

File No:

MEDICAL RESEARCH COUNCIL  
HEADQUARTERS FILE

File No:

S 1516/17

SERIES SUBJECT

PSYCHIATRY.

FILE TITLE

BENZODIAZEPINE DEPENDENCE.

RELATED TO:

REFER TO

Initials

REFER TO

Initials

REFER TO

Initials

Mrs. Rhenius

✓

Dr. James.

21/1

Dr. James

21/2

Dr. Levy

✓

Dr. Davies

✓

Registry

✓

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## **BENZODIAZEPINE DEPENDENCE**

Medical Research Council Headquarters File

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Selected Items from File: Benzodiazepine Dependence,

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THE BETHLEM ROYAL HOSPITAL  
AND  
THE MAUDSLEY HOSPITAL

INSTITUTE OF PSYCHIATRY

DE CRESPIGNY PARK  
DENMARK HILL  
LONDON, SE5 8AF  
01-703 5411

31st October 1980.

Dr. James  
Medical Research Council  
20 Park Crescent  
London W1.

Dear Dr. James,

Further to our discussions today, I am writing to ask if the Medical Research Council would consider holding a half-day meeting to consider the problem of drug dependence with the benzodiazepines. As you know I have been researching in this area for some time and have now evidence that dependence can occur in patients taking normal therapeutic doses of the drugs. In view of the wide-spread usage of benzodiazepines this could mean that hundreds of thousands of patients are physically dependent on these medications. However, the amount of epidemiological evidence is very scanty and it would be necessary to mount two or three studies in order to ascertain the extent of this problem.

To that end might I suggest that the MRC holds a half-day conference, inviting such people as Prof. Shepherd and members of his research group, Prof. Morgan from Bristol and members of his research group, Dr. Skegg from Oxford, perhaps Prof. Parish from Wales. I would be prepared to attend and to present our clinical data with my research assistant, Dr. Petursson. From this conference we would hope that an application could be drawn up to fund epidemiological studies in general practice to ascertain the prevalence of benzodiazepine dependence amongst the population.

Yours sincerely,

*Malcolm Lader*

M.H.Lader.

Extract from minute of visit by Dr James and Dr Sturgess to Professor Lader at the Institute of Psychiatry on the morning of 30 October

S1516/17

Dr James and Dr Sturgess visited Professor Lader at the Institute of Psychiatry on the morning of 30 October. The purpose of the visit was to hear about Professor Lader's current research.

Benzodiazepine dependence

The problem of benzodiazepine dependence was one of his main interests. Dr Petursson and Mr Smokcum, who had reimbursed appointments, had shown that a normal dose dependence relationship operated. A pronounced withdrawal syndrome showed up as a consistent pattern of physiological changes on withdrawal of the drug. HPLC measurements of the levels of catecholamines and their metabolites in plasma and urine indicated that there was a rebound effect as patients were taken off benzodiazepines. This biochemical rebound correlated with clinical observations. The Hospital Biochemistry Department carried out the assays and a recent award of money from the MRC to buy a half-share in a new pump for an HPLC system would allow the measurements to be extended. Mr Smokcum had set up techniques to measure muscimol and benzodiazepine binding to receptors and he assayed benzodiazepines for other people at the Institute. They were also investigating whether oxypertine, a selective catecholamine depletor which had originally been introduced as a psychotropic drug, could be used to attenuate the symptoms of drug withdrawal. Benzodiazepine tolerance was measured by injecting diazepam. In normal people this caused an increase in levels of growth hormone, an effect not seen in dependent patients who had developed tolerance.

Clinical Studies of dependence

Professor Lader considered that the problem of dependence was an important one. The patients he had investigated were self-referred and it was therefore difficult to gauge the extent of the drug dependence. However, from the numbers he had seen, he estimated that about  $\frac{1}{2}$  million people in the United Kingdom, or about  $\frac{1}{2}$  of the patients undergoing benzodiazepine treatment were involved. The magnitude of the problem indicated that it should be of interest to the drug companies. He had lectured at Roche on the subject and had hoped that they might follow up the study. In the absence of any response from them, he suggested that two groups capable of carrying out the study were those of Professor Morgan at Bristol and Professor Shepherd at the Institute of Psychiatry. He wondered whether the survey, which would be 'an epidemiological study of psychotropic drug dependence in general practice', could be organised by the Drug Trials Subcommittee. Dr James said that since the future of the Subcommittee was under discussion, it would be better if an ad hoc meeting were arranged to discuss the matter. Such a meeting could include Professor Lader and some of the people working with him; Dr Tyrer from Nottingham, Dr Skegg from Oxford and Dr Parish. Since the meeting would be under the auspices of the Neurosciences Board, a Board member would probably be needed to chair it. Professor Lader was concerned that when papers which he was preparing appeared in print they would stir the whole matter up and he wanted to be able to say that the MRC had the matter under consideration if questions were asked about it in Parliament.

- 1) Ad hoc meeting on benzodiazepine dependence to be arranged.



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S158/17

13 November 1980

Dear Professor Lader

Many thanks for your letter of 31 October suggesting that we should have a meeting to discuss further studies of benzodiazepine dependence. We will now give this some thought, and I expect Dr Sturgess will get in touch with you again fairly soon.

Yours sincerely

D R James

M H Lader DSc PhD MD FRCPsych  
Professor of Clinical Psychopharmacology  
Department of Pharmacology  
Institute of Psychiatry  
De Crespigny Park  
Denmark  
London SE5 8AF

Re: Meeting on benzodiazepines

Professor Malcolm Lader visited Dr Levy and Dr Sturgess in the office on 10 February 1981 to discuss his proposals that the MRC should hold a half-day meeting on the problems of benzodiazepine dependence. He told us that there had been developments since the Autumn when he had written his letter:

- (a) Roche had approached Professor Lader with suggestions for epidemiological studies; he had in turn put them in touch with Professor Morgan and Professor Shepherd.
- (b) He thought that it was very important, politically, that the MRC should be 'one step ahead'.
- (c) The research would fall into two categories: (i) the epidemiological studies which might be funded by Roche and (ii) more fundamental studies on the biochemistry which might be suitable for MRC funding.

Structure of meeting

The meeting should

- (a) identify problems which were about to arise and
- (b) alert DHSS to the extent of the problem (when the full extent is realised it will probably be the third or fourth largest problem of dependency in the country).

There was considerable international interest, for example from WHO, and the organisation of a half-day meeting by the MRC would be indicative that it was aware of, and concerned about, the problem.

Dr Levy raised the question of whether a half-day meeting would be sufficient to cover the necessary topics. These were:

- (a) the extent of the problem in the country, and the relative position of the United Kingdom; - as background,
- (b) the amounts of benzodiazepines which were prescribed - and why,
- (c) the nature of dependency, - and how it arises,
- (d) the pharmacology.

Professor Lader was of the opinion that a full half-day would be sufficient because, on many of these topics, not very much was known at present, and the discussion would probably not be too contentious. Another point which Professor Lader touched on, was the importance of educating the public about benzodiazepine dependence. He illustrated this by saying that the withdrawal symptoms from valium were much worse than from many other drugs including e.g. heroin. Patients who were withdrawn from benzodiazepines showed flu symptoms, were very jumpy, and experienced perceptual changes. On rare occasion they also might have fits; or full blown psychoses.

/...



continued...

Professor Lader explained that he thought that there was an 'iceberg effect' of benzodiazepine dependence. The withdrawal syndrome which was possibly the result of a catecholamine rebound effect, might be able to be treated with oxypertine (which depletes catecholamines). In biochemical terms, a  $\beta$ -carboline (an intermediary metabolite of the drug) might be responsible for dependence. In answer to a question from Dr Levy, Professor Lader said that nothing much was known at present about the time-scale over which patients became dependent on benzodiazepines. Dr Tyer had done a study in which patients were taken off benzodiazepines once their anxiety symptoms had diminished, but it had not been possible, in that survey, to establish the length of time over which dependence had been established.

The trial which Roche were interested in carrying out would involve following-up patients in general practice, to the stage at which they were removed from benzodiazepines; placebo controls would be included etc. At present, the only indication of the magnitude of the problem had come from a study in the US (by Carl Richarts) which had indicated that about 5% of people initially prescribed benzodiazepines had problems when the drugs were discontinued. Since benzodiazepines were prescribed so widely, this represented about  $\frac{1}{2}$  million people in the UK.

#### Participants

The people who it was suggested should be present at the half-day meeting were:-

Professor Morgan - supported on regional health authority funds - who had done some studies on prescribing.

Professor Shepherd and Dr Paul Williams from his team.

Dr Skegg - who had carried out a study on prescribing benzodiazepines in Professor Sir Richard Doll's Unit, Oxford - paper in BMJ 1978.

- Professor Parish from Swansea, - interested in GP prescribing.
- Dr Tyer - a consultant at Mapperly Hospital, Nottingham, on DHSS support - interested in withdrawal studies.

Professor Lader himself could give a paper on normal dose dependence and preliminary data on oxypertine as a possible treatment for the withdrawal syndrome.

Dr Inman - Drug Surveillance Unit, Southampton - might also be included.

- Professor Lader also suggested that Dr John Marks (Ex-Roche) who has written a review of the topic would be a useful participant - at ~~St Catherine's College, Oxford.~~ - Gilton College, Cambridge. - See letter of 12/3/81.

It was also thought to be useful to invite observers from one or two of the major drug companies - Peter Harris from Roche and ? Tom Hurry from Wyeth were suggested.

To cover the pharmacology, Naylor/Costa from Bradford or Mitchell's group from Bristol perhaps should be contacted.

? addictive behaviour  
epidemiologist.

10 mins

5 to 6 speakers.

Pete

continued....

Timing of meeting

Since Professor Cawley will be asked to chair the meeting, he will need to be consulted about possible dates. It was suggested that May, June or possibly early July should be considered.

Agenda

The structure of the meeting should cover pharmacology, usage and dependence.

Action

1. Draw up lists of suggested participants for discussion with chairman.
2. Discuss possible dates of meeting with chairman.

Professor Lader said he would send us a note, of the names and addresses of some of the people he had mentioned, and would be happy to advise on the agenda.

*Elizabeth Sturgess.*

Elizabeth Sturgess



S1515/17

26 February 1981

Dear Professor Lader,

Meeting on Benzodiazepines

Following your visit to the office and discussion with Dr Levy, we are now trying to arrange a half-day meeting to discuss the benzodiazepines.

When you were here, you very kindly agreed to let me have the names and addresses of the people whom you thought would be valuable participants. It would be a great help if you could send me a note of these, particularly those whom you suggested as observers from the drug companies. It has been suggested that it would be useful to have a epidemiologist at the meeting, - and I would be grateful for your views on whom we should invite, and also who would be suitable to cover the pharmacology. The suggestion has also been made that Professor Griffith Edwards, as an expert in general addictive behaviour, might be invited.

The topics which might be covered are:-

- a) As background; the extent of the problem in the country, and the relative position of the United Kingdom.
- b) The amounts of benzodiazepines which are prescribed, and why.
- c) The pharmacology.
- d) The nature of the dependency, - and how it arises.

But I would welcome any recommendations you have for the agenda.

We hope that we might be able to arrange the meeting for June, and it would be useful, at this stage, if you could let me have a note of any dates which would not be convenient for you during that period.

I look forward to hearing from you soon.

Yours sincerely,

*EAS.*

Elizabeth Sturgess, DPhil

M H Lader, DSc PhD MD FRCPsych,  
Professor of Clinical Psychopharmacology,  
Department of Pharmacology,  
Institute of Psychiatry,  
De Crespigny Park,  
Denmark Hill,  
London, SE5 8AF.

8

SI516/17

3 March 1981

In Confidence

Dear Professor Cawley

Following Professor Lader's recent visit to the office and his discussions with Dr Levy, we are planning a half-day meeting to discuss the benzodiazepines. I believe that Dr Levy has already mentioned this to you and that you have very kindly agreed to chair the meeting.

The topics around which the meeting would be planned would probably include (a) as background, the extent of the problem of benzodiazepine dependence in the country and the relative position of the UK vis-a-vis other countries, (b) the amounts of benzodiazepines which are prescribed, and why, (c) the pharmacology and (d) the nature of the dependency and how it arises. - I would, however, welcome your suggestions on drawing up an agenda.

Among the participants suggested so far, in addition to yourself and Professor Lader, are Professor Morgan (Bristol), Professor Sheppard and Dr Paul Williams from his team (Institute of Psychiatry), Dr Skegg (Oxford), Professor Parish (Swansea), Dr Tyrer (Nottingham), Dr Inman (Southampton), and Professor Griffith Edwards (Institute of Psychiatry). It might be useful to have an epidemiologist and I would welcome your views on whom to invite, and also on who should be asked to cover the pharmacology. As you know, Roche has expressed great interest in an epidemiological study of the benzodiazepines and Professor Lader has promised to write to me with the names of people from Roche and one or two other drug companies who should be invited as observers.

We hope that we might be able to arrange the meeting for June and it would be helpful if you could let me have a note of some dates which would be convenient for you for the meeting during that month.

Yours sincerely

*ES*

Elizabeth Sturgess DPhil

Professor R H Cawley PhD FRCP FRCPsych  
Institute of Psychiatry  
De Crespigny Park  
Denmark Hill  
London SE5 8AF





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Received 5.3.81 9  
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4th March 1981

Dr. Elizabeth Sturgess,  
Medical Research Council,  
20 Park Crescent,  
London W1N 4AL.

Dear Dr. Sturgess,

In reply to your letter of 26th February 1981, the people  
that I would suggest are as follows:

1. Dr. John Marks, M.A., M.D., F.R.C.P., F.R.C.Path., M.R.C.Psych.,  
Girton College, Cambridge.
2. Dr. P. A. Harris, Head of Drug Safety, Roche Products Ltd.,  
P.O. Box 8, Welwyn Garden City, Herts.
3. Dr. T.V.A. Harry, Wyeth Laboratories, Huntercombe Lane South,  
Taplow, Maidenhead, Berks.
4. Dr. Barbara Hunt, D.H.S.S., Alexander Fleming House,  
Elephant and Castle, S.E.1.
5. Professor Peter Parish, Medicines Research Unit, University of Wales,  
Institute of Science and Technology, Cardiff.

The epidemiologist who I think might be appropriate is Dr.  
Peto from Sir Richard Doll's department. The pharmacology might  
be covered by Professor Spencer from Cardiff.

I think the topics covered would be quite appropriate.

I would like my assistant, Dr. Hannes Petursson, to be invited  
as he has had a lot of experience with the clinical problems of  
withdrawal. I should also like Dr. Peter Tyrer from Mapperley  
Hospital, Nottingham to be invited.

I attach a list of the dates which would not be convenient  
for me.

Yours sincerely,

M. H. Lader



# MEDICAL RESEARCH COUNCIL

MRC 81/818

ANNEX

Circulation  
Participants

B81/9

## THE BENZODIAZEPINES

Minutes of the ad hoc meeting held on Wednesday, 23 September 1981 at 20 Park Crescent, London, W1N 4AL

### Present

Professor R H Cawley (Chairman)  
Dr P A Harris  
Dr T V A Harry  
Professor M H Lader  
Dr J Marks  
Dr I Martin  
Dr Pamela G Mason (DHSS Observer)  
Dr A T B Moir (SHHD Observer)  
Professor H G Morgan  
Professor P A Parish  
Dr H Petursson  
Professor M Shepherd  
Professor P S J Spencer  
Mr C Taylor  
Dr P J Tyrer  
Dr P Williams

### MRC Office Staff:

Dr D R James  
Dr Elizabeth Sturgess  
Mrs Julie A Alston

### Apologies for absence:

Mr A Doble  
Professor Griffith Edwards

### 1. Chairman's introduction

After welcoming participants, the Chairman explained why the meeting had been convened. The potential problems of overprescribing and possible dependence on benzodiazepines had been brought to the attention of the office and it had been decided to call a meeting of experts in the field to review existing knowledge of the properties and usage of these drugs. A report of the meeting, would be submitted to the Council's Neurosciences Board, which would decide, in the light of the report, on any action to be taken.

### 2. The history of benzodiazepines

2.1 Dr Tyrer divided the history of Benzodiazepines into three phases (i) Phase of novelty (ii) Phase of enthusiasm, and (iii) Phase of consolidation and doubt.

2.2 The benzodiazepines were first synthesised in the mid 1950's the first to be clinically tested being chlordiazepoxide. This drug was greeted with great interest, particularly as it appeared to produce no negative reactions or adverse affects.

2.3 The second phase, that of enthusiasm, lasted from the early 1960's through to the mid 1970's. By 1967 benzodiazepines had largely replaced barbiturates for treating anxiety and insomnia; they were also widely used as anti-convulsants and muscle relaxants, as well as being important to anaesthetists. By the end of this period they had become the most commonly prescribed psychotropic drugs, not only in the UK but in most other countries of the world.

2.4 By the early 1970's the dramatic increase in benzodiazepine prescribing was causing some concern. The reasons for over prescription however were difficult to ascertain. Dr Tyrer said the following were possibilities: (i) that doctors were being irresponsible in prescribing drugs: he considered this was unlikely to be the explanation since no other drug was prescribed to a similar extent; (ii) benzodiazepines filled a vacuum as they were an effective anti-anxiety drug without detectable side effects, and these properties could not be claimed for any other drug; (iii) perhaps more cases of anxiety were being diagnosed and treated; (iv) a very large number of benzodiazepine compounds were marketed so the G.P. had many to choose from and could switch patients from one to another without actually changing their treatment; (v) the number of long-term users gradually grew and this led to a build-up in the number of prescriptions.

2.5 In discussion it was suggested that one possible reason for the high rate of prescription of benzodiazepines might be that they were known to be relatively safe if overdoses were taken and there was therefore a minimal risk of abuse. It was further noted that from the early '70s numbers of prescriptions for benzodiazepines had levelled off in most countries and that in the last few years there had been a slight fall in numbers issued.

### 3. Pharmacology of benzodiazepines

3.1 Professor Spencer began his description of the pharmacology of benzodiazepines by explaining the differences between long-acting and short-acting benzodiazepines, the length of action being determined by the half-life ( $T_{1/2}$ ) of active metabolites as well as that of the prescribed drug. Long-acting benzodiazepines, such as diazepam, ( $T_{1/2}$  about 32 hours) and desmethyldiazepam ( $T_{1/2}$  about 65h) showed varied activities from one individual to the next; whereas short-acting benzodiazepines with shorter half-lives (e.g. triazolam with  $T_{1/2}$  2h) showed effects which were more easily predicted.

3.2 He went on to describe the four main activities of benzodiazepines: muscle relaxation, anti-convulsant activity, anxiolytic activity and sedative/hypnotic properties. He explained that although pharmacologically they were considered to be separate activities, there were potentiating effects (at present poorly defined) between them.

3.3 The specificity of benzodiazepines had been demonstrated by animal experiments where anti-anxiety effects could be obtained at doses which do not cause depression of the central nervous system. One way of demonstrating this was through their effects on Leptazol-induced convulsions. Other animal tests showed that exploratory activity and conflict-attenuated behaviour were both increased following the use of benzodiazepines.

3.4 Professor Spencer then described the possible mode of action of benzodiazepines. At a cellular level, GABA receptors were widely distributed in the brain and GABA activity was enhanced by benzodiazepines; it was thought



however that benzodiazepines do not bind to GABA receptors but that they interfere with and prevent the effect of a second, naturally occurring substance (GABA-Modulin). Over the last two years it had been suggested that there were at least two benzodiazepine receptors, one of low and one of high affinity. It was thought that there was a natural ligand at the high affinity site, although so far this had not been identified, leading to speculation whether the benzodiazepines were 'agonist' or 'antagonist' agents at their receptors, 'agonists' being the more likely. The  $\beta$ -carbolines were possible contenders as the endogenous ligand, but Professor Spencer did not think any of those currently identified was a strong candidate for the role.

3.5 Professor Spencer pointed out that to date there was no good evidence for benzodiazepine dependence in laboratory animals, although this was difficult to test reliably. He reminded the meeting that it was not until 1962 that a method had been discovered for identifying dependence on opiates. There was, however, evidence of tolerance to benzodiazepines in laboratory animals as shown by a sedative effect on lever pressing, the potentiation of barbiturate sleep, a reduction in spontaneous motor activity, muscle relaxant activity etc.

3.6 Professor Spencer suggested that tolerance resulted from intracellular adaption once a threshold level of drug had been established. A withdrawal syndrome would be manifested if the tissue concentration of the drug fell substantially. Thus it would be dependent on the relative speeds of reversal of adaptive changes and rate of loss of drug. Withdrawal symptoms were thus less likely with drugs with long half-lives since their concentration would fall relatively slowly. Experiments carried out in Germany by Herz and his colleagues had demonstrated that the relatively long-acting partial agonist buprenorphine could be shown to induce dependence (after 4-5 days administration), although this did not become apparent unless the shorter-acting morphine was substituted for it for one day, before naloxone administration.

3.7 Professor Spencer mentioned several possible avenues for future work on benzodiazepines: (i) to establish whether the high affinity benzodiazepine receptor was linked to anxiolytic activity; (ii) to study receptor function; (iii) to identify the endogenous ligand(s); and (iv) to use the new Roche antagonists to precipitate withdrawal reaction and to study the components of withdrawal.

3.8 Dr Martin was then asked to comment on the subject of benzodiazepine receptors. He said that the relationship of GABA and the benzodiazepines was very complex, novel and exciting. Most people in the field now thought that there was only one GABA-related benzodiazepine receptor with two states, active and inactive: benzodiazepines binding to the active form and  $\beta$ -carbolines to the inactive. The benzodiazepine receptor appeared to possess the unusual property of being able to influence GABA-mediated transmission both positively and negatively. A further level of complexity of interaction between benzodiazepines and GABA was indicated, and it was postulated that an endogenous ligand for the benzodiazepine receptors could displace benzodiazepines and  $\beta$ -carbolines competitively.

3.9 It was noted in discussion that, so far, only quantitative rather than qualitative differences between different species reactions to benzodiazepines had been found. The question was raised as to whether any changes in receptors could be found in cases of over prescribing or prolonged benzodiazepine use. This was answered with reference to two experiments, one of which showed a reduction in binding capacity for the benzodiazepines of



about 15% after very large doses of flurazepam over seven days while the other showed approximately 50% reduction of binding capacity at the GABA and muscarinic cholinergic receptor in certain brain areas after low doses of diazepam for 30 days. A paper by Hollister suggested that the greatest risk of dependence came from the use of a drug with a half-life of 12-15 hours. Concern was expressed about the ethical and safety aspects of withdrawal precipitation in humans by the administration of antagonists.

#### 4. Usage of benzodiazepines

4.1 Professor Parish spoke about the medical usage of benzodiazepines. He began by drawing attention to the limitations of studies based on prescribing patterns, one of which was that these studies gave no indication of the reasons for prescription. 15-20% of all prescriptions were for psychotropic drugs and half of these were for benzodiazepines; at any one time 10% of the population were taking psychotropic drugs. Benzodiazepines were prescribed for a multitude of physical and emotional disorders; it was known that consumption increased with age and that twice as many women as men used them, although these facts applied also to many other drugs. There did not appear to be any correlation of the increased use of benzodiazepines with social factors. There was however evidence of overprescribing as shown by the high percentage of benzodiazepines present in "unused drug" collections. Only one in three patients actually took the drugs as prescribed; the ease of obtaining repeat prescriptions increased with increasing length of use (over 6 months) and in many cases repeat prescriptions were issued without the patient being seen by the GP.

4.2 Professor Parish suggested various questions that needed to be answered: (i) how effective were benzodiazepines in relieving common distress and anxiety; (ii) how effective were they in protecting patients from further stress and from physical illness; (iii) and how could the benefits be effectively balanced against the risks? Benzodiazepines were often prescribed for emotional and social problems; compliance was influenced by the patient's social environment which was an important variable, and this would naturally influence the outcome of any study. Indeed the problems encountered in formulating studies in this area were formidable, because of the complexity of the situation and the inter-relationship between different factors.

4.3 Dr Williams then spoke about three studies of psychotropic drugs being conducted by the General Practice Research Unit at the Institute of Psychiatry. The first was a prescription audit carried out in a South London Health Centre for one month (February, 1978). During that time 9382 prescriptions were issued, 718 were for tranquilisers of which 480 were benzodiazepines, 417 prescriptions were for hypnotics of which 304 were benzodiazepines; this meant that 8.5% of all prescriptions were for benzodiazepines, nearly half of which were for diazepam. Dr Williams stressed again the point made by Professor Spencer, that the number of prescriptions issued was not an indication of how many people actually used the drugs.

4.4 The second study was a community study in West London to investigate the 2-week prevalence and correlates of psychotropic drug use. This study confirmed the sex difference in consumption with twice as many women as men being prescribed psychotropic drugs. Dr Williams made several suggestions as to why this might be: (i) that alcohol and drugs were complementary tranquilisers; distressed men turned to drink and distressed women to drugs. An American study, however failed to detect an increase in alcohol consumption on an Indian reserve where psychiatric drugs had been banned; (ii) most

doctors were men, and perceived women and their problems in a different light; (iii) that there was a greater occurrence of neuroses in women than in men. The participants in Dr Williams' study had been given the General Health Questionnaire (GHQ) to establish their level of neuroses; it showed that the occurrence of neuroses was higher in women than in men, although this difference did not account for the consumption rates.

The use of the GHQ also highlighted the fact that only 47% of those in this study who were prescribed psychotropic drugs showed evidence of neurosis: many had probably recovered from the symptoms but were still taking the drugs.

4.5 The third study was a six month longitudinal study of new psychotropic drug users. Here 88% of the patients were rated on the Symptom Rating Test as neurotic, about 30% had physical problems as well and in about 60% of the cases the doctor knew of social problems which affected their patients' health. After four weeks of the study only 40% were still receiving the drugs, the falling off rate flattened out very gradually after this. Long-term use was seen to be related to age, previous psychotropic drug use and social problems. It appeared that the probability of coming off the drug was reduced enormously if they were prescribed for longer than about four months.

4.6 The third study described by Dr Williams was discussed at length. For example, was it possible that those patients who had stopped taking the drugs during the first four weeks, achieved recovery through counselling (ie talking over their problems with the doctor) rather than through taking the drugs; this was considered to be a possibility. It was also pointed out that social variables may well have influenced the speed with which patients felt they had recovered, and therefore were ready to give up the drugs.

There were also cultural influences on the patient's expectations about drug prescribing and some studies had suggested that the prescribing of benzodiazepines had no strict criteria and could be very haphazard; in the cases studied by Dr Williams all of the prescriptions had been initiated by the GP, although only 40% of the patients had asked for drugs.

4.7 Finally, Dr Williams contrasted the use of benzodiazepines with anti-depressants. He said that many patients would stop taking anti-depressants quite quickly, although the reasons were unclear. However many would resume taking them within a month, reflecting the treatment policy of continuing medication for three months. For the benzodiazepines there was a gradual fall off over the first four months.

## 5. Benzodiazepine dependence

5.1 Dr Marks presented an analysis of recent studies of benzodiazepine dependence. It appeared that evidence of withdrawal symptoms from long-acting benzodiazepines could only be found when the patient had been taking them for one year or longer (about 10% of patients were affected). With short-acting benzodiazepines the problem could occur after about six months (5-10% of patients were affected after 1 year). Abrupt withdrawal did not cause problems for the majority of patients, although some showed evidence of rebound anxiety/insomnia, later return of anxiety, pseudo dependence and true physical or psychological dependence.

5.2 Another feature of Dr Marks' analysis was that between 1967 and 1978 the number of long-term repeat prescriptions issued for benzodiazepines each year had more than doubled. It was possible that many of these could be



justified as carriers for other forms of treatment, eg counselling: however 50% of the repeat prescriptions were given without a consultation.

5.3 Dr Marks suggested that four important guidelines for those prescribing benzodiazepines would be: (i) to avoid giving them to those with a known problem of dependence; (ii) to keep the use of benzodiazepines with other sedative drugs to a minimum; (iii) to avoid prescribing them for any period over six months; and (iv) to avoid abrupt discontinuation of the drug.

5.4 Dr Petursson presented the results of an investigation of benzodiazepine withdrawal symptoms, conducted by Professor Lader's team at the Institute of Psychiatry. The study involved thirty-four patients who had been taking benzodiazepines for between 1-16 years, and had found it very difficult to stop. The patients were studied for a period of 10 weeks, and subjected to a battery of physiological and psychological tests. Plasma tests showed drug activity 2-3 weeks after stopping all drug treatment (even with the short-acting lorazepam), which might explain the long duration (8-10 days) of the withdrawal syndrome.

5.5 During withdrawal all patients showed some symptoms, the most common being: sleep disturbance, anxiety, agitation, headache, loss of appetite, nausea, weight loss and impaired concentration. However these had all subsided to pre-withdrawal levels within two to four weeks.

## 6. General discussion

6.1 Professor Lader opened the general discussion by recapitulating some of the points made during the morning. As a class of drugs, the benzodiazepines showed reassuringly low abuse potential. However, the recent realisation that some patients who were on normal therapeutic doses of benzodiazepines had problems when they tried to stop taking them, indicated the existence of a problem, which had not been recognised earlier in the drug's history. Professor Lader's estimate of the extent of the problem was similar to that of Dr Marks'; the point was made that, despite the relatively low percentage of those taking benzodiazepines developing dependence (or tolerance), the total numbers of people in whom dependence actually developed was of the order of 10-100,000 people because of the very large numbers of patients for whom benzodiazepines were prescribed. He emphasised, however the paucity of well-designed epidemiological studies of benzodiazepine dependence. There was also a need for studies of methods of withdrawing patients from benzodiazepines so that the adverse effects could be kept to a minimum.

6.2 Professor Morgan emphasised the great difficulty in evaluating the effect of various environmental factors on benzodiazepine usage, although it was realised that these would be of fundamental importance in interpreting any study. The possible value of low-key intervention in helping individuals cope with their environment was discussed. There was at present no explanation as to why some people did not show the withdrawal syndrome while others did, although it had been reported that long-term users showed psychological effects in that they appeared to have lost the ability to cope with stress.

6.3 Dr Marks noted that although most studies so far had been on patients for whom benzodiazepines were prescribed during the day, there were some examples of dependence developing in patients for whom nocturnal benzodiazepine (only) was prescribed. Although there were no precise data, it was likely that about 1/3 benzodiazepine prescriptions were for nitrazepam for use as an hypnotic.



6.4 The difficulties of deriving information from total numbers of prescriptions were discussed. These partly arose from the Health Department categorisation of prescribed drugs (in which legal constraints inhibit disclosure of certain types of information which could be held to be contrary to the interests of a particular drug company or commercial concern) and partly because the extent of compliance compared with prescription in the United Kingdom was unknown. American studies showed a considerable discrepancy between the two figures, but the reliability of transposing this information to the United Kingdom which had a completely different health system was unclear.

Dr Mason (DHSS) and Dr Moir (SHHD) expressed their Departments' interest in the problems discussed at the meeting. It was clear that information on the clinical efficacy and potential toxicity were needed particularly on any drugs which were used by large numbers of people and/or over long periods of time. Indeed such information was an essential preliminary to a consideration by Health Departments of whether any action was required and, if so, what form it should take.

## 7. Summary of conclusions and recommendations

7.1 Although the prescription of benzodiazepines has recently shown a slight fall in the UK (and greater falls elsewhere) they remain one of the most commonly prescribed categories of drugs, for this reason the scientific study of their usage and properties is of great importance.

7.2 The neuropharmacological basis of benzodiazepine action is already the subject of extensive investigations which are producing evidence of novel types of interaction of drugs with neurotransmitter receptors.

7.3 As highly effective anxiolytic and sedative agents, benzodiazepines are often prescribed inappropriately for a range of ill defined predicaments in which medical problems are subordinate to social and cultural influences and to the relationship between the general practitioner and his patient. In the absence of defined criteria for prescribing, and with the lack of satisfactory outcome measures, assessment of benefits due to the drugs presents formidable difficulties. There is a need for epidemiological and clinical investigations directed towards characterising these complex variables and other inter-relationships, defining such non-pharmacological treatment regimes as might often be preferred for the common patterns of emotional distress and low grade morbidity met with in general practice, and producing guidance for formulating prescribing policies for benzodiazepines.

7.4 The common practice of supplying repeat prescriptions without consultation may encourage long-term use of benzodiazepines and occasional or regular use of others in addition to those for whom the drugs are prescribed. Symptoms during the withdrawal period are so common as to be the rule and provide a further mechanism to promote long-term use. Although dependence occurs in only a small proportion of benzodiazepine takers the number of patients involved may be substantial. Since any prescribing of benzodiazepines carries risks as well as benefits, research should be continued into the factors which determine long-term usage and dependence, and into methods of withdrawing benzodiazepines from dependent patients.

7.5 The risks of dependence could be reduced by more trained prescribing of benzodiazepines, and there is a continuing need to educate general practitioners about the appropriate use of these drugs.

## **BENZODIAZEPINE DEPENDENCE**

**Medical Research Council Headquarters File**

**Closed until 2014 – Opened 2005**

Selected Items from File: Benzodiazepine Dependence,

File no: S1516/17 National Archives ref: FD23/4512

Submission of Additional information (CT scans)

January 1982

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THE BETHLEM ROYAL HOSPITAL  
AND  
THE MAUDSLEY HOSPITAL

# INSTITUTE OF PSYCHIATRY

DE CRESPIGNY PARK  
DENMARK HILL  
LONDON, SE5 8AF  
01 - 703 5411

6th January 1982

Professor R. H. Cawley,  
Institute of Psychiatry.

Dear Professor Cawley,

I am writing to you in your capacity as chairman of the meeting on the benzodiazepines held at the Medical Research Council on Wednesday 23rd September 1981. I am enclosing some additional information which I would have presented at that meeting if it had then been available. I understand that you are presenting the report of that meeting to the Neurosciences Board in the near future and you may consider that my supplementary information could be included.

As you will see from the table, 2 of our 14 patients have definite cortical atrophy, 5 have a borderline abnormality and the rest are normal. However, I am led to believe that the analysis of the radiologist was fairly crude and that more refined techniques might reveal further problems. Accordingly I think that the amount of abnormality is probably an underestimate.

Several of the patients are still on benzodiazepines but some have been off for quite some time.

Yours sincerely,

*Malcolm Lader*

M. H. Lader

cc Dr. James  
Dr. Sturgess



Rec'd 18.1.82

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ACADEMIC DEPARTMENT OF PSYCHOLOGICAL MEDICINE  
(KING'S COLLEGE HOSPITAL MEDICAL SCHOOL and INSTITUTE OF PSYCHIATRY)

UNIVERSITY OF LONDON  
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THE BETHLEM ROYAL HOSPITAL  
AND  
THE MAUDSLEY HOSPITAL

PROFESSOR ROBERT CAWLEY  
DR. H. STEVEN GREER

INSTITUTE OF PSYCHIATRY,  
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LONDON, SE5 8AF  
01-703 5411

RHC/uml

14 January 1982

Professor Malcolm Lader  
Institute of Psychiatry

Dear Malcolm

Thank you for your letter of 6 January and enclosures, in which you report information about your series of fourteen patients, previously on benzodiazapines for long periods, who had CAT scans.

I note that you have sent copies to Dr James and Dr Sturgess at the Medical Research Council. The Neurosciences Board, at its meeting on Tuesday 12 January, received the report of the ad hoc meeting we held in September 1981. I attended for that item and drew the Board's attention to the new data: so I can assure you that the Board is aware of the position.

Yours sincerely

*Bob*

R H Cawley

cc Dr D James  
Dr E Sturgess

*File away on benzodiazapine*  
*S. . . .*

*[Signature]*

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File No.

S1516/17

File Note

24 / 2 / 82 87

I spoke to Prof Lader concerning the para. relating to his CAT scan studies in the minutes. I read the sentences to him & asked if he objected to the minutes being circulated to all participants at the meeting. He said that the para. was quite innocuous & could do no harm go ahead & circulate.

Julie Alston.



PATIENT	SEX	AGE	BZ. YEARS	ON/OFF BZs. AT TIME OF SCAN	RADIOLOGIST'S REPORT
G.Q.	M	37	16	OFF 2/12	Normal appearances
D.W.	M	23	3½	OFF 2/12	Normal scan
G.H.	F	40	2½	ON	Normal scan
L.M.	F	35	6	(ON)	Normal scan
M.L.	M	27	7	OFF 12/12	Normal scan
A.G.	M	76	20	ON	The sulci are marginally prominent but within normal limits considering the patient's age. The lateral ventricles are normal.
S.E.	M	58	30	ON	Scan appearances are normal for the age of the patient.
A.T.	M	50	8	ON	There is some widening of the interhemispheric fissure but no other evidence of cerebral atrophy. No focal lesion seen.
W.H.	M	43	11	OFF 10/12	There is minor prominence of the anterior interhemispheric fissure. There is no evidence of gross atrophy.
R.C.	M	59	16	OFF 10/12	The anterior interhemispheric fissure is widened as are occasional sulci over the frontal lobe only. The lateral ventricles are normal and the posterior aspects of the hemispheres are also normal.

PATIENT	SEX	AGE	BZ. YEARS	ON/OFF BZs. AT TIME OF SCAN	RADIOLOGIST'S REPORT
J.H.	M	34	12-15	ON	Superficially sulci are very minimally prominent considering the patient's young age. No focal abnormality is shown.
M.M.	M	40	11	ON	There is no definite cerebral atrophy present. The sulci are visible but probably just within normal limits for the patient's age.
J.M.	M	32	10	OFF 2/12	Superficial sulci in the highest most 5B cut are relatively prominent considering the patient's young age, do imply some early atrophy. The anterior interhemispheric fissure is also slightly wider than usual. Summary: There is evidence of mild cortical atrophy affecting both hemispheres superficially.
M.F.	F	39	14	ON	There is no displacement of any part of the ventricular system. The left lateral ventricle is dilated and there is widening of the left sylvian fissure. The sulci of both hemispheres are wide. There is enlargement of the superior cerebellar cistern. Conclusions: Cerebral atrophy, the left hemisphere being more affected than the right.



# MEDICAL RESEARCH COUNCIL

MRC: IN CONFIDENCE

Neurosciences: MRC 81/818  
January 1982

## THE BENZODIAZEPINES

Report of an ad hoc meeting held on 23 September 1981

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### 1. Papers

Annex 1 - minutes of the ad hoc meeting

Annex 2 - details of relevant MRC supported research

### 2. Background

The potential problems of overprescribing and possible dependence on benzodiazepines had been brought to the attention of the office by Professor M H Lader. After discussion with the then Board Chairman, Professor R H Cawley, it was agreed to hold an ad hoc meeting of experts in the field to review existing knowledge of the properties and usage of the drugs with special reference to the question of dependence; and in the light of research already in progress, to consider whether further studies were desirable and feasible.

The meeting took place on 23 September 1981, under the Chairmanship of Professor Cawley, and the minutes are at annex 1.

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### 3. Action required

- (i) Consideration of the report of the ad hoc meeting.
- (ii) Decision whether to endorse the conclusions and recommendations from the meeting (annex 1 paragraphs 7.1 - 7.5).

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DBM: Professor E S Paykel  
S1516/17

25. The benzodiazepines - report of an ad hoc meeting held on 23 September 1981 (MRC 81/818)

The Board received the minutes of the meeting on the benzodiazepines, which had been convened to discuss the problems of possible overprescribing and dependence on these drugs.

In introducing the paper, Professor Paykel drew attention to the studies of psychotropic drugs conducted by the General Practice Research Unit at the Institute of Psychiatry as being of particular interest. He also mentioned that extensive investigations of the neuropharmacological basis of benzodiazepines were already in progress. He then identified the two most important recommendations contained in the report. Firstly, the need for studies directed towards characterising the complex reasons for prescribing these drugs, and for producing guidelines for formulating prescribing policies. Secondly, since any prescribing of benzodiazepines carried risks as well as benefits, research should be continued into the factors which determine long-term usage and dependence, and into methods of withdrawing benzodiazepines from dependent patients.

Professor Cawley, who had been invited to attend the Board for this item as Chairman of the benzodiazepine meeting, answered questions raised by Board members. He expanded on the question of the type of research which needed to be done, laying emphasis on the related problems of tolerance and dependence and the medico-sociological factors. He suggested that research into methods of withdrawing the drugs and into non-pharmacological methods of treatment of some of the problems might be of value and agreed that research should be done to determine the actual efficacy of benzodiazepines. He emphasised the difficulty of conducting good research in this important field.

Professor Cawley presented some additional information to the Board which he had received from Professor Lader who had conducted CAT scans on some patients treated with benzodiazepines. The preliminary results suggested the need for further and more extensive studies.

The Chairman thanked Professor Cawley for attending the meeting.

Decision

The Board noted the report of an ad hoc meeting on the benzodiazepines and accepted its conclusions.



MRC Supported Research related to BenzodiazepinesMRC Establishments

1. MRC Clinical Pharmacology Unit, Oxford (Director: Professor D Grahame-Smith)  
- Neuropharmacology: Biochemical pharmacology of brain monoamines and effect of therapeutic agents
2. MRC Neurochemical Pharmacology Unit, Cambridge (Director: Dr L L Iversen)  
Neurophysiological studies of transmitter receptors in mammalian (NS) actions of psychoactive drugs
3. Professor M H Lader (ESS) London, - Psychophysiological and biochemical measures in the assessment of psychotropic drug effects.

Programme Grants

1. Professor Sir William Paton (Pharmacology, Oxford)  
Chronic Effects of Centrally active Drugs and their Metabolites on Brain Chemistry and Structure.