

Cannabinoids in Palliative Medicine

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PALLIATIVE CARE

Definition: Palliative Care

Palliative Care is an approach that improves the **quality of life** of **patients** and their **families** facing the problem associated with **lifethreatening illness**, through the **prevention** and **relief of suffering** by means of early identification and impeccable assessment and treatment of pain and other problems, **physical, psycho-social and spiritual**.

WHO 2002

Palliative Care

What do palliative patients expect?

S Good symptom control

E Decisions: mostly shared decision making

N Networking: cooperation of the professionals, proxies and the volunteers

S Support for the teams and the proxies

=> But it begins mostly with good symptom control

PAIN

Pain: knowledge

J Neuroimmune Pharmacol
DOI 10.1007/s11481-015-9600-6

INVITED REVIEW

Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials

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Abstract An updated systematic review of randomized controlled trials examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to PRISMA guidelines for systematic reviews reporting on health care outcomes. Eleven trials published since our last review met inclusion criteria. The quality of the trials was excellent. Seven of the trials demonstrated a significant analgesic effect. Several trials also demonstrated improvement in secondary outcomes (e.g., sleep, muscle stiffness and spasticity). Ad-

Introduction

Chronic pain is a growing public health problem affecting approximately one in five people and predicted to increase to one in three over the next two decades (Blyth et al. 2001; Moulin et al. 2002; Breivik et al. 2006). The prevalence of chronic pain is likely to increase as the population ages and as medical advances continue to improve survival related to cancer, serious injury and dis-

Pain: knowledge

Clinical Crossroads

Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems A Clinical Review

Kevin P. Hill, MD, MHS

IMPORTANCE As of March 2015, 23 states and the District of Columbia had medical marijuana laws in place. Physicians should know both the scientific rationale and the practical implications for medical marijuana laws.

OBJECTIVE To review the pharmacology, indications, and laws related to medical marijuana use.

EVIDENCE REVIEW The medical literature on medical marijuana was reviewed from 1948 to March 2015 via MEDLINE with an emphasis on 28 randomized clinical trials of cannabinoids as pharmacotherapy for indications other than those for which there are 2 US Food and Drug Administration–approved cannabinoids (dronabinol and nabilone), which include nausea and vomiting associated with chemotherapy and appetite stimulation in wasting illnesses.

FINDINGS Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence. Six trials that included 325 patients examined chronic pain, 6 trials that included 396 patients investigated neuropathic pain, and 12 trials that included 1600 patients focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications.

CONCLUSIONS AND RELEVANCE Medical marijuana is used to treat a host of indications, a few of which have evidence to support treatment with marijuana and many that do not. Physicians should educate patients about medical marijuana to ensure that it is used appropriately and that patients will benefit from its use.

JAMA. 2015;313(24):2474-2483. doi:10.1001/jama.2015.6199

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+ CME Quiz at jamanetworkcme.com and CME Questions page 2489

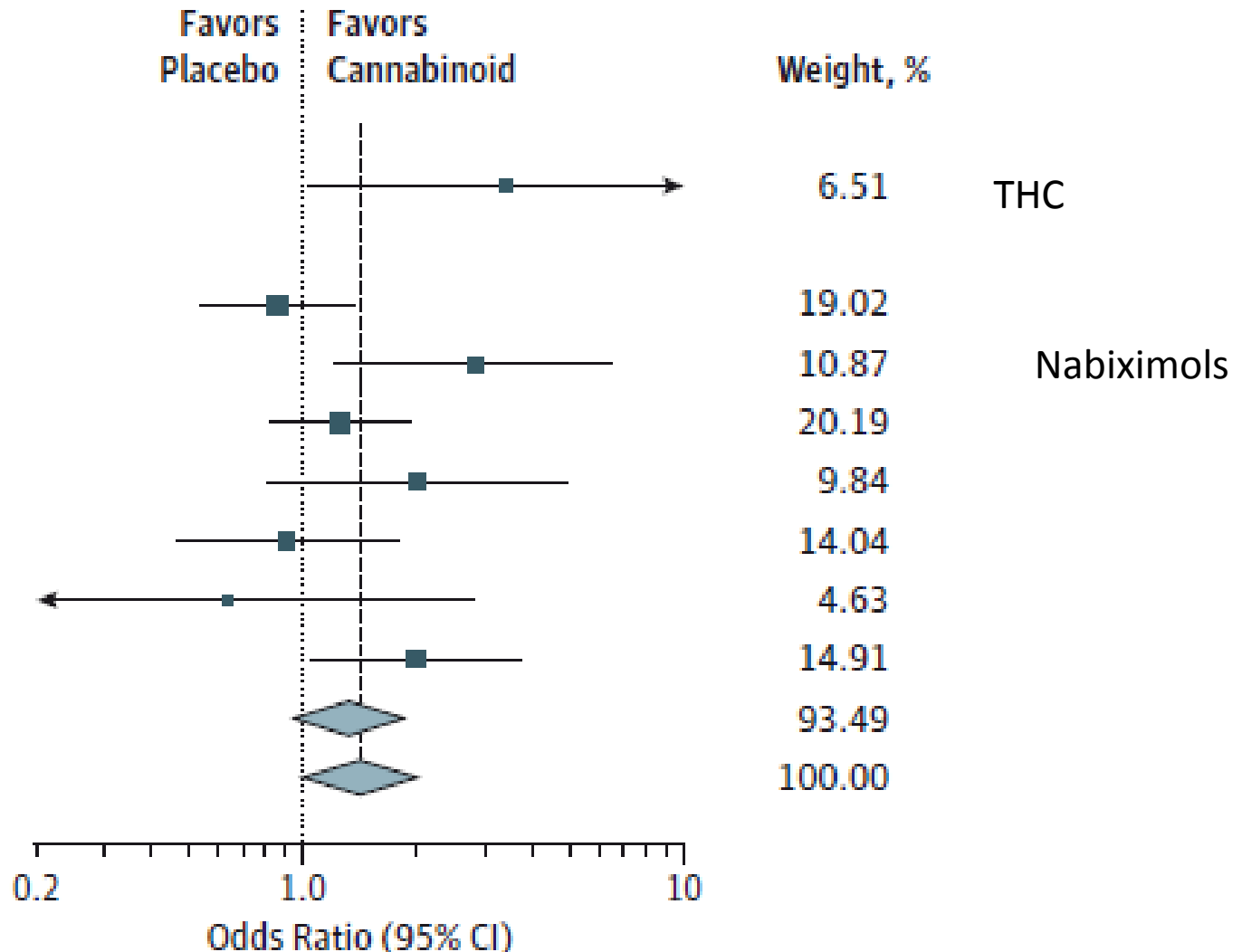
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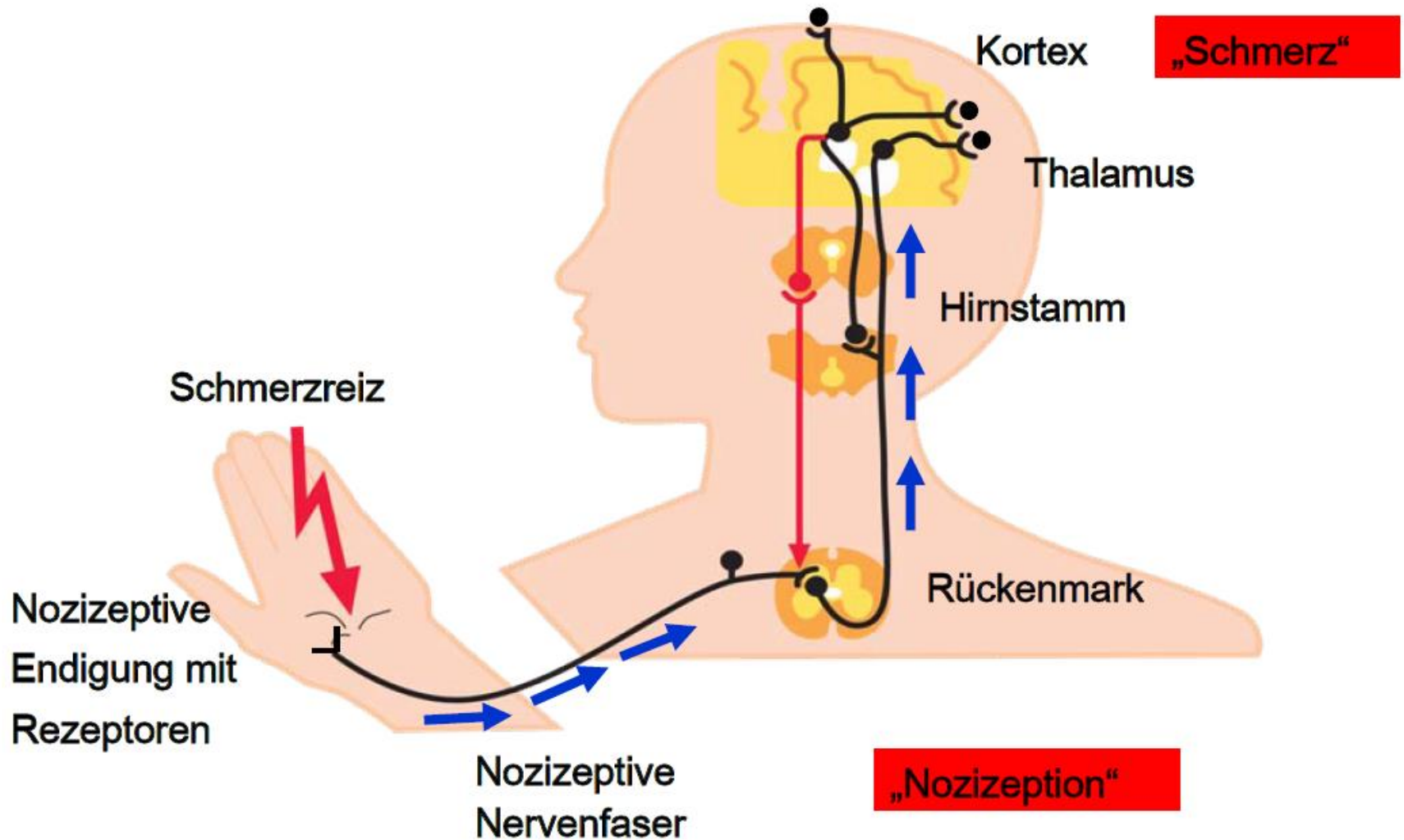
Chronic Pain

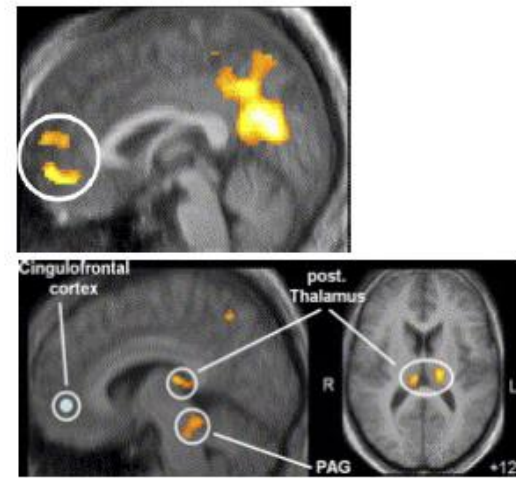
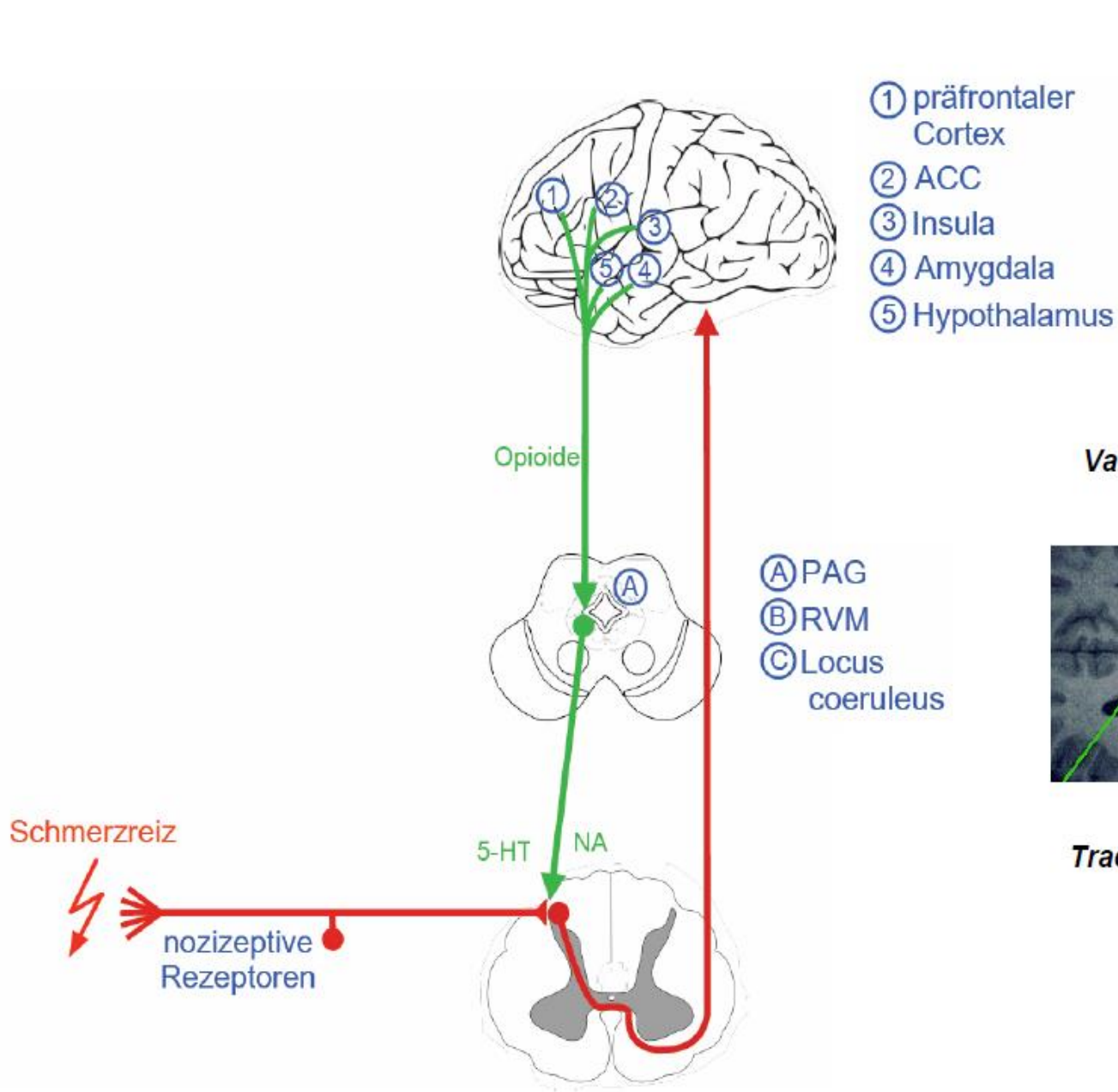
Penny F. Whiting et al. Cannabinoids for Medical Use: a systematic review and meta-analysis. JAMA. 2015;313(24):2456-2473.



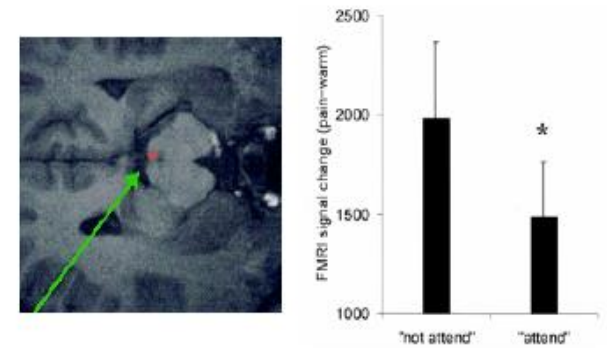
Pain: pathophysiology

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Valet et al. 2004 Pain 109:399



Tracey et al. 2002 J Neurosci 22:2748

Pain therapy in palliative medicine: expert's opinion

Cannabinoids play a little but interesting role for pain therapy in palliative medicine

- In specific (e.g. MS, ALS) diseases cannabinoids might be helpful
- Pathophysiology of pain is very diverse
- We know too little about which cannabinoid for which pain
- Goal is: clear in mind and low in pain

NAUSEA & VOMITING

Nausea & vomiting: knowledge

Limited evidence is available to support the use of cannabis-based medicines (dronabinol, nabilone, THC) in multifactorial nausea in advanced cancer patients.

Cannabinoids (nabilone, dronabinol, THC) are comparable to standard antiemetics for chemotherapy-induced nausea and vomiting that were used before the development of 5-HT₃ antagonists (mostly prochlorperazine, chlorpromazine, domperidone).

Limited evidence is available to support the use of cannabis-based medicines in the therapy of radiotherapy-related

Nausea & Vomiting: Literature

Duran M, Pérez E, Abanades S, et al. (2010) Preliminary efficacy and safety of an oromucosal

standardized cannabis extract in chemotherapy-induced nausea and vomiting. *Br J Clin Pharmacol.* 70(5):656-663

Machado Rocha, F.C., Stefano, S.C., de Cassia Haiek, R., Rosa Oliviera, L.M.Q., da Silveira, D.X. (2008): Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care*, 17:431-443

McCabe M, Smith FP, Macdonald JS, Woolley PV, Goldberg D, Schein PS (1988). Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy. *Invest New Drugs* 6(3):243-246.

Meiri, E., Jhangiani, H., Vredenburg, J.J., Barbato, L.M., Carter, F.J., Yang, H.M., Baranowski, V. (2007): Efficacy of dronabinol alone and in combination with ondansetron versus ondasetron alone for delayed chemotherapy-induced nausea and vomiting. *Curr Med Res Opinion*, 23:533-543.

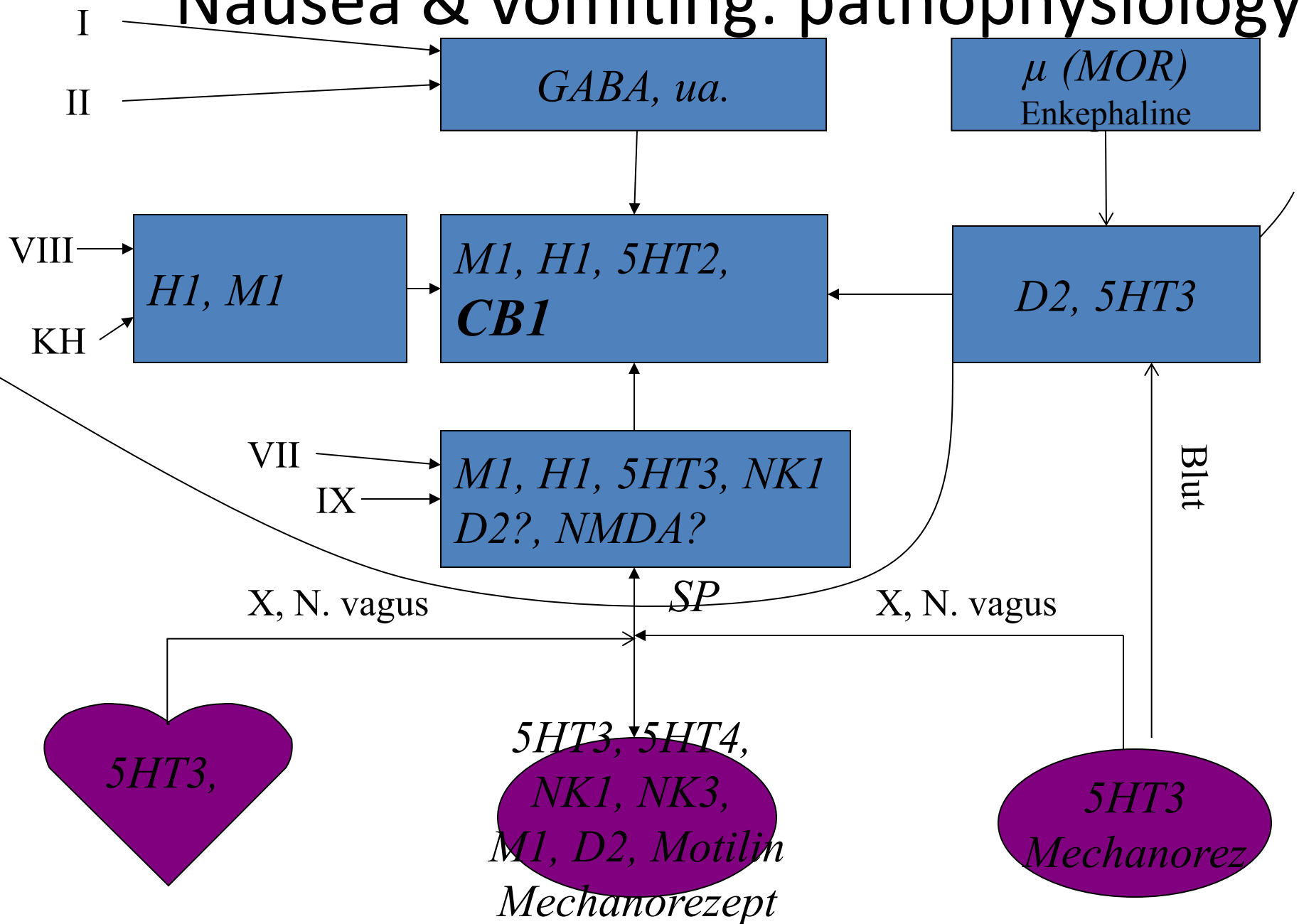
Phillips, R.S., Gopaul, S., Gibson, F., Houghton, E., Craig, J.V., Light, K., Pizer, B. (2010): Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. Cochrane Database of systematic reviews 2010, Issue 9, Art. No. CD007786. DOI: 10.1002/14651858.CD007786.pub2

Priestman,S.G., Priestman,T.J., and Canney,P.A. (1987): A double-blind randomised cross-over comparison of nabilone and metoclopramide in the control of radiation-induced nausea. *Clinical Radiology*, 38:543-544.

Solvay Pharmaceuticals. Dronabinol versus standard ondansetron antiemetic therapy in preventing delayed-onset chemotherapy-induced nausea and vomiting. ClinicalTrials.gov. <http://ClinicalTrials.gov/show/NCT00642512> Accessed April 7, 2014.

Tramer,M.R., Carroll,D., Campbell,F.A., Reynolds,D.J.M., Moore,R.A., and McQuay,H.J. (2001): Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ*, 1-8.

Nausea & vomiting: pathophysiology



Nausea & vomiting: expert's opinion

Cannabinoids have a place in the era of modern antiemetic medication for palliative patients with refractory nausea and vomiting (Case reports for otherwise therapy refractory nausea)

Further research is warranted which cannabinoid for which situation

ANOREXIA & CACHEXIA

Anorexia & cachexia: knowledge

The use of cannabis-based medicines for anorexia and cancer cachexia is at present still unclear, since results of trials were heterogeneous and trials were criticised for methodology (including heterogeneity in stages of cachexia and use of cannabinoids)

THC showed some evidence in weight gain in patients with HIV/AIDS (but megestrol was better), limited evidence suggested increased appetite

Anorexia & cachexia: literature

Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Ann Intern Med.* 2003;139(4):258-266.

Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage.* 1995;10(2):89-97.

Jatoi,A., Windschitl,H.E., Loprinzi,C.L., Sloan,J.A., Dakhil,S.R., Mailliard,J.A., Pundaleeka,S., Kardinal,C.G., Fitch,T.R., Krook,J.E., Novotny,P.J., and Christensen,B. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol.* 2002;20:567-573.

Strasser,F., Lueftner,D., Possinger,K., Ernst,G., Ruhstaller,T., Meissner,W., Ko,Y.D., Schnelle,M., Reif,M., Cerny,T. Comparison of orally administered cannabis extract with and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: A multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *J Clin Oncol.* 2006;24:3394-3400.

Struwe M, Kaempfer SH, Geiger CJ, et al. Effect of dronabinol on nutritional status in HIV infection. *Ann Pharmacother.* 1993;27(7-8):827-831.

Tazi, E., Errihani, H. Treatment of cachexia in oncology. *Indian Journal of Palliative Care.* 2010;16(3): 129-137.

Timpone JG,Wright DJ, Li N, et al; Division of AIDS Treatment Research Initiative. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome: the DATRI 004 Study Group. *AIDS Res Hum Retroviruses*.1997;13(4):305-315.

Anorexia & cachexia: pathophysiology

Involvierte pathogenetische Mechanismen:

- Entzündung
- Neuro-hormonelle Veränderungen
- Hypermetabolismus

(diese sind nicht gänzlich von einander zu trennen)

Führen zu:

- Inappetenz, verminderter Nahrungszufuhr
- Kataboler Stoffwechsellage
- Muskelabbau: verminderter Muskelmasse und -kraft

Tumorkachexie: Stadieneinteilung

adaptiert nach Fearon K (2011) Lancet Oncology

normal	Präkachexie	Kachexie	Refraktäre Kachexie	Tod
	Monitoring Präventive Interventionen	Tumortherapie, Multimodales Management, Ernährungstherapie	Symptomkontrolle	
	Gewichtsverlust <5%	Gewichtsverlust > 5% in 6 Monaten oder BMI < 20 und Gewichtsverlust > 2%	Variabler Grad der Kachexie	
	Anorexie	Häufig reduzierte Nahrungszufuhr		
	metabolische Veränderungen: Insulinresistenz, pathologische Glucosetoleranz	Systemische Entzündung	SW katabol und Tumor non-reponsiv auf Therapie tiefer Funktionsst. WHO 3 o. 4 Erwartete Lebensdauer < 3 Mt	

Anorexia & cachexia: expert's opinion

- In early stage of cachexia: cannabinoids might be helpful
- In late stage of tumor cachexia: cannabinoids might have little to no effect
- In respect to pathophysiology:
 - CBD is more promising than THC in late stage of tumor cachexia
 - Cannabinoids might have more effect on anorexia than on cachexia
- In patients with HIV/AIDS with cachexia and cardiovascular risk factors we have to think about cannabinoids

CANNABIONOIDS: LAST HOPE

Cannabinoids: last hope

Many patients contact us with the question of cannabinoids as tumorspecific therapy

- We aren't as far yet
- We shouldn't create illusion that cannabinoids stop or even cure cancer
- If we «try» a tumor-specific therapy with cannabionoids we should do it in research trials

BARRIERS TO CANNABINOIDS IN PALLIATIVE MEDICINE

Why are cannabinoids so rarely used in Swiss Palliative Care

Administrative barriers

- Palliative medicine => reacts quickly on situations

Knowledge barriers

- We aren't used to use cannabinoids

Patient's barriers are less often than barriers of professionals

- We are more often asked by patients if we could use cannabinoids than we offer cannabinoids to them

OUTLOOK

Visions

- Good research with good concepts
- Cannabionoids as accepted drugs
- Good networking