Systematic review of therapeutic interventions in human prion disease
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CRD summary
The authors concluded that little progress had been made in identifying and evaluating potentially useful treatments for patients with prion disease and that future patients must be evaluated within a structured framework. The authors’ conclusions seem suitably cautious and their recommendation for further research appears appropriate.

Authors’ objectives
To identify the existing evidence on treatments and their effects on patients with human prion disease.

Searching
MEDLINE was searched from 1966 to 2007 for publications in any language. Search terms were reported. Abstracts from relevant and recent conference proceedings were handsearched. ClinicalTrials.gov, mRCT, CenterWatch Drugs in Clinical Trials Database and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for ongoing or completed studies. Reference lists of identified studies were searched, as was a sample of relevant reviews to determine whether all reviews required handsearching.

Study selection
Clinical studies that assessed interventions for treatment of prion disease (sporadic, inherited or acquired) in humans were eligible for inclusion. Studies of well-defined groups of untreated patients were eligible for inclusion and were discussed in the review.

Included studies were conducted in various countries (such as UK, USA, Israel, Spain, France, Japan, Italy, Germany and Finland). There was substantial variation in patient age; all appeared to be at least 18 years old. Prion disease included early, mid and late stage Creutzfeldt-Jakob disease (CJD) (familial, variant, iatrogenic, sporadic, unspecified). Disease duration ranged from two months to six years. Interventions were antiviral drugs (acyclovir, amantadine, vidarabine), antimalarial drugs (quinacrine/mepacrine), anticoagulant drugs (pentosan polysulphate), antifungal drugs (amphotericin), biological response modifiers (interferon), antidepressant drugs (clomipramine), anticonvulsant drugs (levetiracetam, topiramate/phenytoin) and antioxidants. Reported outcomes were change in signs and symptoms, survival and treatment toxicity.

Two reviewers independently screened abstracts for inclusion. Discrepancies were resolved by consensus and by obtaining full papers.

Assessment of study quality
The authors did not state that they performed a validity assessment.

Data extraction
One reviewer extracted data, which were checked by a second reviewer. Data were extracted on definite (neuropathologically confirmed according to techniques and criteria accepted at the time) and probable cases (as reported in each paper).

Discrepancies were resolved through discussion or referral to a third reviewer.

Methods of synthesis
Data were presented as a narrative synthesis and in tables. Antiviral drugs, anticoagulants, anticonvulsants and antioxidants were reported in more detail.

Results of the review
Thirty-three studies of treated patients (n=149) were included in the review: four comparative studies (one RCT) and
29 case reports/patient series. The RCT was double blinded. One other comparative study was blind to assessors. Survival of treated patients was within the ranges of those reported in surveillance datasets and untreated patients.

One RCT (n=28) found that flupirtine significantly reduced deterioration in dementia tests compared to controls. There was no difference in survival rates.

Two case reports found no statistically significant benefit from acyclovir and one reported no evidence of toxicity, but the patient died. Two comparative studies (n=17) and six case reports (n=7) showed conflicting findings for amantadine; four showed benefit and four showed no treatment effect. Studies of pentosan polysulphate (three case series plus 23 treated patients) and quinacrine (one comparative study, nine case reports/case series) showed mixed findings; 10 studies reported toxicity (for example, liver dysfunction).

Vidarabine, amphotericin, interferon, clomipramine, levetiracetam, topiramate/phenytoin and antioxidants were reported in single studies of three or fewer patients.

Authors' conclusions
Evidence suggested that patients with prion disease had been treated in a poorly co-ordinated manner that resulted in little progress in identifying and evaluating potentially useful treatments. Disease course and treatment of patients needed evaluation within a structured framework.

CRD commentary
The review question was clear and supported by appropriate inclusion criteria for study design, intervention and population. Outcomes were not clearly defined. A number of relevant sources were searched for published and unpublished studies in any language, which reduced risks of language bias and of missing relevant articles. The authors acknowledged potential for publication bias due to the subjective nature of case series. The authors did not formally assess study validity, but they acknowledged that many of the included studies were flawed or poorly described and needed to be interpreted with caution. The reviewers undertook study selection and data extraction in duplicate, which reduced potential for reviewer error and bias. A narrative synthesis was appropriate. Access to the supplementary material improved the transparency of the review process. The available evidence was very limited.

The authors’ conclusions seemed suitably cautious and their recommendation for further more structured research is appropriate.

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

Research: The authors stated that randomised controlled trials were needed to evaluate the benefits of treatments and national and international collaboration to enable an international "joined-up" approach to monitoring and treatment evaluation.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.