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[Intervention Review]

Topical phenytoin for treating pressure ulcers

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ABSTRACT

Background

Pressure ulcers are common in clinical practice and pose a significant health problem worldwide. Apart from causing suffering to patients, they also result in longer hospital stays and increase the cost of health care. A variety of methods are used for treating pressure ulcers, including pressure relief, patient repositioning, biophysical strategies, nutritional supplementation, debridement, topical negative pressure, and local treatments including dressings, ointments and creams such as bacitracin, silver sulphadiazine, neomycin, and phenytoin. Phenytoin is a drug more commonly used in the treatment of epilepsy, but may play an important role in accelerating ulcer healing.

Objectives

To assess the effects of topical phenytoin on the rate of healing of pressure ulcers of any grade, in any care setting.

Search methods

In September 2016, we searched the following electronic databases to identify relevant randomized clinical trials: the Cochrane Wounds Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library); Ovid MEDLINE; Ovid Embase; and EBSCO CINAHL Plus. We handsearched conference proceedings from the European Pressure Ulcer Advisory Panel, European Wound Management Association and the Tissue Viability Society for all available years. We searched the references of the retrieved trials to identify further relevant trials. We also searched clinical trials registries to identify ongoing and unpublished studies. There were no restrictions with respect to language, date of publication or study setting.

Selection criteria

We included all randomized controlled trials (RCTs) addressing the effects (both benefits and harms) of topical phenytoin on the healing of pressure ulcers of any grade compared with placebo or alternative treatments or no therapy, irrespective of blinding, language, and publication status.

Data collection and analysis

Two review authors independently selected studies, extracted information on participants, interventions, methods and results and assessed risk of bias using Cochrane methodological procedures. For dichotomous variables, we calculated the risk ratio (RR) with 95% confidence interval (CI). For continuous variables, we calculated the mean difference with 95% CI. We rated the quality of the evidence by using Grading of Recommendations, Assessment, Development and Evaluation approach (GRADE).

Topical phenytoin for treating pressure ulcers (Review)

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Main results

Three small RCTs met our inclusion criteria and included a total of 148 participants. These compared three treatments with topical phenytoin: hydrocolloid dressings, triple antibiotic ointment and simple dressings. In the three RCTs, 79% of participants had grade II ulcers, and 21% of participants had grade I ulcers; no participants had grade III or IV ulcers. Two RCTs had a high risk of bias overall and the other RCT was at unclear risk of bias due to poor reporting. Two RCTs had three intervention arms and the other had two intervention arms.

Two studies compared topical phenytoin with hydrocolloid dressing (84 participants analysed). The available data suggest that hydrocolloid dressings may improve ulcer healing compared to topical phenytoin (39.3% ulcers healed for phenytoin versus 71.4% ulcers healed for hydrocolloid dressings (RR 0.55, 95% CI 0.33 to 0.92; 56 participants, 1 study; low quality evidence). We downgraded the evidence twice: once due to serious limitations (high risk of bias) and once due to the small sample size and small number of events. Two studies compared topical phenytoin with simple dressings (81 participants analysed). From the available data, we are uncertain whether topical phenytoin improves ulcer healing compared to simple dressings (39.3% ulcers healed for phenytoin versus 29.6% ulcers healed for the simple dressing (RR 1.33, 95% CI 0.63 to 2.78; 55 participants, 1 study; very low quality evidence). This evidence was downgraded once due to serious limitations (high risk of bias) and twice due to the low number of outcome events and resulting wide CI which included the possibility of both increased healing and reduced healing. We therefore considered it to be insufficient to determine the effect of topical phenytoin on ulcer healing. One study compared topical phenytoin with triple antibiotic ointment, however, none of the outcomes of interest to this review were reported. No adverse drug reactions or interactions were detected in any of the three RCTs. Minimal pain was reported in all groups in one trial that compared topical phenytoin with hydrocolloid dressings and triple antibiotic ointment.

Authors' conclusions

This review has considered the available evidence and the result shows that it is uncertain whether topical phenytoin improves ulcer healing for patients with grade I and II pressure ulcers. No adverse events were reported from three small trials and minimal pain was reported in one trial. Therefore, further rigorous, adequately powered RCTs examining the effects of topical phenytoin for treating pressure ulcers, and to report on adverse events, quality of life and costs are necessary.

PLAIN LANGUAGE SUMMARY

Topical (applied to the skin) phenytoin for treating pressure ulcers

Review question

We reviewed the evidence about the effect of phenytoin (a medication used orally to treat epilepsy) when used as a cream or in a dressing applied directly to pressure ulcers. We wanted to find out if phenytoin affected ulcer healing, and if it had any harmful side effects.

Background

Pressure ulcers (also known as bed sores, pressure sores and decubitus ulcers) are areas of skin and underlying tissue that have been damaged by prolonged pressure and/or exposure to shear forces (e.g. the forces exerted on the skin when someone is pulled into a more upright position in a bed or chair). People at risk of developing pressure ulcers include those with spinal cord injuries, and those who are immobile or who have limited mobility - such as elderly people and people who lie in bed for long periods due to short-term or long-term medical conditions. Pressure ulcers frequently take a long time to heal. People with pressure ulcers often suffer extended periods of pain and treatment that make it difficult to carry out their basic daily activities; this has an impact on their quality of life and can lead to additional costs for their health care.

Oral phenytoin is a medicine that is used to control epileptic seizures. It has been suggested that topical (applied directly to the skin) phenytoin may help in the healing of pressure ulcers, as it has been used topically to heal and reduce pain and swelling (inflammation) in a range of wounds, including those resulting from traumatic injury, other types of ulcers, and burns. A topical medication can be applied in the form of a cream, a lotion, or a medication-impregnated dressing.

Study characteristics

In September 2016 we searched for randomised controlled trials (RCTs) that compared topical phenytoin against other treatments for treating pressure ulcers. We found three small RCTs that included a total of 148 people with pressure ulcers. The average age of participants in two studies was 45 years and 75 years in one study. Twenty-one per cent of participants had grade I ulcers (the least severe type, with swollen but unbroken skin) and 79% had grade II ulcers (slightly more severe). No one had grade III or IV ulcers (the most severe types). The trials compared topical phenytoin with three other treatments for pressure ulcers: hydrocolloid dressings, triple antibiotic ointment, and simple dressings. The results of one study suggested that hydrocolloid dressings may slightly improve ulcer healing compared to topical phenytoin. However, we are uncertain whether topical phenytoin improves ulcer healing compared to simple dressings. The study which compared topical phenytoin with triple antibiotic ointment did not report any outcomes of interest to this review.

Quality of the evidence

It is uncertain whether topical phenytoin improves ulcer healing for patients with grade I and II pressure ulcers. No adverse events were reported from three small trials and minimal pain was reported in one trial. The trials did not report on some other measurements that we were interested in, such as cost of treatment and quality of life. Two RCTs had a high risk of bias overall, which might have affected the results, and another RCT did not report sufficient details about how it was conducted. Further rigorous, adequately powered RCTs are needed to find whether topical phenytoin is a helpful medication for treating pressure ulcers.

This plain language summary is up to date as of September 2016.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Topical phenytoin compared with hydrocolloid dressing for pressure ulcers

Topical phenytoin compared with hydrocolloid dressing for pressure ulcers

Patient or population: people with a pressure ulcer

Settings: family homes or nursing homes

Intervention: topical phenytoin

Comparison: hydrocolloid dressing

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with hydrocolloid dressing	Risk with topical phenytoin				
Time to complete healing	See comments	See comments				The study data reported did not provide a suitable representation of the outcome of interest
Proportion of ulcers healed within trial period (eight weeks)	714 per 1000	393 per 1000 (236 to 657)	RR 0.55 (0.33 to 0.92)	56 (1 study)	⊕⊕⊕⊕ low ¹	
Adverse events	See comments	See comments	Not estimable	84 (2 studies)		No adverse drug reactions or interactions were detected in the included RCTs.
Pain	See comments	See comments	Not estimable	28 (1 study)		Minimal pain was reported in all groups in one study. Study authors made this statement without any data to support it.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** risk ratio; **SD:** standard deviation

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1. Downgraded two levels: serious limitation (risk of bias), serious imprecision (small number of events)

Summary of findings 2. Topical phenytoin compared with triple antibiotic ointment for pressure ulcers

Topical phenytoin compared with triple antibiotic ointment for pressure ulcers

Patient or population: people with a pressure ulcer

Settings: nursing homes

Intervention: topical phenytoin

Comparison: triple antibiotic ointment

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with triple antibiotic ointment	Risk with topical phenytoin				
Time to complete healing	See comments	See comments				The study data reported did not provide a suitable representation of the outcome of interest
Proportion of ulcers healed within trial period (eight weeks)	See comments	See comments				This outcome was not reported for this comparison
Adverse events	See comments	See comments	Not estimable	28 (1 study)		No adverse drug reactions or interactions were detected in the included RCT.
Pain	See comments	See comments	Not estimable	28 (1 study)		Minimal pain was reported in all groups in one study. Study authors made this statement without any data to support it.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** risk ratio; **SD:** standard deviation

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 3. Topical phenytoin group compared with a simple dressing for pressure ulcers

Topical phenytoin compared with a simple dressing for pressure ulcers

Patient or population: people with a pressure ulcer

Settings: family homes or nursing homes, and a hospital

Intervention: topical phenytoin

Comparison: a simple dressing

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with a simple dressing	Risk with topical phenytoin				
Time to complete healing	See comments	See comments				This outcome was not reported for this comparison
Proportion of ulcers healed within trial period (eight weeks)	296 per 1000	394 per 1000 (187 to 824)	RR 1.33 (0.63 to 2.78)	55 (1 study)	⊕⊕⊕⊕ very low ¹	
Adverse events	See comments	See comments	Not estimable	81 (2 studies)		No adverse drug reactions or interactions were detected in the included RCTs.
Pain	See comments	See comments				This outcome was not reported for this comparison.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** risk ratio; **SD:** standard deviation

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1. Downgraded three levels: once for serious limitation (risk of bias), and twice for very serious imprecision (small number of events and a wide confidence interval which includes the possibility of both increased healing and reduced healing)

BACKGROUND

Description of the condition

A pressure ulcer can be defined as localised injury to the skin or underlying tissue, or both, usually over a bony prominence, as a result of pressure, or pressure in combination with shear. A number of contributing or confounding factors are also associated with pressure ulcers; the significance of these factors has yet to be elucidated (EPUAP/NPUAP/PPPIA 2014). Pressure ulcers are a widespread, expensive and painful healthcare problem, with prevalence rates that range from 8.8% to 53.2% (Gallagher 2008; Moore 2012), and incidence rates that vary from 7% to 71.6% (Scott 2006; Moore 2011). Mean prevalence has been reported as 21% in acute care settings and as 12% in long-stay settings (Moore 2013a). Prevalence among hospice patients has been reported as 35.7%, and in community care patients as 0.04% and 4% (Moore 2013a). Similarly, mean incidence has been reported as 17.6% in an acute care setting, 6.63% in a long-stay setting and 20.4% in a hospice setting (Moore 2013a). Pressure ulcers represent a major concern as they can take a long time to heal, reduce quality of life for many people, and are a burden on healthcare systems and society.

The cost of pressure ulcer treatment is substantial. Pressure ulcers represent a significant cost burden in the UK, both to patients and to healthcare providers. The cost of treating a pressure ulcer varies from GBP 1214 (grade I - least severe type of pressure ulcer) to GBP 14,108 (grade IV - most severe) (Dealey 2012). Costs will increase with the severity of the ulcer, and the incidence of complications is higher in more severe cases (Dealey 2012). In the USA, it has been reported that the average hospital treatment cost associated with grade IV pressure ulcers and related complications was USD 129,248 for hospital-acquired ulcers during one admission, and USD 124,327 for community-acquired ulcers over an average of four admissions; this is much more than previously estimated (Brem 2010). In the Netherlands, pressure ulcers are thought to be the third most expensive health problem (Haalboom 2000). In Flanders, the mean cost of local treatment per patient per day varied between EUR 2.34 and EUR 77.36 in hospitals, and between EUR 2.42 and EUR 16.18 in nursing homes (Demarré 2015). Pressure ulcers impose a heavy burden on healthcare systems in terms of cost, patient suffering, and the need for skilled medical intervention.

Pressure ulcers can be graded according to criteria established by the European Pressure Advisory Panel and National Pressure Ulcer Advisory Panel as follows (EPUAP/NPUAP/PPPIA 2014):

- Grade I: non-blanchable erythema (redness) of intact skin. Discolouration of the skin, warmth, oedema (swelling), induration (hardness) may also be used as indicators, particularly on individuals with darker skin.
- Grade II: partial-thickness skin loss involving epidermis, dermis, or both. The ulcer is superficial and presents clinically as an abrasion or blister.
- Grade III: full-thickness skin loss involving damage/necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia (layers).
- Grade IV: extensive destruction, tissue necrosis (death), or damage to muscle, bone, or supporting structures with or without full-thickness skin loss.

A variety of risk factors for pressure ulcer formation have been identified in different populations. Besides unrelieved pressure, shearing forces and friction, endogenous (personal) conditions that predispose people to pressure ulcers include old age, diabetes, terminal illness, sepsis, neurological and vascular diseases (Bliss 1999). Other risk factors include incontinence, immobility, altered mental status, lower blood pressure and higher body temperature (Allman 1986; Bergstrom 1992; Armstrong 2001; Schouchoff 2002; Benoit 2012).

Description of the intervention

A variety of methods have been used for treating pressure ulcers, such as pressure relief using beds, mattresses or cushions and patient repositioning (NICE 2014; Gillespie 2014; McGinnis 2014; McInnes 2015; Moore 2015); biophysical strategies such as electrical stimulation, ultrasound, ultraviolet irradiation, massage therapy, and laser treatment (Nussbaum 1994; Akbari Sari 2006; Aziz 2012; Chen 2014; Zhang 2015); nutritional supplementation (Hartgrink 1998; Langer 2014); debridement (removal of dead tissue) (Witkowski 1991; Moore 2013b); topical (skin surface) negative pressure (Philbeck 1999; Dumville 2015a); and local treatments including hydrocolloid dressings and phenytoin (Hollisaz 2004; Dumville 2015b). Hydrocolloid dressings are advanced wound dressings designed to control the environment with the aim of promoting wound healing; examples include Granuflex and Duoderm.

Phenytoin is an effective anti-epileptic medication. The possibility of using phenytoin for wound healing was first recognised in 1939 when it was observed that patients receiving oral phenytoin had a side-effect of gingival hyperplasia (increase in the size of the gums) (Kimball 1939). In 1958, Shapiro carried out the first controlled clinical trial examining the effects of oral phenytoin on periodontal (mouth) wounds and reported that phenytoin accelerated wound healing and reduced pain and inflammation (Shapiro 1958). The first double-blind, placebo-controlled clinical study involving topical phenytoin treatment in venous stasis ulcers demonstrated that, when compared with controls, the use of phenytoin promoted wound healing (Simpson 1965). Since this study, a number of other studies have suggested the effectiveness of topical phenytoin in the treatment of a variety of wounds including diabetic ulcers (Pai 2001), trophic ulcers in leprosy (Bhatia 2004), chronic leg ulcers (Carneiro 2003), pressure ulcers (Rhodes 2001), and superficial burn wounds (Carneiro 2002). The topical application of phenytoin can be usually administered as either powder, via an impregnated dressing, or as cream (Fonseka 2010; Pereira 2010; Hokkam 2011; Shaw 2011).

How the intervention might work

It has been reported that phenytoin may promote ulcer healing by stimulating the following processes: fibroblast proliferation (cells that play a central part in wound healing) (Shapiro 1958; Cloyd 1994; Margolis 1995; Eser 2012); collagen deposition (Margolis 1995; Habibipour 2003; Beigom Taheri 2015); vessel ingrowth (Dill 1997; Simsek 2014; Sayar 2014); glucocorticoid antagonism (reduces inflammation) (Margolis 1995; Baharvand 2014; Simsek 2014), and antibacterial activity (Dill 1997; Patil 2013); as well as enhancing the number of macrophages in the wound (cells that 'eat' cellular debris) (Song 1997; Sehgal 2014).

Why it is important to do this review

Previous systematic reviews reported evidence about topical phenytoin for treating pressure ulcers (Reddy 2006; Reddy 2008; Reddy 2011; Smith 2013), but the data were inconsistent and insufficient to enable conclusions to be drawn. In addition, they did not report the outcomes in detail. The effects of topical phenytoin on the healing of pressure ulcers is not known, therefore it is important to undertake a comprehensive assessment of all the available evidence.

OBJECTIVES

To assess the effects of topical phenytoin on the rate of healing of pressure ulcers of any grade, in any care setting.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomized controlled trials (RCTs), including cluster trials, that addressed the effects (both benefits and harms) of topical phenytoin on the healing of pressure ulcers of any grade, irrespective of blinding status, language, and publication status.

Types of participants

We included studies involving people of any age, of any gender and race/ethnicity, and in any care setting, who were described as having a pressure ulcer (pressure sore, bed sore or decubitus ulcer) of any grade.

Types of interventions

The topical application of phenytoin (administered as either powder, impregnated dressing, cream and/or other preparation) to treat pressure ulcers compared with placebo or alternative treatments or no therapy.

Types of outcome measures

Primary outcomes

- Time to complete healing (we defined complete healing as intact skin)
- Proportion of ulcers healed within trial period.

Secondary outcomes

- Adverse events, such as any drug allergies and adverse drug reactions
- Pain, measured using tools such as a visual analogue scale
- The overall cost of healing pressure ulcers in different grades of pressure ulcers
- Quality of life, using tools such as the Nottingham Health Profile.

Search methods for identification of studies

Electronic searches

We searched the following databases with the assistance of Cochrane Wound's Information Specialist:

- the Cochrane Wounds Specialised Register (searched 10 September 2016);
- the Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library 2016, Issue 9);
- Ovid MEDLINE (1946 to 27 September 2016);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations) (searched 27 September 2016);
- Ovid Embase (1974 to 27 September 2016);
- EBSCO CINAHL Plus (1937 to 27 September 2016).

CENTRAL was searched using the strategy in Appendix 1. This strategy was adapted where appropriate for the Cochrane Wounds Specialised Register. The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity and precision-maximizing version (2011 revision) (Lefebvre 2011). The Embase and CINAHL Plus searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2015). There was no restriction on the basis of date or language of publication.

The search strategies for Ovid MEDLINE, Ovid Embase and EBSCO CINAHL Plus are listed in Appendix 1.

Searching other resources

We handsearched conference proceedings from the European Pressure Ulcer Advisory Panel, the European Wound Management Association and the Tissue Viability Society from inception to 27 September 2016. We searched the reference sections of the retrieved trial reports to identify further relevant trials.

We also searched the following clinical trials registries for any ongoing and unpublished studies (searched 27 September 2016):

- Clinical Trials.gov (clinicaltrials.gov);
- WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/en);
- Chinese Clinical Trial Registry (ChiCTR) (www.chictr.org.cn/searchprojen.aspx).

Data collection and analysis

We carried out data collection and analysis according to methods stated in the published protocol (Hao 2010), which were based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Selection of studies

Two review authors (XYH and YFS) identified the trials for inclusion according to the selection criteria independently of each other. When it was unclear from the title or abstract whether a paper fulfilled the criteria, we obtained a copy of the full text and the two review authors jointly decided whether the study met the inclusion criteria. We listed the excluded studies with the reasons for their exclusion. We resolved disagreement by discussion with a third review author (TKG). We set out a study flow diagram as recommended by the PRISMA statement to illustrate the process of screening and selecting studies for inclusion in the review (Figure 1) (Liberati 2009).

Figure 1. Study flow diagram.

Data extraction and management

Two review authors (XYH and YFS) independently extracted the following data from each study:

- first author
- year the trial was conducted
- year of publication
- country
- inclusion and exclusion criteria
- baseline characteristics such as age, sex ratio, concurrent disease, and presence of existing pressure ulcers on entering the study (site, number, grade and size of ulcer(s)), by treatment group
- description of interventions and co interventions and number of participants in each group
- data for the primary and the secondary outcomes
- risk of bias (described below)
- duration of follow-up
- source of funding.

We sought any unclear or missing information by contacting the authors of the individual trials. If there was any doubt about whether the trials shared the same participants, completely or partially (by identifying common authors and centres), we contacted the authors of the trials to clarify whether the trial had been published in duplicate. We resolved any differences in opinion through discussion.

Assessment of risk of bias in included studies

Two review authors (XYH and YFS) independently assessed each included study using the Cochrane tool for assessment of risk of bias (Higgins 2011a). This tool addresses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (e.g. extreme baseline imbalance; see Appendix 2 for details of criteria on which the judgements were based). Blinding and completeness of outcome data were assessed for each outcome separately. We completed a 'Risk of bias' table for each eligible study. We discussed any disagreement amongst all review authors to achieve a consensus.

We have presented an assessment of risk of bias using a 'Risk of bias' summary figure, which presents all of the judgments in a cross-tabulation of study by entry. This display of internal validity indicates the weight the reader may give the results of each study.

Measures of treatment effect

We carried out this systematic review according to Cochrane methods (Higgins 2011a), and used the Cochrane software package Review Manager 5 (RevMan 2014). For dichotomous variables, we calculated the risk ratio (RR) with 95% confidence interval (CI). For continuous variables, we calculated the mean difference (MD) with 95% CI. We carried out the analysis according to the number of pressure ulcers in each group. For time to complete healing, we checked the time to complete healing of participants who reached complete healing in each intervention group, and these original data were then presented and analysed in this review.

Unit of analysis issues

We considered individual participants as the unit of analysis. We checked how participants, or ulcers, had been randomized and whether there was evidence that more than one pressure ulcer on a single person had been analysed by examining the number of participants and the number of pressure ulcers in each trial. We did not include any cluster-randomized studies and cross-over trials in this review.

Dealing with missing data

We attempted to contact the original investigators of trials to request information re missing data. As we received no response, we assessed the risk of attrition bias according to our risk of bias criteria and based on available data (Higgins 2011b). We reported the number and percentage of dropouts/withdrawals. Studies that had missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups, we assessed as being at a low risk of bias for attrition. If the percentage of dropouts/withdrawals was less than 10%, we classed the trial as being at a low risk of bias, but if dropouts/withdrawals exceeded 10%, we classed the trial as being at high risk of bias.

Where we considered data to be missing at random, we analysed the available information. Where outcome data were missing, we used an available-case analysis, based on the numbers of participants for whom outcome data were known. We also addressed the potential impact of the missing data on the findings of the review in the discussion section (Higgins 2011c).

Assessment of heterogeneity

We intended to explore heterogeneity using the Chi² test, with P values of less than 0.1 considered to be statistically significant, and to measure heterogeneity using the I² statistic (Higgins 2003). We considered that an I² value greater than 50% represented substantial heterogeneity. We intended to explore clinical heterogeneity by examining potentially influential factors, for example, care setting or participant characteristics. No studies were pooled in this review, but this was largely due to a lack of suitable data for pooling rather than because of heterogeneity.

Assessment of reporting biases

In future, if 10 or more studies are included for meta-analysis, we will assess visual asymmetry of funnel plots to identify any potential reporting or publication bias (Sterne 2011).

Data synthesis

We had decided to use a fixed-effect model to pool all results when there was no evidence of heterogeneity between studies (DeMets 1987). If there was evidence of heterogeneity, we would have used a random-effects model (DerSimonian 1986). Where pooling was not appropriate, because there was substantial heterogeneity or lack of suitable data for pooling, we presented the outcomes in a descriptive way. No pooling of results occurred in this review due to a lack of suitable data.

'Summary of findings' tables

We present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes

(Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE approach. The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We presented the following outcomes in the 'Summary of findings' tables:

- time to complete healing;
- proportion of ulcers healed within trial period;
- adverse events;
- pain.

RESULTS

Description of studies

Results of the search

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

We identified 26 relevant citations through database searches. After we had removed duplicates, 19 citations remained. We excluded ten of these on the basis of their title and abstract. We assessed 9 full-text articles for eligibility and excluded six because they did not meet our detailed inclusion criteria. This left us with three studies that we included in this review (see [Figure 1](#) for Study flow diagram).

Included studies

Three RCTs met the inclusion criteria. These had recruited a total of 148 participants (Subbanna 2007, 26 participants; Rhodes 2001, 39 participants; Hollisaz 2004, 83 participants). Only Hollisaz 2004 reported an a priori sample size estimation and showed the full details of the sample size estimation. The trials were published between 2001 and 2007. The studies were conducted in America (Rhodes 2001), Iran (Hollisaz 2004), and India (Subbanna 2007), and they were all single-centre studies. The studies were carried out in nursing homes (Rhodes 2001), family homes or nursing homes (Hollisaz 2004), and a hospital (Subbanna 2007).

Hollisaz 2004 and Subbanna 2007 restricted recruitment to people with spinal cord disorders, while Rhodes 2001 excluded people with spinal cord disorders and did not report the cause of the pressure ulcers. All trials provided detailed information on patient exclusion criteria. Subbanna 2007 and Hollisaz 2004 included relatively young participants with a mean age of 45 years. Rhodes 2001 included participants with a mean age of 75 years. The mean duration of ulcers before treatment in Hollisaz 2004 and Subbanna 2007 was six and 10 weeks, respectively; mean duration

was not reported in Rhodes 2001. Subbanna 2007 and Rhodes 2001 included only participants with grade II pressure ulcers; Hollisaz 2004 included participants with grade I and grade II ulcers. Pressure ulcers were all classified according guidance provided by the National Pressure Ulcer Advisory Panel (NPUAP 1995). The trials considered three comparators to topical phenytoin: triple antibiotic ointment (Rhodes 2001); hydrocolloid dressing (Rhodes 2001; Hollisaz 2004); and simple dressings (Hollisaz 2004; Subbanna 2007). The triple antibiotic ointment contained three antibiotics - bacitracin, neomycin, and polymyxin B sulphates. The simple dressings intervention involved covering the ulcer with a wet saline gauze dressing after it was cleaned. In the three RCTs, two RCTs have three intervention arms respectively and another RCT has two intervention arms. The participants of every group in each comparison were comparable. The concentration of phenytoin solution was 5 mg/mL in Subbanna 2007 and 20 mg/mL in Rhodes 2001; the concentration used was not reported in Hollisaz 2004. Rhodes 2001 reported on time to complete healing and pain, while Hollisaz 2004 reported on proportion of ulcers healed within trial period. All three RCTs reported adverse events. None of the included studies reported costs or quality of life. The Rhodes 2001 study did not report the sources of funding, but the Hollisaz 2004 study received financial support from the Jaonbazan Medical and Engineering Research Center, and the Subbanna 2007 study received financial support from the intramural research funds of the Christian Medical College, Vellore, India.

Excluded studies

We excluded six studies and provided details of the reasons for their exclusion in the [Characteristics of excluded studies](#) table. These six studies were excluded because they did not meet detailed inclusion criteria after we had retrieved them in full text for more detailed evaluation (el Zayat 1989; Lodha 1991; Agarwal 1998; Chauhan 2003; Shaw 2010; Panahi 2015). Two of the excluded trials, Agarwal 1998 and el Zayat 1989 were not randomized trials. Chauhan 2003 included only participants with venous ulcers, diabetic ulcers and mixed wounds. Lodha 1991 included only participants with abscess wounds. Shaw 2010 included only participants with diabetic foot ulcers. Panahi 2015 included 60 participants (41 with pressure ulcers, 13 with diabetic wounds and 6 with venous ulcers). The included 60 participants were divided into two groups (Aloe vera-olive oil combination cream group and phenytoin cream) by simple randomization rather than stratified randomization based on the type of the three diseases (pressure ulcers, diabetic wounds and venous ulcers). Therefore, participants with pressure ulcers in Panahi 2015 failed to meet the inclusion criteria for this review.

Risk of bias in included studies

An overall summary of the methodological quality of the included trials can be found in [Figure 2](#) and [Figure 3](#). The studies were either at high or unclear risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hollisaz 2004	+	+	-	+	+	+	?
Rhodes 2001	?	?	?	?	-	+	?
Subbanna 2007	+	+	+	+	?	+	?

Allocation

The participant was the unit of randomization in the included trials. [Subbanna 2007](#) used a computer-generated randomization list and [Hollisaz 2004](#) used a random-number table to ensure random assignment to the groups. [Hollisaz 2004](#) and [Subbanna 2007](#) used appropriate methods of concealment of allocation sequence that prevented foreknowledge of intervention assignments. [Hollisaz 2004](#) reported that the treatment category for each participant was prepared by a statistician and contained within an opaque sealed envelope that was then opened by the general practitioner to determine which treatment would be used at the start of the study. [Subbanna 2007](#) reported that the treatments were prepared and labelled using the randomization number provided by pharmacists from the institution's pharmacy. The nursing staff who administered pressure ulcer dressings were blinded to treatment assignment. [Rhodes 2001](#) did not report sufficient details about sequence generation or allocation concealment to assess whether the study used appropriate methods. Therefore,

the methods used for generating the allocation sequence and concealing the group allocation were of low risk of bias in [Subbanna 2007](#) and [Hollisaz 2004](#) but were unclear in [Rhodes 2001](#).

Blinding

[Subbanna 2007](#) reported successful blinding at all levels; the phenytoin solution was indistinguishable from the normal saline in presentation, colour, density, and odour, therefore, blinding of participants was achieved. So we judged [Subbanna 2007](#) to be at a low risk of performance bias. The nursing staff were blinded to treatment assignment and undertook changes of the pressure ulcer dressings. Outcome assessors were also reported as blinded to treatment allocation. [Hollisaz 2004](#) reported blinding of personnel and outcome assessors, but due to significant differences across the three treatment methods, blinding of participants was considered impossible and so we judged the study to be at a high risk of performance bias. [Rhodes 2001](#) did not report whether participants, personnel and/or outcome assessors were

blinded and so we judged this trial to be at an unclear risk of bias for these domains.

Incomplete outcome data

Two participants (7% of the included participants) in [Subbanna 2007](#) were lost to follow-up. Eight participants (17% of the included participants; three in the phenytoin group, three in the Duoderm group, and two in the triple antibiotic ointment group) did not complete the study in [Rhodes 2001](#). We contacted the original investigators and there were no response. The final analysis in both trials did not include these dropouts/withdrawals; there was therefore a high risk of attrition bias in the estimates, especially in [Rhodes 2001](#). [Hollisaz 2004](#) reported that all participants completed the study, with no losses to follow-up or treatment withdrawals. So we judged [Hollisaz 2004](#) to be at a low risk of attrition bias.

Selective reporting

The included studies did not provide enough information to permit us to make a judgement regarding selective reporting, or to permit identification of any problem that might introduce bias. All of the trials provided information on the outcomes identified in their trial methods, so we considered them to be at a low risk of reporting bias.

Other potential sources of bias

We identified no other potential sources of bias in the included studies.

Effects of interventions

See: [Summary of findings for the main comparison Topical phenytoin compared with hydrocolloid dressing for pressure ulcers](#); [Summary of findings 2 Topical phenytoin compared with triple antibiotic ointment for pressure ulcers](#); [Summary of findings 3 Topical phenytoin group compared with a simple dressing for pressure ulcers](#)

Comparison 1: Topical phenytoin compared with hydrocolloid dressing (two trials)

Summary of findings for the main comparison

Two trials with 28 participants ([Rhodes 2001](#)), and 56 participants ([Hollisaz 2004](#)) respectively, compared phenytoin with a hydrocolloid dressing.

Time to complete healing

In [Rhodes 2001](#), the mean time to complete healing in the phenytoin group was 35.3 ± 14.3 (mean $\pm$ standard deviation (SD)) days compared with 51.8 ± 19.6 (mean $\pm$ SD) days for the hydrocolloid dressing (Duoderm) group. However, time to complete healing is a type of time-to-event data and the study data reported do not provide a suitable representation of the outcome of interest. Due to uncertainty regarding the number of participants covered by the reported data, this result is not appropriate for use. [Hollisaz 2004](#) did not report data on the time to complete healing.

Proportion of ulcers healed within trial period

The [Hollisaz 2004](#) trial reported that 20 out of 28 (71.4%) participants' ulcers had completely healed at eight weeks in the hydrocolloid dressing group compared with 11 out of 28 (39.3%)

participants in the topical phenytoin group. The results suggest that hydrocolloid dressings may improve ulcer healing at eight weeks compared with topical phenytoin (RR 0.55, 95% CI 0.33 to 0.92; 56 participants, 1 study; [Analysis 1.1](#)). [Rhodes 2001](#) did not report data on the ulcers healed at eight weeks. This evidence is low quality; we downgraded it once for risk of bias due to lack of blinded participants and once for imprecision due to the small trial size and low number of events.

Adverse events

No adverse drug reactions or interactions were detected in the included RCTs.

Pain

Minimal pain was reported in all groups in [Rhodes 2001](#). This statement was made by study authors. No data were available to support it.

Costs and quality of life

None of the included RCTs in this comparison reported on costs or quality of life.

Comparison 2: Topical phenytoin compared with triple antibiotic ointment (one trial)

Summary of findings 2

One trial with 28 participants compared phenytoin with triple antibiotic ointment ([Rhodes 2001](#)).

Time to complete healing

The mean time to healing in the topical phenytoin group was 35.3 ± 14.3 (mean $\pm$ SD) days compared with 53.8 ± 8.5 (mean $\pm$ SD) days for the triple antibiotic ointment group. However, time to complete healing is a type of time-to-event data and the study data reported do not provide a suitable representation of the outcome of interest. Due to uncertainty regarding the number of participants covered by the reported data, this result is not appropriate for use.

Proportion of ulcers healed within trial period

This outcome was not reported for this comparison.

Adverse events

No adverse drug reactions or interactions were detected in the included RCT.

Pain

Minimal pain was reported in all groups in [Rhodes 2001](#). This statement was made by study authors. No data were available to support it.

Costs and quality of life

The included RCT in this comparison did not report on costs or quality of life.

Comparison 3: Topical phenytoin compared with a simple dressing (two trials)

Summary of findings 3

Two trials compared phenytoin with a simple dressing ([Hollisaz 2004](#), with 55 participants; [Subbanna 2007](#), with 26 participants).

Time to complete healing

This outcome was not reported for this comparison.

Proportion of ulcers healed within trial period

The [Hollisaz 2004](#) trial reported that 11 out of 28 (39.3%) participants had completely ulcers healed at eight weeks in the topical phenytoin group compared with eight out of 27 (29.6%) participants in the simple dressing group. We are uncertain whether topical phenytoin improves ulcer healing compared with simple dressings (RR 1.33, 95% CI 0.63 to 2.78; 55 participants, 1 study; [Analysis 2.1](#)). This evidence is very low quality, we downgraded once for risk of bias due to lack of blinded participants and twice for imprecision due to the small number of events and wide confidence intervals that include the possibility of both increased healing and reduced healing. [Subbanna 2007](#) did not report data on the proportion of ulcers healed within the trial period.

Adverse events

No adverse drug reactions or interactions were detected in the included RCTs.

Pain

Pain was not reported for this comparison.

Costs and quality of life

None of the included RCTs in this comparison reported on costs or quality of life.

DISCUSSION

Summary of main results

The objective of our systematic review was to assess the effects of topical phenytoin on the rate of healing of pressure ulcers. However, only one study reported quantitative data suitable for a meta-analysis ([Hollisaz 2004](#)). We have presented 'Summary of findings' tables with GRADE ratings for the relevant outcomes ([Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#)). The conclusions are based on the results of three small RCTs that compared topical phenytoin to either hydrocolloid dressings, triple antibiotic ointment, or simple dressings. The results of one study suggest that hydrocolloid dressings may slightly improve ulcer healing compared to topical phenytoin (low quality evidence). We are uncertain whether topical phenytoin improves ulcer healing compared to simple dressings (very low quality evidence). One study compared topical phenytoin with triple antibiotic ointment, however, none of the outcomes of interest to this review was reported suitably to allow data to be considered further. The evidence for both comparisons for which there are data is of low to very low quality due to the paucity of data and risk of bias, therefore, we considered the available evidence to be insufficient to determine the effect of topical phenytoin for treating pressure ulcers. Adverse drug reactions or interactions were negligible in all three RCTs. Minimal pain was only reported in all groups in [Rhodes 2001](#). Study authors made this statement. There were no data to support it. For time to complete healing, the study data reported did not provide a suitable representation of the outcome of interest. It was not possible to address the other

outcomes of this review, for example, costs and quality of life, because data on these were not reported.

Overall completeness and applicability of evidence

As the main results were from one study of 56 participants, it is highly unlikely that the results are generalisable. Pressure ulcers that penetrate only into the epidermis or dermis can heal through tissue regeneration, whereas deeper wounds that extend through the dermis, heal by the formation of scar tissue, since subcutaneous tissues, glands, and hair follicles cannot regenerate ([Sieggreen 1987](#)). In the three included RCTs, 79% of participants had grade II ulcers, and 21% participants had grade I ulcers; no participants had grade III or IV ulcers. Therefore, we are uncertain if effectiveness would be similar in participants with grade III or IV ulcers, and further research in this area needs to be conducted. Time to complete healing was not reported as time-to-event data, therefore, the effect of topical phenytoin on this outcome, together with costs and quality of life, are unknown.

Quality of the evidence

The quality of the evidence for each outcome was low to very low. While this analysis provided an estimate of the best available evidence, this review was based on only three RCTs with small sample sizes that were underpowered to detect significant differences. Also, only [Hollisaz 2004](#) reported an a priori sample size estimation and showed the full details of the estimation. In addition, some methodological limitations may have affected the validity of this review. An overall summary of the methodological quality of the included trials can be found in [Figure 2](#) and [Figure 3](#). The main reasons for downgrading our estimation of the quality of the evidence were risk of bias, and imprecision. The results available came from one study that analyzed a small number of participants (56 participants). This resulted in the study recording a small number of events, which can give rise to imprecision. We downgraded a second time for imprecision where there was a small number of events and wide confidence intervals that included the possibility of both increased and reduced healing.

Potential biases in the review process

We searched databases and trial registries comprehensively, together with reference lists of relevant studies for published RCTs, with no restrictions on language. However, the possibility of publication bias still cannot be excluded. For time to complete healing, as we were unable to verify whether all the participants' ulcers completely healed during the study, we presented the original data as a narrative summary.

Agreements and disagreements with other studies or reviews

Our results concur with [Mao 2010](#) and [Shaw 2011](#). [Mao 2010](#) reported that, from the available published data, routine use of topical phenytoin in pressure ulcer treatment cannot be recommended until more data from rigorously-designed studies become available. [Shaw 2011](#) conducted a randomized, controlled, double-blind, clinical trial to evaluate the effect of topical phenytoin on healing in diabetic foot ulcers. This study did not support the topical application of the phenytoin-containing alginate-based, hydrogel dressing in the treatment of diabetic foot ulcers compared with alginate-based dressing. However, [Rhodes 2001](#) and [Anstead 1996](#) were in disagreement with our

result. [Rhodes 2001](#) reported that topical application of phenytoin demonstrated more rapid results in all aspects of ulcer healing. [Anstead 1996](#) described that people with large Grade IV pressure ulcers responded rapidly to treatment with topical phenytoin after conventional treatments were unsuccessful, and suggested that topical phenytoin was effective in wound healing and deserved further investigation. Additionally, [Pitiakoudis 2004](#) reported that topical phenytoin enhanced wound healing by stimulating lymphocytic chemotaxis and up-regulation of angiogenesis.

AUTHORS' CONCLUSIONS

Implications for practice

This review has considered the sparse evidence available from three small randomized controlled trials. Their results show that it is uncertain whether topical phenytoin improves ulcer healing for people with grade I and II pressure ulcers; the quality of the evidence is low to very low. No adverse events were reported in these three small trials; minimal pain was reported in one trial.

Implications for research

Further rigorous, adequately powered RCTs are necessary to examine the effects of topical phenytoin for treating pressure ulcers, and to determine whether there is an additional benefit in combining topical phenytoin with other established therapies in people with pressure ulcers of different grades (severity). We suggest the following features for the design and reporting of future RCTs in order to overcome the methodological limitations of the studies we included in this review:

- participants with all four grades of ulcers should be enrolled;
- the sample size must be sufficient to detect a significant difference compared to the control group;
- the follow-up period should be long enough to capture the completion of the healing process in the majority of participants and detect the outcomes of interest;

- details of trial methodology, such as blinding and allocation concealment, should be reported more clearly, in line with the Consolidated Standards of Reporting Trials statement (CONSORT) ([Schulz 2010](#));
- uniform diagnosis of all relevant outcome measures should be carried out and all the outcomes should be reported in line with CONSORT;
- future research should be in accordance with guidance from the European Pressure Advisory Panel and National Pressure Ulcer Advisory Panel;
- changes in pressure ulcer status should be measured using the Pressure Ulcer Scale for Healing ([PUSH Tool 3.0](#)) developed by the National Pressure Ulcer Advisory Panel;
- the optimal concentration of phenytoin solution, the dose-effect relationship, the used of full-time trained personnel, and the compliance of participants should be taken into account;
- adequate randomization should be carried out;
- outcome assessors and data analysts (e.g. statisticians) should be thoroughly blinded, as well as the participants and investigators, and bias in outcome assessment should be minimised by presenting the photographic evidence of the ulcer;
- outcomes should include adverse events, quality of life and costs.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by year of study]

Rhodes 2001

Methods	<p>randomized controlled trial</p> <p>Random sequence generation: method of randomization unspecified</p> <p>Allocated concealment: not described</p> <p>Blinding: not described</p> <p>Year of conduct of the trial not reported</p>
Participants	<ul style="list-style-type: none"> N = 39 Phenytoin group (grade II ulcers = 15); Duoderm group (grade II ulcers = 13); triple antibiotic ointment group (grade II ulcers = 11) Setting: Veterans Administration nursing home, USA Numbers of men and women not clearly reported Mean age of participants: phenytoin group = 75.5 years; Duoderm group = 78.4 years; triple antibiotic ointment group = 76.5 years Inclusion criteria: age > 60 years, with a grade II decubitus ulcer. (A grade II decubitus ulcer is defined by the Agency for Health Care Policy and Research (AHCPR) Pressure Ulcer Guideline panel (AHCPR 1992) as "a partial thickness skin loss presenting as an abrasion, blister, or shallow crater involving the epidermis and/or dermal skin layers.") Exclusion criteria: participants with signs and symptoms of wound infection at the start of treatment, anaemia, malnutrition, folate deficiency, chronic use of immunosuppressant medications (e.g. pred-

Rhodes 2001 (Continued)

nisone), immobility (i.e. spinal cord injuries), those receiving oral phenytoin for any concurrent medical problem, or a history of adverse effects caused by phenytoin

Interventions	<ul style="list-style-type: none"> Phenytoin group: the ulcers were debrided as necessary, cleansed with 0.9% NaCl and hydrogen peroxide, dried, and covered with 100 mg phenytoin suspension daily. A single 100 mg phenytoin capsule was opened and placed in a small plastic dosage administration cup containing 5 mL of sterile 0.9% NaCl to form a phenytoin–NaCl suspension. Sterile gauze was then soaked in the suspension and placed over the wound, followed by a layer of dry sterile gauze. Treatment continued until total closure of the ulcer occurred, without evidence of residual exudate or inflammation. Duoderm group: the ulcers were debrided as necessary, cleansed with 0.9% NaCl and hydrogen peroxide, and dried; then the protective backing from the Duoderm dressing pad was removed and the pad placed over the wound with the edges extending 1¼ inch beyond the wound. The dressings were checked at each shift and left in place for up to 7 days, unless they became uncomfortable, leaked, or clinical signs of infection were detected. The dressings were continued for 1-2 weeks after apparent wound healing had occurred. Triple antibiotic ointment group: the ulcers were debrided as necessary, cleansed with 0.9% NaCl and hydrogen peroxide, and dried. Triple antibiotic ointment was then applied to the ulcer in a uniform layer, followed by a sterile gauze covering. This dressing was checked and changed daily, except in cases that required removal and reapplication (e.g. when spillage, contamination, or patient bathing).
Outcomes	<ul style="list-style-type: none"> Time to complete healing Time to formation of granulation tissue Serum phenytoin sodium concentrations Adverse treatment effect Pain <p>Duration of follow-up: 90 days</p>
Notes	Funding source: did not report the sources of funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quotation: "The patients were matched for age, gender, and size and severity of wounds and placed in one of the three groups based on the treatment preference of the randomly assigned physician prescribing the treatment plan."
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	High risk	8 participants did not complete the study. In the phenytoin group, 1 participant had ulcers that continually recurred shortly after healing, and 2 participants died. 3 participants dropped out of the Duoderm group: 1 left the facility, and 2 died. In the triple antibiotic ointment group, 2 participants did not complete the study because 1 transferred to another facility and 1 died. No participants withdrew from the study secondary to adverse treatment effects. Hence, the final analysis sample did not include them in further analyses.

Rhodes 2001 (Continued)

Selective reporting (re-reporting bias)	Low risk	Study aims were stated in the paper and reported in the Results section.
Other bias	Unclear risk	Unclear

Hollisaz 2004

Methods	<p>randomized controlled trial</p> <p>Random sequence generation: used a random-number table</p> <p>Allocated concealment: delivered in an opaque sealed envelope bearing only the number of the participant</p> <p>Blinding: blinding of personnel and outcome assessors, not participants</p> <p>The study took about 10 months from proposal to final analysis (November 2001-September 2002)</p>
Participants	<ul style="list-style-type: none"> • N = 83 • Phenytoin group (grade I ulcers = 9; grade II = 19); hydrocolloid dressing group (grade I = 12; grade II = 16); simple dressing group (grade I = 10; grade II = 17) • Information on power calculation: before the study, the authors assumed response rates of 30%, 40% and 80% for simple dressing, phenytoin cream and hydrocolloid dressing, respectively. Thus, based on the 40% difference, power of 0.85, 95% confidence level and estimated follow-up loss of 10%, 29 patients were required for each study group. • Setting: family homes or nursing homes, Iran • Numbers of men and women not clearly reported • Mean age of participants (years $\pm$ SD): phenytoin group (36.5 ± 4.99); hydrocolloid dressing group (36.81 ± 6.71); simple dressing group (36.6 ± 6.17) • Inclusion criteria: paraplegia caused by spinal cord injury; pressure ulcer grade I and II according to Shea classification (Shea 1975) or National Pressure Ulcer Advisory Panel (NPUAP 1989); patient's informed consent; smoothness of ulcer area to establish whether adhesive could be used at the site • Exclusion criteria: addiction; heavy smoking (more than 20 cigarettes a day or more than 10 packs per year; concomitant chronic disease (e.g. diabetes mellitus or frank vascular disease such as Buerger's disease)
Interventions	<p>Necrotic tissue was debrided before treatment; all debridements preceded ulcer tracing and assignment of participants to the trial groups. No debridement was allowed after treatment had started. No concomitant topical or systemic antibiotic, glucocorticoid or immunosuppressive agents were allowed during the treatment period.</p> <ul style="list-style-type: none"> • Phenytoin group: daily dressing and cleaning of ulcer were similar to the simple dressing group (see later), except that a thin layer of phenytoin cream was applied to the ulcer before the dressing was applied. • Hydrocolloid group: daily dressing and cleaning of ulcer were similar to the simple dressing group, after which the hydrocolloid adhesive dressing was applied to the ulcer area. The adhesive dressings were changed twice a week. • Simple dressing group: the ulcer was cleaned and washed 3 times with normal saline, then dried with a sterile gauze and, depending on the size of the ulcer, covered with wet saline gauze dressing. This was done twice a day.
Outcomes	<ul style="list-style-type: none"> • Complete healing • Partial healing • Without improvement • Worsening • Adverse treatment effect

Topical phenytoin for treating pressure ulcers (Review)

Hollisaz 2004 (Continued)

Duration of follow-up: 6 months

Notes Funding source: received financial support from the Jaonbazan Medical and Engineering Research Center

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotation: "A random-number table was used to generate the random allocation sequence, and stratified randomization was used to achieve balance between the treatment groups and subgroups (ulcer stages and locations)."
Allocation concealment (selection bias)	Low risk	Quotation: "The treatment category for each patient was determined by the statistician and was delivered in an opaque sealed envelope bearing only the number of the patient. These sealed envelopes were delivered to the general practitioners, along with the list of patients' numbers and names. After each patient was visited, the appropriately numbered envelope was opened by the general practitioner to determine whether the SD [simple dressing], PC [phenytoin cream] or HD [hydrocolloid dressing] method would be used, then the appropriate intervention commenced."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quotations: "Because significant differences among the three treatment methods precluded blinding, the patients were also aware of the treatment methods." "the author who enrolled the patients to the study was blind to treatment assignment." "The general practitioners were also blind to the treatment of each patient up to the start of the study, when they opened the sealed envelopes."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotation: "The author who finally assessed the outcomes was also blind to the trial group of each patient."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quotation: "All patients completed the study and there were no losses to follow-up, no treatment withdrawals, no trial group changes and no major adverse events"
Selective reporting (reporting bias)	Low risk	Study aims were stated in the paper and reported in Results section.
Other bias	Unclear risk	Funding: the study was supported by the Jaonbazan Medical and Engineering Research Center, the medical and research section of the official governmental body responsible for spinal cord injury war victims.

Subbanna 2007

Methods A prospective, randomized, double-blind clinical trial

Random sequence generation: computer-generated randomization list

Allocated concealment: prepared and labelled using the randomization number by pharmacists of the institution's pharmacy

Blinding: personnel, outcome assessors, and participants blinded

Subbanna 2007 (Continued)

The study was carried out between October 2005-November 2006.

Participants	<ul style="list-style-type: none"> • N = 26 • Phenytoin group (grade II ulcers = 12); simple dressing group (grade II = 14) • Setting: Christian Medical College (CMC), Vellore, a tertiary care teaching hospital in south India • Numbers of men and women not clearly reported • Mean age of participants (years $\pm$ SD): phenytoin group (34.25 $\pm$ 18.12); simple dressing group (31.64 $\pm$ 12.27) • Inclusion criteria: paraplegic participants aged between 10-55 years, presenting with grade II pressure ulcers without necrotic tissue • Exclusion criteria: people with anaemia, hypoalbuminaemia, elevated serum creatinine, abnormal liver function tests, history of smoking, peripheral vascular disease, diabetes mellitus, malignancy, connective tissue disorders and psychiatric illness
Interventions	<ul style="list-style-type: none"> • Phenytoin group: phenytoin solution (50 mg/mL, Park-Davis) was diluted using normal saline (0.9% NaCl, CMC pharmacy) to prepare a phenytoin solution (5 mg/mL). At this concentration the pH was 7.3–7.4. The preparation was indistinguishable from normal saline in presentation, colour, density, and odour. Participants received sterile gauze soaked with phenytoin solution for dressing their ulcers once daily for 15 days. • Simple dressing group: participants received sterile gauze soaked with normal saline for dressing their ulcers once daily for 15 days.
Outcomes	<ul style="list-style-type: none"> • Reduction in Pressure ulcer scale for healing (Thomas 1997) • Reduction in ulcer size • Reduction in ulcer volume • Systemic absorption of topical phenytoin • Adverse treatment effect <p>Duration of follow-up: 16 days</p>
Notes	Funding source: received financial support from intramural research funds of Christian Medical College, Vellore, India

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotation: "Patients were randomly assigned to the treatment and control groups using a computer-generated randomization list."
Allocation concealment (selection bias)	Low risk	Quotation: "Treatment (phenytoin solution) and control solutions (normal saline) were prepared and labelled using the randomization number by pharmacists of our institutional pharmacy."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotations: "The preparation was indistinguishable from the normal saline in presentation, color, density, and odor." "The nursing staff who administered pressure ulcer dressings were blind to treatment assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotation: "All evaluations were carried out by a single investigator who was blind to the type of intervention."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quotation: "... two patients in the treatment group were lost to follow-up because of discharge from the hospital at patient's request. Hence, the final

Topical phenytoin for treating pressure ulcers (Review)

Subbanna 2007 (Continued)

analysis sample comprised 12 patients in the treatment group and 14 patients in the control group"

Selective reporting (reporting bias)	Low risk	Study aims were stated in the paper and reported in the Results section.
Other bias	Unclear risk	Funding source: received financial support from intramural research funds of Christian Medical College, Vellore, India.

Abbreviation

SD: standard deviation

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Agarwal 1998	Not randomized
Chauhan 2003	Included participants with venous ulcers, diabetic ulcers and mixed wounds
el Zayat 1989	Not randomized
Lodha 1991	Abscess wounds
Panahi 2015	Panahi 2015 included 60 participants (41 with pressure ulcers, 13 with diabetic wounds and 6 with venous ulcers). The included 60 participants were divided into two groups (Aloe vera-olive oil combination cream group and phenytoin cream) by simple randomization rather than stratified randomization based on the type of the three diseases (pressure ulcers, diabetic wounds and venous ulcers). Therefore, participants with pressure ulcers in Panahi 2015 failed to meet the including criteria for this review.
Shaw 2010	Diabetic foot ulcers

DATA AND ANALYSES
Comparison 1. Topical phenytoin versus hydrocolloid dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of ulcers healed within trial period	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Topical phenytoin versus hydrocolloid dressing, Outcome 1 Proportion of ulcers healed within trial period.

Study or subgroup	Phenytoin n/N	Hydrocolloid n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	11/28	20/28		0.55[0.33,0.92]
Favours hydrocolloid				Favours phenytoin

Comparison 2. Topical phenytoin versus simple dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of ulcers healed within trial period	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Topical phenytoin versus simple dressing, Outcome 1 Proportion of ulcers healed within trial period.

Study or subgroup	Phenytoin group n/N	Simple dressing group n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Hollisaz 2004	11/28	8/27		1.33[0.63,2.78]
Favours simple dressing				Favours phenytoin

APPENDICES

Appendix 1. Search strategies

The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*)

#1 MeSH descriptor Pressure Ulcer explode all trees
#2 pressure NEXT (ulcer* or sore*):ti,ab,kw
#3 decubitus NEXT (ulcer* or sore*):ti,ab,kw
#4 (bed NEXT sore*) or bed sore:ti,ab,kw
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Phenytoin explode all trees
#7 phenytoin:ti,ab,kw
#8 (#6 OR #7)
#9 (#5 AND #8)

Ovid MEDLINE

1 exp Pressure Ulcer/
2 (pressure adj (ulcer* or sore*)).tw.
3 (decubitus adj (ulcer* or sore*)).tw.
4 (bed sore* or (bed adj sore*)).tw.
5 or/1-4
6 exp Phenytoin/
7 phenytoin.tw.
8 or/6-7
9 5 and 8

10 randomized controlled trial.pt.
11 controlled clinical trial.pt.
12 randomized.ab.
13 placebo.ab.
14 clinical trials as topic.sh.
15 randomly.ab.
16 trial.ti.
17 or/10-16
18 (animals not (humans and animals)).sh
19 17 not 18
20 9 and 19

Ovid Embase

1 exp Decubitus/
2 (pressure adj (ulcer\$ or sore\$)).tw
3 (decubitus adj (ulcer* or sore*)).tw
4 (bedsore* or (bed adj sore*)).tw
5 or/1-4
6 exp phenytoin/
7 exp phenytoin derivative/
8 phenytoin.tw
9 or/6-8
10 5 and 9
11 Randomized controlled trials/
12 Single-Blind Method/
13 Double-Blind Method/
14 Crossover Procedure/
15 (random\$ or factorial\$ or crossover\$ or cross over\$ or cross-over\$ or placebo\$ or assign\$ or allocat\$ or volunteer\$).ti,ab.
16 (doubl\$ adj blind\$).ti,ab.
17 (singl\$ adj blind\$).ti,ab.
18 or/11-17
19 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
20 human/ or human cell/
21 and/19-20
22 19 not 21
23 18 not 22
24 10 and 23
11 Clinical trial
12 Randomized controlled trials
13 Random Allocation
14 Single-Blind Method
15 Double-Blind Method
16 Cross-Over Studies
17 Placebos
18 Randomized controlled trial\$.tw
19 RCT.tw
20 Random allocation.tw
21 Randomly allocated.tw
22 Allocated randomly.tw
23 (allocated adj2 random).tw
24 Single blind\$.tw
25 Double blind\$.tw
26 ((treble or triple) adj blind\$).tw
27 Placebo\$.tw
28 Prospective Studies
29 or/11-28
30 Case study
31 Case report.tw
32 Abstract report/ or letter
33 or/30-32
34 29 not 33

35 animal
36 human
37 35 not 36
38 34 not 37
39 10 and 38

EBSCO CINAHL Plus

S1 (MH "Pressure Ulcer")
S2 TI (pressure ulcer* or pressure sore*) or AB (pressure ulcer* or pressure sore*)
S3 TI (bed sore* or bedsore*) or AB (bed sore* or bedsore*)
S4 TI decubitus or AB decubitus
S5 S1 or S2 or S3 or S4
S6 (MH "Phenytoin+")
S7 TI phenytoin or AB phenytoin
S8 S6 or S7
S9 S5 and S8
S10 MH "Clinical Trials+"
S11 PT Clinical trial
S12 TI (clinic* N1 trial) OR AB (clinic* N1 trial*)
S13 TI (singl* OR doubl* OR trebl* OR tripl*) OR TI (blind* OR mask*)
S14 AB (singl* OR doubl* OR trebl* OR tripl*) OR AB (blind* OR mask*)
S15 TI (randomi?ed control* trial*) OR AB (randomi?ed control* trial*)
S16 MH "Random Assignment"
S17 TI (random* allocat*) OR AB (random* allocat*)
S18 MH "Placebos"
S19 TI (placebo*) OR AB (placebo*)
S20 MH "Quantitative Studies"
S21 TI (allocat* random*) OR (allocat* random*)
S22 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21
S23 S9 AND S22

Appendix 2. Assessment of risk of bias in included studies

The Cochrane tool for assessing risk of bias

1. Was the allocation sequence randomly generated?

Low risk of bias

The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

High risk of bias

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

Unclear

Insufficient information about the sequence generation process provided to permit a judgement of low or high risk of bias.

2. Was the treatment allocation adequately concealed?

Low risk of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.

High risk of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: use of an open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. envelopes were unsealed, non-opaque, or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

Insufficient information provided to permit a judgement of low or high risk of bias. This is usually the case if the method of concealment is not described, or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias

Any one of the following:

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

High risk of bias

Any one of the following:

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Unclear

Either of the following:

- Insufficient information to permit judgement of low or high risk of bias.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following:

- No missing outcome data.
- Reasons for missing outcome data are unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, a plausible effect size (difference in means or standardised difference in means) among missing outcomes is not enough to have a clinically relevant impact on the observed effect size.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following:

- Reason for missing outcome data are likely to be related to the true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is enough to induce clinically relevant bias in the intervention effect estimate.
- For continuous outcome data, a plausible effect size (difference in means or standardised difference in means) among missing outcomes is enough to induce a clinically relevant bias in the observed effect size.
- 'As-treated' analysis done with a substantial departure of the intervention received from that assigned at randomization.
- Potentially inappropriate application of simple imputation.

Unclear

Either of the following:

- Insufficient reporting of attrition/exclusions to permit a judgement of low or high risk of bias (e.g. number randomized not stated, no reasons for missing data provided).

- The study did not address this outcome.

5. Are reports of the study free of suggestion of selective outcome reporting?

Low risk of bias

Either of the following:

- The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).

High risk of bias

Any one of the following:

- Not all of the study's prespecified primary outcomes have been reported.
- One or more primary outcomes is/are reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified.
- One or more reported primary outcomes was/were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review is/are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear

Insufficient information provided to permit a judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias

Low risk of bias

The study appears to be free of other sources of bias.

High risk of bias

There is at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- has been claimed to have been fraudulent; or
- had some other problem.

Unclear

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias

HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 2, 2017

Date	Event	Description
13 December 2009	Amended	Contact author
28 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Xiang Yong Hao: conceived, designed and coordinated the review; extracted data; checked the quality of data extraction; analysed or interpreted data; undertook and checked quality assessment; checked the quality of the statistical analysis; produced the first draft of the review; approved the review prior to submission; and is a guarantor of the review.

Hong Ling Li: designed and coordinated the review; checked the quality of data extraction; analysed or interpreted data; checked quality assessment; checked the quality of the statistical analysis; produced the first draft of the review; approved the review prior to submission; and is a guarantor of the review.

He Su: designed the review; checked the quality of data extraction; analysed or interpreted data; produced the first draft of the review; approved the review prior to submission; and is a guarantor of the review.

Hui Cai: extracted data; undertook quality assessment; analysed or interpreted data; performed statistical analysis; contributed to writing or editing the review; and advised on the review.

Tian Kang Guo: conceived, designed and coordinated the review; analysed or interpreted data; contributed to writing or editing the review; approved the final review prior to submission; and advised on the review

Ruifeng Liu: analysed or interpreted data; checked quality assessment; performed statistical analysis; contributed to writing or editing the review; and advised on the review.

Lei Jiang: analysed or interpreted data; performed statistical analysis; and contributed to writing or editing the review.

Yan Fei Shen: extracted data; undertook quality assessment; checked the quality of the statistical analysis; contributed to writing or editing the review; and advised on the review.

Contributions of editorial base

Nicky Cullum (Coordinating Editor): edited the protocol and advised on methodology, interpretation and protocol content. Approved the final protocol prior to submission.

Jo Dumville (Deputy Co-ordinating Editor): edited the review and advised on methodology, interpretation and review content. Approved the final review prior to submission.

Sally Bell-Syer (Managing Editor): co-ordinated the editorial process for the protocol and advised on methodology, interpretation and content.

Gill Rizzello (Managing Editor): co-ordinated the editorial process for the review and advised on content.

Ruth Foxlee (Information Specialist): designed the search strategy and edited the search methods section for the protocol.

Reetu Child and Naomi Shaw (Information Specialists): designed the search strategy and edited the search methods section for the review.

Zipporah Ihezor-Ejiofor (Methodologist): advised on methodology, interpretation and review content.

Ursula Gonthier (Editorial Assistant) edited the references and Plain Language Summary.

DECLARATIONS OF INTEREST

Xiang Yong Hao: none known.

Hong Ling Li: none known.

He Su: none known.

Hui Cai: none known.

Tian Kang Guo: none known.

Ruifeng Liu: none known.

Lei Jiang: none known.

Yan Fei Shen: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We added the fact that we searched the following clinical trials registries for ongoing and unpublished studies:
 - Clinical Trials.gov (clinicaltrials.gov),
 - WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictcp/en),
 - Chinese Clinical Trial Registry (ChiCTR) (www.chictr.org.cn/searchprojen.aspx).
- We added a study flow diagram as recommended by the PRISMA statement to illustrate the process of screening and selecting studies for inclusion in the review ([Figure 1](#)) ([Liberati 2009](#)).
- We added a 'Dealing with missing data' section to the review.
- We added a 'Unit of analysis issues' section in to the review.
- For assessment of reporting biases, we updated it as follows "In future, if 10 or more studies are included for meta-analysis, visual asymmetry of funnel plots will be assessed to identify any potential reporting or publication bias ([Sterne 2011](#))."
- We added 'Summary of findings' tables with GRADE ratings.

INDEX TERMS

Medical Subject Headings (MeSH)

*Bandages; Administration, Topical; Anti-Bacterial Agents [administration & dosage]; Bandages, Hydrocolloid; Dermatologic Agents [*administration & dosage]; Ointments; Phenytoin [*administration & dosage]; Pressure Ulcer [classification] [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans