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Pain management for medical abortion before 14 weeks' gestation (Review)

Reynolds-Wright JJ, Woldetsadik MA, Morroni C, Cameron S

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TABLE OF CONTENTS

[Intervention Review]

Pain management for medical abortion before 14 weeks' gestation

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ABSTRACT

Background

Abortion is common worldwide and increasingly abortions are performed at less than 14 weeks' gestation using medical methods, specifically using a combination of mifepristone and misoprostol. Medical abortion is known to be a painful process, but the optimal method of pain management is unclear. We sought to identify and compare pain management regimens for medical abortion before 14 weeks' gestation.

Objectives

Primary objective

To determine if there is evidence of superiority of any particular pain relief regimen in the management of combination medical abortion (mifepristone + misoprostol) under 14 weeks' gestation (i.e. up to 13 + 6 weeks or 97 days).

Secondary objectives

To compare the rate of gastrointestinal side effects resulting from different methods of analgesia

To compare the rate of complete abortion resulting from different methods of analgesia during medical abortion

To determine if the induction-to-abortion interval is associated with different methods of analgesia

To determine if any method of analgesia is associated with unscheduled contact with the care provider in relation to pain.

Search methods

On 21 August 2019 we searched CENTRAL, MEDLINE, Embase, CINAHL, LILACs, PsycINFO, the World Health Organization International Clinical Trials Registry and ClinicalTrials.gov together with reference checking and handsearching of conference abstracts of relevant learned societies and professional organisations to identify further studies.

Selection criteria

We included randomised controlled trials (RCTs) and observational studies (non-randomised studies of interventions (NRSIs)) of any pain relief intervention (pharmacological and non-pharmacological) for mifepristone-misoprostol combination medical abortion of pregnancies less than 14 weeks' gestation.

Data collection and analysis

Two review authors (JRW and MA) independently assessed all identified papers for inclusion and risks of bias, resolving any discrepancies through discussion with a third and fourth author as required (CM and SC). Two review authors independently conducted data extraction, including calculations of pain relief scores, and checked for accuracy. We assessed the certainty of the evidence using the GRADE approach.

Main results

We included four RCTs and one NRSI. Due to the heterogeneity of study designs, interventions and outcome reporting, we were unable to perform meta-analysis for any of the primary or secondary outcomes in this review.

Only one study found evidence of an effect between interventions on pain score: a prophylactic dose of ibuprofen 1600 mg likely reduces the pain score when compared to a dose of paracetamol 2000 mg (mean difference (MD) 2.26 out of 10 lower, 95% confidence interval (CI) 3.00 to 1.52 lower; 1 RCT 108 women; moderate-certainty evidence).

There may be little to no difference in pain score when comparing pregabalin 300 mg with placebo (MD 0.5 out of 10 lower, 95% CI 1.41 lower to 0.41 higher; 1 RCT, 107 women; low-certainty evidence).

There may be little to no difference in pain score when comparing ibuprofen 800 mg with placebo (MD 1.4 out of 10 lower, 95% CI 3.33 lower to 0.53 higher; 1 RCT, 61 women; low-certainty evidence).

Ambulation or non-ambulation during medical abortion treatment may have little to no effect on pain score, but the evidence is very uncertain (MD 0.1 out of 5 higher, 95% CI 0.26 lower to 0.46 higher; 1 NRSI, 130 women; very low-certainty evidence).

There may be little to no difference in pain score when comparing therapeutic versus prophylactic administration of ibuprofen 800 mg (MD 0.2 out of 10 higher, 95% CI 0.41 lower to 0.81 higher; 1 RCT, 228 women; low-certainty evidence).

Other outcomes of interest were reported inconsistently across studies. Where these outcomes were reported, there was no evidence of difference in incidence of gastrointestinal side effects, complete abortion rate, interval between misoprostol administration to pregnancy expulsion, unscheduled contact with a care provider, patient satisfaction with analgesia regimen nor patient satisfaction with abortion experience overall. However, the certainty of evidence was very low to low.

Authors' conclusions

The findings of this review provide some support for the use of ibuprofen as a single dose given with misoprostol prophylactically, or in response to pain as needed. The optimal dosing of ibuprofen is unclear, but a single dose of ibuprofen 1600 mg was shown to be effective, and it was less certain whether 800 mg was effective. Paracetamol 2000 mg does not improve pain scores as much as ibuprofen 1600 mg, however its use does not appear to cause greater frequency of side effects or reduce the success of the abortion.

A single dose of pregabalin 300 mg does not affect pain scores during medical abortion, but like paracetamol, does not appear to cause harm. Ambulation or non-ambulation during the medical abortion procedure does not appear to affect pain scores, outcomes, or duration of treatment and so women can be advised to mobilise or not, as they wish.

The majority of outcomes in this review had low- to very low-certainty evidence, primarily due to small sample sizes and two studies at high risk of bias. High-quality, large-scale RCT research is needed for pain management during medical abortion at gestations less than 14 weeks. Consistent recording of pain with a validated measure would be of value to the field going forward.

PLAIN LANGUAGE SUMMARY

Pain management for medical abortion before 14 weeks' gestation

Key Messages

• Ibuprofen has the best evidence for managing pain during medical abortion in the first 14 weeks of pregnancy, but the best dose is unclear.

• Further studies are needed along with a robust, consistent way of recording pain.

What is medical abortion?

There are two main types of abortion - surgical or medical. Surgical abortion is carried out by specialist doctors in a clinic. In medical abortion, women take medicine ('abortion pills' consisting of mifepristone and misoprostol) to end their pregnancy. Medical abortion is increasingly common worldwide, but it is known to cause cramping and lower abdominal pain. In the first 14 weeks of pregnancy, medical abortion can take place in a clinic or at home, so it’s important that women have ways of treating themselves for pain.

What did we want to find out?

It is unclear what the best method of treating this pain is. We were interested in what the evidence was for pain relief medicines, such as ibuprofen or opiates, and other non-medicinal methods like hot water bottles or mindfulness.

What did we do?

We looked for studies that compared different pain relief treatments for medical abortion in the first 14 weeks of pregnancy.

What did we find?

We found five different studies, all of them looking at different kinds of treatment. Two studies were conducted in Israel, one of which compared ibuprofen with placebo, and another compared ibuprofen with paracetamol. Two studies were conducted in the USA, one compared ibuprofen given in response to pain or preventatively, and another compared pregabalin with placebo. The final study was conducted in the UK and compared being mobile during treatment with resting.

Main results

We found some evidence for the use of ibuprofen given either routinely with misoprostol, or in response to pain as needed.

The best dose of ibuprofen is unclear, but a single dose of ibuprofen 1600 mg was likely effective, and it was less certain whether 800 mg was effective. Paracetamol 2000 mg was less likely to improve pain scores as much as ibuprofen 1600 mg, however its use did not appear to cause harm, and it did not affect the success of the abortion.

A single dose of pregabalin 300mg may not affect pain scores during medical abortion, but like paracetamol, it did not result in any known harm. Being mobile or resting during the medical abortion procedure may not affect pain scores, or the success of the abortion or the time taken to pass the pregnancy.

Limitations of the evidence

The studies were all relatively small and no study compared the same treatment. As such, we could not compare their results.

How up to date is the evidence?

The evidence is up-to-date to 21 August 2019.

Summary of findings 1. Summary of findings table - Ibuprofen 1600 mg compared to paracetamol 2000 mg for women having medical abortion before 14 weeks? gestation

Ibuprofen 1600 mg compared to paracetamol 2000 mg for women having medical abortion before 14 weeks' gestation

Patient or population: women having medical abortion before 14 weeks' gestation
Setting: clinic, Israel
Intervention: Ibuprofen 1600 mg
Comparison: Paracetamol 2000 mg

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Paracetamol 2000 mg	Risk with Ibuprofen 1600 mg				
Pain score	The mean pain score was **5.67** out of 10	MD **2.26 out of 10 lower** (3 lower to 1.52 lower)	-	108 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	
Gastrointestinal side effects (nausea) - not reported	-	-	-	-	-	
Gastroinestinal side effects (vomiting) - not reported	-	-	-	-	-	
Gastrointestinal side effects (diarrhoea) - not reported	-	-	-	-	-	
Complete abortion rate	837 per 1000	**915 per 1000** (766 to 973)	**OR 2.11** (0.64 to 6.92)	108 (1 RCT)	⊕⊕⊖⊖ Low[b]	
Induction to expulsion interval - not reported	-	-	-	-	-	
Unscheduled contact with care - not reported	-	-	-	-	-	
Patient satisfaction with analgesia - not reported	-	-	-	-	-	
Patient satisfaction with abortion care overall - not reported	-	-	-	-	-	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_419478415248553147.

[a] Downgraded 1 level for imprecision: small sample size.
[b] Downgraded 2 levels for imprecision: small sample size and 95% confidence intervals include no effect.

Summary of findings 2. Summary of findings table - Pregabalin 300 mg compared to placebo for women having medical abortion before 14 weeks? gestation

Pregabalin 300 mg compared to placebo for women having medical abortion before 14 weeks' gestation

Patient or population: women having medical abortion before 14 weeks' gestation
Setting: clinic, USA
Intervention: pregabalin 300 mg
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with pregabalin 300 mg				
Pain score	The mean pain score was **5.5** out of 10	MD **0.5 out of 10 lower** (1.41 lower to 0.41 higher)	-	107 (1 RCT)	⊕⊕⊖⊖ Low[a]	
Gastrointestinal side effects (nausea)	808 per 1000	**781 per 1000** (581 to 902)	**OR 0.85** (0.33 to 2.19)	107 (1 RCT)	⊕⊕⊖⊖ Low[a]	
Gastrointestinal side effects (vomiting)	577 per 1000	**509 per 1000** (323 to 690)	**OR 0.76** (0.35 to 1.63)	107 (1 RCT)	⊕⊕⊖⊖ Low[a]	

Gastrointestinal side effects (diarrhoea)	558 per 1000	**508 per 1000** (324 to 689)	**OR 0.82** (0.38 to 1.76)	107 (1 RCT)	⊕⊕⊖⊖ Low[a]
Complete abortion rate - not reported	-	-	-	-	-
Induction to expulsion interval - not reported	-	-	-	-	-
Unscheduled contact with care - not reported	-	-	-	-	-
Patient satisfaction with analgesia	686 per 1000	**680 per 1000** (479 to 829)	**OR 0.97** (0.42 to 2.21)	104 (1 RCT)	⊕⊕⊖⊖ Low[a]
Patient satisfaction with abortion care overall	608 per 1000	**740 per 1000** (554 to 867)	**OR 1.84** (0.80 to 4.22)	105 (1 RCT)	⊕⊕⊖⊖ Low[a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
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See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_419478335724549023.

[a] Downgraded 2 levels for imprecision: small sample size and 95% confidence intervals include no effect.

Summary of findings 3. Summary of findings table - Ibuprofen 800 mg compared to placebo for women having medical abortion before 14 weeks? gestation

Ibuprofen 800 mg compared to placebo for women having medical abortion before 14 weeks' gestation

Patient or population: women having medical abortion before 14 weeks' gestation
Setting: clinic, Israel
Intervention: Ibuprofen 800 mg
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Ibuprofen 800 mg				
Pain score	The mean pain score was **5.4** out of 10	MD **1.4 out of 10 lower** (3.33 lower to 0.53 higher)	-	61 (1 RCT)	⊕⊕⊖⊖ Low[a]	
Gastrointestinal side effects (nausea)	594 per 1000	**690 per 1000** (436 to 865)	**OR 1.52** (0.53 to 4.37)	61 (1 RCT)	⊕⊕⊖⊖ Low[a]	
Gastrointestinal side effects (vomiting)	281 per 1000	**69 per 1000** (15 to 275)	**OR 0.19** (0.04 to 0.97)	61 (1 RCT)	⊕⊕⊖⊖ Low[a]	
Gastrointestinal side effects (diarrhoea) - not reported	-	-	-	-	-	
Complete abortion rate	875 per 1000	**828 per 1000** (543 to 952)	**OR 0.69** (0.17 to 2.85)	61 (1 RCT)	⊕⊕⊖⊖ Low[a]	
Induction to expulsion interval - not reported	-	-	-	-	-	
Unscheduled contact with care - not reported	-	-	-	-	-	
Patient satisfaction with analgesia - not reported	-	-	-	-	-	
Patient satisfaction with abortion care overall - not reported	-	-	-	-	-	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_419429983861681120.

[a] Downgraded 2 levels for imprecision: small sample size and wide 95% confidence intervals including no effect or very small effects.

Summary of findings 4. Summary of findings table - Ambulation compared to non-ambulation for women having medical abortion before 14 weeks? gestation

Ambulation compared to non-ambulation for women having medical abortion before 14 weeks' gestation

Patient or population: women having medical abortion before 14 weeks' gestation
Setting: clinic, UK
Intervention: ambulation
Comparison: non-ambulation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non-ambulation	Risk with ambulation				
Pain score	The mean pain score was **2.4** out of 5	MD **0.1 out of 5 higher** (0.26 lower to 0.46 higher)	-	130 (1 observational study)	⊕⊖⊖⊖ Very low[a,b]	
Gastrointestinal side effects (nausea) - not reported	-	-	-	-	-	
Gastrointestinal side effects (vomiting) - not reported	-	-	-	-	-	
Gastrointestinal side effects (diarrhoea) - not reported	-	-	-	-	-	
Complete abortion rate	Not pooled	Not pooled	Not pooled	(1 observational study)	⊕⊖⊖⊖ Very low[a,c]	Complete abortion rate 100% in both study groups
Induction to expulsion interval	The mean induction to expulsion interval was **233** minutes	MD **2.3 minutes lower** (38.78 lower to 34.18 higher)	-	130 (1 observational study)	⊕⊖⊖⊖ Very low[a,b]	

Unscheduled contact with care - not reported	-	-	-	-	-
Patient satisfaction with analgesia - not reported	-	-	-	-	-
Patient satisfaction with abortion care overall - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
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See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_419478490479686846.

[a] Downgraded 2 levels for risk of bias: high risk of bias from confounding and participant selection.
[b] Downgraded 2 levels for imprecision: small sample size and the 95% confidence intervals include no effect.
[c] Downgraded 1 level for imprecision: small sample size.

Summary of findings 5. Summary of findings table - Therapeutic ibuprofen 800 mg compared to prophylactic ibuprofen 800 mg women having medical abortion before 14 weeks? gestation

Therapeutic ibuprofen 800 mg compared to prophylactic ibuprofen 800 mg women having medical abortion before 14 weeks' gestation

Patient or population: women having medical abortion before 14 weeks' gestation
Setting: multiple clinics, USA
Intervention: therapeutic ibuprofen 800 mg
Comparison: prophylactic ibuprofen 800 mg

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with prophylactic ibuprofen 800 mg	Risk with therapeutic ibuprofen 800 mg				

Pain score	The mean pain score was **7.1** out of 10	MD **0.2 out of 10 higher** (0.41 lower to 0.81 higher)	-	228 (1 RCT)	⊕⊕⊖⊖ Low[a,b]
Gastrointestinal side effects (nausea and/or vomiting)	378 per 1000	**504 per 1000** (376 to 633)	**OR 1.67** (0.99 to 2.83)	228 (1 RCT)	⊕⊕⊖⊖ Low[a,b]
Gastrointestinal side effects (diarrhoea) - not reported	-	-	-	-	-
Complete abortion rate	964 per 1000	**974 per 1000** (892 to 994)	**OR 1.42** (0.31 to 6.50)	228 (1 RCT)	⊕⊕⊖⊖ Low[a,b]
Induction to expulsion interval - not reported	-	-	-	-	-
Unscheduled contact with care	360 per 1000	**367 per 1000** (253 to 499)	**OR 1.03** (0.60 to 1.77)	228 (1 RCT)	⊕⊕⊖⊖ Low[a,b]
Patient satisfaction with analgesia - not reported	-	-	-	-	-
Patient satisfaction with abortion care overall	982 per 1000	**966 per 1000** (831 to 994)	**OR 0.52** (0.09 to 2.89)	228 (1 RCT)	⊕⊕⊖⊖ Low[a,b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
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See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_419478610033865921.

[a] Downgraded 1 level for risk of bias: high risk of bias due to lack of blinding of outcomes assessors
[b] Downgraded 1 level for imprecision: 95% confidence interval includes no effect.

BACKGROUND

Description of the condition

It is estimated that 56 million induced abortions were performed globally each year between 2010 and 2014, 45% of which were unsafe (Ganatra 2017; Guttmacher Institute 2018). Combination medical abortion is the sequential use of mifepristone, a progesterone receptor antagonist, and misoprostol, a prostaglandin E1 analogue (Kulier 2011). It is difficult to accurately estimate the proportion of all abortions performed using medical methods worldwide, due to inconsistency in — or absence of — reporting, and the clandestine use of medical methods in legally restrictive settings. However, in countries where mifepristone is available, an increasing proportion of abortion care is delivered medically, due to the high level of efficacy and relatively low levels of side effects of combination medical abortion (WHO 2018). In Europe, reported rates of combination medical abortion range from 17.8% in Italy to 97.7% in Finland (Ministry of Health 2018; National Institute for Health and Welfare 2019).

Medical abortion is known to be a painful process due to contraction of uterine smooth muscle and passage of the conceptus through the cervix. Approximately 75% of women who undergo early medical abortion before nine weeks use opiate-based analgesia (Penney 2006). Pain is a common reason for dissatisfaction with the method, so adequate pain relief is essential in order to improve access to, and tolerability of, this highly effective and safe method of abortion. Medical abortion under 14 weeks' gestation can occur outside of clinic settings (such as the home) and so pain relief strategies that can be self-administered are important. This review will therefore assess pain management for medical abortion under 14 weeks' gestation; this refers to abortions performed up to and including 13 weeks + 6 days (97 days) of gestation from last menstrual period. A separate Cochrane Review will consider pain management for medical abortion after 14 weeks' gestation.

Description of the intervention

The intervention to be investigated by this review is pain relief, both pharmacological and non-pharmacological, in medical abortion under 14 weeks' gestation. There are a variety of different methods of pain relief and newer classes of pain medications have been investigated in recent years in the management of medical abortion. Additionally, we will consider use of prophylactic versus 'when necessary' pain relief, as well as single and combination interventions, such as multiple drug regimens or drug plus psychological intervention.

How the intervention might work

Medical abortion is a painful process and can impact on the satisfaction with, and tolerability of, medical abortion. Many factors influence perception and expression of pain including gestation, previous pregnancy, chronic pain conditions and anxiety. Excessive pain may lead to unscheduled contact with care providers and admission to a clinical facility. The availability of a range of effective pain relief interventions may enable women to have treatment at home and receive care from more diverse cadres of healthcare providers and therefore broaden access to the method.

Pharmacological interventions may include non-steroidal anti-inflammatory drugs and opiates, and may shorten the induction-to-expulsion interval in medical abortion. Non-pharmacological strategies may include use of a hot-water bottle or heating pad on the lower abdomen or use of a personal supporter or a psychological therapy, such as mindfulness (a meditative therapeutic technique). Optimal analgesia may use a multimodal approach.

Why it is important to do this review

If effective pain management regimens used with medical abortion can be expanded and optimised, this may improve the patient experience and improve uptake and access to medical abortion. Reducing suffering is also a positive outcome on its own. Additionally, there is a degree of heterogeneity in pain relief guidelines at regional, national and international levels. By conducting this review, we aim to provide a clear statement of the evidence for different regimens that can be used to inform recommendations for practice internationally.

OBJECTIVES

Primary objective

- To determine if there is evidence of superiority of any particular pain relief regimen in the management of combination medical abortion (mifepristone + misoprostol) under 14 weeks' gestation (i.e. up to 13 + 6 weeks or 97 days)

Secondary objectives

- To compare the rate of gastrointestinal side effects resulting from different methods of analgesia
- To compare the rate of complete abortion resulting from different methods of analgesia during medical abortion
- To determine if the induction-to-abortion interval is associated with different methods of analgesia
- To determine if any method of analgesia is associated with unscheduled contact with the care provider in relation to pain

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSIs). We decided to include observational studies, as the largest studies are cohort studies and randomised trial evidence is limited. We included studies that reported only on mifepristone–misoprostol combination medical abortion. Mifepristone was first licensed in France in 1988 for use in medical abortion and so studies were restricted from 1988 until 21 August 2019.

Types of participants

Participants were women and girls who had a medical abortion at less than 14 + 0 weeks' gestation (13 weeks + 6 days or 97 days of gestation from last menstrual period) as determined by ultrasound scan or clinical assessment. Inclusion was not limited by participant age, treatment setting or geographical location.

Types of interventions

Interventions included any form of pharmacological, non-pharmacological or multimodal form of analgesia. This included psychological interventions, such as cognitive behavioural interventions, mindfulness or meditation.

Types of outcome measures

Primary outcomes

Self-reported maximal pain score within 24 hours of final dose of misoprostol – this is the time frame when most expulsions of pregnancy will occur, and pain is typically maximal just before expulsion during medical abortion.

On first pass, we included studies only if they have collected pain outcomes using a validated tool, such as the visual analogue scale (VAS). If there was an insufficient number of studies, we included other proxy markers of pain control, such as:

- analgesia intake;
- patient request for analgesia;
- use of level 2 and 3 of World Health Organization (WHO) analgesia ladder medications;
- Likert pain rating versus expectation (e.g. worse than, better than, as expected).

Secondary outcomes

- Incidence of gastrointestinal side effects: proportion experiencing each of the following — nausea, vomiting, diarrhoea from first dose of misoprostol up until 24 hours after last dose
- Complete abortion rate (without the need for surgical intervention) within 14 days of treatment
- Time from initial dose of misoprostol to expulsion of pregnancy (induction-to-abortion interval)
- Unscheduled contacts with care provider (in-person and telephone contact) related to uncontrolled acute pain/pain worse than expected from first dose of misoprostol to 24 hours after last dose
- Patient satisfaction with analgesia regimen (as rated by Likert scale or other tool)
- Patient satisfaction with abortion overall (as rated by Likert scale or other tool)

Search methods for identification of studies

On 21 August 2019 Cochrane Fertility Regulation's Information Specialist conducted a search for all published, unpublished, and ongoing studies, without restrictions on language or publication status. We modelled the search strategies for each database on the search strategy designed for MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily), available in Appendix 1. We checked the bibliographies of included studies and any relevant systematic reviews that we identified for further references to relevant studies. We contacted experts and organisations in the field to obtain additional information on relevant studies. When necessary, we contacted authors of included studies for data clarification and further information. We considered adverse effects described in included studies only.

Electronic searches

We searched the following databases from their inception to 21 August 2019.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 7) in the Cochrane Library (searched 21 August 2019)
- EBM Reviews Ovid
- MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; 1976 to 21 August 2019)
- Embase.com (1974 to 21 August 2019)
- CINAHL (EBSCOHost; 1982 to 21 August 2019)
- LILACs (lilacs.bvsalud.org/en; searched 21 August 2019)
- PsycINFO Ovid (1806 to 21 August 2019)

We searched the following trials registries.

- The World Health Organization International Clinical Trials Registry Platform www.who.int/trialsearch (searched 21 August 2019)
- www.ClinicalTrials.gov(searched 21 August 2019)

Searching other resources

- Secondary reference-checking of included studies (searched 21 August 2019)
- Handsearching of organisations with relevant conferences for abstracts – FIAPAC, FSRH, ESC, NAF, FIGO, RCOG, RANZCOG, ACOG, NFOG, SFP, SOGC, BSACP, SACP (see Appendix 1 for abbreviations in full; searched 21 August 2019).

Data collection and analysis

Selection of studies

Two review authors (JRW and MA) screened the titles, abstracts, citation information, and descriptor terms of citations initially identified through the search strategy. We obtained full-text articles of all selected potentially eligible study abstracts. The same two review authors independently examined these full-text articles for compliance with the inclusion criteria and determination of final study selection. We resolved disagreements by inviting a third member of the team (CM or STC) to arbitrate. We documented this selection process according to PRISMA recommendations (Page 2021).

Data extraction and management

Two review authors (JRW and MA) independently extracted data using standardised data extraction forms, with disagreements resolved by a third or fourth opinion from within the review team (CM and STC).

We collected information from the included studies using data extraction forms on:

- study objectives
- location/setting of abortion/expulsion (i.e. home/clinic/hospital/other)
- geographical location (i.e. state/country/region)
- gestational age reported at treatment

- previous obstetric history
  - number of term pregnancies (≥ 37 ± 0 weeks)
    - mode of delivery (spontaneous vaginal delivery, caesarean section, forceps-assisted delivery, vacuum-assisted delivery)
  - number of previous abortions
    - method of abortion
- number of other pregnancies
- history of dysmenorrhoea (known/unknown cause)
- abortion medication regimen
  - dosages of abortifacients
    - mifepristone
    - misoprostol
    - mifepristone–misoprostol interval
  - route of administration of misoprostol
  - frequency of dosing including use of a loading dose (i.e. in medical abortion after 10 weeks)
- pain management regimen
  - pharmacological
    - type(s) of pain medication – include class and drug name
    - dosages
    - frequency and duration
    - first dose: prophylactic – before misoprostol/with misoprostol/after misoprostol; in response to pain only
  - non-pharmacological
    - type
    - duration/frequency
  - multimodal/unimodal approaches
    - pharmacological – number of different drugs/different classes used per study arm
    - pharmacological + non-pharmacological – combination of strategies used per arm
- study design
  - RCT
  - observational – prospective, retrospective, cohort, case control, cross-sectional
  - blinding process – none, single or double
- sample size
  - total
  - per arm/comparator group
- follow-up periods
  - timing of outcome assessments
- loss to follow-up rates
  - primary outcome – pain score
  - secondary outcomes
- data analysis conducted
- outcome measures
  - pain reported as an outcome – yes/no
  - systematic questioning of participants about pain versus recording pain if reported by participants
  - tool used to report pain outcome – VAS, Likert scale, worst pain, strongest medication used, other pain scores/rating/strongest pain medication used (as reported)
  - complete abortion rate – without need for surgical intervention
  - time from misoprostol to expulsion (if reported)
  - proportion of women reporting gastrointestinal side effects (nausea, vomiting and diarrhoea) from first dose of misoprostol until 24 hours after last dose
  - proportion of women requiring treatment for gastrointestinal side effects (antiemetic/antidiarrhoeal agent)
  - time of pain recording/VAS administration – prospective collection or recall at a delayed interval?
- number of participants in each comparison group (as appropriate for study type)
- type of effect reported – for example relative risk, means
  - effect sizes (if reported)
- confidence intervals (if reported)
- significance levels (if reported)
  - does this meet Cochrane pre-set clinical significance level?
- conclusions
- limitations of studies

We attempted to contact study authors when insufficient information was presented on methods or results, or both.

Assessment of risk of bias in included studies

Two review authors (JRW and MA) independently assessed the risk of bias using the Cochrane RoB 2 tool for RCTs (Sterne 2019), and ROBINS-I for observational studies (NRSIs; Sterne 2016). If there was significant disagreement, a third member of the team assisted (CM).

We assessed the risk of bias of RCTs according to the following domains.

- Bias arising from the randomisation process
- Bias due to deviations from intended intervention
- Bias due to missing outcome data
- Bias in the measurement of the outcome
- Bias in the selection of the reported result
- Other bias

We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trial author, we noted this in the risk of bias table. We did not exclude studies on the grounds of their risk of bias, but clearly reported the bias when presenting the results of the studies.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

We used the ROBINS-I tool to assess the risk of bias for each outcome reported in observational studies according to the following domains.

- Confounding
- Co-interventions
- Selection bias
- Deviations from intended interventions
- Missing data
- Measurements of outcomes
- Selection of the reported result

We judged each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the domains listed.

We will conduct the review according to our published protocol (Reynolds-Wright 2020), and report any deviations from it in the 'Differences between protocol and review' section of the review.

Measures of treatment effect

We pre-set the minimally important difference for each of the outcome measures at 5%. For pain scores reported by VAS, clinical significance was a difference of at least 17 mm (Olsen 2017).

We considered all effect measures reported by individual studies; reporting of outcome measures were not inclusion criteria for the review. Measures of treatment effect could include risk ratios, odds ratios, number needed to treat for an additional beneficial outcome or for an additional harmful outcome, mean difference, prevalence, or simple descriptive statistics.

If we had found sufficient comparable data to conduct meta-analysis for any of the primary or secondary outcomes, we would have started with fixed-effect models. However, if there were a high level of heterogeneity across studies, we may have changed to a random-effects meta-analysis and presented both analyses.

Unit of analysis issues

For RCTs, we planned to consider the unit of analysis as 'per woman randomised'. Given the nature of abortion care, we did not anticipate cross-over design trials. It was possible that there were cluster-RCTs, in which case we might have needed to conduct analysis on a 'multilevel model', a 'variance components analysis' or with 'generalised estimating equations' (GEEs).

Dealing with missing data

Where we identified missing data, we attempted to contact the study authors to obtain more information.

For studies in which data were missing or incomplete, we reported the findings as 'unclear', or 'high risk' if the missing data raised a potential risk of bias.

Assessment of heterogeneity

If we had found a sufficient number of studies we would have conducted meta-analysis. We planned to assess heterogeneity in meta-analyses using the Chi^2 test (P = 0.10), the I^2 statistic (Higgins 2003), and thresholds, described as follows in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021).

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;
- 75% to 100%: considerable heterogeneity*.

*The importance of the observed value of the I^2 statistic depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a confidence interval for I^2 statistic; Deeks 2021).

If we had identified substantial heterogeneity we would have explored it by prespecified subgroup analysis.

Assessment of reporting biases

A form of reporting bias is unavoidable but, in order to minimise its effect upon this review, we conducted a thorough search of published literature and also trial registries to identify unpublished work; and we contacted authors for data sets appropriate for the review outcomes. We needed to appraise the quality of these unpublished studies — all the review authors have experience of peer review. We would have created a funnel plot to attempt to identify publication bias if at least 10 studies reporting an individual outcome were available.

Data synthesis

We analysed data by outcome, using RevMan Web software (RevMan Web 2020). We would have conducted a meta-analysis if studies presented data on sufficiently comparable outcomes. We would have combined effect sizes in odds ratios using the Mantel-Haenszel method. We planned to transform other measures, such as standardised mean difference, to log odds ratios for the purpose of analysis (Deeks 2021). We presented and analysed RCT data separately from NRSI data.

We conducted a narrative synthesis for outcomes that lacked adequate data to combine studies. This synthesis considered the consequences of possible incomplete reporting on the outcomes of interest, and the strengths and limitations of available studies for evaluating the review questions.

Subgroup analysis and investigation of heterogeneity

If we found sufficient data, we planned to conducted subgroup analyses based on the following.

- Gestations: participants with gestations up to 10 weeks compared to 10 + 1 to 13 + 6 weeks. We have selected above and below 10 weeks as this is the gestational limit licensed by the US Food and Drug Administration (FDA) for use of mifepristone in medical abortion
- Treatment location: home versus in hospital/clinic/other health facility
- Multimodal versus unimodal analgesia
- By age group – under 20 years of age versus over 20 years of age (as per WHO definition of adolescence)
- By parity: nulliparous versus parous
- By timing of analgesia administration: empirical versus as-required analgesia

- By total dose of misoprostol
- By route(s) of misoprostol administration (sublingual, vaginal, buccal, oral)

Sensitivity analysis

We would have conducted sensitivity analyses based upon the data found during the review process. If there had been a high risk of bias in studies, we would have removed them and reanalysed.

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables for the main intervention comparisons and included the seven most important outcomes (self-reported maximal pain score, incidence of gastrointestinal side effects, complete abortion rate, time from initial dose to expulsion of pregnancy, unscheduled contacts with care provider, and patient satisfaction) in order to draw conclusions about the certainty of the evidence within the text of the review. If during the review process we become aware of an important outcome that we failed to list in our planned summary of findings tables, we will include the relevant outcome and explain the reasons for this in the section 'Differences between protocol and review'.

Two review authors independently assessed the certainty of the evidence (high, moderate, low, and very low) using the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias; Guyatt 2008). We used methods and recommendations described in Section 8.5 (Higgins 2011), and Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021), and using GRADEpro GDTsoftware (GRADEpro GDT). We resolved disagreements on certainty ratings by discussion and provided justification for decisions to down- or upgrade the ratings using footnotes in the table and made comments to aid readers' understanding of the review where necessary. We used plain language statements to report these findings in the review (EPOC 2013).

RESULTS

Description of studies

Results of the search

The search retrieved 4065 articles. We retrieved the full texts of 180 potentially eligible articles. Five studies (five articles) met our inclusion criteria. See Characteristics of included studies; Figure 1.

Figure 1.

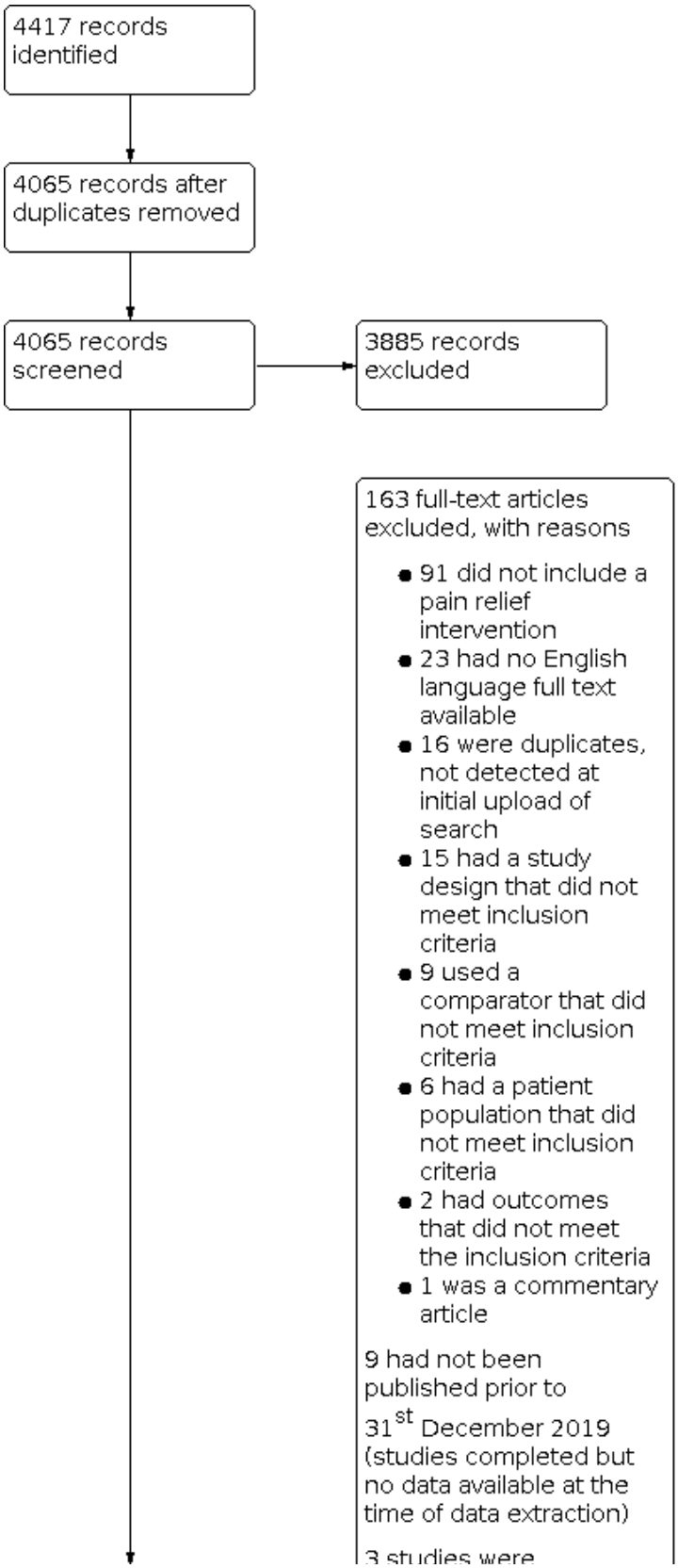
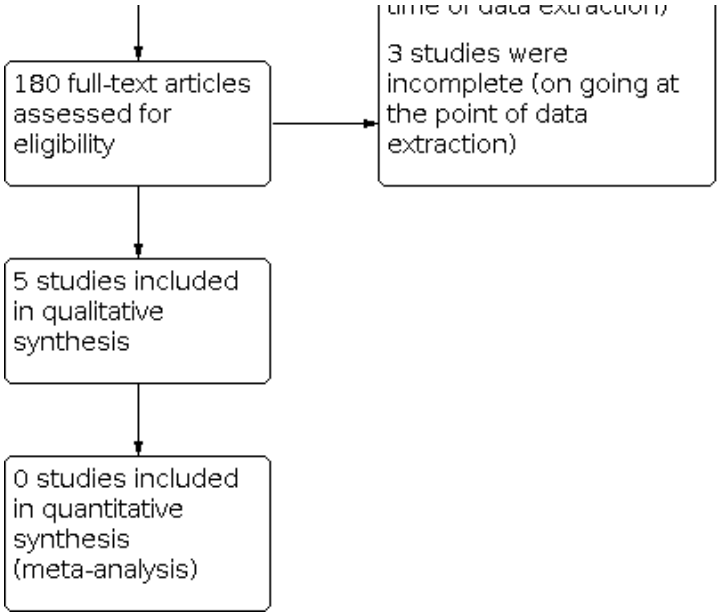


Figure 1. (Continued)



A further 12 studies may have met our inclusion criteria, however three of these were incomplete at the time of data extraction and nine were complete, but no data were available or published. We attempted to contact the authors of these studies, but either had no response or they were unable to provide us with data for inclusion in the review. See Studies awaiting classification; Ongoing studies; Figure 1.

Included studies

Study design and setting

We included four parallel-design RCTs (Avraham 2012; Friedlander 2018; Livshits 2009; Raymond 2013), and one non-randomised clinical trial (Ojha 2012), where women chose the intervention they wished to receive. Two studies were conducted in Israel, two in the USA and one in the UK. Four were single-centre studies conducted in abortion clinics. One study was multi-site, conducted at three centres in the USA.

Participants

The studies included 534 women requesting medical abortion at less than 14 weeks' gestation. There were limited data on important characteristics. Only two studies reported exact gestational age: in Friedlander 2018 the mean gestational age was 55.15 days (standard deviation (SD) 6.9) in the placebo group and 52.51 days (SD 8.16) in the pregabalin group. In Ojha 2012, mean gestational age was 50.5 days (SD 7.7) in the ambulation group and 52.8 days (SD 6.6) in the non-ambulation group.

Only one study reported participants' previous pregnancies: Ojha 2012 reported mean numbers of previous term pregnancies, which were 1.1 (SD 1.3) in the ambulation group and 1.0 (SD 1.4) in the non-ambulation group.

Only three studies reported participant age, and they all used different formats: Ojha 2012 reported mean age per group, which was 27.9 years in the ambulation group and 29.4 years in the non-ambulation group; Friedlander 2018 reported the mean age per group as 27.19 years (SD 6.02) in the placebo group and 27.25 years (SD 5.45) in the pregabalin group; Raymond 2013 reported age bandings per group, with two women aged 16 to 17 years, 52 women aged 18 to 24, and 57 women aged 25 to 44 years in the prophylactic ibuprofen group; and with two women aged 16 to 17 years, 50 women aged 18 to 24, and 65 women aged 25 to 44 years in the therapeutic ibuprofen group.

Interventions

No study used the same intervention or comparator. Three of the RCTs used ibuprofen: one RCT compared prophylactic ibuprofen with prophylactic paracetamol (Livshits 2009); one RCT compared prophylactic ibuprofen with placebo (Avraham 2012); and one compared prophylactic use of ibuprofen to therapeutic use of ibuprofen (Raymond 2013). One RCT (Friedlander 2018), compared prophylactic pregabalin with placebo. The NRSI (Ojha 2012), compared ambulation versus non-ambulation during treatment, from the point of misoprostol administration.

Outcomes

All studies reported pain outcomes, but in different ways. The four RCTs reported pain using an 11-point Likert scale, however two reported pain at two hours post-misoprostol administration (Avraham 2012; Livshits 2009), one reported worst pain in the 24-hour period following misoprostol (Raymond 2013), and one reported pain scores at multiple time points (immediately after misoprostol administration and then at 2, 6, 12, 24 and 72 hours later) (Friedlander 2018). The NRSI (Ojha 2012), used a 6-point Likert scale to report worst pain score pain in the 24-hour period following misoprostol.

Due to the heterogeneity of the outcome measures and interventions, meta-analysis was not possible or appropriate.

All studies also reported at least one secondary outcome of interest, but none included data suitable for meta-analysis.

Excluded studies

We excluded 163 studies from the review, for the following reasons:

- 91 did not include a pain relief intervention
- 23 had no English language full text available
- 16 were duplicates, not detected at initial upload of search
- 15 had a study design that did not meet inclusion criteria
- 9 used a comparator that did not meet inclusion criteria
- 6 had a patient population that did not meet inclusion criteria
- 2 had outcomes that did not meet the inclusion criteria
- 1 was a commentary article

Risk of bias in included studies

We discuss risk of bias separately for the four RCTs using the RoB 2 tool (Table 1; Sterne 2019) and the NRSI using the ROBINS-I tool (Table 2; Sterne 2016). Visual results for RoB 2 and ROBINS-I assessments were created using robvis VISualization tool (Figure 2; Figure 3; McGuinness 2021).

Figure 2. RoB 2 figure

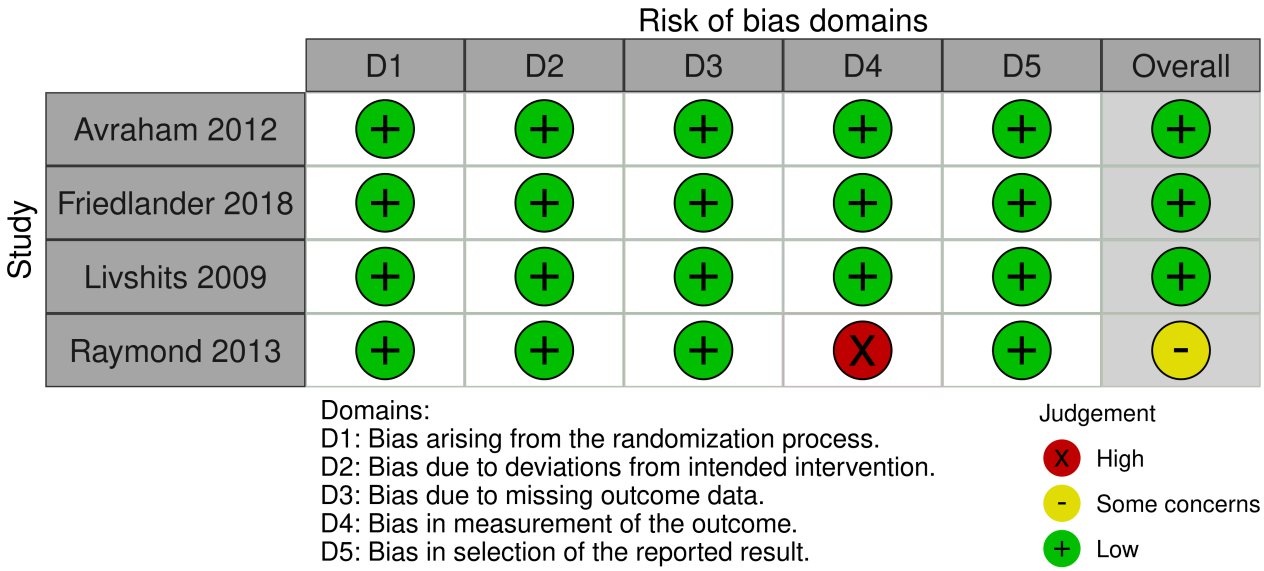
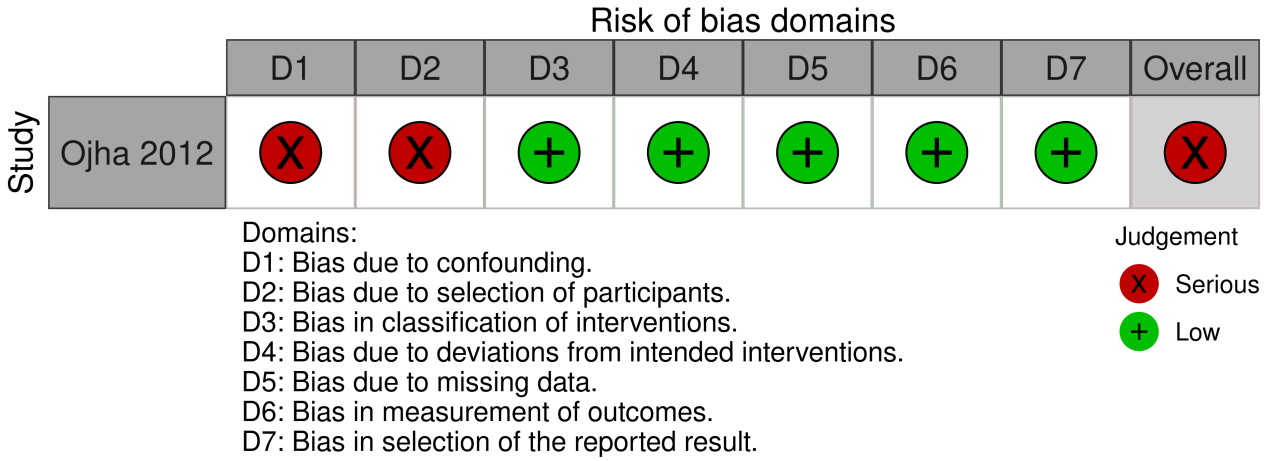


Figure 3. ROBINS-I assessement



Randomized studies of an intervention

Bias arising from the randomisation process

We rated all four studies as low risk of bias due to the randomization process: for sequence generation all four studies used computer-generated randomisation or random number tables; for allocation concealment all four studies used consecutively numbered, sealed opaque envelopes.

Bias due to deviations from intended intervention

We rated all four studies as being at low risk of bias due to deviation from the intended intervention.

Bias in measurement of the outcome

Three studies were at low risk of performance and detection bias due to blinding of both participants and study personnel, and outcomes assessors.

We deemed one study (Raymond 2013), to be at high risk of detection bias due to the outcomes assessors not being blinded. However, we felt that it remained at low risk of performance bias despite not being blinded as we did not consider blinding to influence behaviour.

Bias due to missing outcome data

All four studies included all or most (> 95%) of the randomised women in their analyses, and so we judged these studies to be at low risk of bias due to missing outcome data.

Bias in selection of the reported result

We rated all four studies as at low risk of selective reporting bias. Studies reported all outcomes planned in the protocols and these included pain scores.

Other potential sources of bias

We judged three of the RCTs to be at low risk of other forms of bias. We judged one RCT (Raymond 2013), to be at unclear risk of bias as pain scores were collected by recall for some participants who did not complete the contemporaneous diary. The number and proportion of participants completing their pain diaries at a later date is small and comparable in both groups and so may not affect the overall result, but we cannot say this with certainty as the results were aggregated on presentation.

Non-randomised study of an intervention

Selection of reported result

We rated the single NRSI (Ojha 2012), as low risk of bias due for selection of result reported as this was a prospective trial with prespecified outcomes, albeit not an RCT, rather than a retrospective cohort where results could be 'cherry-picked'.

Confounding

We rated Ojha 2012 as being at high risk of bias due to confounding factors. The study did not appear to use any analytical methods to control for post-intervention and time-varying confounding variables.

Selection of participants

Ojha 2012 was at high risk of bias from selection of participants. Participants at baseline were included in an arm of the study for which they expressed a preference.

Classification of interventions

Ojha 2012 was at low risk of bias for classification of the intervention. Intervention groups were clearly defined and not affected by knowledge of the outcome.

Deviation from intended interventions

Ojha 2012 was at low risk from bias due to deviations from intended intervention – no participants in the study deviated from their intended treatment.

Missing data

Ojha 2012 was at low risk of bias due to missing data. Outcome data were complete and available for all participants.

Measurement of outcomes

We deemed Ojha 2012 to be at low risk of bias for outcome measurement. While the outcomes assessors were not blinded, it is unlikely that awareness of the treatment arm would influence recording of the pain outcome as the pain rating measures were standardised across both study arms and collected prospectively and contemporaneously, as in the RCTs.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Ibuprofen 1600 mg compared to paracetamol 2000 mg for women having medical abortion before 14 weeks? gestation; **Summary of findings 2** Summary of findings table - Pregabalin 300 mg compared to placebo for women having medical abortion before 14 weeks? gestation; **Summary of findings 3** Summary of findings table - Ibuprofen 800 mg compared to placebo for women having medical abortion before 14 weeks? gestation; **Summary of findings 4** Summary of findings table - Ambulation compared to non-ambulation for women having medical abortion before 14 weeks? gestation; **Summary of findings 5** Summary of findings table - Therapeutic ibuprofen 800 mg compared to prophylactic ibuprofen 800 mg women having medical abortion before 14 weeks? gestation

Due to the heterogeneity of study designs, interventions and outcome reporting, we were unable to perform meta-analysis for any of the primary or secondary outcomes in this review.

Primary outcomes

Self-reported maximal pain score within 24 hours of final dose of misoprostol

Only one study (Livshits 2009), found evidence of an effect between interventions on pain score. A prophylactic dose of ibuprofen 1600 mg likely reduces the pain score when compared to a dose of paracetamol 2000 mg (mean difference (MD) 2.26 out of 10 lower, 95% confidence interval (CI) 3.00 lower to 1.52 lower; 1 RCT, 108 women; moderate-certainty evidence; Analysis 1.1).

There may be little to no difference in pain score when comparing pregabalin 300 mg with placebo (MD 0.5 out of 10 lower, 95%

CI 1.41 lower to 0.41 higher; 1 RCT, 107 women; low-certainty evidence; Analysis 2.1; Friedlander 2018).

There may be little to no difference in pain score when comparing ibuprofen 800 mg with placebo (MD 1.4 out of 10 lower, 95% CI 3.33 lower to 0.53 higher; 1 RCT, 61 women; low-certainty evidence; Analysis 3.1; Avraham 2012).

Ambulation or non-ambulation during medical abortion treatment may have little to no effect on pain score, but the evidence is very uncertain (MD 0.1 out of 5 higher, 95% CI 0.26 lower to 0.46 higher; 1 NRSI; 130 women; very low-certainty evidence; Analysis 4.1; Ojha 2012).

There may be little to no difference in pain score when comparing therapeutic versus prophylactic administration of ibuprofen 800 mg (MD 0.2 out of 10 higher, 95% CI 0.41 lower to 0.81 higher; 1 RCT, 228 women; low-certainty evidence; Analysis 5.1; Raymond 2013).

Secondary outcomes

Incidence of gastrointestinal side effects

Three studies (all RCTs) explicitly reported on gastrointestinal side effects.

Friedlander 2018 compared pregabalin 300 mg with placebo. The evidence suggests there is little to no difference in the rate of nausea (odds ratio (OR) 0.85, 95% CI 0.33 to 2.19; 1 RCT, 107 women; low-certainty evidence; Analysis 2.2), vomiting (OR 0.76, 95% CI 0.35 to 1.63; 1 RCT, 107 women; low-certainty evidence; Analysis 2.3) or diarrhoea (OR 0.82, 95% CI 0.38 to 1.76; 1 RCT, 107 women; low-certainty evidence; Analysis 2.4). The study did not report data on anti-emetic/anti-diarrhoeal use.

Avraham 2012 compared ibuprofen 800 mg with placebo. The evidence suggests there is little to no difference in the rate of nausea (OR 1.52, 95% CI 0.53 to 4.37; 1 RCT, 61 women; low-certainty evidence; Analysis 3.2) or vomiting (OR 0.19, 95% CI 0.04 to 0.97; 1 RCT, 61 women; low-certainty evidence; Analysis 3.3). This study did not report data on rates of diarrhoea or anti-emetic/anti-diarrhoeal use.

Raymond 2013 compared therapeutic with prophylactic ibuprofen 800 mg. The evidence suggests there is little to no difference in the rate of nausea or vomiting, or both (OR 1.67, 95% CI 0.99 to 2.83; 1 RCT, 228 women; low-certainty evidence; Analysis 5.2). We could not disaggregate nausea and vomiting. This study did not report data on rates of diarrhoea or anti-emetic/anti-diarrhoeal use.

The fourth RCT, Livshits 2009, compared ibuprofen 1600 mg with paracetamol 2000 mg, and stated that they found no difference between groups with regard to rate of nausea and vomiting, however, they only stated it in the text, they did not present the primary data in the paper.

The NRSI comparing ambulation with non-ambulation did not report gastrointestinal side effects (Ojha 2012).

Complete abortion rate

Four studies (3 RCTs and 1 NRSI) reported on complete abortion rate.

Livshits 2009 compared ibuprofen 1600 mg with paracetamol 2000 mg and suggests that there is little to no difference in complete abortion rate (OR 2.11, 95% CI 0.64 to 6.92; 1 RCT, 108 women; low-certainty evidence; Analysis 1.2).

Avraham 2012 compared ibuprofen 800 mg with placebo and suggests that there is little to no difference in complete abortion rate (OR 0.69, 95% CI 0.17 to 2.85, 1 RCT, 61 women; low-certainty evidence; Analysis 3.4).

Raymond 2013 compared therapeutic with prophylactic ibuprofen 800 mg and suggests there is little to no difference in complete abortion rate (OR 1.42, 95% CI 0.31 to 6.50, 1 RCT, 228 women; low-certainty evidence; Analysis 5.3).

Ojha 2012 suggests that ambulating or not at the time of abortion treatment may have little to no effect on complete abortion rate but the evidence is very uncertain (OR: not estimable, 100% complete abortion in each group).

Interval between misoprostol administration to expulsion of pregnancy

Only the NRSI (Ojha 2012), reported on the interval between misoprostol administration to pregnancy expulsion. Ambulating or not at the time of abortion treatment may have little to no effect on the administration to expulsion interval, however the evidence is very uncertain (MD 2.30 minutes lower, 95% CI 38.78 lower to 34.18 higher; 1 NRSI, 130 women; very low-certainty evidence; Analysis 4.3).

Unscheduled contact with care provider

Only one RCT (Raymond 2013), reported on rates of unscheduled contact with a care provider. There may be little to no difference in unscheduled contact with a care provider with therapeutic compared with prophylactic ibuprofen 800 mg (OR 1.03, 95% CI 0.60 to 1.77; 1 RCT, 228 women; low-certainty evidence; Analysis 5.4).

Patient satisfaction with analgesia regimen

Only one RCT (Friedlander 2018), reported on patient satisfaction with their analgesic regimen. There may be little to no difference in patient satisfaction with the analgesic regimen with pregabalin 300 mg compared with placebo (OR 0.97, 95% CI 0.42 to 2.21; 1 RCT, 104 women; low-certainty evidence; Analysis 2.5).

Patient satisfaction with abortion experience overall

Two RCTs (Friedlander 2018; Raymond 2013), reported on patient satisfaction with abortion care overall. The evidence suggests there is little to no difference in patient satisfaction with abortion when comparing pregabalin 300 mg with placebo (OR 1.84, 95% CI 0.80 to 4.22; 1 RCT, 105 women; low-certainty evidence; Analysis 2.6; Friedlander 2018), or therapeutic with prophylactic ibuprofen 800 mg (OR 0.52, 95% CI 0.09 to 2.89; 1 RCT, 228 women; Raymond 2013).

DISCUSSION

Summary of main results

The review has identified a small number of studies, all with different interventions and comparators. Meta-analysis was not possible for primary or secondary outcomes, however, we believe that we can draw some meaningful conclusions.

Ibuprofen appears to have a greater effect on decreasing pain ratings during medical abortion than both paracetamol and placebo. Use of ibuprofen therapeutically (in response to pain) or prophylactically does not appear to affect pain ratings, acceptability or other outcomes. Use of pregabalin does not appear to have an effect on pain during medical abortion. Ambulating or not ambulating as desired does not appear to affect pain experienced during medical abortion.

Based on the limited evidence found in these studies, the choice of analgesic regimen (ibuprofen, paracetamol or pregabalin) may have little or no effect on the rate of complete abortion. Likewise, choice of analgesic regimen (ibuprofen or pregabalin) may have little or no effect on the rate of gastrointestinal side effects during medical abortion. Future studies need to use consistent methods to gather data on these outcomes to provide greater certainty of the effect of these medications.

There is insufficient evidence to draw meaningful conclusions about the effect of these pain management options on satisfaction with abortion care, satisfaction with analgesia regimen, interval between misoprostol administration and expulsion, and unscheduled contact with care providers.

Overall completeness and applicability of evidence

The condition of pain during medical abortion is understudied, and there is a particular dearth of evidence regarding the use of pain relief interventions during the procedure.

All five included studies were designed to examine if their respective interventions had an effect upon the pain score reported by participants during medical abortion (primary outcome of this review). The selected participants in the studies were reflective of women seeking first trimester abortion care in general and the interventions studied are relevant and would have a plausible effect on pain scores. With regard to the secondary outcomes of the review (incidence of gastrointestinal side effects, complete abortion rate, misoprostol-expulsion interval, unscheduled contact with care provider, patient satisfaction with analgesia regimen and abortion experience overall), these were less consistently reported and possibly reflect the absence of core outcome reporting guidelines in abortion care until recently.

Current pain management practice varies internationally, however WHO guidance does recommend the use of non-steroidal anti-inflammatory drugs, such as ibuprofen. The WHO guidance is based upon one study from this review (Livshits 2009), and several other studies that used different medical abortion regimens and so were excluded from this review. It is unknown, but likely, that many abortion providers advise a lower dose than that used in the studies, that is, the recommended proprietary initial dose of ibuprofen (200 mg to 400 mg), and so well-designed studies examining these dosages are needed to compare with the higher dosages used in the studies in this review (800 mg and 1600 mg) with regard to pain score and other outcomes.

Quality of the evidence

We found four RCTs and one NRSI. We reviewed the certainty of evidence for each of the review outcomes using the GRADE process – we have summarised these in the summary of findings tables per comparison. The highest certainty rating was 'moderate' for the primary outcome of pain score when comparing ibuprofen 1600 mg with paracetamol 2000 mg (Livshits 2009). All other comparisons tested and outcomes reported across the included studies ranged from 'low' to 'very low'. We downgraded them for small sample sizes, 95% confidence intervals that included no effect and being at high risk of bias.

The studies were all conducted in well resourced countries and four of the studies were conducted in inpatient settings. Two studies only included women with pregnancies less than seven weeks' gestation. It is possible that these findings may not translate as well to those receiving medical abortion at home or for those with pregnancies between 7 and 14 weeks' gestation.

Potential biases in the review process

We believe that we have identified all the relevant studies in this search. There were 12 studies at the time of the search and data extraction that were incomplete or unpublished, and these may well be published during the time between the date of data extraction and publication of this review. We have identified these studies for appraisal at the planned update of this review. As this review only included English language papers, it is possible that there are relevant studies on pain and other modalities of management that we have not found, particularly Chinese language papers.

Agreements and disagreements with other studies or reviews

This review reinforces what is already widely known in the field of abortion care – the evidence base for pain management is limited, however non-steroidal anti-inflammatory drugs (i.e. ibuprofen) are the mainstay of treatment for those undergoing medical abortion in the first 14 weeks of pregnancy.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review provide limited support for the use of a single prophylactic dose of ibuprofen given with misoprostol, or in response to pain as needed. One very small study found that there may be no difference in pain scores when comparing ibuprofen (800 mg) with placebo. Another study, however, suggested that pain is probably lower with a higher dose of ibuprofen (1600 mg) when compared with paracetamol (2000 mg). Due to study sample size limitations and inconsistent outcome reporting, the effects of analgesic type and dosages on abortion completion rates and side effects are uncertain.

Implications for research

High-quality, adequately powered clinical research studies are needed to better inform practice. It remains unclear whether paracetamol and ibuprofen combined will have a greater effect than ibuprofen alone. Studies are needed to compare differing strengths of ibuprofen and at different gestational ages. Many clinical guidelines suggest the use of weak or strong opiates, or both, in addition to ibuprofen, however, this review did not identify any studies that examined the use of this in medical abortion prior to 14 weeks' gestation. Further study is needed on the use of stronger non-steroidal anti-inflammatory drugs, such as diclofenac and naproxen. New classes of drugs, such as cannabinoids, also require investigation as potential treatments during early medical

abortion. Non-pharmacological treatments, such as hot water bottles or mindfulness also require investigation. Core outcome sets are needed for medical abortion studies, and consistent measurement of pain would improve the comparability and interpretation of studies. Finally, more methodological research is needed to develop tools to accurately and consistently rate pain during medical abortion care.

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Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al.Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook..

Sterne 2016

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al.ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016;**355**:i4919. [DOI: 10.1136/bmj.i4919]

Sterne 2019

Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al.RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

WHO 2018

World Health Organization.Medical management of abortion. Geneva: World Health Organization, 2018. [ISBN: 9789241550406]

References to other published versions of this review

Reynolds-Wright 2020

Reynolds-Wright JJ, Woldetsadik MA, Morroni C, Cameron S.Pain management for medical abortion before 14 weeks' gestation. *Cochrane Database of Systematic Reviews* 2020, Issue 1. Art. No: CD013525. [DOI: 10.1002/14651858.CD013525]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Avraham 2012

Study characteristics	
Methods	Prospective, double-blind, randomised, controlled study
Participants	61 (29 Ibuprofen, 32 placebo) 61 women who underwent first-trimester termination of pregnancy (29 Ibuprofen, 32 placebo)
Interventions	Women received 600 mg mifepristone orally, followed by 400 µg oral misoprostol 2 days later. They were randomised to receive pre-emptively 2 tablets of 400 mg ibuprofen orally or a placebo, when taking the misoprostol. The women completed a questionnaire about side effects and pain score and returned for an ultrasound follow-up examination 10-14 days after the medical abortion.
Outcomes	Pain score, GI side effects, complete abortion rate
Notes	Trial registration: NCT00997074 (prospective) Dates: October 2009-October 2010 Funding: not reported Conflicts of Interest: none disclosed Contact attempted to gather missing data – no response

Friedlander 2018

Study characteristics	
Methods	A randomised, double-blind, placebo-controlled trial
Participants	107 (55 pregabalin, 52 placebo)

Friedlander 2018 *(Continued)*

	Women initiating medical abortion with mifepristone and buccal misoprostol up to 70 days of gestation
Interventions	Participants were randomised to 300 mg oral pregabalin or a placebo immediately before misoprostol.
Outcomes	Pain score, GI side effects, satisfaction with analgesia, satisfaction with abortion
Notes	Trial registration: NCT02782169 (prospective) Dates: June 2015–October 2016 Funding: Society of Family Planning Research Fund, Grant Award Number SFPRF15-12 Conflicts of Interest: Dr. Soon receives research support from Contramed Pharmaceuticals, Merck Sharpe and Dohme, Mithra Pharmaceuticals, and Gynuity Health Projects. Dr. Tschann receives research support from Contramed Pharmaceuticals, Merck Sharpe and Dohme, Mithra Pharmaceuticals, Gynuity Health Projects, and the National Institutes of Health. Dr. Kaneshiro receives research support from Contramed Pharmaceuticals, Merck Sharpe and Dohme, Mithra Pharmaceuticals, Gynuity Health Projects, and the National Institutes of Health. She is also a consultant for UpToDate. All of these sources of outside research support did not play any role in this project's study design, data collection, analysis, interpretation writing of the report, or decision to submit the report for publication. The other authors did not report any potential conflicts of interest. Contact attempted to gather missing data – no further data provided

Livshits 2009

Study characteristics	
Methods	A prospective double-blind controlled study
Participants	108 (59 ibuprofen, 49 paracetamol) 120 women who underwent first-trimester termination of pregnancy
Interventions	Women received 600 mg mifepristone orally, followed by 400 micrograms of oral misoprostol 2 days later. They were randomised to receive ibuprofen or paracetamol when pain relief was necessary. Women completed a questionnaire about side effects and pain score and returned for an ultrasound follow-up examination 10-14 days after medical abortion.
Outcomes	Pain score, complete abortion rate
Notes	No trial registration Dates: not reported, prior to November 2007 Funding: not reported Conflicts of Interest: none disclosed Contact attempted to gather missing data – no response

Ojha 2012

Study characteristics	

Ojha 2012 *(Continued)*

Methods	An observational prospective patient-preference study
Participants	130 (63 ambulating, 67 non-ambulating) 130 women with pregnancies up to 63 days of gestation
Interventions	The women were given the choice to be ambulatory or non-ambulatory throughout the process of medical termination of pregnancy.
Outcomes	Pain score, complete abortion rate, induction to expulsion interval
Notes	No trial registration Dates: not reported, prior to December 2010 Funding: no external funding Conflicts of Interest: none disclosed Contact made to gather missing data: some additional demographic data gathered

Raymond 2013

Study characteristics	
Methods	RCT
Participants	228 (117 therapeutic ibuprofen, 111 prophylactic ibuprofen) 250 women undergoing first-trimester abortion with mifepristone and misoprostol at 3 clinics
Interventions	Women were assigned to 1 of 2 ibuprofen regimens: therapeutic (800 mg every 4-6 h as needed for pain) or prophylactic (800 mg starting 1 h before the misoprostol dose, then every 4-6 h for 48 h egardless of pain, then as needed)
Outcomes	Pain score, GI side effects, complete abortion
Notes	Trial registration: NCT01457521 (prospective) Dates: October 2011–December 2012 Funding: Society of Family Planning and an anonymous donor Conflicts of Interest: none disclosed Contact made to gather missing data: no further data available

GI: gastrointestinal; **RCT:** randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbas 2016	Wrong intervention
Abbasi 2017	Wrong patient population

Study	Reason for exclusion
Abdel-Aziz 2004a	Wrong intervention
Abdel-Aziz 2004b	Wrong intervention
Aggarwal 2017	Wrong intervention
Ai 2018	Unable to access access full-text
Akin 2005	Wrong comparator
Akin 2009	Wrong intervention
Arvidsson 2005	Wrong intervention
Ashok 1998a	Wrong intervention
Ashok 1998b	Wrong intervention
Ashok 2005	Wrong outcomes
Aubeny 1991	Wrong study design
Avraham 2012	Duplicate
Ayati 2013	Unable to access full text
Bachelot 1992	Wrong study design
Backman 2002	Unable to access full text
Baird 1995	Wrong intervention
Bartley 2002	Wrong intervention
Beckman 1997	Wrong intervention
Bhattacharya 2000	Duplicate
Bjorge 2001	Wrong intervention
Bond 2015	Duplicate
Cameron 2010	Wrong intervention
Cavet 2017	Wrong study design
Cavet 2018	Duplicate
Chen 2002	Unable to access full text
Chen 2013	Wrong intervention
Cheng 2005	Unable to access full text
Colleselli 2015	Wrong patient population

Study	Reason for exclusion
Constant 2014	Wrong intervention
Creinin 2004a	Duplicate
Creinin 2005	Wrong intervention
CTRI/2016/12/007516	Wrong intervention
CTRI/2018/01/011157	Wrong comparator
Dabash 2009	Wrong intervention
Dabash 2012	Wrong intervention
Dalenda 2010	Wrong comparator
De Nonno 2000	Wrong intervention
Ding 2005	Unable to access full text
Dzuba 2016a	Wrong intervention
Dzuba 2016b	Duplicate
el-Refaey 1994	Wrong intervention
Elul 1999	Wrong comparator
Endler 2019	Wrong intervention
EUCTR2009-010277-21-GB 2009	Wrong intervention
EUCTR2018-003675-35-SE 2018	Wrong intervention
Frank 2015	Unable to access full text
Friedlander 2016	Duplicate
Friedlander 2017a	Duplicate
Friedlander 2017b	Duplicate
Garbin 2006	Wrong intervention
Goel 2010	Wrong intervention
Goh 2006	Wrong intervention
Goldstone 2012	Wrong intervention
Goss 2004	Unable to access full text
Gupta 2007	Wrong intervention
Halleb 2012	Wrong intervention

Study	Reason for exclusion
Hamoda 2004	Wrong study design
Hamoda 2005a	Wrong intervention
Hamoda 2005b	Wrong intervention
Hayes 2011	Wrong intervention
Hedqvist 2016	Wrong study design
Honkanen 2004	Wrong study design
ICMR Task Force 2000	Wrong comparator
Ireland 2015	Wrong intervention
ISRCTN97410750	Wrong intervention
Iversen 2003	Wrong intervention
Jackson 2011	Wrong study design
Jensen 1998	Wrong intervention
Joensuu-Manninen 2010	Wrong intervention
Jorgensen 2007	Unable to access full text
Kailash 2015	Wrong intervention
Karasahin 2011	Wrong intervention
Kawonga 2008	Wrong intervention
Kelly 2010	Wrong comparator
Kopp Kallner 2010	Wrong intervention
Kopp Kallner 2012a	Wrong intervention
Kopp Kallner 2012b	Duplicate
Kopp Kallner 2012c	Duplicate
Largeaud 2004	Unable to access full text
Lelaidier 1993	Wrong patient population
Li 2007	Wrong intervention
Li 2009	Wrong comparator
Li 2010	Unable to access full text
Li 2012	Wrong comparator

Study	Reason for exclusion
Liang 2005	Unable to access full text
Liao 2004	Wrong intervention
Lokeland 2012	Wrong intervention
Lokeland 2014	Duplicate
Lord 2018	Wrong study design
Lou 2015	Unable to access full text
Ma 2008	Unable to access full text
Mamers 1997	Wrong intervention
Mukhi 2014	Wrong outcomes
Nawaz 2012	Wrong intervention
NCT00269568	Wrong intervention
NCT00286208	Wrong intervention
NCT00330993	Wrong intervention
NCT00386867	Wrong intervention
NCT00482209	Wrong intervention
NCT00769912	Wrong patient population
NCT00870272	Wrong intervention
NCT00920465	Wrong intervention
NCT00997074	Duplicate
NCT00997347	Wrong intervention
NCT01156688	Wrong intervention
NCT01457521	Duplicate
NCT01856985	Wrong intervention
NCT01966874	Wrong intervention
NCT02018796	Wrong intervention
NCT02314754	Duplicate
NCT02720991	Wrong intervention
NCT02745093	Wrong intervention

Study	Reason for exclusion
NCT02782169	Duplicate
NCT02981030	Wrong intervention
NCT03659045a	Wrong intervention
NCT03727308	Wrong intervention
Ngo 2011	Wrong study design
Pay 2018	Wrong intervention
Priyanka 2014	Wrong intervention
Pud 2005	Wrong patient population
Raghavan 2012	Wrong intervention
Ravn 2005	Wrong intervention
Raymond 2015a	Wrong intervention
Raymond 2015b	Wrong intervention
Robson 2009	Wrong comparator
Rosenblatt 1992	Wrong intervention
Rosseland 2011	Wrong study design
Sang 1994a	Wrong intervention
Sang 1994b	Wrong intervention
Saurel-Cubizolles 2015	Wrong intervention
Schaff 2000	Wrong intervention
Shannon 2005	Wrong intervention
Shannon 2006	Wrong intervention
Sherman 2018	Unable to access full text
Shi 2018	Unable to access full text
Shikha 2011	Wrong intervention
Singh 2005	Wrong intervention
Socolov 2016	Wrong intervention
Spitz 1998	Wrong intervention
Stojnic 2006	Wrong intervention

Study	Reason for exclusion
Suhonen 2011a	Wrong study design
Suhonen 2011b	Wrong study design
Tang 2002	Wrong intervention
Taylor 2013	Wrong study design
Teal 2007	Wrong study design
Thiebaut 2017	Unable to access full text
Thong 1992	Wrong intervention
Ulmann 1994	Unable to access full text
Von Hertzen 2000	Wrong intervention
von Hertzen 2004	Wrong intervention
Von Hertzen 2008	Wrong intervention
Weeks 1995	Wrong intervention
Wells 1991	Wrong study design
Wen 2010	Unable to access full text
Westhoff 2000	Wrong study design
Westhoffa 2000	Wrong intervention
WHO 2000	Duplicate
Wiebe 2018	Unable to access full text
Xu 2007	Unable to access full text
Zhu 2008	Unable to access full text
Zou 2004	Unable to access full text

Characteristics of studies awaiting classification *[ordered by study ID]*

Dragoman 2016

Methods	"We propose a randomized, placebo-controlled trial"
Participants	"576 participants (288 nulliparous; 288 parous) from study sites in Nepal, South Africa and Vietnam"
Interventions	"randomly allocated to one of three treatments: (1) ibuprofen 400 mg PO [orally] and metoclopramide 10 mg PO; (2) tramadol 50 mg PO and a placebo; or (3) two placebo pills, to be taken im-

Dragoman 2016 *(Continued)*

	mediately before misoprostol and repeated once four hours later. All women will be provided with supplementary analgesia for use as needed during the medical abortion"
Outcomes	"We hypothesize that women receiving prophylactic analgesia will report lower maximal pain scores in the first 8 h following misoprostol administration compared to women receiving placebos for medical abortion through 63 days' gestation"
Notes	

EUCTR2014-002974-35-SE

Methods	Randomised trial
Participants	"INCLUSION CRITERIA: Healthy women aged 13-17, seeking medical abortion. Normal pregnancy at the most 9 gestational weeks. Able to have a guardian present at home. Informed consent from guardians. Are the trial subjects under 18? yes"
Interventions	"INTERVENTION: Trade Name: Mifegyne Pharmaceutical Form: Tablet Trade Name: Cytotec Pharmaceutical Form: Tablet Trade Name: Naproxen Pharmaceutical Form: Tablet Trade Name: Alvedon Pharmaceutical Form: Tablet" CONDITION: Therapeutic area: Diseases [C] - Female diseases of the urinary and reproductive systems and pregancy complications [C13] Young women with unwanted pregnancies seeking abortion care
Outcomes	"PRIMARY OUTCOME: Main Objective: To study if home abortion is more acceptable for young women than induced medical abortion at the clinic Primary end point(s): Acceptability measured on questionnaires Secondary Objective: To compare the home abortion group with the clinic abortion group regarding: Pain and use of analgetics; Number of unsceduled visits to the clinic; Acceptability for the guardian; Contraceptive use after six months Timepoint(s) of evaluation of this end point: The day after the abortion and after 3 weeks" "SECONDARY OUTCOME: Secondary end point(s): Pain, bleedings and other complications detected with diaries and from medical records at the clinic; Guardians acceptability measured with questionnaires; Contraceptive use checked after 6 months Timepoint(s) of evaluation of this end point: Diaries filled in from the abortion and another 3 weeks; Questionnaires filled in before the abortion, the day after and after 3 weeks; Contraceptive use after 6 months"
Notes	

EUCTR2015-003760-36-FI

Methods	NR
Participants	"INCLUSION CRITERIA: Patients choosing medical abortion, are first time pregnant, are aged between 15 to 19 years and 25 to 35 years. Attending the study is voluntary Are the trial subjects under 18? yes"
Interventions	"INTERVENTION: Trade Name: oxynorm Product Name: oxynorm Pharmaceutical Form: Solution for injection/infusion Trade Name: oxanest Product Name: Oxanest Pharmaceutical Form: Solution for injection/infusion Trade Name: Oxynorm Product Name: oxynorm Pharmaceutical Form: Oral suspension"
Outcomes	"PRIMARY OUTCOME: Main Objective: Adequate analgesia is crucial in patients undergoing medical abortion. We compare in controlled randomized trial pain management via PCA (patient con-

EUCTR2015-003760-36-FI *(Continued)*

	troller analgesia) to our standard pain management in patients undergoing medical termination of pregnancy with gestational age over 9 weeks. In short we compare different administration routes of oxycodon; We hope to recognize those patients who benefit from more intensive pain management and to create guideline so that all patients receive adequate analgesia in the future. Primary end point(s): Pain management via PCA is more effective (pain VAS [visual analogue scale] is lower) and patient's satisfaction is higher; Teen-aged women profit more on effective pain management than their adult controls. Secondary Objective: Experience of painful and traumatic abortion may affect patients' future plans for pregnancies and childbirth. In addition this may lead patient to choose surgical abortion in case of reapportion, which exposes patient to operative risks. Timepoint(s) of evaluation of this end point: Collecting data takes about 1,5-2 years and is done by the end of the year 2017" "SECONDARY OUTCOME: Secondary end point(s): Predicting factors of pain are patient's young age any longer duration of pregnancy. Timepoint(s) of evaluation of this end point: Data is collected and ready to be evaluated in the end of the year 2017"
Notes	

Louie 2016

Methods	"We enrolled 384 women in states where marijuana is legal for medicinal or recreational purposes on the day they returned to the clinic for medical abortion follow-up. After providing informed consent, women completed a short anonymous Internet-based survey"
Participants	"384 women in states where marijuana is legal for medicinal or recreational purposes on the day they returned to the clinic for medical abortion follow-up"
Interventions	"We surveyed women who underwent first-trimester mifepristone–misoprostol medical abortion to investigate their methods of managing pain during the procedure, including marijuana use"
Outcomes	"We used the data to determine the prevalence, patterns and perceived effectiveness of marijuana use for pain control in medical abortion"
Notes	

NCT02678897

Methods	"Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment"
Participants	"Inclusion Criteria: • Patients who choose medical method of abortion • First pregnancy • Age between 15 and 19 years or 25 and 35 years • Patients volunteer in the study Exclusion criteria for inquiry part are • Patient's serious illness • Known allergy to one of the trial medications • Abortion is done based on foetal abnormality or threat of patient's own health

NCT02678897 *(Continued)*

	Exclusion criteria for intervention part are • Abortion is done based on foetal abnormality or threat of patient's own health • Minor patient does not want to inform guardian • More than one foetus • Patient's serious illness (ASA-class 3 or 4) • Massive obesity (BMI >35 kg/m2) • Known allergy to one of the trial medications • History of opioid abuse • Problems of understanding (Inability of use PCA or to understand VAS) • Active bleeding before intake of first Misoprostol dose • One of next medications: ketokonatsol, erythromycin, claritromycin, verapamil or diltiazem or medication against HIV (CYP3A4-transmitted interaction with oxycodon)"
Interventions	"Drug: Oxynorm on-demand We compare different routes of administration (PCA an oral/intramuscular use of oxynorm) in patients undergoing medical termination of pregnancy. Patients are randomized in two groups (for extra pain medication) 1. If analgesia is inadequate oxycodon (OxyNorm®) (10 mg (less than 80 kg) - 15 mg (over 80 kg) po [orally]. In an hour oxycodon 5-10 mg more po if needed. Intramuscular or intravenous administration if needed. 2. Patient controlled analgesia (PCA pain pump): Oxycodon dose is 3.0 mg (3 ml) and lock-out time 8 min. Maximum four doses in hour. Dose can be lowered or augmented 0,5 [0.5] mg at time between 2.0-4.0 mg and maximal number of doses can be up to 5. • Drug: Oxynorm via PCA We compare different routes of administration (PCA an oral/intramuscular use of oxynorm) in patients undergoing medical termination of pregnancy. Patients are randomized in two groups (for extra pain medication) 1. If analgesia is inadequate oxycodon (OxyNorm®) (10 mg (less than 80 kg) - 15 mg (over 80 kg) po. In an hour oxycodon 5-10 mg more po if needed. Intramuscular or intravenous administration if needed. 2. Patient controlled analgesia (PCA pain pump): Oxycodon dose is 3.0 mg (3 ml) and lock-out time 8 min. Maximum four doses in hour. Dose can be lowered or augmented 0,5 [0.5] mg at time between 2.0-4.0 mg and maximal number of doses can be up to 5."
Outcomes	Primary outcomes: "Patients are less painful using patient controlled analgesia (PCA) [Time-Frame: During drug-induced abortion, in hospital care (1-2days)] Measured in visual analog scale (VAS, 0-100mm). VAS is lower." Secondary outcomes: "Patient satisfaction is higher [Time Frame: just after the abortion and 2-3 weeks after in follow-up visit] Measured in visual analog scale (VAS, 0-100mm), VAS is higher."
Notes	

NCT03480009

Methods	"Allocation: Randomized Intervention Model: Parallel Assignment Intervention Model Description:

NCT03480009 *(Continued)*

	Randomized Controlled Trial Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment"
Participants	"Inclusion Criteria: • Women aged 18 and over • Willing to give voluntary consent • English-speaking • Eligible for medication abortion per Planned Parenthood of Western Pennsylvania protocol • Self-reported reliable cellular phone access for the duration of study participation • Able to receive and reply to a "test" text at time of consent • Willing to comply with the study protocol Exclusion Criteria: • Use of selective serotonin reuptake inhibitors or monoamine oxidase inhibitors due to risk of Serotonin Syndrome • Allergy to any component of the medication abortion regimen or study drug • Has any other condition that, in the opinion of the investigator, would preclude informed consent, make study participation unsafe, complicate the interpretation of the study outcome data, or otherwise interfere with achieving the study objectives • Anticipated use of dextromethorphan during study period"
Interventions	"Drug: Dextromethorphan Hydrobromide Dextromethorphan capsule Other Name: Robitussin, Delsym • Drug: Avicel PH101 (Microcrystalline Cellulose NF) for Compounding Placebo capsule Other Name: Avicel • Drug: Oxycodone Participants may opt for the narcotic receiving arms of the study, before being randomized to dextromethorphan/placebo. Other Name: Tylox, Percodan, OxyContin"
Outcomes	Primary outcomes: "Worst Pain Measurement Via Numeric Rating Scale (NRS-11) [Time-Frame: Over 24 hours starting from misoprostol administration] Self-reported pain measurement via text-messaging system during first 24 hours after misoprostol administration. The scale is from 0 to 10, where 0 represents "no pain" and 10 represents "the worst pain possible". • Analgesic Usage During Medication Abortion [Time Frame: Over 24 hours] Analgesic usage by study arm for women who received dextromethorphan vs. placebo as adjunct to routine pain management during medication abortion; missing data are for participants who did not take the specified pain medication." Secondary outcomes: "Mean Pain Scores Via Numeric Rating Scale (NRS-11) [Time Frame: Marginal mean pain scores over 24 hours]

NCT03480009 *(Continued)*

	Marginal mean pain scores via Numeric Rating Scale (NRS-11) over 24 hours. The scale is from 0 to 10, where 0 represents "no pain" and 10 represents "the worst pain possible". • Number of Participants With Pain Control Satisfaction Via 4-pt Likert Scale [Time Frame: 24 hours after misoprostol administration] Overall satisfaction with pain control, "4" being - "Very good" and "1" being "Very bad""
Notes	

NCT03604341

Methods	"Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment"
Participants	"Inclusion Criteria: • Aged 21 years or older • Consented for elective medical abortion • Pregnancy with intrauterine gestational sac up to 10 0/7 weeks, dated by ultrasound • Able and willing to receive text messages via phone • English speaking • Able and willing to give informed consent and agree to the study terms • Have assistance at home; no motor vehicle use while taking study medications Exclusion Criteria: • Desires to continue pregnancy or currently breastfeeding • Lack of access to cell phone and texting capabilities • Prior participation in this study • Early pregnancy failure • Contraindications to the study medications: Marinol or marijuana derivatives, sesame oil, Ibuprofen • Contraindications to medical abortion with Mifepristone or Misoprostol • History of methadone, buprenorphine or heroin use within the last year • History of a seizure disorder • Used marijuana 5 or more days in the last week • History of any adverse effects associated with prior use of recreational or medical marijuana products, or sensitivity/allergy to Marinol"
Interventions	"Drug: Dronabinol 5mg Cap Subjects randomized to Dronabinol 5mg Cap and ibuprofen 800mg for pain Other Name: Dronabinol • Other: Placebo Subjects randomized to placebo and ibuprofen 800mg for pain"
Outcomes	"Maximum Self-reported Pain Score on a Numeric Rating Scale [Time Frame: 24 hours after misoprostol administration]

NCT03604341 *(Continued)*

	Women will text responds to surveys within 24 hours after misoprostol administration indicating their maximum self-reported pain using an 11-point numeric rating scale (NRS 0-10) where 0=no pain and 10=worst possible pain."
Notes	

NCT03900728

Methods	"Allocation: Randomized Intervention Model: Parallel Assignment Intervention Model Description: This 3-arm randomized trial will assign participants 1:1:1 to receive either of two active treatments (acupuncture or acupressure) or placebo (insert adhesive disks applied to ears). Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Masking Description: A separate investigator will apply the intervention after the initial usual care is complete and participants will go home using the intervention; thus the care provider will not be aware of the treatment. The adhesive disks appear similar for the treatments and the placebo arm; thus the participants will be unaware of their treatment assignment. The research assistant collecting the outcomes data will not know which treatment arm the participant belongs to. Finally, treatment assignment will be coded in the study database until analysis is complete, so that the investigator will be unaware of the treatment assignment until analysis is complete and then un-blinding will occur. Primary Purpose: Supportive Care"
Participants	"Inclusion Criteria: • Pregnant up to 10 weeks (70 days) gestation • Seeking medication abortion with mifepristone and misoprostol • Initial clinical care completed and mifepristone administered • English- or Spanish-speaking • Able to use a mobile phone for follow-up on days 1-4 Exclusion Criteria: • Not a candidate for medication abortion for any reason • Allergy to adhesives"
Interventions	• "Device: Auriculotherapy with needles Single-use 1.2mm acupuncture press needles attach to pre-specified acupoints on the participant's ears with adhesive disk/tape. Other Name: Pyonex needles • Device: Auriculotherapy with beads A trained co-investigator will place the beads onto prespecified acupoints of the participant's ears. An adhesive disk will adhere the beads to the ears. Other Name: Single-use gold-plated 1.2mm beads/balls attach to pre-specified acupoints on the participant's ears with adhesive disk/tape. • Device: Placebo Adhesive disks Single-use adhesive disks without needles or beads.

NCT03900728 *(Continued)*

	Other Name: Placebo disks"
Outcomes	Primary outcomes: "Pain VAS [visual analogue scale] Score [Time Frame: Auriculotherapy is applied on the day of mifepristone. Participants take misoprostol 1-3 days later. Pain scores are recorded following misoprostol at 8pm x 4 days (selecting the highest of the 4 for analysis).] Self-assessed maximum pain reported using a 0-100 mm visual analog scale (VAS), where 100 signifies maximum pain." Secondary outcomes: "Anxiety VAS Score [Time Frame: Auriculotherapy is applied on the day of mifepristone. Participants take misoprostol 1-3 days later. Anxiety scores are recorded following misoprostol at 8pm x 4 days (selecting the highest of 4 for analysis).] Self-assessed maximum anxiety reported using a 0-100 mm visual analog scale, where 100 signifies maximum anxiety."
Notes	

Wiebe 2015

Methods	Survey of women who knew about marijuana use for periods
Participants	Mean age: 30.9 years (range 18-62 years) 72.9% white
Interventions	Survey of target population
Outcomes	Reasons for marijuana use Methods of marijuana use Did marijuana use help
Notes	

NR: not reported

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2017-004083-35-FR 2018

Study name	A double-blind, randomized, multicenter study evaluating 200 mg versus 600 mg of Mifepristone on pain in voluntary abortion by drug prior to 7 SA. DoMy Study
Methods	
Participants	"Female aged 18 or over" "Female with a single intrauterine pregnancy, the term of which is less than 7 weeks on the day of mifegyne intake, estimated by ultrasound with a cranio-caudal length measurement less than or equal to 10 millimeters" "Woman seeking medical abortion in hospital" "A woman who has signed a written informed consent and agrees to abide by the protocol"

EUCTR2017-004083-35-FR 2018 *(Continued)*

	"Are the trial subjects under 18? no"
Interventions	Intervention: trade name: mifepristone 200 mg. Product name: Mifegyne. Product code: mifepristone. Pharmaceutical form: Cachet Pharmaceutical form of the placebo: Cachet. Route of administration of the placebo: oral use pharmaceutical form of the placebo: Cachet route of administration of the placebo: oral use Condition: patient of ≥ 18 years, wishing an abortion with medication before 7 weeks of amenorrhea. Therapeutic area: diseases [C] - immune system diseases [C20]
Outcomes	"PRIMARY OUTCOME: Main Objective: The main objective of this research is to compare the efficacy in reducing the pain of two doses of Mifegyne during medicinal abortion before 7 Weeks of amenorrhea (600 versus 200 mg). Primary end point(s): The primary endpoint of efficacy is the hourly pain for 5 hours after taking misoprostol. The measurement is simple, reproducible, performed with an EN on the side of 0 to 10 (0 absence of pain, 10 maximum of pains felt). The ladder will be explained to the patient. The question asked will be: what is your pain now?" "Secondary Objective: The secondary objectives of this research are to compare the 2 dosages of Mifegyne (600 vs 200 mg) in terms of: *Pain within days of taking misoprostol; *Pain between taking Mifegyne and misprostol; *Failed method; *Additional consultations and gestures following IVG4 consultation; *Tolerance of drug-induced abortion; *Abortion experience documented by the EVAN-LR self-questionnaire; *Impact on the degree of anxiety of the subjects by the questionnaire STAI of anxiety; *Patient satisfaction with an EVA scale and the SF12 questionnaire Timepoint(s) of evaluation of this end point: Patients will be assessed for consultation with the 2 abortion (IVG 2) prior to taking Mifegyne (J1), the next day (D2), IVG3 before taking misoprostol (J3) and the follow-up visit (IVG4) on a digital scale" "SECONDARY OUTCOME: Secondary end point(s): Pains will be assessed at the consultation of voluntary termination of pregnancy 2 (IVG2); before taking Mifegyne (J1), the next day (D2), IVG3 prior to taking misoprostol (J3) and IVG4 on an EN. The questions will be as follows: At the consultation IVG1: "currently, what is your pain? "; At the IVG2 consultation before taking misoprostol: "yesterday, what was the maximum pain felt? "And" currently, what is your pain?; At IVG4: "The day after taking misoprostol and the day after, what was the maximum pain felt in the day? "And" currently, what is your pain? and "since the day after taking misoprostol and so far, what was the maximum pain and how many days have you had trouble"; The use of painkillers on the day of taking misoprostol and the following days, specifying the duration and quantity of ibuprofen and other analgesics taken; Failed method; Failure is defined by the ultrasound presence of a progressive pregnancy at the IVG4 or IVG5 consultation. The means used to enable the diagnosis of the failure will be those used by the investigating centers; Additional consultations and gestures; Additional consultations are planned over a one-month period after taking misoprostol (IVG5 and higher) if the physician deems it necessary to review the patient in relation to the medicinal abortion. It will be specified if it is a simple consultation or the realization of an uterine gesture for retention. The indication of consultation or additional gesture will be carried out according to the habits of the investigating centers; Tolerance; Tolerance will be assessed by the questioning before the end of hospitalization for misoprostol (IVG3). The following signs will be carefully collected: nausea, vomiting, fever, diarrhea, abdominal pain, other (to be specified by the patient); Experience and Anxiety; Assessment of anxiety will be assessed by passing the Anxiety Task Inventory (STAI). The STAI is a self-questionnaire developed by Spielberger (Spielberger, 1983) and validated in French (Gauthier & Bouchard, 1993). It consists of 20 questions, assessing the usual emotional state of the subject. A score is calculated, a high score indicating the presence; anxiety. The experience of the abortion will be done by the EVAN-LR self-questionnaire. This assessment; at IVG2 and IVG consultation 4; Satisfaction; The satisfaction of the subjects will be assessed using an EVA, graduated from 0 to 10, completed by the patient at the IVG4 consultation as well as the questionnaire SF12 completed at the consultation IVG2 and IVG4. Timepoint(s) of evaluation of this end point: The average pain level on the initial time (primary endpoint) will be compared between the 2 groups (Student's t-test or Mann Whitney's test as a function of the parameter distribution). The maximum pain value over the first 5 hours will be compared between the 2 groups, but in secondary analysis; For the secondary endpoints, qualitative variables will be compared between the 2 groups using the exact chi-2 or Fisher test and the continuous variables will be compared is Student's t or Mann Whitney's test depending on the distribution of parameter.

EUCTR2017-004083-35-FR 2018 *(Continued)*

Starting date	2018
Contact information	NA
Notes	

NCT03139240

Study name	Opioid analgesia for MAB
Methods	"Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Masking Description:Double Blind Primary Purpose: Treatment"
Participants	"Inclusion Criteria: • Aged 18 years or older • Seeking elective medical abortion • In good health • Pregnancy with intrauterine gestational sac up to 10 0/7 weeks, dated by ultrasound • Able and willing to receive text messages via phone • Literate in English • Able and willing to give informed consent and agree to the study terms • Have assistance at home; no motor vehicle use while taking study medications Exclusion Criteria: • Lack of access to cell phone and texting capabilities • Early pregnancy failure • Contraindications to the study medications: Oxycodone, Ibuprofen • Contraindications to medical abortion with Mifepristone or Misoprostol • History of methadone or heroin use • Used alcohol in the past 24 hours • Used marijuana >4 times per week • Any opioid in the past 30 days • Using additional pain medications"
Interventions	"Drug: Oxycodone 10mg oral Oxycodone 10mg oral given for pain control in addition to standard of care medications in women undergoing medical abortion Other: Placebo Placebo given in addition to standard of care medications in women undergoing medical abortion"
Outcomes	• "Overall Maximum Self-reported Pain Score [Time Frame: 24 hours after misoprostol administration] Women text responses through two surveys within 24 hours after misoprostol administration indicating their maximum self-reported pain score on an 11-point Numeric Pain Rating Scale (0 = no pain, 5 = moderate pain, and 10 = worst possible pain).

NCT03139240 *(Continued)*

	• <7 Weeks of Gestation - Maximum Self-reported Pain Score [Time Frame: 24 hours after misoprostol administration] Women text responses through two surveys within 24 hours after misoprostol administration indicating their maximum self-reported pain score on an 11-point Numeric Pain Rating Scale (0 = no pain, 5 = moderate pain, and 10 = worst possible pain). • 7-10 Weeks Gestation - Maximum Self-reported Pain Score [Time Frame: 24 hours after misoprostol administration] Women text responses through two surveys within 24 hours after misoprostol administration indicating their maximum self-reported pain score on an 11-point Numeric Pain Rating Scale (0 = no pain, 5 = moderate pain, and 10 = worst possible pain)"
Starting date	01 May 2017
Contact information	Oregon Health and Science University
Notes	

NCT03925129

Study name	Transcutaneous electrical nerve stimulation (TENS) for pain management with medication abortion through 70 days' gestation
Methods	"This is a double-blinded, randomized, placebo-controlled trial evaluating the use of High-frequency Transcutaneous Electrical Nerve Stimulation (HfTENS) compared to sham TENS for pain control during medication abortion with mifepristone and misoprostol through 70 days' gestation."
Participants	"Inclusion Criteria: • Patients seeking medication abortion with a definite, singleton, intrauterine pregnancy (IUP) < 70 days' gestation on ultrasound • Rapid Estimate of Adult Literacy in Medicine-Short Form (REALM-SF)22 score > 4 • Age equal to or greater than 18 years • Provide informed consent to participate • Willing to adhere to study procedures, including access to a smart phone, ability to receive text messages and answer online surveys on smart phone Exclusion Criteria: • Contraindication to medication abortion • Allergy to mifepristone or misoprostol • Contraindication or allergy to ibuprofen • History of cardiac arrhythmia • Presence of an implantable device with electrical discharge, i.e. cardiac pacemaker • History of chronic pain disorder • Any opioid use during previous 30 days • Current or prior use of TENS • BMI [body mass index] > 30"

Interventions	• "Device: high frequency TENS treatment
	  ◦ Treatment with high frequency for minimum of 1 hour after misoprostol administration
	• Device: Sham TENS treatment
	  ◦ Treatment with sham TENS device for minimum of 1 hour after misoprostol administration"

NCT03925129 *(Continued)*

Outcomes	"Pain on numeric rating scale [Time Frame: 8 hours following misoprostol] Maximum pain score on an 11-point numeric rating scale, where 0 is no pain, and 10 is the worst pain."
Starting date	11 June 2019
Contact information	Planned Parenthood of Greater New York
Notes	

NA: not applicable

ADDITIONAL TABLES

Table 1. Risk of bias table for RoB 2 – including judgements

Study, outcome	Bias arising from the randomization process	Bias due to deviations from intended intervention	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall
Avraham 2012	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Pain scores at two hours post-misoprostol administration	Quote: "The 61 women were randomized at the time of misoprostol administration into two treatment groups by providing a sealed envelope, using a computer-generated random list, with serial numbers from 1 to 61."	Quote: "The 61 women were randomized at the time of misoprostol administration into two treatment groups by providing a sealed envelope, using a computer-generated random list, with serial numbers from 1 to 61."	Quote: "Two women, one in each group, did not show up for follow-up, and data about the success of the abortion were not established. They were considered in our analysis as failure of the medical abortion." Comment: missing outcome data between the two groups were similar in proportion and the reason for missing were similar.	Quote: "this was a randomized, placebo-controlled, double-blind trial." Comment: Using ROB2 tool, assessed as 'Probably No' for this domain therefore LOW risk.	Comment: the study was analyzed and reported based on the authors plan	Comment: No other sources of bias were identified
Friedlander 2018	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Pain scores at multiple time points (immedi-	Quote: "A researcher not involved in the conduct of the study used a computer-generated ran-	Quote: "A researcher not involved in the conduct of the study ... placed the allocated study capsule in sequentially num-	Comment: Using ROB2 tool: Domain 5.1 = Yes, 5.2 = No, 5.3 = No	Comment: Using ROB2 tool: Domain 4.1 =No, 4.2 =	Comment: Study appears to have reported on	Comment: No other specific concerns regarding

Table 1. Risk of bias table for RoB 2 – including judgements *(Continued)*

ately after misoprostol administration and then at 2, 6, 12, 24 and 72 hours later)	domization scheme of varied block sizes"	bered bags identified only by study identification number so as to maintain blinding of participants and researchers."		No, 4.3 = No Information, 4.4 = No	all outcomes selected in analysis plan	sources of bias
Livshits 2009	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Pain scores at two hours post-misoprostol administration	Quote: "This was a prospective, double-blind, randomized controlled trial.... We randomized the 120 women into two treatment groups by providing a sealed envelope by using a computer-generated random list that included serial numbers from 1 to 120. The envelope was given by the nurse at the time at which the patient received the misoprostol tablets."	Quote: "This was a prospective, double-blind, randomized controlled trial....We randomized the 120 women into two treatment groups by providing a sealed envelope by using a computer-generated random list that included serial numbers from 1 to 120. The envelope was given by the nurse at the time at which the patient received the misoprostol tablets...The ibuprofen and paracetamol tablets were identical in size, color, and shape."	Quote: "We randomized the 120 women into two treatment groups by providing a sealed envelope by using a computer-generated random list that included serial numbers from 1 to 120. The envelope was given by the nurse at the time at which the patient received the misoprostol tablets...The ibuprofen and paracetamol tablets were identical in size, color, and shape."	Comment: Appears nurses were assessing outcomes and also blind to nature of trial medications	Comment: ROB2 Tool Domain 5.1 = Probably Yes, 5.2 = No, 5.3 = Probably No. The authors listed all analyses for table 2 but only show the ones that were significant, but can infer from text that remaining were not significant.	Comment: There did not appear to be any other significant sources of bias
Raymond 2013	**Low**	**Low**	**Low**	**High**	**Low**	**Some concerns**
Worst pain in the 24-hour period following misoprostol	Quote: "The one-to-one randomization scheme was stratified by site and used randomly permuted blocks with sizes of eight and 20 generated by computer by the study statistician before the start of enrollment."	Quote: "If she was eligible, staff assigned her to either the prophylactic regimen group or the therapeutic regimen group by opening the next unused consecutively numbered opaque envelope containing a random assignment."	Comment: Missing data accounted for and any sections missing identified in results tables. All variables analysed as ordinal - nearly all data available.	Comment: ROB2 tool questions 4.1 = No, 4.2 = No, 4.3 = Yes, 4.4 = Yes, 4.5 = Probably Yes.	Comment: ROB2 tool questions 5.1 = Probably Yes, 5.2 = Probably No, 5.3 = Probably No	Comment: Recall scores of pain for those who did not complete diary will be affected by recall bias, however the number of participants doing this in both groups is small and so may not affect over-

Table 1. Risk of bias table for RoB 2 – including judgements *(Continued)*

							all result, but cannot tell as results aggregated.

Table 2. Risk of bias table for ROBINS-I – including judgements

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Ojha 2012	Serious	Serious	Low	Low	Low	Low	Low	Serious
Rationale for judgement	Comment: ROBINS-I tool questions 1.1 = Yes, 1.2 = Probably No, 1.4 = Probably No, 1.6 = Probably No, 1.7 = Probably No, therefore Judgement = serious risk of bias	Comment: Discussed within review team and felt that as participants could self-select intervention, at serious risk of bias.	Comment: ROBINS-I tool questions 3.1 = Yes, 3.2 = Yes, 3.3 = No, therefore Judgement = Low	Comment: ROBINS-I questions 4.1 = Probably No, 4.3 = Probably Yes, 4.4 = Probably Yes, 4.5 = Probably Yes, therefore Judgement = Low	Comment: ROBINS- I questions 5.1 = Yes, 5.2 = Probably No, 5.3 = Probably No, therefore Judgement = Low	Comment: Discussed within review team and felt that outcome measurements were unlikely to be significantly biased	Comment: ROBINS-I tool questions 7.1 = No, 7.2 = Probably No, 7.3 = Probably No, therefore Judgement = Low	Comment: More than one domain at serious risk of bias therefore study considered to be 'serious' risk of bias overall

Intervention: ambulation versus non-ambulation.
Outcome: worst pain in the 24-hour period following misoprostol

HISTORY

Protocol first published: Issue 1, 2020

CONTRIBUTIONS OF AUTHORS

JJ Reynolds-Wright: conceiving the protocol; designing the protocol, co-ordinating the protocol, designing search strategies, writing the protocol, providing general advice on the protocol, securing funding for the protocol, performing previous work that was the foundation of the current review

MA Woldetsadik: conceiving the protocol; designing the protocol, co-ordinating the protocol, designing search strategies, writing the protocol, providing general advice on the protocol, securing funding for the protocol, performing previous work that was the foundation of the current review

C Morroni: conceiving the protocol; designing the protocol, co-ordinating the protocol, designing search strategies, writing the protocol, providing general advice on the protocol, securing funding for the protocol, performing previous work that was the foundation of the current review

S Cameron: conceiving the protocol; designing the protocol, co-ordinating the protocol, designing search strategies, writing the protocol, providing general advice on the protocol, securing funding for the protocol, performing previous work that was the foundation of the current review

DECLARATIONS OF INTEREST

JJ Reynolds-Wright: none known

MA Woldetsadik: none known

C Morroni: none known

S Cameron: none known

SOURCES OF SUPPORT

Internal sources

- No internal sources of support, Other

  There were no internal sources of support

External sources

- Medical Research Council , UK

  Two of the authors were based at the MRC Centre for Reproductive Health, which is supported by grant MR/N022556/1

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Given the dearth of evidence and heterogeneity of the studies, meta-analysis was not possible. We added information on our approach to the narrative synthesis required for this review since the protocol focused only on quantitative synthesis.

We removed the secondary outcome ‘type of analgesia’ as we felt that this was a feature of interventions rather than an outcome in itself. We further specified a timeframe for complete abortion without surgical intervention of 14 days from misoprostol administration.

Otherwise, the review has been conducted per protocol.

NOTES

The timeline for this publication was disrupted by the COVID-19 pandemic and the need for authors to be redeployed to clinical duties. As a result, the review publication is later than planned, relative to the search date. The scheduled update for the review in imminent and so rather than repeating the search at this stage, we will capture any new studies in the scheduled update.

INDEX TERMS

Medical Subject Headings (MeSH)

*Abortion, Induced [adverse effects]; *Abortion, Spontaneous; Acetaminophen [therapeutic use]; Ibuprofen [adverse effects]; Mifepristone [adverse effects]; *Misoprostol [adverse effects]; Pain [drug therapy] [etiology]; Pain Management [methods]; Pregabalin

MeSH check words

Female; Humans; Pregnancy