Review

The pharmacological management of cancer pain
Part 1: The role of non opioid and adjuvant drugs

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Incidence, causes and prevalence of cancer pain

Cancer-related pain afflicts some 9 million people worldwide annually and is often inadequately managed [1].

The incidence of pain among 5,410 patients at various stages of the disease was 51%, whereas among 9,007 patients with advanced metastatic or at terminal phase of cancer was 74% [1]. Furthermore, published data show that among advanced cancer patients with pain, the symptom is moderate to severe in about 40%–50% and very severe or excruciating in 25%–30% [2–4] and that most advanced-cancer patients have two or more types and/or etiologies of cancer-related pain [3–8].

One-third of adults and children with metastatic cancer report pain that interferes with and reduces their activity level and requires the use of analgesics [9]. The frequency of chronic cancer pain is related to the initial cancer site and varies from 85% (bone) to 5% (leukemia) [4].

Foley [4] found that among 143 cancer in patients referred for pain therapy, the pain was due to cancer in 78% and to cancer therapy in 19%.

The nociceptive stimulus may be somatic (e.g., metastatic to bone, pleura involvement), visceral (e.g., distended bowel proximal to obstruction) or neuropathic as a result of aberrant processes in the peripheral or central nervous system that result from injury to neural pathways. Some of these neuropathic pains are due to deafferentation and may result from tumor infiltration of nerves (e.g., brachial plexopathy due to Pancoast’s tumor) or surgical intervention (e.g., phantom limb pain). Table 1 summarizes various cancer-related pain syndromes.

Assessment of cancer pain is essential in evaluating the current status of the patient, the pain and its impact on the patient as well as the efficacy of pain therapy over time. Different types of pain evaluation are available, as per the review by Chapman and Syrjala [10] and other papers [11–13].

Table 1. Pain syndromes in cancer patients.

<table>
<thead>
<tr>
<th>1. Pain due to direct tumor involvement</th>
<th>Vertebral body metastases</th>
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<tbody>
<tr>
<td>A. Tumor invasion of bone:</td>
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<tr>
<td>Base of the skull metastases</td>
<td>Atlantoaxial syndrome</td>
</tr>
<tr>
<td>Jugular foramen syndrome</td>
<td>C7-T1 syndrome</td>
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<td>Clivus syndrome</td>
<td>L1 syndrome</td>
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<tr>
<td>Sphenoid sinus syndrome</td>
<td>Sacral syndrome</td>
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<tr>
<td>Cavernous sinus syndrome</td>
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<tr>
<td>Occipital condyle syndrome</td>
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<tr>
<td>Other bone involvement:</td>
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<td>pelvis and long bones</td>
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<td>B. Tumor invasion of nerves:</td>
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<tr>
<td>Peripheral nerve syndromes</td>
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<tr>
<td>Paraspinal mass</td>
<td>Chest wall mass</td>
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<tr>
<td>Retroperitoneal mass</td>
<td>Painful polyneuropathy</td>
</tr>
<tr>
<td>Brachial, lumbar, sacral plexopathies</td>
<td>Leptomeningeal metastases</td>
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<tr>
<td>Epidural spinal cord compression</td>
<td></td>
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<tr>
<td>C. Tumor invasion of viscera</td>
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<tr>
<td>D. Tumor invasion of blood vessels</td>
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<tr>
<td>E. Tumor invasion of mucous membranes</td>
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2. Pain due to cancer therapy

<table>
<thead>
<tr>
<th>Postoperative pain syndromes</th>
<th>Postchemotherapy pain syndromes</th>
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<tbody>
<tr>
<td>Post-thoracotomy</td>
<td>Steroid pseudorheumatism</td>
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<tr>
<td>Post-mastectomy</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Post-radical neck resection</td>
<td>Aseptic necrosis of bone</td>
</tr>
<tr>
<td>Post-amputation</td>
<td>Mucositis</td>
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<tr>
<td>Postiradiation pain syndromes</td>
<td>Mucoitis</td>
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<tr>
<td>Radiation myelopathy</td>
<td>Radiation-induced peripheral nerve tumors</td>
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<tr>
<td>Radiation necrosis of bone</td>
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<tr>
<td>Radiation fibrosis of brachial or</td>
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<tr>
<td>lumbosacral plexus</td>
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</table>

3. Pain indirectly related or unrelated to cancer

| Paraneoplastic syndromes              |                                 |
| Myofascial pain syndromes             |                                 |
| Postherpetic neuralgia                 |                                 |
| Dehility, constipation, bed sores, rectal or bladder spasm, gastric distension Osteoporosis | |

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Cancer pain management

The first approach to cancer pain management is to eliminate the tumor. In a study of nearly 3500 patients with pain caused by advanced cancer referred to the Pain Therapy Division of the National Cancer Institute of Milan, 1423 patients had histories of chronic pain lasting more than 2 weeks. Of these, about 75% had obtained partial or complete pain relief by anticancer therapy consisting of radiation, chemotherapy, hormone therapy and/or surgery [14].

The pharmacological approach proposed by the World Health Organization (WHO) is a rather simple one. It is based on the use of a sequential three-step ladder.

The first step involves the use of non-opioid analgesics; the second combines non-opioids with weak opioids and the third step combines strong opioids with non-opioid analgesics [4, 8, 15]. Therefore, depending on the individual case, the oncologist may choose to use either of these three drug groups in combination with adjuvant drugs.

Here are some basic principles worth pointing out:
- These drugs are to be taken at regular intervals, based on their analgesic duration;
- When results are unsatisfactory, the patient should move on to the next therapeutic step;
- When an analgesic ceases to be effective, a stronger drug should be used rather than one of equal potency;
- ‘As required’ drugs may be prescribed for breakthrough pain, in addition to drug administration at fixed intervals;
- Drug doses should be determined individually for each patient;
- Side effects (i.e., constipation) should be pharmacologically prevented whenever possible;
- Patients and family members should be informed about the use of the drug and its main side effects.

Non-opioid drugs

Aspirin, acetaminophen and the nonsteroidal anti-inflammatory drugs (NSAIDs), given as single analgesic treatment, constitute the first step of the analgesic ladder proposed by the WHO. Selected NSAID drugs are listed in Table 2.

They are commonly defined as ‘peripheral’ analgesics, although there is increasing evidence that they have a central or not exclusively prostaglandin-mediated action [16–18]. It has been shown that the analgesic effect of some NSAIDs is, in some types of pain, similar to that produced by narcotic analgesics [19].

Acetaminophen (paracetamol) induces a central analgesic effect [20]; it has proven as effective and potent as aspirin in single-dose studies in cancer pain [21].

NSAIDs have been shown to be effective against specific cancer pain due to stimulation of the free nerve endings of tissues such as myofasciae, joints, serous membranes or periosteum, while their activity is reduced in pain caused by the lesion of large nerves and is virtually non-existent with respect to deafferentation pain [22].

In some patients, NSAIDs are particularly effective in the management of bone pain secondary to tumor metastases [23], but their effect is unpredictable. The analgesia is presumably due to a reduction of the oedema which increases the intraosseous pressure or stretches the periosteum as well as to a reduction of prostaglandin-induced pain sensitization [24].

There is considerable variation in response to NSAIDs, even with drugs of the same chemical group, because of two factors: 1. the differences among the members of this class of drugs in their effects on arachidonic acid metabolism and on the release of inflammatory mediators from polymorphonuclear leucocytes; and 2. the intersubject pharmacokinetic differences [25]. In the only placebo-controlled clinical trial, no significant difference was demonstrated between placebo and flurbiprofen in patients with bone metastases due to breast cancer [26].

NSAIDs can only be used, however, for a limited time because of an increasing incidence of side effects.

<table>
<thead>
<tr>
<th>Table 2. Non-opioid analgesics.</th>
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<tbody>
<tr>
<td><strong>Drugs</strong></td>
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<tr>
<td>Acetaminophen</td>
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<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Diflunisal</td>
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<tr>
<td>Ibuprofen</td>
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<tr>
<td>Naproxen</td>
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<tr>
<td>Naproxen sodium</td>
</tr>
<tr>
<td>Ketoprofen</td>
</tr>
<tr>
<td>Indomethacin</td>
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<tr>
<td>Piroxicam</td>
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<tr>
<td>Diclofenac</td>
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<tr>
<td>Ketorolac</td>
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<tr>
<td>GI = gastrointestinal, A P = antiplatelet effect, + mild, ++ moderate, +++ severe.</td>
</tr>
</tbody>
</table>
and because their analgesia is characterized by a ceiling dose, beyond which additional increments fail to give greater pain relief [27, 28]. The ceiling dose limits the utility of the NSAIDs used alone for mild to moderate pain, but provide additive analgesia when combined with 'weak' and strong opioids in the treatment of more severe pain [21, 22, 29, 30]. The most common NSAID-related side effects are summarized in Table 2. They involve the gastrointestinal tract, the kidneys, the liver, the skin and the blood [27, 31, 32].

Clinical results

Two different studies showed that after 5 weeks of treatment the efficacy of NSAIDs decreased when they were used alone or in combination with adjuvant drugs [22, 33] and that after 6 months, only 6% of the patients were able to continue pain treatment using NSAIDs administered alone. The treatment was discontinued in 44% of the patients because of the ineffectiveness of analgesic therapy, in 40% due to side effects and in 16% owing to death not related to treatment. The chief side effect manifested during treatment was damage to gastric mucosa, which included gastralgia, nausea, vomiting, pyrosis and bleeding.

In a retrospective study on the use of the sequential analgesic ladder as proposed by the WHO, it was reported that in 292 patients the average length of treatment for NSAIDs alone was 19.2 +/- 24.5 days. A need to either discontinue the NSAIDs or to add a narcotic analgesic occurred because of side effects in 48% of cases or because of ineffectiveness of analgesia in 52% [34]. There are no conclusive studies showing which non-opioid is more effective in cancer pain, and neither the proper dose nor route of administration have been established in prospective trials. The great inter-individual variability in response to different drugs suggests that a favorable previous exposure to a particular agent is an indicator that the same drug will be effective again. Ventafridda et al. [35] compared the efficacy and tolerability of acetylsalicylic acid, paracetamol, diclofenac, ibuprofen, indomethacin, piroprofen, sulindac, naproxen and suprofen in the treatment of cancer pain. The most effective drugs for the relief of severe pain [21, 22, 29, 30]. The results show the similar analgesic effect of the two drugs (pain intensity and duration decreased by half in the first week of treatment) and a comparatively low morbidity rate.

Even though it is not statistically significant, the treatment lasted longer for sodium naproxen: over 2 weeks in 42% of cases vs. 25% of patients on sodium diclofenac. The causes for the switch to the second WHO ladder step were the lack of analgesic effect in 77% of cases due to the onset of physical side effects in 14% of cases, and to both in 9% of cases. The four most frequent side effects were gastralgia, drowsiness, dry mouth and dyspepsia.

Adjuvant drugs

Adjuvant analgesic agents constitute another group of drugs used to control cancer pain. Table 3 shows their indications for some pain syndromes. These drugs produce analgesia in certain types of pain by mechanisms that are not clearly understood and not directly related to the opiate receptor system. In some instances, analgesic effects have been established in controlled clinical trials, but for most of these

| Table 3. Guidelines for the use of adjuvant drugs. |
|----------------|----------------|----------------|
| Drugs          | Dose (mg/day)  | Therapeutic effects |
| Corticosteroids|                |                  |
| Prednisone     | 5-15 oral      | perineural oedema |
| Dexamethasone  | 4-12 oral      | anorexia          |
| Chlorpromazine | 10-25 oral     | vomiting          |
| Haloperidol    | 2.5-5 oral     | decreases confusion|
| Prochlorperazine| 5-10 oral     | vomiting          |
| Amitriptyline  | 25-100 oral    | neuropathic pain  |
| Chlorimipramine| 25-100 oral   | tumor, postherpetic neuralgia, phanthon limb pain |
| Carbamazepine  | 200-600 oral   | neuropathic pain  |
| Phenytoin      | 200-300 oral   | nerve compression, plexus neuropathy, postherpetic neuralgia |
| Valproate sodium| 200-600 oral |                  |
| Diazepam       | 10-20 oral     | anxiety, muscle spasm, stiffness |
| Midazolam      | 10-60 SCb      | terminal delirium, multifocal myoclonus, muscle relaxation |
| Local anesthetics|             | neuropathic pain, diabetic |
| Mextetine      | 10/kg          | polyradiculopathy, trigeminal neuralgia |
| Tocainide      | 20/kg          |                  |

a: i.v. : Intravenous.
b: SC : Continuous subcutaneous infusion.
drugs, anecdotal data or clinical surveys provide the rationales for their use, and these are sometimes controversial.

Corticosteroids

In pain therapy, corticosteroids do not necessarily display a direct analgesic action. In some situations, however, they seem to show beneficial co-analgesic effects [37].

The mechanism of action of steroids is not well understood. It is possible, however, to hypothesize a two-fold mechanism: a peripheral effect owing to their anti-inflammatory properties, and a central effect mediated by several neurotransmitters.

Uncontrolled studies have indicated that corticosteroids (CS) reduce pain and the need for narcotics, and increase appetite and mobility in advanced cancer patients [38, 39].

The analgesic effect of these drugs is very apparent when they are used for treating the pain of compressed nerve tissue in closed or narrow cavities, such as headaches due to endocranial hypertension or tumor infiltrations in the brachial and lumbo-sacral plexus [40]. Dexamethasone appears to be significantly stronger than prednisolone in treating pain due to nerve compression [4].

Many controlled clinical studies substantiate the effectiveness of methylprednisolone in terms of improving appetite. They also show that its activity is accompanied by a marked reduction in pain and in the use of analgesics [41-44].

Corticosteroids play a key role in reducing metastatic bone pain, though as yet there are no controlled studies on this topic [45, 46].

Endocranial hypertension symptoms improve within 4-5 hours of corticosteroid administration, and the symptoms progressively stabilize for several days [47]. All available corticosteroids produce an antiedemic effect, but dexamethasone was the preferred corticosteroid thanks to its minimal sodium-retention activity and increased potency when compared with other corticosteroids [48].

The results of a study conducted by the Radiation Therapy Oncology Group in patients with brain metastases highlighted that, from a clinical standpoint, patients receiving combination therapy improved faster than patients who received only radiation therapy [40].

In some pain syndromes, such as epidural medullary compressions, 67% of the patients who received dexamethasone (no significant difference was found between standard and high doses of dexamethasone) in combination with radiotherapy reported significant pain reduction within 24 hours of the drug’s administration, combined with a considerable reduction in the need for analgesics [50].

Corticosteroids can produce adverse side effects in cancer patients. The most frequently encountered are immunosuppression with related consequences [40] and mental disorders including affective disorders (depression, mania), psychotic reactions (steroid psychosis) and global cognitive impairment (delirium) [51]. The rate at which these mental disorders occurred ranged from 3% to 50% [52], becoming severe in 5% of the patients [53].

Biphosphonates

These substances are endowed with a marked antiosteoclastic activity, capable of interfering with the bone reabsorption typical of metastatic bone sites [54, 55]. In addition, in vitro tests showed that these substances actually reduce the production of lactic acid, and inhibit lysosomal enzymatic activity as well as the synthesis of bone prostaglandins. They also appear to interfere with the replication of bone macrophages and with the recruitment of osteoclasts [56]. These substances present a remarkable anti-hypercalcemic activity and might be active also in preventing the development of osteolytic lesions [56].

Some substances from this class of drugs are currently available: etidronate and chlodronate, and the most recent arrival, pamidronate disodium (APD). Of the first two drugs, chlodronate appears to be endowed with both anti-hypercalcemic and analgesic activity. It is also effective when administered orally. A single slow intravenous administration of the drug is as effective as a one-week parenteral administration [57]. APD also appears to be very promising [58].

The analgesic effectiveness of these drugs varies: a reduction in the consumption of analgesics was obtained in approximately 50%-60% of the patients mainly in those with bony metastases [56, 59, 60]. The onset of pain relief is somewhat slow, approximately 6-8 days; but is sustainable for prolonged periods of time or several months [56].

Table 4 shows the suggested biphosphonate therapeutic regimens: their clinical effectiveness appears to be similar. These drugs do not have significant side effects [56, 61, 62]. Their interaction with other kinds of therapy, namely, radio-chemotherapy, hormone therapy and supportive therapy, need to be further explored.

### Table 4. Biphosphonates therapeutic regimens.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Starting dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlодronate</td>
<td>300–600 mg by slow intravenous infusion (4–6 hrs)* for 6–8 days</td>
<td>300 mg weekly by slow intravenous infusion (4–6 hrs)* or 400–2400 mg/day by oral route for 3–4 weeks</td>
</tr>
<tr>
<td>APD</td>
<td>30–60 mg by slow intravenous infusion (4–6 hrs)* weekly for 4 weeks</td>
<td>30 mg every 2 weeks by slow intravenous infusion (4–6 hrs)*</td>
</tr>
</tbody>
</table>

* 500 ml 5% glucose or saline solution.
Calcitonin

In recent years several open studies have suggested that calcitonin is a good or excellent analgesic in patients with pain due to metastatic bone diffusion [25].

The few recent controlled clinical studies of this issue have reappraised this opinion in light of the slight analgesic effect, the cost, and the absence of improvement in patient mobility [25]. Its widespread use for the treatment of bone pain cannot be justified by available clinical data.

Tricyclic antidepressants

Antidepressant drugs are being used in pain therapy either alone or in combination with opiates [63] but there is still some debate about the intrinsic analgesic power of these drugs.

Several clinical studies have shown that the analgesic effect of antidepressants is not related to their effect on concomitant depression, and experimental studies have confirmed these results.

Moreover, some authors agree that the doses needed for analgesia are lower than those needed for antidepressant effects [4]. A single administration of chlorimipramine provided a good analgesic effect in acute postoperative pain [64], in contrast to observations concerning the effects of these drugs on depression, which require 2/3 weeks of administration to become apparent.

Tricyclic antidepressants have been found useful in neuropathic pain syndromes. In prospective controlled trials amitriptyline and desipramine were effective in the management of post-herpetic neuralgia [65, 66] and their effect was unrelated to mood changes.

One placebo-controlled study in terminal cancer patients showed a decrease in morphine requirement for equal pain relief in patients receiving imipramine [67]. Their mechanism of action is not clearly understood; a potentiation of descending inhibitory pathways by blockage of the re-uptake of serotonin has been suggested. Ventafridda et al. in two studies on humans and animals found an increase in bioavailability of morphine when administered in association with antidepressants [68, 69], the same result which was obtained with methadone in rats [70].

The adverse effect of these drugs are xerostomia, postural hypotension, somnolence and confusion. Such symptoms can aggravate the suffering in already debilitated patients. For this reason it is important to evaluate the costs and benefits of a treatment with antidepressant drugs given to control cancer pain.

Anticonvulsant drugs

The main indications for analgesic therapy are neuropathic pain and pain due to deafferentation, whether idiopathic or secondary [71, 72], although the mechanism of pain relief is still poorly understood.

Pain symptoms such as these are described by words such as burning, stabbing, throbbing, gripping, lancinating, or jabbing pain. Neuropathic pain may also ensue from damage to the more centrally located somatosensory pathways [73].

The most widely used drugs in pain therapy are diphenylhydantoin, carbamazepine, and valproic acid [74].

The mechanism of action of these drugs is linked to the stabilization of neural membranes (phenytoin), to sodium canal activity (carbamazepine) and to interaction with the GABA system (valproate sodium). The most significant side effects are vertigo, nausea and drowsiness. Treatment with carbamazepine requires a careful monitoring of blood values because of the risk of agranulocytosis and thrombocytopenia.

Local anesthetics-antidysrhythmics

In recent years some of these drugs have been further developed for use in selected pain syndromes such as diabetic polyradiculopathy, trigeminal neuralgia and neuropathic pain [75]. The ones most widely used for this purpose are lidocaine, mexyletine and tocainide. Lidocaine is primarily used intravenously, while the other two are administered orally. The pharmacological and pharmacokinetic properties of local anesthetics are also well known [76]. However, oral administration of some local anesthetics used as analgesics is quite new [77]. Tocainide and mexyletine administered orally are absorbed well through the gastrointestinal tract with good bioavailability (88%-100%) [77, 78], but the incidence of side effects is quite high for these drugs, especially tocainide. Their use in cancer pain is still controversial: two recent controlled clinical trials produced negative findings on the use of intravenous lidocaine [79, 80].

In our view, more controlled clinical trials are needed on the use of these drugs in cancer pain management.

Benzodiazepines

These drugs have anxiolytic, sedative, hypnotic and amnesic properties [81]. The specific receptors of benzodiazepines are well known and distributed throughout the CNS including the spinal cord and other organ tissues, namely, the liver, kidneys and lungs [82].

In the field of cancer pain treatment, no studies have so far been conducted on the effectiveness of benzodiazepines when used as analgesic. Nevertheless, these drugs are very often used as adjuvants in the treatment of chronic pain [83], and are also beneficial, especially diazepam, when used as relaxants for muscle spasms [84].

Midazolam is a short-acting water-soluble benzodiazepine. It is an anxiolytic sedative with anticonvulsant properties. It is used as a muscle relaxant and anticonvulsant (in particular for multifocal myoclonus) and to reduce terminal agitation [85].
References


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