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Editorial comment

Keeping an open mind: Achieving balance between too liberal and too restrictive prescription of opioids for chronic non-cancer pain: Using a two-edged sword

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In this issue of the *Scandinavian Journal of Pain* a highly respected, internationally known clinical pain researcher discusses his extensive experience with long-term opioid treatment of complex pain patients [1]. Watson describes 10 patients illustrating that, in expert hands, relatively high doses of potent opioids can continue to be beneficial for selected patients for many years without developing tolerance, hyperalgesia, uncontrollable drug-seeking behaviour, or other serious adverse effects [1].

The "hot" topic of opioid therapy for chronic non-cancer pain is increasingly focused on adverse effects and serious complications – from gastrointestinal dysfunction to addiction [2–4]. Most of us, even scientific journal editors [5], suffer from "confirmation bias", in various degrees: It is natural to favour information that confirms our own experience, regardless of whether the information is true [5]. Confirmation-bias prevails also in the pro- and contra-discussion of prolonged opioid-therapy for chronic non-cancer pain. Watson has a point in the title of his paper: The story of five blind men and an elephant [1]!

1. Do we know how to treat chronic non-cancer pain patients with opioids?

Our "evidence-based" knowledge about long-term opioid treatment is limited: Most randomized-controlled-trials (RCTs) on this subject are short-term studies of selected patient groups, lasting from a few days up to 3 months [6]. The longest ever double blind placebo controlled potent opioid study lasted 6 months [7]. Therefore, the recommendations in guidelines on long-term opioid therapy for chronic non-cancer pain are mostly based on weak evidence from "experts' opinions". This is true even for the most recently updated guidelines [8,9].

Almost everybody with some experience agrees that there are patients who obtain meaningful pain relief from stable, low or moderate doses of opioids [3]. Pain intensity may not decrease dramatically, but patients experience a positive "global impression of change" [7], improved mood and quality of life [10]. However, about one-third to one-half of patients who are allowed to remain on long-term opioid therapy discontinue their opioids within a few months because of lack of meaningful effects on their pain or because adverse effects overshadow any beneficial effects on pain intensity [7,11].

The dictum that slow release, long-acting opioids 24 h/day should cause less risk of complications than immediate release and short-acting opioids taken as needed has been a medical "truth" for more than two decades. It was borrowed from management of cancer-related pain in terminal, palliative care where this principle is well established. It is recommended in most guidelines on opioid therapy for chronic non-cancer pain (e.g. [8,9]). However, even this basic rule of opioid-therapy for chronic non-cancer pain is now being challenged [12]: Opioids around the clock result in a higher daily opioid doses compared with a "as needed" dosing regimen [13]. Most adverse effects of opioids are dose-related.

2. Serious adverse effects of long-term opioid therapy

Gastrointestinal dysfunction (nausea and constipation), fatigue, loss of libido, and a number of other unpleasant side effects are common and often reduce the quality of pain relief [11]. Medical use of opioids has increased dramatically during the last two decades in the USA [14], in Canada [15], less so in parts of Europe [16], and Australia. Increases in opioid-related deaths have occurred in parallel with the more liberal prescription of opioids in the USA and Canada [14,15,17]. Problematic opioid use and prescription opioid addiction have increased [2,3,18,19].

3. Iatrogenic problematic opioid use and addiction: rare or frequent complications – depends on definitions

Ballantyne and LaForge describe the definitions of these complications given by the American Pain Society, The American Academy of Pain Medicine, and the American Society of Addiction Medicine [3]:

(1) True addiction is a serious "primary, chronic neuro biologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviours that include one or more of the following:

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impaired control over drug use, compulsive use, continued use despite harm, and craving". They emphasise that *physical dependence* and *tolerance* are not part of the definition of addiction in pain patients on long term opioid therapy because these states are always present, although in varying degrees [3]:

> "*Physical dependence* is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist".
>
> "*Tolerance* is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time".

(2) *Problematic opioid use* is an aberrant behaviour much less serious than true addiction: "Patients who deviate from a prescribed program of opioid treatment can be categorized as patients with problematic opioid use (also sometimes called *opioid misuse*)" [3]. This is problematic opioid-seeking behaviour that does not meet the criteria for opioid addiction. The patient develops patterns of overwhelming focus on opioid issues, early refills, multiple telephone calls and unscheduled clinic visits to request more opioids, lost medication, spilled medication, stolen medication, multi-sourcing [3].

Reported prevalence varies widely, depending on the definition and diagnostic criteria, selection of patients for opioid therapy, and how thoroughly the patients are informed and monitored [3,4]. When some reports conclude that 50% of patients on opioid therapy develop "addiction", they must confuse physical dependence, tolerance, and problematic opioid use with the primary biologic disease *addiction* – see above [2,3]. In our experience about 5–10% of our patients on long term opioid therapy develop *problematic opioid use* [20,21], less than 1–2% develop serious drug seeking behaviour or true addiction [3,20]. Many factors influence the development of these complications of pain management [3,4,22–24]. Some medical doctors who have experienced these serious side effects get "cold feet", destroy their prescription forms for controlled medicines, and thereafter they have an easy excuse for not prescribing opioids at all.

4. Outcome of treatment of iatrogenic opioid addiction

Problematic opioid use can often be handled successfully by information and strict control of the patient's drug regimen. *Addiction* is a serious complication with which most GPs and even pain specialists need assistance from addiction medicine specialists [3].

In experts' hands, outcome of treatment of iatrogenic opioid addiction can be favourable: Annica Rhodin in Torsten Gordh's Pain Centre in Uppsala, Sweden reported that 5 of 60 patients with severe prescription opioid addiction treated in a methadone maintenance program (daily doses of methadone ranged from 10 mg to 350 mg) recovered well enough to be able to go back to work [23]. Unfortunately, 10 of 60 patients failed treatment because of intractable nausea (4), diversion (4), and methadone related cardiac arrhythmia (1) [23]. An impressive 75% had good pain relief, 25% had moderate pain relief, and global quality of life improved in most of the 50 patients continuing in the methadone treatment program [23].

However, we must admit that the treatment of prescription opioid addiction may be difficult, and even unsuccessful, also in experienced hands. Some patients with problematic opioid use started their treatment in situations that were not optimal, and later both the patient and the doctor lost control of the opioid treatment. Often an undiagnosed previous addiction problem, serious mental health problem, or personality disorder can be found when analyzing such patients with "problematic opioid use" [23,24].

5. Red flags for development of problematic opioid use or addiction

When more than "normal" doses – up to about 200 mg morphine equivalents/day are needed to obtain pain relief, Ballantyne [3] and others [4] warn that this is a "red flag". Just escalating the dose does not usually cause more beneficial effects, but it does increase the risk of serious adverse effects [3,18,19]. Many doctors are now afraid of breaching this dose barrier for fear of causing iatrogenic addiction and risking prosecution by drug enforcement authorities. Watson's paper clearly shows that there is not an absolute upper limit of daily opioid dose [1]

6. "Politically correct" practice of opioid-treatment of chronic pain has varied between too strict and too liberal

After a many decades long period with much too strict regulations of opioid prescriptions, the WHO-analgesic ladder for cancer pain in 1986 began the latest area of more liberal regulations of opioids for patients with advance cancer. This liberal prescription of opioid treatment eventually filtered into the treatment of chronic non-cancer pain. Clearly, the pendulum has been swinging too much towards liberal prescription of opioids for chronic non-cancer pain in the USA and Canada [19]. The Drug Enforcement Agency (DEA) in the USA is stepping up their control measures [26]. Opinions of lay people, health policy makers, and drug-enforcement agencies will bring the pendulum back to the restrictive opioid drug regulations we had in our part of the world in the middle of the 20th century unless the prescription of opioids is brought under better control.

It is no longer *comme il faut* to publish case reports indicating that opioid treatment, when well controlled prescribing, even with relatively high doses, can be effective when all other available therapies have failed. In the Nordic countries, Denmark has had a policy of liberal prescription by GPs of opioids for chronic non-cancer pain since the late 1980s. They have seen the unwanted adverse effects of liberal prescriptions and haphazard follow-up of opioid treatment. This is a "prescription for problematic opioid use". Per Sjøgren and co-workers are worried [27].

7. Efforts to bring balance in policies of opioid treatment for chronic non-cancer pain

We believe it is crucial that we do not end up faced with too restrictive opioid regulations and practice. This is bound to deprive those patients who will benefit from opioids of the only therapy that may help them [1,22,25]. We need to be reminded that there are indeed patients who do benefit from opioid therapy when this is performed by experienced pain doctors taking full responsibility for every aspect of the patient's complex health situation [1,18].

We must also avoid the other extreme in which some patients and some doctors in the USA appear to find themselves: too liberal prescription of opioids in uncritically selected patients and, crucially, not following up and/or not monitoring the beneficial as well as unwanted effects of opioids [17]. And not stopping prescription of opioids before the situation deteriorates and the doctor and the patient find themselves in a complex and difficult situation.

8. Opioid therapy for chronic non-cancer pain is a two-edged sword

Thus, we must admit that long term treatment with strong opioids to patients with chronic non-cancer pain really is a two-edged sword. The treatment may go on for decades and some patients continue to benefit from it, without any complications. But for others, opioids create new and serious problems, and unfortunately, the pain is still there. In spite of this they have great difficulties stopping the opioid treatment due to physical dependence causing break-through pain when the opioid dose is reduced, and also due to the opioids' addictive properties. Many in the latter group would probably have done better without the opioid treatment. In reality it is difficult to see beforehand who will benefit and who will develop complications and not benefit. That both outcomes exist, side by side, is obvious for any doctor engaged and experienced in the treatment of this group of patients [17,23,24].

9. Continuous quality improvement of guidelines for opioid treatment of chronic non-cancer pain

Guidelines on how to select patients who may benefit, how to inform the patients of all risks, benefits and responsibilities, and how to prescribe opioid treatment for patients with chronic non-cancer pain conditions have been published by several national and regional pain societies and national medicines agencies. They were all based on weak evidence from expert opinion. These guidelines need continuous quality improvement. Prolonged opioid therapy is not only about renewing prescriptions. It is an ongoing battle in which it is mandatory that the pain relief obtained by the opioid analgesic drug be exploited. The patient must use the periods with less pain to be socially active, perform appropriate physical activities, and resist the temptation to just slumber and waste away the periods with less pain intensity in passive relaxation.

We find that Watson's paper published in this issue of the scientific journal of the *new Scandinavian Association for the Study of Pain* is an important reminder that this complex issue is not simply a question of "for or against" opioid treatment [1]. He emphasises strongly that the quantifiable, regular follow-up of his patients is a prerequisite for effective and safe opioid therapy. It is also an important part of his message that the resources of a multidisciplinary pain centre at a university hospital may be necessary for these most complex chronic pain patients, especially when they need doses higher, even much higher than the "normal" range of morphine equivalents. A single GP in the countryside, even an experienced pain specialist practicing alone, most likely does not have the resources needed when opioid therapy is not straight forward with satisfactory pain relief and increased function and wellbeing using "normal" opioid doses. Watson's ten patients, selected from a larger group of successful long-term opioid treated chronic pain patients [28], illustrate well several different aspects of this challenging problem. We can all learn something from his patients [1].

Suggested updated guidelines for opioid treatment of chronic non-cancer pain must emphasise the following

1. Prolonged treatment with opioids of selected patients with severe chronic non-cancer pain is still medically accepted "good practice".
2. Long term opioid treatment can be undertaken by the patient's GP who knows the patient and his social situation well. Support from organ-disease specialists and a pain-specialist, and even an addiction medicine specialist, must be available when needed.
3. Patients and doctors must be informed and must fully realise, before starting a trial of opioid therapy, that long-term opioid treatment requires considerable effort by both patient and doctor. If this is not possible, opioid treatment will be doomed to failure. All parties involved must be aware of red flags of possible serious adverse effects developing, and they must know what to do when difficulties occur.
4. Qualified resources must be available to handle "problematic prescription opioid use" and the more serious, chronic neuro biological disease "addiction", should these complications arise.

The case report by Watson in this issue of the *Scandinavian Journal of Pain* illustrates well how these issues are well taken care of in an "ideal world" by a pain clinician with knowledge, experience, and wisdom, able to treat successfully with opioids patients with the most complex pain conditions during periods of up to 18 years. Closely monitored opioid-treatment enabled these patients to function well and have an acceptable quality of life [1].

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