Allegato al Decreto del Commissario ad ACTA

n. 109/2016 del 28 SET. 2016

POLITICHE DELLA SALUTE - IL COMMISSARIO AD ACTA

ALLEGATO A

Revisione della letteratura

REFERENZE DEGLI ANNI 2015 E 2016

1 Walitt B1, Klose P, Fitzcharles MA, Phillips T, Häuser W. Cannabinoids for fibromyalgia. Cochrane Database Syst Rev. 2016 Jul 18;7:CD011694.

2 Rock EM, Parker LA. Cannabinoids As Potential Treatment for Chemotherapy-Induced Nausea and Vomiting Front Pharmacol. 2016 Jul 26;7:221. doi: 10.3389/fphar.2016.00221. eCollection 2016.

3 Davis MP. Cannabinoids for Symptom Management and Cancer Therapy: The Evidence. J Natl Compr Canc Netw. 2016 Jul;14(7):915-22.

4 Richard J. Schrot & John R. Hubbard Cannabinoids: Medical implications. Annals of Medicine Volume 48, 2016 - Issue 3

5 Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. JAMA. 2015 Jun 23-30;313(24):2474-83. doi: 10.1001/jama.2015.6199.

6 Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. Can Fam Physician. 2015 Aug;61(8):e372-81.

7 Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73.

8 Ostadhadi S, Rahmatollahi M, Dehpour AR, Rahimian R. Therapeutic potential of cannabinoids in counteracting chemotherapy-induced adverse effects: an exploratory review. Phytother Res. 2015 Mar;29(3):332-8. doi: 10.1002/ptr.5265. Epub 2014 Dec 12.

9 Ware MA, Wang T, Shapiro S, Collet JP. COMPASS study team. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). J Pain. 2015 Dec;16(12):1233-42.

10 Andreae MH1, Carter GM2, Shaparin N3, Suslov K4, Ellis RJ5, Ware MA6, Abrams DI7, Prasad H8, Wilsey B8, Indyk D4, Johnson M9, Sacks HS4. Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. J Pain. 2015 Dec;16(12):1221-32.

11 Jensen B, Chen J, Furnish T, Wallace M. Medical Marijuana and Chronic Pain: a Review of Basic Science and Clinical Evidence. Curr Pain Headache Rep. 2015 Oct;19(10):50.

12 Baron EP. Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been .... Headache. 2015 Jun;55(6):885-916.

13 Penny F. Whiting; Robert F.Wolff; Sohan Deshpande, et al. Cannabinoids for Medical Use A Systematic Review and Meta-analysis. JAMA 2015; vol 313 (24): 2456-2473.

Regione Abruzzo Dipartimento per la Salute e il Welfare

Tabella 1 – Riassunto dei principali risultati della revisione sistematica e metanalisi *"Penny F. Whiting; Robert F.Wolff; Sohan Deshpande, et al. Cannabinoids for Medical Use A Systematic Review and Meta-analysis*. JAMA 2015; vol 313 (24): 2456-2473" per indicazione terapeutica.

GLAUCOMA

Un solo clinical trial crossover ha confrontato THC (5mg), cannabidiolo (20 mg), cannabidiolo spray oromucosale (40 mg) e placebo. I risultati non hanno mostrato alcuna differenza tra il placebo e i cannabinoidi sui valori della pressione intraoculare.

Referenze

Tomida I, et al. Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. J Glaucoma 2006; 15 (5): 349-353.

SINDROME DE LA TOURETTE

Due piccoli studi controllati verso placebo (4 reports; 36 partecipanti) suggeriscono che il THC può essere associato a un miglioramento significativo della severità dei TIC nei pazienti con Sindrome de La Tourette.

Referenze

1.Müller-Vahl KR, et al. Treatment of Tourette syndrome with delta-9 tetrahydrocannabinol (delta 9-THC): no influence on neuropsychological performance. Neuropsychopharmacology.2003;28(2):384-388.
2.Müller-Vahl KR, et al. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. J Clin Psychiatry. 2003; 64(4):459-465.
3.Müller-Vahl KR, et al. Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. Pharmacopsychiatry. 2001;34(1):19-24.
4.Müller-Vahl KR, et al. Treatment of Tourette's syndrome with Delta9-tetrahydrocannabinol (THC): a randomized crossover trial. Pharmacopsychiatry. 2002;35(2):57-61.
5. Müller-Vahl KR. Treatment of Tourette syndrome with cannabinoids. Behavioural Neurology 27 (2013):119-124.

Regione Abruzzo Dipartimento per la Salute il Welfare

SPASTICITÀ DOVUTA A SCLEROSI MULTIPLA (SM) O PARAPLEGIA

'14 studi (33 reports; 2280 partecipanti) hanno valutato la spasticità dovuta a SM o paraplegia. 11 studi (2138) hanno incluso pazienti con SM e 3 pazienti con paraplegia (142 partecipanti) causati da traumi al midollo spinale. 6 studi hanno valutato "nabiximols", 3 dronabinolo, 1 nabilone, 4 THC /CBD (2 di questi anche il dronabinolo) 1 ciascuno per ECP002A e THC fumata. Tutti gli studi erano verso placebo nessuno vs un comparator attivo. Due studi erano a basso rischio di bias, 5 a rischio non chiaro di bias e 7 ad alto rischio di bias. Gli studi suggeriscono che i cannabinoidi sono associati a miglioramenti della spasticità, ma senza raggiungere la significatività statistica in molti studi. Non c'erano differenza chiare nel tipo di cannabinoide. Solo gli studi nei pazienti con SM avevano dati sufficienti a generare stime conclusive. I cannabinoidi sono associati con un miglioramento maggiore nella scala di Ashworth per la spasticità rispetto al placebo, anche se non in maniera statisticamente significativa. Sono inoltre associati a un miglioramento medio della spasticità su scale numeriche.

Referenze

1.Hagenbach U, et al. The treatment of spasticity with D9-tetrahydrocannabinol (D9-THC) in patients with spinal cord injury. Paper presented at: IACM2nd Conference on Cannabinoids in Medicine; September 12-13, 2003; Cologne, Germany.

2.GWPharmaceuticals Ltd. A study of cannabis based medicine extracts and placebo in patients with pain due to spinal cord injury. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01606202. Accessed August 25, 2016.

3.Langford RM, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013;260 (4):984-997.

4.Berman J, et al Sativex Spinal Cord Injury Study Group. Sativex in the treatment of central neuropathic pain due to spinal cord injury: a randomised controlled study. Paper presented at: British Pain Society Annual Scientific Meeting; April 2007; Glasgow: United Kingdom.

5. GWPharmaceuticals Ltd. Sativex versus placebo when added to existing treatment for central neuropathic pain inMS. http://ClinicalTrials .gov/show/NCT00391079

6.Zajicek JP, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry 2005;76(12):1664- 1669.

7. Zajicek JP, et al. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012; 83(11):1125-1132.

8.Corey-Bloom J et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. CMAJ. 2012;184(10):1143-1150.

9. Collin C, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res. 2010;32(5):451-459.

10. Pooyania S, et al. A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. Arch Phys Med Rehabil. 2010;91(5):703-707.

11. Collin C, et al. Sativex Spasticity inMS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol. 2007;14(3):290-296.

12. Freeman RM, et al. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomized placebo-controlled trial (CAMS-LUTS). Int Urogynecol J Pelvic Floor Dysfunct. 2006;17(6): 636-641.

13. Wade DT, et al. Do cannabis-based medicinal extracts Cannabinoids for Medical have general or specific effects on symptoms in multiple sclerosis? a double-blind, randomized, placebo-controlled study on 160 patients. Mult Scler. 2004;10(4):434-441.

14. Vaney C, et al. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. Mult Scler. 2004;10(4):417-424.

15. Zajicek J et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomized placebo-controlled trial. Lancet. 2003;362(9395): 1517-1526.

16. Killestein J, et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS.Neurology. 2002; 58(9):1404-1407.

17. Hobart JC, Zajicek JP. Cannabis as a symptomatic treatment for MS: Clinically meaningful MUSEC to the stiffness and walking problems of people with MS. Paper presented at: 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; October 10-13, 2012; Lyon: France. Mult Scler. 2012; 18(4 suppl 1):247.

Regione Abruzzo Dipartimento per la Salute e il Welfare
REGIONE ABRUZZO

18. Zajicek J, et al. Cannabis extract in the treatment of muscle stiffness and other symptoms in multiple sclerosis—Results of the MUSEC study. Paper presented at: 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; September 9-12, 2009; Dusseldorf: Germany. Mult Scler. 2009;15(9) (suppl S):S274 doi:10.1177/1352458509107025.
19. Killestein J et al. The effects of orally administred cannabinoids in multiple sclerosis patients: a pilot study. Mult Scler. 2000;6(1 suppl 1):S28 doi:10.1177 /135245850000600101.
20. Zajicek J, Reif M, Schnelle M; UK MUSEC Study Investigators. Cannabis extract in the treatment of muscle stiffness and other symptoms in multiple sclerosis – results of the MUSEC study. Paper presented at: IACM5th Conference on Cannabinoids in Medicine; October 2-3, 2009; Cologne, Germany.
21. Collin C, et al. A randomised controlled study of Sativex® in patients with symptoms of spasticity due to multiple sclerosis. Paper presented at: 22nd Congress of the ECTRIMS; September 27-30, 2006; Madrid, Spain.
22. Robson P,et al. Cannabis-based medicinal extract (Sativex) produced significant improvements in a subjective measure of spasticity which were maintained on long-term treatment with no evidence of tolerance. Paper presented at: IACM 3rd Conference on Cannabinoids in Medicine; September 9-10, 2005; Leiden, the Netherlands.
23. Center for Medicinal Cannabis Research. Short-term effects of medicinal cannabis therapy on spasticity in multiple sclerosis. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00248378. Accessed August 25, 2016.
24. Institut fur Klinische Forschung Germany; Weleda AG. Multiple Sclerosis and Extract of Cannabis (MUSEC) study. ClinicalTrials.gov. http: //ClinicalTrials.gov/show/NCT00552604.
Accessed August 25, 2016.
25. GWPharmaceuticals Ltd. A study of Sativex® for relief of spasticity in subjects with multiple sclerosis. ClinicalTrials.gov.http://ClinicalTrials.gov/show/NCT00711646. Accessed August 25, 2016..
26. GWPharmaceuticals Ltd. A study to evaluate the efficacy of Sativex in relieving symptoms of spasticity due to multiple sclerosis. ClinicalTrials.gov.http://ClinicalTrials.gov/show
/NCT01599234. Accessed August 25, 2016.
27. GWPharmaceuticals Ltd. An investigation of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in multiple sclerosis patients. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01610700. Accessed August 25, 2016.
28. University of Manitoba, Valeant Canada Limited. Randomized double blind cross over study for nabilone in spasticity in spinal cord injury persons. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00623376. Accessed August 25, 2016.
29. Medical Research Council (MRC). A multiple randomised controlled trial of cannabinoids on spasticity in multiple sclerosis (MS).metaRegister of Controlled Trials. http://www.controlled-trials.com/ISRCTN39371386. Accessed August 25, 2016.
30. Gesellschaft fuer klinische Forschung e.V. Multiple Sclerosis and Extract of Cannabis (MUSEC): a randomised, double-blind, placebo-controlled phase III trial to determine the efficacy and safety of a standardised oral extract of cannabis sativa for the symptomatic relief of muscle stiffness and pain in multiple sclerosis. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctrsearch/search?query=eudract_number:2005-005263-29. Accessed August 25, 2016..
31. Corey-Bloom J, et al. Short-term effects of medicinal cannabis on spasticity in multiple sclerosis. Neurology. 2008;70(11)(suppl 1):A86-A87.
32. Leocani L, et al. Effect of THC-CBD oromucosal spray (Sativex) on measures of spasticity in multiple sclerosis: a double-blind, placebo-controlled, crossover study. Paper presented at: Joint Americas Committee for Treatment and Research in Multiple Sclerosis ACTRIMS—European Committee for Treatment and Research in Multiple Sclerosis ECTRIMS Meeting; September 10-13, 2014; Boston,MA. Mult Scler. 2014;20(1 suppl 1):498 doi:10.1177/1352458514547846.
33. Van Amerongen G, et al. Individualized dosing of a novel oral DELTA9-THC formulation improves subjective spasticity and pain in patients with progressive multiple sclerosis. Paper presented at Joint Americas Committee for Treatment and Research in Multiple Sclerosis ACTRIMS—European Committee for Treatment and Research in Multiple Sclerosis ECTRIMS Meeting; September 10-13, 2014; Boston,MA. Mult Scler. 2014;20(1)(suppl1):478-479 doi:10.1177/1352458514547846.

Regione Abruzzo Dipartimento per la Salute il Welfare

NAUSEA E VOMITO DA CHEMIOTERAPIA

28 studi hanno valutato nausea e vomito da chemioterapia. 14 studi hanno valutato il nabilone e 3 il dronabinolo, 1 "nabiximols", 4 levonantradol, 6 THC. Due studi includevano anche una combinazione di dronabinolo con ondansetron e proclorperazina. 8 studi erano vs placebo, 3 verso un comparator attivo. I comparator attivi più comuni erano proclorperazina (15 studi), clorpromazina (2 studi) e domperidone (2 studi). Altri comparator (alizapride, idroxizina, metoclopramide e ondansetron) sono stati valutati in singoli studi. Dei 28 studi, 23 erano ad alto rischio di bias, non chiaro per 5. Tutti gli studi suggeriscono un maggiore beneficio dei cannabinoidi rispetto ai comparator attivi e al placebo, ma non si raggiunge la significatività statistica in nessuno.

Referenze

1. Broder LE, Lean NL, Hilsenbeck SG. A randomized blinded clinical trial comparing delta-9-tetrahydrocannabinol (THC) and hydroxizine (HZ) as antiemetics (AE) for cancer chemotherapy (CT). Proc Am Assoc Cancer Res. 1982;23:514.
2. Long A,Mioduszewski J, Natale R. A randomized double-blind cross-over comparison of the antiemetic activity of levonantradol and prochlorperazine. Proc Am Soc Clin Oncol. 1982;1: C-220
3. Duran M, Pérez E, Abanades S, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapyinduced nausea and vomiting. Br J Clin Pharmacol. 2010;70(5):656-663.
4. Meiri E, Jhangiani H, Vredenburgh JJ, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin. 2007;23(3):533-543.
5. Lane M, Vogel CL, Ferguson J, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. J Pain SymptomManage. 1991;6(6):352- 359.
6. McCabe M, Smith FP, Macdonald JS,Woolley PV, Goldberg D, Schein PS. Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy. Invest New Drugs. 1988;6(3):243-246.
7. Chan HS, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. Pediatrics. 1987;79 (6):946-952.
8. Pomeroy M, Fennelly JJ, Towers M. Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis. Cancer Chemother Pharmacol. 1986;17(3):
285-288.
9. Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: an alternative antiemetic for cancer chemotherapy. Arch Dis Child. 1986;61(5):502-505.
10. Niederle N, Schütte J, Schmidt CG. Crossover comparison of the antiemetic efficacy of nabilone and alizapride in patients with nonseminomatous testicular cancer receiving cisplatin therapy. Klin Wochenschr. 1986;64(8):362-365.
11. Niiranen A, Mattson K. A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. Am J Clin Oncol. 1985;8(4):336-340.
12. HeimME, QueisserW, Altenburg HP. Randomized crossover study of the antiemetic activity of levonantradol and metoclopramide in cancer patients receiving chemotherapy. Cancer Chemother Pharmacol. 1984;13(2):123-125.
13. Hutcheon AW, Palmer JB, Soukop M, et al. A randomised multicentre single blind comparison of a cannabinoid anti-emetic (levonantradol) with chlorpromazine in patients receiving their first cytotoxic chemotherapy. Eur J Cancer Clin Oncol. 1983;19(8):1087-1090.
14. George M, Pejovic MH, Thuaire M, Kramar A, Wolff JP. [Randomized comparative trial of a new anti-emetic: nabilone, in cancer patients treated with cisplatin]. Biomed Pharmacother. 1983;37(1): 24-27.
15. Jones SE, Durant JR, Greco FA, Robertone A. A multi-institutional phase III study of nabilone vs placebo in chemotherapy-induced nausea and vomiting. Cancer Treat Rev. 1982;9(suppl B):45-48. 16. Wada JK, Bogdon DL, Gunnell JC, Hum GJ, Gota
CH, Rieth TE. Double-blind, randomized, crossover trial of nabilone vs placebo in cancer chemotherapy. Cancer Treat Rev. 1982;9(suppl B):39-44.
17. Johansson R, Kilkku P, Groenroos M. A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. Cancer Treat Rev. 1982;9(suppl B):25-33.
18. Orr LE, McKernan JF. Antiemetic effect of delta 9-tetrahydrocannabinol in chemotherapyassociated nausea and emesis as compared to placebo and compazine. J Clin Pharmacol. 1981;21(8-9 suppl):76S-80S.
19. Einhorn LH, Nagy C, Furnas B, Williams SD. Nabilone: an effective antiemetic in patients receiving cancer

Regione Abruzzo Dipartimento per la Salute e il

chemotherapy. J Clin Pharmacol. 1981;21(8-9 suppl):64S-69S.
20. Orr LE, McKernan JF, Bloome B. Antiemetic effect of tetrahydrocannabinol: compared with placebo and prochlorperazine in chemotherapyassociated nausea and emesis. Arch Intern Med. 1980;140(11):1431-1433.
21. Steele N, Gralla RJ, Braun DWJr, Young CW. Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. Cancer Treat Rep. 1980;64(2-3):219-224.
22. Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. N Engl J Med. 1980;302(3):135- 138.
23. Frytak S, Moertel CG, O'Fallon JR, et al. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy: a comparison with prochlorperazine and a placebo. Ann Intern Med. 1979;91(6):825-830.
24. Ahmedzai S, Carlyle DL, Calder IT, Moran F. Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. Br J Cancer. 1983;48(5):657-663.
25. Ungerleider JT, Andrysiak T, Fairbanks L, Goodnight J, Sarna G, Jamison K. Cannabis and cancer chemotherapy: a comparison of oral delta-9-THC and prochlorperazine. Cancer. 1982;50 (4):636-645.
26. Sheidler VR, Ettinger DS, Diasio RB, Enterline JP, Brown MD. Double-blind multiple-dose crossover study of the antiemetic effect of intramuscular levonantradol compared to prochlorperazine. J Clin Pharmacol. 1984;24(4):155-159.
27. Harden-Harrison MM, MunsellMF, Fisch MJ, et al. Dronabinol for the prevention of nausea from cyclophosphamide and/or adriamycin. Paper presented at: International MASCC/ISOO Symposium: Supportive Care in Cancer; June 28-30, 2012; New York, NY. Support Care Cancer. 2012;20:S209-S210.
28. Grunberg SM, MunsellMF, Morrow PKH, et al. Randomized double-blind evaluation of dronabinol for the prevention of chemotherapy-induced nausea. Paper presented at: Annual Meeting of the American Society of Clinical Oncology (ASCO); 1-5 Jun 2012; Chicago, IL. J Clin Oncol. 2012;30(15)(suppl 1):9061.
29. Lane M, Vogel CL, Ferguson J, et al. Dronabinol and prochlorperazine in combination are better than either single agent alone for treatment of chemotherapy-induced nausea and vomiting. Proc Am Soc Clin Oncol. 1989;8:326.
30. LevittM. Nabilone vs placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients. Cancer Treat Rev. 1982;9(suppl B): 49-53.
31. Chan HS, MacLeod SM, Correia JA. Nabilone vs prochlorperazine for control of cancer chemotherapy-induced emesis in children. Proc Am Soc Clin Oncol. 1984;3:108.
32. 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.
33. Frytak S, Moertel CG, Ofallon JR. Comparison of delta-9-tetrahydrocannabinol (THC), prochlorperazine (PCP) and placebo as anti-emetics for cancer-chemotherapy. Proc Am Assoc Cancer Res. 1979;20:391.
34. Jhangiani H, Vredenburgh JJ, Barbato L, et al. Dronabinol or ondansetron alone and combined for delayed chemotherapy-induced nausea and vomiting (CINV). Blood. 2005;106(11, part 2):477B.
35. McCabe M, Smith FP, Goldberg D, et al. Comparative trial of oral 9 tetrahydrocannabinol and prochlorperazine for cancer chemotherapy related nausea and vomiting. Proc Am Assoc Cancer Res and Am Soc Clin Oncol. 1981;22:416.
36. Herman TS, Einhorn LH, Jones SE, et al. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. N Engl J Med. 1979;300(23):1295- 1297.
37. Melhem-Bertrandt AI, MunsellMF, Fisch MJ, et al. A randomized, double-blind, placebo-controlled trial of palonosetron plus dexamethasone with or without dronabinol for the prevention of chemotherapy-induced nausea and vomiting after moderately emetogenic chemotherapy [Unpublished manuscript]. 2014:1-23

Regione Abruzzo Dipartimento per la Salute il Welfare - Regione Abruzzo

DOLORE CRONICO

E' stato valutato in 28 studi l'effetto dei cannabinoidi sul dolore cronico (63 report; 2454 partecipanti): 13 hanno valutato i "nabiximols", 4 THC fumata, 5 nabilone, 3 THC per via oromucosale, 2 dronabinolo, 1 cannabis vaporizzata (includendo 2 dosi), 1 capsule di acido ajulemico e 1 THC orale. Un trial ha confrontato il nabilone con l'amitriptilina; tutti gli altri studi erano verso placebo.

Le condizioni che causano dolore cronico variano tra gli studi e includono dolore neuropatico (centrale, periferico, o non specificato in 12 studi), 3 dolore oncologico, 3 neuropatia periferica diabetica, 2 fibromialgia, 2 neuropatie sensoriali HIV-associate, 1 studio per ciascuna delle seguenti indicazioni: dolore refrattario nella SM o altre patologie neurologiche, nella artrite reumatoide, nel dolore non-oncologico (nocicettivo e neuropatico), nel dolore centrale, nei problemi muscoloscheletrici, e nel dolore indotto da chemioterapia.

Due studi erano a basso rischio di bias, 9 a rischio non definito, e 17 ad alto rischio. Gli studi suggeriscono miglioramenti del dolore associati all'uso dei cannabinoidi ma senza raggiungere la significatività statistica in molti studi. Il numero medio di pazienti che ha riportato una riduzione del dolore di almeno il 30% era maggiore nel gruppo a cui erano somministrati cannabinoidi rispetto al placebo (OR 1.41 [IC 95% 0.99-2.00]. Un trial ha valutato il THC fumato e ha riscontrato i maggiori benefici (OR 3,43 [IC 95% 1.03-11.48] e 7 trial hanno valutato "nabiximols". In questi studi è stato valutato l'effetto su dolore neuropatico (OR 1.38 [IC95%0.93-2.03]; 6 trial) e dolore oncologico (OR 1.412 [IC95% 0.99-2.00]; 2 trial) senza differenze chiare tra le tipologie di dolore.

"Nabiximols" è anche associato con una riduzione media maggiore nel Numerical Rating Scale valutazione del dolore (differenza media pesata (WMD), -0.46 [IC 95% -0.80 a -0.11]; 6 trial), short form breve per la valutazione del dolore, indice complesso di severità (WMD, -0.17 [IC95%, -0.50 a 0.16]; 3 trial), dolore neuropatico (WMD, -3.89 [IC 95% -7.32 a -0.47]; 5 trial) e la proporzione di pazienti riportanti miglioramenti su una impressione globale di cambio di punteggio (OR 2.08 [IC 95%, da 1.21 a 3.59]; 6 trial) in confronto a placebo. Ci sono alcune evidenze a supportare questi dati ma non sono consistenti nei vari trial. Non c'è differenza nella media di punteggi di qualità di vita misurati con l'indice di stato di salute EQ-5D (WMD, -0.01 [IC95%, -0.05 to 0.02]; 3 trial) tra nabiximols e placebo. Due degli studi inclusi nella metanalisi per il NRS (scala da 0 a 10) hanno valutato pazienti con dolore oncologico, tutti gli altri studi hanno valutato il dolore neuropatico.

Referenze

1. GWPharmaceuticals Ltd. A study of cannabis based medicine extracts and placebo in patients with pain due to spinal cord injury. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01606202.
2. Center for Medicinal Cannabis Research. Efficacy of inhaled cannabis in diabetic painful peripheral neuropathy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00781001.
3. GWPharma Ltd. A double blind, randomised, placebo controlled, parallel group study of Sativex in the treatment of subjects with pain due to diabetic neuropathy. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2004 -002530-20.
4. GWPharmaceuticals Ltd. A study to evaluate the effects of cannabis based medicine in patients with pain of neurological origin. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01606176
5. WareM, FitzcharlesMA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Paper presented at: Canadian Rheumatology Association Meeting; February 18-21, 2009; Kananaskis, AB: Canada. Abstract 149 *J Rheumatol*. 2009;36(11):2607.
6. WareMA, FitzcharlesM-A, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Anesth Analg*. 2010;110(2):604-610.
7. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled parallel group study of THC/CBD oromucosal sprayin combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol*. 2013;260 (4):984-997.
8. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain*. 2013;14(2):136-148.
9. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain*. 2012; 13(5):438-449.
10. WareMA,Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ*. 2010;182(14): E694-E701.
11. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, FallonMT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in

Regione Abruzzo Dipartimento per la Salute e il Welfare ABRUZZO

patients with intractable cancer-related pain. *J Pain SymptomManage*. 2010;39(2):167-179.
12. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S.
Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. *Diabetes Care*. 2010; 33(1):128-130.
13. Ellis RJ, ToperoffW, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34(3):672-680.
14. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain*. 2008;9(6):506-521.
15. Narang S, Gibson D,Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain*. 2008;9(3): 254-264.
16. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J Pain*. 2008;9(2):164-173.
17. Frank B, Serpell MG, Hughes J, Matthews JNS, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ*. 2008;336 (7637):199-201.
18. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain*. 2007;133(1-3):210-220.
19. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007;68(7):515-521.
20. Pinsger M, SchimettaW, Volc D, Hiermann E, Riederer F, PölzW. [Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain—a randomized controlled trial]. *Wien KlinWochenschr*. 2006;118(11-12):327-335.
21. Blake DR, Robson P, Ho M, Jubb RW,McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)*. 2006;45(1):50-52.
22. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 2005;65(6):812-819.
23. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain*. 2004;112(3):299-306.
24. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? randomised double blind placebo controlled crossover trial. *BMJ*. 2004;329 (7460):253.
25. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA*. 2003;290(13): 1757-1762.
26. Noyes R Jr, Brunk SF, Baram DA, Canter A. Analgesic effect of delta-9-tetrahydrocannabinol. *J Clin Pharmacol*. 1975;15(2-3):139-143.
27. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. *J Pain SymptomManage*. 2014;47(1):166-173.
28. Wallace M, Atkinson J, Gouaux B, Marcotte T, Umlauf A. Effect of smoked cannabis on painful diabetic peripheral neuropathy. Paper presented at: 32nd Annual Scientific Meeting of the American Pain Society;May 9-11, 2013; New Orleans: LA. *J Pain*. 2013;14(4)(suppl 1):S62 doi:10.1016/j.jpain.2013.01 .587.
29. Berman J, Bosworth T, Guy G, Stott C; Sativex Spinal Cord Injury Study Group. Sativex in the treatment of central neuropathic pain due to spinal cord injury: a randomised controlled study. Paper presented at: British Pain Society Annual Scientific Meeting; April 2007; Glasgow: United Kingdom.
30. SerpellM, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J Pain*. 2014;18(7): 999-1012.
31. FitzcharlesMA, Shir Y, Joseph L,Ware MA. The effects of nabilone on insomnia in fibromyalgia: results of a randomized controlled trial. Paper presented at: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting (ACR/ARHP 09); November 6-11, 2009; Atlanta: GA. *Arthritis Rheum*. 2009;60:1429.
32. McGill University Health Center. Nabilone versus amitriptyline in improving quality of sleep in patients with fibromyalgia. ClinicalTrials.gov. http: //ClinicalTrials.gov/show/NCT00381199
33. GWPharmaceuticals Ltd. Sativex versus placebo when added to existing treatment for central neuropathic pain inMS. http://ClinicalTrials .gov/show/NCT00391079.
34. Svendsen KB, Jensen TS, Bach FW. [Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis–secondary publication]. *Ugeskr Laeger*. 2005;167(25-31):2772- 2774.
35. Salim K, Schneider U, Burstein S, Hoy L, Karst M. Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. *Neuropharmacology*. 2005;48(8):1164-1171.
36. Pinsger M. Benefit of an add-on-treatment with a synthetic cannabinomimeticum on patients with chronic back pain-a

randomized controlled trial. Paper presented at 8th International Conference on Early Psychosis: From Neurobiology to Public Policy; October 11-13, 2012; San Francisco: CA. *Eur Spine J*. 2012;21(11):2366 doi:10.1007/s00586-012-2522-6.
37. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ. A multi-centre, double-blind, randomized, controlled trial of oro-mucosal cannabis based medicine in the treatment of neuropathic pain characterized by allodynia. *Neurology*. 2005;64(suppl 1):A374.
38. Issa MA, Narang S, Jamison RN, et al. The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. *Clin J Pain*. 2014;30(6):472-478.
39. Abrams DI, Jay CA, Vizoso H, et al. Smoked cannabis therapy for HIV-related painful peripheral neuropathy: results of a randomized, placebo-controlled clinical trial. Paper presented at: IACM 3rd Conference on Cannabinoids in Medicine; September 9-10, 2005; Leiden, the Netherlands.
40. Young CA, Rog DJ. Randomised controlled trial of cannabis based medicinal extracts (CBME) in central neuropathic pain due to multiple sclerosis. Paper presented at: IV Congress of the European Federation of IASP Chapters (EFIC); September 2-6, 2003; Prague, Czech Republic.
41. Berman J, Lee J, Cooper M, et al. Efficacy of two cannabis-based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomized controlled trial. Paper presented at: Pain Society Annual Meeting; April 1-4, 2003; Glasgow, United Kingdom. *Anaesthesia*. 2003;58(9):938
42. Center for Medicinal Cannabis Research. Effects of smoked marijuana on neuropathic pain.ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00254761. Accessed April 7, 2014.
101. Center for Medicinal Cannabis Research. Medicinal cannabis for painful HIV neuropathy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00255580
43. University of California Davis. Center for Medicinal Cannabis Research, VA Northern California Health Care System. Effects of vaporized marijuana on neuropathic pain. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01037088.
44. Center for Medicinal Cannabis Research. Marijuana for HIV-related peripheral neuropathy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00046722. Accessed April 7, 2014.
45. GWPharmaceuticals Ltd. A study of Sativex® for pain relief in patients with advanced malignancy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00530764
46. GWPharmaceuticals Ltd. A study of sativex® for pain relief in patients with advanced malignancy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00674609
47. GWPharmaceuticals Ltd. A study of sativex® for relief of peripheral neuropathic pain associated with allodynia. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00711880
48. GWPharmaceuticals Ltd. A study of sativex in the treatment of central neuropathic pain due to multiple sclerosis. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01604265.
49. GWPharmaceuticals Ltd. A study of sativex® for pain relief due to diabetic neuropathy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00710424
50. GWPharmaceuticals Ltd. A study of Sativex® for pain relief of peripheral neuropathic pain, associated with allodynia. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00710554.
51. Mary Lynch, Capital District Health Authority Canada. Sativex for treatment of chemotherapy induced neuropathic pain. ClinicalTrials.gov. http: //ClinicalTrials.gov/show/NCT00872144.
52. Brigham **andWomen's** Hospital; Solvay Pharmaceuticals. Study to evaluate the efficacy ofdronabinol (Marinol) as add-on therapy for patients on opioids for chronic pain. ClinicalTrials.gov. http: //ClinicalTrials.gov/show/NCT00153192.
53. Winnipeg Regional Health Authority; Valeant Canada Limited. A trial assessing the effect of nabilone on pain and quality of life in patients with fibromyalgia. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00272207.
54. GWPharma Ltd. A double blind, randomised,placebo controlled parallel group study of cannabisbased medicine extract (CBME), in the treatment of peripheral neuropathic pain characterised by allodynia. metaRegister of Controlled Trials. http: //www.controlled-trials.com/ISRCTN38250575.
55. Montreal General Hospital. Pilot study of smoked cannabis for chronic neuropathic pain. metaRegister of Controlled Trials (mRCT), http://www.controlled-trials.com/ISRCTN68314063.
56. GWPharma Ltd. A double blind, randomised, placebo controlled, parallel group study of Sativex, in the treatment of subjects with peripheral neuropathic pain associated with allodynia. EU Clinical Trials Register. https://www. .clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2004-002531-32.
57. Cambridge Laboratories Ltd. A randomised, crossover, double blind comparison of the analgesic effect and patient tolerability of nabilone and dihydrocodeine in chronic neuropathic pain. metaRegister of Controlled Trials. http://isrctn.org /ISRCTN15330757
58. Selvarajah D, Gandhi RA,Witte D, Bowler H,Emery C, Tesfaye S. Treatment of painful diabetic neuropathy with Sativex (a cannabis based medicinal product)—results of a randomized placebo controlled trial. *Diabetologia*. 2006;49 (suppl 1):671-672
59. Rog DJ, Nurmikko T, Young C, Sarantis NS. Randomized controlled trial of sativex, a cannabis based medicine (CBM) in

Regione Abruzzo Dipartimento per la Salute e il Welfare

central neuropathic pain due to multiple sclerosis, followed by an open-label extension. *Neurology*. 2006;66(5):A31.
60. Ventegodt S, Merrick J. Psychoactive drugs and quality of life. *ScientificWorldJournal*. 2003;3:694-706
61. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. *J Pain*. 2015;pii:S1526- 5900(1515)00601-X

STIMOLAZIONE DELL'APPETITO IN PAZIENTI CON HIV

4 studi hanno valutato la stimolazione dell'appetito in pazienti con infezione HIV /AIDS (4 reports; 255 partecipanti). Tutti gli studi hanno valutato dronabinolo, 3 vs placebo e 1 vs megastrol acetato. Ci sono alcune evidenze che il dronabinolo sia associato con aumento di peso rispetto al placebo. Evidenze più limitate che sia anche associato ad aumento di appetito, aumento massa grassa, riduzione di nausea, e miglioramento dello stato funzionale. Sono singoli studi che però non raggiungevano significatività statistica

Referenze

1. Abrams DI, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled trial. Ann Intern Med. 2003;139(4):258-266.
2. Timpone JG, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wqasting syndrome: the Drati 004 Study Group. AIDS Res Hum Retrovuirus. 1997;13(4):305-315.
3. Struwel M, et al. Effect of dronabinol on nutritional status in HIV infection. Ann Pharmacother. 1993; 27(7-8):827-831.
4. Beal JE, et al. Dronabidiol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptoms Manage. 1995; 10(2):89-97.

Dipartimento per la Salute e il Welfare - Regione Abruzzo