

Buprenorphine Use and Risk of Abuse and Diversion

Michael Soyka^{1,2*}

¹Department of Psychiatry, Ludwig Maximilian University, Munich, Germany

²Private Hospital Meiringen, Willigen, CH 3860 Meiringen, Switzerland

Abstract

Opioid maintenance therapy with methadone or buprenorphine is a well-established first-line treatment for opioid dependence. However, risk of diversion and drug-related mortality are critical issues during maintenance therapy. These issues are discussed controversially in both the scientific and public arenas and are a matter of concern also among medical authorities. In addition to a formulation containing buprenorphine alone, a combination formulation with buprenorphine and naloxone in a 4:1 ratio is available. The combination formulation was developed with the aim to prevent intravenous use or diversion. This critical review summarizes data on the risk of abuse and diversion of buprenorphine.

Keywords: Buprenorphine; Diversion; Abuse; Mortality; Naloxone; Opioids; Opioid dependence

Introduction

Opioid dependence is a chronic relapsing disorder with an excess mortality rate [1-4]. Over than 90% of the estimates relate to heroin, as demonstrated in a global literature review by Degenhardt et al. [5]. Opioid maintenance treatment has proven efficacy in reducing opioid consumption and psychosocial and medical morbidity and in increasing treatment retention rates and social functioning in opioid addicts [6]. Nevertheless, there are persistent and in part increasing concerns about diversion of maintenance drugs, concomitant drug use, and mortality in opioid-maintained patients [1,7,8]. Diversion may be understood differently by clinicians and patients [9]. Usually, it is defined as the unauthorized re-routing or appropriation of a drug. Misuse, on the other hand, is defined as any use of a prescription drug that deviates from medical practice. Risks of diversion and misuse include increased patient morbidity and mortality [10], overdose and fatal respiratory depression [11,12], non-fatal overdose and related emergency admissions [10], blood-borne viruses and infections [13,14], and numerous other complications associated with injection drug use [15,16]. Other considerations include a possible negative impact on the prescribers' practice, threatened reputation of treatment services, and compromised public acceptance for the drug and maintenance treatment [17], as is currently the case in Austria, for example. The economic costs of the non-medical use of prescription opioids are enormous [18].

The misuse of prescription opioids, especially oxycodone but also methadone and others, is very common among street drug users in the USA, UK, and other countries [19-21]. Many patients misuse street methadone to reduce unpleasant addiction-related effects [22]. To diminish the risk of diversion, many countries have implemented regulations on maintenance treatment, which in return restrict access to treatment, among other things [23].

Buprenorphine in Opioid Maintenance Treatment: A Brief Update

Buprenorphine is an established first-line medication for the treatment of opioid dependence (see APA guidelines [24]; WFSBP guidelines [25]; New South Wales clinical guidelines [26]; the British Association for Psychopharmacology guidelines [27]; World Health

Organization guidelines [28,29]; for reviews on the risk of buprenorphine diversion and misuse, see Mammen and Bell [30], Orman and Keating [31] and Yokell et al. [32]. In the US, buprenorphine was approved by the FDA in October 2002 for the treatment of addiction.

Buprenorphine is a partial mu-opioid receptor agonist and kappa antagonist with a long half-life of 24-60 hours; it is administered sublingually in opioid replacement therapy [33]. Extensive first-pass liver metabolism results in low bioavailability after oral administration. Dosages of 4 to 16 or 24 mg/day are usually given for maintenance therapy. Two forms of buprenorphine are available: A tablet containing only buprenorphine, and one that combines buprenorphine with the opioid antagonist naloxone in a 4:1 ratio. Naloxone has poor oral bioavailability, which means that after sublingual administration the concentration is too low to cause severe and protracted withdrawal symptoms [34]. However, it has good parenteral bioavailability, with an elimination half-life in plasma of about 30 min [35]. Consequently, if a combination buprenorphine-naloxone tablet is dissolved and administered intravenously, it precipitates an immediate opioid withdrawal syndrome in the majority of patients [36]. This effect is thought to reduce the abuse potential of buprenorphine and improve its safety. The combination tablet has been found to significantly reduce the risk of diversion [24], but it does not eliminate intravenous misuse [30].

Buprenorphine effectively suppresses opioid withdrawal. Clinical studies of the detoxification effects of methadone, primarily in moderate dosages (50-60 mg), and buprenorphine (12-16 mg) have generally demonstrated comparable efficacy for the two drugs [37-39]. For more details on the use of buprenorphine in opioid dependence, see Soyka et al. [25].

***Corresponding author:** Michael Soyka, MD, Private Hospital Meiringen, P.O. Box 612, CH 3860 Meiringen, Switzerland, Tel: +41(0)339 728 295; Fax: +41(0)339 728 291; E-mail: Michael.Soyka@privatklinik-meiringen.ch

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Aims

This review was performed to evaluate the existing literature concerning the abuse potential and risk of diversion (and illicit use) of buprenorphine and buprenorphine-naloxone (rates of diversion and illicit use and relevance for overdose/mortality in different countries).

Methods

A systematic literature search was performed in the Medline and Pubmed databases to identify studies on the misuse or diversion of buprenorphine. The search was not limited to certain years or languages. The indexing terms were “buprenorphine AND diversion” (123 citations) and “buprenorphine AND misuse” (132 citations) and “buprenorphine AND diversion” (23 citations). Studies were also identified by examining previous reviews on this issue [32,40,41].

Results

Routes of administration

Buprenorphine is usually misused by the sublingual or intravenous route, but there are also reports of buprenorphine inhalation or intranasal application [42,43]. Intravenous misuse has been recorded since the mid-1980s [44,45]. The consensus seems to be that by far the most common method of abuse is to crush the sublingual tablets and inject the resulting extract [46], which causes morphine-like effects [47].

The abuse potential of buprenorphine, which has been demonstrated in experimental and clinical settings [48-50], is generally considered to be less than that of full opioid agonists [51,52]. Buprenorphine can cause euphoria [53,54], although to a lesser degree than full opioid agonists [31,53-55], and has reinforcing effects, again to a lesser degree than full opioid agonists [56-62]. However, under experimental conditions, buprenorphine was found to be as effective as methadone in producing reinforcing and subjective effects [50,54].

In a randomized, double-blind, placebo-controlled, cross-over study, Middleton et al. [43] evaluated the pharmacokinetic and pharmacodynamic profile and subjective and physiological effects of buprenorphine and buprenorphine/naloxone (crushed tablets) in 10 healthy adults who abused opioids intranasally, but were not physically dependent on them. Subjects reported higher ratings and street values for 8 mg buprenorphine than for the 8 mg buprenorphine/2 mg naloxone combination, but these differences were not statistically different. No significant formulation differences in peak plasma buprenorphine concentration or time course were observed. The authors speculated whether greater bioavailability and faster onset of pharmacodynamic effects compared to sublingual administration might motivate intranasal misuse in non-dependent opioid abusers and concluded that “Significant naloxone absorption from an intranasal buprenorphine/naloxone administration may deter the likelihood of intranasal misuse of buprenorphine/naloxone, but not buprenorphine, in opioid-dependent individuals” [43].

Extent of the problem in the US and non-European countries

Many related studies have been conducted in the US and Australia, but far fewer in Europe and other parts of the world. Data from the US indicate an increasing risk of buprenorphine misuse and diversion [63]. A recent survey indicated that 40% of clinicians believe that the diversion of the buprenorphine-naloxone combination is a dangerous problem [64]. Buprenorphine was introduced to the US market in 2002 and is classified as a Schedule III medication [65]; it is the first-line

option for office-based treatment [66,67]. Comparatively low levels of abuse have been found, and buprenorphine and buprenorphine/naloxone rank among the least abused or misused opioids [68-72]. Buprenorphine/naloxone diversion is rather limited, and the drug is used in a “therapeutic,” non-medically supervised manner [73-75]. As part of a national post-marketing surveillance program, applicants to substance abuse treatment and physicians certified to prescribe buprenorphine were surveyed about their perceptions of buprenorphine/naloxone diversion and abuse [76]. Measures of diversion and abuse of buprenorphine/naloxone increased from 2005 to 2009. The results from the applicant survey showed that the perceptions of the extent of diversion and abuse were lower than for the positive controls—methadone, oxycodone, and heroin—but higher than for the negative control, amitriptyline. By 2009, 46% of the physicians believed that buprenorphine/naloxone was diverted, 44% believed illegal use was for self-management of withdrawal, and 53% believed the source of the medication was substance-abusing patients. Other measures from national databases showed similar results. When adjusted for millions of tablets sold per year, slopes for measures of diversion and abuse were reduced. The authors concluded that the increases in diversion and abuse measures indicate both the need to take active attempts to curb diversion and abuse and the need for continuous monitoring and surveillance of all buprenorphine products and that “Finding a balance of risk/benefit (i.e. diversion and abuse versus expanded treatment) remains a challenge” [76]. Interestingly, the black market prices for prescription opioids, including buprenorphine, generally follow clinical equianalgesic potency and accurately predict the relative pharmacologic potency of opioid molecules [77].

A recent comprehensive post-marketing postal survey of Australian authorized opioid substitution treatment prescribers [78] found that prescribers perceived that more buprenorphine patients removed supervised doses (7%) and diverted unsupervised doses (20%) than did methadone patients (1% and 4%, respectively) and buprenorphine-naloxone patients (3% and 2%, respectively). In addition, prescribers reported that significantly more buprenorphine and buprenorphine-naloxone patients injected doses (each 5%) than methadone patients did (2%). All in all, the rates reported seem rather low, and the authors discuss that the prescribers may underestimate the levels of diversion.

About one third of injecting drug users in Australia reported injecting buprenorphine in the last 3-6 months [53,79]. Only 10% of injecting drug users (IDUs) reported buprenorphine as the primary drug of abuse [53].

Opioid maintenance drugs are nearly exclusively misused by individuals under substitution treatment who have a history of drug dependence [40] and substance use diagnoses in addition to opioid dependence [80].

An interesting study was performed recently in the US by Lofwall and Havens [81]. The study examined the frequency and source of and risk factors for diverted buprenorphine use over a 6-month period in an Appalachian community sample of prescription opioid abusers. Of the 503 participants at baseline, 471 completed the study. Psychiatric disorders and demographics, drugs use, and social network characteristics were ascertained at baseline and follow-up. Multivariable logistic regression was performed over the 6-month period. Results indicate that lifetime buprenorphine use “to get high” was 70.1%; 46.5% used diverted buprenorphine over the 6-month period; and 9.6% were daily users and 50%-60% sporadic users (1-2 uses over the 6 months). The most common sources were dealers (58.7%) and friends (31.6%). Predictors of increased risk of use of diverted buprenorphine

included inability to access buprenorphine treatment (AOR: 7.31), meeting criteria for generalized anxiety disorder, and use in the past 30 days of oxycodone, methamphetamine, and/or alcohol. The authors concluded that these results “suggest that improving, rather than limiting, access to good quality affordable buprenorphine treatment may be an effective public strategy to mitigate buprenorphine abuse. Future work should be an effective public health strategy to mitigate buprenorphine abuse” [81].

Aitken et al. [53] performed a prospective cross-sectional study in 316 injecting drug users in Australia. More than 10% of participants reported buprenorphine as the drug they had most often injected, and 32% had injected buprenorphine at least once in the 3 months before the interview. Sharing a used needle was associated with buprenorphine injection.

Previously, a study reported at the 2006 Australian National Drug Trends Conference showed that of 914 injection drug users asked, 1% cited buprenorphine as their drug of choice, and 6% said that it was the drug they had injected most often in the preceding month [82].

A study examining abuse of buprenorphine with and without naloxone by untreated injection drug users found a strong preference for the formulation without naloxone [54].

Bazazi et al. [74] performed a qualitative epidemiological survey in the US in 51 IDUs and 49 non-injecting opioid users. Seventy-six percent of participants reported having obtained buprenorphine/naloxone illicitly. Diversion was more frequent in IDUs than in non-IDUs (86% vs. 65%). The reasons for use were treatment of withdrawal symptoms (74%), having stopped using other opioids (66%), and not being able to afford drug treatment (64%). The authors concluded that particularly IDUs used diverted buprenorphine for reasons consistent with its therapeutic use, such as alleviating opioid withdrawal symptoms and reducing the use of other opioids.

A US post-marketing surveillance study on methadone and buprenorphine found that between 2003 and 2007, rates of abuse, misuse, and diversion of both compounds increased steadily [83]. Rate ratios (per 100,000 population per quarter) of abuse, misuse, and diversion were consistently higher for methadone than buprenorphine.

A retrospective comparison in Australia of untreated regular IDUs and patients receiving medication-assisted therapy found that buprenorphine/naloxone was injected less frequently than buprenorphine, especially when the rate was corrected for medication availability [84].

An Australian multi-site cross-sectional survey in 508 clients, 442 receiving supervised methadone and 66 buprenorphine, found that the prevalence of recent diversion was more than 10 times higher among those receiving buprenorphine than among those receiving methadone, with 23.8% of buprenorphine-maintained participants reporting diverting their dose in the preceding 12 months [85]. Seventeen percent of methadone clients had injected methadone in the preceding 12 months compared with 9.1% of buprenorphine clients over the same time period. The authors concluded that the higher prevalence of buprenorphine diversion compared to methadone diversion is likely to be due to its sublingual tablet formulation and the difficulty associated with supervising its consumption compared to that of an oral liquid. The authors further discussed that “methadone diversion is also less prevalent likely due to the high levels of methadone take-away provision, which also helps to explain the higher levels of recent methadone injecting compared to buprenorphine injecting. A

clearer understanding of the motivations for diversion and injection of opioid pharmacotherapies, and the relationship between them is required” [85].

Gwin Mitchell et al. [86] conducted a qualitative epidemiological survey in 515 opioid-dependent individuals reporting diversion. The study included self-report data on diversion and semi-structured qualitative interviews. Of the total sample, 84 (16%) reported using diverted (street) methadone 2-3 times/week for six months or more. A subsample (n=22) indicated that street methadone was more widely used than street buprenorphine and that both drugs were largely used as self-medication for detoxification and withdrawal symptoms.

In Singapore, Ho et al. [16] conducted a retrospective data analysis and found that pulmonary hypertension may be a potential comorbidity among intravenous buprenorphine users, among many others.

The question of whether the buprenorphine/naloxone combination lowers the risk of diversion and intravenous use was addressed in Australia in a cross-sectional survey by Larance et al. [87]. Results showed that levels of injection among regular IDUs were lower for buprenorphine/naloxone than for buprenorphine, but comparable to those for methadone. Among patients, fewer buprenorphine/naloxone-treated patients (13%) reported recent injection of their medication than buprenorphine-treated (28%) and methadone-treated patients (23%). Overall, buprenorphine/naloxone was less commonly and less frequently injected than buprenorphine, but both were more frequently diverted than methadone.

Another Australian study [88] in 448 opioid-dependent individuals found that about one fourth of patients had ever injected buprenorphine. The rates of diversion in the 12 preceding months were higher among participants receiving buprenorphine (15.3%) than among those receiving methadone (4.3%).

A US/Canadian cross-sectional survey by Monte et al. [75] in 51 treatment-seeking opioid-individuals tried to characterize buprenorphine/naloxone diversion practices in a region with a high prescribing prevalence. One hundred per cent of patients had diverted buprenorphine/naloxone to modulate withdrawal symptoms arising from attempted “self-detoxification,” insufficient funds to purchase preferred illicit opioids, or inability to find a preferred source of drugs.

In summing up the existing literature, Yokell et al. [32] concluded that buprenorphine is effective in opioid dependence treatment and harm reduction. The combination with naloxone may limit its injection misuse potential.

The issue of diversion and abuse of buprenorphine was addressed in a report by Maxwell [41] to the Substance Abuse and Mental Health Services Administration (SAMSHA) that was based on a literature review of papers published since 2002 (n=347). With respect to abuse potential, Maxwell [41] pointed out that while early reports of findings from animal studies suggested that buprenorphine would have minimal abuse potential, varying levels of diversion and abuse were predicted by early investigations in humans [89,90].

Concerning incidence and prevalence of buprenorphine abuse, on the basis of findings from two established informant networks Cicero and Inciardi [46] reported that the level of buprenorphine abuse remained relatively low through the first quarter of 2005 and appeared to be at a much lower level than seen with methadone or oxycodone. In a second report, this group ranked buprenorphine last among other opioids of abuse [68].

Diversion and abuse of buprenorphine in the US is not only restricted to opioid-dependent users: Chronic pain patients may also be affected, because of an increasing amount of nonmedical use of prescription opioids [91]. There are dramatic data concerning emergency department visits due to buprenorphine or other opioids in the US [92,93]. The relative benefit from buprenorphine was discussed by Mendelson et al. [92] in light of the epidemic misuse of prescription opioids. The authors stressed minimal problems with diversion or adverse clinical events, referring to a 2006 SAMSHA/CSAT Evaluation of the Buprenorphine Waiver program.

In their overview of the National Drug Abuse Treatment Clinical Trials Network by the National Institute on Drug Abuse (NIDA), Ling et al. [94] concluded that with the advent of a sublingual tablet containing both buprenorphine and naloxone to mitigate abuse and diversion, buprenorphine appeared poised to be the first-line treatment for opioid addiction.

Findings from a small sample (N=41) in Malaysia suggest that the introduction of the buprenorphine/naloxone combination did not decrease injection-related risk behaviors and was associated with increased benzodiazepine use [95]. A more systematic study in Malaysia, a two-wave survey of buprenorphine IDUs, found that both buprenorphine and buprenorphine/naloxone intravenous misuse occurred in heroin IDUs [60]. Focus group participants reported that buprenorphine/naloxone was not as desirable as buprenorphine, but widespread misuse nevertheless continued. The authors concluded that “the introduction of buprenorphine/naloxone and withdrawal of buprenorphine may have helped to reduce, but did not eliminate the problems with diversion and abuse” [60]. Buprenorphine misuse has been reported also in India [96-98].

Other studies found that switching patients from buprenorphine to buprenorphine/naloxone is an effective measure to reduce diversion and misuse. Amato [99] studied 78 patients for one year after they had switched from buprenorphine to buprenorphine/naloxone and found that the switch had a positive impact on diversion/misuse. Patients were satisfied with treatment and reported improved psychosocial functioning.

Winstock and Lea [88] conducted a survey in 448 clients receiving opioid maintenance treatment. Not surprisingly, the buprenorphine diversion rate in the preceding 12 months was over three times higher among those receiving supervised buprenorphine (15.3%) than among those receiving supervised methadone (4.3%). While 26.5% of participants currently prescribed buprenorphine reported ever injecting buprenorphine, 65.9% of those prescribed methadone reported ever injecting methadone.

Recently, Genberg et al. [100] conducted one of the few systematic assessments of street-obtained buprenorphine use in a community-based sample. Of the 602 respondents, only 9% reported street-obtained buprenorphine use, and only 2% reported getting high. Among active opioid users, 3% reported recent use of diverted buprenorphine. Most patients took street-obtained buprenorphine to avoid withdrawal symptoms.

European Studies

There are reports of buprenorphine misuse/diversion from many European countries, including France, Germany, Spain, the UK, Ireland, and the Scandinavian countries [101-106]. The misuse/diversion of opioid analgesics in the European community was addressed in a recent systematic review of the literature by Casati et

al. [40]. Methadone and buprenorphine were considered as medicines used for opioid substitution treatment. The authors stated that both drugs have high rates of misuse, including doctor shopping, i.e. seeing multiple treatment providers to procure prescription medications illicitly; illicit intravenous application; snorting; and buying or selling on the black market [107-110].

Buprenorphine is widely used in France, and one study reported that up to 20% of buprenorphine patients misuse the drug intravenously [111]. Another study in France found that 27% of IDUs were exclusively buprenorphine injectors, while another 37% reported polydrug use [112]. Some of these IDUs purchased their buprenorphine from individuals with a prescription [113], while others obtained it by altering or forging prescriptions [51,114,115]. Similar results were provided by Obadia et al. [116]. Intravenous misuse is by far the dominant method in France, but there are also cases of buprenorphine sniffing [117,118].

Guichard et al. [119] reported data of a cross-sectional study on illicit drug use and injection practices among drug users receiving methadone (N=197) and buprenorphine (N=142) treatment in France. Injection was more common among buprenorphine-maintained individuals than among those treated with methadone (40.1% vs. 15.2%, $p>0.01$). Multivariate analyses indicated that the type of substitution drug was not associated with illicit drug use. Rather surprisingly, the risk of injection increased with dosage in the buprenorphine group but not in the methadone group.

In many cases, methadone and buprenorphine misuse begins even before a subject enters an opioid maintenance treatment program. Cazorla et al. [120] reported that 84000 opioid users have undergone maintenance treatment in France since 2001. Among these patients, 88% were being treated with buprenorphine, and 35% reported having used buprenorphine for the first time without having a prescription for it. An Irish study [109] found even higher rates of methadone misuse before treatment entry among patients in maintenance therapy: 73% of participants reported methadone misuse before starting treatment, while 55% reported methadone misuse during treatment. The main reasons for misuse were management of withdrawal symptoms and hedonistic effects.

German data from patients admitted for detoxification showed that 53.5% misused medical opioids, especially methadone [110], mainly because of difficulty in acquiring heroin.

A recent Italian study by Moratti et al. [107] on heroin-dependent patients in maintenance therapy reported intravenous misuse of buprenorphine by 23.1% of patients. Not surprisingly, patients receiving buprenorphine maintenance therapy were significantly more likely to inject buprenorphine intravenously than those receiving methadone (35.5% vs. 17.8%, respectively). About half (50.7%) of the patients reported injecting buprenorphine to treat their withdrawal symptoms, while only 12.7% of patients reported doing so to experience pleasure or euphoria. In addition, participants were asked to assess the number of patients receiving buprenorphine who had attempted to take it intravenously: 45.9% of participants thought that at least 50% of patients on buprenorphine replacement therapy had injected buprenorphine intravenously, suggesting that the initial results may have underestimated the problem. The authors concluded that misuse was most common among patients currently receiving buprenorphine treatment and among younger patients. “For the majority of patients, the reason for intravenous misuse was to treat their dependence. We believe that the prevalence for buprenorphine misuse could be reduced

by adopting appropriate clinical practices and treating patients with the buprenorphine/naloxone combination rather than buprenorphine alone” [107].

A group in Sweden [101] studied buprenorphine misuse among patients in a syringe exchange program and found that 43% of heroin and amphetamine users reported intravenous misuse of buprenorphine and 29% snorting. In addition, 11% of heroin users reported buprenorphine use to induce euphoria compared to 62% of amphetamine users. A Finnish study on the abuse liability of buprenorphine-naloxone tablets among untreated intravenous drug users found that buprenorphine is the most misused intravenous opioid in Finland and that misuse increased sharply in 2001 as heroin availability coincidentally decreased [54]. In order to curb buprenorphine misuse, many treatment centers crush tablets before administering them to patients. Simojoki et al. [121] found that this practice does not significantly alter the clinical effect of the drug, indicating that it is an appropriate method to reduce misuse.

Doctor shopping is a means of acquiring more maintenance drugs than required and is a widespread problem. Some countries, e.g. Germany, have introduced central patient registers to prevent patients obtaining multiple treatments. On the basis of data from the General Health Insurance System in one area of Southern France, Pauly et al. [108] found that 13.2% of the reimbursed high-dose buprenorphine was dispensed with prescriptions obtained from doctor shopping. In addition, results revealed that the more deviant a patient’s behavior, the higher the risk for doctor shopping. Another French study on buprenorphine maintenance treatment [122] found that practitioners’ attitudes influence the likelihood of doctor shopping, not the other way around: Doctor shopping was lower among general practitioners who induced buprenorphine maintenance treatment with 8 mg/day or more of buprenorphine, as compared with those who prescribed a lower initial dosage; also, doctor shopping was more common among general practitioners with more stringent, “conservative” attitudes towards patients.

An online questionnaire revealed that 72% of 300 opioid-prescribing practitioners in Germany, Italy, France, and the UK believed that buprenorphine or methadone misuse was a huge or significant problem [123]. The results also suggest that often subtherapeutic doses of maintenance drugs were used.

France has quite “liberal” prescribing regulations for buprenorphine, the predominant maintenance medication, which may account for buprenorphine’s diversion into the black market [124]. Prescription-monitoring programs may reduce the risk for doctor shopping [125]. The risk of buprenorphine misuse (and benzodiazepine misuse and rates of depression) is underestimated by physicians, as shown in a cross-sectional study by Lavie et al. [126]. Data from France from 2006 show that up to 25% of French buprenorphine doses were diverted into the black market (Narcotics Control Board 2006).

In Germany in 2008, 80%-85% of injecting drug users reported finding it easy to access methadone or buprenorphine on the black market [127].

In a cross-sectional survey in Udine/Italy, Moratti et al. [107] studied opioid-dependent patients treated with methadone (n=214) or buprenorphine (n=93). Significantly more buprenorphine patients (35.5%) than methadone-maintained patients (17.8%) admitted intravenous misuse; the main reason given was self-treatment. Also in Italy, a cross-sectional survey by Montesano et al. [128] studied the effect in 43 opioid-dependent patients of 24 weeks’ treatment

with buprenorphine/naloxone after the patients had switched from buprenorphine alone. Only 2% of patients attempted to misuse buprenorphine/naloxone intravenously, and none of them experienced any gratifying effects.

Interestingly, a survey in Finnish intravenous opioid users showed that buprenorphine was the drug most frequently used intravenously (73% of the respondents) [54]. More than 75% used intravenous buprenorphine to self-treat addiction or withdrawal. Most individuals (68%) had tried the buprenorphine/naloxone combination, but 80% reported having a “bad” experience with it. Also interestingly, the street price of buprenorphine/naloxone was less than half that of buprenorphine alone. The authors concluded that buprenorphine/naloxone appears to be a feasible tool for decreasing intravenous abuse of buprenorphine.

A recent Swedish study based on surveys and structured interviews of adolescents and young adults indicated that illicit use of methadone and buprenorphine is rare, only 0.1% of the cohorts sampled had tried these substances, and misuse and diversion of both was not seen as a serious problem by professionals [129].

Risk factors of abuse, which may not be specific for buprenorphine, are younger age, intravenous use of opioids, poor social conditions such as unemployment and withdrawal symptoms, among others [93,130]. Buprenorphine is also cheaper than heroin in many areas [53].

Role of Take-home Doses

Take-home doses of buprenorphine can be prescribed in most countries. In some cases, patients are given take-home doses after they are stabilized, and in others a less than daily dosage of buprenorphine is possible for patient convenience [26]. Advantages of at-home use include saving time for travel, facilitating social integration, emphasizing and promoting patient responsibility for treatment, reinforcing compliance, improving a trusting relationship between staff and patients, engaging in normal day activities, and reducing workload for the dispenser. Some of the apparent risks are the risk of diversion to another person and injection of the oral medication. Patients who should not be candidates for take-home doses include those with repeated intoxication on presentation for dosing at the clinic, concerns about child welfare and safety, current chaotic and unpredictable behavior, risk of self-harm, and hazardous use of opioids [26].

Curcio et al. [131] reported data from a large sample (N=3812) in Italian outpatient centers, 81.5% of whom were treated with methadone and 18.5% with buprenorphine. Patients on buprenorphine treatment were switched to buprenorphine/naloxone, and all patients were followed for about 1 year. The number of patients still in treatment was similar in both groups, but the buprenorphine/naloxone patients reported a significantly greater improvement than the methadone patients in social life status, educational level, and especially toxicological conditions.

In the UK, the number of deaths related to methadone dose clearly declined after the introduction of supervised methadone dosing [132].

Recently, a Finnish study investigated whether electronic medicine dispensers may reduce the risk of diversion of take-home buprenorphine-naloxone, but the authors concluded that further research on this topic is required [133].

Genetics

Recently, the role of genetic variants for treatment response and

risk of diversion in buprenorphine maintenance therapy was examined by Gerra et al. [134]. While there was no evidence that genetic variants of the kappa receptor are relevant, a distinct variant of the dopamine transporter gene (DAT 1 allele 10) was more frequent in buprenorphine non-responders. These results must be seen as very preliminary and need confirming.

Risk of Fatal Poisoning/Mortality

A fairly recent scholarly review of 58 prospective studies reporting mortality rates from opioid-dependent samples [135] revealed remarkable mortality rates (all-cause mortality of 2.09 per 100 person years, PY), but confirmed that overall maintenance treatment significantly reduces mortality rates as compared to untreated heroin dependence (1%-3% per year, <50% attributable to heroin overdose). The reasons for death varied, depending on the methodology, but most patients died from overdose; the risk was highest for male patients and during out-of-treatment periods. Although this finding confirms previous reports, core issues remain unresolved, such as mortality risk by type of substitution medication, the degree to which the substitution drug is involved, and mortality during and after dropping out of maintenance. Additional data from Australia also suggest that the majority of deaths in opioid-dependent people are drug related [136].

The general consensus is that overdoses caused by buprenorphine alone are rare [8,137,138]. In an epidemiological review, Okie [139] concluded that deaths from unintentional drug overdoses in the US have risen sharply since the early 1990s and are the second leading cause of accidental death (27,658 in 2007). The increase has been propelled by a rising number of overdoses of opioids, which in 2007 alone caused more deaths than heroin and cocaine combined. Other data show that most of the drug-related unintentional deaths in the US are related to methadone (31%), hydrocodone (19%), alprazolam (15%), and oxycodone (15%) [140]. In general, deaths due to unintentional overdoses of methadone or other opioid analgesics are associated with poverty, unemployment, and prescription opioid drug rates [93].

Very few corresponding data are available from European studies. From 1991 to 2007, the numbers of drug-related deaths due to methadone poisoning increased in Nordic countries [141]. Buprenorphine was the most frequent cause of death among drug-dependent subjects in Finland (25% of all fatal intoxications in 2007), while methadone was the most frequent cause of death in Denmark (51%). Multidrug use was very common in drug-related deaths.

A large German naturalistic follow-up study (N=2694) on one-year outcome in opioid-dependent maintenance patients found an annual mortality rate of 1.04% for methadone- and buprenorphine-treated patients [142]. The study was a nationally representative, prospective, longitudinal naturalistic study program with three waves (baseline, 1 year, 5-7 years) and was based on a nationwide representative sample of physicians and their opioid-dependent patients [143]. During the six-year follow-up phase, n=131 patients died. Mortality rates were 1.2% (n=28/2284) after one year and 5.7% (n=131/2284) after 6 years. The mean crude annual mortality rate was 1.0%, or 1.2 per 100 PY. Mortality rates did not differ significantly between men and women [144]. The most frequent causes of mortality were somatic disorders (n=57, 36.6%), e.g. HIV/Aids (14 cases), cancer (6 cases), cardiovascular disease (6 cases: 5 [0.3%] in the methadone group and 1 [0.2%] in the buprenorphine group, difference not significant); drug overdose (n=37, 28.3%), e.g. heroin, cocaine, benzodiazepine, 6 cases with more than one drug, including the substitution drug; and suicide (16%). Fatal overdose of substitution drugs was almost never

the exclusive reason (n=2, 1.5%), and interactions of the substitution drug with other concomitant drugs were relatively rare as well (n=6, 6.1%). The majority of deceased patients were not in maintenance treatment (n=73, 55.7%) in the weeks before death, either because the treating physician had decided to discontinue maintenance or because the patient had stopped attending appointments. Consistent with this finding, rates of overdose appeared to be elevated for those who died outside treatment. Of the 58 (44.3%) patients who died during maintenance treatment, 52 of a total of 1,690 treated with methadone at baseline were on methadone medication, and 6 out of 578 treated with buprenorphine at baseline were on buprenorphine medication. In this study, buprenorphine patients had a significantly lower mortality risk (OR: 0.27, p=.005) than methadone patients. These results indicated a comparably low mean crude annual mortality rate of 1.0% and a standardized mortality rate of 1.2 per 100 PY. This rate is lower than the annual mortality rate for opioid users indicated by a recent and very comprehensive meta-analysis by Degenhardt et al. [135], possibly reflecting the beneficial effect of the particular characteristics of German maintenance treatment.

In contrast to the meta-analytic findings, the most frequent reason for death in this study was somatic morbidity, followed by fatal overdose/intoxication of multiple substances. The substitution drug itself was rarely (1.5%) involved in premature mortality. Suicide (16%) was another major contributor. Accidents or other violent causes of death were rare (4.6%). Interestingly, the annual mortality rate decreased only moderately over time and not as much as one might have expected and was highest in the first year of the study. Other long-term studies also indicate persistently high mortality among opioid-dependent patients [1] that appears to change over time.

Just over half of the patients (55.7%) were no longer in maintenance treatment at the time of death. In line with previous studies [4], discontinuation for any reason and being out of treatment were the major predictors for death. Also in line with previous studies that addressed shorter follow-up periods [8,135], well-known predictors such as unemployment, higher age, longer opioid use, and comorbid mental or somatic disorders were confirmed in this study.

The substantially lower rate of premature mortality among buprenorphine-treated patients at the 6-year follow-up was remarkable [144]; buprenorphine was found to be a significant predictor for survival. These data are consistent with other findings, especially French and German forensic autopsy data that indicate a low mortality risk with buprenorphine [145,146]. Bell et al. [7] reported that buprenorphine may be safer in the induction phase. In a recent study on risk of death in a large cohort of patients, Cornish et al. [147] found a crude mortality rate of 0.7 per 100 PY among patients in treatment and 1.3 per 100 PY among patients out of treatment. Unlike the mortality risk in the German study, mortality risk was twice as high in men and also higher in the first two weeks of treatment. Variations in outcome and mortality may have been explained also by differences in the clinical samples and by an allocation of severely affected patients to the methadone group, as possibly indicated by a higher rate of baseline comorbid psychiatric diagnosis [148].

Laberke and Bartsch [11] reported that most methadone-associated deaths in Switzerland (N=176) occurred during substitution treatment or illicit intake of methadone. The majority of cases (76%) were related to polydrug intoxication.

Degenhardt et al. [135] estimated the overall reduction in mortality produced by substitution programs to be 29%.

Especially in the US, buprenorphine poisoning and unintentional exposure in children and toddlers has been recognized as a major health problem, because of the increasing number of reports of emergency visits. In nearly all cases, intoxications are nonfatal (4 of 4879 in children under 6, for recent review see [149]). Similar data were published by Lavonas et al. [150], who reported 4 deaths among 2380 cases of unintentional exposures to buprenorphine in children up to 6 years old.

Discussion and Conclusions

Substance use and risk of diversion are central problems in opioid maintenance therapy. All drugs with opioid agonist effects have an abuse potential. Like other “illegal” behaviors, the issue of abuse/diversion is difficult to study. Relevant outcome data do not come from clinical studies, but from surveys of physicians and their clients or poison control centers, among others. With respect to countries, data about opioid misuse, especially prescription opioids, are available predominantly from the US and Australia, and much fewer data are available from Europe. There are significant differences in rates of reported illicit buprenorphine use and diversion between countries. Concerns persist about the increasing misuse and diversion of prescription opioids, especially methadone, oxycodone and others, but to a lesser extent also of buprenorphine, as indicated by a dramatic increase in emergency room visits linked to opioid overdose. To date, this issue is a matter of great public concern in the US, but not in Europe. Rates of diversion depend also on different legal regulations, the “drug market” availability of different drugs, and other factors. One of the apparent advantages of buprenorphine is the very low risk of fatal (mono-) intoxications, at least compared to other opioids. In France, where buprenorphine is by far the most frequently prescribed drug in opioid maintenance therapy, data from 2006 indicate that up to 25% of French buprenorphine doses were diverted into the black market.

Buprenorphine and buprenorphine/naloxone are administered sublingually. A novel buprenorphine film has been developed, but so far it is available only in the US and Australia [151]. Buprenorphine tablets are usually crushed and misused intravenously, and are smoked or inhaled only rarely. The combination buprenorphine/naloxone was developed to diminish the risk for intravenous use. Naloxone is inactive when taken orally, but immediately precipitates opioid withdrawal when injected, so the combination aims to reduce the risk of abuse/diversion; some data support the effectiveness of the combination in fulfilling this aim. The buprenorphine/naloxone combination is less liked by intravenous opioid users. It may not have eliminated the problem of buprenorphine abuse, but it has clearly decreased it. Fatal intoxications are extremely rare with the combination form and are mostly due to polyintoxications with other CNS depressants. Risk factors for buprenorphine abuse/diversion are younger age, intravenous use of opioids, poor social conditions, and withdrawal symptoms, i.e. all-in-all the typical picture of a polydrug user. Insufficient control of withdrawal symptoms has consistently been reported by buprenorphine abusers as a reason for use. In some cases, a higher dose of buprenorphine and adequate dosing may be helpful to control withdrawal and diminish the risk for buprenorphine misuse.

Careful assessment and supervision of patients given take-home doses of buprenorphine is important for clinical success. If take-home dosing is permitted and the patient is an appropriate candidate, treatment should be initiated with supervised administration and should progress to unsupervised administration when the patient’s clinical stability permits. During treatment induction, closer supervision of dosing is

recommended to ensure proper sublingual placement of the dose and to observe the patient’s response to treatment as a guide to effective dose titration. As the patient becomes stabilized on treatment, longer intervals between patient assessment may be appropriate, depending on patient compliance, effectiveness of the treatment plan, and overall patient progress. It is also recommended that when determining the prescription quantity for unsupervised administration, the frequency of patient visits and the patient’s ability to manage supplies of take-home medication are taken into consideration.

In some cases, crushing the tablets before giving them to patients may be a simple approach to reduce risk of misuse, as shown in Scandinavian studies. In general, one must consider that a reduced risk of buprenorphine/naloxone misuse can be balanced and outweighed by the risk of abusing other drugs, e.g. other opioids, alcohol, or benzodiazepines, which may have an even higher risk for fatal intoxications. A very “conservative” attitude of the treating physician and too low dosages of buprenorphine may encourage doctor shopping and related behaviors, as shown in French studies. On the other hand, too “liberal” regulations may also enhance risk of diversion.

From a scientific point of view, in particular more European studies on the risk of diversion and toxicological studies on safety issues are warranted.

Conflict of Interest

The author has worked as a consultant or has received research grants from Sanofi, Cephalopharm, Phoenix, Reckitt Benckiser, and Lundbeck.

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