Effect of buprenorphine dose on treatment outcome
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CRD summary
This review concluded that there was strong evidence that higher buprenorphine doses may improve retention in buprenorphine maintenance treatment in opioid dependence. The authors' conclusions seem overstated given the unclear quality of the evidence, analysis method used and lack of information about study participants and may not be reliable.

Authors' objectives
To compare treatment outcomes for high dose (16mg or more per day) with lower dose buprenorphine (less than 16mg per day) in opioid dependence.

Searching
MEDLINE and PsycINFO were searched from 1960 to December 2010. The search term was buprenorphine (all fields). Only studies published in English were included. Reference lists of retrieved articles and tables of contents of journals on drug abuse included in the psychiatry and substance abuse listing 2010 of Journal Citation Reports were searched.

Study selection
Eligible studies were randomised controlled or double-blind clinical trials with a buprenorphine maintenance treatment period of three weeks or more where the dosing regimen was clearly stated. For studies with a flexible dosing regimen the average or upper limit (if there was a range) was used. Studies had to report at least one of the outcomes: retention rates, illicit opioid use based on analytical determination of drugs of abuse (natural and synthetic opioids) in urine samples and illicit cocaine use based on analytical determination in urine samples. Studies of opioid detoxification were excluded.

Daily doses of buprenorphine in the included studies ranged from 1mg to 29.6mg. Treatment duration ranged from three to 48 weeks. Higher dose was classed as 16mg/day or above and lower dose was less than 16mg/day.

The authors did not report how many reviewers performed the study selection.

Assessment of study quality
Study quality was assessed with the five-item Jadad scale of randomisation, blinding and description of withdrawals (maximum score of 5). Studies that scored 3 or more were included in the meta-analysis.

The authors did not report how many reviewers performed the quality assessment.

Data extraction
Results were extracted or estimated from text, graphs and tables.

Three reviewers performed the data extraction which was checked by another reviewer.

Methods of synthesis
Characteristics of patients who received high or low dose buprenorphine were compared with a t-test. For the outcome of retention in treatment, univariate analyses were used to assess whether dose, treatment duration, opioid and cocaine use were predictors; if they were found to be statistically significant they were included in a multivariate model. The analysis method was the same for illicit opioid use but retention in treatment was a possible predictor instead of opioid use.

Results of the review
Twenty-one studies (2,703 participants, range 16 to 472) were included in the meta-analysis. Patients who received higher doses of buprenorphine had significantly greater retention in treatment than those on lower doses (69% versus...
51%, p=0.006).

**Retention in treatment**: Buprenorphine dose and urine drug screens were significant predictors for retention status in the univariate analysis. Both remained statistically significant in the multivariate analysis. A higher dose had better retention (p=0.009) and positive urine drug screens for opiates predicted dropping out of treatment (p=0.01).

**Illicit opioid use**: Buprenorphine dose, retention in treatment and urine drug screens for cocaine use were significant predictors for illicit opioid use in the univariate analysis. Retention in treatment and urine drug screens for cocaine remained statistically significant in the multivariate analysis. Better retention in treatment predicted less illicit opioid use (p=0.033) and positive urine drug screens for cocaine predicted more illicit opioid use (p=0.021).

**Authors’ conclusions**
Based on 21 randomised clinical trials, strong evidence existed that higher buprenorphine doses may improve retention in buprenorphine maintenance treatment.

**CRD commentary**
This review had clear inclusion criteria for study design, interventions and outcomes. Only published studies in English were included which put the review at risk of language and publication biases. Study data were extracted by three reviewers and checked by another to reduce bias and error; it was unclear whether this also applied to study selection and quality assessment. The results of the quality assessment were not reported so the reliability of the evidence was unclear. The meta-analysis did not use an appropriate statistical method as it did not maintain the randomisation within trials.

The authors conclusions seem overstated given the unclear quality of the evidence, analysis method used and lack of information about study participants and may not be reliable.

**Implications of the review for practice and research**
**Practice**: The authors stated that clinicians needed to consider using a higher dose (more than 16mg per day) of buprenorphine for patients who would not respond to a lower dose, particularly if they have intense opioid cravings. Due to increased patient monitoring for diversion and increased medication costs clinicians needed to consider the pros and cons of the higher dose range when making clinical decisions.

**Research**: The authors did not state any implications for research.

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