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Review Article

Pain management for medical abortion before 14 weeks' gestation: A systematic review ☆,☆☆

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ABSTRACT

Introduction: 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.

Study Design: We conducted our search in August 2019 and included randomized controlled trials (RCT) and observational studies of any pain relief intervention (pharmacological and non-pharmacological) for mifepristone-misoprostol combination medical abortion of pregnancies less than 14 weeks' gestation.

Results: We included four RCTs and one observational study. Due to the heterogeneity of study designs, interventions and outcome reporting, meta-analysis was not possible.

Only one study found evidence of an effect between interventions on pain score: a prophylactic dose of ibuprofen 1600mg likely reduces the pain score when compared to a dose of paracetamol 2000mg (MD 2.26/10 [CI 3-1.52 lower]).

For other interventions (pregabalin 300mg vs placebo; ibuprofen 800mg vs placebo; therapeutic vs prophylactic administration of ibuprofen 800mg; ambulation vs non-ambulation during treatment) there appeared to be little to no difference with comparator.

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 1600mg was shown to be effective and it was less certain whether 800mg was effective.

1. Introduction

It is estimated that 56 million induced abortions were performed globally each year between 2010 and 2014, 45% of which were procured with less safe or least safe methods [1,2]. Combination medical abortion is the sequential use of mifepristone, a progesterone receptor antagonist, and misoprostol, a prostaglandin E1 analogue [3]. 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 [4]. In Europe, reported rates of combination medical abortion range from 17.8% in Italy [5] to 97.7% in Finland [6].

Medical abortion is known to be a painful process due to contraction of uterine smooth muscle and passage of the conceptus through the cervix, with approximately 75% of women undergoing early medical abortion before nine weeks using opiate-based

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analgesia [7]. 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. The World Health Organization recommends that medical abortion under 14 weeks' gestation can occur outside of clinic settings (such as the home) [4] 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.

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 [8]. 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 be more comfortable during medical abortion, improving experience and satisfaction with 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.

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.

This review was commissioned by and conducted in partnership with the Cochrane Fertility Regulation Group following a priority-setting exercise with stakeholders, the public, and patients. Previous reviews of pain management for medical abortion had included now obsolete methods and pain remains an area that is important to the patient experience, and where clinical guidance is often insufficient. 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.

2. Materials and Methods

We conducted this systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [9]. We searched for all published, unpublished, and ongoing studies, without restrictions on language or publication status. We considered adverse effects described in included studies only. We searched the following databases from 1988 (when Mifepristone was first licenced) to August 2019: Cochrane Central Register of Controlled Trials via EBM Reviews (Ovid) [including ClinicalTrials.gov and WHO ICTRP records], MEDLINE ALL (Ovid), Embase.com, CINAHL (EBSCOhost), LILACs http://lilacs.bvsalud.org/en/, PsycINFO (Ovid).

We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant studies. We contacted experts and organizations in the field to obtain additional information on relevant studies, including those that are ongoing. We searched numerous grey literature sites, which are detailed in the full Cochrane Review publication [10]. We also searched clinicaltrials.gov and www.who.int/trialsearch to look for ongoing studies.

We sought studies that compared any form of pain relief intervention for women (of any age) undergoing medical abortion using mifepristone and misoprostol at less than 14 weeks' gestation. Studies published in any language employing the following designs were included: randomized trials (clustered or individually randomized); quasi-experimental designs, such as nonrandomized controlled studies or stepped-wedge design experiments; and cohort studies with a control group comparing a pharmacological or non-pharmacological pain-relief intervention.

The intervention of interest was 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 considered 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. Only studies that provided medical abortion using mifepristone and misoprostol were included.

We downloaded all titles and abstracts retrieved by electronic searching to a reference management database, and removed duplicates. Two reviewers independently screened titles and abstracts for inclusion. We retrieved the full-text study reports or publications, and 2 reviewers independently screened the full text, identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreement through discussion and use of 'tie-break' decisions from the third and fourth reviewer as required.

We collated multiple reports of the same study, so that each study, rather than each report is the unit of interest in the review. We also provided any information we could obtain about ongoing studies. We recorded the selection process in a PRISMA flow diagram (Figure 1).

For randomized trials of interventions, we used the Cochrane Risk of Bias Assessment 2 (ROB-2) tool to assess for selection, performance, detection, attrition, reporting, and other biases [11]. Based on these assessments, we rated studies as low risk, high risk, or some concerns. For included nonrandomized studies we conducted dual, independent assessment of risk of bias using the ROBINS-I tool [12]. The central domains assessed with this tool are bias due to confounding, bias due to selection, information bias, and reporting bias. An overall judgment of low, moderate, serious, or critical risk of bias was made.

We used Cochrane GRADE methods and GRADEpro to assess the certainty of the evidence and to prepare "Summary of findings" tables to evaluate the overall certainty of the body of evidence for the review outcomes on effectiveness and side effects of pain relief interventions for medical abortion before 14 weeks' gestation [13,14]. Certainty of evidence was downgraded based on risk of bias assessments and imprecision [14]. One review author worked to judge the evidence certainty (e.g., high, moderate, low, or very low) and refined these judgements through discussion with the whole review team. The reviewers recorded notes to justify, document, and incorporate their judgments into reporting the results of each outcome.

Our primary outcome was self-reported maximal pain score within 24 hours of final dose of misoprostol. Our secondary outcomes were: gastrointestinal side effects: proportion experiencing each of the following — nausea, vomiting, diarrhoea; 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).

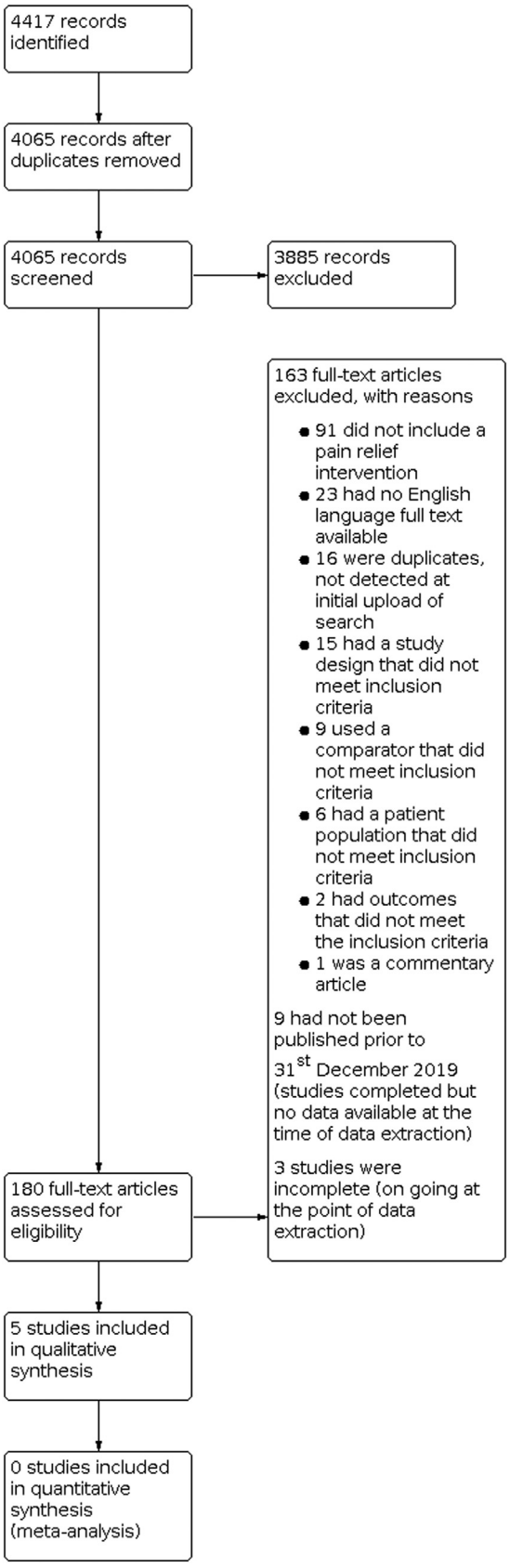

Figure 1. PRISMA Flowchart.

Had we obtained multiple, comparable studies, we would have synthesized intervention effectiveness in a meta-analysis, to produce pooled OR, RR, or mean difference effect estimates with 95% confidence interval (CI). For meta-analysis of nonrandomized studies, we would have sought to pool adjusted effect estimates using the generic inverse variance approach. Narrative synthesis was conducted for outcomes lacking adequate data to combine studies.

3. Results

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

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 Figure 1.

3.1. Study design and setting

We included four parallel-design RCTs [15–18], and one non-randomised clinical trial [19], where women chose the intervention they wished to receive. Two studies were conducted in Israel [15,17], two in the USA [16,18] and one in the UK [19]. Four were single-centre studies conducted in abortion clinics [15–17,19]. One study was multi-site, conducted at three centres in the USA [18].

3.2. 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 et al., 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 [16]. In Ojha et al., 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 [19].

Only one study reported participants' previous pregnancies: Ojha et al., 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 [19].

Only three studies reported participant age, and they all used different formats: Ojha et al., reported mean age per group, which was 27.9 years in the ambulation group and 29.4 years in the non-ambulation group [19]; Friedlander et al., 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 [16]; Raymond et al., 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 [18].

3.3. Interventions

No study used the same intervention or comparator. Three of the RCTs used ibuprofen: one RCT compared prophylactic ibuprofen with prophylactic paracetamol [17]; one RCT compared prophylactic ibuprofen with placebo [15]; and one compared prophylactic use of ibuprofen to therapeutic use of ibuprofen [18]. One RCT [16], compared prophylactic pregabalin with placebo. The NRSI [19], compared ambulation versus non-ambulation during treatment, from the point of misoprostol administration.

3.4. 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 [15,17], one reported worst pain in the 24-hour period following misoprostol [18], and one reported pain scores at multiple time points (immediately after misoprostol administration and then at 2, 6, 12, 24 and 72 hours later) [16]. The NRSI [19], 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.

3.5. 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

3.6. Risk of bias in included studies

We discuss risk of bias separately for the four RCTs using the RoB 2 tool (Table 1; [11]) and the NRSI using the ROBINS-I tool (Table 2; [12]).

3.6.1. Randomized studies of an intervention

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.

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

Three studies were at low risk of performance and detection bias due to blinding of both participants and study personnel, and outcomes assessors [15–17].

We deemed one study, to be at high risk of detection bias due to the outcomes assessors not being blinded [18]. 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.

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.

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.

We judged three of the RCTs to be at low risk of other forms of bias [15–17]. We judged one RCT [18], 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.

3.6.2. Non-randomised study of an intervention

We rated the single NRSI [19] as low risk of bias 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'.

We rated this study 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.

This study 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.

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

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

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

We deemed this study 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.

3.7. Effects of interventions

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.

3.7.1. Primary outcomes

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

Only one study [17], 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, See Table 3).

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; See Table 4) [16].

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; See Table 5) [15].

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; See Table 6) [19].

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; See Table 7) [18].

3.7.2. Secondary outcomes

Incidence of gastrointestinal side effects

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

Friedlander et al., [16] compared pregabalin 300 mg with placebo. The evidence suggests there is little to no difference in

Table 1
Risk of Bias (ROB-2) Table

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 (immediately after misoprostol administration and then at 2, 6, 12, 24 and 72 hours later)	Quote: "A researcher not involved in the conduct of the study used a computer-generated randomization scheme of varied block sizes"	Quote: "A researcher not involved in the conduct of the study ... placed the allocated study capsule in sequentially numbered bags identified only by study identification number so as to maintain blinding of participants and researchers."	Comment: Using ROB2 tool: Domain 5.1 = Yes, 5.2 = No, 5.3 = No	Comment: Using ROB2 tool: Domain 4.1 =No, 4.2 = No, 4.3 = No Information, 4.4 = No	Comment: Study appears to have reported on all outcomes selected in analysis plan	Comment: No other specific concerns regarding 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 overall result, but cannot tell as results aggregated.

Table 2
ROBINS-I Risk of Bias Table

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 Rationale for judgement	Serious 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	Serious Comment: Discussed within review team and felt that as participants could self-select intervention, at serious risk of bias.	Low Comment: ROBINS-I tool questions 3.1 = Yes, 3.2 = Yes, 3.3 = No, therefore Judgement = Low	Low Comment: ROBINS-I questions 4.1 = Probably No, 4.3 = Probably Yes, 4.4 = Probably Yes, 4.5 = Probably Yes, therefore Judgement = Low	Low Comment: ROBINS- I questions 5.1 = Yes, 5.2 = Probably No, 5.3 = Probably No, therefore Judgement = Low	Low Comment: Discussed within review team and felt that outcome measurements were unlikely to be significantly biased	Low Comment: ROBINS-I tool questions 7.1 = No, 7.2 = Probably No, 7.3 = Probably No, therefore Judgement = Low	Serious 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

Table 3
Ibuprofen 1600 mg compared to paracetamol 2000 mg for women having medical abortion before 14 weeks' gestation

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	-	-	-	-	-	

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

the rate of nausea (odds ratio (OR) 0.85, 95% CI 0.33 to 2.19; 1 RCT, 107 women; low-certainty evidence), vomiting (OR 0.76, 95% CI 0.35 to 1.63; 1 RCT, 107 women; low-certainty evidence) or diarrhoea (OR 0.82, 95% CI 0.38 to 1.76; 1 RCT, 107 women; low-certainty evidence). The study did not report data on anti-emetic/anti-diarrhoeal use.

Avraham et al., [15] 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) or vomiting (OR 0.19, 95% CI 0.04 to 0.97; 1 RCT, 61 women; low-certainty evidence). This study did not report data on rates of diarrhoea or anti-emetic/anti-diarrhoeal use.

Raymond et al., [18] 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). 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 [17], 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 [19].

Complete abortion rate

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

Livshits et al., [17] compared ibuprofen 1600 mg with paracetamol 2000 mg and suggests that there is little to no difference in

Table 4
Pregabalin 300 mg compared to placebo for women having medical abortion before 14 weeks' gestation

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]	

Patient or population: women having medical abortion before 14 weeks' gestation
Setting: clinic, USA
Intervention: pregabalin 300 mg
Comparison: placebo
*__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
[a] Downgraded 2 levels for imprecision: small sample size and 95% confidence intervals include no effect.

Table 5
Ibuprofen 800 mg compared to placebo for women having medical abortion before 14 weeks' gestation

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	-	-	-	-	-	

Patient or population: women having medical abortion before 14 weeks' gestation
Setting: clinic, Israel
Intervention: Ibuprofen 800 mg
Comparison: Placebo
*__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
[a] Downgraded 2 levels for imprecision: small sample size and wide 95% confidence intervals including no effect or very small effects.

complete abortion rate (OR 2.11, 95% CI 0.64 to 6.92; 1 RCT, 108 women; low-certainty evidence).

Avraham et al., [15] 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).

Raymond et al., [18] 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).

Ojha et al., [19] suggests that ambulating or not at the time of abortion treatment may have little to no effect on complete abor-

Table 6
Ambulation compared to non-ambulation for women having medical abortion before 14 weeks' gestation

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	-	-	-	-	-	

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

Table 7
Therapeutic ibuprofen 800 mg compared to prophylactic ibuprofen 800 mg women having medical abortion before 14 weeks' gestation

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]	

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
*__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
[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.

tion 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 [19], 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).

Unscheduled contact with care provider

Only one RCT [18], 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).

Patient satisfaction with analgesia regimen

Only one RCT [16], 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).

Patient satisfaction with abortion experience overall

Two RCTs [16,18], 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 [16] (OR 1.84, 95% CI 0.80 to 4.22; 1 RCT, 105 women; low-certainty evidence), or therapeutic with prophylactic ibuprofen 800 mg [18] (OR 0.52, 95% CI 0.09 to 2.89; 1 RCT, 228 women).

4. Discussion

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.

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 [17], 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.

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 [17]. 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.

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.

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.

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.

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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