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Efficacy of pharmacological treatment of dystonia: evidence-based review including meta-analysis of the effect of botulinum toxin and other cure options

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The treatment of both generalized and focal dystonia is symptomatic. There is no evidence-based information about the efficacy of the different methods of the pharmacological therapeutic options currently being applied in dystonia. The specific questions addressed by this study were which treatments for dystonia have proven efficacy and which of them have unproven results. Following evidence-based principles, a literature review based on MEDLINE and the Cochrane Library, augmented by manual search of the most important journals was performed to identify the relevant publications issued between 1973 and 2003. All articles appearing in the professional English literature, including case reports, were considered. In the presence of comparable studies the meta-analysis was performed to obtain pooled information and make a reasonable inference. Based on this review, we conclude: (i) botulinum toxin has obvious benefit (level A, class I–II evidence) for the treatment of cervical dystonia and blepharospasm; (ii) trihexyphenidyl in high dosages is effective for the treatment of segmental and generalized dystonia in young patients (level A, class I–II evidence); (iii) all other methods of pharmacological intervention for generalized or focal dystonia, including botulinum toxin injections, have not been confirmed as being effective according to accepted evidence-based criteria (level U, class IV studies).

Introduction

The prevalence of dystonia is 3.4–29.5 per 100 000 for generalized and focal dystonia (Nutt *et al*., 1988). Amongst the members of the Ashkenazi Jewish community, dystonia occurs approximately five times more often than in the general population (Bressman, 2000). According to The Epidemiological Study of Dystonia in Europe (ESDE) Collaborative group (2000), the crude annual prevalence rate for primary dystonia is 152 per million, with focal dystonia having the highest relative rate at 117 per million. The prevalence rates for the other dystonias were estimated as follows: 57 per million for cervical dystonia, 36 per million for blepharospasm, and 14 per million for writer's cramp. Dystonia is more common than many other neurological diseases, such as Huntington's disease, amyotrophic lateral sclerosis and myasthenia gravis (Marsden and Quinn, 1990). Dystonia can cause significant disability, and the usual therapeutic approach is mainly symptomatic. The possible pharmacological options are oral medications, botulinum toxin injections and intrathecal infusion of baclofen. Thalamotomy, pallidotomy and pallidal deep brain stimulation for dystonia still should to be considered investigational because there are no controlled studies for this indication, the optimal target point is uncertain, and long-term effects are unknown (Krack and Vercueil, 2001; Volkmann and Benecke, 2002). The question what kind of pharmacological treatment is most effective for the treatment of dystonia is undetermined according to evidence-based criteria proposed by the American Academy of Neurology (Table 1). So, the common clinical approach for the treatment of dystonia remains to be 'trial and error' (Adler, 2000).

The criteria outlined in Table 1 were used for the assessment of medical treatment of Parkinson's disease (Miyasaki *et al*., 2002). We believe they can also be applied for the assessment of the treatment of dystonia because of their principle similarity to the commonly used evidence-based classifications used also for the treatment of dystonia (Jost, 2001).

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Methods

The English literature between 1973 and 2003 was studied using MEDLINE and the Cochrane Library

Table 1 Current levels of evidence classification (Miyasaki *et al*., 2002)

Rating of recommendation	Translation of evidence to recommendations	Rating of therapeutic article
A = Established as effective, ineffective or harmful for the given condition in the specified population	Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies	Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: (a) primary outcome(s) is clearly defined; (b) exclusion/inclusion criteria are clearly defined; (c) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; (d) relevant baseline characteristics are presented and substantially equivalent amongst treatment groups or there is appropriate statistical adjustment for differences
B = Probably effective, ineffective or harmful for the given condition in the specified population	Level B rating requires at least one convincing class II study or at least three consistent class III studies	Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets (a)–(d) (above) or an RCT in a representative population that lacks one criteria (a)–(d).
C = Possibly effective, ineffective or harmful for the given condition in the specified population	Level C rating requires at least two convincing and consistent class III studies	Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population where outcome assessment is independent of treatment
U = Data inadequate or conflicting; given current knowledge, treatment efficacy is unproven		Evidence from uncontrolled studies, case series, case reports, or expert opinion.

augmented by manual search of the most important journals, abstracts, seminars and courses of American Academy of Neurology from 1999 to 2002. We included original studies containing documented communications related to pharmacological treatment of primary idiopathic generalized and focal dystonia, including original articles, clinical trials, short reports and case reports. Papers on secondary dystonia as a manifestation of Wilson disease, Huntington's chorea, or tardive dystonia, and hemidystonia as a result of organic brain lesion or known metabolic disorders were excluded. After content analysis of the selected articles, they were rated according to the above-mentioned criteria, and the level of evidence in each was established.

Similar data from various relevant papers were used as primary studies in meta-analysis for obtaining summary information. For the case–control studies log odds ratios were weighted to get a pooled risk difference and its 95% confidence intervals in fixed- and random-effect models. All analyses were conducted with the Review Manager software (version 4.2), recommended by the Cochrane Laboratory for meta-analyses and reviews.

Sixty-nine papers were considered relevant to the aims of this review and their findings were analysed.

Evaluation of the methods of pharmacological treatment of dystonia

Intramuscular injections of botulinum toxin type A

Botulinum toxin is a toxic protein that is produced by the bacterium *Clostridium botulinum*. It blocks the release of acetylcholine in the cholinergic synapse.

Spasmodic torticollis

Six double-blind, placebo-controlled trials, related to the I–II class studies including 158 patients, were encountered. They demonstrate beneficial effect of the botulinum toxin type A (BTX-A) (Botox, 100–280 MU; Allergan Inc., Ontario, Canada) versus the placebo (saline) in repeated injections for a period of 6–16 weeks (Tsui *et al*., 1986; Gelb *et al*., 1989; Blackie and Lees, 1990; Greene *et al*., 1990; Lorentz *et al*., 1991; Moore and Blumhardt, 1991). Subjective response rate has been found better between 66 and 80% as opposed to the placebo in all studies, whereas the degree of objective improvement, appraised according to Tsui scale (Tsui *et al*., 1986) differed from 61 to 74% in five of them. One study, however, revealed lack of

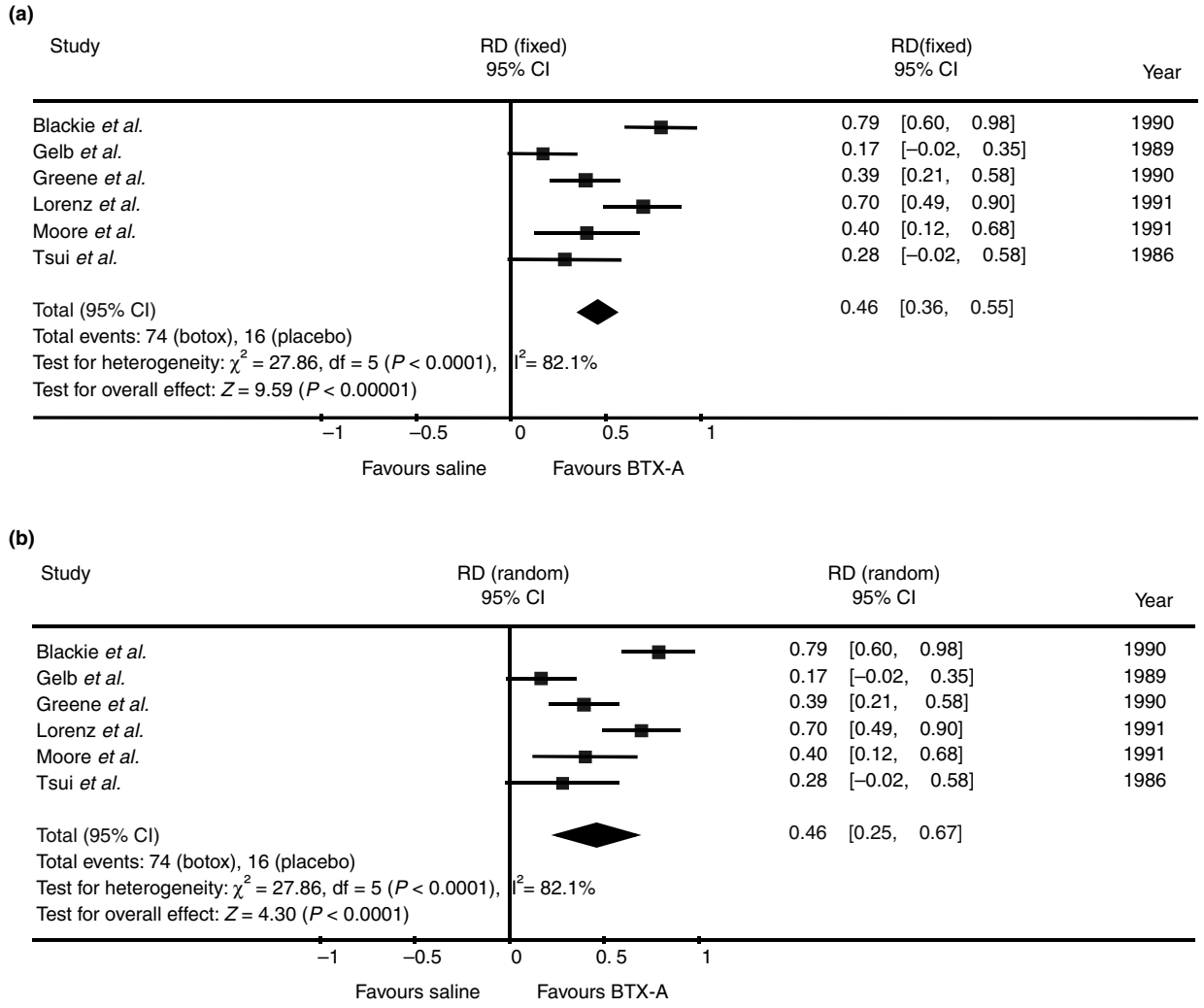

Figure 1 Study-specific and pooled risk differences from case–control studies on BTX-A in patients with spasmodic torticollis: (a) fixed-effect model; (b) random-effect model.

objective improvement comparatively to the placebo in the clinic, although video analysis has demonstrated some improvement (Gelb *et al*., 1989). The most significant side-effect and dose-limiting factor was dysphagia, which was observed up to 36% in one of the above-mentioned investigations (Moore and Blumhardt, 1991). The results of meta-analysis are in Fig. 1a.

Because of lack of homogeneity of results a fixed-effect model is not appropriate for these data and the random-effect model was performed (Fig. 1b).

The above-mentioned meta-analysis shows excellent results sustaining pooled risk difference as 46%, according to both fixed- and random-effect models (Fig. 1a,b) that could definitively confirm positive conclusion for the BTX-A efficacy in patients with torticollis according to selected evidence-based criteria.

Similar results were received in prospective multicentral double-blind placebo-controlled study that was performed in 75 *de novo* patients with rotational torticollis treated by another preparation of BTX-A (Dysport; Ipsen Ltd, Maidenhead, UK) (Poewe *et al*., 1998). The patients were randomly allocated to receive placebo or Dysport in three doses (250, 500 and 1000 MU) for 8 weeks. Objective optimal responses at week 8 (moderate to excellent efficacy with no-moderate adverse effects) were noted by 72% of the 1000 MU group, 44% of the 500 MU and 39% of 250 MU group. Odds ratio showed strong effect size of Dysport for all doses that was statistically significant, only for doses 500 and 1000 MU (Fig. 2).

Subjective improvement was fixed in 79% in the whole group treated by Dysport (Poewe *et al*., 1998). Dysphagia has most serious side-effect in 16 (21.3%) patients treated by Dysport in this study.

Two double-blind studies were devoted to comparison of efficacy of two preparations of BTX-A (Botox

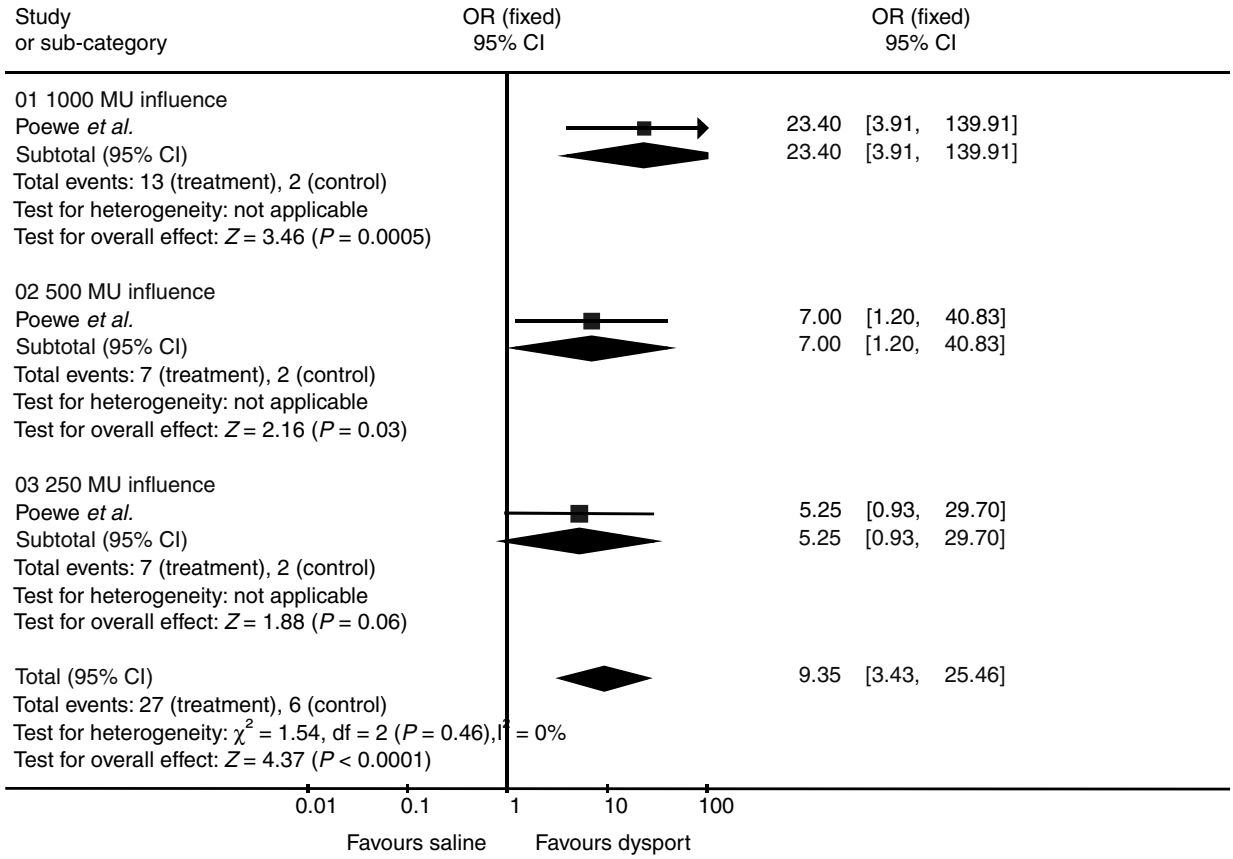

Figure 2 Dose-specific and pooled odds ratio on Dysport influence in patients with spasmodic torticollis (Poewe *et al*., 1998).

and Dysport) for the treatment of spasmodic torticollis (Odergren *et al*., 1998; Ranoux *et al*., 2002). In the first randomized comparative study the patients previously treated with Botox were injected either with usual dose of Botox (35 patients) or equivalent dose of Dysport (38 patients). A ratio of 3 MU of Dysport was assumed to be equivalent to 1 MU of Botox. No differences were revealed in the degree of improvements, assessed according to Tsui scale (Tsui *et al*., 1986) and safety profiles between the two preparations (Odergren *et al*., 1998).

In the second randomized crossover study 54 patients with cervical dystonia also previously successfully treated by Botox were enrolled (Ranoux *et al*., 2002). They were randomly received three treatments: either usually effective dose of Botox or Dysport at the ratios 1:3 or 1:4. The effect was assessed according to Tsui scale (Tsui *et al*., 1986) and Toronto Western Spasmodic Torticollis Scale (TWSTS) (Jancovic and Hallett, 1994). Dysport was shown to be significantly more efficient than Botox for both impairment and pain in cervical dystonia, although with a higher incidence of minor side-effects (dysphagia, dysphonia, asthenia, neck weakness) (Ranoux *et al*., 2002). Both triple and quadriple dose of Dysport have similar medical and side-effect profile without statistically significant differences.

Another botulinum serotype produced by *C. botulinum* – botulinum toxin type B (BTX-B) (NeuroBloc; Elan Pharma International, Shannon, Ireland) was tested in 308 patients with spasmodic torticollis in three multicentre double-blind placebo-controlled trials (Lew *et al*., 1997; Brashear *et al*., 1999; Brin *et al*., 1999). BTX-B has been shown a safe and efficacious agent in the treatment of cervical dystonia in both type A-responsive and A-resistant patients with significant improvement of the TWSTS at the doses 5000 and 10 000 MU. Dysphagia was encountered in 10–28% patients (Lew *et al*., 1997).

The 12-week comparison of the effectiveness of BTX-A (Dysport) performed in two sessions (mean doses 292 and 262 MU) versus trihexyphenidyl (mean dose 16.25 mg/day) in a prospective, randomized, and double-blind design revealed an obvious advantage for BTX-A and with fewer adverse events (Brans *et al*., 1996). Continuation of the BTX treatment as open trial over 12 months has led to maintenance of motor

improvement, stable pain relieve and decrease in disability and social handicap as measured by the TWSTS and the Medical Outcome Study Scale (Stewart *et al.*, 1988; Jancovic and Hallett, 1994). We met no study that assessed the long-term effect of BTX-A in repeated injections in a double-blind placebo-controlled manner.

Assessment: Spasmodic torticollis can be successfully treated by BTX-A and BTX-B within 6–16 weeks. A-level data (treatment established as effective).

Blepharospasm

The positive effect of BTX-A versus saline on blepharospasm was repeatedly confirmed by three double-blind study and one single-blind study (Sampaio *et al.*, 1997) that covered 73 patients in total. A beneficial effect of various degrees lasting more than 2–3 months was observed in all (100%) patients treated by BTX-A (Fahn *et al.*, 1985; Jankovic and Orman, 1987; Park *et al.*, 1993).

Assessment: Blepharospasm can successfully be treated by BTX-A within 2–3 months. A-level data (treatment established as effective).

Oromandibular dystonia

A single placebo-controlled double-blind study was performed. Improvement of oromandibular-cervical dystonia after BTX-A injections was demonstrated in three (37.5%) of eight patients (Jankovic and Orman, 1987).

Assessment: U-level data (treatment efficacy is unproven).

Writer's cramp

The use of BTX-A to treat writer's cramp was assessed in a placebo-controlled manner in two studies. In the study of Yoshimura *et al.* (1992) an objective improvement was seen in five (59%) patients, but this effect was not significant versus placebo, registered in three (38%) patients in video-type analysis. A large degree of interobserver variability was observed.

In the study of Tsui *et al.* (1993) speed and accuracy of pen control in two directions improved in seven of 20 patients with the bias to the patients with the distortion of wrist posture. The above-mentioned meta-analysis shows positive results sustaining pooled risk difference as 31% according to fixed-effect model (Fig. 3) that could confirm positive conclusion for some BTX-A efficacy in patients with writer's cramp.

Assessment: C-level data (possibly effective for the given condition in the specified population).

Laryngeal dystonia

Despite the clinical impression that BTX-A is highly effective for the treatment of laryngeal dystonia in more than 900 patients, no controlled study has been performed to date (Blitzer *et al.*, 1998; Gibbs and Blitzer, 2000).

Assessment: U-level data (treatment is unproven).

Trihexyphenidyl

Anticholinergic drugs block the action of acetylcholine on the central muscarinic receptors. These drugs are administered orally and are commonly used to treat focal, segmental, and generalized dystonias. Trihexyphenidyl is the only anticholinergic agent that was proved effective by a double-blind, randomized, placebo-controlled trial for the symptomatic treatment of segmental and generalized dystonia (mean dose of 30 mg/day) in young patients (mean age 18.9 years, range 9–32) (Burke *et al.*, 1986). The best clinical effect could be achieved if the treatment initiates within the

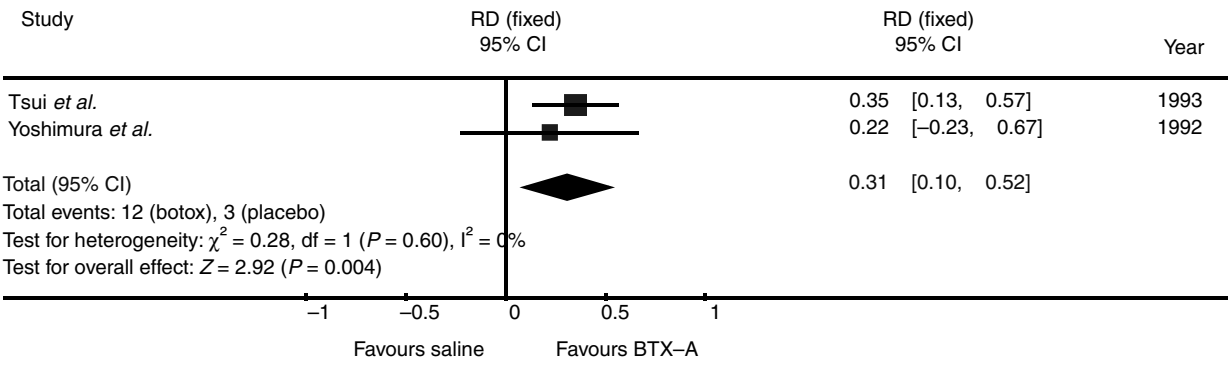

Figure 3 Study-specific and pooled risk differences from case–control studies on BTX-A in patients with writer's cramp. Fixed-effect model.

first 5 years after symptoms onset (Fahn, 1983). This investigation supports numerous observations that had been made previously in open trials and integrates clinical experience for this specific group of patients (Greene *et al*., 1988). Adults do not exhibit the same benefit because of poorer efficacy and/or intolerable adverse effects (Fahn, 1983; Marsden *et al*., 1984).

There is no controlled trial on the effect of trihexyphenidyl in the adult population with generalized dystonia. Nutt *et al*. (1984) had found trihexyphenidyl to be indistinguishable from placebo in eight of nine patients with cranial dystonia in double-blind crossover study.

Assessment: A-level data (treatment established as effective) for young patients with generalized and segmental dystonia. U-level data (treatment is unproven) for cranial dystonia.

Levodopa and dopamine agonists (apomorphine, bromocriptine, lisuride)

Early uncontrolled attempts to treat generalized dystonia with levodopa reached contradictory conclusions. Whilst some studies reported improvement in dystonia (Hongladarom, 1973; Rajput, 1973), others found that levodopa exacerbated dystonia and its natural history (Cooper, 1972). According to a brief questionnaire, the majority of both physicians and patients concluded that levodopa has no influence on generalized dystonia (Eldridge *et al*., 1973). The greatest value of these trials, however, was the discovery of dopa-responsive dystonia (DRD) (Segawa *et al*., 1976). Since then, an empiric trial of levodopa has become indicated in all patients with generalized dystonia to exclude possible DRD cases Nygaard *et al*., 1988). At the same time, for want of a controlled trial for establishing efficacy and dosing of levodopa in DRD, the dramatic effect of levodopa on DRD has not been supported by evidence-based data.

Apomorphine is insufficiently explored for the treatment of dystonia. There are only single case reports about improvement of generalized (Braham and Sarova-Pinhas, 1973; Zuddas *et al*., 1996) and focal dystonia (Tolosa and Lai, 1979; Vidailhet *et al*., 1993). The apomorphine test, however, was suggested for the assessment of dopaminergic sensitivity of dystonic symptoms following the double-blind placebo-controlled study (Langkafel *et al*., 1991; Zuddas *et al*., 1996).

Bromocriptine in high doses (50–80 mg/day) improved both generalized and focal dystonia, but these results were obtained in uncontrolled studies (Lees *et al*., 1976; Stahl and Berger, 1982; Obeso and Luquin, 1984). Lisuride (2–3 mg/day orally), in contrast, has been shown in two randomized placebo-controlled trials as a drug with an 'inconclusive' effect, affording improvement in some patients but having no effect on others (Quinn *et al*., 1985); it was considered as 'a drug of limited use' in focal dystonias (Nutt *et al*., 1985).

Assessment: U-level data (treatment is unproven) for apomorphine and bromocriptine; B-level data (treatment is probably ineffective) for lisuride.

Tetrahydrobiopterin

Tetrahydrobiopterin, as a cofactor for hydroxylation of tyrosine, phenylalanine, and tryptophan, was shown to have a mild to moderate effect in patients with progressive dystonia with diurnal variation in two uncontrolled studies (LeWitt *et al*., 1986; Fink *et al*., 1989).

Assessment: U-level data (treatment is unproven).

Tetrabenazine

Tetrabenazine was shown to be effective in various types of generalized and focal dystonia in a small double-blind crossover study (Jankovic, 1982). These results have been confirmed repeatedly in large open studies and by retrospective data analysis conducted by the same investigators (Jankovic and Orman, 1988; Jankovic and Beach, 1997). They consider this agent to be an effective drug for the treatment of a variety of hyperkineses. Moreover, in some patients, tetrabenazine might be combined with lithium or levodopa, which may help to lessen side effects such as slowed movements and depression (Jankovic and Orman, 1988; Giladi and Melamed, 1999).

Assessment: U-level data (treatment is unproven).

D-2 dopamine antagonists

Dopamine-blocking agents have been used to treat some patients with dystonia (Marsden *et al*., 1984; Marsden and Quinn, 1990). The possible positive effect of these agents is paradoxical as dopamine blockers may cause both acute dystonic reactions, mostly in young patients, and the tardive dystonia (Jimenez-Jimenez *et al*., 1997; Raja, 1998; Rodnitzky, 2003). Dramatic improvement of motor functions during the treatment of psychosis by oral perphenazine (8–12 mg/day) were observed in a case report presenting one patient with generalized dystonia (Harel and Giladi, 1990).

Five patients with generalized dystonia responded to intravenous infusion of tiapride, a selective D-2 dopamine antagonist, in an open trial (Arlazoroff *et al*., 1991). Two open trials with clozapine (12.5–300 mg/day) failed to establish any improvement in spasmodic torticollis (Thiel *et al*., 1994; Burbaud *et al*., 1998).

Another neuroleptic agent, risperidone (1.5–3 mg/day), however, decreased both duration and amplitude of involuntary movements in segmental and generalized dystonia in two uncontrolled studies (Zuddas and Cianchetti, 1996; Grassi *et al*., 2000).

Assessment: U-level data (evidence from uncontrolled studies).

Oral Baclofen

Baclofen, a pre-synaptic GABA agonist, was reported as being effective for the treatment of dystonia in two retrospective studies conducted by the same group (Greene and Fahn, 1992b; Greene, 1992a). Dramatic improvement in symptoms, especially in gait, was found in about 30% of 31 children and adolescents with idiopathic primary dystonia when given at doses ranging from 40 to 180 mg daily. In patients with DYT1 dystonia baclofen therapy improved leg dystonia and gait in 14 of 33 children in dosage over 50 mg daily, and in nine of them have had stable and prolonged benefit (Anca *et al*., 2003). The response to baclofen of adults with focal dystonia was less impressive. One series of 60 adults with cranial dystonia found sustained benefit in 18%. A smaller series did not find significant benefit in adults with focal dystonias (Greene, 1992a).

Assessment: U-level data (evidence from uncontrolled studies).

Intrathecal baclofen injection

According to a number of uncontrolled studies (Narayan *et al*., 1991; Penn *et al*., 1995; Albright *et al*., 1996; Ford *et al*., 1996; Paret *et al*., 1996; Hou *et al*., 2001; Jaffe and Nienstedt, 2001) intrathecal baclofen (ITB) has been successfully used to treat dystonia. In a retrospective study with blinded rating of the effect of ITB, however, nine of 14 patients had no objective clinical benefit and three of them felt only subjective improvement (Walker *et al*., 2000).

In clinimetric placebo-controlled study, Van Hilten *et al*. (1999) stressed the importance and significance of a placebo effect when using ITB, which may continue up to 2 days after a number of placebo bolus injections. Only four (50%) patients in this small study had a significant proven effect of ITB and they received pump implantation.

Assessment: U-level data (data inadequate or conflicting).

Benzodiazepines

Benzodiazepines are commonly used to treat dystonia, but no controlled trial has been performed to evaluate this therapeutic approach. There are several open studies in which improvement of blepharospasm and dystonic choreoathetosis was demonstrated with clonazepam treatment (Jankovic and Ford, 1983; Hughes *et al*., 1991). Intravenous diazepam (5–10 mg) was reported as being effective for the treatment of spasmodic torticollis (Ahmad and Meeran, 1979). Improvement in spasmodic torticollis was, however, also seen following withdrawal from high doses of lorazepam in patients who initially experienced improvement of the torticollis with lorazepam that later ceased being effective (Lal, 1989).

Assessment: U-level data (treatment is unproven).

Mexiletine

In an open-label case study, both intravenous and oral lidocaine (mexiletine) 450–1200 mg/day led to clinical improvement, confirmed by video and EMG examinations, in nine patients who had had spasmodic torticollis for 6 months and more (Ohara *et al*., 1998). These data were later confirmed by a 6-week open trial with tapering of oral mexiletine up to 800 mg/day. A significant improvement was observed in the rating scale for dystonia and in blindly performed videotape ratings (Lucetti *et al*., 2000).

Assessment: U-level data (treatment is unproven).

Riluzole

The effect of riluzole was assessed by only one 6-week open-label study without placebo, but it did have a controlled arm of six patients with cervical dystonia unresponsive to BTX-A and oral treatment (trihexyphenidyl, tetrabenazine, sulpiride, tiapride) (Muller *et al*., 2002). Three patients improved by more than 30% according to the Tsui scale (Tsui *et al*., 1986).

The authors suggested that riluzole might be helpful in patients with spasmodic torticollis refractory to other therapies (Muller *et al*., 2002).

Assessment: U-level data (treatment is unproven).

Lithium

There are isolated reports about successful treatment of spasmodic torticollis and of generalized dystonia with 1200–1500 mg lithium salts (Couper-Smartt, 1973; Marti-Masso *et al*., 1982). These early results were not confirmed by a double-blind, placebo-controlled study on six patients (two with torticollis, two with Meige syndrome, one with generalized dystonia and one with tardive dystonia). No statistically significant differences were found from baseline values for either placebo or lithium therapy (Koller and Biary, 1983).

Assessment: U-level data (data inadequate or conflicting).

Carbamazepine

Early attempts to treat torsion dystonia with carbamazepine in an open trial reported mild to moderate improvement in three of the 16 patients (18.75%) who were treated (Isgreen *et al*., 1976). In another uncontrolled open study, three patients with probable autosomal dominant form of generalized dystonia were successively treated with 400–800 mg/day (Garg, 1982).

Assessment: U-level data (data inadequate or conflicting).

Alcohol

In a single open study focused upon applying alcohol for the treatment of dystonias, an intravenous infusion of 250-ml 10% ethanol improved the symptoms of spasmodic torticollis in five of seven patients, but had no effect on generalized dystonia, Meige syndrome, or tardive dystonia (Biary and Koller, 1985).

Assessment: U-level data (treatment is unproven).

Nabilone

In a double-blind, randomized placebo-controlled crossover study, nabilone, a synthetic cannabinoid receptors agonist, was ineffective in reducing dystonia in 15 patients with generalized and segmental primary dystonia (Fox *et al*., 2002).

Assessment: U-level data (only one prospective matched group cohort study, class II).

Conclusions

According to selected evidence-based criteria and power analysis we determined that all preparations of botulinum toxin has obvious benefit for the treatment of cervical dystonia and blepharospasm. Trihexyphenidyl in high dosages is effective for the treatment of segmental and generalized dystonia in children and in patients younger than 30 years.

However, all other methods of pharmacological intervention for generalized or focal dystonia, including botulinum toxin therapy for another types of dystonia have not been confirmed as being effective.

This survey of literature had led us to conclude that more lines of investigation into the use of new pharmaceuticals and of heretofore-unexplored surgical approaches to patient management in dystonia are warranted.

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