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Subcutaneous drugs and off-label use in hospice and palliative care: a scoping review

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Keywords
subcutaneous drug administration, off-label use, hospice care, palliative care, medication safety

Running Title

Off-label subcutaneous drug administration

Key Message

This scoping review summarizes clinical aspects of 17 drugs that are commonly administered subcutaneously in hospice and palliative care despite not holding a marketing authorization for this route of administration (off-label use). The identified lack of structured practice guidelines and pharmacokinetic data indicate a need for further research.

Tables, figures, references, word count

- 3 tables (see p. 14-17)
- 1 figure (see p. 18)
- 82 references (see p. 11-14)
- word count (251 Abstract + 2908 text body= 3159 incl. titles, 'insert table/figure X here', and references)

Background: Subcutaneous drug administration is an interesting approach for symptom control in hospice and palliative care. However, most drugs have no marketing authorization for subcutaneous administration and are therefore used off-label. In order to meet the requirements of a safe and effective drug therapy, especially in highly vulnerable patients, it is essential to investigate the scope of evidence of these common practices.

Objectives: The purpose of this scoping review was to provide an overview of available data on the tolerability and/or effectiveness of subcutaneously administered and off-label used drugs.

Method: We performed a scoping review according to the PRISMA extension to identify data available on the tolerability and/or effectiveness of 17 predefined drugs that are commonly administered subcutaneously in Swiss hospices and hospice-like institutions and that have no marketing authorization (*off-label use*).

Results: The scoping review identified 57 studies with most data available on their tolerability (68% local, 54% systemic), clinical effects (82%), details on dosage (96%) and routes of application (100%). Information on pharmacokinetic properties was mostly missing and only available for fentanyl, levetiracetam, midazolam, and ondansetron. For seven drugs, less than five articles were identified and no studies on codeine or clonazepam were available.

Conclusion: This work provides an overview of current evidence on subcutaneous and off-label used drugs in hospice and palliative care. Although both are common practices, evidence on tolerability and effectiveness, particularly pharmacokinetic data, is limited and the identified information gaps need to be closed. This work establishes a basis for further research in this area.

Introduction

Subcutaneous (SC) drug administration offers a minimal invasive alternative to oral drug administration for symptom control, preferably when oral intake of drugs is severely limited (e.g., due to dysphagia, vomiting or impaired consciousness). [1] It is less invasive than intravenous administration and less painful than intramuscular injections [2], which complies with the comfort-oriented considerations of hospice and palliative care, provided only drugs well-tolerable for SC administration with measurable effect are applied. [3-5] A decline in patients' cognition may lead to a shift in preferences between routes of administration, from mainly oral medication towards parenteral medication. Therefore, the SC administration route becomes increasingly important. [6, 7]

Parenteral drugs can be administered as bolus injection or via infusion. Continuous SC infusions deliver drugs individually or in some cases as a mixture, usually over a period of 24 hours, using a syringe pump. [8] Many drugs used in palliative care hold no marketing authorization for SC administration and are thus used *off-label*. [9] Even though off-label use is a common practice in palliative care, precise requirements and structured practice guidelines for SC drug administration are lacking. [10-12]

In Switzerland, the term *off-label use* is not regulated by law. The Swiss Academy of Medical Sciences (SAMW) defines *off-label use* as «the use of readily available drugs with marketing authorization in Switzerland that deviate from the purpose approved by Swissmedic[1] and from characteristics published in the Swiss drug compendium». [13] The definition thus includes administration of a drug that deviates from its registered and approved indication, dosage, route of application, duration of therapy, and administration in specific patient groups (e.g., children). Off-label use is permissible provided that due diligence is done and there is compliance with established best practice guidelines. [14] The responsibility for the off-label use rests solely with the prescribing physician. To be able to justify off-label uses within the meaning of federal requirements, the physician must demonstrate that the decision is evidence-based or based on solid recommendations (i.e., guidelines of professional associations), and the benefit must clearly exceed any risk. Affected patients must be adequately informed and consent to the treatment must be obtained. [14, 15] As cost coverage of off-label prescriptions is limited, off-label use requires prior approval by the

individual's health insurance provider according to the Swiss Health Insurance Ordinance. [16] Off-label use should not be confused with *unlicensed use*, which alludes to drugs for which no marketing authorization for any indication has been granted by the relevant licensing authority (i.e., Swissmedic). Examples are the import from countries where the drug is licensed by authorities with comparable regulatory drug control or pharmaceutical modifications to registered and approved drugs (e.g., crushing tablets to prepare a solution) and dispensing it in a different form. [13, 17, 18]

[1] Swissmedic is the Swiss national authorization and supervisory authority for drugs and medical products.

To meet the requirements of a safe and effective drug therapy, especially in highly vulnerable patients, it is essential to investigate the scope of evidence of these common practices. The purpose of this scoping review was to obtain a scope of evidence from the literature on the tolerability and/or effectiveness of drugs that are administered subcutaneously and off-label in Swiss hospices and hospice-like institutions.

Method

A protocol was used to document the process of the scoping review that was performed and documented according to the PRISMA extension. [19] The protocol was not previously published. Based on a previous survey study performed in Swiss hospices and hospice-like institutions, we identified 14 drugs that are used subcutaneously and off-label. [20] Additionally, three representatives of the therapeutic drug group of PPIs (esomeprazole, omeprazole, pantoprazole) were included in the scoping review, as a particular request for information on this drug group emerged from the survey (see *Table 1*).

insert Table 1 here

Information sources and search

We performed a scoping review searching in PubMed, Embase, and CINAHL databases. The search string was designed using two topic blocks "Palliative Care Setting" and "Subcutaneous Drug Administration", using MeSH terms and keywords. It was initially developed in PubMed and then translated for use in Embase (using Emtrees) and CINAHL (using Subject Headings). The full electronic search strategy from the search in PubMed is available as a *Supplemental file.* No filters were applied. If a full text article was not available online, employees of the university's library were contacted for procurement.

Selection sources of evidence

The final search was performed on April 6th, 2021. After removing duplicates, title-abstract screening was performed according to the eligibility criteria (see *Eligibility criteria, Table 2)* by two independent reviewers (FD, UW); any discrepancies were resolved through discussion until consensus was reached. In reviews that were excluded according to the pre-defined eligibility criteria, 'backward citation chasing' was applied to identify potentially missed studies. Full text screening was performed by one reviewer (FD) and discussed with two additional reviewers (UW, CMM).

Eligibility criteria

Eligibility criteria are listed in *Table 2*. Included were all publications reporting tolerability and/or effectiveness (clinical effect, blood plasma or serum levels) of the 17 pre-defined drugs of interest (SC administration and off-label use). No restrictions for time of publication were defined. Hypodermoclysis (i.e., SC fluid infusions) was excluded as this scoping review aimed at putting an emphasis on the administration of drugs only.

insert Table 2 here

Data charting process and data items

A detailed table was created for data extraction (i.e., study type, drug, number of patients, tolerability, clinical effect, details on drug administration, and references) with one row for each included publication. The detailed table is provided by the authors upon special request. The charted data was transferred to another, less detailed table (see *Synthesis of results).*

Data was charted independently by one reviewer (FD) and independently repeated in n=6 (approximately 10%) randomly selected studies by a second reviewer (UW). The charted data was discussed among all three reviewers (FD, UW, CMM) to resolve any discrepancies.

Synthesis of results

To summarize the charted data, a table was created (see *Results of individual sources of evidence, Table 3*). References investigating the same drug were grouped and shaded to make them more discernible in the table.

Results

Selection sources of evidence

A total of n=58 identified articles were included for data extraction. Two of the articles were written by the same author [21, 22] and reported the same findings but they were published in different journals at different times. The two articles were combined for data extraction leading to a total of N=57 included articles (see *Figure 1*).

insert Figure 1 here

Characteristics of sources of evidence

Of the included sources, 57.9% (n=33/57) were of European origin. Almost half and thus the majority of the European sources (48.5%, n=16/33) originated from the United Kingdom [21-37] followed by Spain (n=7/33, 21.2%) [38-44] , France [45-47] and Germany [48-50] (both with n=3/33, 9.1% each). Other represented countries were Denmark [51], Italy [52], Portugal [53], and Norway [54], each contributing one source. Australia was the second most represented continent with n=12/57 (21.1%) sources [55-66], followed by North America, with n=7/57 (12.3%) sources. Of those, 57.1% (n=4/7) originated from Canada [67-70] and 42.9% (n=3/7) from the United States [71-73]. One Canadian article [69] was a collaboration with a palliative care unit in Switzerland. The remaining articles originated from South America (n=3/57, 5.3%) with one contribution each from Argentina [74],

Brazil [75], and Uruguay [76]. 3.5% (n=2/57) were of Asian origin, with one article each from China [77] and Japan [78].

Of the included articles, 17.5% (n=10/57) were intervention studies [29, 52, 59-63, 71, 74, 76]. Eight of them were either 12.3% (n=7/57) prospective uncontrolled open-label (pilot) studies [29, 52, 60, 62, 71, 74, 76] respectively one audit [63] published as either clinical notes [71], short/brief reports [60, 76], or original articles [29, 52, 62, 63, 74]. One randomized placebo-controlled double-blind trial [59] and one randomized double-blind cross-over trial [61] were identified. The other articles (n=47/57, 82.5%) were observational studies with more than a third (n=21/57, 36.8%) case reports or series [23, 24, 28, 31, 32, 35, 36, 38, 39, 43, 45, 46, 53-55, 57, 58, 66, 72, 73, 75], followed by 17.5% (n=10/57) descriptive analyses/reports [21, 22, 27, 30, 33, 34, 37, 40, 44, 47-50, 56, 64, 65, 67-70, 77, 78], with nine of those specifically performing either prospective or retrospective reviews/audits of patient records [30, 33, 34, 37, 40, 49, 65, 69, 70], one analyzing case notes [26], and one reviewing service improvement data [25]. Another study [51] performed a cohort study subsequently after retrospectively reviewing patient records. Stability analyses were performed in two studies [41, 42] and only one study performed a pharmacokinetic (PK) analysis [76] that followed a prospective intervention study.

Results of individual sources of evidence

In *Table 3* an overview of the charted data from the literature is presented. The brackets indicate that information presented in the studies was not entirely conclusive or that some of the patients received the reported drug in a drug mixture instead of single drug administrations.

insert Table 3 here

Synthesis of results

The drugs most commonly investigated in the studies were midazolam (n=14/57, 24.6%), levetiracetam (n=8/57, 14.0%), haloperidol (n=8/57, 14.0%), furosemide (n=7/57, 12.3%), and ketamine (n=7/57, 12.3%). Haloperidol was mostly reported as part of a drug mixture. None of the included articles contained studies on subcutaneously administered clonazepam or codeine.

Information on local, systemic and/or general tolerability of the investigated drugs was identified in n=47/57 (71.9%) articles. Most of the patients tolerated SC drug administration well and there were no or only mild reactions such as redness, induration, pain, or edema at the injection site. In most of the reported cases, the reactions could be avoided by changing injection site or increase dilution of the infusion/injection solution. More severe local side effects were described in a few individual study patients, which in some cases required discontinuation of therapy or initiation of antibiotic treatment. The reactions included painful indurations [47, 54] as well as local infections and abscesses [25, 26, 33, 37, 62, 63, 66]. One patient treated with a mixture of levomepromazine and diamorphine developed a necrotic ulcer [28]. Although such severe local reactions usually occurred only in a few individuals, they were primarily described in studies on furosemide [25, 26, 37] and ketamine [54, 62, 63]. Clinical effects were reported in n=47/57 (82.5%) articles. Most of these effects were reported for midazolam (n=8), levetiracetam (n=7), and furosemide and ketamine, both with six studies reporting clinical effects (see *Table 3*).

Information on PK properties (i.e., plasma levels) was available for fentanyl, levetiracetam, midazolam, and ondansetron. Three articles reported plasma concentrations of SC levetiracetam [39, 49, 76], but only one study

performed a full PK analysis for SC levetiracetam [76]. This was the only PK analysis identified among the totally N=57 included articles.

Discussion

This scoping review provides the first overview on important clinical aspects (i.e., tolerability and effectiveness) of SC drug administration in hospice and palliative care. These clinical aspects need to be considered in order to meet the requirements of safe and effective symptom management, especially if drugs are used off-label. The identified scope of evidence reflects that SC administration is essential for symptom control in hospice and palliative care. If in compliance with best practice guidelines [14], off-label use offers treatment options for patients with special symptom control needs for whom conventionally approved routes of administration are inadequate. Hence, in hospice and palliative care, SC drug administration is often associated with off-label use.

Summary of evidence

Information gaps on the tolerability and/or effectiveness (clinical effect, blood plasma or serum levels) of the drugs of interest became evident in the scoping review. Considering the substantial number of drugs of interest, only a rather small number of sources qualified for inclusion and data extraction. For seven drugs (ceftriaxone, esomeprazole, metamizole, olanzapine, omeprazole, ondansetron, pantoprazole), less than five studies were included. Interestingly, all three representatives of the therapeutic group of proton pump inhibitors, that were included in the scoping review upon request, were among these seven drugs. For two drugs (clonazepam, codeine), no studies were identified at all. However, both substances seem to have become less important in hospice and palliative care. The most recent "Model List of Essential Medicines" [79], published by the WHO in 2021, lists only codeine tablets for oral administration among the medicines considered essential for hospice and palliative care, clonazepam is not listed at all. Although the evidence remains low, both drugs are still used in Swiss hospices and hospice-like institutions. The lack of identified information in the literature on the SC administration of most included drugs of interest reflects the need for more evidence to support clinical decision-making by hospice and palliative care physicians, as the responsibility for off-label use rests solely with them. Decisions need to be evidence-based or based on solid recommendations, and the benefits must clearly exceed any risk.

It is particularly important to increase medication safety in highly vulnerable patients. Evidence-based structured guidelines can help to improve medication safety in clinical settings. A lack of structured guidelines on SC drug administration and off-label use pertaining to hospice and palliative care was identified in this scoping review. Structured guidelines are desirable to support clinical decision-making, especially when drugs are used off-label. Guidelines are preferably based on evidence from studies that have investigated the safety and/or effectiveness of drug administration, particularly when administered to highly vulnerable patients, in order to prevent adverse drug events that may affect quality of life.

Even though SC drug administration is usually well-tolerated, there are substances among the 17 investigated drugs that are associated with severe adverse drug reactions (e.g., haloperidol) that can be misinterpreted as symptoms (e.g., extrapyramidal movements). Potentially life-threatening adverse drug reactions (e.g., qt-time prolongation)

may occur. [60] More severe local side effects were also described in individual patients where initiation of antibiotic treatment was required, albeit occurring rarely. [25, 26, 33, 37, 47, 54, 62, 63, 66]. A potentially resulting prescribing cascade must be avoided as this is somewhat contradictory to the approach of maintaining quality of life.

The number of randomized double-blind placebo-controlled or cross-over clinical trials, which are considered to provide the highest level of evidence, was scarce. This study design is particularly difficult to perform in patients of hospice and palliative care due to the complexity and high frailty of this patient population. [80] Randomization into different treatment arms is impractical and blinding is often unethical. Comparison among drugs is nearly impossible due to the high inter-patient variability and required daily doses vary greatly between patients. [76] Drug therapy regimens are adapted to current requirements in symptom control and thus, can change frequently. This lack of high-level evidence results in a deficit of structured guidelines for evidence-based clinical decision-making. As a result, current recommendations on dosage and route of administration to guide drug choice and/or dose tailoring to individual patients are rarely supported by high-level evidence. [81]

Guidelines may also be based on well-documented clinical experience shared among institutions. In Switzerland, no database to facilitate the exchange of clinical experience pertaining to SC drug administration among institutions is available. As a result, most off-label prescriptions and SC drug administration remain low in evidence and are often limited to clinical experience at an institutional level. Available guidelines (e.g., *BIGORIO* Best Practice Guidelines) cover only a part of the broad spectrum of safety and effectiveness of drug administrations in palliative care. [82]

The identified information gaps establish a basis for further research to support clinical decision-making. To provide evidence that subcutaneous drug administration, especially used off-label, is safe and effective in hospice and palliative care patients, studies providing pharmacokinetic data are required.

Limitations

The basis for selection of the drugs of interest was a previously performed survey study in Swiss hospices and hospice-like institutions. Hospice and palliative care physicians and nurses were asked to list all drugs that are subcutaneously administered in their institutions. Findings are therefore mainly of interest for institutions that use a similar list of SC drugs in hospice and palliative care patients. The clinical trial register was not searched for ongoing studies; therefore, the low number of intervention studies potentially underrepresents current progress in research on this topic.

Conclusion

To our knowledge, this is the first scoping review that provides an overview of clinical aspects on subcutaneous drug administration and off-label use in hospice and palliative care. Evidence on tolerability and effectiveness is limited, resulting in a lack of structured guidelines. Although both are common practices, in-depth knowledge is deficient, and the scoping review revealed a need to close existing information gaps, especially on pharmacokinetic properties of commonly used drugs.

Authors' Contributions

All authors contributed to the study conception and design. Preparation, data collection and analysis for the scoping review were performed by FD, CMM and UW. They were supported by SJPM, who contributed her specialist knowledge from hospice care to this project. FD performed the scoping review (support by UW and CMM). Title-abstract screening was performed by FD and UW. The first draft of the manuscript was written by UW and all authors commented on all versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts to disclosure. All authors declare no competing interests nor personal financial interests.

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Tables

Table 1: Drugs that were identified to be used subcutaneously and off-label in Swiss hospices and hospice-like institutions

Drugs used subcutaneously and off-label in Switzerland (n=17)	
• ceftriaxone • codeine • clonazepam • esomeprazole [a] • fentanyl • furosemide • haloperidol • ketamine • levetiracetam	• levomepromazine • metamizole • metoclopramide • midazolam • olanzapine • omeprazole [a] • ondansetron • pantoprazole [a]
[a] additionally added n=3 representatives of proton pump inhibitors	

Table 2: Eligibility criteria for inclusion and exclusion of studies in scoping review

eligibility criteria IN	**eligibility criteria OUT**
• primary literature (intervention and observational studies including case reports and case series)	• non-primary literature (e.g., reviews), editorials, conference abstracts, expert opinions
• studies reporting local and/or systemic tolerability and/or effectiveness (clinical effect, blood plasma levels) of n=17 pre-defined drugs	• reports of drugs that are not among the pre-defined drugs
• drug administration and investigation in patients ≥18 years that receive palliative care	• drug administration and investigation in patients <18 years, non-palliative, or healthy study subjects
• referral of reported tolerability and/or effectiveness (clinical effect, blood plasma levels) to a specific drug or a mixture of active substances that contains at least one of the n=17 drugs of interest, must be feasible	• hypodermoclysis • other routes of application
• language English, French or German	• other languages

Table 3: Overview of extracted data from N=57 articles

References *(see below)*			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Study type																																																												
observational	47	82		x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x				x	x		x	x	x	x			x	x	x	x	x	x		x	x	x		x	x	x	x	x
intervention	10	18	x														x															x	x	x			x					x	x							x				x					
Investigated drug																																																											
ceftriaxone	2	4																																																				x	x			
clonazepam	0	0																																																									
codeine	0	0																																																									
esomeprazole	1	2																	x																																							
fentanyl	5	9																																			x	x	x	x																x			

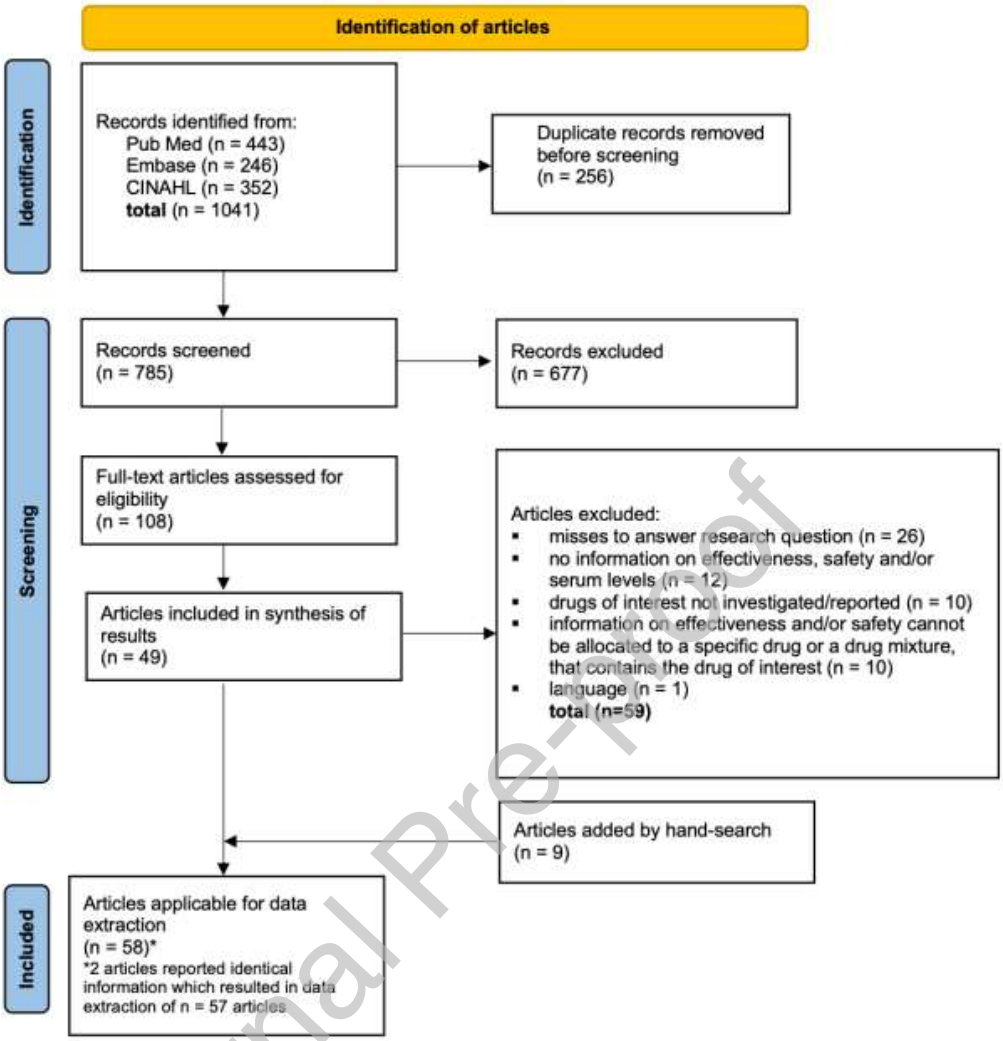
furosemide	7	12									x	x	x	x	x	x																																							x			
haloperidol	8	14																																														x	x	x	x	x		x	x	x	
ketamine	7	12																												x	x	x	x	x	x																			x			
levetiracetam	8	14	x	x	x	x	x	x	x	x																																															
levomepromazine	5	9																																						x	x	x												x	x		
metamizole	1	2																																					x																		
metoclopramide	5	9																																									x	x										x		x	x
midazolam	14	25																		x	x	x	x	x	x	x	x	x	x																									x	x	x	x
olanzapine	2	4														x																																						x			
omeprazole	1	2																	x																																						
ondansetron	4	7																																											x	x	x							x			
pantoprazole	2	4															x																																					x			
Tolerability																																																									
local	39	68	x	x	x	x		x	x	x	x	x			x	x	x	x	x			x					x	x		x		x	x	x	x	x		x				x	(x)	x		x	x	x	x	x	x		x		x	x	x	x	x
systemic	31	54	x	x	x	x		x		x							x	x	x								x	x	x	x	x	x	x	x	x	x	x	x				x	x		x	x				x	x	x		x	x			x	
general information	8	14					x													x	x					x			x										x						x													x
Effectiveness																																																									
clinical effect	47	82	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x		x	x	x	x	x	x	x	x	x	x		x	x	x	x		x	x	x	x	x	x	x		x	x				(x)	
plasma or serum level	6	11	x						x	x														x														x										x										
Information on administration																																																									
dosage	55	96	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	x	x	x	x	x	x	x	x	x	x	x	x	(x)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)			x	x
route of administration	57	100	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
duration of study or of therapy	45	79	x		x	x	x	x	x	x	x	x			x	x	x	x	x	x	x	x					x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x		x	x		x	x	x			x	x
administered in a drug mixture	17	30					x		(x)																	(x)	(x)	(x)	(x)	x											(x)			x				(x)			x	x	x	x		(x)		x	(x)

References: 1 [76] , 2 [33] , 3 [53] , 4 [34], 5 [32], 6 [35], 7 [49], 8 [39], 9 [25], 10 [26], 11 [43], 12 [72], 13 [37], 14 [38], 15 [71], 16 [46], 17 [45], 18 [55], 19 [58], 20 [73], 21 [36], 22 [56], 23 [69], 24 [57], 25 [30], 26 [21], 27 [23], 28 [27], 29 [75], 30 [59], 31 [62], 32 [63], 33 [54], 34 [78], 35 [61], 36 [70], 37 [64], 38 [65], 39 [50], 40 [74], 41 [29], 42 [28], 43 [67], 44 [68], 45 [44], 46 [66], 47 [31], 48 [60], 49 [41], 50 [24], 51 [42], 52 [52], 53 [47], 54 [51], 55 [48], 56 [40], 57 [77]

( ) information presented in the studies was not entirely comprehensible or some of the patients received the drug in a drug mixture and not as individual administration

Figures

Figure 1: Flowchart of articles identified in scoping review



Adapted from: *Page MJ et al. (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews [19]*