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THE QUALITY ASSESSMENT OF ONCOLOGICAL PAIN MANAGEMENT CLINICAL TRIALS IN THE CONTEXT OF A LIMITED NUMBER OF META-ANALYSIS OF OPIOID FORMULATIONS

W. Giermaziak [*1], Ż. Bondaryk [2], A Markowska [2] and T Faluta [3]

PhD, Main Medical Library [1], Chocimska Street 22, 00-791Warsaw, Poland
Main Medical Library [2], Chocimska Street 22, 00-791Warsaw, Poland
PhD Student, Military Institute of Medicine [3], Szaserów Street 128, 04-141 Warsaw, Poland

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Correspondence to Author:
Wojciech Giermaziak

Main Medical Library, Chocimska Street 22, 00-791Warsaw, Poland

E-mail: sekretariat@gbl.waw.pl

ABSTRACT: Treatment ofcancer painis mainly based on the use of opioidanalgesics.This study includes opioids commonly used in Polish clinical practice, such as: dihydrocodeine, tramadol, buprenorphine, morphine, fentanyl, oxycodone and methadone. The purpose of our research is performing a quality assessment of the available clinical trials concerning opioids efficacy and an evaluation of the cause of the limited quantity of systematic reviews in form of meta-analysis. The quality of methodology used in included trials was assessed by Jadad scale. The following databases was searched: Medline (PubMed), Cochrane Library and websites of agencies included in INAHTA (The International Network of Agencies for Health Technology Assessment in Heath). A wide variety of drug dose, dosage forms, routs of administration and pain measuring scales resulted an impossibility of performing a meta-analysis comparing opioids in terms of their effectiveness. Collected studies were assessed for analgesic effect and side effects of opioids therapeutic use, refer to other drugs and depending on doses, frequency of administration, dosage forms (modified/immediate release). The analysis of safety was performed by evaluating the drug-related side effects that resulted an exclusion from the study and general adverse reactions associated with treatment.

INTRODUCTION: The range of the evidence-based researches concerning effectiveness of opioid analgesia used in oncological pain treatment isn't raising doubts. However, we have to take note of deficiency of wide systematic reviews assessing hierarchies of the effectiveness of opioids taking the methodology of meta-analysis into account. A quality assessment of the available clinical research concerning opioid analgesics efficacy and an evaluation of the cause of the limited quantity of systematic reviews in meta-analysis form are the purpose of this study.

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MATERIALS AND METHODS:

A study includes opioids commonly used in Polish clinical practice, such as: dihydrocodeine, tramadol, buprenorphine, morphine, fentanyl, oxycodone and methadone.

For the systematic review of literature following researches were chosen: retrospective, prospective, randomized clinical controlled trials, single/double-blind trials or open-label trials. In the analyzed problem individual opioids, opioids from the same group but varies routes of administration or placebo were used as comparators.

Studies were excluded due to following reasons: theoretical or review type of the publication, too small number of participants (sample size ≤ 10) and also researches focused on mechanisms of disease or mechanisms of the treatment drop-outed of the

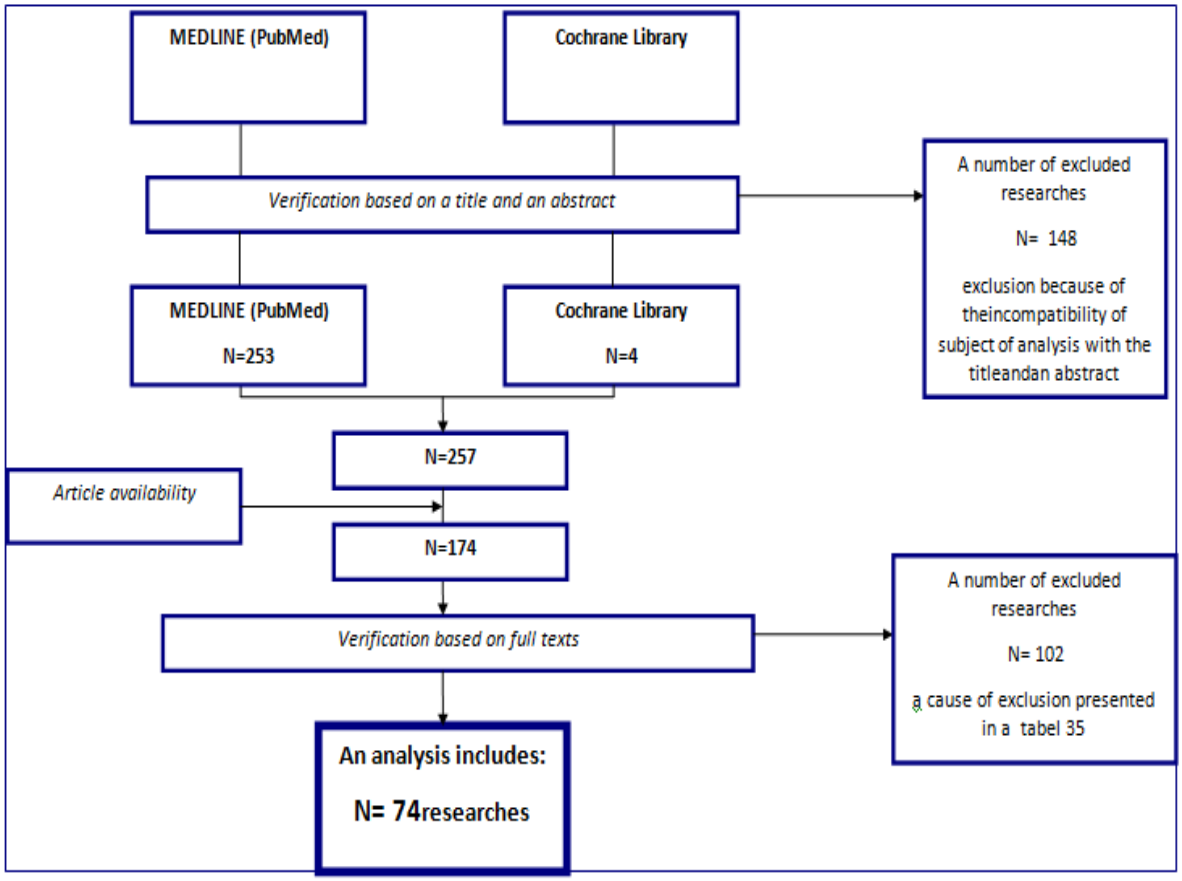
study. The main endpoint of the study is a grade of the analgesic effect of opioids used in neoplasm pain management.

A selection of information was based on a detailed protocol developed before searching and data compilation. Independently of each other, two researchers searched databases and selected the data. The protocol assumed, that in case of the inconsistency between researchers, there will be a discussion all the way to reaching an agreement.
The quality of methodology used in included trials was assessed by Jadad scale. Additionally, the studies were evaluated for the size of the study groups.

The following databases was searched:

- Medline (PubMed)
- Cochrane Library
- Websites of agencies included in INAHTA (The International Network of Agencies for Health Technology Assessment in Heath).

Additionally, researchers used references found in primary and secondary researches. 257 studies were identified, whose full texts were evaluated according to criteria of inclusion or exclusion from the systematic review. A diagram, according to QUOROM, presents the successive stages of searching and selection of primary and secondary research (Fig.1). Finally, for the systematic review of clinical trials included 72 publications.



RESULTS: The evaluation of endpoints of compared intervention was based on assessment of analgesic effect of opioids. A wide variety of drug dose, dosage forms, routs of administration and pain measuring scales before/after opioids administration, resulted an impossibility of performing a meta-analysis comparing opioids in terms of their effectiveness. The results of overview are captured in **Table 1.** The study received a high rate of quality on Jadad scale, from 2to 5 points, with the arithmetic mean of 4, 1 points. The results for morphine trials are captured in **Table 2**.

TABLE 1: THE SUMMARY OF THESCALESOF PAIN MEASURED IN PATIENTS TAKING OPIOIDS INCLUDED IN THE REPORT, ORPLACEBO.

Opioid	Drug dose	Routes of drug administration	Pain measure scale
MOR	15-200 mg/day	oral, mouthwashes, intravenous, subcutaneous, rectal	VAS – visual analog scale McGill pain questionnaire PRT-percentage rating scale VRS – visual rating scale NRS – numeric rating scale CAT- categorical scale BS scale
MET	9-960 mg/day	oral, intravenous	VAS – visual analog scale; McGill pain questionnaire NRS – numeric rating scale
BUP	70 mcg/hours 0,3mg/episodically	transdermal, sublingual, epidural	VAS – visual analog scale NRS – numeric rating scale
FEN	25-400 mcg/hour; 100-800 mg/episodically	transdermal, buccal, oral mucosal, sublingual, intranasal, subcutaneous	MAUC – max area under the pain-time curve; VAS – Visual analog scaleand EORTC card; NRS- Numeric Rating Scale; 5-degree total pain release scale; VAS – visual analog scale
OKS	Different doses	Oral	VRS – visual rating scale; VAS – visual analog scale; CAT- categorical scale
TRA	50-600 mg/day	oral, rectal	VRS - verbal rating scale; VAS - visual analog scale; NRS - numeric rating scale

TABLE 2: THE QUALITY ASSESSMENT OF INCLUDED PRIMARY TRIALS ABOUT MORPHINE, ACCORDING TO JADAD SCALE.

Trials	Randomisation	A double-blinde method	A description of patients retreated or excluded	A summary points on Jaded scale
Mignault 1995[1]	1	1	1	3
Goughnour 1989[2]	2	2	1	5
Portenoy 1989[3]	1	2	1	4
Thirwell 1989[4]	2	2	1	5
Moolenaar 2000[5]	2	2	1	5
Gourlay 1991[6]	1	0	1	2
Cerchetti 2003[7]	2	2	0	4*
Hanks 1995[8]	2	2	1	5
Klepstad 2003[9]	2	2	1	5
De Conno 1995[10]	2	1	0	3*
Ridgway 2010[11]	2	2	1	5
Bruera 1995[12]	2	1	1	4
Elsner 2005[13]	1	0	1	2
Babul 1998[14]	2	1	1	4
O'Brien 1997[15]	2	1	1	4
Hagen 2005[16]	2	1	1	4
Broomhead 1997[17]	2	2	1	5
Currow, 2006[18]	2	1	1	4
Vaino&Tigersted1988[19]	1	0	1	2*

2* a blinde method was not used

Primary researches about morphine:

Collected studies were assessed for analgesic effect and side effects only in case of morphine therapeutic use, refer to other drugs and depending on doses, frequency of administration, dosage forms (modified/immediate release). According to these criteria, [19] researches were included. Two of these studies compared morphine admistered orally with modiefied release (MR) and immediate release (IR) [4, 9]. Thirwell [4] in study focused on immediate released mophine in concentrated form. In five

studies, researches considered the pharmacological action of morphine admistered orally MR, depending on the frequency of administration: every 12 hours versus every 24 hours – 3 studies [15, 16, 17], every 8 hours versus every 24 hours – 1 study[1], every 4 hours versus every 24 hours – 1 study[2]. Another group consists of studies evaluating the effects of morphine MR depending on different power. We included studies which compared following doses: 15mg versus 30mg [11], 100mg versus 3x30mg[3], 100 mg versus 200 mg [8]. One of studies evaluated efficacy of morphine admistered orally efficacy depending on time of day – morning / evening [18]. Three studies [5, 10, 14] compared morphine administered orally versus rectally, which the last two studies took into account modified release forms. One of studies assessed the efficacy of morphine administered orally in form of mouth washes [7]. Four included studies compared drug administration routes: - morphine administrated orally (p.o.) versus morphine administered epidurally versus morphine administrated epidurally with catheter [19]; morphine administered intravenously in bolus (i.v). versus intravenous infusion [6]; - morphine MR administered rectally versus morphine administered subcutaneously (s.c.) [12]. The last study [13] compared morphine IR administered intravenously with morphine IR administered subcutaneously. These data were summarized in Table 3**.**

TABLE 3: MORPHINE -SUMMARY OFCOMPARED INTERVENTIONS FROM PRIMARY RESEARCH.

	Compared interventions	Number of trials
1.	MOR p.o.MR vs MOR p.o. IR	2
3.	MOR p.o.MR vs MOR p.o. MR –various frequency of drug administration	5
4.	MOR p.o.MR vs MOR p.o. MR –various drug doses	3
5.	MOR p.o.MR vs MOR p.o. MR – varioustime of drug administration	1
6.	MOR p.o. MR vs MOR p.r.	3
7.	MOR p.o.vs MOR p.o. - mouthwashes	1
8.	MOR vs MOR- various route of administration (1 study IR vs. IR)	4
	The total number of primary researches	**19**

The analgesic effect was most often measured by VAS scale, which was used in 11 of the 19 studies. In other works, the following scales was used: CAT [3], PPI [4], 10-points NRS [1] and 11-points NRS [11]; BS – 11-points [15]. In Carchetti study 7, researchers measured the time required to achieve analgesic effect defined as good or complete. Table 4 shows the types of intervention and types of morphine analgesic effect assessment scales used in the studies. With these data, it appears that due to the diversity of research and applied scales we can nonperformer meta-analysis.

TABLE 4: MORPHINE - THE SUMMARY OF TYPE OF INTERVENTIONS AND ANALGESIC EFFECT SCALE (PAIN SCALE) USED IN STUDIES.

Compared interventions	Trials	Scales	The number of trials, in which the same scale was used/the total number of trials
1. MOR p.o.MR vs MOR p.o. IR	Klepstad 2003[9]	VAS	0/2
	Thirwell 1989[4]	PPI	
MOR p.o.MR vs MOR p.o. MR- different frequency of drug administration	O'Brien 1997[15]	BS-11 points	4/5
	Hagen 2005[16]	VAS	
	Broomhead1997[17]	VAS	
	Mignault 1995[1]	VAS	
	Goughnour 1989[2]	VAS	
MOR p.o.MR vs MOR p.o. MR- different power(drug doses)	Portenoy 1989[3]	VAS	2/3
	Hanks 1995[8]	VAS	
	Ridgway 2010[11]	NRS	
MOR p.o.MR vs MOR p.o. MR- different time of drug administration	Currow, 2006[18]	VAS	1/1
MOR p.o. MR vs MOR p.r.	De Conno 1995[10]	VAS –percentage change	0/3
	Babul 1998[14]	VAS	

	Moolenaar 2000[5]	NRS	
MOR p.o.vs MOR p.o. - mouthwashes	Cerchetti 2003[7]	Time required to achieve analgesic effect	1/1
MOR vs MOR- different routes of drug administration	Vaino & Tigersted 1988[19]	VAS	4/4
*trial IR vs. IR	Gourlay 1991[6]	VAS	
	Bruera 1995[12]	VAS	
	Elsner 2005[13]	VAS	

Primary research about oxycodone:

This group included eight studies considered oxycodone administered orally. Two studies [20-21] compared modified release oxycodone administered every twelve hours and the immediate released oxycodone. In the remaining six studies [22-27] researchers evaluated the analgesic efficacy of oxycodone modified release in comparison to modified release morphine. Two studies [26-27] described oxycodone and morphine administered every 12 hours. Table 5 presents the summary of these studies.

TABLE 5: OXYCODONE - THE SUMMARY OF TYPE OF INTERVENTIONS.

	Compared interventions	The number of trials
1.	OKS *p.o.*CR vs OKS *p.o.* IR	2
3.	OKS *p.o.*CR vs MOR *p.o.* CR	6
	The total number of primary researches	**8**

In the group which compares oxycodone CR versus oxycodone IR, visual rating scale (VRS) [20] and other 5 – points unspecified scale [21] were used. The second group was less variety in terms of scale which were used. In three researches [22, 24, 25] the VAS scale was used. In Bruera study [27], the intensity of pain was measured by both, VAS and CAT scale. Researchers Heiskanen&Kalso[23] used 4 – points VRS scale, Mucci-LoRusso [26] measured pain by CAT scale. Table 5 presents the summary of type of interventions and analgesic effect scale used in studies.

TABLE 6: OXYCODONE – THE SUMMARY OF TYPE OF INTERVENTIONS AND ANALGESIC EFFECT SCALE (PAIN SCALE) USED IN STUDIES

Compared interventions	Trials	Scales	The number of trials, in which the same scale was used/the total number of trials
OKS *p.o.*MR vs OKS *p.o.* IR	Kaplan 1998[20]	VAS	**0/2**
	Stambaugh 2001[21]	5 points scale	
OKS *p.o.*MR vs MOR *p.o.*MR	Heiskanen 2000 [22]	VAS	**4/6**
	Kalso&Vainio 1990[24]	VAS	
	Lauretti 2003[25]	VAS	
	Bruera 1998 [27]	VAS/CAT	
	Heiskanen&Kalso 1997[23]	VRS	
	Mucci-LoRusso 1998[26]	CAT	

Uniformity of interventions could indicate that implementation of meta-analysis is possible, however, due to the diversity of scales which were used (type, sample size) to measure the effectiveness of analgesic effect, meta-analysis is not possible to perform. Primary research about methadone: This group included three studies [28-30] which present methadone efficacy in comparison to morphine effectiveness. In Grochow study [28], researcher compared methadone and morphine administered intravenously. Two other studies presented methadone and morphine administered orally: morphine SR [29], morphine IR [30]. Table 7 below presents the summary of these studies.

TABLE 7: METHADONE - THE SUMMARY OF TYPE OF INTERVENTIONS.

	Compared interventions	The number of trials
1.	MET *i.v.*vs MOR *i.v.*	1
2.	MET *p.o.*vs MOR *p.o.*	2
	The total number of primary researches	**3**

In each research, analgesic effect was measured by different scale: Grochow [28] - PII (MC Gill Pain Questionnaire), Mercadante [29] – VAS scale, Bruera [30] – differences in the elimination of pain. Table 8 presents the summary of type of interventions and analgesic effect scale used in studies with methadone.

TABLE 8: METHADONE - THE SUMMARY OF TYPE OF INTERVENTIONS AND ANALGESIC EFFECT SCALE (PAIN SCALE) USED IN STUDIES.

Compared interventions	Trials	Scales	The number of trials, in which the same scale was used/the total number of trials
MET *i.v.*vs MOR *i.v.*	Grochow 1989[28]	PII (Mc Gill pain Questionnaire)	**1/1**
MET *p.o.*vs MOR *p.o.*	Mercadante 1998[29]	VAS	**0/2**
	Bruera 2004[30]	-	

The data summared in Table 8 show that meta-analysis is not possible to carry out, due to the diversity of scales which were used to measure the effectiveness of analgesic effect: scale, no scale, type of scale. Primary research about buprenorphine in the buprenorphine group two researches were included: first which compares buprenorphine admistered cutaneously versus placebo [31] and second which compares buprenorphine admistered epidurally versus morphine administered epidurally [32]. Table 9 presents the summary of these studies.

TABLE9: BUPRENORPHINE – THE SUMMARY BASED ON COMPARED INTERVENTIONS.

	Compared interventions	The number of trials
1.	BUP *s.c.*vs placebo	1
2.	BUP *epidural*vs MOR *epidural*	1
	The total number of primary researches	**2**

In both studies, analgesic effect was measured by NRS scale. Table 10 presents the summary of type of interventions and analgesic effect scale used in studies with buprenorphine.

TABLE10: THE SUMMARY OF TYPE OF INTERVENTIONS AND ANALGESIC EFFECT SCALE (PAIN SCALE) USED IN STUDIES.

Compared interventions	Trials	Scales	The number of trials, in which the same scale was used/the total number of trials
BUP s.c.vs placebo	Paulain 2008[31]	NRS	**1/1**
BUP epiduralvs MOR epidural	Pasqualucci 1987[32]	NRS	**1/1**

Although using the same scales in both studies, a meta-analysis is not possible to perform, due to the diversity of forms of buprenorphine and comparators.

Primary researches about fentanyl: This group included twenty primary trials [33-52]. Five publications concerned basic oncological pain management [33-37], and fifteen of them focused on breakthrough pain [38-52]. Among the analyzed publication, three of them compared fentanyl administered transdermally and modified release (SR) morphine administered orally 35-37. Allthese studies refered basic pain. The Kongsgaard study34 compared fentanyl administered transdermally withplacebo in the treatment of basic pain. The following publications concentrated on analysis of OTFC – oral transmucosal fentanyl citrate –

Coluzzi [38], in comparison to immediate-related morphine administered orally – Mercadante [39], morphine administered intravenously – Portenoy [40], other different opioids (MOR, OKS and other) and also with placebo - Farrar [41].

The three researches considered the difference in efficacy and safety between fentanyl buccal tablet (FBT) and placebo [42-44]. A fentanyl pectin nasal spray (FPNS) was compared to modified release morphine administered orally [45-46], as well as placebo[47-48].

An individual studies described intranasal fentanyl spray (INFS) in comparison to oral transmucosal fentanyl citrate (OTFC) [49] or placebo [50].

In two studies [51-52] researched fentanyl buccal soluble film (FBSF) analgetic effectiveness and safety in terms of a placebo. Slatk in [43] compiled fentanyl buccal tablet (FBT) and placebo. One research contained a comparison of subcutaneous fentanyl with morphine subcutaneously administered [33]. Table 11 contains these data.

TABLE 11: FENTANYL - SUMMARY OF INTERVENTION COMPARED IN THE ORIGINAL RESEARCH.

	Compared interventions	The number of trials
1.	TDF vs MOR p.o. SR	3
2.	TDF vs placebo	1
3.	OTFC vs MOR p.o. IR	1
4.	OTFC vs MOR *i.v.*	1
5.	OTFC vs placebo	1
6.	OTFC vs various opioids (MOR, OKS and other)	1
7.	FBT vs placebo	3
8.	FPNS vs MOR p.o. SR	2
9.	FPNS vs placebo	2
10.	INFS vs OTFC	1
11.	INFS vs placebo	1
12.	FBSF vs placebo	1
13.	FBT vs placebo	1
14.	FEN *s.c.*vs MOR *s.c.*	1
	The total number of primary researches	**20**

An analgesic effect was measured mostly in 11-degree NRS scale (used it in 15 trials), in three publications a VAS scale was used [34, 37, 52]. In other researches this effect was measured by following scales: MAUC [36] and a 10-degree NRS scale [41]. Table 12 presents all types of intervention for fentanyl and types of scales used to evaluate analgesic effect, which was analysed in this report. The following data shows that despite of similar scales used to measure an analgesic effect of opioid, its comparators were different, which made it impossible to perform a meta-analysis.

TABLE 12: FENTANYL - SUMMARY OF THE TYPE OF INTERVENTIONS AND THE SCALE OF ANALGESIC EFFECT ASSESSMENT.

Compared interventions	Trials	The type of scale	The number of trials, in which the same scale was used/the total number of trials
TD-F vs MOR p.o. SR	Van Seventer 2003[36]	MAUC	**2/3**
	Ahmedzai 1997[37]	VAS + EORTC card	
	Mercadante 2008 [35]	11-degree NRS	
TDF vs placebo	Kongsgaard 1998[34]	VAS	**1/1**
OTFC vs MOR p.o. IR	Coluzzi 2001[38]	11-degree NRS	**1/1**
OTFC vs MOR i.v.	Mercadante 2007[39]	11-degree NRS	**1/1**
OTFC vs placebo	Farrar 1998[41]	10-degree NRS	**1/1**
OTFC vsvarious opioids (MOR, OKS and other)	Portenoy 1999[40]	11-degree NRS	**1/1**
FBT vs placebo	Portenoy 2006[42]	11-degree NRS	**3/3**

	Slatkin 2007[43]	11-degree NRS	
FBT vs placebo	Zeppetella 2010[44]	11-degree NRS	**3/3**
FPNS vs MOR p.o. SR	Fallon 2011[45]	11-degree NRS	**2/2**
	Davies 2011[46]	11-degree NRS	
FPNS vs placebo	Portenoy 2010[47]	11-degree NRS	**2/2**
	Taylor 2010[48]	11-degree NRS	
INFS vs OTFC	Mercadante 2009[49]	11-degree NRS	**1/1**
INFS vs placebo	Kress 2009[50]	11-degree NRS	**1/1**
FBSF vs placebo	Rauck 2010[51]	11-degree NRS	**1/1**
FBT vs placebo	Lennernas 2010[52]	VAS	**1/1**
FEN s.c.vs MOR s.c.	Hunt 1999[33]	11-degree NRS	**1/1**

Primary researches about tramadol:
According to inclusion criteria, four studies assessing tramadol analgesic effect in neoplasms patients, were included Table 13. Two studies compare tramadol and morphine, both administered orally [53-54]. One study [55] evaluated efficacy of treatment using tramadol modified release and dihydrocodeine. One study [56] compared following interventions: oral dose of immediate and slow release tramadol.

TABLE 13: TRAMADOL – THE SUMMARY OF TYPE OF INTERVENTIONS.

	Compared interventions	The number of trials
1.	TRA *p.o.*vs MOR *p.o*	2
2.	TRA MR vs DHC	1
3.	TRA *p.o.*IR+IR vs TRA *p.o.*IR+SR	1
	The total number of primary researches	**4**

The table below presents different type of scales used to measure analgesic effect of opioids. A VAS scale was used in two studies [54-55], which presented various formulations of tramadol. A Wilder-Smith research [53] measured effectiveness of opioids by VRS scale while Mercadante [56] use 11-points NRS scale. Table 14 presents the summary of type of interventions and analgesic effect scale used in studies with tramadol.

TABLE 14: TRAMADOL - THE SUMMARY OF TYPE OF INTERVENTIONS AND ANALGETIC EFFECT SCALE (PAIN SCALE) USEDIN STUDIES.

Compared interventions	Trials	Scales	The number of trials, in which the same scale was used/the total number of trials
TRA *p.o.*vs MOR *p.o*	Wilder- Smith 1994[53]	VRS	**0/2**
	Leppert 2001[54]	VAS	
TRA MR vs DHC	Leppert 2010[55]	VAS	**1/1**
TRA *p.o.*IR+IR vs TRA *p.o.*IR+SR	Mercadante 2005[56]	11 points - NRS	**1/1**

Due to variety of tramadol dosage forms as well as differences of analgesic effect scale type, a meta-analysis was not feasible.

An assessment of drug safety: The analysis of safety was performed by evaluating the drug-related side effects that resulted an exclusion from the study and general adverse reactions associated with treatment. These studies led to development general profile of typical side effects of opioids such as:

- constipation
- nausea
- vomiting
- dizziness
- somnolence
- sweating
- dementia
- weakness

- confusion
- asthenia.

The highest percentage of patients excluded on account of adverse effect was observed in group using tramadol – 23% and the lowest percentage in group where buprenorphine was used – 1%. Those available results came from small populations (including 107 patients - buprenorphine and 70 patients - tramadol). In the case of morphine, fentanyl and oxycodone - opioids with the largest sample size, the percentage of patients excluded due to side effects developed as follows: 8% - fentanyl, 4% - morphine, 9% - oxycodone. All the results are illustrated in the Fig. 2.

The most common side effects reported during trials and the number of patients excluded due to side effects are listed in Table 15.

TABLE 15: THE MOST COMMON SIDE EFFECTS REPORTED DURING TRIALS, THE NUMBER OF PATIENTS EXCLUDED DUE TO SIDE EFFECTS

Opioid	The most common side effects	Percentage of excluded patients [%]	The number of patients excluded because of side effects	The number of patients involved in the study
MOR	dizziness, nausea, vomiting, somnolence, constipation	4	29	815
MET	sedation, nausea, vomiting, constipation	13	14	107
BUP	constipation, nausea, vomiting, weakness, dizziness, sweating	1	1	106
FEN	constipation, nausea, vomiting, weakness, dizziness, sedation, asthenia	8	151	1908
OKS	nausea, constipation, vomiting, asthenia, dementia, sweating	9	40	439*
TRA	insomnia, dizziness, constipation, nausea, vomiting, confusion, sweating	23	16	70**

* Laurettiresearch [25] excluded because of no information, of which group the patient was excluded(OKS or MOR)
** Wilde- Smith research [53] excluded because of no informations, of which group the patient was excluded (TRAS or MOR)

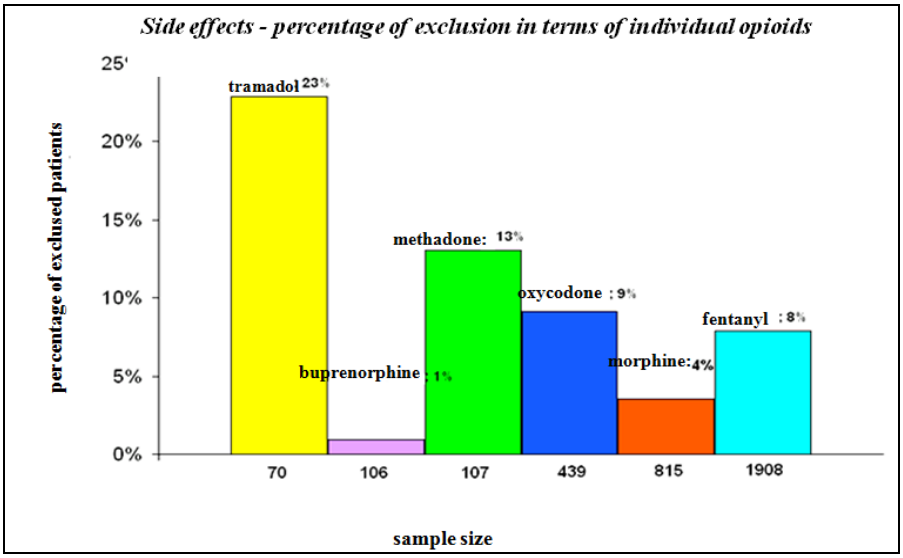


FIG.2: SIDE EFFECTS OF OPIOIDS – PERCENTAGE OF EXCLUSION FOR INDIVIDUAL OPIOIDS.

DISCUSSION: Identified primary studies provide high-quality data. An average rating on Jadad scale is as follows: morphine-3.95; oxycodone-3,38; fentanyl-3.45; methadone-3.33; buprenorphine-3.5

and tramadol-3. While the average for all primary publications achieves 3,43. The main limitation of the study is the fact that searching was carried out without access to the Embase database, which resulted a limited number of research involved. Another limitation is the availability of "head to head" type of research for all analyzed opioids. A morphine is the most commonly used analgetics according to the WHO, and so there are a lot of trials which evaluate its effectiveness in comparison to oxycodone, methadone, fentanyl and tramadol.

Beyond that, even within the group of opiods, there was a wide variety of forms of drug administration. It should also be noted – a various time of analgesic effect intervals (a daily average, an average after stable analgesic effect achievement) and the diversity of pain intensity scales. This had a direct impact on the inability to perform a meta-analysis.
Another limitation is the sizeof population related to the results for various opioids. The smallest number of patients was involved in studies about buprenorphine, methadone and tramadol (less than 250 people for each opioid). Researches about oxycodone included more than 400 patients, about morphine over 800, and fentanyl just over 1900.

In addition to the above, more restrictions which could have a significant impact on the study results, have not been identified.

CONCLUSIONS: The analysis of clinical trials evaluating the efficacy of opioids used in oncological pain treatment is a high-quality research by Jadad scale. They are mostly clinical controlledtrials, with a randomization and single/double-blind method.

The study includes opioids commonly used in the Polish clinical practice, such as: tramadol, buprenorphine, morphine, fentanyl, oxycodone and methadone. An individual studies suggest the effectiveness of various opioids, however, different types of pain intensity assessment scales and the diversity of the studies groups make it impossible to present the meta-analysis. This is probably the main reason for which the number of systematic reviews, especially with a meta-analysis is limited for this therapy. This research confirms the inability to perform a meta-analysis on the basis of the available primary studies, because of important differences in drug dosage, doses and pain assessment scales.

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