



Drug safety and adverse drug reaction reporting behavior related to outpatient opioid replacement therapy: Results from a survey among physicians



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ABSTRACT

To study drug safety and the reporting behavior of adverse drug reactions (ADR) related to agents used for opioid replacement therapy (ORT) we conducted a cross-sectional questionnaire-based telephone survey among physicians who provide outpatient ORT in Germany ($n = 176$; response rate = 55.7%). Most respondents ($n = 97/55.1\%$) reported that they observe ADR related to buprenorphine, (dihydro)codeine, and (levo)methadone rarely ($n = 38/21.6\%$), very rarely ($n = 39/22.2\%$) or never ($n = 20/11.4\%$). Methadone was reported to be most frequently associated with the occurrence of ADR ($n = 82/46.6\%$), followed by levomethadone ($n = 33/18.8\%$), buprenorphine ($n = 6/3.4\%$), and dihydrocodeine ($n = 3/1.7\%$). Frequently observed ADR related to these agents were gastrointestinal, nervous system/psychiatric disorders, and hyperhidrosis. Methadone and levomethadone (not buprenorphine) were frequently associated with fatigue, weight gain, and sexual dysfunction. Hundred twenty nine participants (73.3%) stated that they never report ADR related to ORT; $n = 19$ (10.8%) did so when referring to ADR related to their complete medical practice ($X^2 = 141.070$; $df = 1$; $p < 0.001$). Similar patterns of ADR related to outpatient ORT as those reported in the product information or in pain therapy were found. Motivation to report ADR related to ORT may be reduced compared to ADR related to the general medical practice.

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1. Introduction

Opioid replacement therapy (ORT) is a well-established pharmacological treatment for patients with opioid dependence (Bell, 2014). Several agents are used for ORT at present. *Methadone*, a μ -opioid receptor agonist and antagonist at the *N*-methyl-D-aspartate (NMDA) receptor (Nguyen, Hahn, & Strakowski, 2013), that was used for treating opioid withdrawal symptoms already in the 1950s (Joseph, Stancliff, & Langrod, 2000), has become the mainstay in ORT since the 1960s (Novick et al., 1988). *Levomethadone* (or R-(−)-methadone) is the active enantiomer of racemic methadone (with twice the potency of methadone) is primarily used for ORT in Europe (Verthein et al., 2005). In the last decades other pharmacological agents as *buprenorphine* (Robinson, 2002) (a non-selective, mixed agonist-antagonist opioid receptor modulator (Jacob, Michaud, & Tremblay, 1979) with partial agonism at the μ -opioid receptor, an antagonist

and weak partial agonist at the κ -opioid receptor, an antagonist at the σ -opioid receptor, and a weak partial agonist at the nociceptin receptor [ORL-1] (Huang, Kehner, Cowan, & Liu-Chen, 2001) that is combined with the opioid antagonist *naloxone* in several formulations (Bell, Byron, Gibson, & Morris, 2004), *diacetylmorphine* (heroin) (Ferri, Davoli, & Perucci, 2011), *(dihydro-)codeine* (Hall & Mattick, 2007), *hydromorphone* (Oviedo-Joekes et al., 2010), *naltrexone* (an antagonist at μ -, κ -, and σ -opioid receptors) (Krupitsky et al., 2011) and *slow-release oral morphine* (Beck et al., 2014) are also in use for ORT or studied for this indication. However, methadone (respectively levomethadone in Europe) is by far the most frequently used agent in ORT (Bell, 2014), followed by buprenorphine formulations (Nguyen et al., 2013).

Surprisingly, there is little data regarding drug safety related to ORT despite the medical, legal and social importance of this therapeutic regimen. Apart from methadone and levomethadone (Bell & Zador, 2000; Schoofs et al., 2014), the knowledge regarding drug safety or adverse drug reactions (ADR) associated with the above mentioned substances essentially originates from studies with non-opioid-dependent patients (e.g. various pain syndromes, restless legs syndrome, alcohol

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dependence). However, patients with opioid dependence feature several characteristics (e.g. tolerance, potentially abuse of other psychotropic agents, somatic comorbidities) which may not be that frequent among other patient groups and, in addition, may have impact on the kind and severity of ADR related to agents used in ORT. Furthermore, doses of the respective substances may vary considerably depending on their indication (ORT vs. pain management) (Kress, 2009; Trescot et al., 2008). Taking into account these differences, type and frequency of ADR related to ORT may differ from opioid-related ADR in patients without opioid dependence. Finally, the existing safety and tolerability data related to agents used for ORT does not originate from naturalistic treatment settings; this makes the evaluation of the factual safety profile of agents used in ORT setting difficult.

Furthermore, one factor contributing to the limited knowledge on drug safety related to agents used for ORT may be underreporting (incorrectly low reporting rates of ADR) (Hazell & Shakir, 2006) in the context of ORT. The spontaneous reporting of ADR to national pharmacovigilance institutions (that systematically record and analyze spontaneously reported ADR) is of essential for the improvement of drug safety of agents in the postmarketing setting. The reporting behavior of physicians related to ADR occurring in ORT has not yet been studied.

In this regard we developed a questionnaire and performed an explorative survey within a not representative sample of physicians who perform outpatient ORT. We thus intended to retrieve naturalistic data on the physician's perspective on drug safety related to ORT. Besides, we evaluated the physician's reporting behavior concerning ADR related to ORT in order to study, if increased underreporting (Hazell & Shakir, 2006) may be a factor contributing to the lack of knowledge regarding drug safety in ORT in naturalistic treatment settings.

2. Materials and methods

2.1. Study design

A cross-sectional questionnaire-based telephone survey was conducted.

2.2. Study population

All physicians who perform outpatient ORT in Baden-Württemberg (a federal state of Germany with a population of approximately 10.7 million inhabitants in 2014) were considered for the study. Inclusion criterion for physicians was: performance of outpatient ORT in Baden-Württemberg. Identification of these individuals was performed in January 2015 by using an online platform (www.arztsuche-bw.de) that is run by the association of statutory health insurance physicians of Baden-Württemberg ("Kassenärztliche Vereinigung Baden-Württemberg"). This online platform represents a regularly updated information system on physicians working in outpatient care in Baden-Württemberg. It features public access and is controlled by regulatory authorities. It allows to retrieve information related to particular physicians as address of workplace, contact data, medical specialization etc.

2.3. Survey and data collection

A telephone survey among eligible physicians was performed between January and April 2015. Consultation of the local Ethics Committee of the University of Ulm (institutional review board) was performed before starting the survey. As no patients were interviewed and data obtained from the physicians was documented anonymously an ethical approval was not necessary according to the local standards. The identified physicians were contacted by telephone without prior notification using their publicly available business telephone numbers. Within a short introduction physicians were informed about the

purpose of the survey and asked to participate (informed consent). A questionnaire (see below) was completed during the telephone interview (answers were documented by the interviewer). Interviews were conducted in German language. Rejection of participation by an eligible physician was recorded; a failed contact attempt was recorded if an eligible physician could not be contacted on three independent days during the survey period.

2.4. Questionnaire

A standardized questionnaire was created including open questions (free answers), multiple choice questions and questions with seven-point Likert scales (specified response options). The questionnaire was written in German language and not validated before usage. The questionnaire comprises three parts: (i) basic and personal data related to the interview and the respondent (date of the interview; age and sex of the respondent; working as a general practitioner: yes/no; title of medical specialization, if acquired), (ii) items regarding aspects of the participant's ORT practice, frequency and type of observed ADR, and the reporting behavior in regards to ADR associated with outpatient ORT (seven questions; for further elucidation see next paragraph), and (iii) three questions regarding the respondent's reporting behavior of ADR in general (one questions with a seven-point Likert scale, one open question, and one multiple choice question with the possibility to give an additional open answer) [the third part was only partly considered for this study].

The second part of the questionnaire contained the following seven questions: (1) "How many years have you been performing outpatient opioid replacement therapy" (open question); (2) "How many patients with outpatient opioid replacement therapy do you currently treat in your practice?" (open question); (3) "Which of the following substances do you use for outpatient opioid replacement therapy?" (multiple choice question with the following response options [substances that are used/approved for ORT in Germany]: "methadone"/"levomethadone"/"buprenorphine"/"diamorphine"/"codeine"/"dihydrocodeine"); (4) "How frequently do you observe adverse drug reactions related to outpatient opioid replacement therapy performed with one of the above mentioned substances?" (specified response options [seven-point Likert scale]: "always"/"very often"/"often"/"occasionally"/"rarely"/"very rarely"/"never"); (5) "At which of the following substance(s) do you most frequently observe adverse drug reactions in outpatient opioid replacement therapy?" (multiple choice question with the following response options: "methadone"/"levomethadone"/"buprenorphine"/"diamorphine"/"codeine"/"dihydrocodeine"/"I have not noticed any difference between the mentioned substances regarding the frequency of adverse drug reactions."); (6) "At which substance have you already observed which adverse drug reactions in outpatient opioid replacement therapy?" (open answer; the participant is proposed the already mentioned substances ["methadone"/"levomethadone"/"buprenorphine"/"diamorphine"/"codeine"/"dihydrocodeine"] and may indicate any ADR related to one of these substances that he has already observed); (7) "How often do you normally report adverse drug reactions which occur within outpatient opioid replacement therapy performed with one of the above mentioned substances to the competent authority?" (specified response options [seven-point Likert scale]: "always"/"very often"/"often"/"occasionally"/"rarely"/"very rarely"/"never").

Before starting the third part of the questionnaire the respondent was explicitly advised that the following questions refer to her/his complete medical practice and not only to outpatient ORT. For the current analysis only the first questions of the third part was considered: (1) "How often do you normally report adverse drug reactions which you have observed to the competent authority?" (specified response options [seven-point Likert scale]: "always"/"very often"/"often"/"occasionally"/"rarely"/"very rarely"/"never"). (Translation of the above

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