



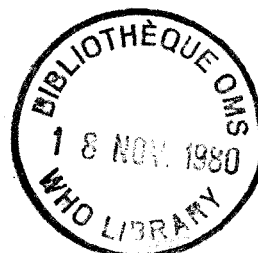
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REVIEW OF PSYCHOACTIVE SUBSTANCES FOR INTERNATIONAL CONTROL

Geneva, 22-24 September 1980

Appetite depressants

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1. Introduction

On behalf of the Director-General of WHO, Dr N. Sartorius, Director, Division of Mental Health welcomed the participants and expressed the concern of the organization to discharge its functions and responsibilities with regard to the Convention on Psychotropic Substances, 1971. He drew attention to the need for devising appropriate procedures for the review of groups of substances which may come within the purview of that Convention.

The advice of the Group was sought with regard to further review groups and possible procedures to deal expediently with notifications which are expected in increasing numbers. The Group was also requested to review and advise from signatories (or member nations) on possible contributions from the WHO Collaborating Centres, other co-operating organizations and the pharmaceutical industry.

2. Scope of Meeting

The Group was informed that at its 6th Special Session, the UN Commission on Narcotic Drugs took the following action regarding the recommendations of WHO:

- a) Dextropropoxyphene was placed in Schedule II of the Single Convention on Narcotic Drugs, 1961, as recommended;
- b) Sufentanil was placed in Schedule I of the Single Convention on Narcotic Drugs, 1961, as recommended but was not concurrently placed in Schedule IV of the same Convention as recommended;
- c) Tilidine was placed in Schedule I of the Single Convention on Narcotic Drugs, 1961, as recommended;
- d) Mecloqualone was placed in Schedule II of the Convention on Psychotropic Substances, 1971, as recommended;
- e) Phencyclidine remained in Schedule II of the Convention on Psychotropic Substances, 1971, as recommended;
- f) The three analogues of Phencyclidine (TCP, PHP, and PCE) were placed in Schedule I of the Convention on Psychotropic Substances, 1971, as recommended;

In September 1979, the previous Advisory Group had suggested WHO, in the future consider anxiolytics, non-barbiturate hypnotics, anorectics and the agonist/antagonist opioid analgesics. Accordingly, WHO convened the present Group to review the pharmacological, medical, epidemiological and data relevant to the dependence potential and abuse liability of the nine anorectics suggested for review by the previous group (phenmetrazine, phentermine, amfepramone, phendimetrazine, benzphetamine, mazindol, chlorphentermine, chlortermine and fenfluramine), and to recommend appropriate measures of control, if needed, under the Convention on Psychotropic Substances, 1971. Further, the Group was requested to add to its agenda the review of (a) the notification by the Government of Austria, under Article 3, para 1 of the 1961 Convention, that pentazocine be placed in Schedule I; (b) a notification from the Government of the Federal Republic of Germany, under Article 3, para 2 of the Single Convention on Narcotic Drugs, 1961, for the inclusion in Schedule III of preparations of dextropropoxyphene containing 150 mg or less per dosage unit.

The Representatives of the UN Division on Narcotic Drugs reviewed the procedures for instituting control under the Conventions of 1961 and 1971. The Representative of the International Narcotics Control Board presented statistical data on the anorectics under review, which had been requested from 140 countries many of whom not being parties to the 1971 Convention. It was noted that, generally, information had been received only on the two anorectic agents already under international control.

Similarly, the International Criminal Police Organization had requested its members to provide information on the frequency of identification of anorectics in seizures. The majority of replies received were negative.

The Group was informed that, pursuant to Article 3, para 8 of the Single Convention on Narcotic Drugs, 1961 and the 1972 Protocol amending that Convention, a request from the Government of Spain to review the decision of the Commission on Narcotic Drugs to include dextropropoxyphene in Schedule II of that Convention, was in the course of being processed. At the time of this meeting, no formal notification to this effect had been received from the Secretary-General. However, in the course of the first day of the meeting, a file was transmitted unofficially to WHO by the General Directorate of Pharmacy and Medicine of the Ministry of Health and Social Security of the Government of Spain containing what they considered as relevant information upon which this request for review was based. No action was taken pending receipt of a formal notification.

A representative of the UN Division on Narcotic Drugs reviewed the status of the various notifications listed on the agenda.

3. Review of Anorectic Substances

The Group reviewed the data submitted in the various background papers on the nine anorectics. It was decided that data on the pharmacology, dependence potential, animal and human toxicity, clinical pharmacology, abuse liability, degree and extent of therapeutic usefulness, evidence of illicit traffic, as well as evidence of public and social consequences in both the developed and developing countries, needed to be considered prior to making recommendations. The Group discussed each drug individually with regard to Article 2, para 1 and 4 of the 1971 Convention to determine if the drug merited controls. Factors taken into account were the capacity to produce dependence of the amphetamine type, to produce a toxic psychosis of the amphetamine type, to determine whether the substance had produced abuse and ill effects similar to those brought about by the substances already controlled, such as dexamphetamine, phenmetrazine and amfepramone; and whether the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

The following conclusions were reached:

(a) Phenmetrazine: Using the criteria described above, there was evidence that the drug had an abuse liability similar to that of dexamphetamine and had given rise to similar public health and social problems. The Group concluded that currently there was no evidence to recommend a change in its level of control under the 1971 Convention.

(b) Amfepramone: Using the criteria described above, there was evidence that this drug had a definite abuse liability of the amphetamine type, but lesser than that of dexamphetamine, giving rise to similar, but lesser public health and social problems. The Group concluded that currently there was no evidence to recommend a change in its level of control under the 1971 Convention.

(c) Phendimetrazine: Using the criteria described above, there was evidence that this drug had a dependence potential and abuse liability similar to, but less than those of dexamphetamine giving rise to similar, but lesser public health and social problems. The Group concluded that there currently was adequate evidence to recommend control under Schedule IV of the 1971 Convention.

(d) Phentermine: Using the criteria described above, there was evidence that this drug had a dependence-potential and abuse liability similar to, but less than those of dexamphetamine giving rise to similar, but less public health and social problems. The Group concluded that there currently was adequate evidence to recommend control under Schedule IV of the 1971 Convention.

(e) Benzphetamine: Using the criteria described above, there was evidence that this drug had a dependence potential and abuse liability similar to, but less than those of dexamphetamine giving rise to similar, but lesser public health and social problems. The Group concluded that there currently was adequate evidence to recommend control under Schedule IV of the 1971 Convention.

(f) Mazindol: Using the criteria described above, there was evidence that this drug had a dependence potential and a likelihood of abuse liability similar to, but less than those of dexamphetamine giving rise to similar, but lesser public health and social problems. The Group concluded that there currently was adequate evidence to recommend control under Schedule IV of the 1971 Convention.

(g) Fenfluramine: Using the criteria described above, there was evidence that this drug did not have amphetamine like abuse liability nor was there evidence of significant public health and social problems. The Group further recognized that fenfluramine was the prototype of anorectics with a pharmacological profile, dependence potential and mechanism of action distinct from those of dexamphetamine. The Group concluded that there currently was insufficient evidence to recommend control under the 1971 Convention.

(h) Chlorphentermine: Using the criteria described above, there was evidence that this drug did not have amphetamine-like abuse liability, nor was there evidence of significant public health and social problems. Evidence was presented that the mode of action of the drug more closely resembles that of fenfluramine than that of dexamphetamine. The Group concluded that there currently was insufficient evidence to recommend control under the 1971 Convention.

(i) Clortermine: Using the criteria described above, there was evidence that this drug did not have amphetamine-like abuse liability, nor was there evidence of significant public health and social problems. Evidence was presented that in respect of the mode of action the drug may more closely resemble fenfluramine than dexamphetamine. The Group concluded that there currently was insufficient evidence to recommend control under the 1971 Convention.

4. Review of the PCP Analogues

The Group reviewed the need for control of PCP analogues and homologues in addition to those listed in Schedule I of the 1971 Convention. The Group concluded that there was sufficient pharmacological evidence that numerous other analogues and homologues had a dependence liability of the PCP type. However, they felt that there was no evidence to indicate that any of these analogues and homologues have appeared in the illicit market nor was there evidence to indicate the existence of public health or social problems of a magnitude to require international control of these substances.

5. Review of Requests for Changes in Scheduling

5.1 Preparations

The Group reviewed, in accordance with Article 3, para 4 of 1971 Convention on Psychotropic Substances, the list of preparations which the Government of the People's Republic of Bulgaria has decided to exempt in accordance with Article 3, para 3 of that Convention.

The Group examined each of these preparations in regard to the evidence that they were compounded in such a way that they present no, or a negligible, risk of abuse and that the substance cannot be recovered by readily applicable means in a quantity liable to abuse so that the preparation does not give rise to public health and social problems.

(a) Barbamil[®]: The information received indicated that this preparation as described, was the sodium salt of amobarbital in normal therapeutic doses and did not represent a preparation that had a lesser risk of abuse than amobarbital itself, nor lesser liability to be recovered. The Group recommended the termination of this exemption.

- (b) Hexadorm-Calcium[®]. The information received indicated that this preparation as described was the calcium salt of cyclobarbital in normal therapeutic doses and did not present a preparation with a lesser risk of abuse than cyclobarbital itself, nor lesser liability to be recovered. The Group recommended the termination of this exemption.
- (c) Hexobarbital-Natrium[®]. Hexobarbital is not controlled under the 1971 Convention therefore the information as provided, contains an apparent technical error. The Group recommended deferment of review until clarification of the supporting information was received.
- (d) Glutethimide[®]. The information received indicated that this preparation as described is a formulation of the normal therapeutic dose and did not represent a preparation that had a lesser risk of abuse than glutethimide itself, nor lesser liability to be recovered. The Group recommended the termination of this exemption.
- (e) Brevinarcon[®]. The information received contained an apparent technical error in the description of the composition of the preparation since there was a discrepancy between the name of the designated substance under control and the description of the composition of the preparation. The Group recommended deferment of the review until clarification of the supporting information was received.
- (f) Thiopental[®]. Thiopental is not subject to control under the 1971 Convention and the information as provided contains an apparent technical error. The Group recommended deferment of the review until clarification of the supporting information was received.
- (g) Antiacid[®]. The information received indicated that the preparation contained a small dose of phenobarbital compounded in such a way that it presents a negligible risk of abuse, and is unlikely to be recovered by readily applicable means in a quantity liable to abuse. The Group recommended that the exemption not be terminated.
- (h) Antiacid B[®]. The information received indicated that the preparation contained a small dose of phenobarbital compounded in such a way that it presents a negligible risk of abuse, and is unlikely to be recovered by readily applicable means in a quantity liable to abuse. The Group recommended that the exemption not be terminated.
- (i) Barbiphan[®]. The information received indicated that the preparation contained a small dose of phenobarbital compounded in such a way that it presents a negligible risk of abuse, and is unlikely to be recovered by readily applicable means in a quantity liable to abuse. The Group recommended that the exemption not be terminated.
- (j) Bellergamin[®]. The information received indicated that the preparation contained a small dose of phenobarbital compounded in such a way that it presents a negligible risk of abuse, and is unlikely to be recovered by readily applicable means in a quantity liable to abuse. The Group recommended that the exemption not be terminated.
- (k) Pyraminal[®]. The information received indicated that the preparation contained a small dose of phenobarbital compounded in such a way that it presents a negligible risk of abuse, and is unlikely to be recovered by readily applicable means in a quantity liable to abuse. The Group recommended that the exemption not be terminated.

The Group reviewed, in accordance with Article 3, para 4 of 1971 Convention on Psychotropic Substances the list of preparations which the Government of the Republic of Mexico has decided to exempt in accordance with Article 3, para 3 of that convention.

The Group examined each of the preparations with regard to the evidence that the preparations were compounded in such a way that they presented a negligible risk of abuse and that the substances cannot be recovered by readily applicable means in a quantity liable to abuse, so that the preparation does not give rise to public health and social problems.

(a) Almotracina (suppository): The information received indicated that this preparation contains a small amount of methamphetamine compounded in such a way that it presents a negligible risk of abuse and is not recoverable in a quantity liable to abuse. The Group recommended that the exemption not be terminated.

(b) Almotracina "S": The information provided indicates that the preparation contained 500 mg of methamphetamine per 100 gms. There is no evidence to indicate that the preparation is compounded in such a way to prevent ready recovery of the substance in a quantity liable to abuse. The Group recommended that this exemption be terminated.

(c) Dilacorán[®]: The information received indicates that this preparation contains a sedative dose of pentobarbital. No evidence was presented to indicate that this preparation is compounded in such a way to present a negligible risk of abuse. The Group recommended that the exemption be terminated.

(d) Fenadrops[®] and Sedadrops[®]: The information provided on these two preparations indicates a similar composition and it was assumed that these present two trade names for similar preparations. It was noted that the preparation as described contains 8 mg of pentobarbital and 16 mg of phenobarbital per ml. No information was provided to indicate the unit dose or the total package dispensed. There is, therefore, insufficient evidence to indicate that the pentobarbital cannot be recovered in a quantity liable to abuse. The Group recommended that the exemption be terminated.

(e) Visparax[®]: The information provided indicates that this compound contains secobarbital in a sedative dose. No evidence was presented to indicate that this preparation is compounded in such a way to present no, or a negligible risk of abuse. The Group recommended that the exemption be terminated.

Recommendations for future review of preparations

On the basis of the review of exempted preparations, the Group recommended that, at a minimum, certain information be provided on each preparation for which a request is reviewed. This should include: (a) the proprietary name of the preparation; (b) the international non-proprietary name and chemical name of all active ingredients; (c) the amount of these ingredients; (d) specification of the unit dosage; (e) specification of the total package dispensed; (f) description of the formulation; and (g) therapeutic indication(s).

5.2 Pentazocine

The Group reviewed the request of the Government of Austria dated 22 August, 1980 that pentazocine be included in Schedule I of the 1961 Convention. The Group noted that the late receipt of this notification did not provide sufficient time for members of the Group to prepare for discussions on this request. The Group noted that WHO, in previous meetings of Expert Committees on Drug Dependence and Advisory Groups on Drug Dependence^{1,2,3} had noted the dependence potential and abuse liability of pentazocine and concluded that there was

1 WHO Technical Report Series, No.437, p.24

2 WHO Technical Report Series, No.407, 1969

3 Review of psychoactive substances for international control, Sept. 1979, WHO document MNH/79.33, p.6

insufficient evidence of public health and social concerns to warrant international control. Further, the Group noted that pentazocine represents the prototype of the agonist/antagonist opioid analgesics and that there is an important need to review this entire group of drugs. Further, there is need to consider in addition to the data provided in the notification from Austria, additional data to be collected from many countries using pentazocine in legitimate medical practice. Such information is not immediately available. The Group recommended that the consideration in respect of the control of pentazocine be placed within the framework of the whole group of agonist/antagonist opioid analgesics and the previous notification be considered by WHO after data on the extent of medical and non-medical use of pentazocine is made available.

4.3 Dextropropoxyphene preparations

The Group reviewed the request of the Government of the Federal Republic of Germany concerning the inclusion in Schedule III of the Single Convention on Narcotic Drugs, 1961 of preparations containing 150 mg or less of dextropropoxyphene per dosage unit. After extensive deliberations, the Group decided to recommend exemption of oral preparations containing not more than 150 mg of dextropropoxyphene per dosage unit or with a concentration of not more than 2.5 per cent in undivided preparations, and, if compounded with other substances then these substances should not be those controlled by the Convention on Psychotropic Substances, 1971.

6. Opioid agonist/antagonist mixtures

The Group was informed that a request for scheduling of an agonist/antagonist mixture was in process by the Government of Belgium. Material received unofficially by WHO served as a basis for the continuation of the general discussion initiated in 1979 meeting by a Group reviewing Psychoactive Substances for International Control (MNH/79.33), concerning such mixtures as therapeutic agents with lesser abuse potential. After extensive discussions the Group concluded that in the future information on such mixtures was needed in the following areas:

- (i) epidemiological data on the incidence of abuse;
- (ii) multiple dose studies with the mixture;
- (iii) clinical pharmacological and human toxicity data;
- (iv) studies on the chemical extractability of the agonist from the mixture.

The Group recommended that WHO initiate efforts to collect information prior to reviewing scheduling of such mixtures for international control.

7. Thebaine

With financial support from the United Nations Fund for Drug Abuse Control (project no. ACB-90117), a literature review and a study of the dependence potential of thebaine were carried out by WHO, Division of Mental Health with the assistance of a group of advisers, several of whom contributed ad hoc experimental work. This work demonstrates that thebaine has limited reinforcing properties in monkeys and produces a form of physical dependence. It was suggested that these actions might be attributable to the metabolites of thebaine. Since oripavine was found to be one of the major metabolites, studies on the pharmacological effects and dependence potential of oripavine were conducted. These studies demonstrated that:

- (i) oripavine is a pharmacologically active substance;
- (ii) its analgesic potency as assessed in mice is comparable to that of morphine;
- (iii) it possesses a weak morphine-antagonistic property as evidenced by its partial precipitation of the morphine withdrawal signs in morphine-dependent and non-withdrawn monkeys;
- (iv) its physical dependence potential as assessed by 72 hours of hourly intravenous administrations at a submaximal, tolerable dose (4 mg/kg) to rats is almost comparable to that of morphine at 0.5 mg/kg, but lower than that of morphine at 2 mg/kg and of codeine at 2 mg/kg;

- (v) its reinforcing effect is demonstrable in intravenous cross self-administration procedures in rhesus monkey.

Based on these findings, oripavine was suggested to be a metabolite which may contribute to the dependence potential of thebaine.

Further pharmacological studies of other metabolites of thebaine such as northebaine and nororipavine were recommended by the Group.

8. Khat

The Group reviewed recent progress of the pharmacological studies on (-) cathinone, the principal active alkaloid of khat. Based on the data obtained in these studies the Group concluded that (-) cathinone possesses a high dependence potential comparable to that of dexamphetamine.

The Group decided to submit the summaries of these studies together with suggestions for epidemiological studies of khat consumption to the UN Bulletin on Narcotics for publication.

9. Recommendations

1. The Group was convinced that the work before them was enormous due to the large number of psychoactive drugs newly introduced into therapeutics besides those which have been in use for some time. Parties to the 1971 Convention have also addressed notifications to the Secretary-General of the United Nations concerning combination products containing psychotropic substances under Article 3 of the 1971 Convention. This adds to the workload of this group to give opinions on the merit of these exemptions. Thus, the group proposed that in future years two meetings annually should be convened.

2. The following groups of substances were recommended for future review:

- (a) opioid agonists / antagonists
- (b) benzodiazepines
- (c) sedatives and hypnotics
- (d) new analgesics
- (e) hallucinogens
- (f) precursors.

3. The Group fully supported the recommendation expressed during the Expert Committee, Geneva, 15-20 September 1980, that WHO develop new mechanisms and strengthen existing ones, to obtain information on drugs which are under review by WHO. In particular, the data on utilization of drugs and the harm they produce in many societies, especially in the developing countries is needed. This can be done through WHO Collaborating Centres, Regional Offices and Member States, Members of the WHO Expert Advisory Panels including involvement of the non-governmental organizations, etc.

4. This gigantic and important job ahead of WHO requires resources and manpower. The Group appreciated the views expressed by Professor Rexed, Executive Director UNFDAC, during the Expert Committee, to give priority to this type of activity in his programme.

5. The Group considered it important that WHO continue to involve the concerned pharmaceutical companies in obtaining information for the review meetings. Mechanisms were discussed which WHO may consider to further involve, in an even closer association, with the pharmaceutical industry together with the various consumers interested in the safe and effective use of psychotropic substances.

10. List of Participants

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Dr P. Kalix, Ecole de Médecine, Department de Pharmacologie, Geneva, Switzerland

LIST OF BACKGROUND DOCUMENTS

1. MNH/78.1 - Consultation on the Convention on Psychotropic Substances. Review of Articles 3 and 10
2. MNH/79.32 - The Dependence Potential of Thebaine. Report of a WHO Advisory Group
3. MNH/79.33 - Review of Psychoactive Substances for International Control
4. MNH/80.1 - Study Guidelines for the Exemption of Preparations under Article 3 of the Convention on Psychotropic Substances, 1971 by Dr E. Widerlov and Dr T. Lewander
5. MNH/80.17 - Neurochemistry of Anorectic Drugs: Differentiation between those mediated by serotonergic and dopaminergic or adrenergic systems by Dr J. Knoll
6. MNH/80.19 - Review of Background Information for the Discussion on Anorectic Substances by Dr I. Khan and Dr P. Kalix
7. MNH/80.20 - Considerations on the Abuse Potential of Pharmaceutical Preparations Combining Tilidine with Naloxone by Dr P. Kalix
8. MNH/80.21 - The Availability, Use and Abuse Potential of Some Psychoactive Anorectic Substances in Nigeria by Dr O. A. Sogunro and Dr O. O. Ogunremi
9. MNH/80.22 - A Review on Khat by Dr T. Yanagita
10. MNH/80.23 - A Review on the Reinforcing Properties of Several Anorectics as assessed by Self-Administration Studies in Animals by Dr T. Yanagita
11. MNH/80.24 - General Pharmacology and Toxicity of Anorectic Drugs by Dr L. S. Harris and Dr C. R. Schuster
12. MNH/80.25 - Comparative Clinical Pharmacology of the Anti-Obesity Drugs by Dr D. R. Jasinski
13. MNH/80.26 - Interdisciplinary Studies on Phencyclidine by Dr Jasinski, Dr Shannon, Dr Cone, Dr Vaupel, Dr Risner, Dr McQuinn, Dr Su and Dr Pickworth
14. MNH/80.27 - Additional Report to Thebaine Study - Dependence Potential of Oripavine by Dr T. Yanagita
15. DND411/1(2) WHO - Reports compiled by the Division of Narcotic Drugs (July and September, 1980)