Brit. J. Psychiat. (1970), 116, 599–619

Methodological Problems of Prophylactic Trials in Recurrent Affective Disorders

BY P. GROF, M. SCHOU, J. ANGST, P. C. BAASTRUP and P. WEIS

During the past year the question of lithium prophylaxis has been the subject of lively debate (Blackwell and Shepherd, 1968; Hullin *et al.*, 1968; Houghton, 1968; Baastrup and Schou, 1968a; Lader, 1968; Sargant, 1968; Saran, 1968; Baastrup and Schou, 1968b; Melia, 1968; Fieve and Platman, 1968; Cole, 1968; Kline, 1968; Kerry, 1968; Editorial, 1968; Berlyne, 1968; Silverman, 1968; Laurell and Ottosson, 1968; *Lancet* Editorial, 1969; Whybrow, 1969; Melia, 1969; Angst *et al.*, 1969c). This discussion has revealed considerable uncertainty about the design and assessment of prophylactic trials, and there have been misunderstandings on important points.

The present paper contains a general discussion of the methodology of prophylactic trials in recurrent affective disorders. Later papers report the results of a prophylactic trial with lithium (Angst *et al.*, 1970) and discuss pharmacological and clinical problems of lithium prophylaxis (Schou *et al.*, 1970).

Experimental Design

The methodology of prophylactic trials differs in important respects from that of conventional therapeutic experiments, and the time factor is of special importance. In therapeutic trials the treatment periods usually last only a few weeks; in prophylactic trials they must run over periods of months and years. The trial must therefore be designed with particular attention to factors which influence the outcome of long-term investigations.

Controlled prophylactic trials may be carried out in two different ways:

(1) Studies with two (or more) groups where the disease course is followed simultaneously in comparable groups of patients. One group is treated with the prophylactic agent, while the patients in the other are given placebo or a different drug.

(2) Studies on one group, in which the disease course is followed in the same patients during one or more control periods and during one or more prophylactic periods. The control period may come before the prophylactic period (which will usually be the case) or after it, or control and prophylactic periods may alternate.

Simultaneous comparison of two groups of patients

With this procedure, comparability of the two patient groups is essential. The requirement is the same as in therapeutic two-group studies, but in prophylactic trials comparability is much more difficult to achieve. There must be the same risk of relapse in the two groups; comparisons which neglect this point may yield erroneous results. Random allocation of patients to the two groups does not ensure comparability unless the samples are very large. The groups should therefore be matched regarding factors which influence the course of recurrent affective disorders: diagnostic sub-group, age at first episode, number of previous episodes, etc. Such matching leads to rather small patient groups, and drop-outs during the necessarily long observation period of a prophylactic trial may further reduce the possibility of reaching conclusions of general validity.

Prophylactic trials which involve the use of control groups, i.e. groups of patients who do not receive the putative prophylactic agent, may give rise to ethical problems. In therapeutic trials with treatment periods of a few weeks, it may be defensible to allocate patients randomly to different treatment groups even if there is evidence that the drug under investi-

https://doi.org/10.1192/bjp.116.535.599 Published online by Cambridge University Press

gation is superior to other available treatments. However, in prophylactic trials, when the treatment periods must extend over months and years, it seems ethically more questionable to deprive groups of patients of the treatment that is most effective according to available evidence. The use of a control group is ethical only as long as the investigators remain sincerely sceptical about the effectiveness of the agent under investigation.

This problem was discussed by Baastrup and Schou (1967) and Laurell and Ottosson (1968), but it has been disregarded by those who in discussions on lithium prophylaxis called for control groups treated with control medication. When dealing with painful and dangerous diseases such as recurrent depressive or manic-depressive psychoses, one cannot dismiss the ethical aspect lightly but must consider carefully whether the necessary information can be obtained with other experimental designs. Laurell and Ottosson (1968) and Lehmann (1969) interrupted double blind two-group studies on lithium prophylaxis because they felt that continuation would have been unethical.

Studies on one group of patients

Prophylactic trials with one group of patients avoid the problem of a control group from which lithium is withheld. With this design, the main issue is that of quantitative prediction of the course of the disease.

Studies on the course of recurrent affective disorders have been carried out during the last fifty years (Kraepelin, 1913; Lange, 1942; Lundquist, 1945; Kinkelin, 1954; Kielholz, 1959; Matussek *et al.*, 1965; Taschev, 1965), but until recently they did not lead to clear-cut results. The earlier studies were mainly concerned with the mean duration of episodes and intervals, but the data do not follow a normal distribution, and the use of arithmetic means therefore distorts the picture. Most affective episodes last less than six months; the arithmetic mean is nevertheless higher than six months because a small number of patients have very long episodes. (An *episode* is the time between beginning and end of a manic or depressive attack. An *interval* covers the time from the end of one episode to the beginning of the next. A *cycle* is the time from the beginning of one episode to the beginning of the next.)

Since the introduction of electroconvulsive therapy and treatment with psychotropic drugs, representative groups of untreated patients are no longer available for studies of the spontaneous disease course; such studies must therefore be based on case histories that are several decades old. An extensive study of this type (Matussek *et al.*, 1965) indicated that in patients of the middle age groups the duration of episodes had a tendency towards prolongation, while in patients above 69 the tendency was towards shortening of episodes. Kielholz (1959), on the other hand, found that the episodes became gradually longer with progression of the disease. There is better agreement concerning the intervals: most authors find that these become shorter as the disease progresses (Kraepelin, 1913; Lange, 1942; Kinkelin, 1954; Kielholz, 1959).

The term 'spontaneous course' is employed in the following for the course in patients receiving treatment during psychotic episodes only, not during intervals. The treatment alleviates the intensity of the symptoms and may suppress them entirely. This makes it very difficult to decide when an episode has ended; even without treatment many episodes show a gradual disappearance. It may therefore be a dubious procedure to base studies of the disease course on the duration of episodes and intervals. The duration of cycles seems a better indicator.

Angst and Weis (1967) based a study of the disease course in recurrent affective disorders on the duration of cycles. The data were subjected to multiple regression analysis. With observations from 372 patients a statistical regularity in the periodicity was established. It was noted that the duration of cycles decreased as the number of previous cycles increased, and this gradual shortening of cycles was noted in different types of affective disorder. The course of the disease differed, however, among the diagnostic categories (Fig. 1). In manic-depressive and schizo-affective psychosis the first cycle was shorter but the shortening of cycles with increasing number of previous cycles somewhat less pronounced than in recurrent depressive psychosis. The duration

https://doi.org/10.1192/bjp.116.535.599 Published online by Cambridge University Press

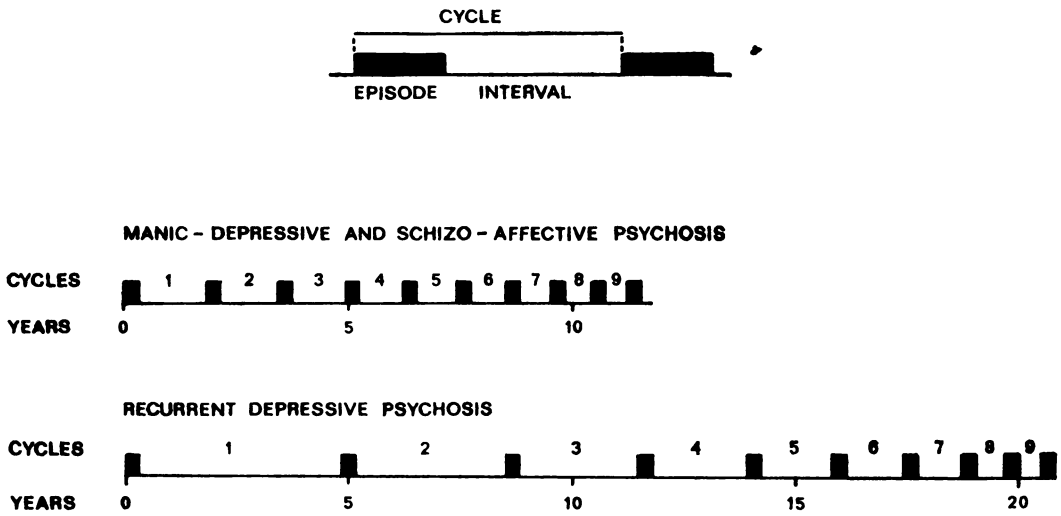


FIG. 1.—The course of recurrent affective psychoses. Diagrammatic presentation of changes in cycle length. Episodes are indicated by symbols of constant size.

of the first cycle was further correlated with the patients' age at that time; the cycles were shorter in patients who became ill late in life than in those who had their first attack at an early age.

The findings were later confirmed and consolidated with larger patient samples in studies carried out in collaboration among several psychiatric clinics (Angst *et al.*, 1968; Angst *et al.*, 1969b). The same trends were found valid for patients suffering from schizophrenia with a recurrent course.

These studies demonstrate that an approximate quantitative prediction of outcome is possible for sufficiently large groups of patients. Prophylactic trials may therefore be carried out according to one-group designs. The following paper (Angst *et al.*, 1970) illustrates two methods of conducting such an experiment.

Selection of Patients

Prophylactic studies might, in theory, be carried out with any group of patients suffering from recurrent affective psychosis, but in order to obtain meaningful results with a manageable number of patients and within a reasonable time, it is convenient to study cases with a relatively high risk of relapse.

Such cases could be selected from those having had many previous episodes or whose disease started late in life, since both groups have relatively short cycles. These procedures for patient selection have not yet been utilized.

Patients might also be selected on the basis of the relapse frequency during the years immediately before the start of prophylactic treatment. Baastrup and Schou (1967) and Angst *et al.* (1969d) studied patients who had experienced relapses within the last years before the treatment with a frequency higher than a specified minimum. The validity of this approach is discussed in the following paper.

Criteria for Defining an Episode

The question of defining what constitutes a psychotic episode has not yet been answered satisfactorily. Admission of the patient to a mental hospital is an objective measure, but it can be influenced by factors not related to the disease and also by agents with therapeutic but no prophylactic action (Angst *et al.*, 1968a). Less rigid criteria may be used, including global clinical ratings, observer and patient rating scales, and psychological tests. The use of highly sensitive tests may involve the risk of recording as episodes what are merely normal mood fluctuations.

Whichever criterion or criteria are chosen for recording a psychotic episode, it is essential

https://doi.org/10.1192/bjp.116.535.599 Published online by Cambridge University Press

that their use in the prophylactic experiment be identical during prophylactic periods and control periods.

Non-Pharmacological Factors

In prophylactic as in therapeutic trials, the possible effect of the following factors must be taken into consideration: spontaneous variation of the disease during treatment, psychological effects of the treatment, and observer bias. Spontaneous variation of the disease is of particular importance in prophylactic trials, which necessarily extend over long periods of time. This has been discussed above.

The two other sources of error can, in principle, be fully controlled only in studies that are carried out single or double blind. Properly executed such studies may yield important information. It may, however, be difficult to ensure that patients and observers remain unaware of whether a patient belongs to one or the other drug group. During long observation periods even slight side effects may render the 'blindness' illusory.

In non-blind trials the psychological effects of the treatment are not controlled. Since environmental factors are presumably of some importance in all mental disorders, it may be asked whether this invalidates conclusions drawn from such experiments. There have been claims that manic-depressive psychosis may be favourably influenced, both therapeutically and prophylactically, by psychoanalysis and other types of psychotherapy (Abraham, 1911; Freud, 1917; Fenichel, 1946; Bräutigam, 1969); however, these reports are based on individual case histories. Not a single systematic study has been published which demonstrates with reliable statistical evidence that psychological factors can radically alter the course of recurrent affective disorders over periods of months and years.

The results of a non-blind trial could further be influenced by bias, positive or negative, on the part of the investigator. This source of error might be of importance in cases where the evaluation of whether an episode was present or absent depended on subtle clinical differences, but in studies where only severe relapses are recorded it is hardly significant. In their prophylactic trial, Baastrup and Schou (1967) recorded as relapses only mood changes that were sufficiently severe to necessitate admission to a mental hospital or regular supervision in the home. Decisions about these measures were not made by the investigators (who might have been biased) but by the patient's own doctor (who did not take part in the study).

Another procedure would be to compare results obtained by independent investigators; this was the approach chosen in the study reported in the following paper (Angst *et al.*, 1970).

Summary

Designs used with success in therapeutic experiments are not necessarily suited to prophylactic trials, which offer special problems and require that new experimental procedures and statistical methods are employed.

Controlled prophylactic trials may be carried out in two different ways: (i) Concurrent comparison of the course of the disease in an experimental patient group and a control group, and (ii) studies on a single group of patients during successive control periods and drug periods. Each procedure offers advantages and disadvantages; ethical problems are of particular importance.

Special attention should be given to the definition of patient samples and to the criteria chosen for recording a relapse. Experiments must be designed with consideration of the role played by non-pharmacological factors: spontaneous variation of the disease course during treatment, the psychological effects of the treatment, and observer bias.

References

Abraham, K. (1911). "Notes on the psycho-analytic investigation and treatment of manic-depressive insanity and allied conditions." In *Selected Papers*, 1949. London: Hogarth Press.

Angst, J., and Weis, P. (1967). "Periodicity of depressive psychoses," in *Neuro-Psychopharmacology*. Amsterdam: Excerpta Medica Foundation, I.C.S. 129, p. 703–10.

Angst, J., Grof, P., Hippius, H., Pöldinger, W., and Weis, P. (1968). "La psychose maniaco-dépressive est-elle périodique ou intermittente?" In J. de Ajuriaguerra (Ed.,) *Cycles Biologiques et Psychiatrie*. Paris: Masson & Cie., p. 339–51.

https://doi.org/10.1192/bjp.116.535.599 Published online by Cambridge University Press

ANGST, J., DITTRICH, A., and GROF, P. (1969a). "The course of endogenous affective psychoses and its modification by prophylactic administration of imipramine and lithium." *Int. Pharmacopsychiat.*, **2**, 1–11.

ANGST, J., GROF, P., HIPPIUS, H., PÖLDINGER, W., VARGA, E., WEIS, P., and WYSS, F. (1969b). "Verlaufsgesetzlichkeiten depressiver Syndrome." In *Das Depressive Syndrom*, Ed. Hippius & Selbach. Munich, Berlin & Vienna: Urban & Schwarzenberg, p. 93–100.

ANGST, J., GROF. P., and SCHOU, M. (1969c). "Lithium." *Lancet*, *i*, 1097.

ANGST, J., WEIS, P., GROF, P., BAASTRUP, P. C., and SCHOU, M. (1970). "Lithium prophylaxis in recurrent affective disorders." *Brit. J. Psychiat.*, **116**, 604–14.

BAASTRUP, P. C., and SCHOU, M. (1967). "Lithium as a prophylactic agent. Its effect against recurrent depressions and manic-depressive psychosis." *Arch. gen. Psychiat.*, **16**, 162–72.

BAASTRUP, P. C., and SCHOU, M. (1968a). "Prophylactic lithium." *Lancet*, *i*, 1419–22.

BAASTRUP, P. C., and SCHOU, M. (1968b) "Prophylactic lithium?" *Lancet*, *ii*, 349–50.

BERLYNE, N. (1968). "Lithium in psychiatric disorders." *Brit. med. J.*, *iv*, 517.

BLACKWELL, B., and SHEPHERD, M. (1968). "Prophylactic lithium: Another therapeutic myth? An examination of the evidence to date." *Lancet*, *i*, 968-71.

BRÄUTIGAM, W. (1969). "Psychotherapie der Depressiven." In *Das Depressive Syndrom*, Ed. Hippius & Selbach. Munich, Berlin & Vienna: Urban & Schwartenberg, p. 519–22.

COLE, J. O. (1968). "Lithium carbonate: Some recommendations." *Amer. J. Psychiat.*, **125**, 556–57.

EDITORIAL (1968). "Lithium in psychiatric disorders." *Brit. med. J.*, *iv*, 271–72.

EDITORIAL (1969). "Lithium." *Lancet*, *i*, 709–10.

FENICHEL, O. (1946). *The Psychoanalytic Theory of Neuroses*. London: Routledge & Kegan Paul Ltd.

FIEVE, R. R., and PLATMAN, S. R. (1968). "Prophylactic lithium?" *Lancet*, *ii*, 830.

FREUD, S. (1917). "Trauer und Melancholie." *Gesammelte Werke*, Vol. 10, 1946. London: Imago Publ. Co.

HOUGHTON, A. W. J. (1968). "Prophylactic lithium?" *Lancet*, *i*, 1427–8.

HULLIN, R. P., MCDONALD, R., ANDERSON, W. MCC., and GERAGHTY, S. M. J. (1968). "Prophylactic lithium." *Lancet*, *i*, 1155–56.

KERRY, R. J. (1968). "Lithium—a special clinic?" *Brit. med. J.*, *iv*, 187.

KIELHOLZ, P. (1959). *Klinik, Differentialdiagnostik und Therapie der depressiven Zustandsbilder*. Geigy. Basel.

KINKELIN, M. (1954). "Verlauf und Prognose des manisch-depressiven Irreseins." *Schweiz. Arch. Neurol. Psychiat.*, **73**, 100–46.

KLINE, N. S. (1968). "Lithium comes into its own." *Amer. J. Psychiat.*, **125**, 558–60.

KRAEPELIN, E. (1913). "Das manisch-depressive Irresein." In *Psychiatrie*, 8. ed., vol. III, 2, p. 1183–1395. Leipzig: J. A. Barth.

LADER, M. H. (1968). "Prophylactic lithium?" *Lancet*, *ii*, 103.

LANGE, J. (1942). "Zirkuläres (manisch-depressives) Irresein." In *Handbuch der Erbkrankheiten*, vol. 4. (ed. A. Gütt.) Leipzig.

LAURELL, B., and OTTOSSON, J.-O. (1968). "Prophylactic lithium?" *Lancet*, *ii*, 1245–46.

LEHMANN, H. E. (1969). Personal communication.

LUNDQUIST, G. (1945). "Prognosis and course in manic-depressive psychoses. A follow-up study of 319 first admissions." *Acta psychiat. (Kbh.)*, suppl. 35.

MATUSSEK, P., HALBACH, A., and TROEGER, U. (1965). *Endogene Depression*. München & Berlin: Urban & Schwarzenberg.

MELIA, P. I. (1968). "Prophylactic lithium." *Lancet*, *ii*, 519–20.

MELIA, P. I. (1969). "Lithium." *Lancet*, *i*, 889–90.

SARAN, B. (1968). "Prophylactic lithium?" *Lancet*, *ii*, 284–85.

SARGANT, W. (1968). "Prophylactic lithium?" *Lancet*, *ii*, 216.

SCHOU, M. (1968). "Lithium in psychiatric therapy and prophylaxis." *J. psychiat. Res.*, **6**, 67–95.

SCHOU, M., BAASTRUP, P. C., GROF, P., WEIS, P., and ANGST, J. (1970). "Pharmacological and clinical problems of lithium prophylaxis." *Brit. J. Psychiat.* **116**, 615–19.

SILVERMAN, G. (1968). "Lithium in psychiatric disorders." *Brit. med. J.*, *iv*, 517.

TASCHEV, T. (1965). "Statistiches über die Melancholie." *Fortschr. Neurol. Psychiat.*, **33**, 25–36.

WHYBROW, P. C. (1969). "Lithium." *Lancet*, *i*, 839.

https://doi.org/10.1192/bjp.116.535.599 Published online by Cambridge University Press