Brit. J. Psychiat. (1964), 110, 514–519

Differential Inter-drug Analysis: A Preliminary Study*

By L. R. C. HAWARD

Introduction

During the past decade so many psychotropic drugs have been produced that the psychiatrist is often faced with a bewildering choice; for some mental disorders no fewer than a dozen preparations claim to remove or alleviate the symptoms. The work of La Verne (1962, 1963) and Jacobsen (1963) has been of considerable value in providing a "compendium of psychopharmacological agents"—a comprehensive classification of psychiatric drugs to assist the prescriber. Nevertheless, there are seldom any clear or universally accepted indications within a class (e.g. antidepressives or antipsychotics) why one drug should be prescribed rather than another. Many preparations share a common basic chemical formula, such as the phenothiazines, and/or a common biochemical function, like the monoamine oxidase inhibitors. The manufacturers themselves, anxious to cover every therapeutic possibility, suggest such a wide range of possible indications that their product often becomes a broad spectrum panacea, inviting increasing scepticism from the physician and concealing any potential advantage it may have for alleviating a particular symptom. Since personal experience determines choice more positively than any number of published reports, the psychiatrist gives most new products an informal trial, but tends to settle down with a limited few of proved usefulness and empirically confirmed indications. This is not a particularly efficient method for obtaining one's personal range of chemotherapeutics, but it is the one most generally used in practice. Its disadvantage lies in the idiosyncratic nature of some drugs, which may work well in one patient but ineffectively, or even adversely, in the next. On the basis of a few short and unsatisfactory trials, sometimes of only one, a potentially useful preparation may be discarded in favour of an older well-tried alternative which may be less therapeutically effective in the long run.

It would seem appropriate, therefore, to re-examine current psychotropic agents, not only for their overall clinical efficacy, which in many cases is not yet completely established, but more particularly for their specific advantages relative to symptoms and symptom clusters. This would not only make the selection of a chemotherapeutic regimen more efficient, it would highlight some of the more subtle disadvantages which deserve consideration on a long-term view and which may only become apparent by a detailed psychometric examination (Editorial, *Medical World*, 1960). While long-term psychological side-effects (Haward, 1958) may be relatively unimportant in the case of a strikingly successful drug like chlorpromazine, they can be important when assessing the merits and demerits of two similar preparations possessing not dissimilar clinical efficacy.

Methodology

The study to be described examines some psychological differences between two currently-prescribed antipsychotic agents. Chlorpromazine was chosen because it is perhaps the most widely used of the relevant drugs (*cf.* Bonafede, 1955; Denbar, 1954; Friedgood, 1955). The other was haloperidol, a comparatively new preparation, for which potent antipsychotic properties have been claimed (Brandrup, 1961; Delay, 1960; Jacobs, 1959; Papuay, 1960; Samuels, 1961; and others). The null hypothesis was raised that there

* Adapted from a paper read at the Annual Conference of the British Psychological Society, Reading University, on 29 March, 1963.

https://doi.org/10.1192/bjp.110.467.514 Published online by Cambridge University Press

would be no difference in the changes in *status psychologicus* produced by the two drugs.

Sample

In this pilot study fifty hospitalized psychotics were used. All possessed delusions of a basically paranoid kind but otherwise had fairly intact personalities. The sample was divided into two groups with fifteen males and ten females in each, matched approximately for age, chronicity of illness and intensity of delusions (see below). Since the "difference between differences" technique was to be used, psychiatric variables other than the above were not considered important, but to improve homogeneity the two groups were adjusted so that there was no statistically significant difference in terms of rating scale scores between the two groups. Two recently devised rating scales (Overall and Gorham, 1962; Turner, 1962) were used for this purpose and both showed intergroup equality.

Five behavioural areas were sampled. Delusional intensity was quantified, using the special psychogalvanic technique detailed elsewhere (Haward, 1963). Special regard was paid to the nature and degree of the effect of the two drugs upon delusions, since a careful study of the relevant literature suggested that it was in this area that the difference between the action of the two drugs would possibly lie. In addition to P.G.R. recording, four other means were used. A ward activity scale (Venables, 1957) was administered to assess the degree of psychomotor sedation produced by the drug, since this would possibly affect the sensitivity of the P.G.R. and probably inhibit the overt expression of delusional intensity. An information test (Roth, 1953) affording a measure of mental clarity was used to examine the relationship between delusional thinking, loss of insight and mental confusion. A projective test modified from Rosenzweig (1947) and scored for direction and degree of verbal aggression was included, since this was particularly relevant to the typical behaviour of the paranoid deluded patient (Cramond, 1958) and had previously been shown to be altered by chlorpromazine (Haward, 1958). Finally a respiratory stress test (Haward, 1953, 1955, 1957, 1959, 1962) was administered in order to determine any changes in stress tolerance and to relate this to altered reactions to delusional frustration. At the commencement of the trial the patients were first tested, and then either chlorpromazine or haloperidol prescribed, according to the group they were in. Since only objective measures were used (with the exception of the Venables Scale) no attempt was made to carry out a double-blind trial, and this gave the psychiatrist responsible for the patients complete freedom to adjust dosage levels to obtain the best response. In this situation both clinical necessity and trial requirements were congruent. No attempt was made to control or interfere with ward management, the principle being to adjust dosage levels to suit the individual patient with a view to obtaining optimum benefit (i.e. maximal relief of symptoms with minimal side-effects). The latter were also minimized where necessary by additional medication such as an anti-Parkinsonian agent. The two groups were re-tested after a period of four weeks or after cessation of treatment, whichever came first.

Results

Table I shows the results obtained from the two groups receiving chlorpromazine and haloperidol respectively, and in Table II the differences between the test-retest differences for both groups are themselves compared.

It will be seen that both drugs reduce ward activity, but to a different degree. Chlorpromazine reduces activity to a more sedated level, with some degree of hypomotility in patients receiving the higher dosage levels. Haloperidol, on the other hand, could be said to "normalize" activity, reducing hypermotility to a normal—but not subnormal—level, and increasing overall activity in the few patients who were under-active before the commencement of the trial. Thus while both drugs *altered* the level of activity by a significant degree, the difference between the action of the two drugs in this respect was itself statistically significant.

There was no significant change in mental clarity, but this was not unexpected since in

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TABLE I

Variable	Before*	After	Significance†
Psychometric Effect of Chlorpromazine			
Ward activity	41·3	26·0	0·01
Mental clarity	7·5	6·3	N.S.
Delusional intensity	18·5	9·8	0·05
Stress reaction	0·89	1·87	0·05
Aggression, intropunitive	4·1	8·6	0·05
Aggression, extropunitive	11·0	4·8	0·01
Aggression, total	15·1	13·4	N.S.
Psychometric Effect of Haloperidol			
Ward activity	42·8	32·1	0·05
Mental clarity	5·9	7·5	N.S.
Delusional intensity	18·1	5·6	0·01
Stress reaction	0·86	2·01	0·01
Aggression, intropunitive	4·9	5·1	N.S.
Aggression, extropunitive	9·7	4·7	0·05
Aggression, total	14·6	9·8	0·05

* Raw scores.

† "Difference between means" (Saunders and Fleming, 1957).

TABLE II

Chlorpromazine Compared with Haloperidol

Variable	Effect of Chlorpromazine	Effect of Haloperidol	Significance of Difference
Ward activity	−15·3	−10·7	0·05
Mental clarity	−1·2	+1·6	N.S.
Delusional intensity	−8·7	−12·5	0·05
Stress reaction	0·98	1·15	0·05
Aggression, intropunitive	+4·5	+0·2	0·05
Aggression, extropunitive	−6·2	−5·0	N.S.
Aggression, total	−1·7	−4·8	0·05

this particular sample there was little initial evidence of mental confusion. The two preparations tended to change the mental clarity scores in opposite directions, but since the differences in test-retest results were not statistically significant in either group there would be no value in discussing this suggestive contrast.

Three measures of verbal aggression were used—intropunitive, extrapunitive and total. In chlorpromazine, the total verbal aggression was reduced, but not by a significant amount; on the other hand, extrapunitive aggression was significantly reduced and intropunitive aggression correspondingly increased. As one would expect, overt clinical behaviour paralleled this trend, the reduction in manifest aggression being characteristic of chlorpromazine and frequently reported in the literature. Haloperidol produced a substantial decrease in both extrapunitive and total aggression, but no significant increase in the opposite direction. Again a parallel was found in ward behaviour, with overt aggression considerably reduced and in some cases eliminated. Both drugs thus reduce verbal aggression but appear to do so in significantly different ways.

Delusional intensity, as defined in terms of P.G.R., was significantly decreased in all

https://doi.org/10.1192/bjp.110.467.514 Published online by Cambridge University Press

subjects irrespective of the group to which they belonged, but a clear difference between the effects of the two drugs was nevertheless apparent. The use of this measure was of especial interest when it was found that the number of patients who had lost their delusions during treatment was not appreciably different between the two groups. Such a crude dichotomy on a small sample is not a statistically reliable method of assessing change in major symptoms. Moreover, those whose delusions succumbed most readily to the medication tended to produce the highest intensity scores, the really chronic paranoid patients showing relatively little emotional involvement with their delusions. Intensity as a continuous variable therefore appears to be important in assessing the action of drugs on delusional thinking.

Finally stress tolerance decreased after treatment with either drug; more so in the case of haloperidol, which produced rather stronger stress reactions on retesting than were found in the chlorpromazine treated group.

Discussion

From the psychometric point of view the reduction in delusional intensity was the central factor in response to these drugs. Was this merely a concomitant to overall psychiatric improvement, a non-specific effect of a centrally acting drug which has altered the hypothetical biochemical base of the psychosis? In this case there should be a high correlation between the intensity of the delusion and the degree of clinical disturbance. But measuring the latter in terms of a psychiatric rating scale yields no significant correlation, and the recent work of Court and Cameron (1963) provides similar evidence, for they found that delusions cleared up quite independently of the affective disturbances. Alternatively, was the reduction in delusional intensity due to reduced activity of the autonomic nervous system, remembering that chlorpromazine has both an anticholinergic effect and an adrenergic blocking action (Rubin, 1962)? But haloperidol has no measurable effect upon the A.N.S. (Gerle, 1961), yet it reduces delusional intensity (measured specifically via the A.N.S.) even more than in the case of chlorpromazine. Does this reduction, then, reflect the overall chemical restraint produced by the drugs? For this to be true, some positive correlation must be shown between intensity and activity. As would be predicted from an examination of Tables I and II a positive correlation does exist, but this is much smaller in the haloperidol treated group than in those receiving chlorpromazine. While the latter reduced both activity and delusional intensity, the former normalized activity without an apparent sedating effect. Some patients, indeed, lost their delusions *and* increased their overt activity at the same time, and there is thus nothing to support the suggestion of a causal relationship between these two variables. There is, however, a positive relationship between delusional intensity and total verbal aggression. Both are reduced significantly by either drug, yet logically we can apply a causal notion only in the opposite direction. As intensity of feelings about delusions is reduced, one would expect verbal aggression, expressing the hostility aroused by the interviewers' contradiction of belief, to be reduced also. It is contrary to our knowledge of psychodynamics to suppose that intensity of feeling is reduced by a more limited expression of that feeling. Experience tells us that often the converse is the case. What is particularly significant is the increase in stress reactivity. From a typically psychotic score obtained prior to treatment, both groups of patients show a marked development of sensitivity to and awareness of stress four weeks later, when they react with normal affectivity to induced hypoxia. Thus, reduction in intensity of delusions has occurred, not with affective blunting but with a marked sharpening of affect.

In the circumstances, therefore, it would not be implausible to hypothesize a specific action of the antipsychotic agent upon the neurophysiological substrata of deluded thought processes. Richter (1961) has emphasized the importance of relating the action of psychotropic drugs to physiological mechanisms in the brain, for without such knowledge the development of new and more effective drugs must be at best an arbitrary process. Two approaches

https://doi.org/10.1192/bjp.110.467.514 Published online by Cambridge University Press

relevant to this problem have been made. Overall and Gorham (1961) have provided a factor-analytic theory of psychiatric change in which thought distortion (which includes delusional thinking) appears on statistical analysis to be a secondary factor and not part of the primary psychotic process. Furthermore, they show that this factor of thought distortion *varies independently* from psychoticism according to the nature of the change-producing treatment. This implies that psychotropic drugs should have a differential effect upon symptoms or symptom clusters irrespective of their overall clinical efficacy, and this is indeed the case. The notion that delusional thinking has an existence separate from that of psychoticism carries with it so many important psychological and psychiatric implications that replication of this and other relevant studies is a sine qua non before seeking valid explanations in this direction. Some support for the idea comes from earlier factor-analytic studies of H. J. and S. B. G. Eysenck (1956, 1957, etc), from delusion-producing drugs discussed by McKellar (1957) and from various neurophysiological and anatomical studies such as those of Stein (1963) in which the respective functions of the reward and punishment centres of the hypothalamus and their differential response to various psychotropic agents have been examined. The brain-stem reticular formation is certainly differentially involved in these studies, for Killam (1957) has shown how chlorpromazine changes the intensity of the sensory input by altering the modulator repeater system of the B.S.R.F. The ensuing shift in the recovery cycle produces a reduced responsiveness which to some extent mimics, but is different from barbiturate sedation. The difference between the sedation effect produced by chlorpromazine and haloperidol may thus be due to the respective degree of involvement with the B.S.R.F. If true, this would help to explain why delusion intensity was decreased by a significantly different amount by the two drugs. Davis (1957) explains the delusion as a defence mechanism, which suppresses evocation of the objective significance of the percept, reducing its information value and thus allowing the neural signal to be loaded with intra-personal significance. The intensity of a delusion should thus be reduced by any process which augments the alerting response of the B.S.R.F. corticopetal pathways or which diminishes the suppressor channels of the peripheral nervous system. Further scope for prediction of experimentally-accessible variables is therefore possible. Measures of body schema and peripheral sensitivity by sensory threshold measurement, of projective facility by projective tests such as the Rorschach and Object Relations Techniques, and of attention and concentration by standard cognitive measures might all be expected to produce inter-drug differences if levels of exteroceptor awareness are involved. Certainly the increase in stress reactivity described earlier supports the view that sensory processes have been accentuated. However, any formal hypothesis derived from this study would be premature: the investigation has been an exploratory study designed to demonstrate that psychotropic drugs possessing not dissimilar clinical indications and efficacy may act in psychologically different ways. Replication and extension of such psychometric evaluations of currently used psychiatric drugs are required to validate the concepts raised in this commentary and to provide material for a new approach to the neurophysiological substrata of psychotropic medication.

Summary

A limited psychometric analysis is made of the action of two psychotropic drugs, chlorpromazine and haloperidol. While both drugs have a similar antipsychotic action and overall clinical efficacy, results of this study indicate that they achieve their effects in psychologically different ways. Special attention is directed to their action on delusional intensity, defined in objective terms and measured psychophysiologically. Hypothetically related variables including verbal aggression, ward activity, and stress reactivity were also measured and an inter-drug differential effect demonstrated. The concept of delusional thinking as a process relatively distinct from psychoticism is considered and some speculative neurophysiological implications are discussed.

https://doi.org/10.1192/bjp.110.467.514 Published online by Cambridge University Press

ACKNOWLEDGMENT

The author wishes to express his thanks to Miss Ann Collins, London School of Economics, for her extensive help in interviewing and testing all patients during the pilot study.

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https://doi.org/10.1192/bjp.110.467.514 Published online by Cambridge University Press