Contemporary pharmacologic treatments for spasticity of the upper limb after stroke: a systematic review

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CRD summary
The review concluded that botulinum toxin appeared to be an effective and well-tolerated focal treatment for reducing tonicity in patients with upper limb spasticity after stroke and the results supported guideline recommendations. Small sample sizes in some trials, potential clinical heterogeneity across studies and some methodological problems with the review mean that caution is warranted when interpreting the authors' conclusions.

Authors' objectives
To assess the benefits and adverse effects of contemporary pharmacological treatments for spasticity of the upper limb after stroke.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from January 1995 to July 2010 for articles published in English. Search terms were reported. Reference lists of identified articles were searched.

Study selection
Clinical trials of at least 10 participants that evaluated treatments for upper limb spasticity secondary to stroke in adults were eligible for inclusion. Studies of treatment for both lower and/or upper limb spasticity were included if the results for patients with upper limb spasticity were reported separately. Case reports, case series, cost-effectiveness analyses, meta-analyses, pooled analyses, systematic reviews, commentaries, editorials and abstracts were excluded. Also excluded were studies that involved lower extremity spasticity only, used botulinum toxin (BTX) formulations not commercially available in USA, focused on treatments for spasticity secondary to diseases other than stroke or included a majority of patients whose spasticity was not secondary to stroke.

The included trials primarily studied BTX (onabotulinumtoxinA, abobotulinumtoxinA and rimabotulinumtoxinB). Some studies also considered tizanidine (TZD) or intrathecal baclofen (ITB). Controls were primarily placebo; some studies used an active comparator such as triamcinolone acetonide or TZD. The reported outcomes included muscle tone and/or spasticity as assessed using the Modified Ashworth Scale or the Ashworth Scale and disability, range of motion, pain, quality of life, adverse events and other clinical outcomes.

One reviewer performed study selection. Any uncertainties were resolved by consensus of the review team.

Assessment of study quality
Studies were assigned a level of evidence based on Oxford Centre for Evidence-Based Medicine criteria to grade studies from 1b (randomised controlled trial) to 5 (expert opinion). The ratings took methodological quality into account. No details of the quality of individual studies were reported.

One reviewer performed the assessment of level of evidence. Any uncertainties were resolved by consensus of the review team.

Data extraction
Data were extracted on muscle tone/spasticity, other clinical outcomes, adverse events and quality of life.

One author performed data extraction. Any uncertainties were resolved by consensus among the review team.
Methods of synthesis
A narrative synthesis was presented. Studies were grouped by outcomes. Differences between studies were discussed in the text and were evident from tables.

Results of the review
Fifty-four studies (51 studies of BTX) were included in the review (n=2,411 participants): 23 RCTs and 31 open-label trials, non-randomised trials and observational studies. The level of evidence was variable and studies ranged from level 1b to level 4. Sample sizes ranged from 10 to 333 participants (42 studies had fewer than 50 participants).

Thirty-eight studies reported a significant reduction in spasticity with BTX, either compared with baseline or with placebo (p<0.05). Two studies of ITB reported significant reductions in upper limb spasticity after 12 months of treatment. One study of tizanidine reported significant reductions in upper limb spasticity after 16 weeks of treatment. A head-to-head comparison found a significant reduction in spasticity with BTX injections compared with oral TZD.

The most commonly reported adverse events were general or local weakness, injection-site pain and fatigue with BTX type A and dry mouth with BTX type B. No serious or life-threatening adverse events were reported in any trial of BTX.

Authors’ conclusions
Botulinum toxin appeared to be an effective and well-tolerated focal treatment for reducing tonicity in patients with upper limb spasticity after stroke; the results supported guideline recommendations.

CRD commentary
Inclusion criteria for the review were reasonably clearly defined. Several relevant data sources were searched. There was potential for language bias as only articles in English were included. Publication bias was not assessed and could not be ruled out. Only one reviewer conducted study selection, data extraction and level of evidence assessment, which may have introduced error and bias into the review. Study quality was assessed only in terms of an indicator of bias in conjunction with level of evidence, which made it difficult to assess the reliability of the evidence base. Sample size in most studies was fewer than 50 participants and there appeared to be clinical heterogeneity across studies, which the authors acknowledged.

Data limitations and methodological problems mean that caution is warranted when interpreting the authors’ conclusions.

Implications of the review for practice and research
Practice: The authors stated that the review supported practice guidelines; however, important differences between formulations of BTX must be considered (the latter point did not appear to be derived directly from the review, which did not include studies that compared different formulations).

Research: The authors stated that health-related quality of life and active function should be measured more rigorously to determine whether treatments offered benefits beyond reduction in spasticity. Further head-to-head studies were needed to provide additional information about relative benefits of treatment.

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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.