

group there was a slight decrease before crossover and until the end of the trial. The mean pulse rate in both groups decreased slightly before and until after crossover. This decrease and increase may be explained as the patients became less or more tense in the course of the trial.

The dose used in this trial is very low: 9 mg Lexotan a day. Tjandra and Kusumanto Setyonegoro (5) in an open trial on Lexotan gave 18 mg - 20 mg a day to most of their patients, followed by a group with 24 mg. - 30 mg. a day and their result was 50.8% very good and good.

SUMMARY

A double blind crossover trial on Lexotan or Bromazepam (Ro 05-3350 of Hoffmann-La Roche Laboratories) versus placebo was done in the treatment of patients with predominant psychophysiological symptoms on an ambulatory basis.

The average duration of the disorders happened to be considerably longer in the Lexotan group (129 weeks) than in the group starting with placebo (68 weeks).

Lexotan did much better than placebo with a decrease in the average morbidity score expressed as the percentage fall in mean of 57.0 for Lexotan before crossover to placebo and a rise (deterioration) of 58.1 after crossover to placebo, against a fall of 40.5 for placebo before crossover and a further fall (improvement) of 42.9 after crossover to Lexotan.

Lexotan scores better for the somatic than for

the psychic symptoms as the percentage fall in mean morbidity scores show 61.8 against 46.7 before crossover (4-week treatment) and 50.8 against 28.1 after crossover (2-week treatment).

Minimal undesirable concomittant effects were found.

Lexotan or Bromazepam, a new benzodiazepine derivative, may be of valuable help in the treatment of patients with psychophysiological disorders.

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THE MANAGEMENT OF GILLES DE LA TOURETTE'S SYNDROME BY CHEMOTHERAPY

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INTRODUCTION

The syndrome of multiple tics accompanied by explosive utterances was originally described by Itard in 1825 and was later differentiated into a syndrome by Gilles de la Tourette (1885) when he described eight cases. The following features are considered essential for the diagnosis of Gilles de la Tourette's syndrome, namely:

1. Childhood onset (below the age of 16)
2. Multiple motor tics
3. Unprovoked loud utterances, which may progress to the forced shouting of obscenities (coprolalia).

According to Fernando (1967), the illness usually commenced with multiple motor tics sometimes accompanied by utterances (vocal tics).

The more common tics were the motor tics usually affecting the head, face and neck, while the less common were the abnormal movements of the limbs and trunk muscles. The disease progressed rapidly after onset with an increase in the variety of motor tics such as head retraction, rolling, blinking, grimacing, twisting of the neck, shrugging of the shoulders and flexion or extension of the arms or legs. Other tics, like smiling, teeth grinding and tongue protrusion were sometimes reported, but more complex movements like the slapping of the face or genitalia were rarer.

Less than 200 cases (Shapiro, 1971) have been reported in world literature. Morphew and Sim (1969) described six cases for study, while Fenichel (1945) observed the sexualization of speech and interpreted it as a form of compulsive neurosis. When the distinction between coprolalia and vocal tics were difficult, where sounds made were often partially resembling obscenities, it might be more appropriate to diagnose the case as a Gilles de la Tourette's disease (Corbett et al., 1969).

The prognosis has been described (Chapel, et al., 1964) as 'sinister' and uniformly poor, with a relentless clinical course and Faux (1966) described the tragedy of life-long institutionalization where treatment previously had been mainly socio-psychiatric methods. However spontaneous improvements in late teens and twenties have been reported by Bockner (1959) and Heuscher (1953) and remissions were said to have lasted several years.

The illness has a marked social impact. Patients seen often sought help for social, personality and behavioural difficulties. When treatment failed, their behaviour often worsened and psychopathic behaviour resulted.

AETIOLOGY

a) *Psychogenic Theory*

The aetiology of the syndrome is unknown. Belief in a psychological aetiology was based on the medical vogue to a diagnostic 'waste-paper basket' labelled 'psychogenic'. There is little agreement about psychological factors common to patients, except for frequent reports of compulsivity and inhibited aggression. Several authors (Ascher, 1948; Eisenberg et al., 1959; Dunlop, 1960 and MacDonald, 1963) suggested that the underlying psychodynamic cause may be a suppressed hostility to parents or to other significant persons. Downing et al., (1964) described a female patient with elements of obsessive-compulsive, hysteric and schizophrenic-like psychopathology in the family.

Likewise, Fernando's report (1967) showed that 57% of all cases had marked obsessional tendencies, and the majority (Morphew et al., 1969) had some precipitating psychological stress such as a tonsillectomy or a circumcision.

Otto Fenichel (1945) commented on the stuttering, saying that the strong anal-sadistic component of speaking and utterances of obscenities was an aggressive act directed at the listener. He postulated that there was a 'magical' temptation to utilize obscene or profane words to attack the listener violently or sexually.*

b) *Organic Theory*

An organic aetiology has been suggested by several authors (Corbin, 1968; Wagner, 1970; and Shapiro & Shapiro, 1971) although there is no evidence of a consistent association between the onset of tics and any physical illness. Some similarity can be observed between the syndrome and symptoms of clearly established illnesses like Sydenham's Chorea, Huntington's Chorea, Encephalitis Lethargica, Manganese poisoning and Acanthocytosis. All that is known is that the basal ganglia may be the probable site of disturbance. The only positive autopsy case (Claus and Balthason, 1954) showed an immature cell structure of the striatum. Generally positive neurological findings are rare in all reported cases, although abnormal EEG findings were reported in a quarter of all cases analysed.

c) *Neuro-physiological Theory*

Several lines of evidence (Snyder et al., 1970) suggested that symptoms of the disease may be related to brain dopamine in the corpus striatum. Recently the dramatic therapeutic responses have been obtained with the butyrophenone, Haloperidol. Phenothiazines and butyrophenones markedly accelerate the turn over of dopamine in the corpus striatum. This mechanism of accelerated turn over is thought to be due to the blockade of dopamine receptors in the striatum, causing enhancement of a postulated feedback of the pre-synaptic dopamine neurones, which respond by increasing dopamine synthesis. Thus, both the symptoms of idiopathic and drug-induced Parkinsonism can be attributed to relative deficiency of dopamine at receptor sites in the striatum. The fact that Haloperidol is unique in its great potency for blocking dopamine receptors and that it is effective in Gilles de la Tourette's Syndrome may account for a pathophysiology of the condition. It is proposed that in the corpus striatum of such patients, there is a hyperactivity of dopaminergic

systems. Whether this is produced by enhanced release of dopamine, impaired inactivation of dopamine, or hypersensitivity of receptors is a matter for speculation. The proposed hypothesis would account for the resemblance of symptoms of Gilles de la Tourette's Syndrome to the side effects of L-Dopa therapy. This would also explain the specific therapeutic efficacy of Haloperidol.

Although the syndrome cannot definitely be attributed to an organic aetiology until more neuro-physiologic or anatomic pathology is evident, the clinical manifestation suggest that the condition is a bizarre organic neuro-physiologic impairment of the central nervous system.

Treatment with Haloperidol

A large number of psychotropic agents have been administered to such patients with discouraging results. In 1961, Seignot reported using R1625 (Haloperidol) in a case of Tourette's disease with dramatic symptomatic improvement. Its effectiveness was further proven by Challas and Brauer in 1963, by Chapel et al., in 1964 and by Shapiro in 1968. However, whenever Haloperidol was discontinued, relapses occurred.

The Present Study

a) Aim

The aim of the study was to observe and measure the degree of symptomatic improvement of 4 cases of Gilles de la Tourette's Syndrome treated with Haloperidol.

b) Methodology

Four cases of Gilles de la Tourette's Syndrome (see Table I) were treated by the author with

Haloperidol. As a controlled measurement of symptomatic improvement, all four patients were video-taped for 10–15 minutes prior to treatment. The patients were then treated with varying doses of Haloperidol at gradually increasing doses until symptomatic improvement was observed. The doses of Haloperidol ranged from 6 mg to 33 mg per day (see Table II). The increasing dosage was stopped when side effects of the drug interfered with the patient's functioning. The side effects of Haloperidol were drowsiness, parkinsonism, poor concentration and blurring of vision. Parkinsonism was controlled with Benzhexol, dosage ranging from 12 mg. to 36 mg. per day. Approximately one month later, they were subsequently video-taped and the degree of improvement was measured.

c) Case Histories

Case I

A 19 year old Chinese male, a fishmonger, developed the illness at 8 years old when he felt an urge to clear his throat frequently. This progressively worsened as he started producing grunting noises. By 14 years old, he felt a compulsive urge to frequently hit his abdomen with his hands. Two years later, he started grimacing and shouting out obscene names of his friends repetitively. He left school at this juncture because of his anti-social symptoms. By the time he reached 17 years old, he was compulsively shouting obscenities, indecently gesticulating with his hands and repeatedly stamping his feet. He eventually gravitated his corprolalia to women essentially and this behaviour was reinforced when he was assaulted by their husbands.

Table I: Characteristics of patients with Gilles de la Tourette's Syndrome

	Case I	Case II	Case III	Case IV
Ethnic Group	Chinese	Chinese	Chinese	Chinese
Sex	Male	Male	Male	Female
Age	19 years	25 years	22 years	16 years

Table II: Maximum doses of Haloperidol and Benzhexol/day duration of medication in treatment of Gilles de la Tourette's Syndrome.

	Case I	Case II	Case III	Case IV
Maximum dose of Haloperidol/day	31.5 mg	33.0 mg	6.0 mg	9.0 mg.
Maximum dose of Benzhexol/day	36 mg	24 mg	12 mg	12 mg
Duration of test period	27 days	33 days	30 days	28 days

He gave a history of having frequently observed his parents performing coitus, when he was 7 years old. He developed hostile feelings towards his father and would attempt to sleep in between his parents to prevent coitus and deliberately made throat sounds to distract his parents. His symptoms appeared to have been precipitated by witnessing the primal scene.

By the time he was admitted to hospital, he was depressed, ashamed of his symptoms and harboured strong sado-masochistic tendencies.

Case II

A 25 year old Chinese male, a motor car mechanic, developed insidious symptoms of coughing at 16 years old. His concentration deteriorated and he developed insomnia. Very soon he started cursing in an explosive manner and compulsively cursed obscenities directed mainly at his mother. He felt more relaxed after corprolalia. Later he began gesticulating obscenely within his hands. The symptoms became progressively worse, with echolalia, corprolalia and indecent gesticulations several hundred times per hour. He would hit his testes until they hurt and stamp his feet repeatedly. Eventually, he learnt to distort his obscene corprolalia by swallowing the 'four letter word' and by sucking his thumb. This resulted in pressure headaches which he suffered for many years.

He blamed excessive masturbation for his illness and was unable to stop the habit which he indulged in 3-4 times per day. The symptoms had a devastating social effect on his life. He isolated himself socially, avoided female company and female clients avoided him. He felt very ashamed of his symptoms, which he was unable to control and became very depressed and desperate during the time of admission to hospital.

Case III

A 22 year old male Chinese, a College student, gave a history that at the age of 17 years old he witnessed his parents performing coitus. This traumatic experience made him hate his parents and he became depressed each time he spoke to them and painstakingly avoided staying at home. He became so obsessed by the sexual act that he ruminated over the incident even until the time of consultation. Since then his relationship with his parents has been cold and distancing. This incident coincided with a female neighbour, whom he was infatuated with, and who had left the neighbourhood.

Soon after that incident, he started coughing

and making queer noises in this throat. This was followed by the wrinkling of his nose, the repeated winking of his eyes and active nodding of his head. At times, while walking, he would stamp his feet. These symptoms developed gradually and fluctuated in intensity. Occasionally he would compulsively blow his nose and make semi-purposeful movements.

His symptoms interfered with his studies, caused him untold embarrassment and he socially isolated himself. His concentration deteriorated and he became nervous and depressed by this uncontrollable disorder.

Case IV

A 16 year old student, a female Chinese, was brought by her father who noted that she had insidiously developed fidgetiness at 13 years old. Initially she developed a blocked nose and started a sneezing habit, with a twitching of the nose. This subsequently spread to mouth twitching and grinding of her teeth. One and a half years later, she developed jerky limb movements and was unable to control hitting herself.

Her symptoms increased and she became withdrawn. Her self-hitting became more severe and spread to hitting her mother and grandmother. Frequently she would make grunting noises and swear curse words under her breath and then feel most embarrassed and repentant. During the time of admission she had obsessive-compulsive rituals, corprolalia, echolalia, stamping of feet and had learnt compensatory movements to dampen her gesticulations.

Her father described her as a reticent girl who fared poorly at school. He had taken her to approximately 100 doctors, native healers and mediums in a search for a cure to this strange malady.

d) The Video-tape Technique of Recording

The video-tape recording system provided a continuous observation and a permanent recording of the frequency and quality of tics in each case. It is unfortunate that the measurement of man's behaviour cannot be done adequately in man's natural environment because of insurmountable technical difficulties, and because variant conditions cannot be controlled out in the natural environment. Hence to achieve stable environment conditions, thereby excluding variability, an experimental studio situation was utilized. This unfortunately, while it controls environmental variables, destroys the naturally occurring contexts of behaviour of the patient.

Table III: Inter-rater reliability: Scoring agreement between two observers.

	Before Treatment	After Treatment
Case I	70.8%	96.4%
Case II	81.8%	94.8%
Case III	94.3%	100%
Case IV	91.1%	97.2%

Each video-tape recording was thus done in a similar controlled studio condition. Patients were given exact instructions to behave naturally in a sitting position. The number of helpers remained constantly the same.

e) Operational Definitions

The recording of the nature and frequency of the tics and body movements were divided into 8 body components representing different parts of the body. They were:

- | | |
|-------------------|-------------------|
| 1. Head | 5. Lower Limb (R) |
| 2. Grimace | 6. Lower Limb (L) |
| 3. Upper Limb (R) | 7. Trunk |
| 4. Upper Limb (L) | 8. Vocalization |

Each body component was graded (by standard criteria) for its movements or tics i.e.

- Code 0 No Movement
- | |
|---------------------------|
| 1 Minor movements |
| 2 Moderate movements |
| 4 Major or mass movements |

f) Scoring and Inter-Rater Reliability

The scoring of body movements was recorded by two independent observers every fifteenth second (with the aid of a metronome) before and after treatment with Haloperidol. Raw data was collected from the first minute to the 3½ minute (i.e. total observation period of 2½ minutes of 12 observations each) and from the 6th minute to the 8½ minute (i.e. 2½ minutes observation) before and after treatment with Haloperidol.

Since the major problem of scoring was the reliability of different observers' scores, the reliability of two independent observers scoring the raw data simultaneously was calculated by simple percentage agreement-disagreement of raters scores (see Table III).

The range of percentage agreement was:—

- | | |
|------------------------|----------------|
| (i) Before treatment: | 70.8% to 94.3% |
| (ii) After treatment : | 94.8% to 100% |

Percent agreement was a vigorous method of testing inter-rater reliability because even small deviances of one point were more apparent than in a correlation technique where small deviances simply contributed to small correlation coefficient.

The first task was training in scoring and the determination of maximum possible level of agreement was set by a learning curve at which the flattening of the curve indicated maximum scorers' agreement. Hopefully, the minimum acceptable percent agreement was 80 – 90%.

Low inter-rater agreement occurred in Case I because this was the first scoring session and a satisfactory level of agreement was reached as scorers became more used to the scoring system.

High inter-rater agreement was reached after treatment due to the marked reduction of the frequency and nature of tics.

g) Results of the Study

i) *Correlated 't' test of significance for sequential observations of tics before treatment:* The χ^2 is a test commonly used to evaluate significance with a nominal or ordinal scale. However, independence of each score is a basic assumption of the χ^2 test of significance. The data obtained does not meet the criteria because within each 15 seconds of observation, the scores are highly related and dependent. This excludes the possibility of using a χ^2 to test statistical significance.

Instead a correlated t test of significance was used so as to determine whether significant changes occurred before the administration of Haloperidol during the first 2½ minutes of observation and the subsequent second 2½ minutes certain items from the data of the two observations were analysed. The reason for selecting only certain items was because the changes appeared significant, while the items not selected for testing showed minimal change. (See Table IV).

The correlated t test in each of the 4 cases was significant ($p < 0.05$ level) in certain body components of movement.

It is interesting that the patients showed increased or decreased frequency of tics during the second 2½ minutes before treatment, in the different body components of their tics.

Yates (1955) experimentally demonstrated that mass negative practice resulted in a significant decline in the frequency of tics. This method of

Table IV: Correlated 't' test for significance in different body components of movement in Cases I - IV.

Patient	Scores of 1st 2½ mins.	Scores of 2nd 2½ mins.	't' test
<i>Case I</i>			
Head Mov.	20	9	t = 2.24, p < 0.05, df = 11 (significant)
Upper Limbs (L)	19	13	t = 1.67, p > 0.05, df = 11 (not sig.)
L Limb (L)	21	10	t = 1.84, p > 0.05. df = 11 (not. sig.)
<i>Case II</i>			
Head Mov.	20	15	t = 0.59, p > 0.05, df = 11 (not sig.)
L. Limb (R)	2	12	t = 3.46, p < 0.01, df = 11 (significant)
<i>Case III</i>			
U. Limb (R)	16	8	t = 1.29, p > 0.05, df = 11 (not sig.)
U. Limb (L)	7	18	t = 2.49, p > 0.05, df = 11 (Significant)
<i>Case IV</i>			
L. Limb (L)	2	11	t = 1.92, p > 0.05, df = 11 (not sig.)

Table V: Mean scores of different body components of movement in Cases of Gilles de la Tourette's Syndrome before and after treatment with Haloperidol.

	Head Mov.		Grimacing		Upp. Limbs		L. Limbs		Trunk	
	Bf. Tr.	Af. Tr.	Bf. Tr.	Af. Tr.	Bf. Tr.	Af. Tr.	Bf. Tr.	Af. Tr.	Bf. Tr.	Af. Tr.
Case I	29	5	32	3	52	8	56	10	33	4
Case II	35	5	26	12	43	7	28	13	9	1
Case III	9	0	13	1	49	0	47	0	26	0
Case IV	24	16	14	4	29	25	61	22	10	2
Mean scores	24.0	6.5	21.3	5.0	43.3	10.0	48.0	11.3	19.5	1.8

Overall mean score before treatment = 156.1

Overall mean score after treatment = 34.6

treatment essentially utilizes the reactive inhibition and drive reduction theory of Hull (Yates, 1970). This theory states that reactive inhibition would be generated as mass negative practice continues and the dissipation of reactive inhibition would be reinforcing, thereby effecting a reduction in tics. Although the patients were not told to deliberately evoke their tics, nonetheless the theory suggested that there will be drive reduction thus resulting

in a significant diminution of tics during the second 2½ minutes of observation.

The results of the correlated t test may give an indication as to why mass negative practice does work in certain cases of Gilles de la Tourette's Syndrome, and in only certain body components of the tics. In another patient (not quoted in this paper) the author found that mass negative practice seemed to reduce the quality

Table VI: Percentage Improvement in various body components of tics in Cases of Gilles de la Tourettes' Syndrome following Treatment with Haloperidol.

	Head Move (%)	Grimacing (%)	Upp. Limbs Mov. (%)	Low Limbs Mov. (%)	Trunk Mov. (%)	Overall Improv. (%)
Case I	82.8	96.7	84.6	82.1	87.9	86.8%
Case II	88.9	53.9	83.7	53.6	88.7	73.8%
Case III	100.0	92.3	100.0	100.0	100.0	98.5%
Case IV	33.3	71.4	13.8	64.0	80.0	52.5%

of tics but did not seem to affect the frequency of tics.

ii) Degree of Percentage Improvement following Haloperidol Therapy The total mean scores of all 4 cases for each body component of movement before and after treatment with Haloperidol was noted. (See Table V).

	Tot. Mean Scores Before Treatment	Tot. Mean Scores after Treatment
Head movements	24.0	6.5
Grimacing	21.3	5.0
Upper limbs movements	43.3	10.0
Lower limbs movements	48.0	11.3
Trunk movements	19.5	1.8
Overall mean scores before treatment	= 156.1	
Overall mean scores after treatment	= 34.6	

There was a marked reduction in scores for each body component of movement after treatment. The overall percentage improvement of tics after treatment with Haloperidol ranged from 52.5% (in Case IV) to 98.5% (in Case III). There was a remarkable improvement in terms of reduction of tics in all components of the body following treatment with Haloperidol (See Table VI).

CONCLUSION

Four cases of Gilles de la Tourette's Syndrome were treated with varying doses of Haloperidol for an average period of 4 weeks. The technique of video-tape recording to measure the degree of improvement following chemotherapy was discussed. Paired independent observers coded the raw data from video-taped recordings before and after the administration of Haloperidol. The inter-rater reliability for scoring agreement ranged from 70.8% to 100%.

The correlated t test of significance for sequential observation of frequency and quality of tics, before treatment, indicated varying significant

improvements of symptoms in certain body components. Results of this observation gave an indication to supporting the reactive inhibition theory of mass negative practice, but showed that only tics in certain body components were reduced by mass negative practice.

The overall percentage improvement of the 4 cases of Gilles de la Tourette's Syndrome following Haloperidol therapy was dramatic in terms of reducing the quality and the frequency of tics.

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A CLINICAL TRIAL OF R6218 IN THE TREATMENT OF OBSESSIVE-COMPULSIVE NEUROSIS

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In this paper a clinical trial of the new neuroleptic Janssen R6218 (fluspirilene) in the treatment of obsessional states, involving 8 male, Malaysian, patients is reported. The patients ranged in age from 14 to 32 years with a mean of 23 years and the duration of their illness ranged from 1 to 11 years with a mean of 6 years. They had previously been treated with benzodiazepines, tricyclic antidepressants and in some cases with Haloperidol and other drugs with amelioration in anxiety and depression without the basic symptoms of the illness being affected directly as a result of drug therapy and those who spoke

English (and thus could converse with the therapist) had had an exposure to various forms of psychotherapy, chief among their being paradoxical intention with defocussing technique, but for one reason or another had failed to derive any benefit from it.

In this trial, which was mainly exploratory in nature, a new chemical compound was being tested, for the first time perhaps, to determine if it could basically alter the dominating symptoms of these patients, viz. their obsessive thoughts and compulsive actions. As such, the conditions of trial were (except in the case of one patient -T.S.D.)