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Anabolic steroids for treating pressure ulcers (Review)

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[Intervention Review]

Anabolic steroids for treating pressure ulcers

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ABSTRACT

Background

Pressure ulcers, also known as bed sores, pressure sores or decubitus ulcers develop as a result of a localised injury to the skin or underlying tissue, or both. The ulcers usually arise over a bony prominence, and are recognised as a common medical problem affecting people confined to a bed or wheelchair for long periods of time. Anabolic steroids are used as off-label drugs (drugs which are used without regulatory approval) and have been used as adjuvants to usual treatment with dressings, debridement, nutritional supplements, systemic antibiotics and antiseptics, which are considered to be supportive in healing of pressure ulcers. Anabolic steroids are considered because of their ability to stimulate protein synthesis and build muscle mass. Comprehensive evidence is required to facilitate decision making, regarding the benefits and harms of using anabolic steroids.

Objectives

To assess the effects of anabolic steroids for treating pressure ulcers.

Search methods

In March 2017 we searched the Cochrane Wounds Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE (including In-Process & Other Non-Indexed Citations); Ovid Embase and EBSCO CINAHL Plus. We also searched clinical trials registries for ongoing and unpublished studies, and scanned reference lists of relevant included studies as well as reviews, meta-analyses and health technology reports to identify additional studies. There were no restrictions with respect to language, date of publication or study setting.

Selection criteria

Published or unpublished randomised controlled trials (RCTs) comparing the effects of anabolic steroids with alternative treatments or different types of anabolic steroids in the treatment of pressure ulcers.

Data collection and analysis

Two review authors independently carried out study selection, data extraction and risk of bias assessment.

Main results

The review contains only one trial with a total of 212 participants, all with spinal cord injury and open pressure ulcers classed as stage III and IV. The participants were mainly male (98.2%, 106/108) with a mean age of 58.4 (standard deviation 10.4) years in the oxandrolone group and were all male (100%, 104/104) with a mean age of 57.3 (standard deviation 11.6) years in the placebo group. This trial compared oxandrolone (20 mg/day, administered orally) with a dose of placebo (an inactive substance consisting of 98% starch and 2% magnesium stearate) and reported data on complete healing of ulcers and adverse events. There was very low-certainty evidence on the relative effect

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of oxandrolone on complete ulcer healing at the end of a 24-week treatment period (risk ratio RR) 0.81, 95% confidence interval (CI) 0.52 to 1.26) (downgraded twice for imprecision due to an extremely wide 95% CI, which spanned both benefit and harm, and once for indirectness, as the participants were mostly male spinal cord injury patients). Thus, we are uncertain whether oxandrolone improves or reduces the complete healing of pressure ulcers, as we assessed the certainty of the evidence as very low.

There was low-certainty evidence on the risk of non-serious adverse events reported in participants treated with oxandrolone compared with placebo (RR 3.85, 95% CI 1.12 to 13.26) (downgraded once for imprecision and once for indirectness, as the participants were mostly male spinal cord injury patients). Thus, the treatment with oxandrolone may increase the risk of non-serious adverse events reported in participants.

There was very low-certainty evidence on the risk of serious adverse events reported in participants treated with oxandrolone compared with placebo (RR 0.54, 95% CI 0.25 to 1.17) (downgraded twice for imprecision due to an extremely wide 95% CI, which spanned both benefit and harm, and once for indirectness, as the participants were mostly male spinal cord injury patients). Of the five serious adverse events reported in the oxandrolone-treated group, none were classed by the trial teams as being related to treatment. We are uncertain whether oxandrolone increases or decreases the risk of serious adverse events as we assessed the certainty of the evidence as very low.

Secondary outcomes such as pain, length of hospital stay, change in wound size or wound surface area, incidence of different type of infection, cost of treatment and quality of life were not reported in the included trial.

Overall the evidence in this study was of very low quality (downgraded for imprecision and indirectness). This trial stopped early when the futility analysis (interim analysis) in the opinion of the study authors showed that oxandrolone had no benefit over placebo for improving ulcer healing.

Authors' conclusions

There is no high quality evidence to support the use of anabolic steroids in treating pressure ulcers.

Further well-designed, multicenter trials, at low risk of bias, are necessary to assess the effect of anabolic steroids on treating pressure ulcers, but careful consideration of the current trial and its early termination are required when planning future research.

PLAIN LANGUAGE SUMMARY

Anabolic steroids for treating pressure ulcers

Review Question

We reviewed the evidence about the effect of anabolic steroids (medicines designed to increase muscle mass) for treating people with pressure ulcers.

Background

Pressure ulcers are also known as bed sores, pressure sores or decubitus ulcers. Pressure ulcers are a common medical problem amongst people confined to a bed or wheelchair for long periods of time. Lack of movement and sustained pressure on the skin over bony parts of the body such as the hips, heels, lower back and elbows can cause the skin to break down and an ulcer to form. People at risk of pressure ulcers include those with spinal cord injuries, elderly people and people with long-term illnesses. Pressure ulcers affect quality of life and can have serious complications such as infection, if they do not heal. As well as being painful and troublesome to patients, pressure ulcers represent a significant cost to healthcare systems due to the nursing time involved in treatment. There are a variety of treatments that are usually used for pressure ulcers including wound dressings and specially-designed beds and cushions to reduce pressure on certain areas of the body.

Anabolic steroids are a type of medicine used to increase muscle mass. They can be used as an alternative to, or alongside, conventional treatments for pressure ulcers. They are thought to promote the growth of skeletal muscle and to restore muscle mass, which could help pressure ulcers to heal. However, it has been found that oxandrolone (a commonly-used anabolic steroid) can cause potential liver damage. Anabolic steroids may also increase the risk of heart attack or stroke. We wanted to find out whether anabolic steroids were effective in treating pressure ulcers, and if they had any harmful effects.

Study characteristics

In March 2017, we searched for randomised controlled trials, which compared the use of anabolic steroids with other treatments for pressure ulcers. We found only one trial involving a total of 212 participants. This trial compared the effects of an anabolic steroid (oxandrolone capsules) with a placebo (dummy treatment containing no active medicine) on pressure ulcer healing in people with spinal cord injuries. The participants were mostly male (98.2%) with a mean age of 58.4 years in the oxandrolone group, which was comparable with the participants in the placebo group (male: 100%; mean age: 57.3 years). The trial was conducted over 24 weeks with a further follow-up for eight weeks.

Key results

The trial was ended early as the trial authors deemed that the interim results suggested that there was unlikely to be a benefit from treatment with oxandrolone. Because of the limited data available from one trial, we remain uncertain whether anabolic steroids have beneficial effects on pressure ulcer healing, whether the treatment causes increased serious adverse events and if the treatment may increase the risk of non-serious adverse events.

Quality of the evidence

Overall, the evidence from this study was judged to be of very low quality. More, better-designed studies are necessary to provide evidence as to whether anabolic steroids are beneficial or not in treating pressure ulcers.

This plain language summary is up to date as of March 2017.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Anabolic steroids for treating pressure ulcers

Anabolic steroids for treating pressure ulcers

Patient or population: people with pressure ulcers

Settings: any

Intervention: anabolic steroids

Comparison: placebo or no anabolic steroids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Anabolic steroids			
Proportion of wounds completely healed at 24 weeks	298 per 1000	241 per 1000 (155 to 376)	RR 0.81 (0.52 to 1.26)	212 (1 trial)	⊕⊕⊕⊕ very low ^{1,2,3}
Non-serious adverse events	29 per 1000	131 per 1000 (33 to 443)	RR 3.85 (1.12 to 13.26)	212 (1 trial)	⊕⊕⊕⊕ low ^{2,3,4}
Serious adverse events	154 per 1000	83 per 1000 (38 to 180)	RR 0.54 (0.25 to 1.17)	212 (1 trial)	⊕⊕⊕⊕ very low ^{1,2,3}

*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

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

¹A wide 95% CI, which spanned both benefit and harm.

²Most of the participants in the oxandrolone group (98.2%) and all participants in the placebo group (100%) were men.

³Total sample size (n = 212) was lower than the original target sample size (n = 400): not downgraded as early stopping according to futility stopping criteria will not lead to substantial bias.

⁴A wide 95% CI.

BACKGROUND

Description of the condition

Pressure ulcers (also known as bed sores, pressure sores or decubitus ulcers) are a common medical problem and often develop when people are confined to bed or a wheelchair for long periods of time. A pressure ulcer is commonly defined as "a localised injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure or in combination with shear" (EPUAP/NPUAP 2009). The classification of pressure ulcers agreed by the National Pressure Ulcer Advisory Panel and European Pressure Ulcer Advisory Panel (NPUAP-EPUAP) consists of four stages (EPUAP/NPUAP 2009): stage I - non-blanchable redness of intact skin; stage II - partial thickness skin loss or blister; stage III - full thickness skin loss, fat visible; and stage IV - full thickness tissue loss, with muscle/bone visible (see [Appendix 1](#) for details). Pressure ulcers are a complication associated with acute illness, injuries and immobility (Kaltenthaler 2001). They develop rapidly and are dependent upon the amount of time soft tissue is compressed against underlying bone, as well as the amount of pressure exerted on the patient's skin (Versluysen 1986). Both of these factors eventually result in ischaemia (lack of blood flow to an area) and necrosis (tissue death). It has been estimated that, at any point in time, pressure ulcers affect between 4.7% and 32.1% of hospitalised patients and between 4.6% and 20.7% of people living in nursing homes (Kaltenthaler 2001).

Although it is difficult to determine the true estimates, prevalence of pressure ulcers is an established quality indicator of health care (Gunningberg, 2012), regardless of settings. It has been estimated that in the UK alone, around 412,000 people annually are likely to develop a new pressure ulcer, which is equivalent to one in every 150 people in the general population, and one in 23 people in the population aged over 65 years (Bennett 2004). A recent study estimated the point prevalence of people with pressure ulcers across a large UK city to be 0.31 people per 1000 (95% CI 0.28 to 0.36) (Cullum 2016). In a prospective cohort study in the USA, around one-third of people with hip-fractures ($36.1 \pm 2.5\%$, standard error (SE)) experienced one or more new pressure ulcers in the course of 32 days following hospitalisation (Baumgarten 2009). This highlights the risk of developing pressure ulcers. A recent Norwegian study amongst 1209 inpatients reported an average of 1.6 (range 1 to 1.7) pressure ulcers per person. The overall prevalence was 18.2% for pressure ulcer categories I to IV and 7.2% for categories II to IV (Bredesen 2015). This was comparable with a Swedish study in which prevalence of pressure ulcer was 16.6% in hospitals and 14.5% in nursing homes (Gunningberg, 2012).

Two cost-analysis studies in the UK reported that treatment costs depend upon ulcer severity, the time taken to heal and the incidence of complications (Bennett 2004; Dealy 2012). According to an estimation in 2011, costs per ulcer healed ranged from GBP 1214 (category 1, comparable to stage I) to GBP 14,108 (category 4, comparable to stage IV) (Dealy 2012). Treating pressure ulcers represents a very significant resource cost to the health and social care system in the UK and elsewhere (Bennett 2004; Dealy 2012). For instance, in 1999 to 2000, the total cost of pressure ulcer care was GBP 1.4 billion to 2.1 billion, which was roughly 4% of the total National Health Service expenditure. As the majority of these costs were attributable to nursing time, any reduction in the nursing time required to manage pressure ulcers could provide a reduction in overall cost of treatment. Moreover, patients'

suffering is an intangible cost, which is not possible to measure in monetary terms. Pressure ulcers from any underlying cause in any country could impair the quality of life of the person, and the burden extends to their family, society and the nation as a whole. Additionally, it is noted that people with pressure ulcers are usually at risk of developing additional pressure ulcers (EPUAP/NPUAP 2009). The impact on the cost of patient management of the transition from having no pressure ulcers to having the first pressure ulcer is greater than the impact of any increase in the number of pressure ulcers beyond the first. This is because the first pressure ulcer triggers the need for treatment interventions, as well as the prevention of subsequent pressure ulcers (Baumgarten 2009). A study in the UK has documented that the mortality of people with and without pressure ulcers in the study hospitals was 11.1% and 3.3%, respectively (Lyder 2012). In order to reduce morbidity and mortality related to pressure ulcers, it is crucial to detect an ulcer early and thus prevent progression to stage IV ulcers (Brem 2010).

Description of the intervention

Treatments that are usually used for pressure ulcers include nutrition supplementation and hydration, pressure redistribution devices (McInnes 2011), dressings (BNF 2017), debridement (EPUAP/NPUAP 2014) and systemic antibiotics and antiseptics (Norman 2016). There are a variety of regimens, which have been promoted for use as an adjuvant therapy (that supplements 'usual/conventional' treatment) in treating pressure ulcers. Anabolic steroids are used as off-label drugs (drugs that do not have regulatory approval for use in treating pressure ulcers) and categorised into the group of adjuvants, which are considered to be supportive in healing of pressure ulcers.

Anabolic steroids are synthetic derivatives of the hormone testosterone that have anabolic (building up) and androgenic (male) properties. The USA lists many derivatives of anabolic steroids in the [Designer Anabolic Steroid Control Act 2014](#); however, only a few are in therapeutic use, and these include nandrolone, oxandrolone and oxymetholone, which are synthetic derivatives of testosterone. A clinically important point is that there are no separate receptors for anabolic and androgenic effects and therefore, the anabolic effect cannot be entirely separated from the androgenic effect. Amongst anabolic steroids, some are more anabolic than others, for example, oxandrolone has six times the anabolic potency of methyltestosterone (Fox 1961). Anabolic androgenic steroids are widely abused in the sports world, and among high school students (FDA 2013), because of these muscle mass effects (Franke 1997).

How the intervention might work

People with severe pressure ulcers have weight loss and lean body mass resulting from a catabolic (breaking down) state. It is highly possible that wound healing will be delayed until these catabolic processes are corrected (Collins 2004b). Anabolic effects enhance the effectiveness of protein synthesis in tissues - including skeletal muscle. The anabolic effect of oxandrolone, for example, is used in people with severe burns (Hart 2001).

A clinical concern associated with oxandrolone administration is an increase in liver enzymes (Jeschke 2007). This effect might limit the use of anabolic steroids in treating pressure ulcers in those with impaired liver function such as the elderly or people with

chronic illness. A prospective study on 27,892 postmenopausal women showed that hormone replacement therapy (oral oestradiol in combination with testosterone-like progestin) may increase the risk of cholecystectomy (i.e. gallbladder removal - often as a result of impaired liver function) (Nordenvall 2014).

Why it is important to do this review

Pressure ulcers are a large problem in people who are in a catabolic state. Anabolic steroids, which have anabolic effects might be useful in promoting healing of pressure ulcers.

Studies report that weight loss associated with protein depletion is directly related to poor wound healing and increased surgical risk (Windsor 1988). Clinically, the anabolic effect of steroids on the growth of skeletal muscle (and bone) is potentially beneficial for the restoration of muscle mass. This is particularly useful in people with cachexia (loss of weight and muscle wastage) attributable to chronic illnesses such as HIV/AIDS (Bhasin 2000), rheumatoid arthritis (Lemmey 2013) and in the elderly with wasting (Morley 2008).

On one hand investigators have suggested that treatment of pressure ulcers with anabolic steroids might be effective for promoting lean body mass and appendicular skeletal muscle mass (combined lean body mass from all four limbs) (Sattler 2011), healing of a wound after a major operation (Jiang 1989) or chronic cutaneous wounds (Demling 2001a; Demling 2001b), and for stage IV ulcers (Collins 2004a).

On the other hand, there have been reports on the undesirable effects of the use of anabolic steroids. For instance, testosterone, as a treatment, may produce a modest increase in prostate-specific antigen level, but does not cause changes in the signs or symptoms of prostate hyperplasia (enlargement) (Kenny 2011). A non-Cochrane systematic review on 27 randomised controlled trials (n = 2994) reported that testosterone administration to older men increased the risk of a cardiovascular-related event (odds ratio 1.54, 95% CI 1.09 to 2.18) (Xu 2013). An individual study on men who underwent coronary angiography reported that the use of testosterone therapy had 29% (95% CI 4% to 58%) increased risk of adverse outcomes (Vigen 2013). The generalisability of these findings to people with pressure ulcers is not known. It is, therefore, important to undertake a comprehensive assessment of all the available randomised controlled trial data on the benefits and harms of anabolic steroids in treating pressure ulcers.

OBJECTIVES

To assess the effects of anabolic steroids for treating pressure ulcers.

METHODS

Criteria for considering studies for this review

Types of studies

We considered published and unpublished randomised controlled trials (RCTs) of anabolic steroids for the treatment of pressure ulcers. RCTs of anabolic steroids for the prevention of pressure ulcers were not considered.

Types of participants

We included studies with participants having a pressure ulcer (bed sore, pressure sore or decubitus ulcer) of any grade in any healthcare setting, regardless of age and underlying clinical conditions. Pressure ulcers vary in severity ranging from stage I to stage IV as classified by the National Pressure Ulcer Advisory Panel and European Pressure Ulcer Advisory Panel (NPUAP-EPUAP) (EPUAP/NPUAP 2009). We excluded studies in which participants with a pressure ulcer were receiving systemic corticosteroids, immunosuppressive agents, anticancer agents or any radiation therapy, because these therapies can prevent or delay wound healing, which has an impact on the effect of anabolic steroids.

Types of interventions

Eligible interventions included an anabolic steroid compared with another anabolic steroid, non-anabolic steroid therapy, placebo or alternative treatments (with or without usual pressure ulcer management). We also considered different regimens of the same anabolic steroid and different mode(s) of anabolic steroid administration.

The term 'anabolic steroid' includes testosterone and its esters, nandrolone (as the decanoate ester), oxandrolone (also known as oxandrin), mesterolone and oxymetholone, which are used clinically. Studies were only eligible for inclusion, if the use of an anabolic steroid (or an aspect of anabolic steroid use) was the only systematic difference between treatment arms. If people in different treatment arms within a trial experienced other systematic differences in co-interventions, the study was excluded.

Types of outcome measures

Primary outcomes

The primary outcomes for this review were complete wound healing and all reported adverse events.

Complete wound healing was measured by:

- time to complete healing/rate of healing (as defined in the trial);
- proportion of wounds completely healed in a specified time period (as defined in the trial).

Healing is defined as "re-epithelialisation to a cicatrix [area of new connective tissue] with a dry surface and 0 cm square of open area for a minimum of 96 hours" (Bauman 2013).

If the studies reported data on adverse events, we extracted and categorised these as either 'non-serious adverse events' or 'serious adverse events' as stated in the trial. If the trial had explicitly reported that participants experienced no adverse events in both arms, this statement was listed.

Secondary outcomes

- Pain (as measured by a validated pain measurement scale)
- Length of hospital stay
- Change in wound size or wound surface area
- Change in pressure ulcer volume
- Incidence of different type of infection
- Cost of treatment

- Quality of life (as measured by the trial investigators or measured by a validated scale).

Search methods for identification of studies

Electronic searches

We searched the following databases to identify relevant RCTs:

- Cochrane Wounds Specialised Register (searched 3 March 2017);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (in the Cochrane Library 2017, Issue 2) (searched 3 March 2017);
- Ovid MEDLINE (including In-Process & Other Non-Indexed Citations, MEDLINE Daily and Epub Ahead of Print) (1946 to 3 March 2017);
- Ovid Embase (1974 to 3 March 2017);
- EBSCO CINAHL Plus (1937 to 3 March 2017).

The search strategies for the Cochrane Wounds Specialised Register, CENTRAL, Ovid MEDLINE, Ovid Embase and EBSCO CINAHL Plus can be found in [Appendix 2](#). We combined the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) ([Lefebvre 2011](#)). We combined the Embase search with the Ovid Embase filter developed by the UK Cochrane Centre ([Lefebvre 2011](#)). We combined the CINAHL search with the trial filters developed by the Scottish Intercollegiate Guidelines Network ([SIGN 2017](#)). There were no restrictions based on language, date of publication or study setting.

We also searched the following clinical trials registries:

- [ClinicalTrials.gov](#) (searched 9 March 2017);
- [WHO International Clinical Trials Registry Platform](#) (searched 9 March 2017);
- [EU Clinical Trials Register](#) (searched 9 March 2017).

Search strategies for clinical trials registries can be found in [Appendix 2](#).

Searching other resources

Searching reference lists of included trials and relevant reviews

We aimed to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, as well as relevant systematic reviews, meta-analyses and Health Technology Assessment reports.

Handsearching

We searched the reference lists of relevant reviews and included studies to identify further relevant trials.

Contacts

We contacted an expert in this field and the author of the included study in this review (Professor William A Bauman) to request further information about his trial and whether there were any unpublished or ongoing trials.

Conference Proceedings

We searched for conference proceedings from the European Pressure Ulcer Advisory Panel and European Wound Management Association. Our searches were carried out within the [Wounds UK](#) (WUK) database from inception to 2015.

Adverse effects

We did not perform a separate search for adverse effects of interventions used, we considered adverse effects described in included studies only.

Data collection and analysis

Data collection and analysis were carried out according to methods stated in the published protocol ([Naing 2014](#)), which were based on the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2011a](#)).

Selection of studies

Two review authors independently screened the titles and abstracts of citations yielded from the searches in electronic databases and retrieved full-text copies of all potentially relevant articles. The two review authors independently checked the full articles for eligibility. Any disagreement was resolved by consensus. If the eligibility of the study or the information given in the study was unclear, we contacted study authors. We recorded the reasons for excluding studies from the full-copies retrieved. We completed a PRISMA flow chart to summarise this process ([Liberati 2009](#)).

Data extraction and management

The two reviewers extracted information from the included studies using a piloted data extraction sheet.

We extracted the following data where possible:

- author;
- country;
- publication year of study;
- setting of study (e.g. primary care, hospital);
- participants' characteristics;
- intervention and comparison;
- co-interventions ;
- treatment regimen (drug, dosage, route of administration, frequency, duration);
- outcomes data for primary and secondary outcomes by groups;
- method of outcome measurements;
- risk of bias assessment (e.g. methods of randomisation, allocation concealment, blinding, follow-up, dropouts);
- duration of follow-up;
- adverse events;
- pain data;
- quality-of-life data;
- length of hospital stay;
- cost of treatment.

Outcome data were collected for relevant time points as described above in the type of outcome measures.

Where studies had duplicate publications, we extracted the maximum amount of data from the available publications. We

resolved disagreements by discussion. If we deemed the studies eligible but there was no clear information, we contacted the study author to obtain additional information.

Assessment of risk of bias in included studies

Two review authors independently assessed the included study using the Cochrane tool for assessing risk of bias (Higgins 2011b). The tool addresses six specific domains, namely: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias. One other bias specific to this review was comparability of ulcer surface area between treatment groups at baseline (i.e. extreme baseline imbalance). We assessed blinding (participants, trial investigators and outcome assessors) and completeness of outcome data separately for each outcome because assessment on wound healing can be subjective. We completed a 'Risk of bias' table for each included study. We discussed any disagreement amongst all review authors to achieve a consensus.

We presented the assessment of risk of bias using a 'Risk of bias' summary figure, which presents all of the judgements in a cross-tabulation of the study by entry. We classified each domain as being at high, low or unclear risk of bias (See Appendix 3 for details).

Measures of treatment effect

For dichotomous outcomes, we reported the risk ratio (RR) and its 95% confidence intervals (CI). For continuous outcomes such as mean and standard deviation (SD), we planned to use the mean difference (MD) or standardised mean difference (SMD) and their corresponding 95% CIs. We would have used SMD if trials used different scales of measurement.

For studies with time-to-event outcomes (e.g. time to healing), we planned to report hazard ratio (HR) and its 95% CI. If the studies identified for the present review did not report HR, we planned to compute these following the formulae of Parmar 1998, implemented in a spreadsheet (Tierney 2007).

Unit of analysis issues

We recorded whether the trial measured outcomes in relation to an ulcer or a participant, or whether multiple ulcers on the same participant were randomised. We also recorded occasions where multiple ulcers on a participant had been incorrectly treated as independent without taking into account the interdependence of the ulcers. We reported this as a part of the 'Risk of bias' assessment. Unless otherwise stated, where the number of ulcers appeared to equal the number of participants, we treated the ulcer as the unit of analysis.

Dealing with missing data

We performed an intention-to-treat analysis whenever possible (Newell, 1992). If there were missing standard deviations (SDs) for continuous outcomes, we planned to contact the corresponding author to see if data were available. If not available, we planned to calculate these using case-analysis such as imputing SDs from SEs, CIs, t-values or P values (as appropriate) that related to the differences between means in two groups, following the guidance described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

When there was insufficient information available to calculate the SDs, we planned to impute them. If SDs had been available from other studies included in this review for the change from baseline for the same outcome measures, we planned to use these as the missing SDs. If this approach was not applicable, assuming correlation coefficients from the two intervention groups were similar (this is reasonable for an RCT), we planned to impute an SD of the change from baseline for the experimental intervention, following a formula as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

Assessment of heterogeneity

We planned to assess studies for clinical heterogeneity based on the participants, intervention, control, outcome and study design elements, and then to tabulate this in the 'Characteristics of included studies' table. We planned to assess statistical heterogeneity using the Chi² test and the I² statistic (Higgins 2003). The I² statistic examines the percentage of total variation across studies due to (statistical) heterogeneity rather than to chance (Deeks 2011). Values of I² over 50% indicates the presence of a higher level of heterogeneity. In the absence of clinical heterogeneity and in the presence of statistical heterogeneity (where I² was greater than 50%), we planned to choose a random-effects model.

When there was no clinical heterogeneity or low statistical heterogeneity (I² less than 50%), we planned to use a fixed-effect model.

Assessment of reporting biases

If there had been a sufficient number of studies (minimum 10 RCTs), we would have assessed publication bias by creating a funnel plot. In the absence of publication bias, the plot should resemble a symmetrical inverted funnel. However, an asymmetrical funnel plot may also be due to other biases such as differences in methodological quality among studies. Even when there is a symmetrical funnel plot, it does not necessarily mean there is an absence of publication bias (Sterne 2011).

Data synthesis

We planned to combine information from included studies narratively where possible. Based on assessment of clinical and methodological heterogeneity, we planned to consider meta-analysis of outcome data in Review Manager 5 (RevMan 5) (RevMan 2014).

'Summary of findings' tables

We presented the main results of the review in a 'Summary of findings' table. This table presents key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' table also includes an overall grading of the evidence related to each of the main outcomes using the GRADE approach, which 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 true 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:

- complete wound healing;
- adverse events.

Sensitivity analysis

We planned to perform a sensitivity analysis by removing studies with high and unclear risk of bias from the meta-analyses. Therefore, the analysis would have only included studies at low risk of bias in all key domains, namely, adequate generation of the randomisation sequence, adequate allocation concealment and blinding of outcome assessor for the estimates of treatment effect.

RESULTS

Description of studies

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

Results of the search

The search generated 34 records after duplicates were removed. Of these, we excluded 11 records after screening titles and we reviewed the full texts of 23 studies. We included only one study in this review and excluded the remaining 22 studies ([Figure 1](#)). In order to ensure ongoing studies were included in this review, we contacted an expert in this field and also checked clinical trials registries. We did not identify any ongoing studies.

Figure 1. Study flow diagram

Included studies

This review included only one RCT ([Bauman 2013](#)), a multicenter study at 16 Veteran Affairs (VA) medical centres providing services for inpatients with spinal cord injury (SCI) in the USA. The pressure ulcers were open wounds of stage III or IV in all participants. Conventional treatments given to these participants were cleaning with normal saline or approved wound care cleaners at each dressing change, debridement, use of dressings to keep the pressure ulcer bed continuously moist and the surrounding intact skin dry, and relief of pressure on the pressure ulcer. Neither nutritional supplements nor special diets were given. Any adjuvant therapies such as ultraviolet light, laser or hyperbaric oxygen therapy were discontinued before the treatment phase was commenced.

The trial compared orally-given oxandrolone (20 mg/day) with matching doses of placebo capsules (an inactive substance, which consisted of starch 98% and magnesium stearate 2%). The participants were mainly male (98.2%, 106/108) with the mean age of 58.4 (standard deviation 10.4) years in the oxandrolone group. The age and sex distribution of participants in the placebo group was comparable with the intervention group (male: 100%, 104/104) and the mean age was 57.3 (standard deviation 11.6) years.

Excluded studies

We excluded 22 studies from this review. The main reasons for exclusion were:

- duplicate data (one study: [Bauman 2009](#));
- not a randomised controlled trial (seven studies: [Crane 2013](#); [Demling 2001a](#); [Demling 2001b](#); [Generali 2013](#); [Spungen 2001](#); [Vennits 1966](#); [Williams 2013](#));
- reviews only (three studies: [Chiu 2011](#); [Mader 2000](#); [Morley 2002](#));
- studies were on nutritional-related issues (six studies: [Bauman 2001](#); [Collins 2004a](#); [Collins 2004b](#); [Himes 1999](#); [Mikulin 2001](#); [Phillips 2003](#));
- not on pressure ulcers (two studies: [Sowers 1996](#); [Wolf 2006](#));
- editorials or guideline on published studies (three studies: [Phillips 2005](#); [Salcido 1999](#); [Salcido 2005](#)).

Risk of bias in included studies

[Figure 2](#); [Figure 3](#)

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

Random sequence generation: [Bauman 2013](#) had a low risk of bias, as the randomisation process used a computer-generated randomisation sequence. We deemed the method of sequence generation adequate.

Allocation concealment: [Bauman 2013](#) had a low risk of bias, as the participants and investigators could not foresee assignment because allocation was via an automated central telephone system. The Clinical Research Pharmacy Coordinating Center (CSP) distributed the medication or placebo through the individual pharmacy services at each participating VA medical centre.

Blinding

Blinding outcome assessment: We deemed [Bauman 2013](#) to be at low risk of performance and detection bias because participants, clinical care providers, research study staff and statistical analyses were blinded to treatment assignment.

Incomplete outcome data

[Bauman 2013](#) was at low risk of attrition bias as the trial report suggested that an intention-to-treat approach had been conducted. This was confirmed through contact with the study author (Professor William A Bauman).

Selective reporting

We deemed [Bauman 2013](#) to be at low risk of selective reporting bias, as the outcomes reported were specified in the protocol.

Other potential sources of bias

We deemed [Bauman 2013](#) to be at unclear risk of other potential sources of bias, as potential centre-specific differences in rate of healing outcomes were not addressed due to limited participant numbers in each centre.

Early stopping with futility-stopping criteria will not lead substantial bias, according to simulation evidence ([Wason 2015](#)).

The trial reported the VA institutions as its primary funding source, however, it did not mention whether the sponsor agency was involved in any processes of this study or otherwise.

Effects of interventions

See: [Summary of findings for the main comparison Anabolic steroids for treating pressure ulcers](#)

Oxandrolone compared with placebo (one study, 212 participants)

[Bauman 2013](#) compared orally-given oxandrolone (20 mg/day) with placebo (an inactive substance, which consisted of starch 98% and magnesium stearate 2%). In total, [Bauman 2013](#) randomised 212 people with SCI who had pressure ulcers. We classed the study as being at low risk of selection bias, detection bias, attrition bias and reporting bias and at unclear risk of other bias. The randomised groups were similar for the baseline demographic, SCI characteristics and pressure ulcer history as well as the number of active smokers, participants with cardiovascular disease, including peripheral vascular disease and those with osteomyelitis.

Primary outcome: complete healing at week 24 of treatment

Completed ulcer healing at week 24 was measured in terms of re-epithelialisation to a cicatrix with a dry surface and 0 cm² of open area for a minimum of 96 hours; 26 participants in the oxandrolone group (24%; 26/108) and 31 participants in the placebo group (30%; 31/104) had a completely healed ulcer. We are uncertain whether oxandrolone increases or decreases the effect of complete healing compared with placebo (RR 0.81, 95% CI 0.52 to 1.26) ([Analysis 1.1](#)). GRADE assessment: very low-certainty evidence, downgraded twice for imprecision (an extremely wide 95% CI, which spanned both benefit and harms) and once for indirectness (mostly male SCI participants).

Primary outcome: non-serious adverse events and serious adverse events

[Bauman 2013](#) reported non-serious adverse events ([Table 1](#)) and serious adverse events ([Table 2](#)). Treatment with oxandrolone

may increase the risk of non-serious adverse events compared with placebo (11.1%; 12/108 versus 2.9%; 3/104, RR 3.85, 95% CI 1.12 to 13.26) ([Analysis 1.2](#)). The non-serious adverse events were largely measured via biochemical or clinical assessment (e.g. measurement of liver enzyme function) and most were assessed as being possibly related to oxandrolone. GRADE assessment: low-certainty evidence, downgraded once for imprecision (an extremely wide 95% CI in one direction) and once for indirectness (mostly male SCI participants).

We are uncertain whether oxandrolone increases or decreases the risk of serious adverse events reported in participants (8%; 9/108 versus 15%; 16/104, RR 0.54, 95% CI 0.25 to 1.17) ([Analysis 1.3](#)). Despite serious adverse events including eight deaths (three in the oxandrolone group and five in the placebo group), the trial investigators judged that none of these serious adverse events were related to oxandrolone. GRADE assessment: very low-certainty evidence, downgraded twice for imprecision (an extremely wide 95% CI, which spanned both benefit and harm) and indirectness (mostly male SCI participants).

Secondary outcomes

[Bauman 2013](#) did not report any of our secondary outcomes (pain, length of hospital stay, change in wound size or wound surface area, change in pressure ulcer volume, incidence of different types of infection, cost of treatment, quality of life).

DISCUSSION

Summary of main results

See [Summary of findings for the main comparison](#)

We included only one trial with 212 people with SCI who had pressure ulcers in this review.

[Bauman 2013](#) compared an anabolic steroid (oxandrolone) with placebo. The distribution of age and sex of participants was comparable in the two groups. We are uncertain whether oxandrolone is better than placebo in promoting complete healing of pressure ulcers at 24 weeks of treatment. We classed the evidence as very low certainty. The trial reported that oxandrolone may increase the risk of non-serious adverse events by approximately four times compared with placebo. We classed this evidence as low certainty.

In summary, there is uncertain evidence on the relative effectiveness of anabolic steroids (oxandrolone) for healing pressure ulcers. We downgraded the evidence because of imprecision, with wide 95% CIs and indirectness with imbalance of male/female participants and the single trial that included those with SCI. It is very likely that further research will have an important impact on our confidence in the estimate of effect, and is likely to change the estimate. Treatment with oxandrolone may increase the risk of non-serious adverse events: this is low-certainty evidence, which is also very likely to be impacted by further research.

Overall completeness and applicability of evidence

The participants in the included trial were hospitalised patients with SCI. They were not likely to be representative of people seen in clinical practice with pressure ulcers as there might be elderly

people with chronic illnesses other than SCI, or female SCI patients with pressure ulcers.

We identified only one trial ([Bauman 2013](#)) for inclusion in this review. Although the search strategy was comprehensive, the effect of publication bias cannot be ruled out. This trial reported uncertain treatment benefits and suggested that more non-serious adverse events may occur in those receiving anabolic steroids. The included study was terminated after a futility analysis which was reported by the study authors to show there to be a low probability of detecting a significant difference between the groups with continued recruitment. The study authors planned to recruit 400 participants and the trial was terminated after 164 participants were recruited. The authors reported that the futility analysis indicated that the amount of healing would have had to increase in the oxandrolone group to greater than 50% (from the current figure of 25%) and decrease in the placebo group from 31% to 20% to attain a significant effect for oxandrolone administration (conditional probability of occurrence; $P = 0.001$) ([Bauman 2013](#)). It may be the case that the inclusion of unpublished data would add further useful information to this body of evidence. Moreover, withdrawal rates were relatively high and similar between the two groups; hence, it is likely that the people with SCI themselves were prone to develop complications that were independent of the study drugs.

Quality of the evidence

We included only one trial ([Bauman 2013](#)), which recruited 164 participants and then was terminated based on a futility analysis. Overall, we are uncertain whether oxandrolone improves complete healing and impacts on serious adverse events, as the certainty of the evidence has been assessed as very low. We used the GRADE approach to assess evidence quality. We downgraded all outcomes for indirectness and imprecision of outcomes. RCTs need to be adequately powered to detect meaningful differences, if they exist, between the experimental drug and placebo or alternatives. Although we noted in this case the futility analysis suggested that further recruitment was unlikely to change the findings.

Potential biases in the review process

We performed a thorough search of the literature and we were able to identify only one trial. Our search was not limited by language nor publication status. We also contacted the author of the trial that we included in this review (Professor William A. Bauman) for clarification of study design, and any unpublished or on-going studies in this field. The trial author provided comprehensive information that (i) this trial was intention-to-treat analysis; (ii) the Data Safety Monitoring Committee performed a futility analysis and it showed the study was not going to yield a positive result to the primary objective, and thus the trial was stopped early; (iii) both participants and physicians were blinded to drug/placebo treatment and (iv) the study team investigated another study on chronic pressure ulcer in people with SCI, which was a local study and did not assess the efficacy of an anabolic agent. It is possible that there might be studies that were conducted in earlier years but were not reported before the date of the establishment of mandatory registration for clinical trials.

Agreements and disagreements with other studies or reviews

This is the first systematic review focused solely on anabolic steroid-based products for treatment of pressure ulcers. A case study on nine people with pressure ulcers showed complete healing in 89% of cases at three to 12 months after administration of 20 mg oxandrolone (Spungen 2001). Because this was a small sample study with no rigorous methodology and no control group, it provided limited evidence. We were not able to identify any recent systematic reviews focusing on participants with pressure ulcers that evaluated anabolic steroid-based products.

AUTHORS' CONCLUSIONS

Implications for practice

A comprehensive review of currently available evidence provides uncertain evidence on whether anabolic steroids improve the healing of pressure ulcers and the risk of serious adverse events when compared with placebo. This means we cannot draw conclusions about the potential benefits or serious harms of this treatment on treating pressure ulcers. There was low-certainty evidence that treatment with anabolic steroids may increase the risk of non-serious adverse events. This evidence was from one randomised controlled trial (RCT) that stopped before reaching the planned recruitment target. The trial was stopped, as the trialists planned to recruit 400 participants but a futility analysis after recruitment of 164 participants suggested that further recruitment would not alter the study findings. There are no further RCT-related data on outcomes such as cost, infection or patient quality of life on which to base treatment decisions.

Implications for research

Current evidence is uncertain regarding the potential benefits of using anabolic steroids to treat pressure ulcers and there is low-certainty evidence that the treatment may increase the risk of non-serious adverse events. Well-designed, multicenter RCTs with adequate sample size are needed in this area. Any future research must ensure uniform wound care is practised among treatment centres, trials should follow a standard protocol and adhere to good clinical practice guidelines for implementation and reporting so that any data produced can be used by healthcare users, health professionals and health policy makers. Future RCTs should also focus on safety to take account of the potential increase in adverse events related to anabolic steroids. The trial included in this review calculated that many more healing events than were observed would have been needed to show in favour of treatment for healing. This might affect the feasibility of future research and the type of participants and anabolic steroid regimes that are investigated.

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REFERENCES

References to studies included in this review

Bauman 2013 {published data only}

Bauman WA, Spungen AM, Collins JF, Raisch DW, Ho C, Deitrick GA, et al. The effect of oxandrolone on the healing of chronic pressure ulcers in persons with spinal cord injury. A randomised trial. *Annals of Internal Medicine* 2013;**158**(10):718-26.

References to studies excluded from this review

Bauman 2001 {published data only}

Bauman WA, Sprungen AM. Body composition changes and anabolic hormone considerations with advancing age and in persons with spinal cord injury. *Top Spinal Cord Injury Rehabilitation* 2001;**6**(3):22-36.

Bauman 2009 {published data only}

Bauman WA, Spungen AM, Collins JF. Lack of efficacy of oxandrolone to increase the percent of healed pressure ulcers in persons with SCI: VA Cooperative Study. *Journal of Spinal Cord Medicine* 2009;**32**(4):458.

Chiu 2011 {published data only}

Chiu H-Y, Tsai T-F. Topical use of systemic drugs in dermatology: a comprehensive review. *Journal of the American Academy of Dermatology* 2011;**65**(5):1048.e1-22.

Collins 2004a {published data only}

Collins N. The right mix: using nutritional interventions and an anabolic agent to manage a stage IV ulcer. *Advances in Wound Care* 2004;**17**(1):36, 38-9.

Collins 2004b {published data only}

Collins N. Nutrition and wound healing: strategies to improve patient outcomes. *Wounds* 2004;**16**(Suppl 9):S12-18.

Crane 2013 {published data only}

Crane D, Hall B. Pressure relief. *PN/Paraplegia News* 2013;**67**(1):24-7.

Demling 2001a {published data only}

Demling RH, DeSanti L. The anabolic steroid, oxandrolone, reverses the wound healing impairment of exogenous corticosteroid use in corticosteroid-dependent burn and wound patients. *Advances in Wound Care* 2001;**14**(5):369.

Demling 2001b {published data only}

Demling RH. Involuntary weight loss, protein-energy malnutrition, and the impairment of cutaneous wound healing. *Wounds* 2001;**13**(Suppl 4):3-21D.

Generali 2013 {published data only}

Generali J, Cada D. Oxandrolone: pressure (decubitus) ulcers in spinal cord injury. *Hospital Pharmacy* 2013;**48**(8):642-3.

Himes 1999 {published data only}

Himes D. Protein-calorie malnutrition and involuntary weight loss: the role of aggressive nutritional intervention in wound healing. *Ostomy/Wound Management* 1999;**45**(3):46, 48-51, 54-5.

Mader 2000 {published data only}

Mader JT, Shirtiff ME, Bergquist S, Cathoun JH. Bone and joint infections in the elderly: practical treatment guideline. *Drugs and Aging* 2000;**16**(1):67-80.

Mikulin 2001 {published data only}

Mikulin L. Notes on practice: nutrition and its role in wound healing. *Ostomy/Wound Management* 2001;**47**(9):17-18, 20.

Morley 2002 {published data only}

Morley JE. Orexigenic and anabolic agents. *Clinics in Geriatric Medicine* 2002;**18**(4):853-66.

Phillips 2003 {published data only}

Phillips EM. Effective use of the anabolic agent, oxandrolone, in the treatment of involuntary weight loss associated with pressure ulcers: why nutrition matters. *Topics in Spinal Cord Injury Rehabilitation* 2003;**9**(2):24-37.

Phillips 2005 {published data only}

Phillips E. Pressure ulcer management in traumatic injuries: guideline for selecting a patient for oxandrolone therapy and appropriate nutritional interventions. *Neuro Rehabilitation and Neural Repair* 2005;**19**(4):373.

Salcido 1999 {published data only}

Salcido R. Anabolic steroids and wound healing. *Advances in Wound Care* 1999;**12**(8):391.

Salcido 2005 {published data only}

Salcido R. Anabolic steroids for pressure ulcers revisited. *Advances in Wound Care* 2005;**18**(7):344-6.

Sowers 1996 {published data only}

Sowers M, Hochberg M, Crabbe JP, Muhich A, Crutchfield M, Updike S. Association of bone mineral density and sex hormone levels with osteoarthritis and the hand and knee in premenopausal women. *American Journal of Epidemiology* 1996;**143**(1):38-47.

Spungen 2001 {published data only}

Spungen AM, Koehler KM, Modeste-Duncan R, Rasul M, Cytryn AS, Bauman WA. Clinical cases of nonhealing pressure ulcers in patients with spinal cord injury treated with an anabolic agent: a therapeutic trial. *Advances in Wound Care* 2001;**14**(3):139-44.

Vennits 1966 {published data only}

Vennits HW, Viskum P. Local treatment of decubitus with methandienone (Dianabol cream). *Ugeskrift for Læger* 1966;**128**(32):930-3.

Williams 2013 {published data only}

Williams R. Relieving the pressure. *Nursing Older People* 2013;**25**(1):39.

Wolf 2006 {published data only}

Wolf SE, Edelman LS, Kemalyan N, Donison L, Cross J, Underwood M, et al. Effects of oxandrolone on outcome measures in the severely burned: a multicenter prospective randomised double-blind trial. *Journal of Burn Care and Research* 2006;**27**(2):131-9,140-1.

Additional references
Baumgarten 2009

Baumgarten M, Margolis DJ, Orwig DL, Shardell MD, Hawkes WG, Langenberg P, et al. Pressure ulcers in elderly patients with hip fracture across the continuum of care. *Journal of the American Geriatrics Society* 2009;**57**(5):863-70.

Bennett 2004

Bennett G, Dealey C, Posnett J. The cost of pressure ulcers in the UK. *Age and Ageing* 2004;**33**(3):230-5.

Bhasin 2000

Bhasin S, Storer TW, Javanbakht M, Berman N, Yarasheski KE, Phillips J, et al. Testosterone replacement and resistance exercise in HIV infected men with weight loss and low testosterone levels. *The Journal of American Medical Association* 2000;**283**(6):763-70.

BNF 2017

British Medical Association, Royal Pharmaceutical Society. British National Formulary. Wound management products and elasticated garments. bnf.nice.org.uk/wound-management/ (accessed 19 June 2017).

Bredesen 2015

Bredesen IM, Bjørø K, Gunningberg L, Hofoss D. The prevalence, prevention and multilevel variance of pressure ulcers in Norwegian hospitals: a cross-sectional study. *International Journal of Nursing Studies* 2015;**52**(1):149-56.

Brem 2010

Brem H, Maggi J, Nierman D, Rolnitzky L, Bell D, Rennert R, et al. High cost of stage IV pressure ulcers. *American Journal of Surgery* 2010;**200**(4):473-7. [DOI: [10.1016/j.amjsurg.2009.12.021](https://doi.org/10.1016/j.amjsurg.2009.12.021)]

Cullum 2016

Cullum N, Buckley H, Dumville J, Hall J, Lamb K, Madden M, et al. Wounds research for patient benefit: a 5-year programme of research. *Programme Grants for Applied Research* 2016;**4**(13):1-316.

Dealy 2012

Dealey C, Posnett J, Walker A. The cost of pressure ulcers in the United Kingdom. *Journal of Wound Care* 2012;**21**(6):261-2, 264, 266.

Deeks 2011

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 9: Analysis data and undertaking meta-analyses. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Designer Anabolic Steroid Control Act 2014

United States Congress. Designer Anabolic Steroid Control Act of 2014. www.congress.gov/113/plaws/publ260/PLAW-113publ260.pdf (accessed 10 June 2016).

EPUAP/NPUAP 2009

European Pressure Ulcer Advisory Panel (EPUAP), National Pressure Ulcer Advisory Panel (NPUAP). Pressure ulcer treatment: quick reference guide. www.epuap.org/epuap-guidelines/2009-epuap-multilanguage-quick-reference-guides/ (accessed 16 November 2016).

EPUAP/NPUAP 2014

European Pressure Ulcer Advisory Panel (EPUAP), National Pressure Ulcer Advisory Panel (NPUAP). Pressure ulcer treatment: quick reference guide. www.npuap.org/wp-content/uploads/2014/08/Quick-Reference-Guide-DIGITAL-NPUAP-EPUAP-PPPIA.pdf (accessed 16 November 2016).

FDA 2013

US Food, Drug Administration (FDA). Teens and steroids: a dangerous combo. www.fda.gov/forconsumers/consumerupdates/ucm373014.htm (accessed 1 June 2014).

Fox 1961

Fox M, Minot AS, Liddle GW. Oxandrolone: a potent anabolic steroid of novel chemical configuration. *Journal of Clinical Endocrinology and Metabolism* 1961;**22**(9):921-4.

Franke 1997

Franke WW, Berendonk B. Hormonal doping and androgenisation of athletes: a secret program of the German Democratic Republic Government. *Clinical Chemistry* 1997;**43**(7):1262-79.

Gunningberg, 2012

Gunningberg L, Donaldson N, Aydin C, Idvall E. Exploring variation in pressure ulcer prevalence in Sweden and the USA: benchmarking in action. *Journal of Evaluation in Clinical Practice* 2012;**18**(4):904-10. [DOI: [10.1111/j.1365-2753.2011.01702.x](https://doi.org/10.1111/j.1365-2753.2011.01702.x)]

Hart 2001

Hart DW, Wolf SE, Ramzy PI, Chinkes DL, Beauford RB, Ferrando AA, et al. Anabolic effects of oxandrolone after severe burn. *Annals of Surgery* 2001;**233**(4):556-64.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2011a

Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated

March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b

Higgins JP, Altman DG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011c

Higgins JP, Deeks JJ, Altman DG, editor(s). Chapter 16: Special topics in statistics. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Jeschke 2007

Jeschke MG, Finnerty CC, Suman OE, Kulp G, Mlcak RP, Herndon DN. The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase post burn. *Annals of Surgery* 2007;**246**:351-62.

Jiang 1989

Jiang ZM, He GZ, Zhang SY, Wang XR, Yang NF, Zhu Y, et al. Low-dose growth hormone and hypocaloric nutrition attenuate the protein-catabolic response after major operation. *Annals of Surgery* 1989;**210**(4):513-24.

Kaltenthaler 2001

Kaltenthaler E, Whitfield MD, Walters SJ, Akehurst RL, Paisley S. UK, USA and Canada: how do their pressure ulcer prevalence and incidence data compare?. *Journal of Wound Care* 2001;**10**:530-5.

Kenny 2011

Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. *Journal of Gerontology* 2011;**56**(5):M266-72.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J, editor(s). Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Lemmey 2013

Lemmey AB, Elamanchi SR, Marcora SM, Casanova F, Maddison PJ. Chapter 12: Efficacy of nandrolone decanoate in treating rheumatoid cachexia in male rheumatoid arthritis patients. In: Matsuno H editor(s). *Innovative Rheumatology*. Online open access. InTech, 2013:271-85. [cdn.intechopen.com/pdfs-wm/40832.pdf]

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate

healthcare interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700. [DOI: doi.org/10.1136/bmj.b2700]

Lyder 2012

Lyder CH, Wang Y, Metersky M, Curry M, Kliman R, Verzier NR, et al. Hospital-acquired pressure ulcers: results from the national medicare patient safety monitoring system study. *Journal of the American Geriatrics Society* 2012;**60**(9):1603-8. [DOI: [10.1111/j.1532-5415.2012.04106.x](https://doi.org/10.1111/j.1532-5415.2012.04106.x)]

McInnes 2011

McInnes E, Dumville JC, Jammali-Blasi A, Bell-Syer SE. Support surfaces for treating pressure ulcers. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: [10.1002/14651858.CD009490](https://doi.org/10.1002/14651858.CD009490)]

Morley 2008

Morley JE. Sarcopenia: diagnosis and treatment. *Journal of Nutrition Health and Aging* 2008;**12**(7):452-6.

Newell, 1992

Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology* 1992;**21**(5):837-41.

Nordenvall 2014

Nordenvall C, Oskarsson V, Sadr-Azodi O, Orsini N, Wolk A. Postmenopausal hormone replacement therapy and risk of cholecystectomy: a prospective cohort study. *Scandinavian Journal of Gastroenterology* 2014;**49**(1):109-13. [DOI: [10.3109/00365521.2013.858180](https://doi.org/10.3109/00365521.2013.858180)]

Norman 2016

Norman G, Dumville JC, Moore ZE, Tanner J, Christie J, Goto S. Antibiotics and antiseptics for pressure ulcers. *Cochrane Database of Systematic Reviews* 2016, Issue 4. [DOI: [10.1002/14651858.CD011586.pub2](https://doi.org/10.1002/14651858.CD011586.pub2)]

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sattler 2011

Sattler F, Bhasin S, He J, Chou CP, Castaneda-Sceppa C, Yarasheski K, et al. Testosterone threshold levels and lean tissue mass targets needed to enhance skeletal muscle strength and function: the HORMA trial. *Journal of Gerontology* 2011;**66A**(1):122-9. [DOI: [10.1093/gerona/glq183](https://doi.org/10.1093/gerona/glq183)]

Schünemann 2011a

Schünemann HJ, Oxman AD, Higgins JP, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version

5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Schünemann 2011b

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

SIGN 2017

Scottish Intercollegiate Guidelines Network (SIGN). Search filters. www.sign.ac.uk/methodology/filters.html#random (accessed 19 June 2017).

Sterne 2011

Sterne JA, Egger M, Moher D, editor(s). Chapter 10: Addressing reporting biases. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Tierney 2007

Tierney JF, Stewart LA, Gherzi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**7**(8):16.

Versluysen 1986

Versluysen M. How elderly patients with femoral fracture develop pressure sores in hospital. *BMJ* 1986;**292**(6531):1311-3.

Vigen 2013

Vigen R. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *Journal of the American Medical Association* 2013;**310**(17):1829-36.

Wason 2015

Wason J. Randomized designs with treatment selection. In: Oleksandr Sverdlov editor(s). *Modern Adaptive Randomized Clinical Trials: Statistical and Practical Aspects*. New York: Chapman and Hall/CRC Biostatistics Series, 2015:387-400.

Windsor 1988

Windsor JA, Hill GL. Weight loss with physiologic impairment: a basic indicator of surgical risk. *Annals of Surgery* 1988;**207**(3):290-6.

Xu 2013

Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomised trials. *BMC Medicine* 2013;**11**:108. [DOI: [10.1186/1741-7015-11-108](https://doi.org/10.1186/1741-7015-11-108)]

References to other published versions of this review

Naing 2014

Naing C, Whittaker MA, Aung K, Racloz V. Anabolic steroids for treating pressure ulcers. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: [10.1002/14651858.CD011375](https://doi.org/10.1002/14651858.CD011375)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bauman 2013

Methods	<p>RCT</p> <p>Parallel-group (1:1), placebo-controlled</p> <p>A separate screening and treatment phase without a crossover</p> <p>Undertaken in 16 Veteran Affairs (VA) medical centres providing services for inpatients with spinal cord injury (SCI) in the USA</p>
Participants	<p>212 participants completed at least 4 weeks of treatment.</p> <p>Oxandrolone: 108; placebo: 104</p> <p>Inpatients with SCI and stage III or IV pressure ulcers</p> <p>Inclusion criteria: inpatients who were ≥ 18 years old with SCI or equivalent spinal cord damage and at least 1 stage III or IV pressure ulcer of the ischial, trochanteric, perineal, and sacral regions of the pelvis and provided written informed consent for the treatment and follow-up phases</p> <p>Exclusion criteria (screening phase)</p> <p>Patients for</p> <ul style="list-style-type: none"> Reconstructive flap surgery of the targeted pressure ulcer Unresolved osteomyelitis

Bauman 2013 (Continued)

- Psychopathology

Patients with:

- Active malignant disease
- Skin cancer at the targeted pressure ulcer site
- History of radiation therapy in the targeted pressure ulcer field
- Life expectancy < 12 months
- Nephrosis, haemodialysis, or chronic ambulatory peritoneal dialysis
- Advanced AIDS
- Administration of oxandrolone or another anabolic agent (except testosterone replacement therapy) within the past 6 months
- Hypersensitivity to anabolic steroids
- Atherosclerosis, congestive heart failure, or a history of myocardial Infarction
- Inability/unwillingness to provide informed consent

Exclusion criteria (treatment phase)

Patients having:

- Targeted pressure ulcer > 200 cm² of the surface area of the pelvic region
- Clinical impression that the targeted pressure ulcer is not expected to heal
- Flap surgery of the targeted pressure ulcer during the screening phase
- Multiple full-thickness pressure ulcers with > 500 cm² in total body surface area
- Evidence suggestive of prostate cancer
- Elevated liver enzyme levels
- Hemoglobin A1c level > 8.0%
- Receiving systemic corticosteroids, immunosuppressive agents, anticancer agents, or any radiation therapy within 30 days prior to randomisation or going to receive during this study participation
- Initiating or continuing therapy with appetite stimulants
- On treatment for hepatitis B or C virus infection
- Hypercalcaemia

Patients who were:

- Pregnant or lactating mothers
- Women of child-bearing potential and unwilling to agree to abstain from sexual intercourse or use 2 reliable forms of contraception during the study
- Men unwilling to agree to abstain from sexual intercourse or use a condom during the study
- On initial treatment with oral anticoagulants (e.g. warfarin) during the screening phase
- With atherosclerosis, congestive heart failure, or history of myocardial infarction
- On another active treatment clinical trial
- Not willing to provide informed consent

Interventions

Group A (treatment group): orally-given oxandrolone (10 mg, twice daily with morning and evening meals

Participants remained in the treatment phase until full healing of the ulcer

Targeted pressure ulcer healing at 24 weeks.

Group B (control group): placebo capsules

1500 mg (294 mg starch: 6 mg magnesium stearate, 98% and 2%)

In screening phase: participants were enrolled in a 28 ± 2 day observation period to identify hard-to-heal pressure ulcers (i.e. wound healed ≤ 30% during the 1-month screening phase). Non-drug adjunctive therapies were allowed

Bauman 2013 (Continued)

In treatment phase: the targeted pressure ulcers were examined and measured weekly. Participants remained until full healing of the targeted pressure ulcer or 24 weeks. Any adjunctive therapies were not allowed.

If targeted pressure ulcer healed in treatment phase, participants were followed up at 4 and 8 weeks after termination of the treatment phase to determine whether the targeted pressure ulcer remained closed.

Outcomes	Primary outcome The percentage of participants who had complete healing of the targeted pressure ulcer by 24 weeks (defined as re-epithelialisation to a cicatrix with a dry surface and 0 cm ² of open area for a minimum of 96 hours) Secondary outcome VA Nutrition Status Classification (NSC) score at 12 and 24 weeks	
Notes	Study period was between 1 August 2005 and 30 November 2008 Trial was reviewed when complete data for 164 participants were obtained. Based on the findings of a futility analysis, this study was terminated. The original sample size was 400. Trial stopped 2 months later and 7 participants (3 Oxandrone and 4 placebo) completed only 4 weeks instead of 24 weeks Source of funding: The Veterans Affairs Clinical Science Research and Development Service, Cooperative Study #535; Rehabilitation Research and Development, National Center of Excellence for the Medical Consequences of Spinal Cord Injury (B2648C, B4162C, and B9212C); and Department of Veterans Affairs, Spinal Cord Injury Services.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation process used a computer-generated randomisation sequence. Comments: method of sequence generation deemed adequate
Allocation concealment (selection bias)	Low risk	Comments: allocation concealment deemed appropriate as the participants and investigators could not foresee assignment because an automated central telephone system was used. The Clinical Research Pharmacy Co-ordinating Center (CSP) distributed the medication or placebo through the individual pharmacy services at each participating VA medical centre.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, clinical care providers, research study staff and statistical analyst were blinded to treatment assigns" Comments: blinding of outcome assessment deemed adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	40% (43/108) of the participants in group A and 36% (37/104) in group B did not complete the treatment. Details were listed. All 212 were included in the current data analysis according to the intention-to-treat principle. Comments: an intention-to-treat approach was followed; this was confirmed the trial investigator

Bauman 2013 *(Continued)*

Selective reporting (re-reporting bias)	Low risk	Many outcomes listed in methods were reported
Other bias	Unclear risk	Potential centre-specific differences in targeted pressure ulcer healing by 24 weeks or in targeted pressure ulcer healing $\geq 30\%$ at 4 weeks were not explored due to limited participant numbers at each centre. Comment: site-specific healing not addressed

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

Study	Reason for exclusion
Bauman 2001	A study on anabolic hormones on body composition changes in spinal cord injury
Bauman 2009	Duplicate data
Chiu 2011	A review
Collins 2004a	Nutrition assessment on people with pressure ulcers
Collins 2004b	Nutrition assessment on people with pressure ulcers
Crane 2013	Not an RCT
Demling 2001a	Not an RCT
Demling 2001b	Not an RCT
Generali 2013	Not an RCT
Himes 1999	Review on the role of protein in anabolic action in wound healing
Mader 2000	A treatment guideline
Mikulin 2001	Assessed nutrition on wound healing
Morley 2002	A review
Phillips 2003	Not an RCT; study on nutritional assessment to determine the need of using anabolic agents in wound healing
Phillips 2005	Not RCT; guideline information of oxandrolone and nutritional assessment
Salcido 1999	An editorial on anabolic steroids of published studies
Salcido 2005	An editorial on anabolic steroids of published studies
Sowers 1996	Not an RCT and assessed people with osteoarthritis
Spungen 2001	A single arm trial of oxandrolone with no comparator drug
Vennits 1966	Not an RCT, although double-blind assessment was done

Study	Reason for exclusion
Williams 2013	Not an RCT; an awareness initiative programme for the risks and preventive strategies of pressure ulcers
Wolf 2006	RCT of oxandrolone on people with severe burns

DATA AND ANALYSES

Comparison 1. Oxandrolone compared with placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Completed healing at 24 week	1	212	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.52, 1.26]
2 Non-serious adverse events	1	212	Risk Ratio (M-H, Fixed, 95% CI)	3.85 [1.12, 13.26]
3 Serious adverse events	1	212	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.25, 1.17]

Analysis 1.1. Comparison 1 Oxandrolone compared with placebo, Outcome 1 Completed healing at 24 week.

Analysis 1.2. Comparison 1 Oxandrolone compared with placebo, Outcome 2 Non-serious adverse events.

Analysis 1.3. Comparison 1 Oxandrolone compared with placebo, Outcome 3 Serious adverse events.

ADDITIONAL TABLES

Table 1. List of reported non-serious adverse events

Description	Oxandrolone group n = 108	Placebo group n = 104
Elevated liver enzyme levels	5	1
Deep venous thrombosis	3	0
Elevated prostate specific antigen	0	1
Severe osteomyelitis ^a	1	0
Sepsis, secondary cellulitis ^a	1	0
Medical illness ^a	2	1

^aIn the trial investigators' judgement these events were not associated with oxandrolone

Table 2. List of reported serious adverse events

Description	Oxandrolone group n = 108	Placebo group n = 104
Death ^a	3	5
Myocutaneous flap surgery ^a	5	9
Elevated bladder stone removal liver enzyme levels ^a	1	0
Small bowel obstruction, renal failure ^a	0	1
Oral cancer ^a	0	1

^aIn the trial investigators' judgement these events were not associated with oxandrolone

APPENDICES

Appendix 1. Stages of pressure ulcers

The characteristics of pressure ulcers are categorised into 4 stages ([EPUAP/NPUAP 2009](#)).

Stage I: non-blanchable redness of intact skin

Intact skin with non-blanchable erythema of a localised area usually over a bony prominence. Discoloration of the skin, warmth, oedema, hardness or pain may also be present. Darkly pigmented skin may not have visible blanching.

Stage II: partial thickness skin loss or blister

Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled or sero-sanguinous filled blister.

Stage III: full thickness skin loss (fat visible)

Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Some slough may be present. May include undermining and tunnelling.

Stage IV: full thickness tissue loss (muscle/bone visible)

Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present. Often include undermining and tunnelling ([EPUAP/NPUAP 2009](#)).

Appendix 2. Search strategies

Cochrane Wounds Specialised Register

```
1 MESH DESCRIPTOR Pressure Ulcer EXPLODE ALL AND INREGISTER
2 (pressure next (ulcer* or sore* or injur*)) AND INREGISTER
3 (decubitus next (ulcer* or sore*)) AND INREGISTER
4 (bedsore* or (bed next sore*)) AND INREGISTER
5 #1 OR #2 OR #3 OR #4
6 MESH DESCRIPTOR Anabolic Agents EXPLODE ALL AND INREGISTER
7 MESH DESCRIPTOR testosterone EXPLODE ALL AND INREGISTER
8 MESH DESCRIPTOR Oxandrolone EXPLODE ALL AND INREGISTER
9 MESH DESCRIPTOR Nandrolone EXPLODE ALL AND INREGISTER
10 MESH DESCRIPTOR Mesterolone EXPLODE ALL AND INREGISTER
11 MESH DESCRIPTOR Oxymetholone EXPLODE ALL AND INREGISTER
12 (anabolic next (steroid* or agent*)) AND INREGISTER
13 testosterone AND INREGISTER
14 oxandrolone AND INREGISTER
15 nandrolone AND INREGISTER
16 mesterolone AND INREGISTER
17 oxymetholone AND INREGISTER
18 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19 #5 AND #18
```

The Cochrane Central Register of Controlled Trials (CENTRAL)

```
#1 MeSH descriptor: [Pressure Ulcer] explode all trees
#2 (pressure next (ulcer* or sore* or injur*)):ti,ab,kw
#3 (decubitus next (ulcer* or sore*)):ti,ab,kw
#4 (bedsore* or (bed next sore*)):ti,ab,kw
#5 {or #1-#4}
#6 MeSH descriptor: [Anabolic Agents] explode all trees
#7 MeSH descriptor: [Testosterone] explode all trees
#8 MeSH descriptor: [Oxandrolone] explode all trees
#9 MeSH descriptor: [Nandrolone] explode all trees
#10 MeSH descriptor: [Mesterolone] explode all trees
#11 MeSH descriptor: [Oxymetholone] explode all trees
#12 (anabolic next (steroid* or agent*)):ti,ab,kw
#13 testosterone:ti,ab,kw
```

Anabolic steroids for treating pressure ulcers (Review)

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#14 oxandrolone:ti,ab,kw
#15 nandrolone:ti,ab,kw
#16 mesterolone:ti,ab,kw#17 oxymetholone:ti,ab,kw
#18 {or #6-#17}
#19 #5 and #18

Ovid MEDLINE

1 exp Pressure Ulcer/
2 (pressure adj (ulcer* or sore* or injur*)).tw.
3 (decubitus adj (ulcer* or sore*)).tw.
4 (bedsore* or (bed adj sore*)).tw.
5 or/1-4
6 exp Anabolic Agents/
7 exp Testosterone/
8 exp Oxandrolone/
9 exp Nandrolone/
10 exp Mesterolone/
11 exp Oxymetholone/
12 (anabolic adj (steroid* or agent*)).tw.
13 testosterone.tw.
14 oxandrolone.tw.
15 nandrolone.tw.
16 mesterolone.tw.
17 oxymetholone.tw.
18 or/6-17
19 and/5,18
20 randomised controlled trial.pt.
21 controlled clinical trial.pt.
22 randomi?ed.ab.
23 placebo.ab.
24 clinical trials as topic.sh.
25 randomly.ab.
26 trial.ti.
27 or/20-26
28 exp animals/ not humans.sh.
29 27 not 28
30 19 and 29

Ovid Embase

1 exp decubitus/
2 (pressure adj (ulcer* or sore* or injur*)).tw.
3 (decubitus adj (ulcer* or sore*)).tw.
4 (bedsore* or (bed adj sore*)).tw.
5 or/1-4
6 exp anabolic agent/
7 exp testosterone/
8 exp testosterone ester/
9 exp epitestosterone/
10 exp testosterone derivative/
11 exp methenolone/
12 exp methyltestosterone/
13 exp testosterone propionate/
14 exp oxandrolone/
15 exp nandrolone/
16 exp mesterolone/
17 exp oxymetholone/
18 (anabolic adj (steroid* or agent*)).tw.
19 testosterone.tw.
20 oxandrolone.tw.
21 nandrolone.tw.
22 mesterolone.tw.

Anabolic steroids for treating pressure ulcers (Review)

23 oxymetholone.tw.
24 or/6-23
25 and/5,24
26 Randomized controlled trials/
27 Single-Blind Method/
28 Double-Blind Method/
29 Crossover Procedure/
30 (random\$ or factorial\$ or crossover\$ or cross over\$ or cross-over\$ or placebo\$ or assign\$ or allocat\$ or volunteer\$).ti,ab.
31 (doubl\$ adj blind\$).ti,ab.
32 (singl\$ adj blind\$).ti,ab.
33 or/26-32
34 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
35 human/ or human cell/
36 and/34-35
37 34 not 36
38 33 not 37
39 25 and 38

EBSCO CINAHL Plus

S30 S16 AND S29
S29 S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28
S28 TI allocat* random* or AB allocat* random*
S27 MH "Quantitative Studies"
S26 TI placebo* or AB placebo*
S25 MH "Placebos"
S24 TI random* allocat* or AB random* allocat*
S23 MH "Random Assignment"
S22 TI randomi?ed control* trial* or AB randomi?ed control* trial*
S21 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S20 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S19 TI clinic* N1 trial* or AB clinic* N1 trial*
S18 PT Clinical trial
S17 MH "Clinical Trials+"
S16 S6 AND S15
S15 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S14 TI oxymetholone OR AB oxymetholone
S13 TI mesterolone OR AB mesterolone
S12 TI nandrolone OR AB nandrolone
S11 TI oxandrolone OR AB oxandrolone
S10 TI testosterone OR AB testosterone
S9 TI "anabolic steroid*" OR AB "anabolic steroid*" OR TI "anabolic agent*" OR AB "anabolic agent*"
S8 (MH "Testosterone+")
S7 (MH "Anabolic Steroids")
S6 S1 OR S2 OR S3 OR S4 OR S5
S5 TI (bed sore*) OR AB (bed sore*)
S4 TI bed sore* OR AB bed sore*
S3 TI decubitus or AB decubitus
S2 TI (pressure ulcer*) OR AB (pressure ulcer*) OR TI (pressure sore*) OR AB (pressure sore*) OR TI (pressure injur*) OR AB (pressure injur*)
S1 (MH "Pressure Ulcer+")

US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov)

"anabolic steroid" AND "pressure ulcer"

"anabolic agent" AND "pressure ulcer"

"testosterone" AND "pressure ulcer"

"oxandrolone" AND "pressure ulcer"

World Health Organization International Clinical Trials Registry Platform

"anabolic steroid" OR "anabolic agent" OR "oxandrolone" AND "pressure ulcer"

Anabolic steroids for treating pressure ulcers (Review)

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Appendix 3. Risk of bias assessment criteria

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 to permit 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 randomisation); 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 to permit 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 (participants and outcome assessors)?

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 unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data 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 observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on 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 likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear:

Either of the following:

- Insufficient reporting of attrition/exclusions to permit judgement of low or high risk of bias (e.g. number randomised 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 pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias:

Any one of the following:

- Not all of the study's pre-specified primary outcomes have been reported.
- One or more primary outcomes are reported using measurements, analysis methods or subsets of the data (e.g. sub scales) that were not pre-specified.
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review 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 to permit 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.

CONTRIBUTIONS OF AUTHORS

Cho Naing: conceived and designed the review; extracted data; checked the quality of data extraction; analysed and interpreted data; performed statistical analysis; produced the first draft of the review; contributed to writing and editing the review; approved the final review prior to submission; secured funding; wrote to study author/experts/companies; provided data; and is a guarantor of the review.

Maxine Whittaker: conceived, designed and coordinated the review; checked quality assessment; produced the first draft of the review; contributed to writing or editing the review; approved the final review prior to submission; secured funding; and is a guarantor of the review.

Contributions of editorial base:

Nicky Cullum (Editor): edited the protocol; advised on methodology, interpretation and protocol content.

Jo Dumville (Editor): edited the review; advised on methodology, interpretation and review content.

Gill Rizzello and Sally Bell-Syer (Managing Editors): co-ordinated the editorial process. Advised on interpretation and content; edited the review.

Reetu Child and Naomi Shaw (Information Specialists): designed the search strategy, ran the searches and edited the search methods section.

Ursula Gonthier (Editorial Assistant): Edited the plain language summary and reference sections of the review.

DECLARATIONS OF INTEREST

Cho Naing: none known

Maxine A Whittaker: none known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Only one study was included in this review. Thus, the planned data pooling, assessment of heterogeneity and sensitivity analysis were not possible.

INDEX TERMS

Medical Subject Headings (MeSH)

Off-Label Use; Oxandrolone [adverse effects] [*therapeutic use]; Pressure Ulcer [*drug therapy]; Starch [therapeutic use]; Stearic Acids [therapeutic use]; Testosterone Congeners [adverse effects] [*therapeutic use]; Wound Healing

MeSH check words

Female; Humans; Male; Middle Aged