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From St. Hans Mental Hospital, Department D., Roskilde, Denmark
(A. FAURBYE, M.D.)

Reversible and Irreversible Dyskinesia after Treatment with Perphenazine, Chlorpromazine, Reserpine and Electroconvulsive Therapy*

By
L. UHRBRAND and A. FAURBYE

With 1 Figure in the Text

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Neurological symptoms are often observed as side effects in the treatment of psychoses with psychopharmaca. Such neurological symptoms have hitherto been considered as a minor inconvenience because they disappeared after reduction of the dose or cessation of the treatment but now we have observed that neurological symptoms may persist as irreversible phenomena after cessation of the treatment.

The neurological symptoms which we have observed being irreversible in some cases is a syndrome (bucco-linguo-masticatory dyskinesia) consisting of incessant involuntary munching and masticatory movements of the jaw during which the tongue is protruded at short intervals with vigorous grimaces of the lips (see Fig. 1). In the most serious cases there are also rocking and torsionary body movements and incessant tripping and shuffling movements so that the patient can not stand still.

SHANNON et al. (1957) have noted in patients treated with perphenazine occasional stiffness of the face and neck muscles together with protrusion of the tongue. The attacks disappeared after stopping perphenazine, reduction of the dose or administration of barbituric acid compounds.

CHRISTIAN and PAULSEN (1958) describe the case of a patient who was treated with small doses of prochlorperazine (Stemetil). On the third day of treatment an alarming state developed with protrusion of the tongue, spasms of the neck muscles, and later on opisthotonus and increasing respiratory trouble. Only intravenous injection of a barbituric acid preparation restored the patient.

FREYHAN (1959) describes a "perioral" syndrome arisen under treatment with ataraxica consisting of involuntary protrusion of the tongue accompanied by tonic contraction of the muscles of the face and neck.

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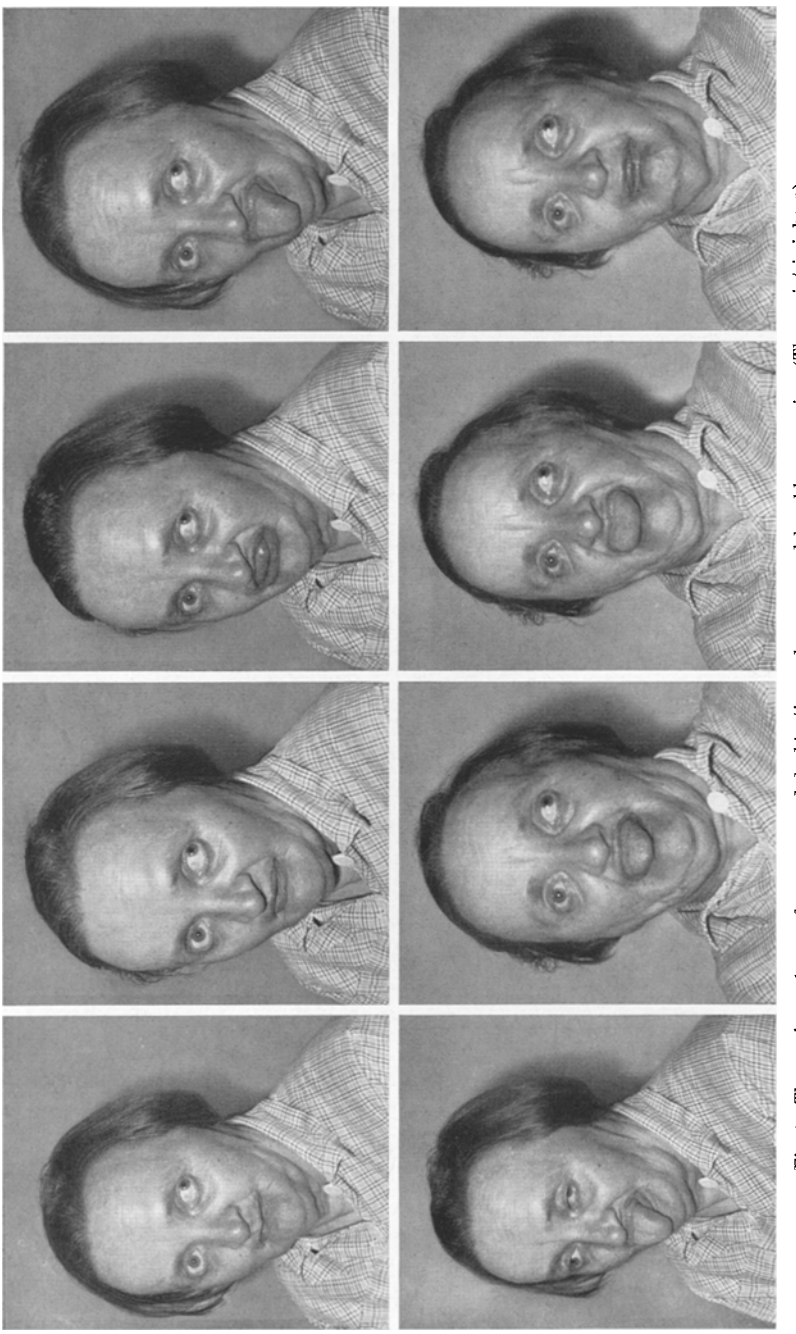

Fig. 1. The various phases of a pronounced dyskinetic syndrome caused by chlorpromazine. (The squint is inborn)

These symptoms were observed in the first stage of the treatment. They disappeared after reduction of the dose and administration of kemadrine (procyclidine hydrochloride). Coffeic potassium benzoate was also effective.

DELAY et al. (1959) have given a comprehensive survey of various neurological symptoms after treatment with neuroleptica. They describe a number of types of dyskinesia as reversible phenomena, including bucco-linguo-masticatory crises, akathisia (difficulty of remaining in sitting position) and tasikinesia (a constant desire to walk).

The bucco-linguo-masticatory dyskinetic syndrome has thus been described more or less completely in the literature but so far only as reversible phenomenon.

In November and December 1957 we observed 2 cases of bucco-linguo-masticatory dyskinesia which arose as a direct result of electroconvulsive therapy. Dyskinesia is still present in these two patients, and is presumably due to some organic lesion.

During the winter and spring of 1959 we became aware of a number of similar syndromes that had developed in patients under pharmacotherapy and in June 1959 a systematical examination of all the about 500 patients of the department, who are all females, proved that a total number of 33 had this dyskinetic syndrome. 4 of these were ascribed to electroconvulsive therapy and 29 to treatment with perphenazine (Trilafon), chlorpromazine (Largactil), and reserpine (Serpasil). A number of the cases of dyskinesia caused by medicine have also proved irreversible. Observation of the patients was completed in October 1959.

15 of the 29 cases of dyskinesia ascribed to psychopharmaca are due to perphenazine (Trilafon), which often has a good effect on the psychic condition, but has proved to have many side effects when taken for some time. After the introduction of perphenazine for the treatment of psychoses a large number of cases of dyskinesia occurred simultaneously, and gradually we became aware of the fact that the dyskinetic syndrome was in some instances an irreversible result of pharmacotherapy with perphenazine.

We have treated altogether 155 patients with perphenazine. In 121 (78 per cent) there were side effects, which were more frequent in elderly patients than in the younger ones. Out of 98 patients under 60 years of age 73 per cent had side effects, and in 57 patients over 60 years of age 88 per cent had side effects. Most of these side effects were, however, slight and temporary. The symptoms in question were the same as described by other authors: rigidity, tremor, paresthesia, oculogyric crises, stridulous respiration, drowsiness, dryness of the mucous membranes, vertigo, and in a few cases nausea and vomiting.

Table 1 describes the 15 patients whose dyskinetic syndrome is ascribed to perphenazine. Most of the patients have taken other psychopharmaca before perphenazine, but only in moderate doses and for short periods, as will be seen from the table. Thus the other drugs have hardly had any important effect, and in 12 of the patients the syndrome arose during or immediately after the perphenazine treatment. It is characteristic of the dyskinesia due to perphenazine observed here that

Table 1. *15 patients with Dyskinetic syndrome after treatment with perphenazine*

Number and name	Age	Diagnosis and duration of disease	Treatment	Average dosis per 24 hours (mg)	Dyskinesia
1. H. K.	55	Schizophrenia. 6 years	1956/58 chlorpromazine for 20 months 1958 perphenazine for 1 month Treatment terminated December 1958	170 35	Dyskinesia observed in December 1958, disappeared 4 months after ceasing treatment
2. M. P.	63	Schizophrenia. 20 years	1958 perphenazine for 8 months Treatment terminated December 1958	28	Dyskinesia observed in November 1958, treatment terminated one month later, dyskinesia disappeared 3 months after ceasing treatment
3. A. C.	61	Schizophrenia (prefrontal leucotomy 1949 and releucotomy 1954). 33 years	1954/55 chlorpromazine for 7 months 1955/57 reserpine for 20 months 1957/58 chlorpromazine for 17 months 1958 perphenazine for 3 months 1958 chlorpromazine for 1 month 1959 perphenazine for $^1/_2$ month Treatment terminated February 1959	270 4.5 265 20 250 60	Tremor was observed during treatment with perphenazine in February 1959. Dyskinesia appeared 10 days after termination of treatment and persists still 8 months later
4. Eb. S.	62	Schizophrenia (severe icterus after chlorpromazine in 1955). 5 years	1955 2 ECT 1956 9 ECT 1956 reserpine for 1 month 1956/57 reserpine for 15 months 1958 perphenazine for 2 months Treatment terminated September 1958	 2 0.5 15	Dyskinesia observed September 1958, disappeared a few weeks after ceasing treatment
5. E. N.	75	Senile dementia. 5 years	1956/57 reserpine for 10 months 1958 perphenazine for 7 months Treatment terminated January 1959	1.5 17	Dyskinesia observed January 1959 persisting 9 months after ceasing treatment
6. L. A.	48	Schizophrenia (prefrontal leucotomy 1949) 30 years	1957 chlorpromazine for 1 month 1958 perphenazine for $2^1/_2$ months Treatment terminated October 1958	150 20	Dyskinesia observed October 1958, disappeared 2 weeks after ceasing treatment
7. L. F.	52	Schizophrenia. 25 years	1955 chlorpromazine for 7 months 1956 chlorpromazine for 9 months 1958/59 perphenazine for 6 months Treatment continues	225 350 40	Very slight degree of dyskinesia observed February 1959, disappeared after administration of brocadisipal and reduction of dose in spite of continuing perphenazine treatment
8. N. O.	64	Schizophrenia. 40 years	1955 chlorpromazine for 3 months 1955/56 reserpine for 11 months 1958 reserpine for $^1/_2$ month 1958/59 perphenazine for $3^1/_2$ months Treatment terminated February 1959	280 4 2.5 45	Dyskinesia observed February 1959, disappeared 4—6 weeks after ceasing treatment

Table 1 (continued)

Number and name	Age	Diagnosis and duration of disease	Treatment	Average dosis per 24 hours (mg)	Dyskinesia
9. G. H.	63	Dementia after meningoencephalitis (prefrontal leucotomy 1956 and releucotomy 1959). 9 years	1952/53 22 ECT 1955 chlorpromazine for 1 month 1955/56 veserpine for 9 months 1956 14 ECT 1956/57 chlorpromazine for 15 months 1957/59 perphenazine for 16 months Treatment terminated March 1959	250 4.5 250 54	Dyskinesia observed in March 1959, 3 weeks after ceasing treatment, unaltered 7 months later, not influenced by leucotomy in July 1959
10. E. S.	60	Schizophrenia (prefrontal leucotomy 1959). c. 20 years	1957 11 ECT 1957 chlorpromazine for 1½ month 1957 reserpine for 3 months 1958 2 ECT 1958 reserpine for 2 months 1958 perphenazine for 8 months One month after termination of treatment with perphenacine the patient resumed treatment with reserpine in varying dosis. April 1959 18 ECT. September 1959 prefrontal leucotomy	 300 5 10 60	Pronounced Parkinsonism occured during treatment with perphenazine, dyskinesia appeared shortly after ceasing this treatment and has since persisted
11. V. A.	63	General paralysis (malaria and penicillin treated). 5 years	1958 chlorpromazine for 1 month 1958 prochlorperazine (Stemetil) for 1 month 1958 chlorpromazine for 3 months 1958 perphenazine for 4 months 1959 reserpine for 4 months Continues treatment with reserpine	75 50 175 46 0.7	Dyskinesia observed in June 1959, persisting unaltered 4 months later
12. H. W.	82	Arteriosclerotic dementia. 2 years	1958 chlorpromazine for 1 month 1958/59 perphenazine for 6 months Treatment terminated May 1959	75 12	Dyskinesia observed in May 1959, persisting 5 months after ceasing treatment
13. A.M.J.	75	Schizophrenia. 52 years	1955 reserpine for 2 months 1958 chlorpromazine for 1 month 1958/59 perphenazine for 9 months Treatment terminated June 1959	3 125 8.5	Dyskinesia observed in June 1959, grimaces having, however, been observed for several years. The dyskinetic syndrome persists 4 months after termination of treatment
14. L. V. J.	53	Chronic epidemic encephalitis (Economo). 24 years	1956 chlorpromazine for 2 months 1957 chlorpromazine for ½ month 1958 perphenazine for 6 months Treatment terminated January 1959	325 325 30	Dyskinesia observed in June 1959, persisting 9 months after ceasing treatment
15. J. M.	80	Senile dementia (hypertensive encephalopathy) 10 years	1959 perphenazine for 1½ month 1959 chlorpromazine for 1 week Treatment terminated April 1959	20 60	Dyskinesia observed in July 1959, persisting 6 months after ceasing treatment

it occurs late in the treatment period. It has at the earliest been observed on the 16th day of treatment. 5 of the patients did not show symptoms until the treatment had lasted for more than 200 days, one patient only after 482 days. In 3 patients (nos. 11, 14, and 15) the syndrome was only observed some time after the termination of the treatment, when the systematic review of all the patients in the department was carried out. We may have overlooked the syndrome in these patients at the time when the treatment with perphenazine was stopped for other reasons, but we have seen several cases of the dyskinetic syndrome becoming more pronounced or even appearing for the first time

Table 2. *10 patients with Dyskinetic syndrome after treatment with chlorpromazine*

Number and name	Age	Diagnosis and duration of disease	Treatment	Average dosis per 24 hours (mg)	Dyskinesia
1. A. O.	79	Senile dementia. 13 years	1956 chlorpromazine for 9 months 1957/59 chlorpromazine for 30 months Continues treatment	225 150	Dyskinesia observed since June 1959, persisting in October 1959
2. R. A.	70	Schizophrenia. 27 years	1956/59 chlorpromazine for 33 months Continues treatment	200	Dyskinesia observed since June 1959, persisting in October 1959
3. A. S.	71	Schizophrenia. 37 years	1956/57 chlorpromazine for 12 months Treatment terminated December 1957	150	Dyskinesia observed June 1956, still persisting in October 1959 22 months after termination of treatment
4. M. B.	76	Manic-depressive psychosis (lymphatic leucemia). 44 years	1955 chlorpromazine for 6 months 1956 chlorpromazine for 2 months 1957/58 chlorpromazine for 12 months 1959 chlorpromazine for 6 months Treatment terminated June 1959	200 225 275 250	Involuntary movements of the jaw observed since 1956. Fully developed dyskinetic syndrome observed in June 1959. The syndrome persists 4 months after cessation of treatment
5. M. F.	67	Dementia arteriosclerotica (emotional instability). 13 years	1955/56 chlorpromazine for 3 months 1957/59 chlorpromazine for 26 months Treatment terminated June 1959	150 200	Dyskinesia observed in June 1959, remains 4 months after termination of treatment
6. A.M.N.	53	Schizophrenia. 23 years	1955/56 chlorpromazine for 6 months 1956/59 chlorpromazine for 28 months Continues treatment	225 275	Dyskinesia observed June 1959, persisting in October 1959
7. E.M.J.	72	Senile dementia. 4 years	1955 3 ECT 1956 9 ECT 1956 chlorpromazine for 1 month 1956 reserpine for 2 months 1957 reserpine for 1 months 1957/59 chlorpromazine for 24 months Continues treatment	 225 4 5 175	Dyskinesia observed June 1959, persisting in October 1959
8. O. H.	77	Senile dementia. 5 years	1956 chlorpromazine for 1 months 1956 chlorpromazine for 4 months 1957 reserpine for 1 month 1957 reserpine for 2 months 1958/59 chlorpromazine for 18 months Continues treatment	75 50 2 1.5 100	Dyskinesia observed June 1959, persisting in October 1959
9. X. N.	54	Schizophrenia. 24 years	1955 reserpin for 2 months 1957/59 chlorpromazine for 18 months Continues treatment	5 150	Dyskinesia observed June 1959, persisting in October 1959
10. L. N.	52	Schizophrenia. 18 years	1956 reserpine for 1 month 1956/59 chlorpromazine for 39 months Continues treatment	1.5 250	Dyskinesia observed July 1959, persisting in October 195

when Parkinsonian rigidity caused by pharmaca diminished after reduction of the dose or termination of the treatment. In two patients (nos. 10 and 11) further treatment with reserpine was indicated, and in both cases dyskinesia still remains unabated. In no. 7 dykinesia disappeared on reduction of the dose of perphenazine.

Perphenazine treatment has terminated in 12 cases, and in 5 of these cases dyskinesia disappeared after a fortnight to 4 months, but in 7 patients dyskinesia still remains at the end of the observation period in

Table 3. *Patient with Dyskinetic syndrome after treatment with reserpine*

Name	Age	Diagnosis and duration of disease	Treatment	Average dose per 24 hours (mg)	Dyskinesia
O. P.	72	Schizophrenia. 27 years	1955/58 reserpine for 35 months 1958/59 reserpine for 10 months Continues treatment	2 3.5	Dyskinesia observed since June 1959 somewhat diminished under treatment with benztropine (Cogentine)

October 1959, respectively 4, 5, 6, 7, 8, 9, and 9 months after the cessation of perphenazine treatment.

Table 2 shows 10 patients in whom the dyskinetic syndrome is ascribed to chlorpromazine. 6 of these patients have not had any other psychopharmaca than chlorpromazine, while 4 have also had small doses of reserpine for short periods, but chlorpromazine treatment was of long duration and predominating in all 10 patients.

In 7 cases further chlorpromazine treatment was indicated in spite of dyskinesia, which still remains unchanged in these 7 patients. In 2 cases treatment ceased in June 1959 but dyskinesia was unchanged at the end of the observation period 4 months later.

No. 3 patient stopped chlorpromazine treatment in December 1957, but dyskinesia was not observed prior to the systematic examination of all patients in June 1959, and then only in a mild degree. As the patient has had no other treatment than chlorpromazine, it is however probable that dyskinesia has been present since the chlorpromazine treatment. The patient shows no sign of encephalitis or other plausible causes of the dyskinetic syndrome.

Table 3 shows one patient with a typical dyskinetic syndrome. The patient has had no other pharmacotherapy than reserpine, small doses being given for a long time. There are no other traceable causes of the dyskinesia, and we may thus presume that it was caused by the reserpine. The patient continues the reserpine treatment which has a good effect on the psychosis. Dyskinesia has diminished under treatment with Cogentine (Benztropine Methanesulfonate).

Table 4 lists 3 patients treated with various psychopharmaca. It is not possible to judge which substance is the principal cause of the syndrome. In no. 1 patient the syndrome disappeared on reduction of the thioridazine (Melleril) dosis. In no. 3 the dyskinesia disappeared in 4 months after the termination of the treatment, but in no. 2 dyskinesia has now persisted for 8 months after the termination of the treatment.

In Table 5 four patients are entered in whom the dyskinetic syndrome is ascribed to electroconvulsive therapy. In the two first cases dyskinesia arose in immediate connection with electroconvulsive therapy,

Table 4. *3 patients with Dyskinetic syndrome after treatment with various drugs*

Number and name	Age	Diagnosis and duration of disease	Treatment	Average dosis per 24 hours (mg)	Dyskinesia
1. H.A.P.	66	Dementia. Encephalopathia atrophicans. 9 years	1957 reserpine for 1 month 1958 chlorpromazine for 2 months 1958 perphenazine for 4 months 1959 thioridazine for 6 months Continues treatment with thioridazine in reduced dose	2 200 20 75	The dyskinetic syndrome which was observed in June 1959 was somewhat atypical, the rhythm being faster than usual. The syndrome disappeared 3 months after reduction of thioridazine dose
2. A. N.	78	Dementia arteriosclerotica. 5 years	1957 chlorpromazine for 7 months 1958 chlorpromazine for 3 months 1958 perphenazine for 1 month 1958/59 thioridazine for 3 months Treatment terminated February 1959	225 125 20 80	Dyskinesia observed in June 1959, still persisting 8 month after ceasing the treatment
3. K. N.	43	Schizophrenia. 20 years	1958 chlorpromazine for 2 months 1958 perphenazine for 6 months 1958/59 thioridazine for 8 months Treatment terminated June 1959	325 50 225	Dyskinesia observed in June 1959, disappeared in 4 months

Table 5. *4 patients with Dyskinetic syndrome after ECT*

Number and name	Age	Diagnosis and duration of disease	Treatment	Average dosis per 24 hours (mg)	Dyskinesia
1. G. P.	71	Manic-depressive psychosis (protracted endogenous depressions). 55 years	1952/54 20 ECT 1955/56 chlorpromazine for 13 months 1956/57 chlorpromazine for 3 months November 1957 12 ECT 1958 chlorpromazine for 7 months	 200 250 200	Dyskinesia arose in immediate connection with ECT in November 1957. The syndrome persisting 23 months later
2. A.H.N.	56	Schizophrenia (prefrontal leucotomy 1949). 15 years	1955/56 chlorpromazine for 16 months 1956 reserpine for 1 month 1957 chlorpromazine for 4 months 1957 chlorpromazine for 5 months December 1957 13 ECT	250 3 300 400	Dyskinesia arose in immediate connection with ECT in December 1957. It persists unchanged 22 months later
3. D. A.	74	Senile melancholia. 8 years	1952/59 a total of 192 ECT 1955 chlorpromazine for 3 months 1955 reserpine for 6 months 1956 chlorpromazine for 2 months 1956/57 reserpine for 1 month 1957 chlorpromazine for 1 month 1958 perphenazine for 1 month ECT treatment once a week continues	 250 3 200 3 200 16	Dyskinesia observed in April 1959, persisting unchanged since then
4. A.M.S.	72	Senile depression. 5 years	1955/58 28 ECT 1958 reserpine for 3 months 1958 chlorpromazine for 1 month April 1959 1 ECT May—July 1959 chlorpromazine for 2 months Chlorpromazine treatment terminated July 1959	 0.75 100 100	Dyskinesia observed in June 1959, has since abated considerably

which is thus undoubtedly the direct cause. Patient no. 3 has had pharmacotherapy for short periods with moderate doses of chlorpromazine, reserpine and perphenazine, but very intensive electroconvulsive

treatment, which treatment is the only one to have recognisable effect on the psychosis. In this patient electroconvulsive therapy is presumably the main cause of the dyskinetic syndrome. Patient no. 4 had so little pharmacotherapy that this can hardly have caused dyskinesia, thus electroconvulsive therapy is presumably the main cause. Dyskinesia dimished in this patient although chlorpromazine treatment continued for one month after the observation of the syndrome, but three months after the termination of the chlorpromazine treatment dyskinesia has, however, not yet completely gone.

Discussion

Out of 29 patients with dyskinesia caused by pharmacotherapy continuation of this therapy was indicated in 12 cases. In 2 of these 12 cases dyskinesia disappeared on reduction of the dose. In the 10 other patients who have continued pharmacotherapy dyskinesia still persists. In some instances dyskinesia has diminished after Cogentine treatment, while treatment with anti-Parkinson compounds such as Brocadisipal (β-dimethylaminoethyl-2-methylbenzhydryletherhydrochlorid) and Aturban was without recognisable effect.

17 patients have stopped pharmacotherapy, and in 6 of them dyskinesia disappeared within 10 days to 4 months after the cessation of the treatment. 5 of these 6 patients had had perphenazine and one patient had had various compounds.

In 11 of the 17 patients who terminated pharmacotherapy dyskinesia has remained after the termination of the pharmacotherapy. 7 of these cases were treated with perphenazine, and dyskinesia persists 4, 5, 6, 7, 8, 9, and 9 months respectively, after the treatment. This group also includes 3 patients treated with chlorpromazine, in whom dyskinesia has so far lasted 4, 4, and 22 months respectively, and one patient treated with various pharmaca in whom dyskinesia has lasted for 8 months. Some of these 11 cases of dyskinesia may disappear, but this is unlikely, since so far no patient shows any sign of improvement.

5 patients with permanent dyskinesia were aware of these involuntary movements, and two of them were much inconvenienced. The remaining patients with permanent syndromes are on account of their psychosis hardly aware of their dyskinesia; at least they do not complain of it. However, dyskinetic patients inevitably attract the attention of their surroundings, and thus these patients are also caused great inconvenience by their ailment.

It seems as if perphenazine is the most toxic of the pharmaca in question, as 15 cases of dyskinesia have been found, including 7 irreversible ones, amongst 155 patients treated with perphenazine.

The relatively large number of cases of dyskinesia caused by chlorpromazine (10, out of which 3 are irreversible) are due to the fact that chlorpromazine has been the chief drug of the department since 1954. Several hundred patients have been treated with chlorpromazine but it is not possible to give the exakt number.

Reserpine is only used as an exception, generally as an experiment when other treatment has no effect. Thus no conclusions may be drawn as to the toxidity of reserpine from the single case of dyskinesia due to reserpine.

Most of our cases of bucco-linguo-masticatory dyskinesia occurred after prolonged treatment while the reversible dyskinetic symptoms described in the literature occurred at an early stage of the treatment.

It should be noted that the patients in which the dyskinetic syndrome occurs are rather old, the average age being 66, and among the younger patients several have an organic brain disease. Therefore it may be presumed that the dyskinetic syndrome occurs most easily in elder persons and in persons with organic brain lesions.

We conclude from the present material that prolonged administration of psychopharmaca carries the risk of manifestation of bucco-linguo-masticatory dyskinesia which in some cases may prove to be irreversible. The risk of manifestation of a dyskinetic syndrome seems greatest in elderly patients and in persons with organic brain diseases[1].

Summary

A dyskinetic syndrome consisting of involuntary grimaces, mastication, and propulsion of the tongue, in some cases in connection with akathisia and tasikinesia, due to electroconvulsive therapy, has been observed in 4 patients.

Moreover 29 cases have been observed, which were due to pharmacotherapy, in 15 cases with perphenazine, 10 cases with chlorpromazine, and one case with reserpine, and in 3 cases with various compounds.

12 patients are continuing the pharmacotherapy and dyskinesia disappeared in 2 of these cases after the dose had been reduced.

17 patients discontinued the treatment, but in 11 of these dyskinesia proved irreversible after an observation period of 4 to 22 months.

[1] Renewed investigation in May 1960 of the 11 patients with "irreversible" bucco-linguo-masticatory dyskinesia showed: In 1 case the dyskinesia disappeared in 6—7 months, in 2 cases the pharmacotherapy was renewed because of the psychotic condition. 4 patients have died, they had all of them dyskinesia when they died 7, 10, 15 and 23 months after cessation of the treatment, in 3 of these cases the brain is undergoing histological investigation which has not yet been finished. 4 patients have still dyskinesia 11, 12, 13 and 16 months after cessation of the treatment respectively. In May 1960 we have further observed 3 cases of the dyskinetic syndrome due to thioridazine (Melleril).

Dyskinesia generally occurred after prolonged treatment in elderly patients and patients with organic brain diseases.

The conclusion is drawn that prolonged administration of psychopharmaca, which cause neurological side effects, carries the risk of lesion of the central nervous system with irreversible dyskinesia, especially in elderly patients and patients with organic brain diseases.

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A. FAURBYE, M.D.
St. Hans Mental Hospital, Department D., Roskilde/Denmark