Recent Developments in Palliative Cancer Care

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Acta Oncologica Vol. 37, No. 7/8, pp. 749–757, 1998

In recent years major developments have taken place in palliative cancer care. Cancer specialists should be familiar with a number of these developments since they can improve symptom control in advanced cancer patients. Some of these developments are discussed in this article, with particular emphasis on the multidimensional assessment of symptom complexes and neurotoxicity of opioids.

Received 6 November 1997
Accepted 11 September 1998

MULTIDIMENSIONAL ASSESSMENT IN PALLIATIVE CARE

The past decade has seen a heightened awareness of the interaction between the numerous physical symptoms and a plethora of psychosocial, cultural and spiritual variables that patients present with. All these appear to have a strong influence on the patients' overall well-being and quality of life (1). Given the complexity of the interaction between the various physical and psychosocial domains, it is becoming generally acknowledged that if a positive impact on the well-being of patients is the goal of palliative care, then the assessment of terminally ill patients requires a multidimensional approach. This approach not only needs to incorporate all these domains, but also needs to be made on a regular and disciplined basis so as to ensure comprehensiveness and consistency. Initiatives to improve the process of research-related data collection are closely related to this approach. To facilitate these multidimensional assessments, numerous tools, systems and questionnaires have been developed or adopted (2).

Pain and symptom assessment

Several factors must be noted when symptoms and problems are being assessed. These include not only the characteristics of the symptoms, such as intensity and frequency, but also the subjectivity and multidimensional nature of the symptom expression, the interaction of many concurrent symptoms on one another, the overall symptom burden and the degree to which symptom distress affects quality of life. Patient self-reports should be the primary source of information for the measurement of symptoms. Observer ratings of symptom severity correlate poorly with patient ratings and are generally an inadequate substitute for patient reporting (3). Studies have consistently demonstrated that clinicians and nurses tend to underestimate patients' symptoms, while family caregivers tend to overestimate the symptom intensity. Objective signs and findings may complement subjective symptom expression, but this is not universal as in the case of dyspnea where the patient's symptom complaints do not necessarily correlate with physical examination or investigations.

In the process of instrument selection, the clinician or investigator must carefully consider the goals of assessment and the practicality and acceptability of the instrument by terminally ill patients (2). Ideally, so as to encourage compliance by both the patient and the caregiver as well as to minimize the burden on the patient, the tools or questionnaires should be simple and brief. On the other hand, it must be noted that simplicity and brevity may limit the ability to capture multidimensional impressions of symptomatology and quality of life.

Simple visual analogue (VAS), numerical rating (NRS) and verbal descriptor scales have proven to be a very effective and reproducible means of measuring pain and other symptoms (4). Despite some shortcomings of these scales (primarily their unidimensional approach), they can be universally implemented and regularly applied in all care settings. The regular application and charting of symptom intensity allows caregivers to assess the impact of therapeutic interventions and the patient to report any changes in the symptom pattern and intensity.

 ISSN 0284-186X

Several validated assessment tools are now available (5–12). The Edmonton Symptom Assessment Scale (ESAS) and the Memorial Pain Assessment Card (MPAC) (5, 7) are examples of tools that meet the criteria of brevity, reproducibility and reliance primarily on patient self-reporting. The ESAS consists of 9 different visual analogue or numeric scales that assess 9 different symptoms. The results can then be recorded on a graphic display in the patient's chart. Certain visual patterns which develop over time on the graphic display can alert clinicians' to the interdependence of various symptoms and psychosocial influences. There appears to be a tendency for patients who experience psychosocial distress on a physical level consistently to rate many of their symptoms at a high level. Recognition of these patterns allows caregiving teams to be proactive and to focus on psychosocial influences as well as addressing physical symptoms. Finally, the ESAS can also be used for quality control. In Edmonton, where there are various settings of palliative care; patients in the Acute Palliative Care Unit complete the ESAS twice daily while those in the hospices complete it on a once-daily basis. Patients who are seen at various other emergency care, oncological, medical, and surgical units complete it at the time of assessment. Patients being cared for at home are encouraged to complete it at least several times a week.

The MPAC is a brief, validated measure that uses the VAS scale to characterize pain intensity, pain relief, and mood, and an 8-point verbal rating score (VRS) to further characterize pain intensity (7). The Memorial Symptom Assessment Scale (MSAS) is a validated, patient-rated measure that assesses various symptoms (8). Although it provides multidimensional information, the 32 physical and psychological symptoms that are characterized in terms of intensity, frequency and distress make it lengthy and inconvenient to apply on a very regular basis. The Rotterdam Symptom Checklist (RSC) is also a validated patient-rated measure that evaluates 30 symptoms (11). Both physical and psychological symptoms are included and some items specifically attempt to define the impact of symptoms on physical activity and function. The main drawback of the RSC is that it does not provide information about symptom intensity or frequency and fails to provide a general pain item. The Symptom Distress Scale (SDS) is a 13-item patient-rated scale that uses a 5-point Likert scale to evaluate 11 symptoms (9 physical and 2 psychological) in terms of frequency, intensity, and distress (12).

The McGill Pain Questionnaire (MPQ) (9) and the Brief Pain Inventory (BPI) (10) are instruments that provide a multidimensional assessment of pain. The MPQ is a self-administered questionnaire that provides global scores and subscale scores that reflect various dimensions of pain. A 5-point verbal categoric scale characterizes the intensity of pain. Further information is collected about the impact of medications and other therapies. Although the MPQ has been extensively evaluated in patients with chronic pain, the utility of the subscale scores has not been demonstrated for cancer pain. The BPI provides information about pain history (in general, at its worst, at its least, and right now), intensity, location and quality. Numeric scales indicate the intensity of pain, while a percentage scale assesses relief gained from therapies. Seven questions determine the degree to which pain interferes with function, mood and enjoyment of life. The BPI, too, is self-administered and has been translated into several languages.

The measurement of symptoms may improve patient outcomes by increasing staff awareness (13). Furthermore, frequent symptom measurement serves as a means of reviewing the quality of patient care (14). The use of assessment tools in the home setting is encouraged so as to promote continuity of pain management in all settings.

The staging of cancer pain

It is now well-recognized that a certain subset of patients will experience difficulty in achieving adequate control of their cancer pain despite the application of well-recognized guidelines. Several prognostic factors have been identified that correlate with poorer pain control. These include the presence of neuropathic pain, incidental pain, psychological distress, a history of alcohol/drug abuse and the rapid development of tolerance to an opioid.

In an attempt prospectively to identify patients unlikely to respond favourably to systemic analgesics, our group incorporated these factors into a staging system. This system, the Edmonton Staging System (ESS) for cancer pain, incorporates the above-mentioned prognostic factors (15). Although the universal development of tolerance to the analgesic effects of opioids does not generally negatively impact on pain control, it is recognized that a small subgroup of patients do develop significant tolerance that can be a challenge to manage effectively (16). It is recognized that a past history of alcohol or substance abuse indicates a maladaptive coping technique that predisposes a patient to cope chemically while facing a psychological distress (15). In initial prototypes of this system, cognitive impairment and the previous opioid dose were included. Results of the multivariate analysis suggested that cognitive function and the previous opioid dose did not have any correlation with outcome and were consequently deleted from the staging system (15). A multicenter validation study found that the system is accurate in predicting the outcome of patients with a good prognosis. However, patients with more difficult pain syndromes can still achieve good pain control in almost half of the cases if the factors are identified early and timely management strategies are implemented. Of 276 evaluable patients, 86/92 Stage I (good prognosis) patients achieved good pain control during a final assessment on day 21 (93%); versus 102/184 Stage II and Stage III (poor prognosis) patients (55%), $p < 0.001$ (17). The ESS also provides researchers

with a common method of stratifying groups of patients in much the same way that staging systems for various cancers have provided researchers and clinicians with a means to stratify various cancers according to prognostic features.

Instruments for the assessment of impaired cognition and delirium

The majority of cancer patients develop severe cognitive failure before death (18). The most common cause of impaired cognition in this population group is delirium. Delirium results in increased morbidity and mortality and frequently impacts negatively on the assessment of cancer pain and its management. Unfortunately, numerous studies have indicated that cognitive impairment and delirium are frequently under-diagnosed and often mismanaged. During the same day in which a patient experienced an episode of major cognitive failure, the clinical examination by the physician and by the nurse failed to detect cognitive failure in almost one in four cases (19). To detect cognitive impairment, various screening tests have been developed (20), including the Mini-Mental State Examination (MMSE) and the Blessed Orientation Memory Concentration test (BOMC). The MMSE has been utilized and tested extensively in patients with cancer (20). It is a simple tool that requires only a few minutes to administer and can easily be performed by minimally trained caregivers. Frequent administrations of the MMSE have been found to be useful in following up patients in a palliative care setting (19). Furthermore, a recent retrospective study suggests that improvement of cognition as indicated by normalization of an MMSE correlates with an increased discharge rate from a palliative care unit (18). The BOMC has not been validated in cancer patients (21).

The screening tools discussed above are sensitive indicators of cognitive impairment, but are not specific for the diagnosis of delirium. Moreover, they do not quantify the severity of delirium and do not provide a phenomenology of delirium. Several instruments have been developed and validated to facilitate the specific diagnosis of delirium. These include the Confusion Assessment Method, the Delirium Symptom Interview, the Saskatoon Delirium Checklist and the Delirium Rating Scale (20). These tools cannot be applied repeatedly and are unable to monitor short-term changes. The Memorial Delirium Assessment Scale (MDAS) has been developed more recently as a method of quantifying the severity of delirium on a frequent basis (22). It appears to have diagnostic properties as well. Other tools to describe the phenomenology of delirium are presently being evaluated.

Assessing alcohol and drug abuse

A history of alcoholism or drug abuse has been identified to be an independent prognosticator for poor pain control. These patients, when faced with life stressors, tend to utilize maladaptive coping strategies. Despite the relatively high frequency of alcoholism in the general population, a recent study suggested that physicians from different specialities missed the diagnosis of alcoholism in the great majority of patients under their care during a hospital admission (23). When the CAGE screening questionnaire was utilized in consecutive admissions to an acute palliative care unit, the prevalence of alcoholism, or a history of it, was found to be 27%. The four key questions in the CAGE questionnaire include: has the patient a) ever been asked to 'cut back' on alcohol intake; b) ever been 'annoyed' by people suggesting alcohol avoidance; c) ever felt 'guilty' about the amount of alcohol consumed; and d) did he/she ever require an 'eye-opening' drink upon awakening in the morning (24). Although classified as a screening tool, the CAGE questionnaire can predict with a high level of specificity and sensitivity the presence of alcoholism in patients who score positively for two or more of the questions. The early detection of alcoholism or drug abuse allows for early intensive counselling. When this proactive management is instituted together with the pharmacological management of cancer pain, the overall outcome of pain control and analgesic consumption was comparable to that of non-alcoholic patients with cancer pain (24).

Instruments for the assessment of functional activities and fatigue

The majority of patients with terminal cancer have an impaired ability to perform everyday functions during the various stages of the disease. Rehabilitation offers interventions to achieve an optimal level of function within the limits imposed by the disease process. An evaluation of functional status is therefore an essential element in the caring of terminally ill patients and, as with the assessment of symptoms, ongoing recording at various intervals is required.

Unfortunately, most of the functional scales utilized in cancer patients are not sensitive enough to reflect major changes in function that occur during the last months and weeks of life. The Karnofsky Performance Status (KPS) scale and the Performance Status Measure of the Eastern Cooperative Oncology Group (ECOG) are two examples of such tools (25, 26). Furthermore, the KPS is unable to evaluate the effects of rehabilitation while the ECOG evaluates physical independence as a single-item only.

With the limitations of the above tools in mind, the Edmonton Functional Assessment Tool (EFAT) was designed to provide comprehensive, ongoing evaluations of functions appropriate to the rehabilitation of patients with terminal cancer (27). The first part of the tool contains 10 items, each describing the functions to be performed, while the second part contains a global rating of functional performance status after the 10 functions are assessed. Each item in the EFAT is worded in behavioral terms to indicate the function to be observed and tested. Each item

is rated using a behaviorally anchored rating scale from 0 to 3: 0 = independent functional performance and 3 = total loss of functional performance. The maximum score is 30, representing a severe decline in independent functioning. Validity studies suggest that the EFAT has excellent potential in the setting of palliative care.

Assessment of constipation

Constipation is highly prevalent among cancer patients. However, even in the palliative care setting, this symptom is often poorly assessed (28). The number and volume of bowel movements is usually poorly recorded and the patient's recollection may not be reliable. A plain x-ray of the abdomen may allow for the rapid assessment of the amount of stool in the colon and a simple technique of dividing the abdomen into four quadrants and assessing the amount of stool in each quadrant has been found to be very useful in a palliative care setting (28).

Assessing quality of life in palliative oncology

The primary goal of palliative care is to optimize the quality of life (QOL) of patients with incurable illness through the control of physical symptoms and through attention to the psychological, social and spiritual domains. The measuring of QOL and its impact on therapeutic interventions remains a major challenge in palliative care. The majority of existing QOL instruments have several major short-comings; these include: an inadequate assessment of the existential domain, excessive focus on the physical domain, most do not adequately attempt to measure positive contributions to QOL and many are too lengthy (29).

It is clear that no instrument is as yet completely adequate and that further research into this crucial aspect of palliative care is needed. However, this does not mean that researchers and clinicians should refrain from using existing QOL instruments, such as the Functional Assessment of Cancer Therapy (FACT) (30), the EORTC Core Questionnaire (26), and the Spitzer Questionnaire (31). More recently, the McGill Quality of Life Questionnaire (MQOL) was developed to overcome some of the previously mentioned short-comings (32). This instrument attempts to measure the existential domain, the physical domain, as well as positive contributions to the QOL. The importance of measuring the existential domain is highlighted by the finding that, of all the subscales, only the meaningful existence subscale correlated significantly with a single item scale rating overall QOL.

Other assessment issues

The psychosocial assessment of a terminally ill patient is imperative and should reflect factors such as personality, coping strategies, and both past and present psychiatric disorders. The clinician must become aware of the patient and family's social resources, financial situation, and the physical environment in which they live. The hopes and expectations of both the patient and family need to be considered since unrealistic expectations may require attention. Screening for major depression remains a challenge. Somatic symptoms of a major depression (weakness, loss of appetite, weight loss) cannot be used as diagnostic criteria since they are commonly the result of advanced cancer per se. Reliance on purely psychological symptoms, on the other hand, loses screening specificity.

OPIOID TOXICITY

Approximately 80% of patients with advanced cancer develop pain before death (33, 34). Several studies have documented the under-treatment of cancer pain with opioid analgesics (35, 36).

During the past 15 years, the World Health Organization, the International Association for the Study of Pain, the American Society of Clinical Oncology and numerous other organizations have emphasized the need to better assess and manage cancer pain with opioid analgesics. A number of useful guidelines have been used by these organizations. As a result of this educational effort, the use of opioids for cancer pain has significantly increased, in both the developed (37) and developing countries (38).

Opioids are now used not only in higher doses, but also at earlier stages of the disease compared with their use 5 to 10 years ago (37). In addition, the adequate assessment and monitoring of cognitive and neuropsychiatric function in advanced patients has received more emphasis in recent years (39, 40).

This highly desirable increase in the use of opioids, combined with increased vigilance on neuropsychiatric status, has resulted in increased detection of several neuropsychiatric side effects.

We will now review some of the literature characterizing key side effects and strategies for the management of these recognized toxicities.

Traditional opioid side effects

In Table 1 we summarize the most common side effects of opioid agonists (33). Most of these effects are rarely a cause for halting analgesic treatment. There is no clear evidence that one particular opioid agonist has a significantly lower prevalence or intensity of sedation, nausea, or constipation compared with other opioid agonists (41, 42). However, there is general consensus that an individual

Table 1

Traditional opioid side effects

— Sedation
— Nausea
— Constipation
— Other (pruritus, sweating, anaphylaxis, urinary retention

Table 2

Emerging side effects of opioids

— Pulmonary edema
— Cognitive failure
— Delirium
— Myoclonus/grand mal seizures
— Hyperalgesia
— Severe sedation—coma

patient may experience fewer severe side effects with a given opioid agonist. Therefore, a change in the type of opioid may help in overcoming some of these common side effects.

Recently recognized side effects

Some of the most recently recognized side effects of opioids are summarized in Table 2. With the exception of pulmonary edema (43), the remaining side effects are of a neuropsychiatric nature. Some of these effects are described in the next section.

Cognitive failure and sedation

Most patients treated with opioid analgesics for the first time develop transient sedation or cognitive failure. These effects appear to be more severe in patients receiving higher doses of opioids or agonist/antagonist opioids as compared to pure agonists, in patients treated with other psychoactive drugs, and in those with borderline cognitive failure (44). In most patients, the cognitive failure is more like the 'slowing down' of cognitive function, than an increase in both the number of errors or major errors in judgement (44).

Hallucinosis and delirium. Several authors have documented that delirium is one of the most frequent neuropsychiatric complications in patients with advanced cancer (39). Patients with delirium present with a combination of cognitive failure, fluctuating level of consciousness, change in the sleep–wake cycle, and variable severity of hallucinations, delusions, other perceptional abnormalities and psychomotor agitation (45).

Delirium is a multicausal syndrome. In cancer patients, problems such as infection, metabolic abnormalities (hypercalcemia, hyponatremia, renal or liver failure), brain metastases, or drugs are all possible causes (41). Centrally acting drugs and anticholinergics are the main non-opioid drugs capable of causing delirium (40, 45). Opioids may be the only cause of delirium in a given patient or may aggravate pre-existing delirium from other causes (46). The possible pharmacokinetic interactions between morphine and other drugs should be considered. The plasma concentration of morphine can increase when it is administered in association with antidepressants (47) or ranitidine (48). Unfortunately, delirium is frequently under-diagnosed in patients with advanced cancer (46) and consequently, it is frequently mismanaged. Simple and reliable instruments allow the screening and monitoring of delirium in advanced cancer patients (41, 46).

Patients receiving opioid analgesics may experience visual hallucinations. Hallucinations may also be tactile and, rarely, auditory. Occasionally, hallucinations occur in patients with no cognitive failure (49). These patients may be reluctant to describe their hallucinations for fear of being considered psychiatrically ill. In some cases a sudden change in the patient's mood (anxiety or depression) rather than obvious hallucinatory activity may indicate the development of organic hallucinosis.

Myoclonus and grand mal seizures. Cases of myoclonus have been described after administration of hydromorphone (50–52), meperidine (53, 54), sufentanil and fentanyl (55). Studies show that high concentrations of these opioids and their metabolites in cerebral spinal fluids (CSF) can cause myoclonus (53).

The likelihood of generalized myoclonus or grand mal seizures may increase in patients who have other aggravating factors such as a history of seizure disorders, brain metastases, or other metabolic abnormalities. These abnormalities improve with opioid rotation (52–56).

Hyperalgesia. Sjogren et al. (57) described hyperalgesia and myoclonus that manifested both as generalized cutaneous hyperalgesia and progressive aggravation of cancer pain in eight patients receiving high doses of intravenous morphine. In another paper the same author described four patients who presented hyperalgesia during morphine administration. Morphine was stopped in all the patients and methadone was administered in two, sufentanil in 1 patient and ketobemidone 1; all of the patients obtained pain control without hyperalgesia (58). These side effects appear to result from the accumulation of active opioid metabolites and respond to a switch in opioid type (58, 59). Thus, patients who experience sudden aggravation of pain or cutaneous hyperalgesia might improve with a change in opioid administration.

Mechanism of neuropsychiatric toxic effects

Animal studies have shown that morphine, morphine-3-glucuronide, normorphine, and hydromorphone can cause allodynia in rats after intrathecal high dosages (60–63). Morphine, hydromorphone, and fentanyl can cause agitation, myoclonus, hyperalgesia, and grand mal seizures in animals when administered systemically (62–66). There is evidence to suggest that both tolerance and hyperalgesia share common neural substrates in the excitatory amino acids (61–66). Animal evidence also suggests that some syndromes such as neuropathic pain link the presence of hyperalgesia with decreased opioid responsiveness (61, 66).

Animal and human studies have found that a variety of opioids including morphine, hydromorphone, and meperidine have active metabolites that can cause significant neurotoxicity. These metabolites are generally produced in the liver and eliminated in the urine. Conditions associated with increased circulating active metabolites include high opioid doses, prolonged treatment, dehydration, renal failure, and drugs that might decrease glomerular filtration. Some metabolites such as morphine-6-glucuronide are potent opioid agonists and therefore are capable of causing the traditional opioid side effects including sedation, and respiratory depression. Other metabolites such as morphine-3-glucuronide and normorphine are generally excitatory and do not bind to the opioid receptor. These metabolites can cause agitation, myoclonus, hyperalgesia, and grand mal seizures. Because of the presence of mixed metabolites, most patients present with mixed syndromes combining sedation with excitation.

A number of animal studies clearly suggest that parent compounds are also involved occasionally in severe neurotoxicity.

MANAGEMENT

A number of strategies that have been proposed for the management of opioid neurotoxicity are summarized in Table 3.

Opioid rotation. If either the parent compound or its active metabolites are suspected to be at least partially responsible for neurotoxic side effects, it would be reasonable to attempt an opioid rotation in order to decrease neurotoxicity. A number of authors have reported significant improvement in neuropsychiatric side effects after opioid rotation (52–54, 56, 59, 67). The results should be interpreted cautiously because of the uncontrolled nature of the studies and the relatively small number of patients. However, in all cases the authors observed significant improvement after the opioid rotation. Most patients had severe symptoms of hyperexcitability. These results clearly justify randomized control trials on opioid rotation and suggest that opioid rotation should be tried in patients with acute neurotoxicity. The ideal alternative opioid has not been characterized. Initially, the trial of an alternative agonist such as hydromorphone or oxycodone is usually effective in patients who develop toxicity to morphine, and vice versa. In cases of severe toxicity after rotation among the most common opioid agonists, second-line drugs such as methadone should be considered. Methadone has the advantages of extremely low cost, recently demonstrated NMDA antagonist properties and no active metabolites. However, its main disadvantages are a long and unpredictable half-life and a poorly defined equianalgesic dose as compared with morphine and hydromorphone (67). Methadone can be absorbed orally and rectally. It has a unique profile among other opioid agonists in that the equianalgesic dose appears to be relatively lower in patients previously exposed to high doses of opioid agonists as compared to patients previously exposed to low dosages (67). These observations suggest that patients receiving other opioid agonists develop only partial cross-tolerance to methadone. Randomized controlled trials on opioid rotation to methadone are currently being carried out. In the meantime, opioid rotation to methadone should only be performed by experienced specialists, and such rotation should take place over several days in order to titrate the new opioid dose appropriately.

Table 3

Management of opioid neurotoxicity

— Opioid rotation
— Dose reduction
— Circadian modulation
— Hydration
— Psychostimulants
— Sedatives

Dose reduction or discontinuation. A number of reports suggest that dose reduction or discontinuation resulted in significant improvement in the patient's neuropsychiatric symptoms (56, 67–69). These observations further support the role of opioids as a cause of the patient's neurotoxic symptoms. Unfortunately, either reduction or discontinuation is rarely possible in patients with advanced cancer.

While complete dose reduction or discontinuation may be impossible, circadian modulation might allow patients to receive lower total dosages without significantly compromising pain intensity. A retrospective study of patients receiving intermittent subcutaneous opioids (70) and a randomized controlled trial in patients receiving slow-release suppositories of morphine (71) both found that in cancer patients not receiving hypnotics, night time opioid requirements are significantly lower. Future studies should assess whether pain-management regimens targeted to the circadian variation in pain intensity might reduce overall opioid administration and the consequent development of tolerance or accumulation of opioid metabolites without jeopardizing pain control. Opioids with very short half-lives, such as fentanyl and its derivatives, might be ideal for such studies.

Hydration. The opioid metabolites are hydro-soluble and thus are likely to accumulate in patients with renal failure or dehydration. For this reason, ensuring that the patients receive adequate hydration will decrease the severity and duration of the central side effects. Hydration can be administered subcutaneously or intravenously (72). If the decision is made not to hydrate a terminally ill patient who is receiving opioid analgesics, it is likely that active opioid

metabolites will accumulate as the patient becomes progressively dehydrated and urine output decreases. These patients require a reduction in opioid dose in conjunction with assessment of pain control. If progressive delirium or hyperaccessibility becomes apparent, these patients might require a switch in opioid type.

Psychostimulants. These medications can counteract opioid-related sedation and cognitive dysfunction, and allow escalation of opioid doses in patients with difficult pain syndromes (73). A number of randomized, controlled trials have demonstrated that methylphenidate, and pemoline have similar effects on opioid-induced sedation. Before prescribing psychostimulants, the clinician should conduct a thorough anamnesis test to exclude any psychiatric disorder. These drugs are contraindicated in patients with a history of hallucinations, delirium, or paranoid disorders. They are also relatively contraindicated in patients with a history of substance abuse.

CONCLUSIONS

An increasing number of authors have recently reported that patients receiving opioids develop neuropsychiatric side effects. These syndromes occur more frequently in patients receiving high doses for prolonged periods, patients with renal failure, and those with underlying delirium or receiving other psychoactive drugs. The most common syndromes described include cognitive failure, sedation, delirium, hyperalgesia, generalized myoclonus, and grand mal seizures. While initial evidence indicates the role of active opioid metabolites, animal and human evidence also suggests the implication of the parent compounds and opioid receptors in these toxic effects.

There is evidence that opioids continue to be underutilized in the treatment of cancer pain, both in the developing and developed countries. However, the studies reported in this paper strongly suggest that in some cases over-enthusiastic opioid titration may be associated with severe neurotoxicity. Our educational efforts must emphasize the need to rapidly identify and manage these complex syndromes.

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