Chronic non-cancer-related pain

Long-term treatment with rapid-release and short-acting opioids in the context of misuse and dependency

The annual reports concerning drug prescriptions in Germany—compiled using prescription data from the German Drug Index—show a continual increase in prescriptions of opioids over the past 10 years. In terms of a defined daily dose (DDD), the total number of opioid analgesic prescriptions increased from 190 million DDD to 389 million DDD between 2000 and 2010, thus representing an increase of >100%. In 2012, 138 million DDD of high potency opioids were prescribed. Although fentanyl (particularly transdermal systems) was the most frequently prescribed of these with 60 million DDD in 2010, this represented a relatively stable prescription volume as compared to 2009 (a marginal increase of +0.9%) and prescriptions of morphine were even reduced in comparison to the previous year (-2.5%). A clear increase in the number of prescriptions for oxycodone was observed (+13.7%). The majority of opioid prescriptions were for low potency preparations. Although tramadol prescriptions remained relatively constant, the number of tilidine combination prescriptions increased by 7% as compared to 2009, to a total of 128 million DDD [67].

Interestingly, around 40% of prescriptions for the latter two substances were for rapid-release preparations [21]. Furthermore, relevant discrepancies that could not plausibly be explained by the health insurance structure arose amongst private prescriptions in 2009. In Germany, approximately 85% of the population belongs to a statutory health insurance scheme, which prompts one to assume that around 15% of prescriptions are dispensed to patients who are privately insured. However, the 2009 sales statistics from the pharmaceutical industry show deviations here of +26% for tramadol and +21% for tilidine combinations. For some drugs these deviations are substantial, as in the case of Valorone N® for example, with +40%. At a private health insurance rate of 15%, this could plausibly result in a deviation of 15% [21]. Even if we cannot currently demonstrate that there is no difference between the morbidity rates of statutorily and privately insured patients, these numbers would seem to imply prescription practices that are not in line with the intended use of these substances, thus representing inappropriate use of a relevant portion of them. On the basis of the medication misuse and medication dependency potential of tilidine—including in fixed combination with naloxone, which permits at least oral misuse—as well as the above described prescription data, the discovery of counterfeit prescriptions [42] and the analysis of data concerning adverse side effects, the expert committee of the Federal Institute for Drugs and Medical Devices has ruled that as of January 1, 2013, rapid-release preparations will be completely covered by the regulations governing anesthetics [9].

Analysis of a data sample from the Hessen AOK insurance providers showed that in 2010, 77% of opioid prescriptions were dispensed to patients not diagnosed with cancer. In addition to this, within the 10-year period between 2000 and 2010, a greater increase in opioid DDD was observed amongst patients without cancer than for those with a cancer diagnosis, thus implying an intensification of opioid therapy for non-cancer-related pain [66]. In terms of rapidly effective, non-retarded opioid preparations, a sharp increase in the number of fentanyl administrations can be observed since 2008. In 2012, one third of rapidly effective non-retarded World Health Organization (WHO) level-III opioids were prescribed to patients without a tumor diagnosis [66]. In this context, it is interesting to note that the volume of non-opioid analgesic prescriptions decreased for the first time since 2004 [67].

A similar trend can be observed in other European countries and North America. Hamunen et al. [37] were able to show an increase in opioid prescriptions for the Scandinavian countries between 2002 and
The increase here is mainly due to more prescriptions of fentanyl and oxycodone, while prescription numbers for morphine and low-potency opioids decreased [37, 44]. In the USA, a clear prescriptions increase was observed amongst the long-acting/extended-release opioids between 2000 (9 million prescriptions) and 2000 (23 million prescriptions), as well as for the rapidly effective/non-retarded forms (2000, 165 million prescriptions; 2009, 234 million prescriptions), particularly in the treatment of non-cancer-related pain. A total of 56% of the long-acting/extended-release and 30% of the rapid-release opioids were prescribed for musculoskeletal and myofascial pain [58]. Interpretation of the prescription data leads to the conclusion that marketing strategies must be playing a major role here. There is no adequate evidence for the superior pharmacological characteristics of WHO level-III oral therapy alternatives as compared to morphine that might justify the preferential prescription of some of these substances [79]. One possible exception to this might be the use of rapid-release fentanyl formulations to treat breakthrough pain in cancer patients, where their faster mode of action may render them preferable to orally administered non-retarded morphine [10, 11, 23, 37, 44, 55].

On the basis of a lack of evidence regarding the efficacy of long-term use of opioids to treat patients with chronic non-cancer-related pain, the data concerning prescription numbers must be viewed critically [1]. In recent years, we at the interdisciplinary University Pain Centre in Dresden have seen an increasing number of patients with non-cancer-related pain, who have been incorrectly treated with rapidly effective non-retarded opioids in the past. In the majority of cases, treatment had not been in accordance with the medication’s intended use and an iatrogenic opioid dependency or practice of medication misuse had developed. The aim of this article is to critically discuss this problem in terms of therapy recommendations and the current literature, which the authors do by referring to four example case reports. The terms dependency, dependency syndrome and addiction are used synonymously and refer in each case to the psychological but not the physical dimensions of the condition.

### Case reports

For purposes of diagnosis and therapy planning, each patient underwent an interdisciplinary pain-therapy assessment of both medical and psychotherapeutic parameters (including standardized psychometric tests) upon admission.

#### Case report 1

A 51-year-old male patient was admitted due to pain caused by diabetic polyneuropathy, experienced predominantly in the legs.

#### Diagnosis

- Chronic pain disorder with somatic and psychological factors (ICD-10 F45.41).
- Psychological and behavioral disturbances due to opioids: dependency syndrome (ICD-10 F11.2).

#### Case history and progression

Based on clinical examinations, the results of chemical laboratory tests and the electrophysiological examination encompassing quantitative sensory testing, we were able to confirm diagnosis of a diabetic polyneuropathy with high level impairment of all sensory qualities. The patient complained of a burning pain in both feet and the permanent sensation of wearing shoes that are too tight. Based on a numerical analog scale (NAS; 0, no pain; 10, most intense pain imaginable), the patient rated the pain as 4–6. The pain had been experienced for approximately 5 years. Particularly apparent was the patient’s severely reduced ability to differentiate between physical and psychological pressure, especially in the context of a demanding occupation. Depending on the context, the level of pain increased in highly stressful situations.

At the time of admission, the medication-based pain management therapy comprised administration of tilidine/naloxone drops at a non-quantified dosage, usually “1 dessertspoonful”, 3–5 times a day. At night, the patient took 900–1200 mg pregabalin in combination with 7.5 mg zopiclone. The patient needed this medication “to relax” and counter sleep disturbances.

As part of an extra-occupational, multi-modal out-patient pain management therapy, the patient was initially sensitized for psychophysical correlations related to stress and the experience of pain. It was possible to motivate the patient to alter the inappropriate stress regulation and also to instill recognition of opioid dependency and medication misuse. As treatment progressed, the pregabalin dose was reduced to 600 mg/day and the patient stopped taking zopiclone completely. An attempt to substitute the tilidine drops with a slow-release preparation was unsuccessful and thus followed up by dependence-specific stationary re-
habilitation. During rehabilitation, the tilidine dosage was successfully reduced to 15 drops taken 3 times a day (total daily dose, approximately 112.5 mg). Additionally, a daily dose of up to 75 mg amitriptyline was prescribed. Despite controlled prescription, the tilidine dosage increased to 30 drops taken 4 times daily (total daily dose, approximately 300 mg) following stationary rehabilitation. A further period of stationary rehabilitation was thus planned.

Conclusion
As a result of the long-term complications of diabetes mellitus, the patient developed neuropathic pain and subsequently a chronic pain disorder with somatic and psychological attributes. Inappropriate approaches to pain management within the context of a demanding lifestyle, physical over-exertion and inappropriate stress regulation led to further intensification of the condition. The consequences of this were an increase in pain intensity, dysphoria and insomnia.

The primarily monocausally oriented and exclusively medication-based pain management therapy must be considered to have fostered chronicification. The continuous prescription of the benzodiazepine-like drug zopiclone did not conform to the intended application of this medication. The combination therapy comprising co-administration of an analgesic and an opioid appeared to be in line with recommendations for the treatment of neuropathic pain, but this was then followed-up by an inappropriate long-term treatment using tilidine drops. As a consequence of the inappropriate management approach, the patient began to misuse the combined medication, characterized particularly by an increase in tilidine and pregabalin use to a level exceeding the prescribed dose. The suggestion that the pharmacological mode of action of pregabalin could potentially lead to substance dependency is supported by early case reports [3]. In terms of opioid administration, medication dependency was manifested by a strong desire to consume the substance to keep withdrawal symptoms and dysphoria at bay, as well as to manage stress. The dependency disorder thus has to be considered iatrogenic and understood to have caused complications in the treatment course, which in turn generated considerable costs in the form of secondary therapies.

Case report 2
A 52-year-old male patient was admitted due to opioid misuse and persistent headache.

Diagnosis
- Headache in the setting of medication overuse (opioid; ICD-10 G44.4)
- Psychological and behavioral disturbances due to opioids: dependency syndrome (ICD-10 F11.2; Tab. 1)
- Harmful misuse of nonaddictive substances: analgesics (ICD-10 F55.2)
- Chronic pain disorder with somatic and psychological factors (ICD-10 F45.41)
- Migraine without aura (ICD-10 G43.0)
- Chronic pain in both knees following arthrodesis of the left knee joint and total prosthetic replacement of the right knee joint (ICD-10 M25.56, Z98.1, Z96.6)
Case history and course
The patient had suffered from headaches since childhood. The pain, described as ranging from aching to throbbing, was frontotemporal and bilateral. The intensity of the pain was rated as NAS 10. A headache usually lasted 12–24 h. The headaches were intensified by physical activity and associated with sensitivity to light. Physical activity, stress and weather influences were reported as triggering factors in the onset of pain. In addition to medication, physical relaxation in a darkened room helped to ease the pain. The headaches fulfilled the diagnostic criteria for a migraine without aura and a symptomat- ic cause was ruled out at an early stage. In addition to the headaches, the patient al- so suffered from multilocular joint pain— particularly in the knees—as a conse- quence of recurrent hemorrhages resulting from a blood disorder.

Due to the pain, the patient had fre- quently been given painkillers as a child and the frequency of this practice in- creased during adolescence. This medica- tion often comprised mixed analgesic preparations. Medication misuse was al- ready evident at this stage and the recom- mended single and maximum daily dos- es were sometimes substantially exceeded. Approximately 10 years previously, the pa- tient was prescribed tilidine drops, which were then preferentially taken to combat the pain caused by headaches. As time progressed, an advanced dose escalation was observed: Upon admission, the pa- tient was taking an average of 200 drops, 4 times daily (total dose, approximately 2000 mg). Prescriptions were made out by up to three different physicians from various departments. The patient gener- ally took the medication in a pain-inde- pendent manner and in stress situations. During short intermittent periods of absti- nence, the patient suffered no physical withdrawal symptoms.

During treatment, the patient ac- knowledged the existence of an opioid de- pendency and made the co-treating phy- sicians aware of the incidence of multiple prescriptions. This resulted in controlled prescriptions being issued exclusively by a single department. In the context of a sta- tionary dependency-specific treatment, the well-motivated patient successfully ac- complished complete opioid withdrawal.

Conclusion
Treatment of the patient with opioids was inappropriate, as these are not recom- mended for the therapy of primary head- ache disorders. Furthermore, a potential- ly dependency-inducing, rapidly effec- tive non-retarded tilidine/naloxone prepar- ation was prescribed to be taken as re- quired. On the basis of a history of anal- gesic misuse prior to opioid therapy, this must be viewed particularly critically. During the course of this long-term and increasingly chronic disorder, the consequent single-approach therapy led to a continuum of medication misuse and re- sultant dependency. The situation was ex- acerbated by dysfunctional management systems that were continuously adhered to and an inadequate appreciation of in- dividual tolerance levels.

Case report 3
A 30-year-old female patient was admit- ted for assessment of medication-based therapy used to treat recurrent abdomi- nal pain.

Diagnosis
- Recurrent abdominal pain due to ul- cerative colitis (ICD-10 R16.4/K51.8) and as a consequence of multiple ab- dominal surgical procedures
- Chronic pain disorder with somat- ic and psychological factors (ICD-10 F45.41)
- Psychological and behavioral distur- bances due to opioids: dependency syndrome (ICD-10 F11.2)
- Psychological and behavioral distur- bances due to sedatives and hypnot- ics (benzodiazepine): substance abuse (ICD-10 F13.1)
- Psychological and behavioral distur- bances due to other stimulants (amp- hetamine): substance abuse (ICD-10 F13.1)

Case history and course
Owing to severe therapy-resistant ulcer- ative colitis, the patient had undergone multiple laparotomies in the past. The pa- tient was unable to make any statements concerning the pre-operative complaints experienced at that time or the peri- and post-operative progression of the condi- tion. The patient was also unable to pro- vide any information regarding the strate- gies employed to manage the disorder and reported only on a period of depression approximately 15 years previously. The patient underwent psychotherapy at that time, but was unable to comment on ei- ther the aspects or outcome of this ther- apy. Since mid 2010, the patient had re- peatedly experienced attacks of abdomi- nal pain several times a week. Paramed- ic treatment and subsequent admission to hospital had been necessary in every in- stance.

To treat the pain, the patient was ad- ministered tramadol intravenously. Treat- ment using transdermal fentanyl at a dos- age of 12.5 µg/h was not tolerated due to side effects (nausea and drowsiness). Fur- ther surgery to treat the primary disorder was performed in 2011, whereby the post- inpatient pain therapy comprised subcu- taneous injections of 10 mg oxycodone solu- tion to be given as required.

Due to persistent cramp-like stom- ach pains with alternating localizations, an outpatient pain management thera- py was devised. The pain was described as beginning suddenly and progressing to reach a crescendo (NAS 10). Occasion- ally the pain also radiated into the patient’s back. The patient was unable to pinpoint factors that increased or diminished the pain. The pain attacks occurred up to twice daily, and were also experienced in the night approximately twice a week. The duration of the attacks could not be defined because the patient injected oxycodone as soon as they began. No corre- lations between the attacks and eating or bowel movements were observed. When questioned as to possible explanations for the pain attacks, the patient referred to comments made by a pre-operative phy- sician who claimed that the pain arose “as soon as the bowel filled”. This was “of lit- tle help” to the patient, who gave the re- mark no further consideration. The pa- tient showed little emotion in dealing with the condition and generally sought to re- press and deny it: no attempt was made to address previous surgical interventions and their consequences, or the special as-
pects of nutrition and physical impairments resulting from the chronic disorder. As well as simply wanting to appear “normal”, the patient could not afford to take any more long-term absences from work and had a son to take care of. On the other hand, the patient spoke of disease-related fears concerning another intestinal obstruction, prolonged phases of disease with sick leave and further advancement of physical impairments. The patient had “always” suffered from bouts of insomnia, plagued by thoughts about “how to go on”. Psychometric analysis and psychological exploration indicated the development of depression. Upon admission, the patient required up to three 10-mg injections of oxycodone a day. Immediately following injection, the patient was relieved of pain and “freed” of dysphoria. The patient was aware of the existence of a medication dependency. Prior attempts at unassisted withdrawal had been unsuccessful and the patient expressed a great fear of inpatient dependency therapy.

Together with the patient’s physician, controlled medication prescription measures were implemented and the patient was motivated to undertake inpatient withdrawal therapy. The patient also made contact with a dependency counseling service. Despite this, a massive dose escalation was observed, to the extent that the patient required 8–10 ampules a day. In this context, the patient attested to intermittent symptoms of respiratory depression. Upon consultation with the dispensing pharmacy, it became apparent that the patient had been obtaining prescriptions from multiple physicians. Consequently, the patient was promptly admitted for inpatient dependency therapy. Drug screening indicated illegal co-consumption of benzodiazepines and amphetamines. Despite successful withdrawal, renewed prescription of oxycodone injection solution was ordered by an outpatient physician shortly following discharge. A course of pain management therapy in a specialist institution was discontinued by the patient.

**Conclusion**

This case once again highlights the problems resulting from a single-approach treatment of a complex chronic pain disorder. Psychosocial factors contributing to instigating and prolonging the pain were completely ignored. At no stage was an attempt made to improve the patient’s acceptance of the disease and no disease-management strategies were discussed. In this context, prescription of opioids in a form with a high potential to cause dependency has to be considered as extremely problematic. Not only did this result in the rash development of dependency, but undesirable effects of the medication also put the patient’s life at risk from an opioid overdose. Evidence for co-consumption of illegal drugs further underlines the impact that pre-existing psychosocial issues can have on the problem as a whole.

**Case report 4**

A 66-year-old female patient was admitted for the assessment of medication-based therapy used to treat chronic anorectal pain syndrome.

**Diagnosis**

- Chronic anorectal pain syndrome (ICD-10 K62.9) in the context of a long-term somatoform pain disorder
- Psychological and behavioral disturbances due to opioids: dependency syndrome (ICD-10 F11.2)
- Psychological and behavioral disturbances due to sedatives and hypnotics (benzodiazepine): substance abuse (ICD-10 F13.1)

**Case history and course**

The patient underwent total hysterectomy during the 1990s. The complications that arose necessitated further laparotomies in the follow-up period. Anal pain was first experienced approximately 3 years after the previous surgical intervention. The pain was localized to a quadratic region between about three and six o’clock in the lithotomy position. The localization, nature and intensity of the pain had remained unchanged since that time. Pain was constant, with an intensity of NAS 4 under continued medication. Without medication, the pain had an intensity of NAS 10. The pain was described as burning, throbbing and stabbing. Pain of the same nature also radiated into the vaginal area with the same intensity.

Several colorectal surgical interventions were carried out but did not provide any relief from symptoms. The condition was classified as neuropathic pain syndrome. The patient was predominantly dependent on constant medication to modulate the pain; sitting, defecation and weather changes enhanced it, whereas distraction (work, television) brought some relief. The medication-based therapy ultimately comprised oral transmucosal fentanyl citrate (OTFC, 1600 µg) to be taken as required, up to a maximum daily dose of 20 lozenges. This medication was only taken during the day, between getting up and going to bed. The sedative triazolam (0.25 mg) ensured that the patient was symptom-free at night.

OTFC had been prescribed for many years. At the start of therapy, a single dose comprised 400–600 µg but tolerance developed rapidly, leading to a dose escalation and a reduction in the interval between doses. An intermittent reduction in OTFC dosage at the patient’s request resulted in renewed unbearable pain and administration of morphine drops (as required; maximally 400 mg/day). Other opioids (tilidine/naloxone, hydromorphone and oxycodone), as well as various non-opioids and co-analgesics were prescribed in extended-release and rapidly effective non-retarded forms; however, none of these achieved an acceptable level of pain relief. Subsequent therapeutic approaches tried out over the years included analgesic infusions and further invasive procedures, as well as medication-free techniques and physiotherapy. Since none of these treatments achieved long-term pain relief, OTFC treatment was restarted.

No lesion of the somatosensory system had ever been identified in connection with the numerous surgical interventions undergone by the patient recently or in the more distant past. The authors were thus unable to confirm the diagnosis of chronic neuropathic pain [75]. Despite numerous unsatisfactory treatment outcomes, an intensive psychological diagnosis had never been performed. This could have contributed considerably to an appropriate choice of therapy by identifying the factors responsible for causing and prolonging the disease. The potentially
relevant factors defined by psychological evaluation included: the patient’s childhood and adolescence spent in a primarily performance-orientated environment; marked avoidance behavior and the negative impact that the disease and its treatment—which the patient had found traumatic—had had on the patient’s life. Consequently, additional pain then developed within the context of a long-term somatoform pain disorder. This pain was at least in part prolonged by the purely somatic management therapies that were employed to manage it. In this context, the patient’s OTFC consumption could be viewed as a strategy to enable pursuit of an over-active lifestyle in order to avoid addressing the psychologically painful aspects of previous life history.

Discussion

During the entire disease course, diagnosis and pain management therapy were once again geared toward a single, exclusively somatic approach. Psychological risk factors were ignored. Opioid-based therapy using OTFC is not intended or appropriate for the treatment of long-term somatoform pain disorders. The patient developed a strong opioid dependency, which, in light of psychological factors and the persistently somatic medical strategies, played a significant role in the further intensification of the pain disorder.

Estimations of the prevalence of medication dependency within the normal German population range from 1.4 to 1.9 million affected individuals. In the majority of cases, the medication concerned is a psychotropic drug or an opioid [21, 69]. According to the results of the 2009 epidemiological dependency survey, painkillers represent the type of medication most frequently taken (usage prevalence, 61.6%). Over a 12-month period, problematic painkiller usage could be identified in 6.2% of cases [54].

On the one hand, these statistics do not allow any definite conclusions to be drawn regarding opioid dependency or misuse in the context of chronic pain management therapy. On the other, the fact that no adequately reliable national or international epidemiological data on the frequency of either disorder within pain management therapy exists should not provide grounds to assume that these problems are of no relevance in daily practice. The four examples discussed here highlight the need to raise awareness to the uncritical and unintended use of opioids in relation to harmful medication misuse and the development of dependency. The “Medication: misuse and dependency” section of the German Medical Association’s guidelines deals thoroughly with the spectrum of topics this touches upon. On the basis of their potential to cause dependency, these guidelines warn against the “ill-considered prescription of opioids for unexplained pain”. In this context, it should also be noted that an exclusively medication-oriented management therapy can not only lead to chronicization of the condition, but also be dependency-promoting [2, 49].

Diagnosing opioid dependency

Further problems are encountered with the terminology and operationalization of opioid dependency in the context of pain management therapy. It is important to distinguish between the diagnoses of harmful opioid misuse (synonym, abuse, ICD-10 F11.1) and dependency syndrome (synonym, addictive disorder, ICD-10 F11.2; [24, 25]). Both disorders are associated with aberrant drug-related behavior in relation to substance consumption and procurement. Amongst other things, this is characterized by: aggressive demands for increased doses or rapid-release preparations; noncompliance with the instructions for administration, including unauthorized dosage increases; alternative methods of application; frequent prescription loss; falsified prescriptions or premature demand for repeat prescriptions; multiple prescriptions from several physicians; as well as by concomitant use of other psychotropic substances [40].

Ballantyne and LaForgue [5] view medication misuse and dependency as both the start and the endpoint of a continuum. They recognize and criticize the fact that diagnostic differentiation between these two disorders can be problematic due to bad operationalization. In this context, they refer to the behavioral pattern amongst illegal-drug user, whereby a full-blown addiction disorder usually develops as a consequence of sporadic drug abuse. In the context of pain management therapy, the initiation and perpetuation of medication misuse does not lie in the hands of the patient, but in the hands of the prescribing physician [41]. All four case reports support this assumption.

In contrast to medication misuse, a dependency syndrome is defined as a chronic disease determined by genetic, neurological, psychosocial and environmental factors, as part of which continued substance use produces a “pleasant” modification of emotions [5, 38, 40, 65]. Three or more of the six criteria for opioid dependency (ICD-10 F11.2; Tab. 1) should have been met for at least 1 month. Since even a state-of-the-art opioid-based pain management therapy can result in withdrawal symptoms or tolerance development in the context of physical dependen-
cy, these criteria ( Tab. 1, points 3 and 4) are unsuitable for the diagnosis of iatrogenic opioid dependency. They are also not necessary for the diagnosis of dependency, as fulfillment of the other four criteria is sufficient. The essential characteristic of an addiction disorder is the compulsion to consume the substance. This does not mean, however, that discontinuing opioid consumption will necessarily lead to the onset of withdrawal symptoms [5, 24, 40, 65].

Incidence of misuse and dependency

Fishbain et al. [32] calculate the incidence of opioid misuse and dependency in the context of long-term treatment of chronic non-cancer-related pain patients to be 3.27%. A Cochrane review published in 2010 assumed an incidence of 0.1–0.3% [52]. However, this review deals with a highly selective patient population; groups at risk from misuse and dependency were excluded. Additionally, these patients were generally given long-acting and slow-release opioids. Owing to the short follow-up period, the relationship between duration of opioid consumption and dose, as well as its influence on the development of dependency remains unclear. Although it can safely be assumed that the risk of medication misuse and dependency is low amongst a well-selected group of patients, the development of these conditions is not treated as an “adverse event” in controlled studies [12, 32]. In a retrospective analysis of medication dependency amongst patients in primary medical care in Wisconsin, the frequency of opioid dependency was 3.8% [33] and thus comparable with the results of Fishbain et al. [32]. Even though the broad cross-sectional experimental design precludes definitive distinction between an opioid dependency that developed in the context of therapy and a pre-existing condition, the calculated value is still 4 times higher than in the general population. Medication dependency also correlated with a higher incidence of co-consumption of illegal drugs (24%; see Case report 3). Additional risk factors included young age and the presence of comorbidities. The most important predictive factor for risk estimation in terms of dependency development was identified as “aberrant drug-related behavior”. This is in agreement with the assumptions made by Ballantyne et al. [5] discussed above and demonstrated by the case reports [33].

Long-term opioid therapy

Various national recommendations on long-term opioid therapy are based on a lack of reproducible data concerning the efficacy of these substances for clinically relevant, long-term pain relief. Particularly evident is the lack of data relating to the pharmacokinetics of these substances and a risk stratification to avoid misuse and dependency [1, 16, 34]. The criticism of American and Canadian guidelines contained in a Chou editorial refers to the fact that the majority of recommendations are not based on reliable clinical studies [13]. The German S3 guideline LONTS recommends “preferred use of opioids with targeted galenics or those which are long-acting, as well as adherence to a therapeutic time scheme that corresponds to the duration of the pharmacological activity of these substances” [1]. Prescribing a medication to be used as required for pain attacks that can be plausibly explained by the case history or nature of the disease and are not due to an error in medication dosage, is at the discretion of the physician in the individual case [1, 61]. On the basis of a lack of evidence, the American guidelines mentioned above also contain only a minor recommendation for the use of rapid-release, fast-acting opioids to manage tumor breakthrough pain. The potential for medication misuse or development of dependency is viewed as a risk of such interventions [16].

As highlighted by the clinical experiences of the four case reports, long-term treatment of chronic pain with rapid-release and short-acting opioids can be problematic. Owing to the neurological mechanisms responsible for the development of addiction, pharmacologically active substances with kinetics and modes of application that produce a rapid and strong effect are characterized by a particularly high risk of causing medication misuse and development of dependency [5, 38, 62, 64]. It is thus all the more surprising that these findings clearly receive inadequate consideration in clinical practice. The currently available evidence does not allow conclusions to be drawn regarding differences between the effects and side effects of short- and long-acting opioids. However, the studies that have addressed this issue have had significant shortfalls in their methodology: development of medication dependency was not investigated and the maximal study duration of 30 days appears too short—even on the basis of a non-proven assumption that medication misuse usually begins with commencement of therapy [15, 57].

Fine et al. observed advantages in the individual tailoring of chronic non-cancer-related pain therapy conferred by administering long-acting opioids in accordance with a time contingent in combination with short-acting preparations. The results demonstrated an improvement in everyday life and a reduction in the degree of disability caused by disease [29]. However, these conclusions are in no way backed-up by argumentation. The case reports presented here could be used to argue the standpoint that such moncausal therapeutic strategies condition patients for medication misuse and resultant dependency [5, 19, 38]. The potential risk represented by rapid-release, short-acting opioids in terms of addictive potential has not been addressed at all. The issue is highlighted to only a limited extent by global indications of a necessity to assess patients for addiction and medication misuse disorders that existed prior to disease [29].

As described above, clinical studies do not usually treat development of dependency in the context of opioid therapy as an outcome criterion. Furthermore, no suitable predictors for operationalization and risk stratification regarding medication misuse are available. This is particularly true for opioid therapy planned in the context of a prior medication dependency, and also during dose titration phases and monitoring of long-term treatment. Last but not least, there is no standardized definition of medication misuse in the context of opioid therapy [14, 17]. Future studies are needed to address not only the long-term efficacy and safety of opioid therapy, but also patients’ quality...
of life, possible complications (with particular reference to emergency treatment) and socioeconomic outcome parameters. The latter factor relates to improvement in quality of life and direct and indirect health costs [12]. The feasibility of such studies within the framework of predominantly industry-financed research remains to be seen [8].

On the basis of the potentially addictive nature of these substances, the German, American and Canadian guidelines cited above all recommend that a benefit vs. risk assessment is carried out before initiating opioid therapy. This is especially important for patients with a pre-existing psychological disorder, including addictive disorders, or who show indications of medication misuse in their case history [1, 16, 34]. As we have demonstrated using case reports, these recommendations clearly receive little attention on a routine clinical basis. At least for North America, there are now reliable data showing that psychological disorders (phobic disorders, depression and dependency disorders), which often accompany pain, are valuable predictors to be considered before initiating opioid therapy for chronic non-cancer-related pain [71]. By analyzing insurance data, Weisner et al. [77] were able to show that patients with a previous history of substance misuse (medication or illegal drugs) generally received higher potency opioids in higher doses. In addition to an uncritical prescriptions practice, this also highlights the absence of a thorough assessment before commencement of therapy and a lack of interdisciplinary communication, since many of these patients had already undergone dependency-specific therapy [27]. A data sample taken from patients beginning a rehabilitation program who had a poor psychological health status and chronic pain showed that medication misuse and dependency had developed as a consequence of routine opioid prescription. A continuum of alcohol and drug abuse in the patients’ case histories was ignored in the run-up to therapy [18], although these are important predictive factors for medication misuse during opioid therapy [39, 51]. In the context of poor psychological health—particularly in the case of phobic disorders and disease accompanied by substance abuse—misuse involved alternative, non-intended methods of application (such as snorting or injection) to achieve rapid release [56]. Thus a patient group that was a priori excluded from studies on opioid therapy for chronic non-cancer-related pain was treated in a manner that did not conform to guidelines [14]. It remains unclear whether these patients were being treated for pain or their psychological symptoms [70].

Complications of opioid therapy

As highlighted by case report 3, a further problem arising from the increases in opioid prescriptions is the risk of overdose, which can be fatal [12]. Doses of ≥100 mg morphine equivalent were shown to be associated with a 9-fold increase in the risk of overdose [26]. Figures for the US attest to more deaths resulting from prescribed opioids than from illegal drug use (cocaine and heroin; [23, 74]). Amongst other determining factors, this is related to non-medical use of prescribed opioids and consumption by non-intended third parties [6, 8, 35]. The risk of fatal overdose became a focus of attention following the appearance of slow-release oxycodone on the market [22, 36]. Although the absolute risk was low, Bohnert et al. [7] demonstrated a strong correlation between high opioid doses (>100 mg morphine equivalent per day) and death rates. Despite the obvious increase in this fatal complication, it is difficult to prove a causal relationship in terms of treatment errors. Many patients, however, are at a retrospectively increased risk of misusing medication [53, 75].

These problems underline the practical necessity and vital importance of an interdisciplinary assessment prior to initiating opioid therapy in the context of chronic non-cancer-related pain treatment. This consensus has now been reached in both the literature and the guidelines [1, 16, 18, 29, 34, 55]. How monitoring measures such as those employed in drug substitution programs [23] with small prescriptions and regular urine tests [45, 55], or greater transparency in the prescription of high-dosage opioids will reduce medication misuse remains to be seen [48].

Does chronic non-cancer-related “breakthrough” pain exist?

Case report 4 describes the development of a severe opioid dependency associated with treatment using a rapid-release, short-acting fentanyl formulation. The strong controversy surrounding the concept of breakthrough pain in chronic non-cancer-related pain in recent years [46, 59, 63, 72] is clearly linked to the appearance of these application forms on the market. Within a highly selected sample of patients with widely varying chronic pain disorders, Portenoy et al. found a 74% incidence of breakthrough pain. This value is comparable to that for cancer-related pain patients in advanced stages of disease. It must be noted, however, that these data were collected retrospectively in telephone interviews using a non-validated questionnaire [59].

The lack of methodology in the aforementioned study throws the results into question. At this point it should also be mentioned that the imprecisely defined term “breakthrough pain” has hitherto been used exclusively in relation to cancer-related pain and refers to a temporary exacerbation of a base-level pain that is otherwise stable and adequately controlled [50]. Simply extending the concept of breakthrough pain to non-cancer-related pain does not appear to be justified [12, 46]. Advanced stages of cancer are usually characterized by severe symptoms. Cancer-related breakthrough pain stands in direct etiologic relationship to the base-level pain. It should be clearly distinguishable as a separate physical correlate, although its perception is clearly subject to individual or context-dependent modulation. In contrast to this, for a large proportion on non-cancer-related pain, no direct relationship between the underlying lesion and the symptoms or the impairments produced by pain can be identified. Far more common here is the maintenance of disease by psychological comorbidities and social factors. Based on the current definition, therefore, it is not possible to precisely define which physical or psychological symptoms of non-cancer-related pain are being treated as “breakthrough pain” using potentially dependency-inducing medication.
Current recommendations concerning opioid therapy for cancer-related pain consistently call for basic opioid-therapy medication to be complemented by the prescription of a rapid-release opioid preparation that can be administered orally, transmucosally or nasally as required, to combat breakthrough pain [10, 20, 79]. In our opinion, this alone defines the current therapeutic significance of the corresponding fentanyl preparations for the treatment of chronic pain. Indeed, this is the only usage of these formulations that has been approved in Germany. In light of the lack of evidence concerning long-term efficacy and possible undesirable effects—particularly in terms of their presumed potential to induce dependency—we do not consider the off-label use of these substances to treat chronic not-cancer-related pain to be justifiable.

A series of industry-financed studies of almost identical design investigated the effectiveness of buccal fentanyl to treat breakthrough pain in opioid-tolerant patients with chronic dorsal and chronic neuropathic pain [60, 68]. In further studies, patients with the most diverse non-cancer-related pain disorders—including dorsal and neuropathic pain, as well as unspcific musculoskeletal and myofascial pain syndromes such as fibromyalgia—were also considered in the analysis [4, 28, 30]. Investigation of such a heterogeneous collective, without detailing aspects such as pain duration, intensification of the condition over time and co-morbidities has to be deemed highly questionable. For at least a proportion of these disorders, opioid treatment may not even be approved. Referring to its rapid action and good tolerability, these studies unanimously state that carefully titrated buccal fentanyl is suitable for the treatment of breakthrough pain in chronic pain disorder patients [28, 60, 68]. Fine et al. [31] comment on and confirm these results in a review, but also point out the need for careful patient selection and monitoring, including weighing up of the benefits vs. risks in relation to misuse, dependency and non-medical use of these substances. Irrespective of this, these studies have serious shortcomings in their methodologies. In most instances, the period of observation is limited to between 3 weeks and a maximum of 3 months. “Breakthrough pain” was defined as a transient increase in the “stable” pain that was already being managed with opioids. Considering the complexity involved in the perception of chronic pain, this simplified definition does not seem to be justifiable. This presumption is supported by the remarkably high drop-out rate during the titration phase, which points to a lack of effectiveness of the substance. The average duration of pain was also unknown. Patients with a history of addiction and psychological disorders were excluded from the study. One study, however, included opioid-tolerant patients, 42% of which had suffered from a phobic disorder in the past. Correspondingly, the primary outcome parameter of this study was pain-related anxiety as measured using the Pain Anxiety Symptoms Scale [76]. In a retrospective analysis of data from five studies, Passik et al. [57] evaluated “aberrant drug-related behavior” associated with buccal fentanyl. Aberrant behavior is taken as an indication of loss of control and medication misuse or dependency. Amongst other things, it is defined as the prohibited passing on of medication to a third person, prescription falsification, simultaneous consumption of alcohol and illegal drugs and repeated unauthorized dosage increases. Although patients with a history of alcohol or drug misuse were excluded from all studies, 11% of the included patients demonstrated aberrant drug behavior that was associated with the buccal fentanyl under investigation. The most commonly reported problems included unauthorized dose escalation (5%) and medication theft (4%). The risk of aberrant drug behavior was independent of therapy duration [57]. It should be noted, however, that this was a retrospective analysis of a highly selected patient collective and that this aspect calls for a defined prospective study with appropriate methods of assessment in the future.

Careful patient selection on the basis of an interdisciplinary assessment, as well as appropriate monitoring programs can also minimize the risk of medication misuse and dependency. A Risk Evaluation and Mitigation Strategy for opioids has been implemented in the US by the Food and Drug Administration (FDA). This concentrates mainly on specific training for physicians who prescribe opioids and supplementary information for patients. A physician’s participation in the program is currently voluntary, but will soon become mandatory for all physicians prescribing strong opioids [58]. However, it is still questionable whether these types of demands and risk-mitigation programs are in any way feasible or effective in the current reality of clinical care, particularly considering the unsatisfactory definition of the concept of breakthrough pain in chronic non-cancer-related. Furthermore, the importance of the individual features of a patient’s condition for the accurate assessment of risk in terms of the development of tolerance, misuse and dependency in the context of a long-term opioid therapy is unclear [5]. A high prevalence (up to 25%) of medication misuse in connection with prior or current substance-specific disorders was observed amongst patients with chronic dorsal pain undergoing opioid treatment, [47]. Even though differentiation between iatrogenic and pre-existing opioid dependency was difficult using this data, these analyses support maintaining a critical standpoint concerning the widespread use of rapid-release, fast-acting fentanyl formulations to treat chronic non-cancer-related pain.

It should not go without mention that a large increase in the number of medical emergencies resulting from opioid consumption was seen in the US between 1994 and 2002. These figures are considered to be indicators of misuse, dependency and non-medical usage. In the case of fentanyl, a 7-fold increase in prescriptions during this period was accompanied by a 50-fold increase in the number of medical emergencies [19]. This can be considered a very clear indicator for the misuse and dependency potential of this substance. As described above, the use of rapid-release, short-acting fentanyl preparations to treat chronic non-cancer-related breakthrough pain could lead to the development of maladaptive management strategies via operant conditioning. This in turn would serve to promote medication misuse and dependency [19].
Conclusions and practical recommendations

- Despite the absence of data on the long-term treatment of chronic non-cancer-related pain using opioids, a rapid increase in prescription volume has been seen in recent years.

- There are indications that opioids are being used inappropriately in therapeutic strategies and that the incidence of undesirable effects such as misuse and dependency is on the increase.

- The use of rapid-release and short-acting opioid preparations can promote opioid misuse and dependency.

- Treating chronic non-cancer-related pain with the relevant preparations can therefore not be recommended on the basis of current knowledge.

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References


