

escaped detection and infected three infants, two of whom developed diarrhoea. The infection was, however, contained within the isolation unit.

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Severe Depressive Mood Changes Following Slow-release Intramuscular Fluphenazine Injection

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Summary: Sixteen patients in whom schizophrenia was initially diagnosed and who were treated with fluphenazine enanthate or decanoate developed severe depression for a short period after the injection. In five cases this depression is thought to have been responsible for suicide. In 8 out of 10 cases the depression responded to electroplexy (E.C.T.). It is recommended that patients who are treated with fluphenazine should be carefully supervised.

Introduction

Slow-release intramuscular fluphenazine, both in the enanthate (Moditen) and in the decanoate (Modecate) form, is increasingly being used in the community treatment of schizophrenia on account of the simplicity of its administration—one injection every two to four weeks—and the assurance it gives that the patient has taken the medication in the dosage prescribed. In the past many chronic schizophrenics who responded to maintenance phenothiazine treatment thwarted efforts to rehabilitate them in the community by neglecting to take their medication orally in the amounts and at the time required. With fluphenazine enanthate many of these patients can now be maintained out of hospital (Bethell *et al.*, 1966; Freeman, 1967). Nevertheless, if injected slow-release drugs are to mean a major advance in psychiatric treatment more attention must be paid to their side-effects as well as to their effects. Lack of knowledge of the precautions with which a drug should be administered can lead to its unwarranted total rejection by doctors if fatal or other adverse effects occur.

This paper describes depressive mood changes which may follow a slow-release injection of fluphenazine. The case

of one patient on whom a trial was conducted is reported in detail and 15 others are discussed, including five who committed suicide.

Trial Case

A 39-year-old unmarried man with a five-year history of mental illness was admitted to a mental hospital via a general hospital casualty department in November 1968 after he had attempted suicide by slashing his wrists.

Personal and Family History.—There was no family history of mental illness apart from one maternal uncle who had a “break-down” after the first world war. Birth, early milestones, and schooling were normal. He was regarded as shy and “highly strung.” At age 16 he became articled to a firm of accountants, qualifying as a chartered accountant at the age of 28. He had worked in this capacity ever since.

Previous Psychiatric History.—In 1963 (aged 34) he began to complain that advertisements in *The Times* were being directed against him and that people were accusing him of being a Communist. The following year these ideas of reference became more pronounced, other typical schizophrenic symptoms appeared, and eventually he had to be admitted to a mental hospital under Section 25 on account of disturbed behaviour. The diagnosis made on this first admission was schizophrenia, and he was treated with chlorpromazine. He was readmitted—never for longer than five weeks—in 1965, 1966, and 1967 with the same diagnosis, and with similar symptomatology. On the last occasion, however, which occurred shortly after his father's death, he was given six treatments with E.C.T. On discharge in March 1967 intramuscular fluphenazine enanthate was prescribed on the grounds that he would not persevere with oral medication. He later moved to East London and arrangements were made with his Sussex general practitioner to give him a fortnightly injection of 25 mg. of fluphenazine enanthate when he came down to visit his mother. No psychiatric supervision was provided.

Present Episode.—For three to four months before admission he had been having recurring bouts of severe depression about every fortnight. The usual pattern was to feel tired and sad on a Sunday evening and to wake up the next morning very depressed and low.

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While in this state he had to force himself to go to work, he shunned people, felt grossly inadequate to cope with anything, and was beset by suicidal ideas. He would remain in this state two or three days, and by Thursday of the same week had returned to normal. During one of these depressive episodes he slashed his wrists and was admitted to hospital. He was at the time working in the City of London and had lodgings in the suburbs but spent the week-ends with his widowed mother. He attributed these depressive episodes to social isolation and feelings of inadequacy at work. On admission to hospital he was co-operative and well-orientated in time and place. He looked depressed and said he felt very low and suicidal. No delusions, ideas of reference, thought disorder, or hallucinations were elicited. The provisional diagnosis on admission was depressive illness. Within 24 hours of admission the mood had returned to normal, he was able to smile and to appreciate a joke, and said that the depression had disappeared. He seemed to be well-mannered, intelligent, and shy. This striking sudden improvement was at the time attributed to the relief of symptoms which is sometimes observed in patients when they are admitted to hospital after a suicidal attempt (Stengel and Cook, 1958).

Inpatient Response to Intramuscular Fluphenazine Enanthate.—A week after admission he received his fortnightly injection. Twenty-four hours later he became withdrawn, refused food, and took to his bed in mid-afternoon. He appeared sad and miserable, and was unwilling to discuss his state of mind. He remained in this depressed state two days. When he returned to normal he said that he had felt the same way as when he attempted suicide. A similar depressive reaction recurred when the injection was repeated a fortnight later. A check on the dates of injection during the previous three months showed that he had had an injection of fluphenazine enanthate four days before his suicidal attempt. In view of the apparent association that had developed in this patient between this drug and the depressive mood swings, the following trial was conducted.

Trial

Stage One.—The patient was not given any medication for four weeks and was observed in hospital in order to exclude spontaneous periodic mood changes. No changes were observed during this period.

Stage Two.—After this period of observation he was given a trial dose of 25 mg. of fluphenazine enanthate intramuscularly, and for 10 days starting five days before the injection he was assessed clinically and psychometrically.

Clinical Assessment

During his stay in hospital he was interviewed by one of us (R. de A.) three times a week. For a week before the injection, on the days he was not due for an interview, his condition was discussed with the chief ward nurse and the nursing reports were perused. He was given the trial injection on a Wednesday at 3 p.m.; by mid-afternoon of the following day he felt low, wanted to be left on his own, and had no desire to talk to anyone, read, or watch television. He took to his bed at about 4 p.m. In the opinion of the charge nurse he was a suicidal risk. When interviewed on the Friday the change in external appearance was striking—he looked gloomy, he did not respond with a smile to a joke, and there was no spontaneous conversation. His answers were limited to what was strictly necessary. He denied any paranoid or hypochondriacal ideas or any feelings of guilt. He simply said that he felt very low and if he were alone in digs he would take his life. By Friday evening there was some improvement, and when he was interviewed again on Saturday he had returned to his usual normal self.

Psychometric Assessment

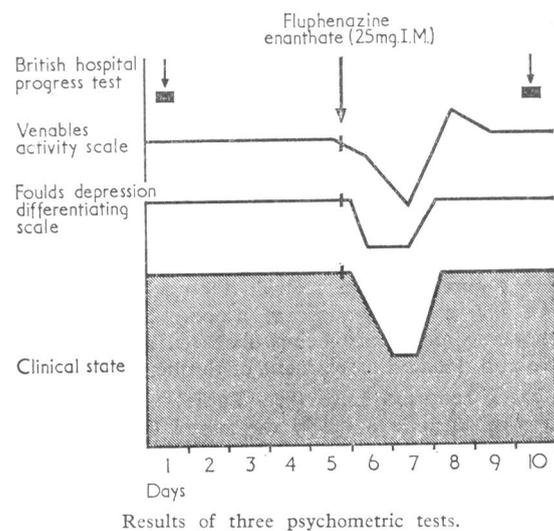
Three tests were used: the Venables Ward Activity Scale and the Foulds Depression Differentiating Scale, which were given daily for seven days starting three days before injection, and the British Hospital Progress Test, which was administered a week before the injection and repeated again on the week after. The following results were obtained:

Venables Ward Activity Scale (Venables, 1957).—The baseline score on the days preceding the injection was 30 points, which went down one point 24 hours after the drug was administered, and descended five points at the 48th hour. It had returned towards the baseline, exceeding it by one point, at the 72nd hour.

Foulds Depression Differentiating Scale (Foulds, 1960).—The scores were negative for all the 14 items during the seven days tested except for the two days after the injection, when items 1 (I feel the future is hopeless), 6 (I feel so low in spirits that I could sit for hours on end), 13 (I feel when I go to bed that I couldn't care if I never woke up again), and 14 (I feel I might do away with myself because I am no longer able to cope) scored positively. This is an unusually sensitive questionnaire scale in which the change recorded by this patient represents a move of about 25 percentiles.

British Hospital Progress Test (Sarwer-Foner et al., 1966).—The readings on both occasions (five days before and after the injection) failed to show the existence of a classical depression, suggesting that the depression noted clinically was of an atypical transitory type. These results helped, together with the other evidence, to confirm the clinical assessment that the depression following the injection, though very severe, was very short-lived.

The Chart portrays graphically the results of these various tests and their relation to the clinical changes.



Other Case Reports

One of us (M. W. P. C.) treated a series of 124 patients diagnosed as schizophrenics with intramuscular fluphenazine and found severe depression of mood associated with its administration in 10 cases (8.06%) (See Table).

Suicide Reports

The notes of five patients who committed suicide while on intramuscular fluphenazine were perused to see if there was a possible temporal association between the injection and the suicidal act.

Case 11.—Man aged 41. Inpatient in a mental hospital for six years. Chronic paranoid schizophrenic, withdrawn, preoccupied with hearing voices, deluded. He was started on intramuscular fluphenazine enanthate 25 mg. every month, which was changed to fluphenazine decanoate three months later. Six days after the first injection of fluphenazine decanoate he cancelled a promising interview for a job and committed suicide by drowning on the 13th day after the injection.

Case 12.—Man aged 46 with a history of 14 admissions to hospital between 1946 and 1968. Diagnosed in an early case conference as a schizophrenic with some affective features. In the course of his various admissions the diagnosis had been either chronic schizophrenia or schizo-affective state. In the doctors' notes through the years remarks can be found that, though on the whole the symptomatology was typically schizophrenic, there were moments when affective features, depressive or hypomanic, pre-

dominated. He had made a suicidal attempt in 1946 and again in 1966. During his last admission he was stabilized on intramuscular fluphenazine enanthate and two months later took a fatal dose of sleeping tablets six days after his last injection.

Case 13.—Man aged 32. Admitted five times to mental hospital between 1957 and 1968. Though schizoid in appearance and showing at times unexplainable and incongruous behaviour and affect, such as trying to strangle his mother for no obvious reason, no overt signs of schizophrenia were found on examination at the time of first admission. He showed guilt and depressive features which called for E.C.T. and thiopentone abreacts, but without great improvement. Nevertheless, on subsequent admissions a schizophrenic impoverishment of personality, thought disorder, and other typical symptoms were obvious from the notes. He gassed himself 26 days after an injection, having been on intramuscular fluphenazine enanthate for four months.

Case 14.—Woman aged 38. Had seven admissions to mental hospital between 1962 and 1968. First admission to hospital was precipitated by a suicidal attempt. The clinical picture through the years showed a combination of schizophrenic and affective features. Fortnightly fluphenazine enanthate was given for three months, and when she became mildly depressed it was changed to monthly fluphenazine decanoate injection. She committed suicide 19 days after the third fluphenazine injection.

Case 15.—Woman aged 46. Had one previous admission when aged 29—schizophrenic. Three months after being stabilized on fluphenazine decanoate she was discharged from hospital, but when seen two weeks after her fourth injection she showed severe extrapyramidal symptoms and her condition had deteriorated. Before she could be readmitted she committed suicide 17 days after this injection.

Discussion

In this report we have restricted ourselves to describing the more severe disturbances of mood. Lesser changes of affect that may occur are being observed as part of a more extensive and detailed assessment of fluphenazine.

The cases reported here (see Table) suggest that some patients may become severely depressed for a short period after an injection of fluphenazine enanthate or decanoate. So far no clear pattern has been established regarding when and in whom this is likely to occur. The lack of adverse effects in the past is no indication that these may not appear in the future. In the trial case, for instance, the patient received fluphenazine enanthate for more than six months before he began to react repeatedly to the injection with severe depression, and the same thing happened with other cases in the series.

We cannot ignore the possibility that patients who become depressed after fluphenazine have been mistakenly diagnosed

as schizophrenic when in fact they were suffering from an affective disorder. In this series three patients (Cases 1, 7, and 8) were found on reassessment to have an affective disorder, and Cases 12 and 13 showed depressive or hypomanic features at some stage of their illness, which was regarded as a schizo-affective disorder. N. Capstick (personal communication, 1969) postulates that patients who react to the injection with depression have a previous history of affective mood swings. Misdiagnosis, however, could be only a partial explanation. In all the patients who showed a depressive reaction to fluphenazine the diagnosis was reconsidered very carefully. Apart from the three cases mentioned above, a typical schizophrenic history and symptomatology was found among all the other patients in this series, and those who had a subsequent psychotic episode while off fluphenazine presented on this latter occasion with schizophrenic and paranoid symptoms and not with a depressive picture.

In the cases reported the temporal association between injection and onset of depression is too close to be disregarded either clinically or theoretically. The clinical manifestations of this depressive episode is similar to that of a primary depressive illness, and, like the latter, it responds to E.C.T. The fact that the drug may convert schizophrenia into an acute depression which can then be resolved by E.C.T. has important theoretical and practical implications, as Hamilton (1965) pointed out when commenting on the cases of schizophrenia changing into depression following the administration of haloperidol, reported by Tewfik (1965). From the point of view of practical therapeutics, in the cases reported in this series fluphenazine enanthate has converted a schizophrenic illness into an affective disorder. This affective disorder responds to treatment, and in those cases in which fluphenazine was restarted on recovery no further schizophrenic psychotic manifestations have been observed so far. Further studies are required, ideally along the lines suggested by Doll (1969), and we also need to know far more about changes and disturbances of mood which may occur in the course of a schizophrenic illness.

Schizophrenia in itself carries some risk of suicide (Fremming, 1951; Helgason, 1964; Markowe *et al.*, 1967) and this risk will be greater if the patient is misdiagnosed as schizophrenia when in fact he is suffering from a depressive illness. Extra care should be taken, therefore, when administering a drug with a potential mood-depressant effect to a patient already at risk.

The case described in detail also provides an example of how the advantages of fluphenazine can turn into disadvantages if they lessen contact with patients who are still in need of such contact and so lead to a neglect of psychiatric supervision.

Case No.	Age and Sex	Duration of Mental Illness	No. of Known Depressive Episodes	Original Diagnosis and Clinical Type	Change of Initial Diagnosis on Reassessment	Months on Intramuscular Fluphenazine Enanthate before Depressive Episode	No. of Days after Injection			Treatment given for Depression	Restabilized on Intramuscular Fluphenazine after Depression	Symptom-free Months since Restabilized on Fluphenazine
							Suicidal Attempt	Admission to Hospital	Seen as Emergency in Outpatient Department			
1	26 F	12 years	1	Paranoid schizophrenia	Manic-depressive	2	2	2	—	E.C.T.	No	—
2	54 F	15 "		Paranoid schizophrenia		7	3	—	—	E.C.T.	Enanthate	9
3	34 F	3½ "		Catatonic schizophrenia		2	11	11	—	E.C.T. and imipramine	Enanthate	6
4	66 M	30+ "		Paraphrenia		6	—	6	3	E.C.T.	Decanoate	1
5	56 F	5 "		Hebephrenic schizophrenia		3	—	9	6	E.C.T.	Enanthate	5
6	19 F	3½ "		Hebephrenic schizophrenia		5	—	9	5	E.C.T. and imipramine	Enanthate	6
7	24 F	5 "		Puerperal psychosis (schizophrenia)	Depression with hysterical features	1½ 3½ (decanoate)	17 21	10 21	13 10	Imipramine	Enanthate Decanoate No	5½ 7 3½
8	54 F	9 "	3	Paraphrenia with excitability	Manic depressive	4	8	—	—	E.C.T.	No	—
9	25 F	3 "		Hebephrenic schizophrenia		2 (decanoate)	—	—	28	E.C.T.	Decanoate	14 days
10	45 F	5 "		Paranoid schizophrenia		7	—	7	6	E.C.T. and imipramine	Decanoate	1

Many psychiatric services have started "Moditen clinics" in general hospitals or day centres. In some of these treatment has gradually been left to persons whose sole function is to give the patient an injection every fortnight and check, perhaps, that no overt extrapyramidal symptoms have appeared since the last treatment. In these circumstances the appearance of psychiatric symptoms or side-effects may be ignored or missed. The same thing may happen when a general practitioner is requested to administer the drug. In the belief that the psychiatrist continues to supervise the treatment he may restrict himself to giving the injection. It appears essential, therefore, to keep the patient who is on intramuscular fluphenazine under careful supervision. Provided that there is this scrupulous follow-up, there appears to be no contraindication to continuing fluphenazine injection to those patients who have previously shown a depressive reaction to the drug. Relatives can be enlisted to help in this supervision, and they can be instructed to watch for external signs indicative of a depressive mood swing, particularly in the days following the injection. In the series studied both patients and relatives have attended the outpatient department for group instruction and discussion of the treatment, its advantages, and its pitfalls.

If intramuscular fluphenazine or other similar slow-release drugs are to be used in an effective and safe way to help keep the schizophrenic out of hospital it should not be done to the detriment of two important elements of the community treat-

ment of psychiatric patients: the regular support of patients and relatives, and the early detection of relapses or changes in the course of the illness.

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Retinopathy at Diagnosis of Diabetes, with Special Reference to Patients under 40 Years of Age

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[WITH SPECIAL PLATE FACING p. 553]

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Summary: Diabetic retinopathy was present in 7.5% of 5,157 newly diagnosed patients seen at the Birmingham General Hospital Diabetic Clinic between 1960 and 1967. Although the condition becomes commoner with increasing age it is found in 1.5% of patients aged 20 to 39 years. The aetiology is discussed, the conclusion being that in young as in elderly diabetics asymptomatic diabetes of long duration is the main factor.

Introduction

Retinopathy is generally acknowledged to be a late complication of diabetes. Nevertheless, it is found at diagnosis in a small number of diabetics, the prevalence in different series varying from 4 to 15% (Lawrence, 1949; Aarseth, 1953; Lundbæk, 1955; Pyke and Roberts, 1959; Whittington, 1968). At the General Hospital, Birmingham, retinopathy at diagnosis has been recorded in 7.5% of patients. This figure is derived from a series of 5,157 newly diagnosed diabetics seen from 1960 to 1967.

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Retinal changes at diagnosis of diabetes have mainly affected older patients, and they are considered to be the result of pre-existing mild diabetes of long duration (Lundbæk, 1955; Pyke and Roberts, 1959). In the present study, however, among the 591 patients aged 20 to 39 years nine had retinopathy at diagnosis—a prevalence of 1.5%.

The purpose of the present paper is to present the figures for retinopathy at diagnosis in the various age groups and to draw particular attention to this group of younger diabetics.

Method

Patients of all age groups except children attend the General Hospital Diabetic Clinic and represent a typical hospital diabetic

TABLE I.—*Classification of Diabetic Retinopathy*

Stage 1:	Venous dilatation and capillary microaneurysms
Stage 2:	Microaneurysms, haemorrhages, and exudates
Stage 3:	Stage 2 plus newly formed blood vessels (neovascularization) and vitreous haemorrhages
Stage 4:	As in stage 3 with fibrotic bands and retinal destruction

outpatient population. At first attendance they give their history and have a physical examination, including a neurological assessment. The fundi are examined by experienced observers in a dark room, a mydriatic being used in one eye. The ophthalmoscopic appearances are graded according to the classification of Fabrykant and Gelfand (1965) (Table I).