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ASSESSMENT OF DRUG-INDUCED EXTRAPYRAMIDAL REACTIONS AND OF DRUGS GIVEN FOR THEIR CONTROL

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Extrapyramidal syndromes have been estimated to occur in about 40% of patients receiving phenothiazine drugs, and thus present a most important complication of treatment (Ayd, 1961).

The common use of phenothiazine drugs, and the frequency of their unwanted effects, has led to attempts to control the effects on the extrapyramidal system. Not unnaturally, it has been assumed that the drugs most likely to be helpful are those which are used in the treatment of Parkinson's disease itself, and some of these, particularly those with anticholinergic effects, have come into widespread use for this purpose. The full implications of this assumption, and the difficulties in testing it, were not apparent to the author until he took part in a trial of the new drug amantadine in the control of drug-induced parkinsonism (Mindham *et al.*, 1972). Amantadine had already been shown to be effective in Parkinson's disease.

From a study of previous trials of substances used in controlling drug-induced parkinsonism we recognized several factors important to the design of such trials: (1) that a failure to take the offending phenothiazine could result in an improvement in its unwanted effects on the extrapyramidal system; in consequence, we must ensure that the provocative substance is taken by patients in a sufficient dosage to produce parkinsonism and in the same dosage throughout the investigation; (2) that phenothiazine drugs vary in their potency in causing drug-induced parkinsonism, so that we must use one drug throughout the study; (3) that the severity of the unwanted effects might decline with continued medication and that this must be allowed for in the design of the study; (4) that control treatments were required for comparison with the trial substance.

The design which resulted is shown in Figure 1. The patients who took part in the study were chronic schizophrenic patients in whom symptoms were well controlled by injections of fluphenazine decanoate alone, every 4 weeks. This mode of administration ensured that the drug had been taken. Dosage of drug used in each patient was known to produce parkinsonism from observing each patient, at the appropriate time after injection, before the study began; and this dosage was kept constant throughout the study. The three treatments given to control drug-induced parkinsonism were amantadine, orphenadrine and placebo; these were administered double-blind and in all possible sequences of administration. Patients were assessed at a time when the symptoms were thought to be maximal, that is, between 3 and 5 days after injection of fluphenazine decanoate (*Drug and Therapeutics Bulletin,* 1970); and in each individual patient this period was kept constant. Assessments were made using a standardized clinical examination, a small battery of performance tests, the Zung mood scale, and a questionnaire on unwanted effects.

We found no differences between treatments with regard to their efficacy in controlling drug-induced parkinsonism. This finding took us completely by surprise and led us to examine the trial carefully for possible errors and to look at earlier studies in greater detail. The design of our own study seemed to have met many of the deficiencies of earlier studies, but it was evident that the methods of assessment used were in many cases crude, subjective reports of symptoms from patients were often unreliable, and the patients' motivation in carrying out performance tests was often inconsistent.

A closer study of previous trials showed that many of the anticholinergic drugs used in Parkinson's disease itself had never been tested against placebo, but more often against each other; and that studies of the control of drug-induced parkinsonism often contained basic methodological weaknesses. Moreover, several studies showed fluctuation or

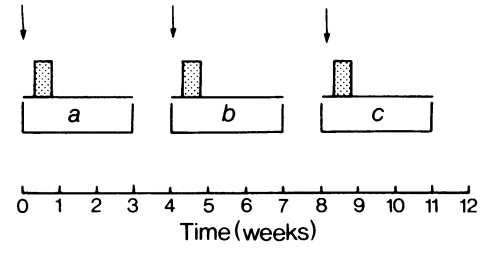

Figure 1 Comparison of amantadine, orphenadrine and placebo in parkinsonism induced by fluphenazine decanoate. Arrows, assessment injection.

decline in unwanted effects (Brumlik *et al.*, 1964); others showed that withdrawal of anticholinergic drugs did not necessarily result in the return of symptoms (Mandel & Oliver, 1961), or that re-introduction of drugs which had previously produced parkinsonism did not always result in the return of the symptoms (Cahan & Parrish, 1960). What is more, some studies failed to show the anticholinergic drugs to be effective (Ekdawi & Fowke, 1966). All these studies concerned the effects of orally administered substances, where the drugs were generally given to prevent the appearance of parkinsonism.

A small series of studies of the effectiveness of intravenously administered anticholinergic drugs failed to show any benefit (Simpson, 1970). In these studies the drugs were given when parkinsonism was already present. The author comments on the difficulties in conducting research in this area but curiously rejects the possibility that the drugs might be ineffective as the cause of his findings.

Our study suggested that amantadine and orphenadrine have no place in the management of parkinsonism induced by fluphenazine decanoate. This conclusion was tempered by caution, as we had become aware of the great difficulties in conducting methodologically sound investigations in this area.

More recently, the opportunity to carry out another study of the use of drugs in controlling drug-induced parkinsonism led us to look for alternative methods of assessing symptoms. A number of clinical methods of assessing patients with parkinsonism have been devised. These have usually been used for assessing the effectiveness of treatment in Parkinson's disease itself, although at least one standardized clinical assessment has been specially devised for use in patients with drug-induced parkinsonism.

A fairly typical example of standardized rating scales for clinical signs and symptoms is the scale developed by Godwin-Austen *et al.* (1969) and consists of the assessment of autonomic function, including seborrhoea and salivation; a clinical examination, which includes assessment of posture, tremor, rigidity and speed of action; together with an assessment of some common activities in daily life, such as dressing, bathing, getting into bed, and so on. All these factors are rated on a four-point scale and the scores added to given a total score referred to as the 'Total Disability Score'. This scale has been used successfully in a number of studies to investigate the effectiveness of new treatments in Parkinson's disease. There are objections to any rating system which involves the addition of scores derived from such a wide variety of observations, but the method seems to work well in practice and has the advantage of covering a wide range of symptomatology, most of it very relevant to the patient's disability. It has been found (Mindham *et al.*, in press) that the 'Total Disability Score' was closely correlated with the scores on three leading clinical signs—tremor, akinesia and rigidity. This finding is not surprising, but it is reassuring to know that the various elements in this scale are so closely related.

A scale specifically designed for use in assessing drug-induced parkinsonism has been developed by Simpson & Angus (1970) over a number of years. This scale is a standardized clinical examination including assessments of rigidity, tremor and salivation. They have attempted to validate the scale by showing that it effectively separates patients on different dosages of a drug which induces parkinsonism, and have also assessed the reliability of the examination between raters; tests of rigidity and the glabellar tap showed a high correlation between raters, other tests showed a lower but generally acceptable degree of correlation.

Similar but often less well standardized and tested methods of clinical assessment have been used by other workers. A deficiency that many of these clinical methods of assessment share is that, although well suited to the assessment of patients with Parkinson's disease where there is a broad spectrum of symptoms and signs of moderate or severe degree, the methods are less well suited for use in patients with less well developed symptoms and signs, as is often the case in drug-induced parkinsonism. This problem, together with difficulties in the reliability of many tests, has led a number of workers to develop tests of performance which might be less susceptible to observer error.

A well established test is to ask the patient to walk 25 yards with a turn in the middle and to measure the time taken to do this. This test is clearly related to clinical disability and probably reflects the severity of rigidity, akinesia, and steadiness of gait.

A test of motor power recommended by Onuaguluchi (1964) is made by blowing up a sphygmomanometer cuff to 60 mmHg and asking the subject to squeeze it with all his power with each hand in turn. This test may be simplified by using the smaller cuffs designed for testing strength of grip in patients suffering from rheumatoid arthritis.

In the grooved-peg-board test, the patient places 25 grooved pegs in grooved holes in a board and the procedure is timed. The grooves require the subject to orientate the pegs before insertion, thus including a cognitive factor as well as being a test of motor function. The test has been investigated by Meier & Martin (1970) and shown to successfully distinguish between patients receiving treatment and placebo for Parkinson's disease.

A somewhat similar test has been developed by Horne (1973) from a method originally described by Talland & Schwab (1964). In this test the subject has to transfer beads from one cup to another using tweezers: sometimes he has to distinguish beads of different colours and sometimes he has to operate a Morse code tapper with the other hand. Various

sequences of these operations may be timed.

Another test which has been used is simply measuring the speed of tapping a stylus on a plate and counting the number of taps in a fixed period. This test can be made more complicated by getting the subject to alternately tap opposite ends of the plate, or make other changes in the procedure. The apparatus used has a timing device, which counts the taps in 10 s after a button is pressed, enabling performance to be measured from a longer run and overcoming the difficulty patients often have in initiating a particular action.

These last three tests clearly measure, amongst other things, speed of action and co-ordination, and are likely to be impaired in the presence of rigidity or tremor.

Finally, there are a number of tests of writing ability. These may simply involve writing a name and address while the operation is timed. Other methods have involved observation of changes in the size and form of handwriting or in the area of paper covered (Angus & Simpson, 1970).

The second study was designed with the shortcomings of the earlier study in mind, and in particular the shortcomings in the methods of assessment used. The trial treatments were piribedil, a new substance said to stimulate dopamine receptors (Corrodi *et al.*, 1971), procyclidine and placebo.

Table 1 Clinical assessment of parkinsonism

(1) Facial expression 0–3 (examine for blinking, movement of face, glabella tap, dysarthria, rapid movement of tongue)

0 = Normal
1 = Detectable immobility, mouth closed
2 = Moderate immobility, able to smile slowly, lips parted some of the time
3 = Fixed facies with severe loss of facial expression

(2) Rigidity

(*a*) Neck 0–3 (examine flexion, extension and lateral movements)

0 = Normal
1 = Detectable
2 = Moderate but full range of movement possible
3 = Severe

R	L

(*b*) Arms 0–3 (examine flexion and extension of elbow, pronation and supination)

(*c*) Legs 0–3 (examine flexion and extension)

(3) Tremor

(*a*) Face (examine face and head, mouth, tongue and titubation)

0 = Absent
1 = Slight and infrequently present
2 = Moderate in amplitude but intermittently present
3 = Severe and persistent

R	L

(*b*) Arms

(*c*) Legs

(4) Associated movements in walking (examine gait)

0 = Normal, both arms swing well
1 = One arm does not swing normally
2 = One arm fails to swing
3 = Both arms fail to swing

(5) Global assessment of physical state

0 = No evidence of parkinsonism
1 = Parkinsonism discernible
2 = Parkinsonism definitely present
3 = Moderate or severe parkinsonism

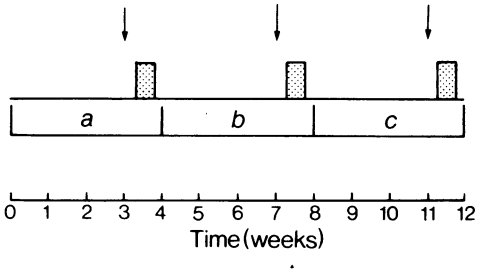

Figure 2 Comparison of piribedil, placebo and procyclidine in parkinsonism induced by fluphenazine decanoate. Arrows, assessment injection.

The general plan was like that already described, except that administration of injections and treatments for extrapyramidal effects were staggered to allow the build up of the effect of each substance (Figure 2). It was believed that for piribedil this mode of administration was necessary to reduce the severity of unwanted effects. Procyclidine was chosen as a control treatment as it is one of the few anticholinergic drugs which has been shown to be more effective than placebo in Parkinson's disease (Strang, 1965).

The methods of assessment were similar to those used in the earlier study and included a clinical examination, performance tests, and an assessment of unwanted effects. The questionnaires assessing symptoms and mood changes were omitted. A battery of pathological tests were used to monitor the toxicity of the substances, together with urine tests for the presence of the substances administered and their metabolites to check that the drugs had been taken. We considered using some of the standardized clinical examinations developed by other authors, but decided that these had no special advantages over the method we had already used. The clinical assessment carried out is shown in Table 1.

Performance tests were the same as those used earlier with two additions: the grooved-peg-board test and the tapping test. In using these tests we hoped to be able to make more objective assessments of the patients' motor function, and at the same time to avoid tests which might be markedly affected by the intelligence of the patients.

Urine tests confirmed that most patients were likely to have taken piribedil in the appropriate dosage when they were supposed to be taking it and, just as important, that they were not taking piribedil when they were supposed to be taking the placebo. Technical problems prevented the detection of piribedil in the presence of procyclidine. The urine tests lent some support to the supposition that patients were taking the treatments as intended.

Procyclidine was more effective than placebo in controlling extrapyramidal unwanted effects of fluphenazine decanoate, and piribedil less so (Mindham *et al.*, unpublished). The clinical assessments and the grooved-peg-board and tapping tests were in agreement, but the differences between the treatments were more clearly shown by the clinical assessments. This finding was a surprise to us, but has been noted by others (Horne, personal communication). The cruder performance tests of walking 25 yards, squeezing the sphygmomanometer cuff, and speed of writing a name and address did not discriminate between the treatments. We were unfortunate in this trial in that one of the substances used was far more unpleasant to take than we had anticipated; this led to difficulties in completing the trial and left it rather unbalanced. This problem is not, of course, specific to trials in this area.

The experience of these two trials left us in a somewhat unsatisfactory position; the results suggest that procyclidine is effective in controlling fluphenazine-induced parkinsonism whereas orphenadrine is not; performance tests which we had hoped to be more reliable than clinical tests were either less sensitive or failed to show differences between treatments which other methods showed. The thing which impressed most, however, was the realization of how insecurely founded are most of the claims that drugs are effective in controlling drug-induced parkinsonism.

There was clearly a need for studies which provide more basic information. We now have a study in progress which simply seeks to study the pattern of extrapyramidal signs in the weeks following the administration of fluphenazine decanoate and at the same time to test the effectiveness of some methods of assessment (Lamb *et al.*, unpublished).

Four questions must be asked: what is the pattern of extrapyramidal signs following injections of fluphenazine decanoate; is this consistent in the individual patient; do different patients show different patterns; is there a fluctuation in severity or a gradual decline?

Patients receiving injections of fluphenazine decanoate alone every 4 weeks have been studied for periods up to 6 months. The severity of extrapyramidal signs has been assessed using a standardized clinical assessment weekly and a number of performance tests (already described) twice weekly. Profiles of symptoms are shown in Figure 3.

The severity of the extrapyramidal signs, as measured by clinical and performance tests, follow similar patterns suggesting that the tests used measure related factors. The severity of signs is greatest in the third week after injection of fluphenazine decanoate and this finding held true in the individual patient during several months of observation and between patients. The absolute severity of physical signs varied from month to month in the same patient although showing the same pattern; this could clearly lead to

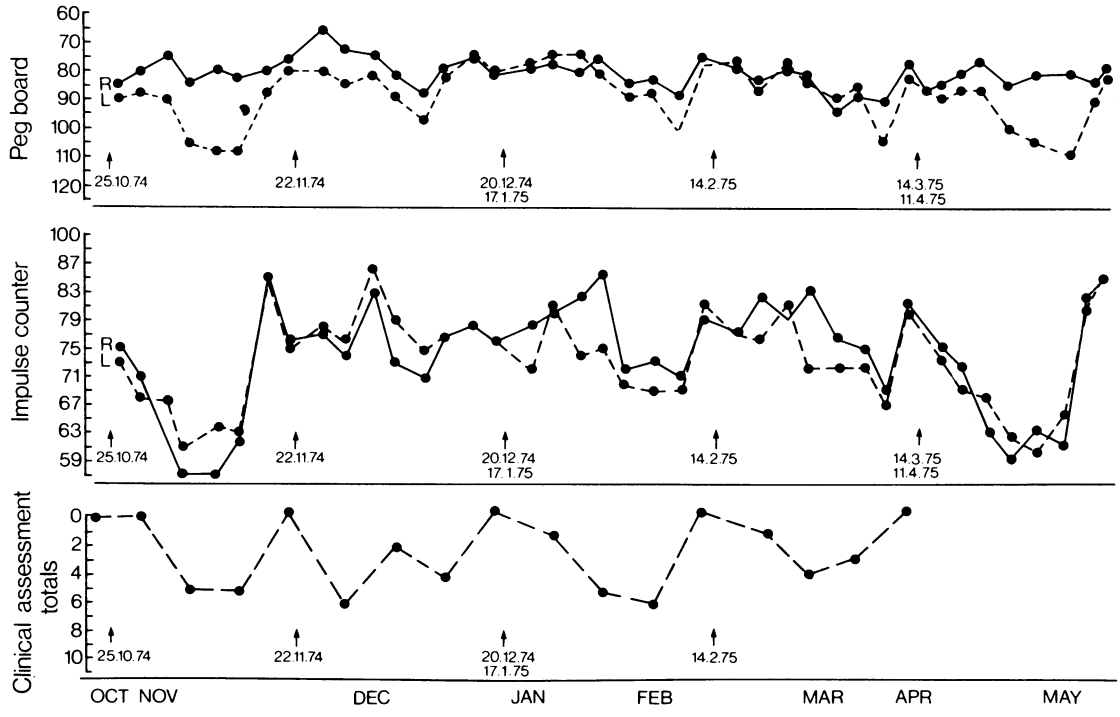

Figure 3 Assessment of symptoms of parkinsonism induced by fluphenazine decanoate over a 6-month period. Arrows, date, fluphenazine decanoate given.

erroneous conclusions in testing substances to control them. There was no evidence of a gradual decline in performance or of a practice effect. The pattern of the assessments may well reflect blood concentrations of fluphenazine and its release from the depôt; but similar problems arise by whatever route a drug is administered. The finding that the signs reach their maximum intensity in the third week is quite contrary to previous statements and clearly has some relevance to the use of drugs to control drug-induced unwanted effects and the assessment of their effectiveness.

Summary

I have tried to bring out some of the important methodological problems found in examining the effectiveness of drugs used in the control of drug-induced parkinsonism by referring mainly to studies in which I have taken part. I hope I have shown that the whole topic is far less well understood than is often assumed. The main points may be summarized as follows: there is doubt as to whether many of the drugs used in controlling drug-induced parkinsonism are really effective; the results of many studies are conflicting; many studies contain serious flaws in design; methods for assessing extrapyramidal signs are not well developed; we are ignorant of the way in which drug-induced extrapyramidal signs change spontaneously.

There is a clear need for further research in this area to improve techniques of assessment, to provide basic information on drug-induced syndromes, and to rigorously examine the efficacy of the drugs used in controlling them.

References

ANGUS, J.W.S. & SIMPSON, G.M. (1970). Handwriting changes and response to drugs. *Acta psychiat. scand.*, suppl., **212**, 28–37.

AYD, F.J. (1961). A survey of drug-induced extrapyramidal reactions. *J. Am. med. Ass.*, **175**, 1054–1060.

BRUMLIK, J. *et al.* (1964). A critical analysis of the effects of trihexyphenidyl (Artane) on the components of the Parkinsonian syndrome. *J. nerv. ment. Dis.*, **138**, 424–431.

CAHAN, R.B. & PARRISH, D.D. (1960). Reversibility of

drug-induced parkinsonism. *Am. J. Psychiat.*, **116**, 1022–1023.

CORRODI, H., FUXE, K. & UNGERSTEDT, U. (1971). Evidence for a new type of dopamine receptor stimulating agent. *J. Pharm. Pharmac.*, **23**, 989–991.

DRUG AND THERAPEUTICS BULLETIN (1970). Long-acting phenothiazine injections. *Drug. Ther. Bull.*, **8**, 69–71.

EKDAWI, M.Y. & FOWKE, R. (1966). A controlled trial of anti-parkinsonian drugs in drug-induced parkinsonism. *Br. J. Psychiat.*, **112**, 633–636.

GODWIN-AUSTEN, R.B., TOMLINSON, E.B., FREARS, C.C. & KOK, H.W.L. (1969). Effects of L-DOPA in Parkinson's disease. *Lancet*, **2**, 165–168.

HORNE, D.J. de L. (1973). Sensorimotor control in parkinsonism. *J. Neurol. Neurosurg. Psychiat.*, **36**, 742–746.

LAMB, P., MINDHAM, R.H.S. & EZZAT, M.A. The pattern of signs in parkinsonism induced by fluphenazine decanoate over a period of time. In progress.

MANDEL, W. & OLIVER, W.A. (1961). Withdrawal of maintenance anti-parkinson drug in the phenothiazine-induced extrapyramidal reaction. *Am. J. Psychiat.*, **118**, 350–351.

MEIER, M.J. & MARTIN, W.E. (1970). Measurement of behavioural changes in patients on L-DOPA. *Lancet*, **1**, 352–353.

MINDHAM, R.H.S., GAIND, R., ANSTEE, B.H. & RIMMER, L. (1972). Comparison of amantadine, orphenadrine and placebo in the control of phenothiazine-induced parkinsonism. *Psychol. Med.*, **2**, 406–413.

MINDHAM, R.H.S., LAMB, P. & BRADLEY, R. A comparison of piribedil, procyclidine and placebo in the control of parkinsonism, induced by fluphenazine decanoate (in preparation).

MINDHAM, R.H.S., MARSDEN, C.D. & PARKES, J.D. Psychiatric symptoms during L-DOPA therapy for Parkinson's disease and their relationship to disability. *Psychol. Med.* (in press).

ONUAGULUCHI, G. (1964). *Parkinsonism*, p. 125. London: Butterworths.

SIMPSON, G.M. & ANGUS, J.W.S. (1970). Drug-induced extrapyramidal disorders. *Acta psychiat. scand., suppl.*, **212**, 11–19.

SIMPSON, G.M. (1970). Controlled studies of antiparkinsonism agents in the treatment of drug-induced extrapyramidal symptoms. *Acta psychiat. scand., suppl.*, **212**, 44–51.

STRANG, R.R. (1965). Kemadrin in the treatment of parkinsonism: a double-blind and one-year follow-up study. *Curr. med. Drugs*, **5**, 27–32.

TALLAND, G.A. & SCHWAB, R.S. (1964). Performance with multiple sets in Parkinson's disease. *Neuropsychologia*, **2**, 45–53.

ZUNG, W.W.K. (1965). A self-rating depression scale. *Arch. gen. Psychiat.*, **12**, 63–70.