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Observational Study

Prevalence of Side Effects of Prolonged Low or Moderate Dose Opioid Therapy with Concomitant Benzodiazepine and/or Antidepressant Therapy in Chronic Non-Cancer Pain

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Background: Opioid use in the management of chronic pain is widespread in chronic pain settings. Opioid prescriptions for non-cancer pain and overall opioid sales have been soaring with the increasing nonmedical use of opioids in the United States. Prolonged use of high dose opioids has been associated with adverse consequences including tolerance, abuse, addiction, hyperalgesia, hormonal effects, and immunosuppression.

Studies of high dose therapy have shown pain relief with a 30% decrease in the intensity of pain and that only 44% of the patients continue the treatment between 7 and 24 months. However, there is no data available on the prevalence of side effects associated with low or moderate dose opioid use in chronic non-cancer pain when administered in conjunction with interventional techniques.

Objective: To evaluate the prevalence of side effects, of low or moderate dose opioid therapy with or without benzodiazepines, antidepressants, and their combinations.

Methods: The evaluation was conducted by interviewing 1,000 patients on stable doses of opioids, with or without benzodiazepines, antidepressants, and their combinations. Patients were categorized into 4 groups with Group 1 receiving opioids only (n = 143), Group 2 receiving opioids and benzodiazepines (n = 159), Group 3 receiving opioids and antidepressants (n = 113), and Group 4 received opioids, benzodiazepines, and antidepressants (n = 118).

Results: Inclusion criteria was met in 533 patients receiving opioid therapy for longer than 6 months. The incidence of side effects in Group 1 was 18%, in Group 2 was 8%, in Group 3 was 17%, and in Group 4 was 14%. The most frequent complications were in patients receiving methadone (52%) followed by oxycodone (41%) and morphine (36%). Patients receiving hydrocodone had the least incidences of side effects with 7.5%. There were no significant differences noted based on the duration of therapy, age of the patient, and gender. Severe side effects accounted for only 14 of 137 instances.

Limitations: Limitations of this study include the inability to incorporate multiple other drugs due to complicated nature with multiple groups and data collection and analysis. The other limitation is that the proportion of patients receiving methadone, oxycodone, morphine, and propoxyphene was low compared to hydrocodone with 77% of the patients.

Conclusion: Moderate or low dose opioid therapy in conjunction with or without benzodiazepines, antidepressants, or in combinations are associated with minor side effects.

Key words: Opioids, benzodiazepines, antidepressants, chronic non-cancer pain, abuse, side effects

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Opioid use in chronic non-cancer patients is controversial (1-3). During the last 25 years, opioids have increasingly been used for the treatment of chronic non-cancer pain in the United States, coupled with exploding medical use, misuse, and abuse (4-9). Three models have been described for the long-term use of opioids and the treatment of intractable pain: 1) scheduled respites from pain, 2) "as needed" opioids for relief of pain exacerbations, and 3) long-acting, scheduled opioids for continuous pain relief (10). Mostly high dose opioids have been recommended and evaluated. Studies of high dose therapy have shown pain relief with a 30% decrease in the intensity of pain, and that only 44% of the patients continued the treatment between 7 and 24 months (1-4,11-15). In a systematic review and meta-analysis of the efficacy and safety of long-term opioid therapy for chronic non-cancer pain (15), the authors concluded that many patients discontinued long-term opioid therapy due to adverse events or insufficient pain relief.

Numerous studies have shown widespread use of opioids in the management of chronic pain in approximately 90% of patients (4-22). Further, 90% of the patients were on opioids prior to presenting to an interventional pain management center (16). Consequently, opioid prescriptions for non-cancer pain and overall opioid sales have been soaring with the increasing nonmedical use of opioids in the United States, which consumes 90% of the global supply of the opioids and 99% of the global supply of hydrocodone (4,5,23). Prolonged use of high dose opioids has been associated with adverse consequences, including tolerance, abuse, addiction, hyperalgesia, hormonal effects, and immunosuppression (1-4,24,25).

In general, the side effects of opioids have been considered to be a barrier to successful pain management (22,23). With high dose long-term opioid therapy, the side effects allegedly limit the titration of analgesics to achieve optimal pain control and decrease the patient's quality of life. Consequently, optimal opioid pharmacotherapy may hinge on finding a satisfactory balance between analgesia and side effects (28). The common side effects associated with the administration of various classes of opioid medications include gastrointestinal (nausea, vomiting, indigestion, constipation), central nervous system (drowsiness, difficulty concentrating, hallucinations/nightmares, light-headedness, poor coordination, lack of energy), and autonomic nervous system effects (urinary retention, xerostomia) (26). It is critically important to understand the relationship between the type of analgesic prescription and its dosage to the prevalence and severity of side effects (26). Most published studies have used opioids as the mainstay of therapy. However, opioids may be used as supplemental therapy to other modalities of treatments, including interventional pain management techniques. Consequently, in the settings in which opioid therapy is not the mainstay of treatment, the effectiveness of opioids may be enhanced with the additive effect of interventional techniques, resulting in a lower dosage with reduced adverse effects. However, no data is available on the prevalence of side effects associated with low or moderate dose opioids in chronic non-cancer pain.

Noble et al (15) provided the best evidence and significant insights into long-term chronic opioid therapy. The results showed that many patients withdrew from clinical trials due to adverse effects or insufficient pain relief. Consequently, they concluded that there is weak evidence that oral opioids reduce pain long-term in the relatively small proportion of individuals with chronic non-cancer pain that continue treatment. In a systematic review of the comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain by Chou et al (12), withdrawal rates due to adverse events ranged from 23% to 25%. Kalso et al (13) showed only 44% of 388 patients on open-label treatment were still on opioids after therapy between 7 and 24 months. Adverse events were a common reason for discontinuation, as well as lack of efficacy. Martell et al (11) showed substance use disorders in aberrant medication-taking behaviors in up to 24% of cases of patients on opioid therapy for chronic low back pain. In addition, studies have shown increasing opiate needs, and prescription drug abuse and illicit drug use in chronic pain patients receiving short-acting or long-acting opioids (29,30). Prescription drug abuse in settings of moderate or low dose opioid therapy, supplemental to interventional pain management, has been well studied (31-38).

We sought to evaluate the prevalence of side effects, other than drug abuse, in patients on long-term opioid therapy of at least 6 months. In this study, the evaluation was limited to only the side effects and no attempt was made to evaluate the effectiveness, drug misuse, abuse, illicit drug use, or tolerance, etc. The study was performed in an interventional pain management setting with patients receiving interventional techniques. Side effects were evaluated in patients

receiving either opioids alone, or in combination with benzodiazepines and/or antidepressants. The effectiveness of drug therapy was not the focus of this study. The side effects of muscle relaxants, antiepileptics, hypnotics, and other drugs were not evaluated.

Methods

The study was performed in a nonacademic interventional pain management tertiary referral center. The multidisciplinary center provides interventional pain management services. Patients are referred to the center from specialty and primary care physicians. The general patient population consists of chronic pain patients, with spinal pain being the most common condition.

All patients signed an informed consent for evaluation of therapy, including random drug testing and publication of any results, as part of the treatment. Appropriate precautions were taken to protect the privacy and identity of patients evaluated for this study. Institutional Review Board approval was not required.

Inclusion criteria were a willingness to participate, stable condition, and participation in a pain management program encompassing interventional techniques and opioid drug administration with or without benzodiazepines and/or antidepressants.

Exclusion criteria were either the inability to understand the consent or refusing to sign the consent, refusing to provide the information or undergo random drug testing, and unstable pain control. Further, patients who were on opioids, but were also on various types of muscle relaxants, hypnotics, or antiepileptics, etc. were also excluded. If patients were receiving higher than the maximum daily doses, they were also excluded.

Patients were characterized into 4 groups, Group 1 consisting of patients receiving opioids only, Group 2 consisting of patients receiving opioids and benzodiazepines, Group 3 consisting of patients receiving opioids and antidepressants, and Group 4 patients receiving a combination of opioids, benzodiazepines, and antidepressants.

Maximum daily doses to be included in this study were hydrocodone, 50 mg; oxycodone, 60 mg; methadone, 60 mg; and morphine, 60 mg, or Fentanyl, 75 mcg per hour or a morphine equivalent not exceeding 90 mg per day.

Data were collected with regards to all the drugs the patient was receiving, the duration of the drugs, demographic information, and side effects including constipation, sedation, impotence, fatigue, dry mouth, insomnia, nausea, vomiting, pleuritis, cognitive dysfunction, dizziness, hyperactivity, ataxia, depression, sluggishness, dreams, peripheral edema, diarrhea, restless legs, headache, decreased appetite, weight gain, memory loss, hyperacidity, urinary retention, and increased frequency of urination.

Statistical Methods

Using Microsoft® Access® 2003, SPSS (version 9.0), the data were tabulated to generate the descriptive tables. Differences in proportions were tested using the chi-squared statistic. Fisher's exact test was used wherever the expected value was less than 5. One-way analysis of variance was used for comparison of means among the 4 groups and Bonferroni correction was done for multiple comparisons. All results were considered statistically significant if the p value was less than 0.05.

Results

Patient Flow

A total of 1,000 consecutive patients presenting for interventional pain management were evaluated during 2006. As illustrated in Fig. 1, data included analyzable and complete information from 987 patients. Of these, 850 patients were on opioids of which 72 patients were on opioids less than 6 months. Further, 234 patients were on opioids with other drugs (or were receiving the doses over described maximum daily doses). Overall, 533 patients met the inclusion criteria, with patients on opioid drug therapy for more than 6 months with or without benzodiazepines and/or antidepressants. These 533 patients were analyzed to investigate for side effects due to the opioids.

Patient Characteristics

Group 1 consisted of patients receiving only opioids (n = 143), Group 2 consisted of patients receiving opioids and benzodiazepines (n = 159), Group 3 consisted of patients receiving opioids and antidepressants (n = 113), and Group 4 consisted of patients receiving a combination of opioids, benzodiazepines, and antidepressants (n = 118).

Table 1 illustrates the demographic characteristics. There was a significantly greater proportion of male patients in Group 1, compared to Group 2, 3, and 4. The age also differed among the groups with a smaller proportion of patients over age of 60 in Group 4, compared to Group 1. Duration of opioid therapy was shorter in Group 3 compared to Group 2.

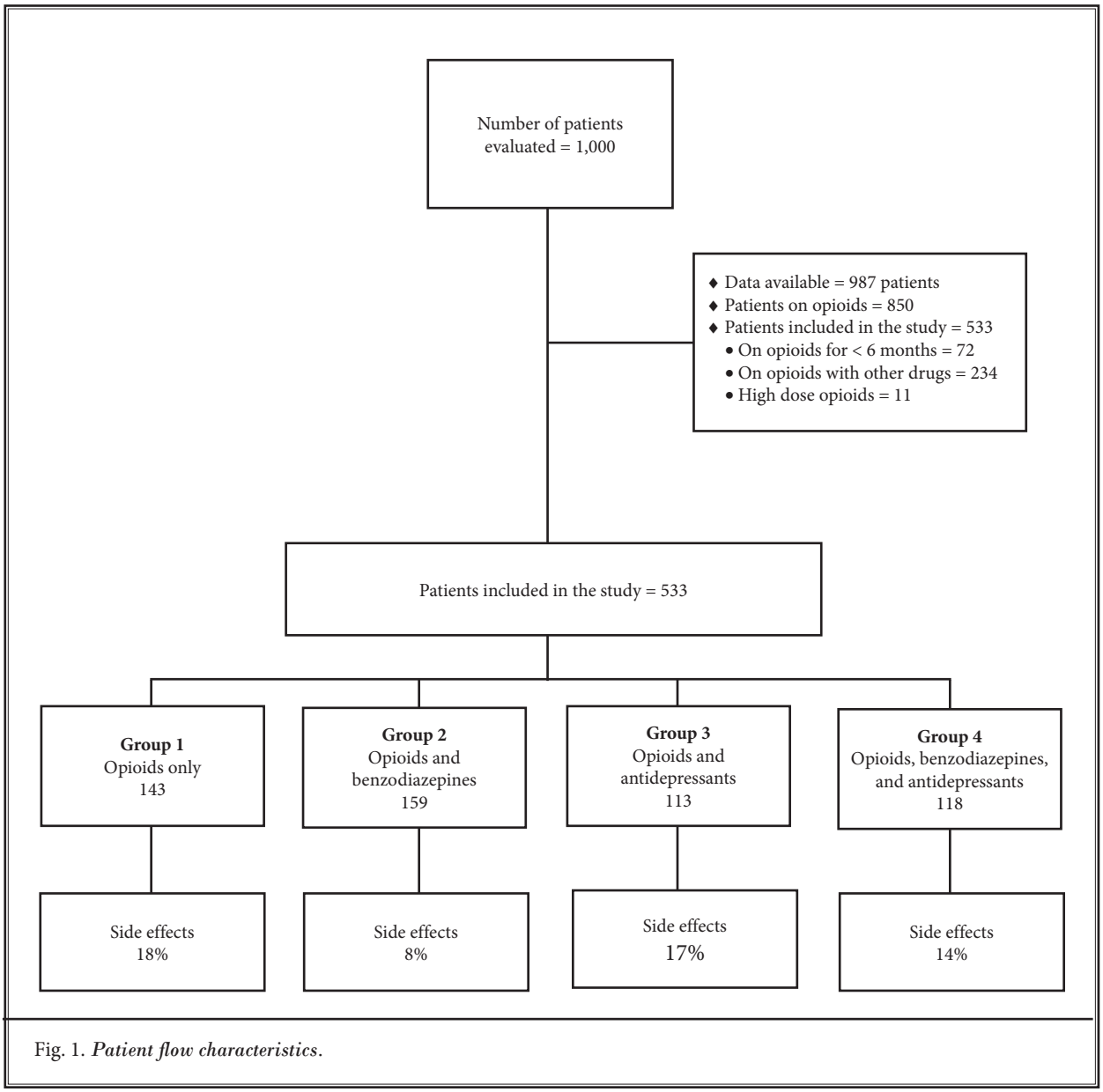

Fig. 1. *Patient flow characteristics.*

Drug Usage Characteristics

Table 2 illustrates characteristics of drug use in the study population. As illustrated in Table 2 opioids were administered to 533 patients with hydrocodone being the most common drug in 77% of the patients followed by methadone in 10%, propoxyphene in 4%, oxycodone in 3%, and morphine in 1.6% of the patients.

Side Effects

A significant proportion of patients were receiving muscle relaxants, antiepileptics, and hypnotics. They were excluded from the study. Some patients were also receiving antihypertensives, which may also influence a side effect profile; however, these patients were in small proportions and were not excluded. Consequently, this evaluation was limited to side ef-

Table 1. *Demographic characteristics of patient population and side effects of opioid drug therapy.*

		Group 1 (143)	Group 2 (159)	Group 3 (113)	Group 4 (118)	Total (533)	*p* value
Gender	Male	57% (81)	43%* (69)	32%*# (36)	28%*# (33)	41% (219)	0.000
	Female	43% (62)	57% (90)	68% (77)	72% (85)	59% (314)	
Age	≤45	31% (44)	31% (49)	30% (34)	36% (43)	32% (170)	0.022
	45 - 60	36% (52)	46% (73)	47% (53)	50% (59)	44% (237)	
	> 61	33% (47)	23% (37)	23% (26)	14%*# (16)	24% (126)	
	Mean ± SD	53 ± 14.7	50 ± 11.8	51 ± 12.3	48* ± 10.8	51 ± 12.6	0.022
Duration of opioid therapy	Mean ± SD	54 ± 29.8	62 ± 28.0	49# ± 29.6	57 ± 27.2	56 ± 28.9	0.002
Prevalence of side effects		18% (26)	8% (13)	17% (19)	14% (16)	14% (74)	0.061

* indicates significant difference with group 1 values
\# indicates significant difference with group 2 values

Group 1 = Patients on opioids only
Group 2 = Patients on opioids and benzodiazepines
Group 3 = Patients on opioids, and antidepressants
Group 4 = Patients on opioids, benzodiazepines, and antidepressants

fects of opioids alone or in combination with benzodiazepines and/or antidepressants. As shown in Table 1, prevalence of side effects were 18% in Group 1, 8% in Group 2, 17% in Group 3, and 14% in Group 4, with an overall rate of 14% with no significant differences noted among the groups. As shown in Table 2, the complication rate was the highest in patients receiving methadone followed by oxycodone, morphine, propoxyphene, and hydrocodone which showed least complications even though it was the most commonly used drug.

There were a total of 137 side effects in 74 patients with 69% or 51 of the patients experiencing one side effect and 31% or 23 experiencing more than one side effect. Table 3 illustrates type and severity of side effects. Constipation was by far the most common complication encompassing 80%, followed by sedation with 15%, dry mouth and fatigue 11%, nausea 9%, cognitive dysfunction 8%, and dreams and peripheral edema in 7% of the patients with all other complications showing an extremely low level prevalence. In addition, the only severe complication was constipation seen in only 14 patients. The most common complications were mild contributing to 64% (87), followed by moderate contributing to 26% (36), and severe contributing to 10% (14) of the 137 incidences.

Table 2. *Opioid use characteristics and prevalence of side effects.*

	Proportion of opioids	Side effects
Hydrocodone	77% (413)	7.5% (31)
Methadone	10% (52)	52% (27)
Propoxyphene	4% (23)	17% (4)
Oxycodone	3% (17)	41% (7)
Morphine	1.6% (11)	36% (4)
Opioids	533	14% (74)

Table 4 illustrates complications and side effects by duration of administration. There was no significant difference noted based on duration of administration of opioids, benzodiazepines, and antidepressants.

Table 5 illustrates side effects by age with no significant differences noted among various age groups. Table 6 illustrates side effects based on gender with no significant differences noted among males and females.

Table 3. *Type and severity of side effects from present opioid drug therapy.*

Side effects	Mild	Moderate	Severe	Proportion of side effects in study population	Proportion of side effects	Proportion of patients with side effects
Constipation	18	27	14	11.1%	43% (59)	80% (59)
Sedation	8	3	0	2.1%	8% (11)	15% (11)
Fatigue	7	1	0	1.5%	6% (8)	11% (8)
Dry mouth	7	1	0	1.5%	6% (8)	11% (8)
Nausea	7	0	0	1.5%	5% (7)	9% (7)
Cognitive dysfunction	6	0	0	1.1%	4% (6)	8% (6)
Dreams	4	1	0	0.9%	4% (5)	7% (5)
Peripheral edema	4	1	0	0.9%	4% (5)	7% (5)
Impotence	4	0	0	0.8%	3% (4)	5% (4)
Ataxia	4	0	0	0.8%	3% (4)	5% (4)
Pruritus	2	1	0	0.6%	2% (3)	4% (3)
Insomnia	3	0	0	0.6%	2% (3)	4% (3)
Hyperactivity	3	0	0	0.6%	2% (3)	4% (3)
Headache	3	0	0	0.6%	2% (3)	4% (3)
Dizziness	1	0	0	0.2%	1% (1)	1% (1)
Anxiety	1	0	0	0.2%	1% (1)	1% (1)
Sluggish	1	0	0	0.2%	1% (1)	1% (1)
Decreased appetite	1	0	0	0.2%	1% (1)	1% (1)
Vomiting	1	0	0	0.2%	1% (1)	1% (1)
Others	2	1	0	0.6%	2% (3)	4% (3)
Total	87	36	14	26% (137/533)	137	14% (74/533)

Table 4. *Side effects by duration of administration of drugs.*

Duration of administration of drugs (yrs)	**Group 1 (143)**	**Group 2 (159)**	**Group 3 (113)**	**Group 4 (118)**	**Total (533)**
1+	20% (6/30)	16% (3/19)	10% (3/30)	18% (3/17)	16% (15/96)
2 - 5	13% (8/60)	6% (4/66)	27% (13/49)	17% (10/60)	15% (35/235)
> 6	23% (12/53)	8% (6/74)	9% (3/34)	7% (3/41)	12% (24/202)
	0.422	0.527	0.673	0.350	0.571

Table 5. *Side effects by age.*

Age (yrs)	**Group 1 (143)**	**Group 2 (159)**	**Group 3 (113)**	**Group 4 (118)**	**Total (533)**
≤45	11% (5/44)	6% (3/49)	24% (8/34)	9% (4/43)	9% (16/170)
46 - 60	21% (11/52)	11% (8/73)	15% (8/53)	15% (9/59)	15% (36/237)
> 60	21% (10/47)	5% (2/37)	27% (7/26)	19% (3/16)	17% (22/126)
	0.370	0.495	0.313	0.555	0.104

Table 6. *Side effects by gender.*

Age (yrs)	Group 1 (143)	Group 2 (159)	Group 3 (113)	Group 4 (118)	Total (533)
Male	22% (18/81)	12% (8/69)	14% (5/36)	18% (6/33)	17% (37/219)
Female	13% (8/62)	6% (5/90)	18% (14/77)	12% (10/85)	12% (37/314)
	0.152	0.168	0.570	0.378	0.093

Discussion

In this study, we evaluated a total of 533 patients receiving opioids or opioids with benzodiazepines, antidepressants, or a combination thereof for over 6 months with low or moderate dose opioid therapy. This sample was derived from 1,000 patients. The patients were characterized into those receiving opioids only (Group 1), opioids and benzodiazepines (Group 2), opioids and antidepressants (Group 3), and opioids, benzodiazepines, and antidepressants (Group 4). Overall, 137 instances of side effects were noted with only 14 cases of constipation being severe. The overall side effect rate was 18% in Group I, 8% in Group II, 17% in Group III, 14% in Group IV with an overall prevalence of side effects of 14% with no significant differences among the patients receiving either opioids alone or in combinations. Constipation was the most common complaint in all the groups, followed by sedation, dry mouth, and fatigue. Only severe constipation required prescription drug therapy. The side effects with opioid therapy in conjunction with interventional pain management, with or without benzodiazepines and antidepressants, are lower than the previous reported rates.

Kalso et al (13) in a systematic review of opioid efficacy and safety described the results of discontinuations and adverse events. Compared to placebo, more patients reported having at least one adverse event (80% versus 60%). They also showed that for every 4 patients treated with opioids, one more would have experienced an adverse event than if they were treated with placebo with a number needed to harm of 4.2 (3.1 to 6.4). They showed a rate of constipation in 41% of the patients, somnolence in 29%, and nausea in 32%, which were most frequently reported with opioids, followed by vomiting in 50% of the patients, dizziness in 20%, and itching in 15%.

The results of this evaluation are different from the side effects described for high dose long-term chronic opioid therapy. No serious side effects were noted in this evaluation. In Kalso et al's (13) systematic review constipation was seen in 41% of the patients. In fact, opioid-induced bowel dysfunction is the most common complaint resulting from the actions of opioids within the gastrointestinal tract (39). However, unlike most other opioid adverse effects, tolerance does not develop with opioid-induced constipation. It is recommended that constipation be treated prophylactically and that all patients on high dose chronic opioid therapy should also have an around-the-clock bowel regimen (40). In the current evaluation, severe constipation requiring therapy was seen in only 14 of 533 patients with a prevalence of 2.6%. Further, none of the patients were on an around-the-clock bowel regimen and only 27 of 533 patients experiencing moderate constipation were taking over-the-counter medication, either a mild bowel stimulant or a stool softener.

In Kalso et al's (13) systematic review somnolence was reported in 29% of the patients. Sedation or somnolence is a commonly encountered central nervous system adverse effect associated with long-term high dose opioid use. However, sedation is typically experienced when opioid therapy is first initiated or when doses are increased. Subsequently patients develop a tolerance to this feature. Often, stimulants such as caffeine dextroamphetamine or methylphenidate are prescribed for opioid induced somnolence or sedation, thus adding another Schedule II drug to the management. In this study, 11 of 533 patients complained of sedation and only one patient complained of sluggishness. None of the patients were provided with any type of stimulants in this evaluation.

Kalso et al (13) reported nausea in 32% of the patients and vomiting in 50% of the patients. Nausea and vomiting may be caused either by opioid-induced bowel dysfunction or by other mechanisms, including

sensitization of the vestibular system or the activation of opioid receptors in the chemoreceptor trigger zone (CTZ) (41). While these effects are often transient in nature and usually subside within a few days following initiation of chronic long-term therapy, they may also be protracted in some patients. Centrally acting antiemetics or metoclopramide have been suggested as treatments for these symptoms of nausea and vomiting. Other recommendations include transdermal scopolamine. In the present study nausea was seen in 7 of 533 patients and vomiting was seen in only one patient, with a prevalence of 0.2% which is lower than the reports with high dose opioid therapy.

Kalso et al's (13) systematic review reported dizziness in 20% of the patients and itching in 15% compared to dizziness in only one patient and itching in only one patient in the present study.

Limitations of this study include the inability to incorporate multiple other drugs due to the complicated nature with multiple groups and data collection and analysis. Even though a significant number of patients were included in each category, the results need to be confirmed in a larger number of patients. Further, this is not a study evaluating the effectiveness of any type of opioids, with or without benzodiazepines and antidepressants, in managing chronic non-cancer pain. In addition, there is no proven evidence of short-acting opioids or interventional techniques providing additive or summating effect.

Even though the evaluation was limited to opioids, benzodiazepines, and antidepressants, it is appropriate as these are the most commonly used drugs. The influence of muscle relaxants, hypnotics, antiepileptics, and various other drugs will be appropriate for evaluation. There is potential for higher doses of opioids to provide additional effect but also increased side effects as shown in the previous studies. Thus, this study is limited only to low dose or moderate dose opioid therapy in only patients who have been on therapy, with or without benzodiazepines and antidepressants, for longer than 6 months. This study also showed a significantly higher proportion of complications, in patients receiving methadone, oxycodone, and morphine as compared to hydrocodone.

Conclusion

The results of this evaluation showed a low prevalence of side effects with low or medium dose long-term opioid therapy, with or without benzodiazepines and/or antidepressants. Thus, it is concluded that long-term low or medium dose opioid therapy with benzodiazepines and/or antidepressants provided in conjunction with interventional techniques is associated with minimal side effects and these side effects are minor. These findings may not be generalizable to high dose long-term opioid therapy. This study has not evaluated the effectiveness of low dose opioid therapy.

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