

Pathophysiology and Pharmacotherapy of Spasmodic Torticollis: A Review

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SUMMARY: *The few existing neuropathological, neurochemical, and neuropharmacological studies have shed little light on the pathophysiology of spasmodic torticollis (ST). The relevance of experimental 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, object-

ive evaluation of response, documentation of key data, and adequacy of duration of follow-up make interpretation of published results difficult. Because of the heterogeneity of ST, investigations aimed at establishing 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 neuropathologiques, neurochimiques et neuropharmacologiques connues ne jettent que peu de lumière sur la physiopathologie du torticollis spasmodique (ST). La correspondance entre le ST expérimental chez l'animal, le ST induit par des médicaments, et le ST idiopathique humain est encore inconnue.*

La plupart des essais pharmacothérapeutiques se sont concentrés sur les médicaments agissant sur les fonctions des noyaux gris centraux. Plusieurs problèmes rendent l'interprétation des résultats pu-

bliés alléatoire: grandeur de l'échantillonnage, hétérogénéité clinique des populations, plans de recherches, évaluation objective des réponses, documentation de données-clef, pertinence 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 aiguë à des doses-essai de divers médicaments cholinergiques, dopaminergiques, sérotoninergiques et GABAergiques, offrirait une base plus valable pour la sélection du traitement approprié.

INTRODUCTION

"Spasmodic torticollis is an involuntary hyperkinesia 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)" (Patterson 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 disease and Huntington's chorea where anatomical, chemical, and pharmacological information may provide a rational basis for therapy, such an underpinning of knowledge in spasmodic torticollis (ST) is lacking. Drug treatment is both advanced and discounted yet published results are few, contradictory, 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 doubtful role in the etiology of ST (Marsden, 1976; Mathews et al., 1978; Cockburn, 1971; Choppy-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-

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lized dystonia (Cassirer, 1922; Wimmer, 1929). However, the relevance of these findings to the development of ST is questioned (Tarlov, 1970). ST has been associated with injury to the cerebral cortex (David et al., 1952), colloid cyst of the third ventricle (Avman and Arasil, 1969), as well as with posterior fossa tumors (Winther, 1930; Boisen, 1979). In the latter, clonic features were not described. These symptomatic cases may indicate that lesions at several levels of the CNS may induce a clinical picture of ST. However, in the majority of cases of ST there is no demonstrable lesion.

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.

2. Experimental ST

Focal brain stems lesions have been known to produce abnormal neck postures in experimental animals (Foltz et al., 1969; Carpenter, 1956; Denny-Brown, 1962; Poirier, 1960; Mori et al., 1975; Battista et al., 1976; Carrea and Mettler, 1955). Interruption of ascending dopamine (DA) fibers from the midbrain tegmentum in the marmoset induces severe torticollis with deviation of the head towards the side of the lesion, but lesions in the pontine tegmentum, which affect ascending noradrenergic neurons, induce contralateral torticollis (Crossman and Sambrook, 1978). Tarlov (1970), examined brain regions that have been implicated in the experimental pathophysiology of ST, but found no histological abnormalities in the single ST brain investigated.

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 pimozide, the catecholamine synthesis inhibitor, alpha-methyl-para-tyrosine, as well as choli-

nergic 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; Cottom 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 Stibler, 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-thalotomy 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 mo 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)

Treatment	Dose ¹	N ⁴	Results	OBS ⁶	Comments ⁷	Authors
1. Anti-cholinergics						
Scopolamine	?	1	Appreciable improvement	?	Post-encephalitic parkinsonism	Urechia & Retezeanu, 1937
Scopolamine	?	17	None-slight improvement	?		Patterson & Little, 1943
Atropine (+ Sodium Iodide)	?	1	Favorable improvement	5-6 mo	Duration ST few dy; only partial relapse on stopping drug.	Krebs, 1939.
Miscellaneous (CT-237, P-189, Cyrimine; Scopolamine)	Var ²	5	2 Sustained improvement	1 yr	Duration ST 4 mo; effect of stopping drug not reported	Foltz et al., 1959
			3 Transient improvement	2½ yr	Post-chicken pox encephalitis; worsened on dose decrease	
Trihexyphenidyl	?	1 ⁵	Remitted	6 mo	Dystonia musculorum deformans in 2 Remission for 10 yr without drugs; recurrence refractory	Barrett et al; 1970
2. Cholinergics						
Deanol	450-900	1	No effect	2 wk		Laterre & Fortemps, 1975 ⁸
3. Anti-dopaminergics						
Haloperidol (and/or amantadine 300 mg/dy)	1.5-14	9	7 good or excellent 2 no effect	3 wk-2 yr; <3 mo in 3	In 2 duration of ST ≤6 mo; 2 responded to amantadine alone	Gilbert, 1971, 1972a, 1972b, 1972c
Haloperidol (+ Trihexyphenidyl ± Amantadine ± Diazepam)	9-30	4	2 recovered 2 markedly improved	?	All familial ST; also on biofeedback	Gilbert 1977a
Haloperidol	3	5 ⁵	No effect	Few wk	Amantadine failures	Bigwood, 1972 ⁸
Haloperidol	3	6 ⁵	1 dramatic improvement 5 no effect	5 mo ?	Improvement maintained on stopping drug; worsened on L-dopa. All L-dopa failures	Shaw et al., 1972
Haloperidol	7	16	8 improved 50%+; 6 improved 25-50% 2 no change	4 wk	Double-blind cross-over; planned randomization of treatment sequence; assessment by rating scale	Couch, 1976a
Prochlorperazine	450	3 ⁵	All improved	Few wk-2 yr	1 ? postencephalitic, with retrocollis	Sigwald et al., 1959
Thiopropazine	200	2 ⁵	Both improved	Few wk	Single blind placebo substitution in 1	Sigwald et al., 1959
Perphenazine	92-108	2	1 improved	Few wk	Retrocollis; torsion dystonia; relapse on dose decrease. Reserpine 4.5 mg/dy; duration ST 6 mo	Blom & Ekblom, 1961
Pimozide	?	2 ⁵	1 no effect 1 transient improvement	?	Siblings; 1 post-thalotomy with segmental dystonia	Korein, 1977
Tiapride	200-500	4	No effect	?		Emile et al., 1977 ⁸

Treatment	Dose ¹	N ⁴	Results	OBS ⁶	Comments ⁷	Authors
Tiapride	400	4 ⁵	1 good results 3 no effect	2 mo <15 dy-3mo	2 neuroleptic treatment failures	Trillet et al., 1977 ⁸
Sulpiride	400	1 ⁵	no effect	?	Tiapride failure	Trillet et al., 1977 ⁸
Tetrabenazine	75-200	3	1 improved 2 no effect	4 wk	'intractable' ST; duration ?; blind film rating	Swash et al., 1972 ⁸
Tetrabenazine	150	9 ⁵	1 transient improvement 8, no effect	?	All L-dopa failures	Shaw et al., 1972
Reserpine	3-6	2 ⁵	No effect	27-30 dy	Placebo substitution and filming in responders	Markham et al., 1963 ⁸
Alpha-Methyl-dopa	1050	3 ⁵	No effect	17-28 dy	as above	Markham et al., 1963 ⁸
4. Dopaminergics						
Amphetamine (+ Scopolamine)	?	1	Responded well	?	Chronic encephalitis	Patterson & Little, 1943
Amphetamine (+ Scopolamine) (± Nicotinic Acid)	60-120	2	Both marked improvement	5 mo 14 mo	Duration ST 1 mo; relapse on stopping drug. Both improved with test dose amphetamine	Myerson & Loman, 1942
Pipradol	35	1	Marked improvement	?		Fabing 1954
Amantadine	300	5 ⁵	No effect	7-10 dy	Haloperidol failures	Bigwood, 1972 ⁸
Amantadine	200	9 ⁵	1 transient improvement 2 worsened 6 no effect	?	All L-dopa failures	Shaw et al., 1972
Amantadine	200	10 ⁵	No benefit	1 mo	Double-blind cross over. Collateral information.	West, 1977
Amantadine (+ Haloperidol 6mg/dy)	300	3 ⁵	No benefit	Few wk	Uncontrolled	West, 1977
L-Dopa	6-8.5G	3 ⁵	No effect	1-6 mo	Open or single blind placebo substitution; film assessment. 2 thalotomy failures	Barrett et 1970
L-Dopa	Max ³	17 ⁵	1 sustained improvement 1 improved but became intolerant of L-dopa 4 transient improvement 11 no effect	2 yr >4 mo ≥1 mo	Retrocollis Placebo substitution and filming in responders. Collateral information.	Shaw et al., 1972
L-Dopa	7.5-8G	6	4 worsened 2 no change	83-142 dy	Instrumental measurement of head rotation and tremor.	Ansari et al., 1972

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

¹Maximum or optimum daily dose in mg/day unless specified. ²Various combinations; names of coded drugs CT-237 and P-189 not given. ³Maximum tolerated dose. ⁴Number of subjects treated. ⁵Subjects 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. ⁶Duration of observations. ⁷All studies are uncontrolled or presumed uncontrolled unless specified; response evaluated by clinical assessment alone unless specified. ⁸Clinical description or information on duration of ST not given.

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 im-

provement 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 spasmodic 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 mea-

sures, 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 cycrimine) was discouraging and Patterson and Little (1943) found slight to no effect in 17 patients treated with scopolamine. In the absence of

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 benzotropine 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 Retezeanu, 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 crossover 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 substi-

tion. 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 GABAergic 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 benzotropine, haloperidol, or

apomorphine, respectively, under controlled conditions. Recent findings suggest that a single intravenous dose of benzotropine and, to a lesser extent, subcutaneous apomorphine may indeed identify potential responders to chronic benzotropine or L-dopa therapy (Lal et al., 1979). This approach could be extended by evaluating potential responders to GABAergic and 5HT drugs by use of a single dose of diazepam or L-tryptophan, respectively. Studies establishing an individual profile of neurotransmitter function by such pharmacological tests may provide a more rational approach to the investigation and treatment of ST.

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