REVIEW ARTICLE

Dependence on Prescription Opioids

Prevention, Diagnosis and Treatment

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SUMMARY

Background: The incidence of initial prescriptions of opioids for chronic non-cancer pain rose by 37% in Germany from 2000 to 2010. Prescribing practice does not always conform with the recommendations of current guidelines. In the USA, 8–12% of patients with chronic non-cancer pain are opioid-dependent.

Methods: This review is based on publications retrieved by a selective PubMed search and on the German S3 guideline on the long-term use of opioids in non-cancer pain.

Results: Patients must be informed and counseled about the effects and risks of opioids before these drugs are prescribed. All opioid prescriptions for patients with chronic non-cancer pain should be regularly reviewed. The risk of abuse is high in young adults (odds ratio [OR] = 6.74) and in those with a history of substance abuse (OR = 2.34). Any unusual medication-related behavior, e.g., loss of prescriptions or increasing the dose without prior discussion with the physician, calls for further assessment by the physician in conversation with the patient. Urine testing for drugs and their metabolites is helpful as well. The goal of treatment of opioid abuse is opioid abstinence by gradual reduction of the dose. If this is not possible on an outpatient basis, hospitalization for drug withdrawal or substitution-based addiction therapy can be offered.

Conclusion: Physicians who know the indications and risks of opioid therapy and the typical behavior of drug-dependent patients will be better able to identify patients at risk and to prevent dependence. Studies on the prevalence of opioid abuse and dependence in German patients with chronic pain can help provide better estimates of the current extent and implications of this problem in Germany.

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Opioids are indispensable for treating severe pain. However, like all active substances, they carry the risk of side effects and complications, which also include misuse, abuse, and dependence (1). Increases in prescription rates (2), and health and economic damage caused by abuse of and dependence on prescription opioids, have brought these topics to the forefront of discussion (3).

A meta-analysis from the United States estimated a dependence rate of 8% to 12% for patients with chronic non-cancer pain (4). Therefore, dependence should be considered as a possible side effect of opioid therapy particularly for this group of patients. According to data from a major German statutory health insurance company, Barmer GEK, in 2010, patients with chronic non-cancer pain received about three-quarters of prescribed opioids in Germany, sometimes despite existing contraindications (5).

This article aims to help practitioners with addiction prevention, by identifying affected patients early and finding an appropriate therapeutic plan for them.

Increased opioid prescribing in Germany

In Germany, the percentage of persons with statutory health insurance who have been prescribed opioids at least once per year has increased from 3.3% in 2000 to 4.5% in 2010. This represents an increase in first-time prescriptions of 37% (2).

According to data from Barmer GEK, prescriptions for strong extended-release opioid analgesics (WHO step III) increased by almost 400% from 2000 to 2010 (5). While opioid were previously used to treat mainly cancer patients, they are now being increasingly used to treat chronic non-cancer pain, such as chronic back pain (5).

However, prescribing behavior does not always follow provided guidelines. For instance, insureds of Barmer GEK who were diagnosed with “headache” received weak opioid analgesics (WHO step II) in 16% of the cases, and strong opioid analgesics (WHO step III) in 7.5% of the cases, despite existing contraindications (5). During 2008 to 2009, about 11% of the insureds diagnosed with fibromyalgia syndrome fulfilled a prescription for a strong opioid at least once quarterly, also in this case despite existing contraindications (5).

A further example is given by the prescribing behavior for transdermal fentanyl preparations (WHO

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BOX 1

Contraindications to opioid therapy

- Opioids are contraindicated for:
 - Primary headaches
 - Pain from functional disorders of organ systems, such as irritable bowel syndrome
 - Fibromyalgia syndrome (with the exception of tramadol, which presumably works as a serotonin-norepinephrine reuptake inhibitor)
 - Chronic pain due to a mental disorder (for example, post-traumatic stress disorder, atypical depression, or generalized anxiety disorder)
 - Inflammatory bowel disease or chronic pancreatitis (with the exception of acute episodes or a therapy shorter than 4 weeks)
 - Comorbidity of severe mood disorders and/or suicidal behavior
 - Irresponsible use of medicines
 - Women who are pregnant or are planning pregnancy

step III), which have high rates of side effects in opioid-naïve patients. Despite these high rates, data from Barmer GEK in 2011 showed that 53% of patients who received a fentanyl patch had not been previously treated with a weak opioid (6).

In general, determining the correct indications for opioid therapy seems to be fraught with uncertainty. In a survey of 226 physicians with a self-described interest in pain therapy, at least 13% gave an incorrect indicator for opioid therapy, while 20% misclassified strong opioids as weak ones (7).

Epidemiology

In the United States, about 15 million people used prescription opioids non-medically in 2014, placing prescription opioids third behind alcohol and marijuana (8). Between 1999 and 2011, the incidence of related deaths rose in the United States from 1.4 per 100 000 to 5.4 per 100 000 (8). The total societal costs in 2007 were estimated at 55 billion US dollars (3). A recent meta-analysis of epidemiological studies ($n = 38$) revealed that patients in the United States with chronic non-cancer pain had rates of misuse between 21% to 29% (95% confidence interval [CI]: 13; 38) and dependence rates between 8% and 12% (95% CI: 3; 17) (4). No comparable meta-analyses have been performed yet in Germany. An expert committee of the Federal Institute for Drugs and Medical Devices found that the risk of misuse for tramadol and tilidine in Germany is low (9). While the situation for other opioids is unclear, estimates from epidemiological data suggest that every practicing physician in Germany attends on average one drug-dependent patient per day (1).

Methods

Based on the aforementioned background, we identified the following research question: “What is the current state of knowledge on the diagnosis, treatment, and dependence prevention for prescription opioids?”

To address this research question, we conducted a preliminary search with the Google Scholar search engine, as well as with a selective literature search of the PubMed database, using the search algorithm “(opioid abuse OR opioid misuse OR opioid dependence OR opioid dependent OR opioid dependency) AND (diagnosis OR therapy OR prevention)” from 1995 to 2015. In addition, we used the results of the current S3 guideline „Langzeitanwendung von Opioiden bei nicht tumorbedingten Schmerzen (Long-Term Opioid Use in Non-Cancer Pain)“ (LONTS).

Results

Prevention

Strategies to prevent prescription opioid dependence include:

- Educating and counseling patients
- Using the correct indications for treatment with regular indication review
- Early identification of patients at risk and risk-taking behavior.

BOX 2

Basic concepts of dependence

- **Dependence:** The perceived effects of using a substance are so positive that it leads to loss of control of its use. Dependence is defined by ICD-10 as the existence of more than three of the following criteria in 12 months: loss of control with respect to use, craving, withdrawal symptoms, development of tolerance with dose escalation, neglect of alternative interests, and continued use despite negative consequences..
- **Harmful use:** According to ICD-10, harmful use causes actual damage to the mental or physical health of the consumer. This is possibly more difficult to detect for opioid abuse than for nicotine or alcohol.
- **Misuse:** Using a substance with another intention than the originally intended one based on indications is misuse. An example is using opioids for inducing sleep, euphoria, or pleasure.
- **Pseudoaddiction:** Patients who suffer from pain but are not adequately treated can have behavior patterns that mimic an addiction. This can occur, for example, if the half-life of the used substances have not been taken into account, or if postoperative opioids are used "sparingly."
- **Tolerance development:** Tolerance is developed by a compensatory reduction in the number and sensitivity of the central nervous system receptors. Development of tolerance is slower for the analgesic effects than for the euphoric effects of opioids.
- **Withdrawal symptoms:** Physical withdrawal symptoms include muscle pain, abdominal cramps, and diarrhea. Psychological withdrawal symptoms include anxiety, insomnia, and a strong craving. Objectifiable symptoms include watery eyes, frequent yawning, acute rhinitis, sweating, chills, and piloerection. Symptoms last for about 5 to 10 days and peak 2 to 3 days after the last intake. Dysphoria and insomnia may persist for months. Opioid withdrawal is not usually associated with medical complications. There is, however, a risk of complications in patients with pre-existing cardiovascular conditions or epilepsy, for example, as well as in pregnant women.
- **Potential for abuse:** The potential for abuse of a substance depends on a rapid onset of action and its euphoric effect. For instance, oxycodone has a higher abuse potential than morphine, and immediate-release formulations have a higher abuse potential than extended-release formulations. However, the speed of onset of action can also be influenced, for instance if an extended-release tablet is crushed.

When is opioid therapy indicated for chronic non-cancer pain?

For most chronic non-cancer pain, the LONTS guidelines give an open recommendation (10). This means that, although opioids may be used, there are currently no high quality studies for proof of efficacy. For instance, for chronic back pain, therapy should be time-limited (<3 months), with an eventual extension upon good response. Even if a patient responds well to treatment, an attempt to stop therapy after six months should be made for re-evaluation. In general, and whenever possible, a therapy with opioid analgesics should use step I analgesics, according to the WHO Pain Ladder, and be accompanied with physical therapy, physiotherapy, and, if indicated, psychotherapy for pain management (11).

Contraindications should be given particular attention (10–12) (*Box 1*). A summary of the LONTS guidelines can be found in Häuser et al. (11).

Diagnosis

Any suspected dependence should be addressed at an early time point and constructively in a direct

patient–physician visit. Diagnosis is made according to ICD-10 (*Box 2*).

Following the LONTS guideline, a quarterly evaluation of the therapy goals, side effects, and misuse is recommended for patients treated with opioids.

As the topic of addiction is often associated with feelings of shame, assessments should be done carefully to avoid that the patient withdraws or changes physicians.

To evaluate for misuse within a medical interview, knowledge about risk factors and typical behavior is helpful. Additional tests can be performed at the discretion of the treating physician.

Abuse and addiction

Opioid dependence is highly stressful for the patient and, in the worst case, could lead to a fatal overdose (13). Further negative consequences include neglect of interests, social isolation, withdrawal symptoms, and social stigma (4). To detect affected patients at an early stage, it is important to know the concepts of dependence, pseudoaddiction, abuse, and tolerance

TABLE

Risk factors for opioid abuse and dependence

Risk factor	OR [95% CI] and n
Case history	
Prior substance abuse (14)	OR = 2.34 [1.75; 3.14], n = 15 160
Prior psychiatric diagnosis (14)	OR = 1.46 [1.12; 1.91], n = 15 160
Daily opioid dose >120 mg (15)	OR = 2.14 [1.75; 2.62], n = 36 605
Demographic factors (15)	
Female sex	OR = 0.82 [0.74; 0.92], n = 36 605
Age 18–30	OR = 6.74 [4.86; 9.33], n = 36 605
Age 31–40	OR = 4.62 [3.43; 6.22], n = 36 605
Age 41–50	OR = 3.27 [2.45; 4.37], n = 36 605
Age 51–64	OR = 1.95 [1.45; 2.62], n = 36 605

OR: odds ratio; 95% CI, 95% confidence interval; n, number of cases

development, as well as the typical withdrawal symptoms (*Box 2*).

Risk factors

In a meta-analysis from 2008, a history of substance abuse was determined to be the most important risk factor (14). The *Table* shows other risk factors and their effect sizes.

Opioid-dependent patients often request dose increases that cannot be explained by the normal development of tolerance by pain patients (16). According to the LONTS guidelines, a daily dose for chronic non-cancer pain should normally not exceed 120 mg of oral morphine equivalents, as a dose increase is associated with an increase in complications, such as falls, confusion, and death. If a dose exceeds this limit, the possibility of misuse should be evaluated (*Table*) (17).

Opioid-dependent patients often show typical behavior patterns, which should be viewed as signs of a medical condition rather than as a behavioral deficit (*Box 3*) (18, 19).

Screening tools

Before using a screening tool, the patient must be informed of the action and provide consent. It is important that the evaluation is seen as positive, as it is intended to protect and avert danger from the patient. The patient should be informed that all results are subject to medical confidentiality.

Numerous questionnaire-based screening tools are available for identifying a dependence of prescription opioids (20). However, a large meta-analysis from 2009

only identified the COMM (Current Opioid Misuse Measure) and SOAPP-R (Screener and Opioid Assessment for Patients with Pain—revised) as tools with qualitatively sufficient evidence to provide a moderately positive and negative predictive value (21).

No validated, questionnaire-based screening tool is currently available for German-speaking areas.

Additionally, routine urine tests are recommended to detect co-use, for example of benzodiazepines, opiates, cocaine, amphetamines, or methadone (16). The creatinine content of the urine sample should always be additionally determined, in order to recognize tampering attempts by dilution of the sample and, if necessary, to allow the values to be calculated correctly. Further testing using sweat, saliva, and hair samples is also possible. Since modern opioids are often difficult to detect with standard screening tests, the laboratory physician should be consulted in case of doubt (22).

Treatment

The ultimate goal of treatment is opioid abstinence. In addition to a structured dose reduction, multimodal pain and addiction treatments should also be made available. These include physiotherapy, occupational therapy, sports, rehabilitation, psychotherapy, support groups, and drug counseling (23).

The treating physician should set clear rules that have to be met for a continued supply of opioids, as well as the dose reduction, until abstinence is achieved (prevention and structured opioid therapy). Recommendations for different patient groups are shown in the *Figure*. If the structured opioid therapy fails due to

BOX 3

Typical behavior patterns in opioid dependence

● Conspicuous

- Hoarding during periods of reduced symptoms
- Requesting new prescription although enough tablets should still be present (based on calculations)
- Receiving similar prescription drugs from other physicians or the emergency room
- Emphatically stating a desire for a dose increase
- Independently using the prescribed opioid to treat other symptoms
- Requesting a specific drug
- Reporting psychological side effects of the opioid
- Up to two unauthorized dose increases

● Very conspicuous

- Selling controlled drugs
- Forging prescriptions
- Repeatedly reporting lost or destroyed prescriptions or tablets
- Repeated unauthorized dose increases
- Obtaining prescription drugs from external sources (relatives, internet, dealer)
- Stealing or “borrowing” tablets from a third party
- Using other routes of administration (such as intranasal or intravenous)
- Abuse of other substances, such as alcohol

lack of patient cooperation, a physician with an additional qualification in “addiction medicine” can be engaged. This thereby presents a patient with all possibilities for addiction treatment. Examples of such treatment are inpatient withdrawal or substitution-based addiction treatment. For these treatments, agreement and cooperation on the part of the patient are essential. Submitting the patients to an abrupt termination of prescribing (going “cold turkey”) should be avoided, but this remains the last resort to be used if patient cooperation is insufficient.

Drug counseling and rehabilitation

In Germany, it is possible to connect patients to psychosocial support through drug counseling, which can lead to sustainable abstinence, among other things (relative risk [RR], 2.43 [95% CI: 1.61; 3.66]) (24). However, it is unclear which patients benefit the most from this.

In addition to inpatient detoxification, further treatment options include a qualified withdrawal treatment (1 to 3 weeks), an inpatient medical rehabilitation (8 to 16 weeks), an outpatient medical rehabilitation (up to 18 months), and connection to a support group (1). The abstinence goal is more readily achieved with inpatient treatment than with outpatient treatment (58% versus 53%) (25). However, these data include heroin users as well, whose outpatient substitution therapies are often long-term, which may distort the results.

Tapering off an opioid

Besides the risks of side effects, long-term treatments with opioids may lead to the development of tolerance

in terms of analgesic effects and increased pain sensitivity (26). Dose reduction can positively influence pain and mood (27). Therefore, the LONTS guidelines recommend a regular attempt at stopping drug intake in order to re-evaluate the treatment situation (10).

In contrast to withdrawal from alcohol or benzodiazepines, withdrawal of opioid analgesics for healthy patients is not dangerous; nonetheless, it can be very unpleasant. Therefore, the so-called “cold turkey” withdrawal method, which is limited to the treatment of vegetative withdrawal symptoms, should only be carried out for easy cases or upon patient request. The preferred method according to the current guidelines is the “warm turkey” withdrawal method, with a tapering of consumed opioids within a structured opioid therapy, as part of a multimodal treatment plan (16, 28).

For dose reduction, the original opioid is discontinued and replaced by an extended-release formulation, such as extended-release morphine; in this step, opioids with a high potential for addiction, such as oxycodone or hydromorphone, should be avoided. Medication intake and treatment adherence are controlled (*Figure*) (16). During this process, a patient requires about 80% to 90% of the previous day’s dose to prevent withdrawal symptoms. The duration of the opioid therapy should determine the speed of tapering—the longer the therapy, the slower the tapering. Clonidine or doxepin can be used for support (10).

Substitution therapy

The fundamental condition for a substitution-based addiction treatment is that the patient fulfils the ICD-10

FIGURE

Structured opioid therapy based on evidence of abuse and dependence

diagnostic criteria for opioid dependence (Box 1). However, this does not mean that every opioid-dependent pain patient should undergo substitution therapy. Indeed, treating dependence with substitution is stigmatizing for the patient and strongly restricts the patient's freedom of movement and ability to organize everyday life.

Substitution therapy should only be considered after a "structured opioid therapy" has failed and if the patient meets the dependence criteria (16, 29).

In Germany, physicians require an additional qualification in "addiction medicine" in order to be able to treat addiction with substitution therapy. However, according to the Directive of the German Medical Association, every licensed physician can initiate a substitution therapy for up to three patients, but this requires consultation with a physician specialized in addiction medicine (consultancy process) (23).

Substitution-based addiction treatment in Germany can be carried out with methadone (46%), levomethadone (30%), and buprenorphine (23%), among other substances, and the addiction therapist is responsible for the substance choice (30). In contrast, in the United States, buprenorphine is usually used for treatment, due to its favorable profile of action and the legal environment. Buprenorphine itself does not produce a euphoric

effect; further, since it has a high receptor affinity with a partially agonistic effect on the μ -receptor, it reduces the euphoric effects and the respiratory depressant effects of co-consumed opioids. The plateau phase starts at a dose of 16 mg in healthy volunteers, and is at approximately 12 breaths per minute at a dose of 32 mg (31, 32).

The optimal duration of substitution therapy in opioid-dependent patients is unclear. In a randomized controlled trial, only 7% of patients (43/653) had a opioid-negative urine test after completing a 4-week buprenorphine therapy. This rate increased significantly, to 49% of patients (177/360), at 12 weeks into the therapy. However, at 8 weeks after therapy completion, the rate dropped dramatically to 9% (31/360) (33). In another randomized controlled trial, a control group with continued buprenorphine substitution over a 14-week interval was compared with an intervention group using a tapering protocol. The control group showed less co-use of other substances including opioids in urine tests. In the intervention group, significantly more patients discontinued therapy (6 of 57 [11%] versus 37 of 56 [66%]; $p < 0.001$) (34). In light of these data, substitution-based addiction therapy can be expected to be a lengthy process even for dependence on prescription opioids. For this reason, patient

compliance is of utmost importance. If a patient violates the substitution requirements already in the first two weeks of treatment, the probability of opioid abstinence at 12 weeks is very low (with a negative predictive value of 94%) (35). In general, compliance for patients who are exclusively dependent on prescription opioids is significantly better than for patients who consume heroin (with opioid-negative urine tests during the trial of 56% compared to 40%, respectively) (36). Altogether, the characteristics associated with an improved outcome are older age, psychiatric comorbidity, opioid use limited to oral and sublingual intake, and no prior opioid dependence treatment (37, 38).

Summary

The high psychological strain on patients with chronic non-cancer pain, and their pronounced desire for treatment, can lead to the use of strong opioids, even when indications are lacking (2, 5, 39).

Prevention of dependence on prescription opioids requires patient education, determining and assessing indications following guidelines, and the early identification of patients at risk as well as of risk-taking behavior (10).

Diagnosing opioid abuse and dependence is based on the criteria of ICD-10, but it is not always possible if patients give incomplete information. Knowing risk factors and typical behavior patterns of affected patients is helpful. Further, questionnaire-based screening tools and urinalysis can help identify patients at risk.

Therapy should involve structured reduction of the opioids with the objective of abstinence, and psychosocial support can be offered (16, 34, 36, 40). If this fails, a physician who is specialized in addiction can be consulted to examine the possibility of an inpatient withdrawal treatment or a substitution therapy (23).

Data on the prevalence of abuse and dependence among German patients with chronic non-cancer pain would allow a better assessment of the extent of the problem.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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KEY MESSAGES

- Opioid prescriptions have increased in Germany—by 37% between 2000 and 2010 alone. Misuse, abuse, and dependence are possible complications of opioid therapy.
- During opioid therapy for chronic non-cancer pain, special attention must be given to the indications, treatment duration, and risk factors for opioid abuse.
- Risk factors for opioid abuse include prior substance abuse (OR = 2.34), being young (18 to 30 years old; OR = 6.74), and high daily doses (OR = 2.14).
- The first choice for therapy is a gradual tapering off of the dose to abstinence. If an attempt at reduction is not successful, an addiction specialist can be consulted. Options include inpatient withdrawal therapy and substitution therapy. Behavioral therapy, psychosocial support, and rehabilitation can also be offered as support.
- Affected patients need help. Their resorting to illegally obtaining opioids and using other substances must be prevented.

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