Drug Therapy for Severe, Chronic Pain in Terminal Illness

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TREATMENT OF PAIN—mild or severe, acute or chronic—is a major component of medical practice. Acute pain is recognized as a useful symptom that alerts the patient and physician to a medical problem. Acute pain is relatively easy to treat; it sharpens and then lessens. Mild pain—even mild, chronic pain—also is relatively easy to treat. The medical profession is armed with a host of analgesic agents that are effective for mild to moderate pain; aspirin is well recognized as the most effective single analgesic for mild to moderate pain (1), and there are several other effective nonnarcotic analgesics.

Perhaps the most difficult pain to treat is the severe, chronic pain of terminal illness. Many of the analgesic agents that are effective against severe pain often have side effects and other complications. Chronic pain adds to the underlying illness and becomes an additional cause for treatment (2). It contributes to serious emotional and behavioral changes, such as depression and insomnia, which themselves require treatment (1). Often there are conflicting remedies for the different needs of terminally ill patients for treatment, for relief from pain and the fear of recurring pain, and for maintenance of as dignified and normal a life as possible. The American College of Physicians, to help physicians and patients maintain a balance among these competing claims, encourages all physicians to learn how best to treat the severe, chronic pain of terminal illness. (Because many terminally ill patients suffering from severe, chronic pain have cancer, much of the data about drug therapy for such pain are from studies of patients with cancer. However, the generic principles hold true for all terminally ill patients.)

Summary of Positions

1. The goal of drug therapy for severe, chronic pain in terminal illness is to make the patient relatively pain-free.

2. Oral administration of narcotic agents (for example, morphine or methadone) on a regular basis will provide most terminally ill patients with relief from severe, chronic pain and from fear of that pain recurring. Some patients, especially those with episodic pain, do better when narcotics are given on an as-needed basis. The American College of Physicians advocates that physicians remain flexible in treating the severe, chronic pain in terminal illness, adjusting administration dosage, route, and frequency to the needs of the patient.

3. There is no clinical evidence that availability of heroin will improve the drug therapy for the severe, chronic pain of terminal illness.

4. Although fear of patients becoming dependent on narcotics has limited the effective use of morphine and other narcotic drugs, such fear is unfounded, because dependence is of little consequence in the context of terminal illness.

5. The American College of Physicians accepts its responsibility to improve the internist's knowledge of narcotic therapeutics and drug therapy for severe, chronic pain in terminal illness.

6. The American College of Physicians supports expanded research in the field of narcotic therapeutics.

Position 1

1. The goal of drug therapy for severe, chronic pain in terminal illness is to make the patient relatively pain-free.

RATIONALE

The scientific literature has begun to verify the anecdotal data well known to most practitioners: management of pain comprises a large portion of a physician's healing arts. In fact, it has been shown that "pain is the most frequent incapacitating complaint of patients seeking medical help" (3). For the terminally ill patient, pain often is the *only* complaint physicians can treat (4). Pain in terminal illness is often severe (5) and chronic (1, 2).

The primary goal of sufficient management of pain is "relief of suffering and restoration of function lost because of pain" (4). The most appropriate treatment to relieve pain depends not only on the cause and nature of the pain, but also on many other factors, including the patient's prognosis for recovery from the underlying condition or illness. Potential side effects caused by the treatment must be balanced against the known side effects caused by pain and the fear of recurring pain. It is well known that severe, chronic pain is associated with sleep disturbances, lack of appetite, and behavioral changes such as anxiety and depression (6). When a patient has a

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terminal illness, the emphasis in these balancing processes should center on the short-term prognosis and immediate effects of therapy. Pain associated with terminal illness "should be managed with the intent of eliminating pain, preserving function, and rehabilitating the patient to a level appropriate with the short-term prognosis" (7).

Many have argued that the most important aspect of treating the terminally ill patient is elimination of pain with resulting preservation of functions. The modern hospice movement has evolved from this tenet and its corollary: palliative care is more appropriate for the terminally ill patient than any attempts at aggressive, curative treatment. In hospices, the primary goal of palliative care is to make patients free from pain and fear of that pain recurring. Yet, pain relief is not to be provided at any expense; the overall physiological and psychological needs of terminally ill patients remain crucial. Physicians working in hospices and other settings where terminally ill patients are treated have discovered that the most effective way to provide relief from severe, chronic pain is to prevent that pain from recurring. Relief is total, and function is preserved at a maximum. Thus, the goal of drug therapy for severe, chronic pain in terminal illness should be alleviation and suppression of existing pain and prevention of any pain recurring. Although this is a goal that modern medicine can meet (8), too often it is not achieved (9, 10).

Positions 2 and 3

2. Oral administration of narcotic agents (for example, morphine or methadone) on a regular basis will provide most terminally ill patients with relief from severe, chronic pain and from fear of that pain recurring. Some patients, especially those with episodic pain, do better when narcotics are given on an as-needed basis. The American College of Physicians advocates that physicians remain flexible in treating the severe, chronic pain in terminal illness, adjusting administration dosage, route, and frequency to the needs of the patient.

3. There is no clinical evidence that availability of heroin will improve the drug therapy for the severe, chronic pain of terminal illness.

RATIONALE

The scientific literature suggests that, in general, severe, chronic pain in cancer and other terminal illnesses is poorly managed. Reasons for this include "a lack of knowledge and an improper application of what is known" (5). Sometimes the severe, chronic pain of terminal illness is treated as acute pain. Sometimes too much or too little narcotic medication is given. It has been recommended that "medications must be administered in adequate doses on a regular basis to control chronic pain. If a patient always has to ask for medication she or he is reminded constantly of dependence on the drugs and the person administering them" (11). Receiving medication on a regular schedule can help the terminally ill patient with severe, chronic pain avoid "peaks and valleys in pain intensity and ensures sustained relief . . ." (12).

Administration of narcotic agents on a regular, scheduled basis, rather than "as-needed," seems to have originated in English hospices. Traditional pain control in American medicine has followed the tenet that narcotics should be used sparingly to avoid addiction and other severe side effects. It has become apparent, however, that when given on a regular schedule, smaller doses of narcotics are needed, because the pain to be managed is constantly at a lower level. Thus, lower total dosages of narcotics are needed when they are administered on a regular schedule (BONICA JJ. Principles of diagnosis: evaluation and definition of patient status and need. Presented at the Conference on the Care of Patients with Severe, Chronic Pain in Terminal Illness. Washington, D.C.: 28 January 1983.).

Although "parenteral narcotic agonists are most useful for controlling sudden, severe pain" (13), many recommend that the *chronic,* severe pain of terminal illness is best treated with oral administration of a narcotic drug (14) on a regular basis (15). Oral narcotic agents also were first used in English hospices. The "Brompton's Mix," consisting of a narcotic analgesic, heroin, phenothiazine, cocaine, and alcohol in a sweetened syrup, which was given to patients on a regular basis with the dose of the analgesic adapted to the individual needs of the patient, was the forerunner of all liquid narcotic analgesics. Clinical studies have indicated that cocaine is not needed as part of the mixture (16) and that morphine can be substituted for heroin in the mix with similar analgesic effects (17). Indeed, Mount and colleagues (18) showed that liquid oral morphine in a 10% alcohol solution, flavored for the individual patient, is effective for controlling pain in terminal illness (19). It appears, then, that the actual advantage of the Brompton's mix was the regular administration of sufficient oral narcotic medication (12). The American College of Physicians suggests that in treating the severe, chronic pain in terminal illness, physicians recognize that oral administration of a narcotic drug on a regular basis will render most terminally ill patients pain-free. The College also advocates flexibility to ensure that administration dosage, route, and frequency are adjusted to the needs of each patient.

In 1980, Kaiko and associates (20) studied the analgesic efficacy of heroin treatments in patients with postoperative pain and with chronic cancer pain, and showed that there were no significant differences between morphine and heroin in their analgesic efficacy, effects on mood, or side effects. Although heroin appears to have identical side effects and therapeutic effects as morphine, it has some different characteristics. Studies have confirmed that heroin has a slightly more rapid onset of action and a slightly shorter duration of effect than morphine (21). Furthermore, heroin appears to be approximately two and one half times more potent than morphine (22) and to have greater solubility (22), meaning that equieffective doses can be administered in a much smaller volume. Despite these differences, which are more significant for parenterally rather than orally administered heroin, researchers have concluded that "there is no unique or special advantage to heroin over

morphine in the management of a cancer or other terminally ill patient" (21). Additionally, other narcotic agents presently available offer some of the advantages heroin claims, such as greater potency. Thus, there is no clinical evidence to support the thesis that availability of heroin is needed to improve the physicians' ability to manage severe, chronic pain in terminal illness.

Although morphine is the mainstay of narcotic therapeutics for preventing severe, chronic pain in terminal illness, some prefer to use other narcotics alone or to supplement oral morphine. Methadone is an opioid that is highly active when administered orally and has a longer duration of action than morphine (13, 23). Dosage therefore need not be as frequent as that with oral morphine, and the likelihood of periods of inadequate pain control is decreased. Although oxycodone is another opioid that is very active when given orally and may prove to be an excellent choice, little experience has been reported with this drug and it is considerably more expensive than morphine. When oral administration of morphine or other narcotic agents is not fully effective, hydrocodone is a useful, although expensive, opioid to supplement control of pain. Because it is more potent than morphine (24), smaller subcutaneous doses can be used. Many terminally ill patients become emaciated near the end of their lives, so the actual volume of any injection must be kept as small as possible.

Adjunctive drugs may be used in combination with narcotics to enhance their analgesic actions and to reduce the doses needed for effective pain control. Aspirin and acetaminophen, although not adequate by themselves to prevent most severe, chronic pain, may serve a "narcotic-sparing" action by their inhibition of prostaglandin synthesis. Prostaglandins play a significant role in many types of pain. Various nonsteroidal antiinflammatory drugs with proven analgesic action may be substituted if aspirin or acetaminophen are troublesome and produce undesirable side effects.

Tricyclic antidepressant agents may be effective against both the depression caused by severe, chronic pain and the pain itself. There is some evidence that antidepressants work because they increase the supply of a naturally produced neurotransmitter, serotonin, decreased amounts of which have long been associated with severe depression. Some evidence also suggests that cells using serotonin are an integral part of a pain controlling pathway that starts with endorphin-rich nerve cells high in the brain and ends with an inhibitor of pain-conducting nerve cells lower in the brain or spinal cord (25).

The combined use of some stimulants (such as dextroamphetamine) and sedatives (such as diazepam) with narcotic analgesic agents may increase the patient's comfort; stimulants may allay the lethargy and somnolence produced by narcotics, whereas sedatives may help the patient sleep better (8). Some evidence also suggests that these drugs may enhance the analgesia produced by narcotics. It is important to realize that not all patients require such adjunctive therapy, and some patients have negative side effects (26).

Clearly there are available to the physician sufficient narcotic agents that, when properly administered, can provide terminally ill patients with relief from severe, chronic pain. The key to proper administration is oral administration on a regular basis. Injectable opiates may be used as adjunctive therapy, but there does not appear to be a clinical need for heroin to improve the drug therapy that can be given to terminally ill patients.

A major concern shared by practitioners treating terminally ill patients is the difficulty physicians and patients often have in obtaining narcotic drugs. The American College of Physicians believes it necessary that terminally ill patients with severe, chronic pain have access to sufficient medication.

Position 4

4. Although fear of patients becoming dependent on narcotics has limited the effective use of morphine and other narcotic drugs, such fear is unfounded, because dependence is of little consequence in the context of terminal illness.

RATIONALE

Studies on the nature of psychological drug dependence and substance abuse have shown that, when properly administered, narcotic agents used therapeutically to prevent pain do not lead to addiction or dependence in terminally ill patients (11, 27). It has been argued that requiring a patient to ask for a narcotic places him in a situation where he is reminded constantly of his dependence and is thus more psychologically dependent on narcotics than a patient who is receiving them regularly (11). "An undermedicated patient who can think only of the next dose of analgesic comes closer to the behavioral definition of an addict than the properly medicated patient who is able to think of other things" (28).

It is thus important that narcotic doses be appropriate for each patient and that dosage schedules be reviewed frequently. Doses of drug, dosage schedules, and modification of these schedules due to tolerance to the analgesic effects must be tailored to the needs of individual patients. Individualization of doses and dosage schedules is axiomatic for all drugs. There is a tendency, however, to pay less attention to these details when treating terminally ill patients. This tendency to ignore terminally ill patients and to assume that all is well because the patient does not complain should be assiduously avoided.

Finally, studies are beginning to find that abuse of therapeutic narcotics is not seen in patients with cancer (the majority of terminally ill patients with severe, chronic pain). Many studies of patients with cancer receiving narcotic analgesic agents for pain relief have demonstrated no evidence of drug abuse (11, 27-29). Indeed, "data suggest that drug use alone is not the major factor in the development of addiction, but other medical, social, and economic conditions seem to play an important role" (29).

Position 5

5. The American College of Physicians accepts its responsibility to improve the internist's knowledge of nar-

cotic therapeutics and drug therapy for severe, chronic pain in terminal illness.

RATIONALE

The above discussions have indicated that severe, chronic pain in terminal illness can be prevented. Terminally ill patients can be relieved of their pain and the fear of that pain recurring. These patients can therefore have much of their functions preserved and can live the remainder of their lives more productively than had previously been thought. This depends, however, on physicians being knowledgeable about pain; its causes, complications, and treatments; and specifically narcotic therapeutics, the mainstay for relief of severe, chronic pain. The American College of Physicians is dedicated to improving the education of physicians in order to improve patient management. Therefore, the College accepts its responsibility to improve the internist's knowledge of narcotic therapeutics and drug therapy.

Position 6

6. The American College of Physicians supports expanded research in the field of narcotic therapeutics.

RATIONALE

Much has been learned lately about the causes of pain and the most effective ways to manage it. Yet, even more information is needed about the comparative effects of narcotic analgesic agents, especially the newly developed analgesics; about the role of antidepressants in pain therapy; about the side effects or drug-drug interactions of analgesics; and about non-drug therapies that might be useful adjuncts to drug therapy for severe, chronic pain. Continued research is needed on these new pain treatments and on the conventional drug therapies so that guidelines of care can be based on controlled observations, not anecdotal reports.

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