previously been reported.

The study was conducted in compliance with International Council on Harmonization Good Clinical Practice, with the ethical principles of the 1964 Helsinki Declaration and its later amendments, and local guidelines. The protocol was reviewed and approved by the Italian Medicines Agency (AIFA) and each participating center's Ethics Committee. Written informed consent was obtained from all patients before enrolment, unless the patient was unable to provide written informed consent, in which case witnessed verbal consent was obtained, with the patient signing the informed consent as soon as they were able.

Participants

Eligible patients were adults aged ≥18 years presenting with trauma (fracture, dislocation, crushing, contusion) to a single limb and requiring analgesia for moderate-to-severe pain (NRS pain score ≥4). Patients had to be medically stable, alert, able to provide informed consent and communicate with the investigator to perform the study activities. Patients receiving ongoing analgesic treatment for chronic pain or who had used any other analgesic in the previous 5 hrs (8 hrs for diclofenac), who were pregnant or lactating, had dynamics of at-risk trauma, contraindications to methoxyflurane administration as per the Summary of Product Characteristics (SPC)[14] or to any of the SAT were excluded from participation. Full eligibility criteria have previously been reported.[25]

Interventions

Treatment randomization was performed in blocks of four, without stratification. Once patient eligibility was confirmed, treatment allocation was performed via a centralized Interactive Web Response System set up within the electronic case report form (eCRF). The study was not blinded because the different routes of administration (inhaled vs IV) would have necessitated a double-blind, double-dummy study design, which was impractical and had ethical implications given the urgent need for rapid analgesia in the study setting.

Study treatment was administered as soon as possible after randomization. Patients randomized to methoxyflurane received one inhaler containing 3 mL of methoxyflurane. The inhaler was prepared by trained study staff by pouring methoxyflurane liquid from the supplied vial into the base of the inhaler, where it is absorbed by a polypropylene wick and vaporizes. The patient was supervised by the investigator and instructed to inhale methoxyflurane intermittently through the inhaler mouthpiece. The patient could control their own level of analgesia by changing the frequency of inhalation or covering the diluter hole with a finger to obtain greater analgesia. The inhaler included an activated carbon chamber that adsorbed any exhaled methoxyflurane when the patient exhaled back into the mouthpiece, preventing environmental release of methoxyflurane resulting in occupational exposure. One methoxyflurane inhaler provided approximately 25 min to 1 hr of analgesia, depending on the frequency of inhalation[14,15] Methoxyflurane was supplied by the study sponsor in single (3 mL dose) packs containing inhaler and methoxyflurane vial.

For patients randomized to the SAT group, the treatment administered was dependent on the patient's baseline pain intensity. Patients presenting with moderate pain (NRS 4–6) received a single IV dose of paracetamol (1 g) or ketoprofen (100 mg), based on local availability and clinical practice, and any contraindications for the patient. Patients presenting with severe pain (NRS ≥7) received a single IV dose of morphine (0.10 mg/kg) and are the focus of this report. The morphine dose selected for the study represents usual clinical practice for severe trauma pain in Italy and is congruent with intersocietary recommendations.[26] All SAT treatments were diluted and infused over 10 mins, and were administered as soon as possible after treatment assignment. Venous access was obtained before randomization according to local clinical practice. All SAT was supplied locally by the study centers as commercially available product.

Rescue medication was permitted if a patient's pain was not adequately controlled by their randomized study treatment. Rescue medication was administered at the discretion of the treating physician according to local clinical practice.

Study Assessments

The primary efficacy variable was the change from baseline in pain intensity over the first 10 min; the changes at 15 to 30 min were assessed as secondary efficacy variables. Pain intensity was measured using a 0–100 mm VAS (where 0=no pain and 100=maximum pain) at baseline and at 3, 5, 10, 15, 20, 25 and 30 min, or until administration of rescue medication if this occurred earlier than 30 min. If a patient was unable to mark the VAS

themselves, a trained HCP could assist the patient to complete the VAS, in which case the patient verified the recording with a signature and date as soon as they were able to. While the NRS was considered adequate for enrolment, VAS pain intensity was chosen as the primary variable because it is a more sensitive tool (allowing the patient to mark a point on the scale that is measured to the nearest mm).

The time from randomization to the onset of analgesic effect (as subjectively reported by the patient) and use of rescue medication were recorded as secondary efficacy variables. Patient- and physician-reported outcomes were global assessments of treatment efficacy and treatment practicality, respectively. Each was recorded on a 5-point Likert scale (poor, fair, good, very good, excellent) at 30 min after randomization.

Safety variables included the incidence of AEs and serious AEs (not related to the trauma presentation), and vital signs (systolic and diastolic blood pressure [SBP and DBP], heart rate and respiratory rate) measured at baseline and 10 and 30 min after randomization. For all efficacy and safety variables, baseline was taken as the time of randomization. This allowed not only the intrinsic efficacy, but also the speed of study drug administration to be evaluated, given the need to act as quickly as possible to relieve the patient's pain and allow continuation of the diagnostic-therapeutic procedure. All study data were entered into an eCRF system accessible via the internet by the investigator or designee, and were monitored by qualified personnel from the contract research organization (YGHEA, Division of Ecol Studio s.p.a., Bologna, Italy).

Statistical Analysis

The change from baseline in VAS pain intensity was compared between study treatments for the severe pain subgroup using a linear mixed-effect model for repeated measures adjusted for VAS baseline score, and the interaction between time point and treatment. The primary analysis was the overall test for treatment effect at 3, 5 and 10 min. For each analysis, the treatment difference (methoxyflurane-morphine) was presented with 95% confidence interval (CI). Non-inferiority of methoxyflurane vs IV morphine was concluded if the upper 95% CI was <1, while superiority was concluded if the upper 95% CI was <0.

The mean change from baseline in VAS pain intensity at each time point after 10 min was estimated for each group and compared between the treatments using the *t*-test for equality of means. The VAS responder rate (the proportion of patients with ≥30% reduction from baseline in VAS pain intensity; post hoc analysis) was compared between treatments using a Chi-squared test. Kaplan-Meier curves were used to present the time to onset of pain relief, with "survival time" representing the event "onset of pain relief". The frequency of administration of rescue medication was compared between the treatments using Fisher's exact test. The efficacy of study treatment rated by the patient and the practicality of study treatment rated by the physician were compared between the treatments using a non-parametric Mann–Whitney *U*-test. Efficacy variables were analyzed using the intention-to-treat (ITT) population, ie, all randomized patients who received study treatment and had at least one post-baseline efficacy measurement. No imputation of missing data was performed.

AEs were coded using the Medical Dictionary for Regulatory Activities version 22.0 and presented for the safety population (based on administered treatment). Statistical programming and analyses were performed using the validated software IBM SPSS Statistics version 23.0.

Sample Size

The sample size calculation for the main study (including patients with both moderate and severe pain, assuming a non-inferiority margin of 1.0, a standard deviation of 2.5 and a significance level of 0.05[25]) estimated that 108 patients per treatment group would provide 90% power to determine non-inferiority of methoxyflurane versus SAT for the change from baseline in VAS pain intensity over the first 10 min of treatment. Allowing for 20% of patients being non-evaluable, it was planned to randomize a total of 136 patients per treatment group.[21] The sample size was not intended to provide enough power to demonstrate non-inferiority of methoxyflurane versus IV morphine in the severe pain subgroup presented in this report (N=93); thus, analyses were performed in an exploratory manner only.

Results

Study Patients

A total of 272 patients were randomized in the whole study and 270 (135 per treatment group) were included in the ITT population.[21] The severe pain subgroup (NRS score ≥7 at baseline) included 93 patients; 49 (18.1%) of those in the methoxyflurane group and 44 (16.3%) of those in the SAT group (Figure 1). Most patients (>95%) in the

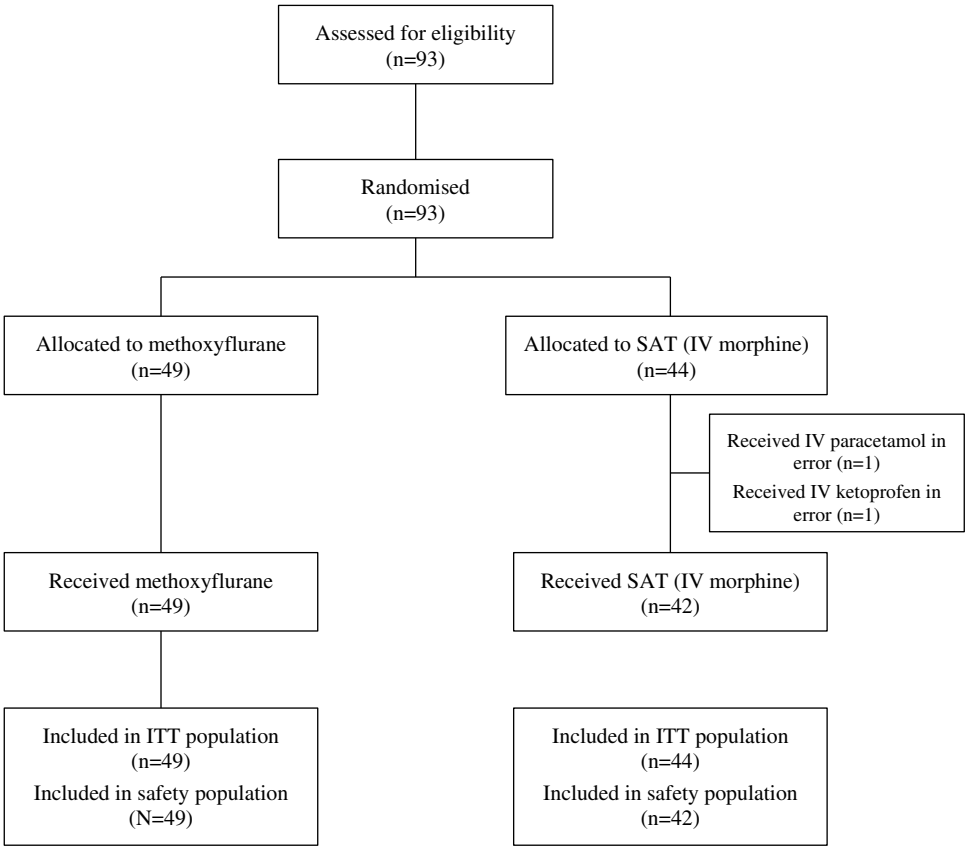


Figure 1 Participant flow (severe pain subgroup).
Abbreviations: ITT, intention-to-treat; IV, intravenous; SAT, standard analgesic treatment.

severe pain subgroup were Caucasian, with a mean age of 53.1 years in the methoxyflurane group and 57.4 years in the SAT group (Table 1). Although the full study population had a relatively even gender split (49% male: 51% female),[21] more patients were female (~63%) in the severe pain subgroup (Table 1). All patients with severe pain in the SAT group were to be administered IV morphine; however, one patient was administered IV paracetamol and one patient was administered IV ketoprofen in error. Under the ITT principle, these patients were included in the SAT group in the severe pain subgroup efficacy analysis but were excluded from safety analyses.

Efficacy Results

Patients with severe pain treated with methoxyflurane achieved a significantly greater reduction in VAS pain intensity compared with patients treated with SAT (IV morphine) in the first 10 min (Table 2). The treatment difference for the overall mean change from baseline at 3, 5 and 10 min was −5.54 mm (95% CI: −10.49, −0.59 mm; p=0.029; Table 2), thus meeting the pre-defined criteria for both non-inferiority and superiority (upper bound of the 95% CI of the difference between estimated marginal means <1 and <0, respectively). At time points beyond 10 min (ie, 15 to 30 min), the reduction from baseline in VAS pain intensity was similar for both treatment groups (Table 2; Figure 2). The proportion of VAS responders was numerically higher for methoxyflurane versus SAT at early time points (3, 5 and 10 min; Figure 3), with a significant treatment difference in the responder rate at 5 min (p=0.021).

The median time to onset of pain relief was shorter for methoxyflurane (9 min; 95% CI: 6.25, 11.76 mins) than SAT (15 min; 95% CI: 12.52, 17.48 min), with the quicker time to pain relief for methoxyflurane evident in Kaplan-Meier curves up to ~24 min (Figure 4). There was no difference between the treatment groups in the proportion of patients who received rescue analgesic medication (methoxyflurane: three patients [6.1%]; SAT: 3 patients [6.8%]; p=1.000).

More than twice as many patients rated the efficacy of study treatment as "Excellent" or "Very good" in the methoxyflurane group compared with the SAT group

Table 1 Patient Characteristics (Severe Pain Subgroup, ITT Population)

Characteristic		Methoxyflurane (N=49)	Standard Analgesic Treatment (IV Morphine) (N=44)
Age (years)	Mean (SD) Range	53.1 (18.42) 19-91	57.4 (19.34) 19–95
Gender [n (%)]	Male Female	20 (40.8) 29 (59.2)	15 (34.1) 29 (65.9)
Race [n (%)]	Caucasian Asian Black	46 (93.9) 1 (2.0) 2 (4.1)	43 (97.7) 0 1 (2.3)
NRS Score at Inclusion [n (%)]	7 8 9 10	13 (26.5) 16 (32.7) 15 (30.6) 5 (10.2)	9 (20.5) 25 (56.8) 6 (13.6) 4 (9.1)
VAS baseline score (mm)	Mean (SD)	81 (15)	79 (14)

Abbreviations: ITT, intention-to-treat; NRS, Numerical Rating Scale; SD, standard deviation; VAS, visual analog scale.

(42.8% vs 18.1%), although the proportion rating study treatment as "Poor" was higher for methoxyflurane than SAT (14.3% vs 6.8%; Figure 5A). Overall, the distribution of patients' efficacy ratings was not significantly different between the treatments (p=0.387). The proportion of physicians rating the practicality of study treatment as "Excellent" or "Very Good" was almost threefold higher for methoxyflurane than SAT (67.3% vs 22.8%; Figure 5B), with a similar proportion of physicians rating the practicality of each study treatment as "Poor" (10.2% for methoxyflurane and 9.1% for SAT). Overall, the physicians' practicality ratings were significantly more favorable for methoxyflurane than SAT (p<0.001).

Safety Results

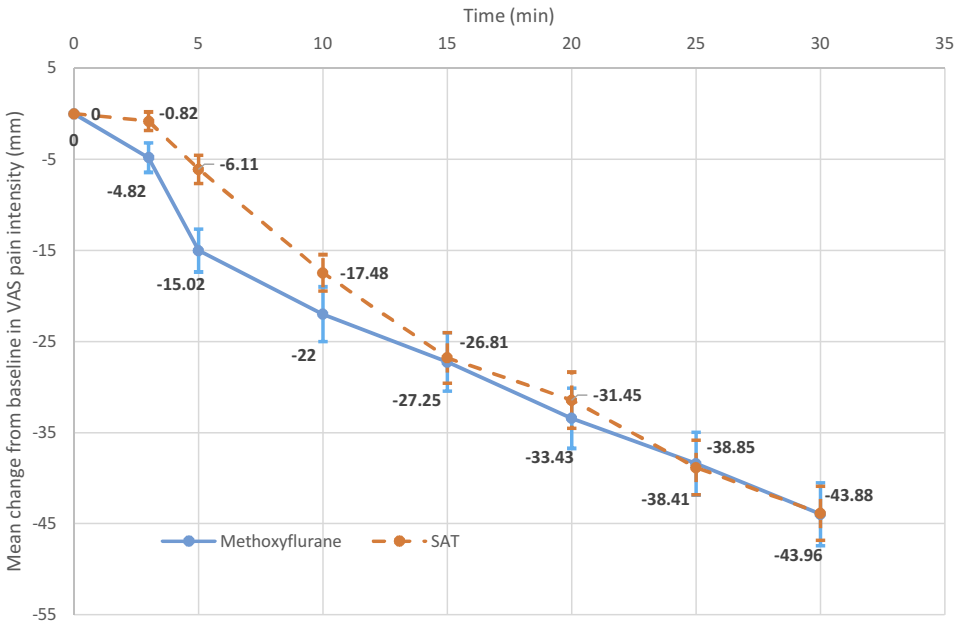
A total of 10 patients (20.4%) treated with methoxyflurane and 2 patients (4.8%) treated with IV morphine experienced AEs (all non-serious; Table 3). All AEs except two (bronchitis in a patient who received methoxyflurane and pruritus in a patient who received IV morphine; both considered unrelated to study treatment by the investigator) resolved by end of study. Three patients (6.1%) discontinued methoxyflurane treatment due to AEs (vertigo and nausea, feeling drunk, and nausea, respectively). Two "bad taste" events in the mothoxyflurane group were classified as "dysgeusia" for lack of more appropriate classification in the MedDRA system.

There were no statistically significant changes in vital signs parameters in the methoxyflurane group. The mean changes from baseline at 10 and 30 mins were 0.19 and −0.69 mmHg for SBP, −0.54 and −1.58 mmHg for DBP, and 0.52 and −2.67 bpm for heart rate. For patients receiving IV morphine, there were statistically significant reductions in SBP of −5.90 mmHg (95% CI: −10.37, −1.44; p=0.011) at 10 min and −7.38 mmHg (95% CI: −12.53, −2.23; p=0.006) at 30 min, and in DBP of −3.44 mmHg (95% CI: −6.86, −0.15; p=0.049) at 10 min and −3.81 mmHg (95% CI: −7.27, −0.35; p=0.032) at 30 min, but non-significant changes of −0.70 bpm at 10 min and 1.51 bpm at 30 min for heart rate; the observed changes in BP are not considered to be clinically

Table 2 Analysis of Change from Baseline in VAS Pain Intensity (Severe Pain Subgroup, ITT Population)

Endpoint	Time Point (min)	Mean Change from Baseline (95% Confidence Interval)[a]		Estimated Treatment Effect (95% Confidence Interval)	p-value
		Methoxyflurane	Standard Analgesic Treatment		
Primary Endpoint	3	−4.69 (−7.27, −2.11)	−0.96 (−3.68, 1.76)	−3.73 (−7.48, 0.02)	0.051
	5	−14.89 (−18.80, −10.99)	−6.26 (−10.38, −2.13)	−8.64 (−14.32, −2.96)	0.003[b]
	10	−21.87 (−26.93, −16.81)	−17.62 (−22.96, −12.28)	−4.25 (−11.61, 3.11)	0.254
	Overall	−13.82 (−17.22, −10.42)	−8.28 (−11.87, −4.69)	−5.54 (−10.48, −0.59)	0.029[b]
Secondary Endpoint	15	−27.25 (22.23)	−26.81 (17.92)	−0.44 (−8.86, 7.98)	0.917
	20	−33.43 (22.49)	−31.45 (20.05)	−1.98 (−11.04, 7.08)	0.665
	25	−38.41 (23.34)	−38.85 (19.16)	0.44 (−8.73, 9.61)	0.924
	30	−43.96 (23.42)	−43.88 (18.96)	−0.08 (−9.23, 9.08)	0.986

Notes: Based on estimated marginal means. [a]Mean change from baseline (standard deviation) is presented for 15, 20, 25 and 30 min time points. [b]Mean difference significant at the 0.05 level (Bonferroni adjustment for multiple comparisons).
Abbreviations: ITT, intention-to-treat; VAS, visual analog scale.



95% CIs (mm)	Time (min)						
	3	5	10	15	20	25	30
Methoxyflurane	-8.08, -1.55	-19.76, -10.28	-28.03, -15.97	-33.70, -20.80	-40.11, -26.76	-45.34, -31.48	-50.91, -37.00
SAT	-2.85, 1.21	-9.26, -2.97	-21.52, -13.43	-32.40, -21.23	-37.70, -25.21	-44.90, -32.81	-49.86, -37.89

Figure 2 Change from baseline in VAS pain intensity (severe pain subgroup, ITT population). Mean change ± standard error.
Abbreviations: ITT, intention-to-treat; SAT, standard analgesic treatment.

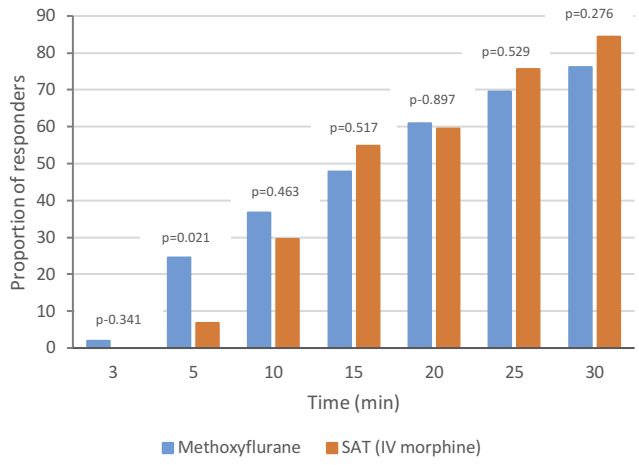


Figure 3 VAS responder rate (severe pain subgroup, ITT population). VAS responder: patient with ≥30% reduction from baseline in VAS pain intensity.
Abbreviations: ITT, intention-to-treat; SAT, standard analgesic treatment; VAS, visual analog scale.

significant. Mean respiratory rate remained constant at 16–17 breaths/min in both groups.

Discussion

This subgroup analysis showed superior efficacy of methoxyflurane compared to IV morphine in terms of the reduction in VAS pain intensity over the first 10 min after randomization, reflecting the convenience of use and rapid onset of action of methoxyflurane. At later time points (15 to 30 min), the reduction from baseline in VAS pain intensity was similar in both treatment groups. Given the urgency of the requirement for pain relief in emergency situations, these results are clinically relevant.

To our knowledge, the results of this subgroup analysis represent the first head-to-head comparison of methoxyflurane and IV morphine for trauma pain in a prospective randomized controlled trial. Recently, Borobia and colleagues reported a larger reduction in pain intensity (NRS_{0-10}) for methoxyflurane than SAT regardless of patients' baseline pain intensity (NRS <7 or NRS ≥7) and class of SAT administered (non-opioids or opioids), although very few patients in the study (N=14) received opioid analgesics.[20] In contrast to our study, two large retrospective comparative trials comparing the effectiveness of IV morphine, intranasal fentanyl and inhaled methoxyflurane in 52,046 adults[27] and 3312 children[28] with moderate-to-severe pain treated by paramedics in the prehospital setting in Australia found that methoxyflurane was less effective

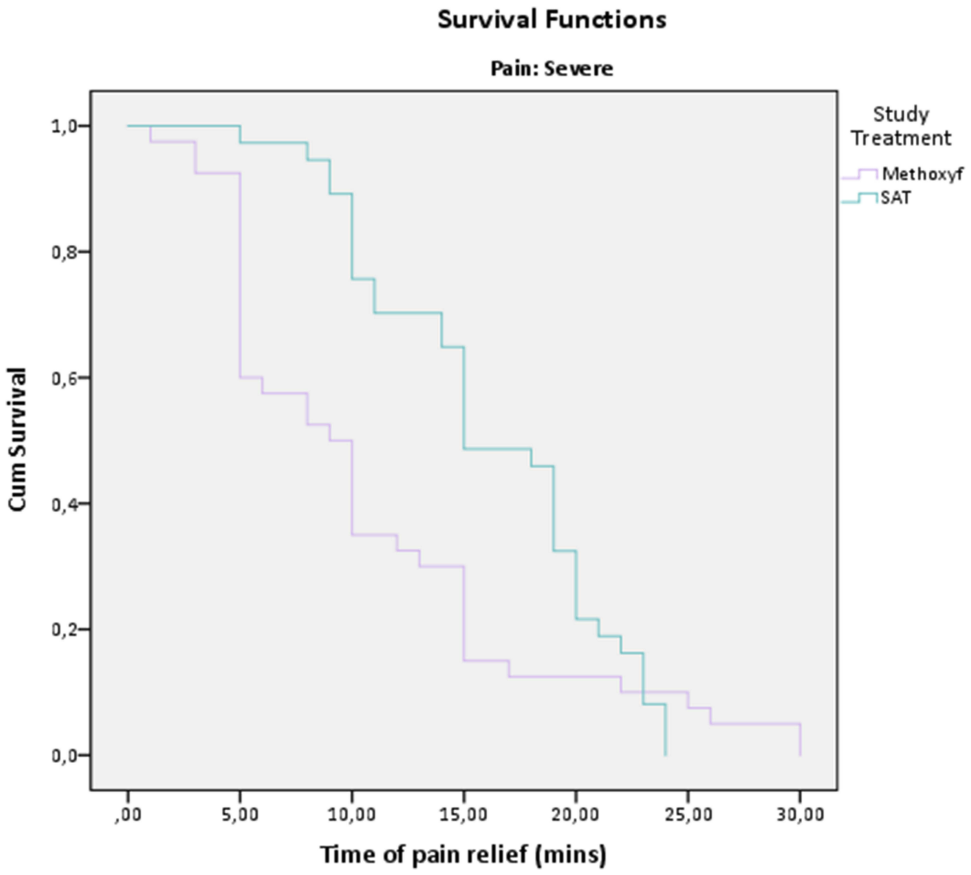


Figure 4 Kaplan-Meier plot of time to onset of pain relief (severe pain subgroup, ITT population). The Kaplan-Meier curve represents an estimate of the cumulative proportion of patients who have not yet experienced onset of pain relief. Higher curves indicate longer time to pain relief. No censoring was performed.

than IV morphine in terms of the proportion of patients achieving effective analgesia (defined as ≥30% reduction in pain using an 11-point verbal NRS). The proportion of adults/children achieving effective analgesia was 81.8%/87.5% for IV morphine and 59.1%/78.3% for methoxyflurane ($p<0.0001$).[27,28] However, these Australian studies noted that both methoxyflurane and IV morphine were individually effective in the majority of patients, and on-scene care time was significantly shorter for patients administered methoxyflurane than for patients treated with morphine.[27,28] Furthermore, methoxyflurane can be used in emergency rescue situations where IV placement may not be possible.

Other factors such as the ease and convenience of administration, particularly at triage, as well as supervision times and safety profile should also be taken into consideration when making treatment decisions. Methoxyflurane does not interfere with other analgesic or anesthetic agents[14] and therefore, used as a first-line treatment, would not limit the choice of subsequent treatments. In addition to the time and materials required to cannulate and infuse treatment, IV administration of opioid analgesics incurs healthcare resource costs in terms of the physiological monitoring required and management of opioid-related AEs.

Administration of methoxyflurane also allows a more patient-centric approach, avoiding the requirement for needles and allowing the patient to control the strength and duration of analgesia according to their individual needs. Consistent with the MEDITA study, the STOP! and InMEDIATE studies both showed high patient satisfaction with methoxyflurane treatment. In STOP!, Global Medication Performance was rated as "Excellent", "Very Good" or "Good" by 77.6% of adult patients.[29] In InMEDIATE, patients scored methoxyflurane a median of 9 out of 10 for pain control, comfort of treatment and safety (AEs), and methoxyflurane treatment exceeded patient's expectations in 77% of cases.[20] Although a larger proportion of patients experienced AEs with methoxyflurane (20%) than IV morphine (5%) in our study, methoxyflurane AEs were mild and transient, and only 6% of patients in the methoxyflurane group discontinued treatment due to AEs.

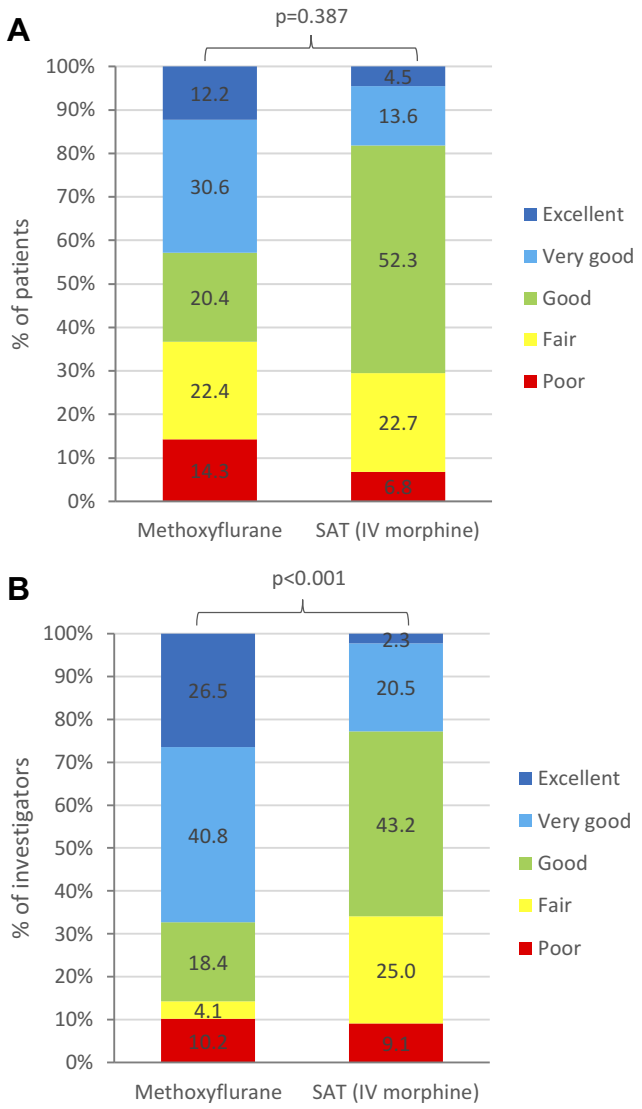


Figure 5 Patient and physician-reported outcomes (severe pain subgroup, ITT population). (**A**) Overall treatment efficacy evaluated by the patient. (**B**) Practicality of using study treatment evaluated by the physician.

A clear limitation of the analysis presented here is that the study was not powered to determine non-inferiority of methoxyflurane versus SAT in the subgroup of patients with severe pain. Nonetheless, our analysis demonstrated a clear benefit of methoxyflurane versus IV morphine over the first 10-min post-randomization. Taking baseline as the time of randomization may have biased the analysis in favor of methoxyflurane, given the ease of use and rapid onset of action of methoxyflurane, and the time taken to infuse IV morphine; however, this allowed not only the intrinsic efficacy, but also the speed of study drug administration to be evaluated, given the importance of rapid pain relief to allow stabilization of the patient in the field or continuation of the diagnostic-therapeutic process in the ED. It should be noted that per standard local procedure, patients were generally already cannulated at the time of randomization. Pain intensity results at later time points (Table 2, Figure 2), when effects of IV morphine would be expected to be maximal, suggest equivalent efficacy of methoxyflurane versus morphine. Although the morphine dose utilized in the study represents standard of care in Italy,[26] as evidenced by participation of multiple emergency centers, it is plausible that a higher dose of morphine could have produced a greater and faster analgesic effect in the SAT group. While the study results are clinically relevant and valid in Italy, they may not be directly applicable in other countries where higher morphine doses are routinely used for severe trauma pain. As previously discussed,[21] the open-label nature of treatment administration in this study also presents an intrinsic bias, but was considered the only practical option due to the urgent requirement for effective analgesia in the emergency setting, the different modes of administration of the treatments being studied, and the characteristic "fruity" smell of methoxyflurane. Given these limitations, further direct head-to-head studies powered to detect treatment differences in the efficacy of methoxyflurane and IV morphine, potentially investigating higher morphine doses, are required to fully assess the risk:benefit of methoxyflurane versus IV morphine in patients with trauma pain.

Table 3 Adverse Events (Severe Pain Subgroup, Safety Population)

Number (%) of Patients	Methoxyflurane (N=49)	IV Morphine (N=42)
Any adverse event	10 (20.4)	2 (4.8)
Nausea	2 (4.1)	0
Feeling abnormal	2 (4.1)	0
Dysgeusia	2 (4.1)	0
Vertigo	1 (2.0)	0
Oral discomfort	1 (2.0)	0
Feeling drunk	1 (2.0)	0
Pyrexia	1 (2.0)	0
Bronchitis	1 (2.0)	0
Presyncope	1 (2.0)	0
Sedation	1 (2.0)	0
Euphoric mood	1 (2.0)	0
Vomiting	0	1 (2.4)
Pruritus	0	1 (2.4)

Notes: AEs are presented by MedDRA preferred term in decreasing order of frequency in the methoxyflurane group, followed by the standard analgesic treatment (IV morphine) group.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; IV, intravenous.

In conclusion, methoxyflurane provided superior pain relief to IV morphine over the first 10-min post-randomization in patients with severe trauma pain. Analysis of pain intensity at later time points up to 30 min suggested equivalent analgesic efficacy of the two treatments. The findings of this subgroup analysis highlight the potential of methoxyflurane as an effective, convenient, non-narcotic analgesic agent to help reduce opioid use in the ED.

Abbreviations

AE, adverse event; AIFA, Italian Medicines Agency; CI, confidence interval; DBP, diastolic blood pressure; eCRF, electronic case report form; ED, emergency department; HCP, health-care professional; ITT, intention-to-treat; IV, intravenous; MEDITA, Methoxyflurane in Emergency Department in ITAly; NRS, numerical rating scale; SAT, standard analgesic treatment; SBP, systolic blood pressure; SPC, Summary of Product Characteristics; VAS, visual analog scale; WHO, World Health Organization.

Ethics Approval and Informed Consent

The trial was approved by the Italian Medicines Agency (AIFA). The co-ordinating ethics committee, Comitato Etico Regione Toscana – Area Vasta Centro, Florence, Italy, approved the trial protocol on 1 December 2017. In addition, all trial documents and procedures were reviewed and approved by the appropriate Ethics Committees at each center. Written informed consent (or verbal witnessed consent) was obtained from all patients before initiation into the trial. The MEDITA trial was registered with EudraCT (2017-001565-25) on 02 March 2018 and ClinicalTrials.gov (NCT03585374) on 13 July 2018.

Data Sharing Statement

The datasets generated, analyzed and reported within this manuscript may be requested in accordance with the Data Sharing Policy of Mundipharma Research Limited available from www.mundipharma-rd.eu.

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Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, and take responsibility for the integrity

of the work as a whole. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

Elisabetta Bonafede is an employee of the clinical research organization that conducted the study. Antonella Sblendido, Amedeo Soldi and Alberto Farina are employees of Mundipharma Pharmaceuticals srl. The authors report no other conflicts of interest in this work.

References

1. Cordell WH, Keene KK, Giles BK, Jones JB, Jones JH, Brizendine EJ. The high prevalence of pain in emergency medical care. *Am J Emerg Med*. 2002;20:165–169. doi:10.1053/ajem.2002.32643
2. Berben SA, Meijs TH, van Dongen RT, et al. Pain prevalence and pain relief in trauma patients in the Accident and Emergency Department. *Injury*. 2008;39:578–585. doi:10.1016/j.injury.2007.04.013
3. Mura P, Serra E, Marinangeli F, et al. Prospective study on prevalence, intensity, type, and therapy of acute pain in a second-level urban emergency department. *J Pain Res*. 2017;10:2781–2788. doi:10.2147/JPR
4. Marinangeli F, Narducci C, Ursini ML, et al. Acute pain and availability of analgesia in the prehospital emergency setting in Italy: a problem to be solved. *Pain Pract*. 2009;9:282–288. doi:10.1111/ppr.2009.9.issue-4
5. World Health Organization. WHO's cancer pain ladder for adults 1986. Available from: http://www.who.int/cancer/palliative/painladder/en/. Accessed January 24, 2020.
6. Diβmann PD, Maignan M, Cloves PD, Gutierrez Parres B, Dickerson S, Eberhardt A. A review of the burden of trauma pain in emergency settings in Europe. *Pain Ther*. 2018;7:179–192. doi:10.1007/s40122-018-0101-1
7. Berben SA, Meijs TH, van Grunsven PM, Schoonhoven L, van Achterberg T. Facilitators and barriers in pain management for trauma patients in the chain of emergency care. *Injury*. 2012;43:1397–1402. doi:10.1016/j.injury.2011.01.029
8. Pierik JG, IJzerman MJ, Gaakeer MI, et al. Pain management in the emergency chain: the use and effectiveness of pain management in patients with acute musculoskeletal pain. *Pain Med*. 2015;16:970–984. doi:10.1111/pme.12668
9. Casamayor M, DiDonato K, Hennebert M, Brazzi L, Prosen G. Administration of intravenous morphine for acute pain in the emergency department inflicts an economic burden in Europe. *Drugs Context*. 2018;7:212524. doi:10.7573/dic.212524
10. Hansen MS, Dahl JB. Limited evidence for intranasal fentanyl in the emergency department and the prehospital setting: a systematic review. *Dan Med J*. 2013;60:A4563.
11. Porter KM, Dayan AD, Dickerson S, Middleton PM. The role of inhaled methoxyflurane in acute pain management. *Open Access Emerg Med*. 2018;10:149–164. doi:10.2147/OAEM.S181222
12. Jephcott C, Grummet J, Nguyen N, Spruyt O. A review of the safety and efficacy of inhaled methoxyflurane as an analgesic for outpatient procedures. *Br J Anaesth*. 2018;120:1040–1048. doi:10.1016/j.bja.2018.01.011
13. Blair HA, Frampton JE. Methoxyflurane: a review in trauma pain. *Clin Drug Investig*. 2016;36:1067–1073. doi:10.1007/s40261-016-0473-0
14. Penthrox® summary of product characteristics. Available from: https://www.medicines.org.uk/emc/medicine/31391. Accessed January 24, 2020.
15. Oxer HF. Effects of Penthrox® (methoxyflurane) as an analgesic on cardiovascular and respiratory functions in the pre-hospital setting. *J Mil Veterans Health*. 2016;24:14–20.
16. Blair HA, Frampton JE. Methoxyflurane inhalation vapour in trauma pain: a profile of its use in the EU. *Drugs Ther Perspect*. 2017;33:403–408. doi:10.1007/s40267-017-0433-7
17. Coffey F, Wright J, Hartshorn S, et al. STOP!: a randomised, double-blind, placebo-controlled study of the efficacy and safety of methoxyflurane for the treatment of acute pain. *Emerg Med J*. 2014;31:613–618. doi:10.1136/emermed-2013-202909
18. Medical Developments International. Penthrox: European Update, 07 February 2017. Available from: https://www.medicaldev.com/wp-content/uploads/2017/02/ASX-Announcement-Penthrox-European-Update-7-Feb-2017.pdf. Accessed January 24, 2020.
19. Medical Developments International. Penthrox is approved in Canada, 10 April 2018. Available from: https://www.medicaldev.com/wp-content/uploads/2018/04/ASX-Announcement-Penthrox-is-approved-in-Canada-100418.pdf. Accessed January 24, 2020.
20. Borobia AM, García Collado S, Carballo Cardona C et al; On behalf of the InMEDIATE investigators group. Inhaled methoxyflurane provides greater analgesia and faster onset of action versus standard analgesia in patients with trauma pain. InMEDIATE: a randomized controlled trial in Emergency Departments. *Ann Emerg Med*. 2019. doi:10.1016/j.annemergmed.2019.07.028
21. Mercadante S, Voza A, Serra S, et al; MEDITA Study Group. Analgesic efficacy, practicality and safety of inhaled methoxyflurane versus standard analgesic treatment for acute trauma pain in the emergency setting: a randomised, open-label, active-controlled, multicentre trial in Italy (MEDITA). *Adv Ther*. 36;2019:3030–3046. doi:10.1007/s12325-019-01055-9
22. Marinangeli F, Reggiardo G, Sblendido A, Soldi A, Farina A; On behalf of The METEORA Group. Prospective, multicentre trial of methoxyflurane for acute trauma-related pain in helicopter emergency medical systems and hostile environments: METEORA protocol. *Adv Ther*. 2018;35:2081–2092. doi:10.1007/s12325-018-0816-8
23. Hartshorn S, Barrett MJ, Lyttle MD, et al; in collaboration with Paediatric Emergency Research in the UK and Ireland (PERUKI). Inhaled methoxyflurane (Penthrox®) versus placebo for injury-associated analgesia in children-the MAGPIE trial (MEOF-002): study protocol for a randomised controlled trial. *Trials*. 2019;20:393. doi:10.1186/s13063-019-3511-4

24. Raccomandazioni Intersocietarie Italiane (SIAARTI, SIMEU, SIS 118, AISD, SIARED, SICUT, IRC) sulla gestione del dolore in emergenza. Available from: http://www.aisd.it/e107_files/downloads/raccintersocietarie_it_complete31052014.pdf. Accessed January 24, 2020.
25. Fabbri A, Carpinteri G, Ruggiano G, et al. Methoxyflurane versus standard of care for acute trauma-related pain in the emergency setting: protocol for a randomised, controlled study in italy (MEDITA). *Adv Ther*. 2019;36:244–256. doi:10.1007/s12325-018-0830-x
26. Savoi G, Coluzzi F, Di Maria C, et al. Italian Intersociety Recommendations on pain management in the emergency setting (SIAARTI, SIMEU, SIS 118, AISD, SIARED, SICUT, IRC). *Minerva Anestesiol*. 2015;81:205–225.
27. Middleton PM, Simpson PM, Sinclair G, Dobbins TA, Math B, Bendall JC. Effectiveness of morphine, fentanyl, and methoxyflurane in the prehospital setting. *Prehosp Emerg Care*. 2010;14:439–447. doi:10.3109/10903127.2010.497896
28. Bendall JC, Simpson PM, Middleton PM. Effectiveness of prehospital morphine, fentanyl, and methoxyflurane in pediatric patients. *Prehosp Emerg Care*. 2011;15:158–165. doi:10.3109/10903127.2010.541980
29. Coffey F, Dissmann P, Mirza K, Lomax M. Methoxyflurane analgesia in adult patients in the emergency department: a subgroup analysis of a randomized, double-blind, placebo-controlled study (STOP!). *Adv Ther*. 2016;33:2012–2031. doi:10.1007/s12325-016-0405-7