This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES
No. 495

OPIATES AND THEIR ALTERNATES FOR PAIN AND COUGH RELIEF

Report of a WHO Scientific Group

WORLD HEALTH ORGANIZATION
GENEVA
1972

PRINTED IN FRANCE

CONTENTS

WHO SCIENTIFIC GROUP ON OPIATES AND THEIR ALTERNATES FOR PAIN AND COUGH RELIEF

Geneva, 9-15 November 1971

*Members:**

Dr M. A. Attisso, Professor, Faculty of Medicine and Pharmacy, University of Dakar, Senegal

Dr M. L. Dhar, Director, Central Drug Research Institute, Lucknow, Uttar Pradesh, India

Dr N. B. Eddy, Consultant on Narcotics, National Institutes of Health, Bethesda, Md., USA *(Chairman)*

Dr M. El-Kattan, Director General of Planning and Scientific Department, Egyptian General Organization for Pharmaceuticals, Cairo, Egypt

Dr K.-J. Hahn, Department of Medicine, University of Heidelberg, Federal Republic of Germany

Dr F. Hoffmeister, Professor of Pharmacology, Head, Department of Pharmacology, Farbenfabriken Bayer A. G., Wuppertal-Elberfeld, Federal Republic of Germany *(Rapporteur)*

Dr E. Hosoya, Professor and Chairman, Department of Pharmacology, Keio University School of Medicine, Shinjuko-Tokyo, Japan

Dr R. W. Houde, Attending Physician, Memorial Hospital for Cancer and Allied Diseases, New York, N.Y., USA *(Rapporteur)*

Dr J. Jacob, Chief, Pharmacology and Toxicology Service, Institut Pasteur, Paris, France *(Vice-Chairman)*

Dr K. Pengsritong, Under-Secretary of State for Public Health, Ministry of Public Health, Bangkok, Thailand

Dr M. H. Seevers, Professor of Pharmacology, University of Michigan Medical School, Ann Arbor, Mich., USA

Representatives of other organizations:

United Nations:

Dr I. Bayer, Division of Narcotic Drugs, United Nations, Geneva, Switzerland

Dr O. J. Braenden, Chief, Scientific and Technical Section, Division of Narcotic Drugs, United Nations, Geneva, Switzerland

International Narcotics Control Board:

Mr L. Manueco-Jenkins, Social Affairs Officer, International Narcotics Control Board, Geneva, Switzerland

Mr S. Stepczynski, Deputy Secretary, International Narcotics Control Board, Geneva, Switzerland

Secretariat:

Dr D. C. Cameron, Chief Medical Officer, Drug Dependence, WHO, Geneva, Switzerland *(Secretary)*

Dr T. L. Chruściel, Medical Officer, Drug Dependence, WHO, Geneva, Switzerland

Dr H. Friebel, Chief Medical Officer, Drug Efficacy and Safety, WHO, Geneva, Switzerland

---

* Unable to attend: Dr E. A. Babajan, Head of the Department for the Introduction of New Drugs and Medical Technology, Ministry of Health of the USSR, Moscow, USSR; Dr Paul Janssen, Janssen Pharmaceutica Research Laboratoria, Beerse, Belgium.

OPIATES AND THEIR ALTERNATES FOR PAIN AND COUGH RELIEF

Report of a WHO Scientific Group

The WHO Scientific Group on Opiates and their Alternates for Pain and Cough Relief met in Geneva from 9 to 15 November 1971. Dr V. Fattorusso, Director, Division of Pharmacology and Toxicology, opened the meeting on behalf of the Director-General and welcomed participants and the representatives of the Secretary-General of the United Nations and of the International Narcotics Control Board. He described the background to the meeting of the Scientific Group, whose task was, in the light of present knowledge, to compare the opiates of natural origin with the available fully synthetic alternates in regard to their effectiveness in pain and cough relief and their adverse effects, including dependence liability, and to suggest areas for research.

1. GENERAL CONSIDERATIONS

1.1 The opiates

For the purposes of this report, opiates are natural substances found in the opium poppy and the semisynthetic alkaloids derived from them. Some 1350 tons of opium are now used annually to meet most of the world's medical needs for morphine, codeine, opium and other opium products.[1,2] It has been estimated that at least another 1200 tons of opium reach the illicit market in one form or another.[3]

It is well known that opium contains two groups of medically useful alkaloids: (1) the phenanthrene alkaloids, e.g., morphine and codeine, which have played a most important role in providing symptomatic relief of pain (analgesics), cough (antitussives) and diarrhoea; and (2) the benzoisoquinolines, e.g., papaverine and noscapine (narcotine), which

---

[1] More than 30 % of all opiates are derived from poppy straw.

[2] International Narcotics Control Board (1971) *Statistics on Narcotic Drugs for 1970* (document E/INCB/15), New York, United Nations, p. ix.

[3] United Nations, Commission on Narcotic Drugs (1969) Document E/4606/Rev.1, para. 128 *(Economic and Social Council: Official Records)*.

are employed to afford relief from spasm of smooth muscle (spasmolytics) and cough, and have played a relatively minor role in medical treatment. From the phenanthrene alkaloids a large number and variety of semi-synthetic analgesic and antitussive compounds have been prepared, some of which have been found to have useful opiate antagonist properties, i.e., the capacity to counteract in varying degrees the morphine-like (agonist) properties of the opiates. Many of these antagonists themselves also produce analgesic and other effects.

Morphine and codeine are considered as the standard reference substances in evaluating the relative effectiveness of other drugs in relieving pain and cough. A major difference in the use of these two opiates is that morphine is more commonly prescribed for the relief of moderate to severe pain and is usually administered parenterally, whereas codeine is most commonly employed for the control of cough or mild to moderate pain and is usually taken orally.

1.2 The synthetic alternates for opiates

Study of the numerous derivates of natural alkaloids has shown that chemical similarity does not guarantee comparable morphine-like pharmacological properties. In the search for improved analgesics, it has been found that some compounds that are fully synthetic and chemically dissimilar have pharmacological properties comparable with those of certain opiates. The extent to which these synthetic drugs are capable of replacing the major natural alkaloids of opium and their derivatives depends on their respective desirable and undesirable properties.

In discussing the suitability of the available synthetic alternates for opiates, the Group considered whether such possible alternates were as effective in relieving the target symptom as the appropriate reference opiates (morphine or codeine) and compared the nature, frequency and severity of adverse side effects, particularly the capacity to produce psychic or physical dependence and tolerance.[1] The Group considered fully only those drugs that had been both adequately and objectively evaluated by controlled clinical trials, and had been marketed and subjected to substantial clinical experience and scrutiny.

[1] *Psychic dependence* is a condition in which a drug produces a " feeling of satisfaction and a psychic drive that requires periodic or continuous administration of the drug to produce pleasure or to avoid discomfort ". *Physical dependence* is " an adaptive state that manifests itself by intense physical disturbances when the administration of the drug is suspended . . . These disturbances, i.e., the withdrawal or abstinence syndromes, are made up of specific arrays of symptoms and signs of psychic and physical nature that are characteristic for each drug type ". (Eddy, N. B., Halbach, H., Isbell, H., & Seevers, M. H., *Bull. Wld Hlth Org.*, 1965, **32**, 723). *Tolerance* is " The state in which repetition of the same dose of a drug has progressively less effect, or in which the dose needs to be increased to obtain the same degree of pharmacological effect as was caused by the original dose ". (Isbell, H. & Chrusciel, T. L., *Bull. Wld Hlth Org.*, 1970, **43**, Suppl., p. 5).

1.3 Clinical evaluation

The essential features of a controlled clinical study are the use of appropriate measures for the control of bias and the use of suitable reference standards to ascertain the validity and/or sensitivity of the experiment. Specifically, studies involving the evaluation of such responses as pain and cough must provide for: (1) the proper selection of the population in which the response is to be evaluated; (2) the use of the double-blind technique; (3) randomization of the assignment of treatments to patients; (4) the inclusion of either an inert and an active standard medication or graded doses of the standard drug; and (5) a means of collecting data in a form that will permit the valid statistical appraisal of the significance of observed differences in results.[1]

The methods used in controlled studies of the opiates and their alternates have varied from one investigation to another, according to the clinical setting, type of patient involved and purposes of the investigation. No generally accepted method of assay has yet been developed for assessing the comparative efficacy of drugs administered over long periods. On the other hand, generally accepted methods are available for determining the efficacy of a single dose or of any one dose in a series of repeated administrations. In the case of the opiates and their alternates, the interpretation of results can also be seriously complicated if tolerance and physical dependence develop during the course of repeated administration,[2] as there are no convenient and reliable methods of quantifying their influence. Yet despite these shortcomings and difficulties, whenever the principles of controlled clinical trials have been closely adhered to, there has been a good measure of agreement in the results of studies of the relative analgesic or antitussive efficacy and relative potency[3] of drugs carried out in different groups of patients and in different clinical settings.

2. PAIN RELIEF

2.1 Moderate to severe pain

2.1.1 *Agonists*[4]

The Group noted that a great many synthetic compounds belonging to different chemical classes have analgesic properties comparable to

[1] For a further discussion of the clinical evaluation of drugs, see *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 403.

[2] The development of tolerance and physical dependence is related to the size of the dose and the frequency of administration.

[3] The reciprocal ratio of the doses of two drugs that produce the same effect.

[4] In this report, agonists are compounds with morphine-like action.

those of morphine.[1] Some of these compounds have been subjected to extensive clinical trials. For others, fewer data are available and their clinical use has been limited.

The pharmacological profile [2] of morphine was taken as the reference standard against which to evaluate the clinical usefulness of synthetic drugs. Morphine is one of the most generally useful analgesics available in that it can afford significant relief from many different kinds of pain resulting from a variety of causes. It also has a number of other pharmacological actions giving rise to effects that may be desirable or undesirable in the particular clinical situation, including a sense of well-being, euphoria, relief from anxiety and modified intestinal activity. On the other hand, some of its properties are almost always undesirable; for example, it is relatively ineffective by oral (as compared with parenteral) administration, and it causes respiratory depression and contraction of smooth muscle, particularly of the biliary and urinary tracts. But its most important limitations are that psychic and physical dependence and tolerance develop on repeated administration. Consequently, in seeking a replacement for morphine and its congeners priority continues to be given to the development of compounds that are relatively free from these disadvantages.

The Group discussed the properties of a substantial number of compounds in different chemical groups, but this report is concerned primarily with prototypes of the various chemical groups reviewed and a few special cases.

Pethidine,[3] the prototype of the phenylpiperidines, is widely used. The analgesic properties of this drug were discovered during a search for atropine-like spasmolytic agents. Although it has only a part of the structural skeleton of morphine, pethidine has strong morphine-like effects in animals and man.

In persons suffering from acute post-operative pain, 75–100 mg of pethidine administered intramuscularly have essentially the same analgesic potency as 10 mg of morphine. Pethidine is one quarter as potent orally as intramuscularly, the corresponding ratio for morphine being about one sixth to one eighth.

Respiratory depression and other side effects of therapeutic doses of pethidine administered for acute pain are essentially the same as those of morphine, but pethidine produces more hypotension than morphine when given intravenously. It induces about the same degree of psychic and physical dependence and tolerance as equally effective doses of morphine. Numerous cases of dependence on pethidine have been reported. The abstinence syndrome resulting from pethidine withdrawal is generally

---

[1] 3,6-dihydroxy-*N*-methyl-4,5-epoxymorphinen-7.

[2] All the signs and symptoms produced by the administration of a drug.

[3] 1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester.

qualitatively similar to that of morphine, and is severe. In some instances it is more dangerous because of an excessive stimulant component. The euphorigenic properties of pethidine are thought by some to be more pronounced than those of morphine, especially following the initial dose.

Some difficulties in the use of pethidine in the treatment of patients with chronic pain arise from the fact that comparatively large volumes of solution are necessary as the dosage requirement increases with the development of tolerance, and local irritation is noted especially at higher doses. This drug may produce incoordination and convulsions at very high dose levels (2–3 g per day), but this is not of major importance in clinical practice because such dose levels are seldom reached.

The often held view that pethidine has a spasmolytic effect has led to its use to control pain arising from spasticity of smooth muscles, particularly of the biliary and urinary tracts. It is not, however, generally more effective than morphine in such conditions.

Pethidine has been well accepted in medical practice. Between 1956 and 1970 the total yearly consumption increased from 13 758 kg to 20 288 kg, while in the same time period the consumption of morphine decreased from 4377 kg to 2474 kg.[1,2] The trends are clear, but caution must be used in drawing conclusions about the relative frequency with which the two drugs are used in medical practice, since seven and a half to ten times as much pethidine as morphine is required to produce equally effective pain relief.

Pethidine has supplied a new model for chemical modification, leading to the synthesis of thousands of compounds. Among these, *alphaprodine* [3] has some limited use in a few countries and *trimeperidine* [4] is used extensively in one. Both have a somewhat shorter duration of action than pethidine but do not differ significantly in their dependence liability. Another phenylpiperidine derivative, *anileridine*,[5] is relatively potent when taken by mouth. The oral effective analgesic dose is only twice the intramuscular dose. Still another member of this group, *fentanyl*,[6] is used almost exclusively in anaesthesia because of the rapid onset and short duration of its action.

Methadone,[7] the prototype of the diphenylpropylamine group of

---

[1] Permanent Central Opium Board (1961) *Report to the Economic and Social Council on the Work of the Board in 1961*, Document E/OB/17, Annex B, p. 41, New York, United Nations.

[2] International Narcotics Control Board (1971) *Statistics on Narcotic Drugs for 1970* (document E/INCB/15), New York, United Nations, Annex B, p. 49.

[3] α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine.

[4] 1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine.

[5] 1-(*p*-aminophenethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester.

[6] 1-phenethyl-4-*N*-propionylanilinopiperidine.

[7] 6-dimethylamino-4,4-diphenyl-3-heptanone.

morphine-like compounds, came into clinical use in the late 1940s. Administered parenterally (intramuscularly), methadone is as effective as morphine, weight for weight, in controlling moderate to severe acute and chronic pain, and the duration of its analgesic action is the same as that of morphine. Administered orally, methadone is four times as potent as morphine and oral methadone is half as effective as parenteral morphine. Methadone thus has some advantage over morphine as an oral analgesic.

Methadone, like morphine, induces psychic and physical dependence and tolerance. In some countries there are significant numbers of persons who self-administer methadone, usually intravenously. Some of them take it as their drug of choice and may not have used other drugs with morphine-like effects. When the drug is withdrawn, methadone-dependent persons present a somewhat delayed, less intense but more prolonged abstinence syndrome than persons dependent on morphine, but the syndromes are qualitatively similar. Methadone will suppress the signs and symptoms of morphine-type abstinence. It is relatively effective orally, as noted above, and when taken by this route has a substantially longer duration of action than morphine in suppressing the abstinence syndrome. The same is true of parenteral methadone, but to a lesser extent. For these reasons, it is being used increasingly as a substitute for heroin and other natural and synthetic narcotics in treatment programmes that include maintenance on morphine-like drugs as one of their therapeutic approaches.[1]

The worldwide consumption of methadone is low as compared with morphine or pethidine. In 1967, 306 kg were consumed, while in 1970 consumption had increased to 930 kg.[2] Nearly all this increase occurred in the last year and can be accounted for by the rapid development of methadone maintenance programmes. Apart from the differences noted in the abstinence situation, the pharmacological profiles of the two drugs are strikingly similar.

There are many synthetic compounds chemically related to methadone. Among them, *dextromoramide* [3] and *dipipanone* [4] have been used to a certain extent. 5 mg of dextromoramide, 20 mg of dipipanone and 10 mg of morphine administered intramuscularly produce comparable analgesia. Dextromoramide, like methadone, is very effective orally. Its pharmacological profile is more or less identical with that of methadone. The world consumption of dextromoramide was 166 kg in 1967 and 158 kg in 1970.[2] This quantity is sufficient to provide approximately the same

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1970, No. 460, p. 20 (section 3.3.2).

[2] International Narcotics Control Board (1971) *Statistics on Narcotic Drugs for 1970* (document E/INCB/15), New York, United Nations, Annex B, p. 49.

[3] (+)-4-[2-methyl-4-oxo-3,3-diphenyl-4-(1-pyrrolidinyl)butyl]morpholine.

[4] 4,4-diphenyl-6-piperidine-3-heptanone.

number of therapeutic doses as the amount of methadone used for analgesic purposes in those years. The 1970 consumption of dipipanone was 91 kg.[1]

Levorphanol[2] is the most used morphinan[3] derivative, although only 4 kg were used during 1970.[1] 2 mg of levorphanol administered intramuscularly is equi-analgesic with 10 mg of morphine. It has morphine-like dependence-producing properties and its overall profile of therapeutic action closely resembles that of morphine except that orally it is relatively more potent. Its parenteral versus oral dose ratio is 1 : 2.

Phenazocine[4] may serve as an example of the agonists among the benzomorphan[5] group of compounds. Consumption was 4 kg in 1970.[1] 3 mg given intramuscularly is equivalent to 10 mg of morphine; orally, 15 mg is required to produce comparable analgesia. Phenazocine produces dependence of the morphine type.

The Group concluded that, *within the four groups of agonists discussed, there are synthetic alternates that can replace, and to a considerable extent have been used in place of, parenterally administered morphine for the relief of moderate to severe pain of both acute and chronic types.* The Group noted, however, (1) that some alternates with relatively greater oral effectiveness than morphine can be used orally for the relief of moderate to severe pain, and (2) that the alternates in the phenylpiperidine group, because of the short duration of their action, are not as useful for pain of long as for pain of short duration.

2.1.2 *Agonist-antagonists*[6]

Pentazocine[7] is an example of a benzomorphan[5] that has both agonist and antagonist properties. Its agonist properties are more prominent at lower dose levels, while at higher doses some of the adverse effects common to antagonists of the nalorphine type begin to appear. The analgesic effect of 30 – 60 mg of pentazocine intramuscularly is comparable to that of 10 mg of morphine. But whereas, over a period of time, the therapeutic dose of morphine can be multiplied several times without severe and limiting acute side effects, an increase in the intramuscular dose

---

[1] International Narcotics Control Board (1971) *Statistics on Narcotic Drugs for 1970* (document E/INCB/15), New York, United Nations, Annex B, p. 53.

[2] (−)-3-hydroxy-*N*-methylmorphinan.

[3] *cis*-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-iminoethanophenanthrene.

[4] 2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan.

[5] 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine.

[6] In this report, agonist-antagonists are substances with morphine-like action that have the capacity to counteract the morphine-like action of other drugs under certain circumstances.

[7] 3-(3-methyl-2-butenyl)-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine.

of pentazocine to only 80 mg may result in limiting side effects characterized by hallucinations and dysphoria. An oral dose of 180 mg of pentazocine is required to provide pain relief comparable to that provided by 10 mg of morphine given intramuscularly. However, in oral doses exceeding 200 mg limiting adverse effects begin to occur. Pentazocine is of somewhat limited use in the control of chronic pain owing to its comparatively short duration of action, its narrow therapeutic range and the possibility of its precipitating abstinence phenomena if another potent analgesic has preceded it. With prolonged use, pentazocine is capable of producing mild morphine-like psychic dependence and somewhat less physical dependence;[1] the latter is qualitatively different from that produced by drugs of the morphine type. Tolerance also develops. Nevertheless, the overall dependence liability of the compound as compared to that of morphine-like substances is low.

The Group concluded that *parenteral pentazocine is a synthetic alternate for parenteral opiates in the treatment of acute moderate to severe pain.* This synthetic alternate is generally less effective for the relief of chronic pain, especially following another potent analgesic.

2.2 Mild to moderate pain

Codeine,[2] a less potent congener of morphine, is widely used as an analgesic, often in combination with antipyretics, other analgesics and caffeine. The total world consumption for the relief of both pain and cough was 157 582 kg in 1970.[3]

The pharmacological profiles of codeine and morphine are qualitatively similar except that codeine has a greater stimulant component, which is particularly manifest at high doses. Parenterally, codeine has about one-tenth to one-thirteenth the analgesic potency of morphine. Orally, it is one-third to one-quarter as potent as morphine. The usual oral therapeutic dose of codeine for pain is 30–60 mg. The effects of such a dose usually last for 3 – 4 hours and any adverse reaction is likely to be minimal. These properties of codeine may account for its popularity in the treatment of mild to moderate pain that is not readily controlled by antipyretic analgesics.

As already noted (p. 6), in medical practice codeine is not often administered parenterally. Analgesic equivalence to 10 mg of morphine administered intramuscularly can be attained orally, but only by increasing the dose of codeine to such an extent that limiting adverse effects are

---

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1970, No. 437, p. 24 (section 6).

[2] 3-methylmorphine.

[3] International Narcotics Control Board (1971) *Statistics on Narcotic Drugs for 1970* (document E/INCB/15), New York, United Nations, Annex B, p. 49.

likely to occur. Tolerance to codeine develops much as with morphine. Qualitatively, codeine and morphine have similar physical dependence-producing properties. However, the actual occurrence of codeine dependence is limited by the physical properties of the drug, its tendency to produce adverse effects as the dose is increased and its apparently general inability to afford as much psychic satisfaction as morphine.

There are synthetic compounds of different chemical classes having analgesic properties possibly comparable with those of codeine. Some are at present undergoing clinical trials, while others have been carefully evaluated and have been in extensive clinical use. The Group took the pharmacological profile of codeine as the reference standard for the evaluation of the clinical usefulness of these compounds in the relief of mild to moderate pain. Primary consideration was given to two prototypes.

Dextropropoxyphene [1] is extensively used in a few countries for the relief of mild to moderate pain. Like codeine, it is often used in combination with antipyretics, other analgesics and caffeine. Because it gives rise to local irritation, it is rarely administered parenterally. Orally, its analgesic potency has been estimated by most investigators to be about half that of codeine. 65 mg of dextropropoxyphene is usually regarded as an effective analgesic dose and, at this level, no severe side effects have been noted. Higher doses (150 mg and more) have sometimes produced a syndrome of mixed central nervous system stimulation and depression. The dependence liability of dextropropoxyphene is low. Cases of dependence do occur; but the frequency of non-medical use is low considering the quantity of the drug used in medical practice.[2] 800 mg orally gives substantial, but incomplete, relief from the abstinence syndrome that occurs on withdrawal from physically dependent persons of a daily intramuscular dose of 240 mg of morphine. When dextropropoxyphene has been administered at high dose-levels (500 mg or more per day) over a long period, a mild abstinence syndrome and some drug-seeking behaviour occur on discontinuation.

Pentazocine,[3] taken orally, has about the same analgesic potency as codeine, 30–60 mg being the usual therapeutic dose. As noted in section 2.1.2, adverse effects begin to be encountered only at doses of 200 mg, that is, some 3–6 times the usual therapeutic dose, and so the oral therapeutic range of this compound for the relief of mild to moderate pain is satisfactory.

The Group concluded that *there are synthetic alternates that can replace, and to a considerable extent have been used in place of, oral codeine for the relief of mild to moderate pain.*

---

[1] α-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol propionate ester.

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1970, No. 437, p. 24 (section 6).

[3] 3-(3-methyl-2-butenyl)-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine.

3. COUGH RELIEF

Although virtually all the potent morphine-like analgesics are also effective antitussives, these drugs are rarely employed to suppress cough because of their higher side effect potentials and dependence-producing risks if used repeatedly. Codeine has been used as an antitussive drug almost from the time of its isolation from opium in 1832 and is still widely employed for this purpose.

Although cough is a frequent and sometimes distressing symptom of a large number of pulmonary, mediastinal and upper respiratory disorders, the indications for employing an antitussive have undergone considerable change and diminution in recent years as more effective, definitive measures have been developed and utilized for controlling the disorders causing cough and some of the environmental sources of inhaled irritants.

Antitussive medications are still employed, however, for the symptomatic relief of both acute and chronic cough. As it is acute cough that most frequently causes discomfort and loss of sleep, antitussives are employed in practice in these circumstances. But such cough tends to be self-limited and so is only infrequently the subject of controlled clinical drug trials. The majority of such trials are conducted on persons with chronic cough — most commonly elderly patients suffering from chronic bronchitis, emphysema or tuberculosis who often appear to be less distressed by cough than those who suffer from the acute type.

Codeine is generally considered the reference standard in evaluating drugs alleged to have antitussive properties. In most studies involving patients with chronic cough, doses of 15–30 mg of oral codeine 3–4 times a day are regularly found to be effective. If these oral doses are not exceeded, the incidence of adverse side effects is very low (for the pharmacological profile of codeine, see section 2.2).

A large number of wholly synthetic drugs belonging to different chemical categories have been claimed to be as effective as, and capable of being substituted for, codeine in the control of cough. Only a few of these drugs have been evaluated by acceptably controlled clinical trials.

Dextromethorphan [1] is a wholly synthetic morphinan [2] having no analgesic properties. It has been tested in a few controlled studies and found to be approximately as effective as codeine in suppressing cough. In the oral doses employed, no side effects of consequence have been encountered. In some countries there have been a number of reports

[1] (+)-*cis*-1,3,4,9,10,10a-hexahydro-6-methoxy-11-methyl-2*H*-10,4a-iminoethanophenanthrene.

[2] *cis*-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-iminoethanophenanthrene.

of non-medical use of this compound. In large doses, it produces mental effects that some persons appear to enjoy. However, the drug has little if any liability to produce dependence of the morphine type and it is not a substitute for morphine in morphine-dependent persons.

A number of drugs from chemical classes unrelated to those usually expected to possess antitussive properties have been reported to be useful antitussives. These drugs include two substances chemically related to the phenothiazines, *dimethoxanate* [1] and *pipazetate*,[2] which have pharmacological profiles different from that of codeine. In controlled clinical studies, both proved approximately as effective as codeine in the doses of 15–30 mg employed. Two others, *clobutinol* [3] and *oxolamine*,[4] have pharmacological profiles which are distinguishable from each other and from that of codeine. Both are less potent than codeine, but with somewhat larger doses each appears to be as capable as codeine of suppressing cough. Such adverse effects as have been reported from these as well as from the other substances assessed in this paragraph have been minimal; there are no reports of their use other than on medical indications. Limitations in the clinical trials carried out for the evaluation of the four above-mentioned drugs do not permit any definitive judgements about their overall usefulness as antitussive agents.

The Group concluded that *there are synthetic alternates that can replace, and to some extent have been used in place of, oral codeine for the relief of cough.*

4. SPECIAL CONSIDERATIONS

4.1 Other indications

The semisynthetic drug *ethylmorphine* [5] has been used in ophthalmological practice as a chemotic to produce vasodilatation and oedema of the conjunctiva in corneal ulcer and other inflammatory conditions of the eyes. This is not a specific opiate action and other more effective drugs are available for this purpose.

Opium and its preparations have been widely used for the control of diarrhoea. Comparable therapeutic effects can be achieved with synthetic compounds such as *diphenoxylate*.[6] This substance is used only

[1] 2-(2-dimethylaminoethoxy)ethyl phenothiazine-10-carboxylate.

[2] 2-(2-piperidinoethoxy)ethyl 10*H*-pyrido[3,2-b][1,4]benzothiazine-10-carboxylate.

[3] *p*-chloro-α-[2-(dimethylamino)-1-methylethyl]-α-methylphenethyl alcohol.

[4] 5-[2-(diethylamino)ethyl]-3-phenyl-1,2,4-oxadiazole.

[5] 3-ethoxy-6-hydroxy-*N*-methyl-4,5-epoxymorphinen-7.

[6] 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester.

as an antidiarrhoeal agent. Its worldwide use has trebled in the last five years to a current level of 1243 kg per year.[1]

Certain synthetic and opiate analgesics can be modified in their molecular structure to produce agonist-antagonists. These substances counteract the respiratory depressant and other effects of opiates and are used as life-saving agents when adverse and toxic effects result from the use of opiates. However, no pure antagonist of the naloxone [2] type is yet available as a synthetic compound.

The endoetheno compounds derived from thebaine, which are over 100 times more potent than morphine, are at present used only in veterinary practice, for the immobilization of large animals. Fully synthetic compounds with similar effects are available and can serve as alternates for these compounds.

The benzoisoquinoline derivatives of opium were noted in section 1.1 to be of relatively little importance in medical practice. Nevertheless they must be considered. *Papaverine* [3] is a smooth muscle relaxant. There are many non-opiate synthetic compounds with at least equal effectiveness. Moreover, papaverine has been synthesized and a large part of the present medical supply is of synthetic origin. In so far as *noscapine* [4] (narcotine) has antitussive activity, it is like codeine, replaceable by synthetic compounds.

4.2 Variations among the opiates and their alternates

Hundreds of modifications have been made in the morphine molecule, with the primary objective of dissociating the useful from the undesirable effects, particularly dependence-producing liability. Intensive study of the structure/activity relationships of the resultant substances has shown wide variations in potency, some differences in duration of action and peak effects, and differences in the relative oral effectiveness of the various derivatives. But little difference has been obtained in the quality or intensity of the adverse effects at equally effective doses. Many modifications have also been made in the molecular structure of possible synthetic alternates, with much the same outcome. Claims have been made concerning special properties of particular substances and numerous pharmacological studies have been carried out. However, there have been no adequate and detailed clinical studies on these special properties,

---

[1] International Narcotics Control Board (1971) *Statistics on Narcotic Drugs for 1970* (document E/INCB/15), New York, United Nations, Annex B, p. 53.

[2] 12-allyl-7,7a,8,9-tetrahydro-3,7a-dihydroxy-4a*H*-8, 9c-iminoethanophenanthro [4,5-*bcd*]furan-5(6*H*)-one.

[3] 6,7-dimethoxy-1-veratryl-isoquinoline.

[4] 5-(6,7-dimethoxyphthalidyl)-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo [4,5-*g*]isoquinoline.

matching particular synthetic alternates with particular opiates. In general, when analgesic effectiveness is increased, so is the dependence liability, unless other limiting adverse effects preclude the use of the drug in amounts necessary to produce dependence.

4.3 Ease of clandestine manufacture

Some, but not all, of the synthetic analgesics can be produced by persons reasonably experienced in carrying out the procedures used in organic synthesis and in handling everyday chemical equipment, particularly if there is little concern about the chemical purity or yields of the compounds produced. The training and experience of qualified chemists is not necessarily required though access to such expertise might be necessary in setting up the manufacturing process.

The basic ingredients for the synthesis of most categories of dependence-producing synthetic alternates are on unrestricted sale in a large number of countries and many are not prohibitively expensive. The ease with which clandestine manufacture could be carried out partly depends on the nature of the equipment required. In the production of impure heroin very little equipment is involved and it is easily transportable. But, for the manufacture of the synthetic alternates for opiates more sophisticated, more bulky and less portable equipment is required. Nevertheless, methadone is known to have been clandestinely manufactured.

The Group therefore concluded that *the clandestine manufacture of many of the dependence-producing synthetic alternates for opiates is technically possible.* The process would be substantially more complex than the clandestine manufacture of certain opiates, particularly the extraction of morphine from opium and the manufacture of heroin.

5. COMMENT

The natural and semisynthetic opiates used for the relief of pain and cough vary in their potency, time/effect relationships and relative oral/parenteral effectiveness. None is fully effective and none is without adverse effects, although the occurrence of adverse effects in relation to the therapeutic dose varies from one drug to another. None of the effective agonist analgesics is without physical dependence liability. Physical dependence of the morphine type will develop in practice unless severe adverse effects or low solubility prevent the intake of enough of the drug. There are opiates of the agonist-antagonist type in which analgesic potency is not associated with liability to produce physical dependence of the morphine type, but none is currently available for practical use as an analgesic.

The synthetic alternates used for pain relief have all these characteristics except that at least one of the available agonist-antagonists is therapeutically useful for the relief of mild to moderate pain. But to some extent at least the benefit of separating analgesia and physical dependence liability is offset by the narrow separation between the dose ranges producing therapeutic effects and those giving rise to adverse effects.

Some synthetic alternates used for the relief of cough do not have significant dependence liability.

6. CONCLUSIONS OF THE GROUP

(1) Synthetic alternates are available that are equivalent to and may, in some respects, be superior to the opiates for the relief of *moderate to severe pain;* and some are being used to a considerable extent.

(2) Synthetic alternates are available that may be equivalent, though none is clearly superior, to the opiates (codeine) for the relief of *mild to moderate pain;* and some are being used to a considerable extent.

(3) Synthetic alternates are available that can be, and to some extent are being, used for the relief of *cough,* and on substantial evidence a few of them rate as equivalent to codeine in effectiveness. Lack of well-controlled clinical trials in most instances prevents a definitive judgement on their relative merits.

(4) Synthetic alternates are available that are equivalent or superior to the opiates for the control of *diarrhoea;* and some are being used to a considerable extent.

(5) There are a few other specific indications (see section 4.1) for which synthetic alternates have been and are being used.

(6) The partial agonist-antagonists have shown the greatest dissociation between therapeutic efficacy and physical dependence liability.

(7) In the light of the foregoing considerations the natural and semi-synthetic opiates may be considered not indispensable in the practice of modern medicine.

7. RECOMMENDATIONS

(1) The Group recommended a substantial increase in research on chemical structure/activity relationships so that the desired analgesic and antitussive effects of drugs may be further separated from their adverse effects, particularly the capacity to produce drug dependence.

(2) The Group noted that controlled clinical trials are essential to the evaluation of the efficacy and adverse effects of analgesics and antitussives. The methodology for single dose assays is well established, but the same cannot be said for studies of the overall effectiveness of a series of doses. The Group further noted that the resources available for controlled clinical studies of analgesics and antitussives are insufficient. It recommended that further emphasis be given to the development of (1) improved methods for assaying the therapeutic efficacy of a series of doses, (2) increased facilities for clinical trials involving both single and repeated administration of drugs, and (3) additional, urgently needed training programmes in this field in clinical pharmacology.

(3) The Group agreed that " many factors have been proposed as playing a part in the initiation, perpetuation, and discontinuation of drug-using behaviour. No single ' cause ' has been demonstrated. A knowledge of the pharmacological interaction between the drug and the organism and of the interaction between the organism and the environment is essential to an understanding of the nature of drug dependence ".[1] It recommended an intensification of research into the causes of drug dependence and the mechanisms of the interaction between drugs and human and animal organisms and between such organisms and their environments.

---

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1970, No. 460, p. 11 (section 3.1.1).

WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES

No.		Price p	$	Sw.fr.
463	(1971) **WHO Expert Committee on Biological Standardization** Twenty-third Report (91 pages)	50	1.75	5.—
464	(1971) **Joint FAO/WHO Expert Committee on Brucellosis** Fifth Report (76 pages)	40	1.25	4.—
465	(1971) **Application and Dispersal of Pesticides** Eighteenth Report of the WHO Expert Committee on Insecticides (66 pages)	40	1.25	4.—
466	(1971) **Methodology for Family Studies of Genetic Factors** Report of a WHO Scientific Group (37 pages)	30	1.00	3.—
467	(1971) **WHO Expert Committee on Malaria** Fifteenth Report (59 pages)	40	1.25	4.—
468	(1971) **Prevention of Rh Sensitization** Report of a WHO Scientific Group (36 pages)	30	1.00	3.—
469	(1971) **Cerebrovascular Diseases: Prevention, Treatment, and Rehabilitation** Report of a WHO Meeting (57 pages)	40	1.25	4.—
470	(1971) **Health Aspects of the Supply and Use of Non-Human Primates for Biomedical Purposes** Report of a WHO Scientific Group (30 pages)	30	1.00	3.—
471	(1971) **Endocrine Regulation of Human Gestation** Report of a WHO Scientific Group (32 pages)	30	1.00	3.—
472	(1971) **Statistical Indicators for the Planning and Evaluation of Public Health Programmes** Fourteenth Report of the WHO Expert Committee on Health Statistics (40 pages)	30	1.00	3.—
473	(1971) **Methods of Fertility Regulation: Advances in Research and Clinical Experience** Report of a WHO Scientific Group (48 pages)	30	1.00	3.—
474	(1971) **Pesticide Residues in Food** Report of the 1970 Joint FAO/WHO Meeting (44 pages)	30	1.00	3.—
475	(1971) **WHO Expert Committee on Insecticides** Nineteenth Report (20 pages)	20	0.60	2.—
476	(1971) **Family Planning in Health Services** Report of a WHO Expert Committee (65 pages)	40	1.25	4.—
477	(1971) **Joint FAO/WHO Expert Committee on Nutrition** Eighth Report (80 pages)	40	1.25	4.—
478	(1971) **The Use of Cannabis** Report of a WHO Scientific Group (47 pages)	30	1.00	3.—
479	(1971) **WHO Expert Committee on Yellow Fever** Third Report (56 pages)	30	1.00	3.—
480	(1971) **Personal Health Care and Social Security** Report of a Joint ILO/WHO Committee (74 pages)	40	1.25	4.—
481	(1971) **Development of Studies in Health Manpower** Report of a WHO Scientific Group (56 pages)	30	1.00	3.—
482	(1971) **Principles for the Testing and Evaluation of Drugs for Mutagenicity** Report of a WHO Scientific Group (18 pages)	20	0.60	2.—