Prevalence and characteristics of patients using opioid analgetics in the emergency department – a retrospective study

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) [1].
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	A

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PROTOCOL SIGNATURE FORM

Study Title	*Prevalence and characteristics of patients using opioid analgetics in the emergency department – a retrospective study*

The project leader has approved the protocol version ***[1.0 (dated 27.08.2019)]***, and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [1, 2], current version of the World Medical Association Declaration of Helsinki [3] and the principles of Good Clinical Practice.

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GLOSSARY OF ABBREVATIONS

BASEC	*Business Administration System for Ethical Committees*
CRF	*Case report form*
FOPH	*Federal Office of Public Health*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
ED	*Emergency Department*

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1 BACKGROUND AND PROJECT RATIONALE

Opioid analgetics are exceedingly used in medicine, with most prescriptions originating from office based settings [PMID 29373155]. Prescription guidelines have been widely utilized [PMID 28663006, 27624507, 26823927], but conflicting data exists regarding a significant effect on prescription practises [PMID 26995800]. Overall there is a decline in prescription opioid related discharges, but a sharp increase in non-prescription related discharges [PMID 28971919].

Opioids are naturally widely used in emergency medicine, but concern is voiced about liberal utilization of opioids before alternative approaches [PMID 29127600] have proven ineffective. The three major concerns are creating dependency, misuse of dispensed drugs and adverse events. To clarify the actual prevalence of medical-use opioid overdose is especially challenging since records show that coding of the ICD diagnosis "opioid intoxication" is often inadequate [PMID 27763703].

Although short term use seems to be unlikely to cause dependency [PMID 26875061], there is evidence that opioid prescription in the ED can lead to dependency in susceptible patients [PMID 28958216, 25534654, 26743334, 20837827].

Opioid misuse is a major concern when prescribing opioid analgetics with rapidly rising prevalence [PMID 29602664], and screening tools for patients at risk for misuse were proposed [PMID 26824227]. It was also shown that patients asking for specific analgetics were at higher risk of misuse [PMID 30013710]. Several studies addressed the increased risk with interventions to a good effect [PMID 27062245, 26056833]. Prescription Drug monitoring systems proved unsuccessful to detect misuse [PMID 26454836], but using data from toxicology infocenters proved successful early detection of misuse behaviour [PMID 24130046].

Regarding adverse events nausea, vertigo and constipation are widely noticed. It could also be shown that patients undergoing opioid therapy have significantly decreased cognitive function measured by MMSE and MOCA [PMID 29137902]. It could also be shown that patients presenting with peripheral vertigo which were also prescribed opioids were at significantly higher risk of fractures than patients without opioids [PMID 28631577]. The incidence of adverse events from opioids prescribed in the ED is generally low and is associated with age, sex and route of administration [PMID 25664538].

It could be shown that opioid overdosing increased in the past ten years, reaching 15.6 per 100 000 population in 2016/17 [PMID 29911820]. It could also be shown that frequent emergency department visits (EDVs) for opioid overdose increased the risk of future overdose and near-fatal events [PMID 24629443]. In another study alcohol was involved in 18.5% of medical-use opioids and 27.2% of benzodiazepine drug abuse-related emergency department visits and 22.1% of medical-use opioids and 21.4% of benzodiazepine drug-related deaths [PMID 25299603].

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There is sparse literature on the characteristics of patients prescribed with opioids and the overall reasons for their emergency department visits. This study aims to clarify the characteristics of patients prescribed with opioids, the indication of the prescription, the dosing and the use of co-analgetics. We want also to clarify the prevalence of opioid related adverse events in our population.

Preliminary studies

- Van Winkle et al found in a retrospective cohort study that advancing age is associated with an increase of opioid prescriptions and higher dosage. Especially white people and females were likely to receive opioids. [PMID 30343960]
- Braden et al analysed administrative claim records and showed that among other conditions the use of schedule II opioids is associated with EDVs and ADEs (alcohol- or drug-related encounters) in adults prescribed opioids for 90 days or more. Short-acting schedule II opioids were associated with increased numbers of EDVs, long-acting schedule II opioids with increased numbers of ADEs. [PMID 20837827]
- In a retrospective cross-sectional study Vijay et al showed that the proportion of prescription of any fentanyl product increased significantly among EDVs and the proportion of prescription of any non-fentanyl opioid product increased significantly among outpatient visits. [PMID 30894321]
- Jones et al revealed that alcohol was commonly involved in EDVs resulting from the abuse of opioids or benzodiazepines as well as in deaths related to these drugs. The percentage of alcohol involvement in EDVs for opioids and benzodiazepines was higher for men compared to women. [PMID 25299603]
- Daoust et al detected that the incidence of adverse events associated with opioid administration in the ED is generally low (12%) and is associated with age (female), sex (65+) and route of administration (iv > sc > po). Additionally, non-opioid co-analgesia with opioid administration did not significantly reduce the risk of adverse events; benzodiazepine use before opioid administration did slightly increase the risk of adverse events. [PMID 25664538]
- In another study, Daoust et al showed that opioid users were more likely to report constipation, nausea/vomiting, dizziness, drowsiness and weakness compared to non-users. A dose-response trend was found for constipation. [PMID 31182367]

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- A data collection of Pedigo et al revealed that the rate of patients with high dose opioid intake and the overall rate of risk of opioid overdose increased significantly from 01/2013 to 10/2016 in the ED of a tertiary care county teaching hospital. [PMID 29602664]
- In a retrospective cohort study it was found by Hasegawa et al that, overall, 53% of the EDVs for opioid overdose resulted in hospitalizations. Furthermore, patients with frequent EDVs for opioid overdose had a higher likelihood of hospitalization. 10% of the EDVs led to near-fatal events; patients with frequent EDVs had a higher likelihood of a near-fatal event. [PMID 24629443]
- By means of a data collection using the ICD-10-CA codes, O'Connor et al found that in Canada hospitalizations and EDVs due to opioid poisoning have increased in the past 10 years, with the greatest increases in rates over the past three years. Patients older than 45 years had the highest rates of opioid poisoning hospitalizations, while patients younger than 45 years had the fastest growing hospitalization rates. [PMID 29911820]
- In contrast, Kay et al showed that in the USA the rates of opioid-related EDVs (not significantly) and hospitalizations (significantly) for patients on chronic opioids have decreased from 2009 to 2015. 2/3 of those with EDVs and nearly ¾ of those with a hospitalization had a co-prescription with benzodiazepines. [PMID 30113319]
- Marco et al identified 70% of the patients presenting with opioid overdose had a history of opioid overdose. The dose of naloxone required was highly variable. A minority reported access to a naloxone kit; most of them stated that their frequency and dosage of opioid use has not changed because of the access to naloxone. [PMID 29776702]
- Choi et al found that compared to non-users, patients who reported use or misuse of opioids had greater odds of any EDV and hospitalization. Those who used (but did not misuse) had more EDVs and longer hospital stays than non-users. [PMID 30585135]
- Doran et al analysed that opioid prescription use was one of the four factors most strongly associated with ED use. Additionally, the percentage of patients who had received a prescription for opioids increased dramatically with increasing ED use. [PMID 23582617]

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

Our study aims to clarify the characteristics of Patients who take opioid analgetics and present themselves to the ED.

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2.2 Primary and secondary endpoints

1. To investigate the prevalence of opioid analgetics in a population of Swiss emergency department patients over 2 years.
2. To clarify the prevalence for each opioid in this population.
3. To evaluate which indications the opioids are taken for.
    a. Cancer
    b. Muscolosceletal
    c. other
4. To clarify whether non-opioid analgetics and co-analgetics were utilized.
5. To identify the proportion of patients in whom the emergency department visit was due to or related to intake of opioids.
6. To clarify the dosages (morphin equivalent) of prescribed opioids
7. To clarify the prevalence of the need to administer naloxone
8. To clarify if opioid users have longer hospitalization than non-users
9. To clarify the prevalence of alcohol and/or benzodiazepine co-intoxikation in the setting of opioid overdosing

2.3 Project design

We plan to conduct a retrospective chart review of all admissions to our Emergency Department (ED) between January 1st 2017 and December 31st 2018. The Department of Emergency Medicine of the Bürgerspital Solothurn is an interdisciplinary Emergency Department treating approximately 35.000 patients per year.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

Inclusion criteria
All patients taking the following medications

- Morphine
- Hydromorphon
- Fentanyl
- Buprenorphin
- Tramadol
- Dihydrocodeine
- Levomethadon
- Methadon
- Oxycodon
- Oxycodon/Naloxon
- Tapentadol
- Tilidin

Exclusion criteria
Patients with age < 18 years.
Patients who withdraw (written or verbally) the right to use their data for scientific purposes.

3.2 Recruitment, screening and informed consent procedure

We plan to conduct a retrospective chart review of all admissions to our Emergency Department (ED) between January 1st 2017 and December 31st 2018. The Department of Emergency Medicine of the Bürgerspital Solothurn is an interdisciplinary Emergency Department treating approximately 35.000 patients per year. Due to the retrospective design of the study and the large patient number in our Dept. of Emergency Medicine (> 35.000 visits/year) a gathering of consent by patients is not feasible.

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3.3 Study procedures

All patient data will be collected by the same persons (PB, BW, GL), and saved coded in a central database. The code does not include the name or date of birth of the individual patients. The database will be accessible only to the persons gathering data and the principal investigator. Of all patients fulfilling the above mentioned inclusion criteria we will gather the following data:

- Demographics (age, sex)
- Comorbidities
- Current Medication
- Indications of the opioid intake
- Reason for current ED consultation and relation to opioid intake
- Need to administer naloxone
- Need of a hospitalization
- Hopsital length of stay
- Mortality
- Presence of alcohol and/or benzodiazepine co-intoxikation
- Creatinine levels

3.4 Withdrawal and discontinuation

Datasets of Patients who withdraw consent or where either written or oral dissent is documented will be deleted from the Database. Overall Number of withdrawn Patients will be stated in the final report.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

Data will be presented as means and standard deviation or medians and interquartile range as appropriate.

Prevalence rates of opioids and respective indications will be given in absolute numbers and percent.

Wilcoxon signed ranked tests will be used for non-normally distributed parameters and t-tests for normally distributed parameters. A p-value of ≤ 0.05 will be considered statistically significant. Statistics will be calculated using PSPP Statistics, published under the GNU General Public License.

4.2. Handling of missing data

Missing Data will be left out in the analysis of the respective Endpoint. If a whole Dataset is missing the Patient will be omitted.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

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This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

5.4 Procedure for investigations involving radiation sources

This Study does not involve radiation sources.

5.5 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.6 End of project

Upon project termination, the Ethics Committee is notified within 90 days. All health-related data are anonymized upon termination of data analysis.

5.7 Insurance

In the event of project-related damage or injuries, the liability of the Bürgerspital Solothurn provides compensation, except for claims that arise from misconduct or gross negligence.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

This is a retrospective study, so no intervention is planned. All data will be coded and only the principal investigators will have insight into the data. Due to the retrospective design of the study and the large patient number in our Dept. of Emergency Medicine (> 35.000 visits/year) a gathering of consent by patients is not feasible.

6.2 Risk-Benefit Assessment

There is no benefit for the participating patients, but since it is a retrospective Data-analysis, we expect no risks.

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

All data handling will be undertaken directly by the investigators. For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

Data will be extracted from the electronic record to a Microsoft Excel file and later transferred to FileMaker Pro. Both files will be password protected stored on a dedicated drive accessible only by the study team. The dedicated drive is part of the Hospital IT Structure and thus subject to data backup procedures, additionally, manual backups will be done regularly. Changes to the files will be tracked and are thus accountable. Unauthorized access is prevented by restrictive access to the dedicated drive and password protection of the files.

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number. The Code will not include any parts able to identify a subject like name or date of birth.
All patient data will be stored in a lockable bin in an office room at the General Hospital Solothurn. Patient data will be entered into a Microsoft Excel database, Microsoft Corporation, Redmond, WA, USA, and stored electronically on a password-protected computer. Electronic patient data will be encrypted and only the investigators (Drs. Woitok, Plüss and Lindner) will be able to identify patients by use of a personal identification number for every patient enrolled in the study. Data will be published anonymously.

7.4 Retention and destruction of study data and biological material

Health related data are stored for 10 years after publication of the research project.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

There is no funding for the project. The Investigators declare no conflict of interest.

9 REFERENCES

1. Ordinance on Human Research with the Exception of Clinical trials (HRO) https://www.admin.ch/opc/en/classified-compilation/20121177/index.html
2. Human Research Act (HRA)
   http://www.admin.ch/opc/en/classified-compilation/20121176/201401010000/810.305.pdf
3. Declaration of Helsinki
   (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects)
4. STROBE statement (http://www.jclinepi.com/article/S0895-4356(07)00436-2/pdf)