Pathophysiology and Pharmacotherapy of Spasmodic Torticollis: A Review

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SUMMARY: The few existing neuropa-thological, neurochemical, and neurophar-macological studies have shed little light on the pathophysiology of spasmodic torticollis (ST). The relevance of experimen-tal ST in animals and drug-induced ST in man to idiopathic ST is unclear. Most pharmacotherapeutic endeavors have focused on drugs affecting basal ganglia function. Unfortunately, problems of sample size, clinical heterogeneity of patient population, research design, objective evaluation of response, documentation of key data, and adequacy of duration of follow-up make interpretation of published results difficult. Because of the heteroge-neity of ST, investigations aimed at esta-blishing a neurotransmitter profile for each patient by observing the acute response to a test dose of drugs affecting cholinergic, dopaminergic, serotonergic, and gamma-aminobutyric acid systems may provide a more rational basis to the selection of treatment.

RÉSUMÉ: Les rares études neuro-pathologiques, neurochimiques et neuro-pharmacologiques connues ne jetent que peu de lumière sur la physiopathologie du torticollis spasmodique (ST). La corres-pondance entre le ST expérimental chez l'animal, le ST induit par des médicaments, et le ST idiopathique humain est encore inconnue.

La majorité des essais pharmacothera-peutiques se sont concentrés sur les médi-caments agissant sur les fonctions des noyaux gris centraux. Plusieurs problèmes rendent l'interprétation des résultats pu-bliés aléatoire: grandeur de l'échantillon-nage, hétérogénéité clinique des popula-tions, plans de recherches, évaluation ob-jective des réponses, documentation de données-clé, perinence de la durée d'observation. À cause de l'hétérogénéité du ST, nous croyons qu'une batterie de tests qui aurait pour but d'évaluer, chez chaque patient, la réponse à des doses-essai de divers médicaments choli-nergiques, dopaminergiques, sérotoniner-giques et GABAergiques, offrirait une base plus valable pour la sélection du traite-ment approprié.

INTRODUCTION

"Spasmodic torticollis is an involuntary hyperkinesis manifesting itself by mobile, tonic or clonic spasms of the neck musculature, and producing a more or less stereotyped deviation of the head into an abnormal position, the chin being rotated to one side or the head bent directly forward (ante-collis) or backward (retrocollis)" (Pat-terson and Little, 1943). The etiology and site of a presumed central nervous system (CNS) lesion is unknown. Most pharmacotherapeutic endeavors have focused on drugs that affect basal ganglia function. Unlike Parkinson’s dis-ease and Huntington’s chorea where anatomical, chemical, and pharmaco-logical information may provide a ra-tional basis for therapy, such an under-pinning of knowledge in spasmodic torticollis (ST) is lacking. Drug treat-ment is both advanced and discounted yet published results are few, contra-dictory, poorly controlled, and often inadequately documented.

The present paper discusses the pathophysiology of ST and reviews in detail the available literature on the pharmacotherapy of this disorder.

PATHOPHYSIOLOGY OF ST

1. Neuroanatomical findings

Psychological factors play a doub-tful role in the etiology of ST (Marsden, 1976; Mathews et al., 1978; Cockburn, 1971; Chopy-Jacolin et al., 1977). On the other hand, demonstration of a consistent pathological lesion remains elusive. Necropsy studies have been few. Lesions in the striatum, amongst other sites, have been described in three autopsied brains (Grinker and Walker, 1933; Foerster, 1933; Alpers and Drayer, 1937) as well as in two cases in which ST was part of a genera-
Spasmodic Torticollis

2. Experimental ST

Collis (Crossman and Sambrook, 1978) which affect ascending noradrenergic lesions in the pontine tegmentum, towards the side of the lesion, but collis with deviation of the head (Foltz et al., 1969; Carpenter, 1956; Hassler and Dieckman, 1970) found significant differences in cerebral hemispheric size on pneumoencephalography in 85% of cases. They speculated that these radiological findings indicated early brain damage which destroyed parts of the putamen (or projections to the putamen) which exert an inhibitory effect on contraversive head movements. This inhibitory action may become ineffective and ST become manifest. Unfortunately, the incidence of hemispheric asymmetry in subjects without ST was not given.

3. Biochemical studies in ST

The absence of anatomical changes does not exclude a biochemical lesion. A few investigations have focused on neuro-transmitter metabolism. Curzon (1973) found a normal mean concentration of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid in lumbar cerebrospinal fluid (CSF) of 9 patients, whereas in a single case reported by Johansson and Roos (1974) there was a lowered value of both acids. In ventricular CSF from 4 patients with ST and 2 with dystonia musculorum deformans, HVA concentrations were intermediate between non-neurological controls and Parkinsonian patients (Papeschi et al., 1972).

4. Endocrinological findings in ST

ST may develop as a consequence of hyperthyroidism and resolve with treatment of the endocrine dysfunction (Gilbert, 1972a). Thyroxine increases catecholamine receptor sensitivity, but whether such a mechanism accounts for the precipitation of ST in a predisposed individual remains conjectural. In a single case of ST, apomorphine, a DA receptor agonist, failed to increase growth hormone secretion (Brown et al., 1973). The significance of this isolated finding is unclear.

5. Neuropharmacological studies in experimental ST

Neurotransmitter dysfunction has been investigated in experimental ST, but results do not lend themselves to ready conclusions. Based on experiments in the monkey (Macaca mulatta), in which ST was produced by electrolytic lesions in the mesencephalic tegmentum, Foltz et al. (1959) postulated that a denervation hypersensitivity of acetylcholine neurons which control postural movements of the head and neck was important in the genesis of ST. However, anticholinergic agents failed to improve the experimental disorder. Anticholinergics, L-dopa, piribedil (indirectly acting DA receptor agonists), and apomorphine were ineffective in improving ST induced by ventromedial mesencephalic tegmental lesions in the African green monkey (Battista et al., 1976). Worsening of symptoms with these agents was not described. On the other hand, the DA receptor blockers haloperidol or pipomoide, the catecholamine synthesis inhibitor, alpha-methyl-para-tyrosine, as well as cholinergic agents and drugs that enhance gamma-aminobutyric acid (GABA) function improved ST.

In the marmoset, in which the ascending DA fibers projecting from the mesencephalic tegmentum to the ipsilateral striatum were lesioned with 6-hydroxy-DA, amphetamine, an indirectly acting DA receptor agonist, worsened ST. Low doses of apomorphine, which may inhibit DA neurotransmission (in contrast to large doses, Tolosa, 1978), alleviated the experimental condition. High doses of apomorphine reversed the direction of ST (Crossman and Sambrook, 1978).

In the mid-brain lesioned cat the 5HT precursor, 5-hydroxytryptophan, worsened ST and L-dopa had no effect (Mori et al., 1975).

6. Drug-induced ST in man

Neuroleptics (Ayd, 1961) as well as the benzamide derivative, metoclopramide (Casteels-van Daele et al., 1970) block DA receptors and induce a variety of dystonic reactions including ST in the early stages of treatment. Clinically, acute drug-induced ST is predominantly tonic in nature. Swett (1975) reported torticollis occurring in 35 out of 1152 patients receiving neuroleptics. In 20 cases of acute phenothiazine toxicity in childhood, four had torticollis (Gupta and Lovejoy, 1967). These dystonic reactions responded rapidly to anticholinergic agents (DiMascio et al., 1976), antihistamines (Gupta and Lovejoy, 1967; Cotton and Newman, 1966), which are also potent anticholinergic agents, as well as to the indirectly acting DA receptor agonists, amantadine (DiMascio et al., 1976) and methylphenidate (Fann, 1966).

ST may also develop as an isolated complication of chronic neuroleptic therapy (Chateau et al., 1966; Harenko, 1967) and can be considered as a form of tardive dyskinesia. However, whether chronic neuroleptic-induced ST pharmacologically resembles the more commonly studied oral form of tardive dyskinesia [i.e. worsening with anticholinergics and DA activating agents, but improvement with cholinergics and drugs that impair DA function (Marsden et al., 1976)] which is the opposite of acute neuroleptic-induced ST, has not been well studied.
In a single case, doses of neuroleptic sufficient to induce Parkinsonism eliminated chronic neuroleptic-induced ST (Chateau et al., 1966). “Parkinsonism medication” was ineffective in 6 patients with retrocollis associated with chronic neuroleptic use (Harenko, 1967).

In addition to chronic neuroleptic treatment which is believed to induce striatal DA super-sensitivity (Marsden et al., 1975), chronic treatment with L-dopa, in Parkinsonian patients at least, may also induce ST (Barbeau et al., 1971; Sigwald and Raymondeaud, 1970). This may suggest that enhanced DA function induces ST. However, improvement of acute neuroleptic-induced ST with drugs that enhance DA function points to the complexity of relating drug-induced ST to idiopathic ST. Nevertheless, drug-induced dystonic reactions resemble spontaneously occurring movement disorders (Marsden et al., 1976; Ayd, 1961) so that it is difficult to believe that they are entirely without relevance to the pathophysiology of idiopathic dystonias, including ST.

7. Neuropharmacological studies in idiopathic ST

Few data are available on the effect of test doses of drugs on ST. Hirschmann and Mayer (1964) in an open study found that L-dopa (25 mg iv) improved all 6 patients with ST including one subject who had associated truncal dystonia. Surprisingly, the beneficial effects lasted up to three days. Tolosa (1978), in a predominantly uncontrolled investigation, noted transient improvement (45-60 mins) in 2 out of 7 patients following apomorphine (1-3 mg sc). In a placebo-controlled observation with film recording in one patient and uncontrolled observations in another, amphetamine (30 mg im) induced improvement within 30 mins on several different occasions which lasted 18-24 hrs. (Myerson and Loman, 1942). These three reports suggest that in some patients DA function is impaired.

Improvement has also been noted after diazepam (5 mg iv), which enhances GABA function, but not the antihistamine, diphenhydramine (50 mg iv), (Bianchine and Bianchine, 1971). Unfortunately, the diagnosis in this single case report remains in doubt. Meprobamate administered over two days in combination with behavior therapy has resulted in amelioration in one patient (Turner et al., 1974), but improvement continued with behavior therapy alone.

PHARMACOTHERAPY OF IDIOPATHIC ST

1. General Comments

Table 1 summarizes the findings of 42 drug treatment trials reported in 33 papers published between 1937-1978 involving approximately 148 individuals. It would appear that 64 of the patients derived clinically significant improvement with drug therapy. Unfortunately, the data are limited in many respects and problems of interpretation are many.

(i) sample size

ST is a relatively uncommon disorder, though basic data on the incidence and prevalence are unknown. Of 42 drug treatment trials, 17 described results in only 1 or 2 patients, 16 in 5 or more and of the latter only 5 reported on series of 10 or more subjects.

(ii) clinical heterogeneity

In a variable number of patients with ST there is a family history of essential tremor, coexisting signs of essential tremor, facial spasms and tics, extranuchal dystonic features, and Parkinsonian symptoms (Patterson and Little, 1943; Couch, 1976b; Marsden, 1976; Critchley, 1939). In others there is a history of encephalitis (Patterson and Little, 1943) or the ST is a manifestation of idiopathic torsion dystonia (Marsden, 1976). In addition, abnormal CSF protein patterns are found in some patients but not in others (Kjellin and Stbler, 1975). Studies on ST include a mixture of patients from this broad clinical spectrum. How far this heterogeneity reflects different etiologies of ST or accounts for dramatic responses to pharmacotherapy in some patients but lack of response in others is unknown. Also, how far the inclusion of post-thalamotomy cases influences outcome to drug treatment is uncertain. In many reports little or no clinical data are given (Table 1).

(iii) research design

Evaluation of treatment should take into account the natural history of the disorder. Meares (1971), in a retrospective study, observed 4 remissions lasting 18 mos - 29 yrs in 24 unoperated patients during the first year of the disorder and Mathews et al. (1978) reported complete or substantial remission in 5 out of 30 patients in the first year of illness. Beyond a year of the disorder, spontaneous remissions are still possible (Meares, 1971; Mathews et al., 1978). In addition, fluctuations in intensity of the symptoms may vary from day to day or hour to hour. Also, the involuntary movements are sensitive to stress as well as to a variety of sensory stimuli (Podvinsky, 1969; Herz and Glazer, 1949). Hence, in the absence of control procedures, interpretation of results is difficult. Of 42 drug treatment reports in Table 1, only 2 have utilized a double-blind placebo-controlled technique (West, 1977; Couch, 1976a). In both, a cross-over design was used. In a further 6 reports, placebo substitution was used but not systematically in all individuals. In 2 other reports, the design involved placebo substitution but only if improvement occurred. In an additional 8 reports, the effect of dose reduction or drug discontinuation was described but not in all subjects. The study of Couch (1976a) is the only one which provides a statistical analysis of results.

Only in exceptional cases are treatment observations beyond 3 mos described. In only 7 patients has this extended to 1 year or more and of these in only 2 subjects was the effect of drug discontinuation, dose reduction, or placebo substitution reported.

(iv) objective evaluation of improvement

Objective assessment of severity of ST is difficult and evaluation is usually limited to clinical impression. Collateral information is sometimes sought (West, 1977). Couch (1976a) used a clinical rating scale of frequency and severity of symptoms and Tolosa (1978) recorded the duration of keeping the head vertical. Film has been used in a few studies but only Swash et al. (1972) and Turner et al. (1974) described the method or process of evaluation. Filming permits
TABLE 1.
Pharmacotherapy of Spasmodic Torticollis (ST)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>N</th>
<th>Results</th>
<th>OBS</th>
<th>Comments</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Anti-cholinergics</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Scopolamine</td>
<td></td>
<td>1</td>
<td>Appreciable</td>
<td>?</td>
<td>Post-encephalitic parkinsonism</td>
<td>Urechia &amp; Retezaneau, 1937</td>
</tr>
<tr>
<td>Scopolamine (+ Sodium Iodide)</td>
<td></td>
<td>17</td>
<td>None-slight</td>
<td>?</td>
<td></td>
<td>Patterson &amp; Little, 1943</td>
</tr>
<tr>
<td>Atropine</td>
<td></td>
<td>1</td>
<td>Favorable</td>
<td>5-6 mo</td>
<td>Duration ST few dy; only partial</td>
<td>Krebs, 1939.</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Var</td>
<td>5</td>
<td>Sustained</td>
<td>1 yr</td>
<td>Duration ST 4 mo; effect of</td>
<td>Foltz et al., 1959.</td>
</tr>
<tr>
<td>(CT-237, P-189 Cyclrimine;</td>
<td></td>
<td></td>
<td>improvement</td>
<td></td>
<td>stopping drug not reported</td>
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<tr>
<td>Scopolamine)</td>
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<tr>
<td>Trihexyphenidyl</td>
<td></td>
<td>1</td>
<td>Remitted</td>
<td>6 mo</td>
<td>Remission for 10 yr without</td>
<td>Barrett et al; 1970</td>
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<td></td>
<td>drugs; recurrence refractory</td>
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<td><strong>2. Cholinergics</strong></td>
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<tr>
<td>Deanol</td>
<td>450-900</td>
<td>1</td>
<td>No effect</td>
<td>2 wk</td>
<td></td>
<td>Laterre &amp; Fortemps, 1975</td>
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<td><strong>3. Anti-dopaminergics</strong></td>
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<tr>
<td>Haloperidol (and/or amantadine)</td>
<td>1.5-14</td>
<td>9</td>
<td>7 good or</td>
<td>3 wk-2 yr; &lt;3 mo in 3</td>
<td>In 2 duration of ST ≤6 mo; 2 responded to amantadine alone</td>
<td>Gilbert, 1971, 1972a, 1972b, 1972c</td>
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<td></td>
<td></td>
<td></td>
<td>excellent</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>2 no effect</td>
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<tr>
<td>Haloperidol (+ Trihexyphenidyl)</td>
<td>9-30</td>
<td>4</td>
<td>2 recovered</td>
<td>?</td>
<td>All familial ST; also on biofeedback</td>
<td>Gilbert 1977a</td>
</tr>
<tr>
<td></td>
<td>± Amantadine</td>
<td>2</td>
<td>markedly</td>
<td></td>
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<tr>
<td></td>
<td>± Diazepam</td>
<td></td>
<td>improved</td>
<td></td>
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<tr>
<td>Haloperidol</td>
<td>3</td>
<td>5</td>
<td>No effect</td>
<td>Few wk</td>
<td>Amantadine failures</td>
<td>Bigwood, 1972a</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6</td>
<td>1 dramatic</td>
<td>5 mo</td>
<td>Improvement maintained on stopping</td>
<td>Shaw et al., 1972</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>improvement</td>
<td></td>
<td>drug; worsened on L-dopa.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>5 no effect</td>
<td>?</td>
<td>All L-dopa failures</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>7</td>
<td>16</td>
<td>8 improved</td>
<td>4 wk</td>
<td>Double-blind cross-over; planned</td>
<td>Couch, 1976a</td>
</tr>
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<td></td>
<td></td>
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<td>50% +; 6</td>
<td></td>
<td>randomization of treatment</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>improved 25-50%</td>
<td></td>
<td>sequence; assessment by rating</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>2 no change</td>
<td></td>
<td>scale</td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>450</td>
<td>3</td>
<td>All improved</td>
<td>Few wk</td>
<td>1 ? postencephalitic, with</td>
<td>Sigwald et al., 1959</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 yr</td>
<td>retrocollis</td>
<td></td>
</tr>
<tr>
<td>Thioproperazine</td>
<td>200</td>
<td>2</td>
<td>Both improved</td>
<td>Few wk</td>
<td>Single blind placebo substitution</td>
<td>Sigwald et al., 1959</td>
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<td>in l</td>
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<tr>
<td>Perphenazine</td>
<td>92-108</td>
<td>2</td>
<td>1 improved</td>
<td>Few wk</td>
<td>Retrocollis; torsion dystonia;</td>
<td>Blom &amp; Ekbom, 1961</td>
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<td></td>
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<td></td>
<td></td>
<td>relapse on dose decrease.</td>
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<td>Reserpine 4.5 mg/dy; duration</td>
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<td></td>
<td></td>
<td></td>
<td>ST 6 mo</td>
<td></td>
</tr>
<tr>
<td>Pimozide</td>
<td></td>
<td>2</td>
<td>1 no effect</td>
<td>?</td>
<td>Siblings; 1 post-thalotomy with</td>
<td>Korein, 1977</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>transient</td>
<td></td>
<td>segmental dystonia</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>improvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiapride</td>
<td>200-500</td>
<td>4</td>
<td>No effect</td>
<td>?</td>
<td></td>
<td>Emile et al., 1977</td>
</tr>
<tr>
<td>Treatment</td>
<td>Dose</td>
<td>N</td>
<td>Results</td>
<td>OBS</td>
<td>Comments</td>
<td>Authors</td>
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</tr>
<tr>
<td>Tiapride</td>
<td>400</td>
<td>4^2</td>
<td>1 good results</td>
<td>2 mo</td>
<td></td>
<td>Trillet et al., 1977^8</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>400</td>
<td>1^2</td>
<td>no effect</td>
<td>&lt;15 dy-3 mo</td>
<td>2 neuroleptic treatment failures</td>
<td>Trillet et al., 1977^8</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>75-200</td>
<td>3</td>
<td>1 improved</td>
<td>4 wk</td>
<td>'intractable' ST; duration ?; blind film rating</td>
<td>Swash et al., 1972</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>150</td>
<td>9^2</td>
<td>1 transient improvement</td>
<td>?</td>
<td>All L-dopa failures</td>
<td>Shaw et al., 1972</td>
</tr>
<tr>
<td>Reserpine</td>
<td>3-6</td>
<td>2^2</td>
<td>No effect</td>
<td>27-30 dy</td>
<td>Placebo substitution and filming in responders</td>
<td>Markham et al., 1963^8</td>
</tr>
<tr>
<td>Alpha-Methyl-dopa</td>
<td>1050</td>
<td>3^2</td>
<td>No effect</td>
<td>17-28 dy</td>
<td>as above</td>
<td>Markham et al., 1963^8</td>
</tr>
</tbody>
</table>

### 4. Dopaminergics

- **Amphetamine (+ Scopolamine)**
  - Dose: 60-120
  - N: 2
  - Results: Both marked improvement
  - OBS: 5 mo
  - Comments: Duration ST 1 mo; relapse on stopping drug. Both improved with test dose amphetamine
  - Authors: Myerson & Loman, 1942

- **Amphetamine (+ Scopolamine) (+ Nicotinic Acid)**
  - Dose: 35
  - N: 1
  - Results: Marked improvement
  - OBS: ?
  - Authors: Fabing 1954

- **Pipradol**
  - Dose: 300
  - N: 5^3
  - Results: No effect
  - OBS: 7-10 dy
  - Comments: Haloperidol failures
  - Authors: Bigwood, 1972^8

- **Amantadine**
  - Dose: 200
  - N: 9^3
  - Results: 1 transient improvement, 2 worsened
  - OBS: 6 no effect
  - Authors: Shaw et al., 1972

- **Amantadine (+ Haloperidol 6mg/dy)**
  - Dose: 300
  - N: 3^3
  - Results: No benefit
  - OBS: Few wk
  - Authors: West, 1977

- **L-Dopa**
  - Dose: 6-8.5G
  - N: 3^3
  - Results: No effect
  - OBS: 1-6 mo
  - Comments: Open or single blind placebo substitution; film assessment. 2 thalamotomy failures
  - Authors: Barrett et al., 1970

- **L-Dopa**
  - Dose: Max^2
  - N: 17^3
  - Results: 1 sustained improvement
  - OBS: 2 yr
  - Comments: Retrocollis
  - Authors: Shaw et al., 1972

- **L-Dopa**
  - Dose: 7.5-8G
  - N: 6
  - Results: 1 improved but became intolerant of L-dopa
  - OBS: >4 mo
  - Comments: Instrumental measurement of head rotation and tremor.
  - Authors: Ansari et al., 1972
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose(^1)</th>
<th>(N)(^4)</th>
<th>Results</th>
<th>OBS(^5)</th>
<th>Comments</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>15-80</td>
<td>10</td>
<td>1 marked improvement</td>
<td>&gt;2 mo</td>
<td>Retrocollis. Prior response to L-dopa. Single blind placebo substitution. Improved with haloperidol (4.5 mg/day) - uncontrolled Placebo substitution.</td>
<td>Lees et al., 1976</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 worsened</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>8 no effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Serotonergics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-5-hydroxytryptophan (± Amantadine)</td>
<td>?</td>
<td>8</td>
<td>7 improved</td>
<td>1-2 wk</td>
<td>Stereotactic surgery failures</td>
<td>Mori et al., 1975(^6)</td>
</tr>
<tr>
<td>6. Gaba-ergics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>6-15</td>
<td>6</td>
<td>Excellent results</td>
<td>5 dy-6 wk</td>
<td>Type of torticollis unspecified. 5 'acute', 1 chronic</td>
<td>Pernikoff, 1964(^4)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>8</td>
<td>1</td>
<td>Recovered</td>
<td>2 wk</td>
<td>Duration ST 8 days. Improvement maintained on stopping drug.</td>
<td>Bianchine &amp; Bianchine 1971</td>
</tr>
<tr>
<td>L-Glutamine + Diazepam +</td>
<td>see text</td>
<td>2(^3)</td>
<td>1 symptom free</td>
<td>&gt;2 mo</td>
<td>Siblings; non-responder post-thalotomy and segmental dystonia</td>
<td>Korein, 1977</td>
</tr>
<tr>
<td>Isoniazid + Pyridoxine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>serum Li 0.9 mM/1</td>
<td>3</td>
<td>Striking improvement in all</td>
<td>1-2 mo</td>
<td>Abnormal CSF protein patterns. Single blind placebo substitution in 2. Duration ST 2 mo in 1.</td>
<td>Kjellin &amp; Stibler, 1975</td>
</tr>
<tr>
<td></td>
<td>1200</td>
<td>1</td>
<td>Improved</td>
<td>few wk</td>
<td>Single blind placebo substitution; independent evaluators. Prior town gas poisoning &amp; neuroleptic therapy.</td>
<td>Couper-Smartt, 1973</td>
</tr>
<tr>
<td>Lithium</td>
<td>?</td>
<td>2</td>
<td>Both responded</td>
<td>?</td>
<td></td>
<td>Patterson and Little 1943(^8)</td>
</tr>
<tr>
<td>Quinine</td>
<td>Max(^3)</td>
<td>6</td>
<td>No benefit</td>
<td>?</td>
<td></td>
<td>Hassin, 1939</td>
</tr>
<tr>
<td>Quinine</td>
<td>2G</td>
<td>1</td>
<td>Practically recovered</td>
<td>2 mo</td>
<td>Duration ST 3 mos; worse on stopping drug</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Maximum or optimum daily dose in mg/day unless specified. \(^2\)Various combinations; names of coded drugs CT-237 and P-189 not given. \(^3\)Maximum tolerated dose. 
\(^4\)Number of subjects treated. \(^5\)Subjects common to more than one treatment trial administered by the same author. Reports of Shaw et al., (1972) and Lees et al (1976) are based on the same patient population. \(^6\)Duration of observations. \(^7\)All studies are uncontrolled or presumed uncontrolled unless specified; response evaluated by clinical assessment alone unless specified. \(^8\)Clinical description or information on duration of ST not given.

The absence of objective measures, side effects reported by the patient may be mistaken for worsening of ST. Improvement may result from non-specific sedative effects rather than from a presumed selective pharmacological action.

2. Effect of anticholinergic agents

Bunts (1960) stated, without details, that treatment with anticholinergic drugs (scopolamine, trihexyphenidyl, and cyclomine) was discouraging and Patterson and Little (1943) found slight to no effect in 17 patients treated with scopolamine. In the absence of frequency counts but amplitude is more difficult to assess. Use of a horizontal grid over a videotape television monitor has been described (Bernhardt et al., 1972), but this has not yet been used in pharmacotherapeutic investigations. Ansari and Webster (1974) described recording devices to quantify head rotation and head tremor in ST, but these have not been widely used (Ansari et al., 1972). Unfortunately, a single recording by whatever technique may not provide an accurate sample of the actual treatment response. Sustained improvement on several measures, namely, on clinical assessment, range of daily activities, collateral information, and an objective recording is required to document improvement, but this is rarely done.

Treatment may result in worsening of the tonic but improvement of the spastic component or vice-versa. Whether such change is considered amelioration, deterioration, or no effect depends on the requirements of the individual in his day to day activities.

In the absence of objective measures, side effects reported by the patient may be mistaken for worsening of ST. Improvement may result from non-specific sedative effects rather than from a presumed selective pharmacological action.
details one can only conjecture that dose and duration of treatment in the latter study were adequate. In contrast, Putnam et al. (1949) recommended atropine for several months and Poppen and Martinez-Niochet (1951) suggested scopolamine before considering surgery. One presumes that some patients were improved by this approach, but the number of subjects treated and the outcome were not given.

Mild relief with benztropine has been incidentally noted (Gilbert, 1972a), but otherwise, apart from the single case reports of Barrett et al. (1970) and of Krebs (1939), in whom spontaneous remissions probably occurred, in only 3 patients has improvement been documented with anticholinergics (Urechia and Reteseanu, 1937; Foltz et al., 1959). Interestingly, in 2 of these 3 patients there was a history of encephalitis. In 2 patients of Foltz et al. (1959), sustained improvement over one year in 1 patient and 2.5 yrs in the other was described. In the former case, spontaneous improvement cannot be excluded as a dose reduction was not tried. In the latter case, several attempts at dose reduction resulted in relapse.

Anticholinergic drugs have frequently been used in combination with other pharmacotherapeutic agents to counteract side effects. The relevance to therapeutic outcome is difficult to assess. Myerson and Loman (1942) reported a potentiating effect of scopolamine on the beneficial effect of amphetamine in one patient and Gilbert (1977b) stated that the therapeutic effect of haloperidol was reduced by co-administration of anticholinergic agents.

3. Effect of antidopaminergic agents

DA receptor blockers as well as directly and indirectly acting DA receptor agonists are reported to improve some cases of ST. This apparent anomaly is further complicated by reports that haloperidol in combination with amantadine results in marked improvement (Gilbert, 1972a). The most convincing report of a therapeutic benefit from DA receptor blockers was from Couch (1976a) who used a placebo-controlled cross-over study in 16 patients. The duration of treatment with the active agent, haloperidol, was 4 weeks. The effect of long-term treatment, however, remains to be documented. The failure with haloperidol reported by some authors (Bigwood, 1972; Shaw et al., 1972) may be due to inadequate doses. Gilbert (1972b; 1972c; 1977b) has emphasized that 14-30 mg or more per day may be needed and in addition co-administration of amantadine may be necessary for successful therapy (Gilbert, 1972a; 1972c; 1977a).

In 2 patients, one on prochlorperazine (Sigwald et al., 1959) and one on haloperidol, amantadine and, trihexyphenidyl (Gilbert, 1972a) improvement for at least 1 year was reported. In neither case was the response to drug withdrawal described.

It is possible that response to DA receptor blockers represents only masking of ST by induction of mild drug-induced Parkinsonism.

Results obtained with benzamide derivatives, depletors of central DA, or alpha-methyl dopa show little that is encouraging.

4. Effect of dopaminergic agents

Putnam et al (1949) and Poppen and Martinez-Niochet (1951) recommended amphetamine as a pharmacological treatment before considering surgery. The former used a dose of 10 mg twice daily. Outcome of this approach was not given. Myerson and Loman (1942) in 2 patients required considerably larger doses of amphetamine than used by Putnam et al (1949) to induce improvement. In two cases reported by Gilbert (1972a) amantadine alone was effective in treating ST. In other cases combination with haloperidol was necessary. In the only double blind study with amantadine no therapeutic effect was demonstrated (West, 1977). However, the dose in this controlled study was less than that found successful by Gilbert (1972a; 1972b). Studies with L-dopa have involved giving the drug to the maximum tolerated dose. In general, no effect or worsening has been reported (Ansari et al., 1972; Shaw et al., 1972; Barrett et al., 1970), though in a single well documented case remarkable improvement occurred on both L-dopa and bromocriptine (Lees et al., 1976) but not on placebo substitution. In one patient, worsening on bromocriptine was followed by improvement on haloperidol (Lees et al., 1976).

The use of DA activating agents resulting in improvement lasting one or more years has been described in only 3 patients, one on amphetamine combined with scopolamine (Myerson and Loman, 1942), one with amantadine (Gilbert, 1972a), and one on L-dopa (Shaw et al., 1972). Only in the latter was dose reduction, drug discontinuation, or placebo substitution reported.

5. Effect of miscellaneous drugs

Evaluation of drugs affecting GABA-ergic or 5HT function have been few. The diagnoses in the cases responding to diazepam described by Pernikoff (1964) and Bianchine and Bianchine (1971) are unclear. Incidental comments pointing to an ineffectual role of diazepam have been mentioned in the literature (Barnett et al., 1970; Gilbert, 1972a). Follow-up of the preliminary work of Korein (1977) who used large daily doses of L-glutamine (40G), diazepam (30mg), isoniazid (150mg), and pyridoxine (150mg) to enhance central GABAergic function is awaited.

All published reports on the use of lithium have found improvement (Kjellin and Stibler, 1975; Gilbert, 1977b; Couper-Smartt, 1973) though long term outcome has not been reported.

POSSIBLE APPROACH TO THE TREATMENT OF ST

The limited and in general poorly documented or conducted research makes any summary conclusion difficult. One possible point of focus worth considering is that ST is a heterogeneous disorder. This would account for the diversity of clinical findings as well as the variable pharmacotherapeutic responses reported. Some patients appear to respond to anticholinergic agents, some to DA receptor blockers, and some to DA receptor agonists though the total numbers may be small. If this is so then it may be possible to identify potential responders to these 3 classes of drugs by observing the response to a single dose of benztropine, haloperidol, or

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Spasmodic Torticollis

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