

Recommendations for the appropriate use of opioids for persistent non-cancer pain

A consensus statement prepared on behalf of the Pain Society, the Royal College of Anaesthetists, the Royal College of General Practitioners and the Royal College of Psychiatrists

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RECOMMENDATIONS FOR THE APPROPRIATE USE OF OPIOIDS FOR PERSISTENT NON-CANCER PAIN

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Persistent pain affects approximately 10% of the population. Many of these patients might be considered for opioid therapy. The consensus group that prepared this document takes the view that the decision to initiate opioid treatment should always be made by the patient in partnership with a doctor. The group acknowledges the valuable role of the other members of the health care team in maintaining and supporting opioid prescribing within agreed boundaries. Opioids are not needed by all patients and are not suitable or effective for some people. However a trial of opioids is worth considering as part of an overall rehabilitation strategy.

This publication has been produced for all health care professionals who are concerned with the use of opioids in the management of patients with persistent non-cancer pain. These recommendations will help to define the appropriate use of opioids in such circumstances. They have been produced for use in both primary and secondary care, and they provide a national framework to support the appropriate use of opioids. They encourage local liaison between primary care, pain and drug services e.g. drug information services and addiction services. The publication contains an information leaflet about opioids for persistent painful conditions prepared for patients and for their paid and unpaid carers. These recommendations have been developed by the Pain Society in collaboration with representatives from the Royal College of Anaesthetists, the Royal College of Psychiatrists, the Royal College of General Practitioners, the Association for Palliative Medicine and the Royal Pharmaceutical Society. The document has been prepared in consultation with the Pain Society Patient Liaison Group. These recommendations were circulated in provisional form in April 2003 and endorsed by the Royal College of Anaesthetists, Association of Anaesthetists and Royal College of General Practitioners. They have since undergone a period of 3 months detailed consultation with health care professionals involved in pain management and other professional bodies and groups.

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1. Executive summary

- **1.1** This document makes recommendations about the appropriate use of opioids in persistent non-cancer pain.
- **1.2** These recommendations apply to all opioids available in the UK. The recommendations do not concern spinally delivered opioids.
- 1.3 Opioids have traditionally been classified as weak e.g. dihydrocodeine or strong e.g. morphine; this division is artificial in some cases, but is still in common use (see table 1). These recommendations were not developed for patients who use weak opioids within the British National Formulary (BNF) dosage range. The recommendations refer to patients who use weak opioids outside the BNF range, and to patients who use or might benefit from using strong opioids.
- **1.4** It is the opinion of the working group that injectable opioids are rarely appropriate in the management of persistent non-cancer pain.
- **1.5** There is a lack of good quality research about the benefits and risks of opioids for persistent non-cancer pain.
- **1.6** There is a need for closer working relationships and good communication between primary and secondary care services about the management of patients who are prescribed opioids (see 7.4).
- 1.7 The primary outcome of treatment should be pain relief. Demonstrable improvements in physical, psychological and social function are important secondary aims. Opioids should not be used as primary anxiolytics or sedatives.
- **1.8** The presence of psychological co-morbidity or a history of alcohol/problem drug use (see section 6) does not preclude the use of opioids. Advice from or referral to a specialised service with experience of managing these patients (e.g. multidisciplinary pain management service or specialised addiction service) is recommended in these circumstances.

- 1.9 Only a registered medical practitioner should make the initial prescription of strong opioids for persistent non-cancer pain. Thereafter other health care professionals may assist with monitoring and maintaining opioid therapy. Health care professionals who prescribe or maintain opioid treatment for persistent non-cancer pain should develop an individualised treatment plan in discussion with the patient.
- 1.10 Patients who are prescribed opioids for persistent non-cancer pain should be assessed regularly at intervals determined by clinical need. Initially it is expected that this assessment would be at least monthly. The assessment should include documented evaluation of: pain relief, physical, psychological and social function, sleep, side effects and signs of problem drug use (see sections 6 and 9). It is important to regularly discuss any concerns that patients have about their opioid use.

Evidence of developing tolerance should prompt referral to a multidisciplinary pain management service or specialised addiction service.

Evidence of problem drug use (see section 6) should initiate prompt consultation with and/or referral to a specialised addiction service.

It is envisaged that this document will stimulate the development of local clinical networks using defined care pathways, such that early referral will lead to prompt specialist intervention.

2. The need for recommendations

2.1 Survey findings show that many people describe themselves as being severely disabled by persistent pain.

Large-scale surveys throughout Europe and in Australia have shown that 5-10% of the population has severe persistent pain (see section 11). A study from Scotland published in 1999 is particularly relevant to the UK population. In this postal survey of 4,400 patients who were randomly selected from a general practice database, 13% were moderately to severely disabled by persistent pain. In a follow up study by the same group four years later, in more than 2000 of those patients, 79% who had pain at presentation still had pain at follow up; pain is commonly persistent.

Broad extrapolation of these figures suggests that 2-6 million people in the UK would describe themselves as having persistent, severe pain not associated with cancer.

- **2.2** Opioids are effective in some patients with persistent non-cancer pain.
- 2.3 More than 20 different opioids are available in the UK. Most opioids are delivered orally. Recently marketing authorisation has been given to transdermal fentanyl and transdermal buprenorphine for use in patients with persistent non-cancer pain.

A number of opioids are used routinely in the management of persistent pain and some, but not all, have a specific marketing authorisation for such use. Licensing of a drug in the UK is mandatory before that drug can be marketed for its licensed indication. Prescribing of drugs outside the product licence (marketing authorisation) is not prohibited under UK law.

- 2.4 Recent high profile legal cases have led to debate about appropriateness of opioid prescription in persistent pain. There have also been cases where patients have taken legal action against health care professionals because of inadequate pain relief.
- 2.5 Problems with opioid use or dosing can develop in some cases. The diversion of prescribed opioids to those who use drugs for non-medical reasons is a significant concern for patients and health care professionals.

3. Opioid pharmacology

- 3.1 Opioids are drugs that exert their activity by acting as agonists at endogenous receptors (opioid receptors), and that elicit the characteristic stereospecific actions of natural morphine-like ligands. These receptors are widespread throughout the central and peripheral nervous system. A number of opioid receptors have been described. Some opioids display differential receptor activity; the clinical relevance of this is not clear.
- **3.2** For prescribing information and approximate potency ratios in adults, refer to the BNF section on "Opioid analgesics". For information about prescribing for children, the source text should be "Medicines for Children" published by the Royal College of Paediatrics and Child Health.
- **3.3** The clinical response to opioids is variable. Switching patients between different opioids may be worthwhile. Dose ratios may vary, and therapy should always be individualised after specialist advice (e.g. specialist pain management or drug information services).
- 3.4 Opioids are classified as strong or weak (see table 1). The distinction between these groups is not always clear and may depend on the dose. The term weak opioid should not encourage lack of caution in prescribing.
- **3.5** These recommendations do not apply to patients who use weak opioids within the BNF dose range. These recommendations do refer to patients who use weak opioids outside the BNF range, and to patients who might benefit from using strong opioids.

Table 1.

Examples of non-injectable opioids available in the UK

Strong opioids

| APPROVED NAME (Some proprietary names) | FORMULATIONS AVAILABLE | |
|---|--------------------------------|--|
| Buprenorphine (Temgesic, Transtec) | Sublingual, Transdermal | |
| Diamorphine (Heroin) | Oral | |
| Dipipanone (Diconal) | Oral | |
| Fentanyl (Durogesic, Actiq) | Transdermal, Transmucosal oral | |
| Hydromorphone (Palladone, Palladone SR) | Oral | |
| Methadone | Oral | |
| Morphine (Oramorph, Sevredol, MST Continus, MXL, Zomorph) | Oral | |
| Oxycodone (OxyNorm, OxyContin) | Oral | |
| Pentazocine | Oral | |
| Pethidine | Oral | |
| Tramadol* (Zydol, Zamadol) | Oral | |
| Oral formulations may be immediate or modified release *Tramadol may behave as a strong or a weak opioid depending on the dose used. | | |

Weak opioids

| APPROVED NAME (Some proprietary names) | FORMULATIONS AVAILABLE |
|---|------------------------|
| Codeine | Oral |
| Dextropropoxyphene | Oral |
| Dihydrocodeine (DF118 Forte, DHC Continus) | Oral |
| Meptazinol (Meptid) | Oral |
| Tramadol* (Zydol, Zamadol) | Oral |

Oral formulations may be immediate or modified release

*Tramadol may behave as a strong or a weak opioid depending on the dose used.

Some of the opioids are presented with paracetamol as compound analgesic preparations e.g. Co-codamol, Kapake, Solpadol, Tylex, Co-dydramol, Remedeine, and Co-proxamol. Some opioids are presented with antiemetics as compound preparations e.g. Diconal is a compound preparation of Dipipanone and cyclizine. See BNF for more details.

4. Benefits of opioids when appropriately prescribed

- **4.1** The primary effect of the appropriate use of opioids in persistent pain is pain relief. There may be a reduction in the use of other analgesics. Patients may also make less use of other health care resources.
- 4.2 Opioids should not be used as primary anxiolytics or as sedatives. However, an improvement in physical, psychological and social function and sleep may occur secondary to pain relief.
- **4.3** Opioids should be used to facilitate a rehabilitation plan with the aim of improving physical and social function. These plans should involve clear goals, with plans for steady progress towards them.

5. Adverse effects of persistent opioid use

5.1 Nausea, vomiting, itching and somnolence are common opioid side effects. These problems usually occur within the first few days of starting opioids and decrease with time in the majority of patients. However, itching may persist and may preclude continuation of the drug. Constipation is common, may be dose related and tends to persist. These potential problems should be discussed with patients prior to starting opioids.

If symptoms occur, they should be managed quickly and appropriately. Persistent symptoms may necessitate discussion regarding treatment withdrawal or opioid switching (see Glossary).

5.2 More serious problems include respiratory depression, weight gain, weight loss, and hormonal effects such as reduced adrenal function, reduced sexual function and infertility. Serious consideration should be given to these potential problems when considering opioid prescribing. Particular care is needed in women of childbearing age. Data are limited, but these reversible effects seem to occur in about 1% of patients on long-term opioids.

All patients should be warned of these side effects and the fact that the problems have been discussed should be documented. Patients on long-term opioids who develop symptoms of adrenal insufficiency, infertility or sexual dysfunction should be investigated by an appropriate specialist service as a matter of urgency.

- 5.3 Any woman taking opioids and planning pregnancy should seek pre-conception advice about potential problems from appropriate health care professionals (e.g. departments of fetal medicine or fetal toxicology). Alternative pain relief may be needed during pregnancy. Patients and their partners should be warned of the effects of maternal opioid consumption on neonatal well being. Babies born to women taking opioids have about a 50% chance of showing symptoms of drug withdrawal. Patients and their partners should be made aware of this possibility. With long acting drugs such as methadone, neonatal withdrawal symptoms may not be manifest for up to five days after birth. This should be taken into account when planning the mother and baby's length of hospital stay after delivery. The possibility of having to treat neonatal withdrawal syndrome should not, in itself, rule out the use of opioids in pregnancy, if these drugs confer significant benefits to the mother.
- **5.4** The immunological effects of using long-term opioids are well described. However their clinical importance is not clear.
- 5.5 Research suggests that patients who have reached a stable dose of opioids are generally fit to drive. Patients should not drive during dose titration, or at any time that they feel cognitively impaired. Patients should be advised that they are responsible for ensuring their own fitness to drive. The only body that can advise a patient about their legal right to hold a driving licence is the Driving and Vehicle Licensing Authority (DVLA). If patients have any doubts about their driving abilities, then they should contact the DVLA and their motor insurance company, especially whilst

escalating onto a stable opioid dose; this is not the responsibility of health care professionals. Patients must be told that opioids enhance the effects of alcohol, and that they must not drive if they have taken opioids with alcohol.

5.6 Patients may need to modify their domestic and work activities whilst getting used to taking opioids. They may need to discuss this issue with their employers.

6. Tolerance, withdrawal, addiction, and problems with opioid use

Patients, carers and health care professionals can confuse the terms tolerance, dependence and addiction. Terms such as "drug abuse", "drug misuse" and "addiction" were developed in the context of drug use in the absence of pain or where pain relief was not the primary goal. These terms apply poorly in the prescribed use of opioids for pain treatment. The term problem drug use is clearer, more descriptive and less judgemental. Clarification with patients of the phenomena described here should be ensured before instituting opioid therapy, as a basis for openness about the effects of opioids during the trial period. It is important to explore and discuss any fears and misconceptions patients and carers have about problem drug use before treatment to try to improve concordance.

- 6.1 **Tolerance** is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Increased doses are then needed to get the same effect. Data are limited, but tolerance to opioids used for chronic pain seems to be uncommon: after a period of dose titration that may take several months, the majority of patients stabilise on a long-term opioid dose.
- 6.2 Withdrawal usually occurs when opioids are stopped suddenly, or an antagonist such as naloxone or naltrexone is administered. Acute withdrawal should be treated with intravenous fluids, glucose, and adrenergic blocking drugs, or with small doses of opioids.
 Withdrawal is easily avoided by gradual reduction of opioid dose.
- 6.3 Addiction consists of the compulsive use of opioids to the detriment of the user's physical and/or psychological health and/or social function. Signs of compulsive use include preoccupation with obtaining and taking opioids, apparently impaired control over their use, and reports of craving. These signs of compulsive use are well established where opioids are

taken not primarily for pain relief but for effects on mood and thinking. The use of opioids prescribed for pain relief probably only rarely results in addiction, although the exact risk is not known. Addiction can only be determined by observing these behaviours over time, not on a single event. Regular and frequent use and/or a high dose do not alone constitute addiction, although they do constitute a criterion for addiction in some diagnostic schedules that explicitly do not apply to the use of prescribed opioids for pain relief.

What is more important is that the fear of addiction can lead to restrictions on prescribing or on taking opioids which thereby restrict pain relief. The term **pseudoaddiction** has been coined to describe behaviours such as drug hoarding, attempts to obtain extra supplies, and requests for early prescription or increased dose which may be mistaken as signs of addiction but are an attempt to obtain better pain relief. When pain is relieved these behaviours cease.

The term **dependence** is also a source of confusion. Physical dependence was defined by withdrawal when the drug was abruptly stopped, and therefore occurred commonly in patients using a stable opioid dose. Psychological dependence was defined by compulsion to use the drug that occurred rarely in patients prescribed a stable dose of opioid for pain relief. Neither of these situations is equivalent to addiction.

Concern that a patient's behaviour may indicate addiction should trigger immediate referral to and/or consultation with a specialised drugs unit.

[®]American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine

7. Patient selection

- 7.1 The evidence base supporting the use of opioids in specific clinical circumstances is sparse. The following should be regarded as general guidance for practitioners treating non-cancer pain.
- 7.2 Opioids should only be considered after the use of other established therapies. For example, there is good evidence for the use of anti-depressant and/or anti-convulsant medication as first line drugs in neuropathic pain. However issues such as toxicity and safety in overdose should be considered.
- 7.3 Other partially effective pain treatments should be continued. For instance, antidepressants and/or anticonvulsants in patients with neuropathic pain who derive partial pain relief from their use. Antidepressants may also be needed for mood elevation.
- 7.4 All patients should undergo a thorough physical, psychological and social assessment before commencing opioids. This should include history, examination, and relevant special investigations. It is important to address patient's beliefs, fears and expectations about their pain and about what opioids can and cannot do.
- 7.5 Patients with persistent non-cancer pain may present with acute exacerbations of pain. Thorough assessment should take place before long-term opioids are started in response to this. Acute pain teams or other hospital services should not start long-term strong opioids without support from a multidisciplinary pain management service and liaison with the patient's primary care team. They must ensure that arrangements are in place to provide long-term supervision for the patient after discharge from hospital.
- 7.6 Consideration of clinical use of opioids should only take place after appropriate specialist assessment of any underlying causes of the pain. For instance, patients with primary hip pain should be referred for a specialist orthopaedic opinion; they will need pain management whilst they are waiting to be seen. Opioids and other drugs should be part of an overall strategy for pain

management that should be multi-professional (e.g. potentially involving physiotherapists, psychologists and nurses).

- **7.7** The following psychological factors do not preclude the use of opioids, but should prompt careful assessment and observation of the patient.
 - Current or previous history of problem drug or alcohol use
 - Current or previous history of relevant psychiatric problems
 - Current major depression or a history of repeated depressive episodes
 - Current psychosis or a history of psychosis
 - Current risk of suicide or relevant history of suicide attempts

Patients should be encouraged to be open with their health care team about any past or present problems with alcohol or drugs. If current problem drug or alcohol use is suspected, evidence should be sought that such a problem exists, and a referral to a specialised service should be considered. If possible, evidence for the extent of the problem should be documented. The CAGE questionnaire is frequently used to screen for problem alcohol use (see Glossary). There is no good questionnaire to screen for problem drug use.

Whilst the following psychosocial factors do not absolutely preclude the use of opioids, there should be careful assessment of the social situation and sensitive discussion about the potential for drug diversion. Usually special arrangements for small and regular opioid supplies would be needed in these situations; this would have to be carefully supervised.

- Household member with current or relevant problem drug or alcohol use
- Household member with current or relevant psychiatric problems

8. Practical aspects of prescribing

- 8.1 Opioids should be considered to be only one aspect of an overall rehabilitative strategy for the patient with persistent non-cancer pain. Effective pain relief should be accompanied by changes in physical, psychological and social functioning. Improved sleep and reduced anxiety alone are not sufficient to justify continuing opioid treatment.
- 8.2 In most cases, day-to-day medical responsibility will lie with a general practitioner once the patient is taking a stable dose of opioid. Hospital based services should start opioid therapy only after discussion and agreement with primary care services. A single practitioner should take primary responsibility for prescribing opioids for individual patients. Fixed supplies of these drugs should be prescribed at fixed intervals.
- 8.3 Patients and health care professionals should develop a treatment plan prior to starting opioid therapy. Patients should be informed adequately so that they can take part in decision making. Information for patients is contained in Appendix 1.
- 8.4 Emphasis should be given to agreeing desirable treatment goals, and the time course over which these goals should be attained. Complete pain relief is rarely achievable, and then only at the expense of side effects such as cognitive impairment. Realistic treatment goals are primary partial pain relief, leading to an improvement in physical and/or psychosocial functioning.
- 8.5 Modified release opioids administered at regular intervals should be used in the management of patients with persistent pain. Drugs may be administered orally or transdermally. Short acting opioids may predispose to tolerance and dependence and in general should not be used for persistent non-cancer pain. However, they may occasionally be needed during opioid titration, but in this situation support from a specialist pain management service should be considered.

- 8.6 Immediate release opioid preparations may be considered in cases of intermittent, transient severe pain where the patient is pain free between episodes. They may also be used for transient exacerbations of pain that is otherwise reasonably controlled (breakthrough pain). Frequent predictable episodes of pain, e.g. on weight bearing, (incident pain) are more appropriately managed by judicious dose adjustment of sustained release preparations. These cases are difficult to manage and specialist advice should be sought. It should be noted that this contrasts with the use of immediate release preparations for the management of incident cancer related pain.
- 8.7 Injectable opioids should not be used in the management of patients with persistent non-cancer pain except in extraordinary circumstances and then only after consultation with a specialised multidisciplinary pain management service.
- **8.8** Patients should be advised to store their opioids carefully and to ensure that children do not have access to them.
- 8.9 Choice of drug depends on clinical circumstance, local experience and expertise. There are no high quality randomised trials that compare different opioids in the management of persistent non-cancer pain. Clinical experience suggests that pethidine is particularly unsuitable for patients with persistent pain. Its high lipid solubility and rapid onset/offset possibly predispose to problem drug use. Its active metabolite norpethidine may lead to serious side effects. It does not produce less smooth muscle spasm than equipotent doses of other opioids and so it is confers no advantage for patients with visceral pain.
- 8.10 Drug doses should be escalated at fixed intervals during an initial period of titration until pain relief is achieved or intolerable side effects occur. The interval between each step of titration will depend on individual drug pharmacology and the patient's response. Controlled release preparations may require quite slow titration, with a number of days between dose increments. Local

protocols need to be developed and updated. This requires cooperation between primary care, and pain management services with support from pharmacists.

- 8.11 Patients should be monitored closely during the dose titration; this should be at least monthly. However, some patients may need more frequent assessment. The primary treatment goal should be pain relief. Changes in pain, sleep, mood and physical, psychological and social function should be discussed and documented, as should side effects and evidence of problem drug use.
- 8.12 Opioid therapy has failed if the primary goal of acceptable pain relief is not attained after reasonable dose adjustments, or if intolerable side effects occur. In some patients it may be possible to improve pain relief and/or reduce side effects by switching to an alternative opioid (see Glossary).
- 8.13 If opioid therapy is a success, the patient should continue to be monitored regularly (see 9.1). Continuing assessment might need to be less frequent than during dose titration.

9. Identifying and managing problems

- **9.1** Patients who are prescribed long-term opioids should be assessed regularly (see 8.13).
- **9.2** Evidence of inadequate pain relief or developing tolerance should prompt referral to a specialist multidisciplinary pain management service. Patients should be told that if they develop problems with opioid use they should make contact with their doctor or other health care professional
- **9.3** Special consideration should be given to patients stabilised on opioids who undergo surgical procedures, are subject to trauma, or develop new painful conditions.

Such patients need careful analgesic management whilst they have acute pain. Local policies should be developed in conjunction with multidisciplinary acute pain management teams.

- 9.4 Opioid-related side effects should be managed promptly. Consideration might be given to opioid switching (see Glossary) or to specialist pain management referral if the patient is in a primary care setting.
- **9.5** Concerns about problem drug use should prompt referral to specialised services. The following behaviours should cause concern.
 - Earlier prescription seeking
 - Claims of lost medication
 - Intoxication
 - Frequent missed appointments
 - Use of other scheduled drugs

Pseudo-addiction can lead to behaviours that do not indicate problem drug use (See section 6). Before starting opioids, patients should be informed that these behaviours will lead to referral for specialist management.

10. Glossary

Persistent pain

Pain that has been present for more than three months: the pain may be continuous or intermittent.

Intermittent severe pain (episodic pain)

Spontaneous episodes of recurrent severe pain: the patient is pain free between episodes. A number of disorders predispose to episodes of intermittent severe pain (Figure 1).



Breakthrough pain

Transient exacerbations of pain occurring on a background of continuous pain that is otherwise satisfactorily controlled.

Incident pain

Frequent, predictable pain episodes brought on by certain activities e.g. weight-bearing, coughing: may occur on a background of continuous pain or the patient may otherwise be pain free.

Opioids

Opioids are drugs that exert analgesic activity by binding to endogenous receptors (opioid receptors) and that elicit the characteristic stereospecific actions of natural morphine-like ligands. Opioid receptors

are found throughout the central nervous system, both within the brain and within the spinal cord, and in the peripheral nervous system.

Available opioids have different pharmacokinetics and potencies. Some have differential activity on different opioid receptors. Some opioids demonstrate a ceiling effect with increasing dose. In many cases the ceiling is above the usual clinical dose range and is not clinically relevant.

Some opioids have agonist activity at certain opioid receptors and antagonist activity at others. There is no clinical evidence that these drugs antagonise pain relief or cause withdrawal when combined with, or used after, full agonist opioids.

Available opioids have differences in their metabolism. Some, such as morphine, have active metabolites that may be a problem in patients with renal impairment. Liver metabolism is important in some cases e.g. methadone metabolism may be affected in those patients with liver enzyme induction.

Constipation

Many patients on persistent opioid therapy become constipated. Using routine simple aperients can usually prevent constipation. An intestinal stimulant and stool-softening agent should usually be prescribed together. Some opioids are less likely to cause constipation than others.

Opioid Switching

Opioid switiching may be used to improve analgesia. If a patient does not respond to an opioid, then an alternative may be tried. There is some evidence that patients who develop intolerable side effects when taking one opioid can experience diminution of these side effects by switching to an equipotent dose of an alternative opioid. Effective opioid switching is best managed in consultation with a specialised multidisciplinary pain management service and advice from drug information units may be of help. *The CAGE questionnaire; screening for problem alcohol use* For alcohol screening, the CAGE is frequently recommended.

There are four questions:

- Have you ever felt you should Cut down on your drinking?
- Have people Annoyed you by criticising your drinking?
- Have you ever felt bad or Guilty about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (*Eye-opener*)?

Answering yes to two is more common in those with alcohol problems; yes to all 4 defines that the patient has a problem with alcohol.

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The working group

The Pain Society is the multi-professional UK representative group for health care professionals and basic scientists involved in pain management and research.

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