Psychotropic drugs

G. W. HANKS
B.Sc., M.B., M.R.C.P.

The Royal Marsden Hospital, Fulham Road, London SW3 6JJ

Introduction

The interaction between the cognitive component (the perception of nociceptive, or painful stimuli) and the affective component of pain is reflected in the overlap between the actions of anti-nociceptive agents (analgesics) and mood-altering drugs (psychotropics) when treating pain patients. Anxiety, depression, fear and sleeplessness may all respond to psychotropic drugs, and this may result in a reduction in pain or a greater ability to cope with it. This may enable a patient's pain to be controlled with a smaller dose of analgesic. In this sense psychotropic drugs have an 'analgesic' effect but it is a misleading use of the word, and has been the source of much misunderstanding.

In the day-to-day management of pain problems the two groups of drugs do have well-defined indications. Acute pain is invariably associated with nociception, and responds to analgesics or other antinociceptive treatments. Chronic pain (except that due to cancer or arthritis) is rarely associated with an identifiable nociceptive stimulus and frequently does not respond to simple antinociceptive measures. Psychotropic drugs (Table 1) play an important part in the management of chronic pain. Cancer pain is a special case. Loeser (1980) and others have proposed that chronic cancer pain should be characterized as long-standing acute pain because it is associated with a continuous nociceptive input and responds better to antinociceptive measures. Psychotropic drugs have a lesser part to play in cancer pain than in other types of chronic pain (Hanks, 1984).

The mode of action of psychotropic drugs in chronic pain

If relief of pain is obtained with psychotropic drugs there are three possible explanations. The pain relief may be secondary to the amelioration of psychological distress or disorder, which may be the primary problem or a result of the persistent pain. It may represent some true intrinsic analgesic action. Or it may be a reflection of a non-specific central nervous system-depressant effect of these drugs: by depressing the general level of arousal the central perception of pain may be modified.

In this review the evidence for intrinsic analgesic activity and the place of psychotropic drugs in the treatment of chronic pain are discussed in the light of the published literature and recent clinical experience.

TABLE 1. The WHO classification of psychotropic drugs

Neuroleptics
Anxiolytic sedatives
Antidepressants
Psychostimulants
Psychodysleptics

Neuroleptics

Neuroleptics are antipsychotic agents of which the prototype is chlorpromazine, a phenothiazine. Moore and Dundee (1961) examined a range of phenothiazines for analgesic activity. They found apparent analgesic effects with trimeprazine, chlorpromazine and promazine but algesic activity with promethazine, pecazine, prochlorperazine and others. The use of an experimental pain technique in this study means that it is not possible to extrapolate directly from these results to the clinical situation. In a controlled clinical study, Houde and Wallenstein (1955) were unable to show any difference between intramuscular injections of morphine alone, and morphine combined with chlorpromazine.

Twycross (1980) has suggested that chlorpromazine may be useful in the management of rectal or bladder 'tenesmoid' pain in cancer. This effect is variable and needs to be explored further. There are no other cancer pain syndromes which appear to respond preferentially to the phenothiazines.

Methotrimeprazine. Interest has been shown in the analgesic action of methotrimeprazine (levomepromazine). Studies in postoperative patients (Lasagna

and DeKornfeld, 1961) and in a variety of other acute and chronic painful conditions (Montilla, Frederik and Cass, 1963) have shown that when given by intramuscular or subcutaneous injection methotrimeprazine 15 mg and morphine 10 mg appear to have equivalent analgesic activity. At these doses sedation is more pronounced with methotrimeprazine.

A recent study showed that, in mice, small non-sedative doses of methotrimeprazine potentiated the analgesic action of morphine (Petts and Pleuvry, 1983). The same authors were unable to show a similar effect in man using an experimental pain technique in healthy volunteers, though the dose they used (7·5 mg i.m.) caused significant sedation.

Evidence of analgesic activity after oral administration is unconvincing, and side effects, particularly sedation, are common (Hanks, 1984). There have been no reliable controlled studies which show that, when given orally, methotrimeprazine has a useful analgesic effect.

Haloperidol. Haloperidol was the first of the butyrophenones to be synthesized, in 1957. It has since become one of the most widely used neuroleptics because it combines high potency and established efficacy with low toxicity. It is chemically related to pethidine. There is some evidence that haloperidol enhances morphine analgesia in animal models (Head *et al.,* 1979) and also that it binds to opiate receptors (Clay and Brougham, 1975) but there is little clinical data to support these effects in man.

A recent study in 34 patients undergoing surgery failed to find any evidence of an analgesic or analgesic-potentiating effect of haloperidol (Judkins and Harmer, 1982). Our own experience in cancer patients has been similar (Hanks *et al.,* 1983).

Neuroleptic/antidepressant combinations. There have been a number of reports of the use of combinations of phenothiazines with tricyclic antidepressants in patients with difficult chronic pain problems. Several series have produced apparently promising results (Merskey and Hester, 1972; Taub, 1973; Kocher, 1976; Clarke, 1981). However the validity of the data is often questionable (Hanks, Evans and Lloyd, 1981). Many different drug combinations have been used. The choice of drugs and the selection of patients does not appear to have been based on any clear rationale other than that the patients had usually failed to respond to more conventional measures. No controlled clinical trials have been carried out. This makes it difficult to draw any useful conclusions about the role and indications for using neuroleptics in this way.

Antidepressants

Antidepressants are widely used in the treatment of chronic *non-cancer* pain (Table 2). Though they have been employed for this purpose for many years controversy still surrounds their use in this way. As with the neuroleptics the results of animal studies have been conflicting, but there is evidence from several different models of an antinociceptive and opiate-potentiating action of the tricyclics (Saarni-vaara and Mattila, 1974; Goldstein *et al.,* 1982). Antidepressants have never been shown to be effective in the relief of acute pain in man or in experimental pain.

TABLE 2. Chronic pain syndromes reported to respond to treatment with antidepressants

Cancer pain
Chronic rheumatic disorders
Migraine
Tension headache
Atypical facial pain
Facial arthromyalgia (tempero-mandibular joint dysfunction syndrome)
Low back pain
Post-herpetic neuralgia
Causalgia
Phantom limb pain
Anaesthesia dolorosa

There are numerous references in the literature to the frequency of pain as a symptom in psychiatric patients and to the common association of chronic pain and depression (Sternbach, 1974). Certain chronic pain syndromes have been specifically regarded as being manifestations of an underlying depressive illness and have been described as 'masked depression' or 'depressive equivalents' (Lopez-Ibor, 1972). Atypical facial pain (Lesse, 1974), facial arthromyalgia (Fine, 1971), and low back pain with no identifiable organic cause (Forrest and Wolkind, 1974) are the conditions which have most often been described in these terms. These syndromes do respond favourably to treatment with antidepressants (Lascelles, 1966; Feinmann, Harris and Cawley, 1984).

Of the other conditions included in Table 2, some of the 'organic' disorders such as rheumatic pain and headache (including migraine and tension headache) have also been shown in well-controlled studies to respond to antidepressants (Hanks, 1981). The efficacy of antidepressants in other varieties of chronic pain is much more open to question. Post-herpetic neuralgia, post-traumatic neuralgia, causalgia, arachnoiditis and phantom limb pain have all been the subject of extravagant claims. But clinical experience

with antidepressants in such patients is often disappointing and clinical trial data are poor. An initial beneficial effect is often seen in these conditions but is rarely maintained and is partly (perhaps largely) explained by a placebo response.

The potential magnitude of the placebo effect in chronic pain patients was clearly demonstrated in a study which examined the possible analgesic activity of the tricyclic antidepressant doxepin. Treatment with this drug produced a dramatic 70% reduction in analgesic requirements in a group of patients with a variety of chronic pain problems. However the placebo group did equally as well (Evans *et al.*, 1973).

Antidepressants, monoamine neurotransmitters and opioid analgesia

Considerable attention has been focussed in recent years on the neurotransmitters involved in pain pathways and on the mechanisms of opioid analgesia. This has been stimulated both by the discovery of stereospecific opioid receptors and their endogenous ligands the endorphins, and also by the finding that electrical stimulation of discrete sites in the brainstem results in analgesia which is akin to that induced by the opioids. Stimulus-produced analgesia (SPA) is elicited by stimulation of the periaqueductal grey area and the nucleus raphe magnus, and injection of opioids into these sites also results in reduced sensitivity to pain. SPA may be abolished or attenuated by specific opioid antagonists.

Pharmacological studies have indicated that monoamine neurotransmitters are involved in mediating both SPA and opioid analgesia. Serotonin (5-HT, 5-hydroxytryptamine) and dopamine (DA) appear to have a facilitatory action, whereas noradrenaline (NA) has an antagonistic action (Akil and Liebeskind, 1975). Serotonin has also been identified as an important transmitter in the descending projections from the brainstem to the dorsal horn of the spinal cord. This neuronal pathway exerts an inhibitory effect on nociceptive transmission (Messing and Lytle, 1977).

The same monoamine neurotransmitters are believed to be involved in the mode of action of antidepressants on mood. All of the tricyclics inhibit the presynaptic reuptake of NA and/or 5-HT and to a much lesser extent DA. In this way they enhance transmission in these synapses. Recently it has become clear that antidepressants also produce changes in the sensitivity and density of pre- and post-synaptic receptors and that their actions on monoaminergic neurotransmission is much more complex than has hitherto been thought.

The involvement of monoamines in the actions of both the opioids and antidepressants has been the basis for rationalising the use of the latter drugs in chronic pain states. Particular attention has been paid to drugs which have a predominant effect on 5-HT because this, of all the amine neurotransmitters, seems to be important in anti-nociceptive mechanisms. Studies with clomipramine and the more selective 5-HT uptake blocker zimelidine have been carried out. L-tryptophan, a precursor of 5-HT, has also been used in chronic pain patients. Unfortunately the results with all of these agents have been generally disappointing. There have been a handful of initial enthusiastic reports, which have not been substantiated by good clinical trials.

The effects on monoamines may be more relevant when antidepressants are used in conjunction with centrally-acting analgesics. Spencer (1976) has drawn attention to similarities in the pharmacological profiles of narcotic analgesics and antidepressants, and has also demonstrated that 5-HT and NA have an enhancing and attenuating action respectively on morphine analgesia in animal models. These results thus support the conclusions derived from SPA models. Spencer's group have gone on to show that clomipramine enhances opioid analgesia whereas maprotiline (a relatively selective NA-uptake inhibitor) attenuates it. Again this fits well with the general hypothesis.

The implications of these findings are important. Spencer's work indicates that some antidepressants may potentiate opioids whilst others antagonise them. In either case the introduction of an antidepressant to a patient on long-term narcotic therapy may produce unforseen, and perhaps unrecognised, consequences.

Psychostimulants

Amphetamines. Dextroamphetamine enhances the analgesic action of morphine in animal models. A similar effect has been shown in normal human volunteers in whom dextroamphetamine also counteracts the psychomotor impairment, respiratory depression, and nausea and vomiting induced by morphine (Ivy, Goetzl and Burrill, 1944). Other experimental work has confirmed these results but has stimulated little interest. There is only a single systematic clinical investigation to be found in the literature: this showed that in postoperative patients intramuscular injection of dextroamphetamine 10 mg with morphine was twice as potent as morphine alone (Forrest *et al.*, 1977). The sedative effects of the narcotic were also reduced. The authors suggest that this combination 'comes much closer than any existing single compound to offering ideal pain therapy for this group of patients'. In spite of this dramatic claim the work has not been followed up.

There have been isolated references to the use of amphetamines to counteract the drowsiness associated with oral narcotics in cancer pain patients but no

studies have been carried out. There is little information about their efficacy when used in this way. The usual suggested dose range is 2·5–5 mg of dextroamphetamine once or twice a day in the morning.

Cocaine and the Brompton cocktail. Cocaine was first used together with morphine in patients with cancer pain as long ago as 1896, to 'sustain vitality' (Snow, 1896). Following its adoption by the Brompton Hospital the mixture became widely used as a means of administering narcotics to patients with terminal illness. Controlled clinical studies have demonstrated that cocaine serves no useful purpose when used in this way and that in common with the other constituents of the elixir is more likely to produce undesirable rather than beneficial effects (Twycross, 1979). The Brompton cocktail is now obsolete: even the Brompton Hospital no longer uses it.

Benzodiazepines

Benzodiazepines are widely used as premedicants and have been shown to reduce postoperative analgesic requirements. As with the neuroleptics there seems to be little doubt that anxiety reduction plays an important part in this situation. Investigations of their possible analgesic properties have produced variable results. Animal studies have either shown no or only mild antinociceptive activity (Bodnar *et al.,* 1980), and experimental pain models in man have demonstrated both elevation of pain thresholds and reduction (Hall, Whitwam and Morgan, 1974).

Clonazepam. Clonazepam is a potent benzodiazepine with a relatively greater anticonvulsant effect than its congeners. Anticonvulsants have been increasingly employed in the management of lancinating (stabbing) dysaesthetic pains ever since the demonstration that phenytoin and carbamazepine are effective in relieving the pain of trigeminal and glossopharyngeal neuralgias. Results from controlled studies are still awaited but initial reports are promising (Swerdlow and Cundhill, 1981). Clonazepam appears to be as effective as the major anticonvulsants but is particularly sedative. Treatment should be started with low doses (0·5 mg nocte) and titrated up according to response and tolerability. The usual maintenance dose is 2–4 mg nocte.

Benzodiazepines as co-analgesics. Anxiolytic and hypnotic agents have an important part to play as co-analgesics in the management of cancer pain. Anxiety, fear, and insomnia are potent pain exacerbating factors and the benzodiazepines are the drugs of choice for coping with them. Effective use of this group of drugs depends on a knowledge of their pharmacokinetics. In particular the potential for accumulation with several members of the group must be borne in mind. This apart, these drugs are characterized by a low incidence of side effects and little potential for interaction with other agents.

Diazepam is still the most generally useful of the group. It need be administered only once a day because of its long duration of action and long-acting major metabolite, though some circumstances will require more frequent dosing. The usual dose is 5–30 mg daily. Clobazam is a useful alternative which has less central depressant effects and produces less impairment of psychomotor performance. It also is long acting and is used in a single daily dose (10–40 mg nocte; 10 mg clobazam is equivalent to 5 mg diazepam). Temazepam is a shorter-acting hydroxylated derivative of diazepam and is a good simple hypnotic for use when an anxiolytic action is not required (10–60 mg nocte).

Muscle spasm is an important mechanism of pain in cancer and the benzodiazepines are effective muscle relaxants. This property is mediated by inhibition of spinal polysynaptic reflexes and diazepam is probably the most potent of the benzodiazepines in this respect. However the sedative effects of diazepam limit its use purely for this purpose; baclofen is preferable because at doses producing comparable muscle relaxation it is much less likely to cause troublesome drowsiness (Young and Delwaide, 1981).

Hydroxyzine. Hydroxyzine is not a benzodiazepine but is included here because it has been in widespread use in North America. It is a sedative antihistamine and has been commonly employed as a preanaesthetic medication. In several studies it has been shown to enhance morphine analgesia in postoperative patients (Hupert, Yacoub and Turgeon, 1980). There is no other evidence that it has analgesic properties and there is a lack of convincing evidence of sustained anxiolytic activity with this drug. This suggests that the most probable explanation for its enhancement of morphine analgesia is its non-specific sedative action.

Psychodysleptics

The most important psychodysleptics are lysergic acid diethylamide (LSD) and cannabis. The unpredictable and dangerous actions of LSD have limited investigations of its therapeutic use and there is no good evidence that it has analgesic properties. The active principle of *Cannabis sativa* is δ-9-tetrahydrocannabinol (THC) which, in common with the synthetic cannabinoids nabilone and levonantradol, has been shown to possess analgesic activity in animal models. This activity is variable and depen-

dent on the model used; in some studies cannabinoids appear to be of similar potency to morphine. Studies in man have also produced inconsistent results. In one study no analgesic action was detectable with THC in normal volunteers, whereas in a clinical trial in patients with advanced cancer the drug appeared to reduce pain. However this was at doses which produced significant side effects in terms of sedation, mental clouding, and depersonalisation (Noys *et al.,* 1975). Levonantradol has been shown to be analgesic when given intramuscularly to postoperative patients.

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