Effectiveness and tolerability of combination treatment of chronic hepatitis C in illicit drug users: meta-analysis of prospective studies

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CRD summary
The review concluded that using antiviral combinations to treat chronic hepatitis C was as efficacious and well tolerated in illicit drug users as in the general population. Differences across the studies, small sample sizes, methodological quality issues and potential for publication bias limit the reliability of the pooled results and caution appears warranted when interpreting the authors' conclusions.

Authors' objectives
To assess the effectiveness and tolerability of combination treatment with ribavirin plus recombinant or pegylated interferon-alpha for the treatment of chronic hepatitis C in illicit drug users.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from 2000 to July 2010 for articles published in English. Search terms were reported. Reference lists of relevant review articles were searched. The abstract books of eight international meetings of hepatologists were manually searched.

Study selection
Prospective studies that reported complete results on sustained virological response of combination treatment with ribavirin plus recombinant or pegylated interferon-alpha for the treatment of chronic hepatitis C in illicit drug users were eligible for inclusion. Definitions were provided in the review. Studies had to have more than 15 participants, provide a clear definition of antiviral schedule for type, dose and duration of treatment and use combination antiviral therapy in the entire study population.

Most participants in the included studies were men. Almost all (96%) participants received opiate substitution treatment. Most studies used a multidisciplinary team approach. The hepatitis C genotype was split 50:50 between unfavourable (genotypes 1 or 4) and favourable (genotypes 2 or 3). The mean age of participants ranged from 30 to 50 years, where reported.

Two reviewers independently performed study selection. Disagreements were resolved by discussion.

Assessment of study quality
Two reviewers independently assessed study quality using a 10-point scale that included an assessment of population sampling and completeness of reporting. Studies that scored less than 8 were deemed poor quality and those that scored 8 or more were deemed high quality. The percentage of agreement between reviewers was estimated.

Data extraction
Data were extracted on the rate of intention-to-treat sustained virological response, drop-out rate and severe psychiatric adverse events and used to calculate prevalence estimates, together with 95% confidence intervals (CIs). Trial authors were contacted for missing data.

Two reviewers independently performed data extraction. Disagreements were resolved by discussion.

Methods of synthesis
A random-effects meta-analysis was used to calculate pooled prevalence estimates, together with 95% CIs. Statistical heterogeneity was assessed with I² and the Q statistic. Subgroup analysis was undertaken for six factors associated with sustained virological response success. Sensitivity analysis was used to assess the influence of each of the illicit drug use studies on the results. Results were compared with the results of two multicentre registration trials of antiviral therapy in non-illicit drug users with chronic hepatitis C. Publication bias was assessed with funnel plots and Egger's test.
Results of the review
Sixteen studies that provided 19 study groups (953 illicit drug users) were included in the review. The study group sample size ranged from 11 to 244 illicit drug users. Methodological quality of the studies varied. Studies of seven interventions were deemed high quality and studies of 12 interventions were deemed low quality.

**Combination therapy:** Prevalence of sustained virological response was 52% (95% CI 44% to 60%; $I^2=86\%$). Prevalence of drop-outs was 26% (95% CI 18% to 35%; $I^2=93\%$). Prevalence of severe psychiatric adverse events that led to discontinuation was 2% (95% CI 1% to 3%; $I^2=21\%$). High $I^2$ values indicated significant heterogeneity for the first two results.

Subgroup analysis indicated that active ongoing drug use negatively affected the success rate and resulted in a prevalence of sustained virological response of 39% (95% CI 30% to 49%; three studies) compared with 55% in studies that had a mandatory drug abstinence period before study entry (95% CI 45% to 64%). Sensitivity analysis did not alter results. There was evidence of publication bias.

Authors’ conclusions
Using antiviral combinations to treat chronic hepatitis C was as efficacious and well tolerated in illicit drug users as in the general population.

CRD commentary
Inclusion criteria for the review were clearly defined and several relevant data sources were searched. The restriction to studies in English limited language bias (the authors considered the actual risk to be low). Publication bias was detected. Attempts were made to reduce reviewer error and bias throughout the review process. Quality assessment indicated that the quality of the studies was variable and most were deemed poor quality. The studies varied considerably in patient characteristics, interventions and study types, which the authors acknowledged. Several studies had small sample sizes. Trials were combined using standard statistical methods. Statistical heterogeneity was assessed and found to be significant for most outcomes, so the studies may not have been suitable for pooling. The studies of non-illicit drug users were not part of the systematic review and were not adequately described and so use of these results as a comparison may not have been appropriate.

Differences between the studies, small sample sizes, methodological quality issues and potential for publication bias limits the reliability of the pooled results and caution appears warranted when interpreting the conclusions.

Implications of the review for practice and research
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that larger prospective trials were needed to determine the most effective antiviral treatment regimens for hepatitis C virus infection in illicit drug users. The choice of opiate-substitution treatment to be associated with antiviral agents needed to be determined.

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