EXPLORING THE ANTICANCER EFFECTS OF OPIOIDS: A SCOPING REVIEW OF THE LITERATURE

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Introduction & Aim

Opioids are the most efficacious analgesics against moderate and severe cancer pain. More than 70% of cancer patients take an opioid at some point during their treatment. Although opioids have been extensively studied for their analgesic effects, we know little about their direct effect on cancer. A few studies have reported mixed effects from different opioids in a variety of cancer cell types as regards to the recurrence & progression of cancer. This study aims to present a review of direct opioid properties in different cancer cells found throughout scientific research performed in the last 27 years.

Methods

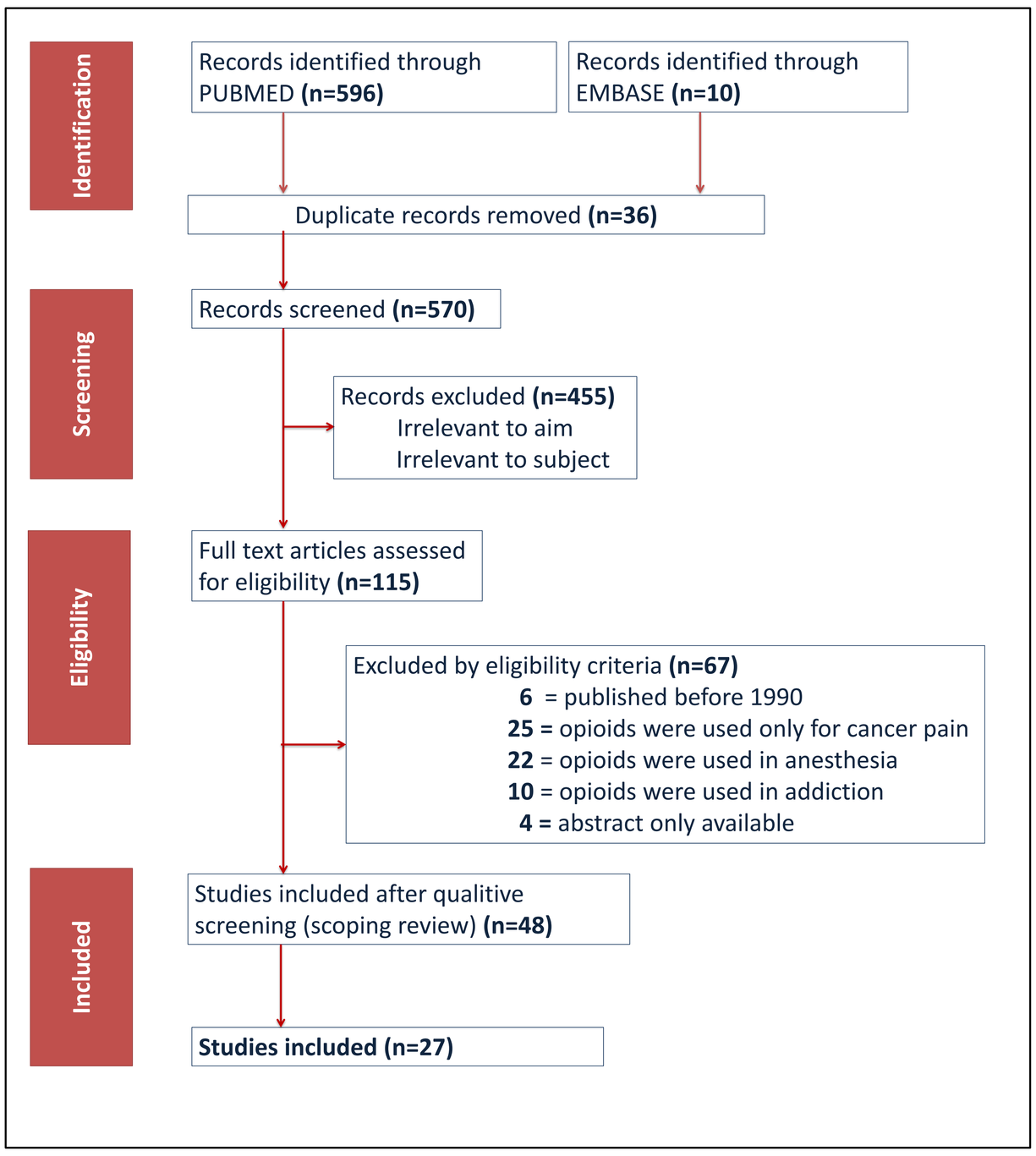

Figure 1. *The PRISMA protocol that was applied as a methodological tool for identifying the relative studies in the literature: we searched PUBMED and EMBASE for original articles using "Opioids and Anticancer Effect" and other relevant keywords. We removed all duplicated articles and screened all records available from which only 115 where relevant to our subject & aim. We then excluded all articles that didn't meet specific inclusion criteria (as shown above) and finally we ended up with a final number of 27 relevant studies to review.*

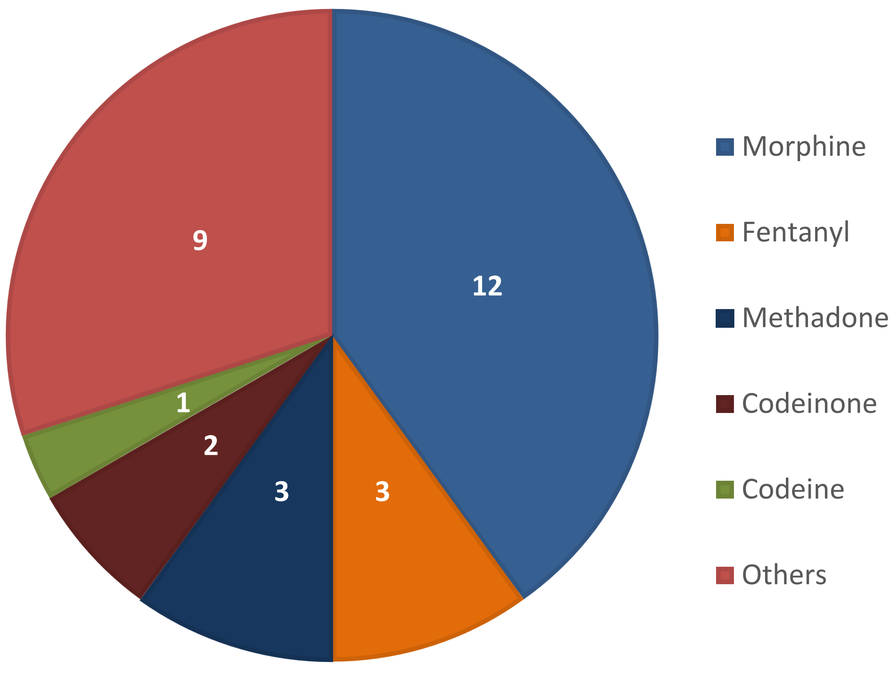

Figure 2. *Pie-chart showing the drugs reported in the studies included in our assessment. The numbers represent the number of studies that provide evidence of anticancer efficacy for each drug.*

Main Results

Drug	Type	Tumor Effect	Reference
Morphine	**Breast cancer cell lines**		
	MCF7	↓ proliferation ↓ growth ↑ apoptosis	Chen, Y. et al.,2017
	Murine 4T1	↓ metastasis ↓ size of nodules	Afsharimani, B. et al., 2014
	T47D	↓ proliferation	Hatzoglou, A. et al., 1996
	Adenocarcinoma cell lines	↑ proliferation ↑ migration of cells	Ecimovic, P. et al., 2011
	Lung cancer cell lines		
	LLC	↓ growth ↓ angiogenesis	Koodie, L. et al., 2014
	Adenocarcinoma - H1975	↓ growth	Kim, JY. et al., 2016
	Human colorectal carcinoma HCT 116	↑ proliferation (6h) ↓ proliferation (12h)	Nomura, Y. et al., 2014
	Human glioblastoma T98G	↓ proliferation ↑ proliferation (>2w)	Lazarczyk, M. et al., 2010
	Human tumor cell lines HL-60 , A549	↑ apoptosis (RM)	Hatsukari, I. et al., 2007
	Gastric cancer cells MGC 803	↓ cell growth ↓ proliferation ↑ apoptosis	Qin, Y. et al., 2012
	Neuroblastoma SH-SY5Y	↑ proliferation (10nM) ↓ proliferation (1μM) (DD)	Gonzalez, V. et al., 2014
	Human prostate cancer LNCaP, DU145, PC3	↓ proliferation	Kampa, M. et al., 1997
Fentanyl	**Human colorectal carcinoma**		
	HCT116	↓ growth ↓ invasion	Zhang, X.-L. et al., 2015
	HCT 116	No effect	Nomura, Y. et al., 2014
	Colorectal cancer	↓ cell invasion ↓ migration	Li, A.X. et al 2015
Methadone	**Leukemia**		
	ALL cells	↑ apoptosis (RM)	Friesen, C. et al., 2013
	HL-60	↑ apoptosis ↓ growth	Friesen, C. et al., 2008
	Lung cancer SCLC	↓ growth	Maneckjee, R. et al., 1992
Codeinone	**Leukemia**		
	HL-60	↑ apoptosis	Hitosugi, N. et al., 2003
	HL-60	↑ apoptosis ↓ proliferation	Takeuchi, R. et al., 2005
Codeine	**Leukemia** HL-60	No effect	Hitosugi, N. et al., 2003
Morphinone	**Leukemia** HL-60	↑non-apoptotic cell death	Takeuchi, R. et al., 2006
Remifentanyl	**Human colorectal carcinoma** HCT116	No effect	Nomura, Y. et al., 2014
U50,488H & TRK820	**HUVECS**	↓ migration ↓ tumor size RM	Yamamizu, K. et al 2013
Biphalin	**Glioblastoma** T98G	↓ proliferation (DD)	Lazarczyk, M. et al., 2010
Protopine	**Prostate cancer** HRPC	↓ proliferation	Chen, C.H. et al., 2012
	Human breast cancer cell MDA-MB-231	↓ cell viability (DD)	Bournine, L. et al., 2013
Noscapine	**Lung Cancer** NSCLC	↑ apoptosis * ↑ p53 expression	Chougule, N. et al., 2011
Buprenorphine	**Lung Cancer** SCC - SCLC – N417 **Breast cancer** MCF-7	↑ apoptosis ↓ cell viability	Yoshida, A. et al., 2000
MNTX	**Lung cancer** LLC	↓ invasion	Mathew, B. et al., 2011

Figure 3*. Major outcomes of opioids on various cancer cell line viability. A549; Adenocarcinoma Human Alveolar Basal Epithelial Cells, ALL; Acute Lymphoblastic Leukemia, DD; dose-dependent manner, HL-60; Human Promyelocytic Leukemia cells, HRPC; Human Hormone Refractory Cancer Cell, HUVEC; Human Umbilical Vein Endothelial cells, LLC; Lewis Lung Carcinoma, MNTX; methylnaltrexone, NSCLC; Non-Small Cell Lung Carcinoma, RM; receptor-mediated effect, SCC; Squamous Cell Carcinoma; (* when administered with cisplatin).*

Limitations & Conclusions

The main **limitations** of our study towards reaching solid conclusions were:

- The relatively low number of studies in the literature for the anticancer effects of opioids
- The diversity in methodology, in tested cell lines tested and in anticancer assays used
- The lack of clinical studies and the limited number of animal studies in the literature

Main conclusions: a number of pre-clinical studies provide preliminary evidence that different opioids can significantly inhibit tumor viability in various experimental settings: Morphine is the most studied opioid for its anticancer effect and there is high consistency in the evidence provided. One of the most used readout of anticancer efficacy is the decrease in cancer cell number (e.g. apoptosis, proliferation, tumor growth), with limited studies looking at other outputs like tumor invasion, metastasis and angiogenesis.

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