Authors' objectives
To assess the impact of different interventions on post-operative fatigue, and to determine whether any of these interventions is effective.

Searching
Two database searches were made. The first was conducted on MEDLINE, EMBASE, CINAHL, PsycINFO, Science Citation Index (via ISI), Social Sciences Citation Index (via ISI), Index to Scientific and Technical Proceedings (via ISI), ASSIA, PREMEDLINE, the Cochrane Library, HealthSTAR and the Index to Theses. These databases were all searched from their inception to July 2001 for English language papers containing surgery-related MeSH or free-text terms in combination with fatigue-related MeSH of free-text terms. The full strategy used is available from the authors. A second search was subsequently made to identify all surgical studies that utilised the profile of mood states (POMS) questionnaire; this questionnaire contains a reliable 7-item fatigue subscale together with scales designed to assess, for example, anger and depression (see Other Publications of Related Interest). This search was performed using the same databases, but substituting 'POMS' or 'profile of mood states' for the fatigue-related terms.

The citations of all papers included in the review were examined for additional studies, as were the reference sections of 88 reviews, editorials and commentaries identified during the review process. Finally, an independent unpublished systematic search for post-operative fatigue-related papers was examined to check the comprehensiveness of the strategy, which had identified 16 relevant RCTs for the period 1966 to 1999.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Any interventions to treat post-operative fatigue were eligible for inclusion in the review. The interventions included related to analgesia, psychosocial, nutritional, surgical, anaesthesia, human growth hormone (HGH), glucocorticoid and 'other' modalities.

The analgesia interventions were: transcutaneous electrical nerve stimulation; epidurals; analgesia via interpleural catheter; self-administered versus nurse-administered analgesia; fentanyl versus morphine; hydromorphone versus morphine; supplemental morphine at night-time; ketorolac versus placebo; and ibuprofen versus placebo.

The psychosocial interventions were emotionally disclosive writing, emotional or psychiatric support, relaxation training, coping skills training and the provision of information.

The nutritional interventions were the provision of dietary advice and protein supplements, immediate enteral feeding, early parenteral feeding, general nutritional supplements and glutamate supplement.

The surgical techniques were laparascopic versus open surgery, and French and American styles of laparoscopy.

The anaesthesia interventions were: ketamine isomers, isoflurane and propofol; 200 mg pethidine versus 100 or 50 mg pethidine, or 250 mg prilocaine local anaesthesia; and thiopentone versus propofol.

The HGH interventions were HGH versus placebo, and Cetoran nutritional supplement versus a formula peptide supplement.

Glucocorticoids administered peri-operatively were also included.
The ‘other’ interventions were: limited versus unrestricted chair-nursing; early versus late mobilisation; day surgery versus overnight stay; high- versus low-volume peri-operative hydration; effortil versus placebo; and lower versus normal haemoglobin threshold for transfusion.

The interventions were compared with routine care or placebo. Specific details of the different interventions and their regimens were provided in the review.

Participants included in the review
Any patients undergoing surgery were eligible for inclusion in the review. Several types of surgery were reported in the review. Studies were excluded if not all the participants had undergone operation, if any of the participants had undergone fatigue-related adjuvant therapy or operation (e.g. chemotherapy, radiotherapy, bilateral adrenalectomy), or if any of the participants had a fatigue-related diagnosis (e.g. chronic fatigue syndrome, fibromyalgia, pregnancy, univentricular heart). Owing to the high frequency of chemotherapy, radiotherapy and immunotherapy used in breast cancer treatment and organ transplantation, all studies specifically examining these procedures were also excluded.

Outcomes assessed in the review
The primary outcome was subjective fatigue following surgery. Only studies using self-report measures of fatigue after operation were eligible for inclusion. These were defined as any attempt to quantify the intensity of subjective fatigue, excluding, for example, single yes/no items. Eligible studies were also required to have assessed fatigue at least once, more than 24 hours after the operation.

How were decisions on the relevance of primary studies made?
One review selected the papers for the review, and any uncertainties were resolved through consultation with the second author.

Assessment of study quality
The methodological quality of the included studies was assessed on four scales relating to the fatigue questionnaire: validity and reliability, blinding, concealment of allocation at enrolment and completeness of follow-up. No points were given when there was insufficient information to assess an aspect of methodological quality. A total quality score of between 0 (worst quality) and 8 (best quality) was then allocated to each RCT. One review assessed the quality of the studies, and any uncertainties were resolved through consultation with the second author.

Data extraction
One reviewer extracted the data, and any uncertainties were resolved through consultation with the second author. Data were extracted on the nature of the participants' surgery, the intervention, and the study findings. Data were pooled within studies to give no more than one outcome at each of the following time-points: same day as surgery to post-operative day 1 (d0-d1); post-operative day 2 to day 7 (d2-d7); post-operative day 8 to day 30 (d8-d30); and post-operative day 31 or later (d31+). Where both routine care and placebo groups were used in a study, the placebo group was taken as the reference point.

Methods of synthesis
How were the studies combined?
The studies were combined statistically in a meta-analysis, where appropriate, using standardised mean differences (SMDs). To facilitate pooling of the study results using different fatigue scales, the overall results were presented as the SMD with 95% confidence interval (CIs). Where meta-analyses could not be undertaken (surgical technique, anaesthesia and glucocorticoids), the studies were combined narratively. Meta-analyses were conducted at each time-point, using a random-effects model, to examine the efficacy of various interventions in comparison with routine care or placebo.

How were differences between studies investigated?
Heterogeneity was assessed with Q tests, using a P-value of less than 0.1 to indicate significant heterogeneity.
**Results of the review**

Sixty-eight papers providing data on 66 RCTs (n=4,289) were included in the review. There were 17 studies (n=1,084) of analgesia, 16 studies (n=1,546) of psychosocial interventions, 8 studies (n=258) of nutritional interventions, 6 studies (n=228) of operative technique, 6 studies (n=324) of anaesthesia, 3 studies (n=64) of glucocorticoids, and 6 studies (n=785) of other interventions.

In general, the quality of the research identified was average to poor.

**Analgesia.**

Eleven comparisons between increased analgesia and routine care or placebo found that increased analgesia reduced post-operative fatigue significantly at d0-d1, with a SMD of -0.21 (95% CI: -0.37, -0.04, P=0.01). Little heterogeneity was observed at d0-d1 (Q=11.21, d.f.=10, P=0.34). Fatigue at other times (d2-d7, d8-d30, d31+) was not significantly affected. Of the 5 comparisons that provided results but were not included in the analyses, none showed any effect of increased analgesia at any time-point. Other results of the heterogeneity tests at different time-points were presented and discussed in the review.

**Psychosocial interventions.**

No significant effects of psychosocial interventions were found at any time-point for which data were available (d2-d7, d8-d30, d31+). No statistically-significant heterogeneity was identified at any time-point. Of the 5 studies that provided results but were not included in the meta-analyses, only one found a significant effect: reduced fatigue was reported during the first post-operative week for cardiac patients engaged in guided imagery.

**Nutritional interventions.**

No significant effects of nutritional interventions were found at any time-point for which data were available (d2-d7, d8-d30, d31+). No significant heterogeneity was identified at d2-d7 or d8-d30; only one study reported results at d31+. Of the 3 studies that provided relevant data but were not included in the analyses, none identified any significant effect of the nutritional intervention.

**Surgical technique.**

No formal meta-analyses could be undertaken for this group since 5 of the 6 studies compared laparoscopic with open surgery; the difference between these approaches in terms of invasiveness depends on the specific procedure under consideration. Three of these 5 studies found no significant difference at d0-d1, while one reported less fatigue in the laparoscopic group. None of the 3 studies that provided data reported a significant difference between the groups at d8-d30. No data were available for d31+. The study that compared French and American styles of laparoscopic cholecystectomy found no significant difference at d0, d1 or d2.

**Anaesthesia.**

No meta-analyses could be undertaken for this group of 6 studies. No differences were identified between different isomers of ketamine or between isoflurane and propofol. However, significantly higher fatigue levels were reported at d0-d1 for 200 mg pethidine compared with 100 or 50 mg pethidine (P<0.05), or 250 mg prilocaine (P<0.05), and for thiopentone compared with propofol at d0-d1 (P<0.01 at 1 hour; P<0.05 at d1). Significantly greater fatigue was also reported for propofol compared with desflurane at d7 (P<0.01), but not at d0 or d1.

**HGH.**

The pooled data from 2 studies found a significant beneficial effect of HGH treatment at d8-d30 (SMD -0.55, 95% CI: -1.13, -0.17, P=0.01). No significant differences were found for the other time-points for which data were available (d2-d7, d31+). Significant heterogeneity was found at d31+ (Q=11.21, d.f.=2, P<0.01), but not at d2-d7 or d8-d30. A further study not included in the meta-analyses reported that the Cetoran nutritional supplement significantly reduced fatigue at day 56, compared with formula peptide nutritional supplement.
Glucocorticoids.

One study reported a significant beneficial effect of glucocorticoids (methylprednisolone) at d1 (P<0.05), but not during d2-d7. A second study found no significant difference between glucocorticoid and placebo groups at d0-d1, d2-d7, or d8-d30. The third study reported an overall beneficial effect of glucocorticoid provision (with neural blockade, post-operative hydrochloride-morphine and indomethacin sodium) versus routine care over d1, d4 and d8 (P<0.05).

Other interventions.

Post-operative fatigue was reduced significantly by limited chair-nursing following lower-limb surgery (P<0.001), by increased peri-operative hydration during dental surgery at d0 (P<0.05), and by the administration of effortil after gynaecological surgery at d1 and d2 (P<0.05). No significant benefits were found for same-day discharge following laparoscopic cholecystectomy, and for a lower haemoglobin threshold for blood transfusion for cardiac patients.

Authors' conclusions

Post-operative fatigue immediately after operation may be attenuated by improved analgesia, peri-operative administration of HGH and glucocorticoids. However, many of the findings in this area require confirmation and extension to other surgical populations. There is much scope for novel interventions, that are not based on the surgical stress model of post-operative fatigue, to be attempted.

CRD commentary

The review question and the study selection criteria were stated clearly. The literature search seemed comprehensive, except for the restriction to publications in English, which may have caused relevant material to be missed. There was adequate information on the literature selection, validation and data extraction processes, and appropriate statistical tests were employed when meta-analyses were carried out. However, the authors did not report a method for assessing publication bias.

The presentation and discussion of the data and findings was clear. The authors' conclusions are appropriate, and are appropriately cautious in the light of the data they present and the methodological limitations of the studies they have reviewed.

Implications of the review for practice and research

Practice: The authors state that post-operative fatigue immediately after operation may be attenuated by improved analgesia, peri-operative administration of HGH and glucocorticoids. However, many of the findings in this area require confirmation and extension to other surgical populations. Further implications for practice were outlined in the review.

Research: The authors state that there remains much scope for novel interventions, which are not based on the surgical stress model of postoperative fatigue, to be attempted. Future research should ensure that an adequate measure of subjective fatigue is employed, possibly in tandem with important objective measures, such as time taken to return to work. Larger clinical trials to verify the HGH finding and to examine overall safety are warranted.

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