Oral Medications for Treatment of Blepharospasm and other Cranial Dystonias

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Given the marked benefit of botulinum injections, the use of oral medications for the treatment of blepharospasm and other cranial dystonias has garnered little interest from clinical researchers over the past 15 years. For example, at the most recent International Congress of Parkinson's Disease and Movement Disorders Meeting in Chicago, not one of the 5 research abstracts on blepharospasm dealt with the subject of oral pharmacotherapy. Among 46 additional abstracts related to the treatment of dystonia, only 2 were focused on oral medications: (1) a small study of dronabinol for cervical dystonia did not generate optimistic results and (2) the other abstract described positive effects of trihexyphenidyl on dystonic posturing in two girls with Rett syndrome. The vast majority of "Dystonia: Treatment" abstracts presented information on deep brain stimulation (DBS) and botulinum toxins. At the present time, many intractable cases of craniocervical dystonia (typically a consequence of immuno-resistance to botulinum toxins) are being treated with DBS without consideration of oral pharmacotherapy.

Most pharmacological treatments for neurological and other medical disorders can be characterized as symptomatic. However, there is growing interest in developing medications to prevent disease onset and slow disease progression. For example, Teva Pharmaceutical Industries has recently released data showing that the monoamine oxidase inhibitor rasagiline slows down the rate of disease progression in Parkinson's disease. At present, there is no data to suggest that rasagiline or any other currently-available prescription medication will slow down the progression of blepharospasm. This is an issue worthy of study since over 50% of patients who develop dystonia of the eyelid closing musculature (i.e., blepharospasm) will exhibit spread to the lower face, jaw musculature, or neck within 5 years of disease onset.

Most published studies of oral medications for treatment of blepharospasm and other cranial dystonias are compromised by small sample sizes (too few patients), heterogeneous populations (mixtures of age-of-onset, distribution and etiology) and otherwise faulty experimental designs. By current standards, proof that a particular drug is effective for a specific medical condition demands two independent, randomized, multicenter, double-blind, placebo-controlled studies. Clearly, NO study of blepharospasm or other adult-onset focal/segmental dystonia has approached these criteria. "Modern" clinical practice as it pertains to oral medications for blepharospasm and other cranial dystonias has been driven by treatments developed for other movement and neurological disorders, small published clinical series, textbook chapters written by dystonia experts, and empiricism.

Most of the oral medications used to treat blepharospasm and other cranial dystonias are listed in Table 1. Evaluating the effects of medications in individual patients must be tempered by consideration of drug-drug interactions, drug dosage, etiology of blepharospasm (primary versus secondary), the occurrence of spontaneous remissions, and duration of treatment. Moreover, it is likely that blepharospasm is biologically/genetically heterogeneous. Consequently, what works for one patient may not work for another! Overall, however, a significant fraction of patients with blepharospasm and/or other forms of cranial dystonia will benefit from trihexyphenidyl, clonazepam, or baclofen.

The drugs presented in Table 1 are divided into major classes based on mechanism of action. In general, drugs that work on the nervous system must be started at low dosages and incremented slowly. Similarly, none of these medications should be discontinued abruptly. If ineffective after an adequate test period, these and most other medications for neurological conditions should be slowly tapered.

Table 1. Oral Medications for Blepharospasm and Other Cranial Dystonias*

CLASS	GENERIC (BRAND) NAMES	MECHANISM(S) OF ACTION	POSSIBLE SIDE EFFECTS
Anticholinergic	trihexyphenidyl (ARTANE), benztropine (COGENTIN)	block acetylcholine receptors	dry mouth, constipation, blurred vision, mild memory impairment
Benzodiazepine	clonazepam (KLONOPIN), lorazepam (ATIVAN), diazepam (VALIUM)	potentiate the effects of GABA on $GABA_A$ receptors	drowsiness, disequilibrium
$GABA_B$ Receptor Agonist	baclofen (LIORESAL)	stimulates $GABA_B$ receptors	drowsiness, disequilibrium, weakness
Dopamine Receptor Agonist	bromocriptine (PARLODEL)	stimulates D_2 dopamine receptors, 5-HT_2 antagonist	nausea, lightheadness, drowsiness
Neuroleptic	pimozide (ORAP) haloperidol (HALDOL)	blocks dopamine receptors ($D_2 > D_3 > D_1$ & D_4)	tardive dyskinesias**
Monoamine Depleter	tetrabenazine (NITOMAN)	inhibits monoamine transporters in the brain	depression, drowsiness, Parkinsonism
Anticonvulsant	levetiracetam (KEPPRA)	binds to the synaptic vesicle protein SV2A	irritability, headaches
Imidazopyridine	zolpidem (AMBIEN)	binds to the benzodiazepine receptor 1	drowsiness, dizziness, headache
Atypical Antipsychotic	clozapine (CLOZARIL)	blocks dopamine receptors ($D_4 >> D_1$, D_2, D_3, & D_5, partial 5-HT_{1A} agonist, cholinergic and histaminergic antagonist	constipation, sedation, agranulocytosis
Serotonin Receptor Antagonist	cyproheptadine (PERIACTIN)	5-HT_2 antagonist, antihistaminic	drowsiness, nausea
Antiarrhythmic Agent	mexiletine (MEXITIL)	inhibits inward sodium currents	nausea, dizziness, tremor

*None of these medications are FDA approved treatments for blepharospasm

**Tardive dyskinesias may be a permanent side effect

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[Discusses use of **tetrabenazine** and **pimozide**]

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