

## Evidence-based Medicine

- Sackett らによる "Evidence-Based Medicine" 1990年以降
- 「エビデンスに基づいた医療」を「臨床経験と患者の価値観を最高の研究によって得られたエビデンスと統合すること」と定義
- 臨床的効果の研究と患者の選択は、エビデンスが重要
- ランダム化比較試験 (RCT) を唯一の価値ある決定的エビデンスとして盲目的に固執するのではなく、より広い範囲の臨床上のエビデンスが検証されている。
- 従来のRCTの他に実際的な臨床結果研究や定性的調査研究が含まれる

ホメオパシーはその作用機序がまだ解明できていないことから、プラセボ効果ではないことを証明することのために多くのRCTが報告されてきた。Linde (1997年)らは、ホメオパシーの肯定的な成果は、解釈バイアスでは説明できないことを示した。Shang et al (2005年) は、trialの質は適応を対応させた現代医療の8%と比較すると、ホメオパシーは19%と高い質であることを示した。

一方、2001年に、欧州議会の指令2001/83/ECの第16条 は、RCTのような臨床データのパラメータをホメオパシー薬に適用することの難しさを認めている。

Community Code Relating to Medicinal Products for Human Use. 2001/83/EC. Strasbourg: European Commission, 2001.

### I. 広範囲なメタアナリシス

1991年以降、ホメオパシーに関する6つの広範なレビューが発表された。

- 1) Kleijnen J, Knipschild P, ter Riet G. Clinical trials of homeopathy British Medical Journal 1991;302:316-323.

説明できる結果をもつ105の研究。有効な基準に基づくメタアナリシス。

- 77%の研究は、ホメオパシーの肯定的な結果を示している。
- これらの結果は、trialの質に関してホメオパシーに好意的。
- ホメオパシーのさらなる評価のために法的な議論が必要である。

- 2) Boissel JP, Cucherat M, Haugh M, Gauthier E. Critical literature review on the effectiveness of homoeopathy: overview of data from homoeopathic medicine trials. Homoeopathic Medicine Research Group. Report to the European Commission. Brussels 1996, 195-210

15の研究。厳密性の高い研究のみを含む（高品質）。

- 15 研究の、組合せp値は有意 ( $p = 0.0002$ )。
- ホメオパシーはプラセボよりも有効であることは明らか。
- 未発表の否定的結果の証拠は、ほとんどない。さらなる研究が必要。

- 3) Linde K e.a. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebocontrolled trial. Lancet 1997;350:834-43

89の研究。

■オッズ比 2.45 (95% CI, 2.05-2.93)はホメオパシーに有利。

■ 最良の26研究の オッズ比 は、1.66。

■ ホメオパシーの臨床効果が、全般的にプラセボに起因することはない。

4) Linde K, Melchart D. Randomized controlled trials of individualized homeopathy: a state-of-the art review. J Alter Complement Med 1998;4: 371-88.

個別性に処方されたホメオパシー(Individualised homeopathy)のみに関する研究を含め32の研究。

■個別性に処方されたホメオパシは、プラセボより有効:組合せ係数の値は1.62だった (95% CI, 1.17-2.23)。

■ さらなる実用的な研究が必要。

5) Cucherat, M. et. al. Evidence of clinical efficacy of homeopathy. A meta-analysis of clinical trials. Eur J Clin Pharmacol 2000;56: 27-33.

プラセボと17の比較を示す16のtrial (Boissel 1996 研究のデータに基づく)。

■ 肯定的な結果を示す研究がいくつかある。期待以上に多くのtrialは肯定的な結果を示している。

■ 出版バイアスはない。

■ 多くの臨床試験が必要。

6) Shang A, Huwiler-Muntener K, Nartey L, Juni P, Dorig S, Sterne JA, Pewsner D, Egger M. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. Lancet 2005;366(9487):726-32.

110のtrialが含まれているが、最終結論は、8つのtrailの選択に基づく。

ただし解析はQUOROM (Quality of Reporting of meta-Analysis) のガイドラインに従っていない

■ファンネル・プロットに差はなかった。出版バイアスはいずれにおいても存在した。

■分析対象を高品質の大規模な trial に限定した場合、ホメオパシーの 8 つの異なる疾患に関する trial のオッズ比は 0.88 (95%CI=0.65-1.19)、6つの現代医療の trial のオッズ比は 0.58 (0.39-0.85) であった:ホメオパシーレメディの特定な効果の証拠としては弱い、現代医療の介入の特定な効果の強力な証拠とした。ただし 6 つの現代医療の trial はホメオパシーの 8 つの trial の疾患に対応したものが不明。

■ ホメオパシーtrialの質は優れている:質の高いtrialはホメオパシーのtrialは21 あり全体の19%、現代医療は9で 8%。

■ ホメオパシーは、急性上気道感染に有効 (オッズ比0.36 [95% CI 0.26-0.50])、解釈バイアス適応なしの8つのtrialに基づく。

## II. その他の系統的レビューもしくはメタアナリシス

15の特定疾患分野におけるホメオパシーRCTを中心とした系統的レビューもしくはメタアナリシスが報告されている。

### **ホメオパシーの効果があるとする論文**

1)Bornhöft G, Wolf U, Ammon K, et al. Effectiveness, safety and cost-effectiveness of homeopathy in general practice – summarized health technology assessment. Forschende Komplementärmedizin, 2006;

13 Suppl 2: 19–29.

2) Jacobs J, Jonas WB, Jimenez-Perez M, Crothers D. Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials. *Pediatric Infectious Disease Journal*, 2003; 22: 229–234

3) Barnes J, Resch K-L, Ernst E. Homeopathy for postoperative ileus? A meta-analysis. *Journal of Clinical Gastroenterology*, 1997; 25: 628–633.

4) Jonas WB, Linde K, Ramirez G. Homeopathy and rheumatic disease. *Rheumatic Disease Clinics of North America*, 2000; 26: 117–123.

5) Wiesenauer M, Lüdtke R. A meta-analysis of the homeopathic treatment of pollinosis with *Galphimia glauca*. *Forschende Komplementärmedizin und Klassische Naturheilkunde*, 1996; 3: 230–236.

6) Taylor MA, Reilly D, Llewellyn-Jones RH, et al. Randomised controlled trials of homeopathy versus placebo in perennial allergic rhinitis with overview of four trial series. *British Medical Journal*, 2000; 321: 471–476.

7) Bellavite P, Ortolani R, Pontarollo F, et al. Immunology and homeopathy. 4. Clinical studies – Part 2. *Evidence-based Complementary and Alternative Medicine: eCAM*, 2006; 3: 397–409.

8) Bellavite P, Ortolani R, Pontarollo F, et al. Immunology and homeopathy. 4. Clinical studies – Part 1. *Evidence-based Complementary and Alternative Medicine: eCAM*, 2006; 3: 293–301.

9) Schneider B, Klein P, Weiser M. Treatment of vertigo with a homeopathic complex remedy compared with usual treatments: a meta-analysis of clinical trials. *Arzneimittelforschung*, 2005; 55: 23–29.

#### **ホメオパシーの効果が不明あるいは否定の論文**

1) Pilkington K, Kirkwood G, Rampes H, et al. Homeopathy for anxiety and anxiety disorders: A systematic review of the research. *Homeopathy*, 2006; 95: 151–162.

2) Pilkington K, Kirkwood G, Rampes H, et al. Homeopathy for depression: a systematic review of the research evidence. *Homeopathy*, 2005; 94: 153–163.

3) Owen JM, Green BN. Homeopathic treatment of headaches: A systematic review of the literature. *Journal of Chiropractic Medicine*, 2004; 3: 45–52.

4) Ullman D. Controlled clinical trials evaluating the homeopathic treatment of people with human immunodeficiency virus or acquired immune deficiency syndrome. *Journal of Alternative and Complementary Medicine*, 2003; 9: 133–141.

5) Long L, Ernst E. Homeopathic remedies for the treatment of osteoarthritis: a systematic review. *British Homeopathic Journal*, 2001; 90: 37–43.

6) Altunç U, Pittler MH, Ernst E. Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials. *Mayo Clinic Proceedings*, 2007; 82: 69–75.

7) Milazzo S, Russell N, Ernst E. Efficacy of homeopathic therapy in cancer treatment. *European Journal of Cancer*, 2006; 42: 282–289.

- 8) Ernst E, Pittler MH. Efficacy of homeopathic arnica. A systematic review of placebo-controlled clinical trials. *Archives of Surgery*, 1998; 133: 1187–1190.
- 9) Lüdtke R, Hacke D. On the effectiveness of the homeopathic remedy *Arnica montana*. *Wiener Medizinische Wochenschrift*, 2005; 155: 482–490.
- 10) Brinkhaus B, Wilkens JM, Lüdtke R, et al. Homeopathic arnica therapy in patients receiving knee surgery: Results of three randomised double-blind trials. *Complementary Therapies in Medicine*, 2006; 14: 237–246.

### **III. RCT (ランダム化比較試験)**

1950年から2009年にかけて74の異なる疾患に対してホメオパシーを用いた142のRCTの論文がある。63の論文でホメオパシーの効果がプラセボと比較してpositiveな内容であり、11の論文でnegativeであった。最も多くの68の論文では結論がでていない。

1980年以降の主なRCTを示す。

#### **Positiveな結果を示す主な論文**

- 1) Jacobs J, Jimenez LM, Gloyds SS, et al. Homeopathic treatment of acute childhood diarrhoea. A randomized clinical trial in Nicaragua. *British Homeopathic Journal*, 1993; 82: 83–86.
- 2) Jacobs J, Jimenez LM, Gloyds SS, et al. Treatment of acute childhood diarrhea with homeopathic medicine; a randomized clinical trial in Nicaragua. *Pediatrics*, 1994; 93: 719–725.
- 3) Jacobs J, Jimenez LM, Malthouse S, et al. Homeopathic treatment of acute childhood diarrhoea: results from a clinical trial in Nepal. *Journal of Alternative and Complementary Medicine*, 2000; 6: 131–139.
- 4) Bell I, Lewis D, Brooks A, et al. Improved clinical status in fibromyalgia patients treated with individualized homeopathic remedies versus placebo. *Rheumatology*, 2004; 43: 577–582.
- 5) Fisher P. An experimental double-blind clinical trial method in homeopathy. Use of a limited range of remedies to treat fibrositis. *British Homeopathic Journal*, 1986; 75: 142–147.
- 6) Relton C, Smith C, Raw J, et al. Healthcare provided by a homeopath as an adjunct to usual care for fibromyalgia (FMS): results of a pilot randomised controlled trial. *Homeopathy*, 2009; 98: 77–82.
- 7) Ferley JP, Zmirou D, D'Adhemar D, Balducci F. A controlled evaluation of a homeopathic preparation in the treatment of influenza like syndromes. *British Journal of Clinical Pharmacology*, 1989; 27: 329–335.
- 8) Papp R, Schuback G, Beck E, et al. Oscillocoquinum in patients with influenza-like syndromes: a placebo-controlled double-blind evaluation. *British Homeopathic Journal*, 1998; 87: 69–76.
- 8) Shealy CN, Thomlinson RP, Cox RH, Borgmeyer RN. Osteoarthritic pain: a comparison of homeopathy and acetaminophen. *American Journal of Pain Management*, 1998; 8: 89–91.
- 9) Shipley M, Berry H, Broster G, et al. Controlled trial of homeopathic treatment of osteoarthritis. *Lancet*, 1983; i: 97–98.
- 10) van Haselen RA, Fisher PAG. A randomized controlled trial comparing topical piroxicam gel with a homeopathic gel in osteoarthritis of the knee. *Rheumatology*, 2000; 39: 714–719.

- 11) Abel S, Laerum E, Dølvik S, Djupesland P. Is homeopathic 'immunotherapy' effective? A double-blind, placebo-controlled trial with the isopathic remedy *Betula 30c* for patients with birch pollen allergy. *British Homeopathic Journal*, 2000; 89: 161–168.
- 12) Abel S. No beneficial effect of isopathic prophylactic treatment for birch pollen allergy during a low-pollen season: a double-blind, placebo-controlled clinical trial of homeopathic *Betula 30c*. *British Homeopathic Journal*, 2000; 89: 169–173.
- 13) Abel S. Prophylactic and acute treatment with the homeopathic medicine *Betula 30c* for birch pollen allergy: a double-blind, randomized, placebo-controlled study of consistency of VAS responses. *British Homeopathic Journal*, 2001; 90: 73–78.
- 14) Kim LS, Riedlinger JE, Baldwin CM, et al. Treatment of seasonal allergic rhinitis using homeopathic preparation of common allergens in the southwest region of the US: a randomized, controlled clinical trial. *Annals of Pharmacotherapy*, 2005; 39: 617–624.
- 15) Reilly DT, Taylor MA. Potent placebo or potency? A proposed study model with initial findings using homeopathically prepared pollens in hayfever. *British Homeopathic Journal*, 1985; 74: 65–75.
- 16) Reilly DT, Taylor MA, McSharry C, Aitchison T. Is homeopathy a placebo response? Controlled trial of homeopathic potency, with pollen in hayfever as model. *Lancet*, 1986; ii: 881–885.
- 17) Wiesenauer M, Häussler S, Gaus W. [Treatment of pollinosis with *Galphimia glauca*]. *Fortschritte der Medizin*, 1983; 101: 811–814.
- 18) Wiesenauer M, Gaus W. Double-blind trial comparing the effectiveness of the homeopathic preparation *Galphimia* potentization D6, *Galphimia* dilution 10-6 and placebo on pollinosis. *Arzneimittelforschung*, 1985; 35: 1745–1747.
- 19) Wiesenauer M, Gaus W, Häussler S. [Treatment of pollinosis with the homeopathic preparation *Galphimia glauca*. A double-blind trial in clinical practice]. *Allergologie*, 1990; 13: 359–363.
- 20) Weiser M, Gegenheimer LH, Klein P. A randomized equivalence trial comparing the efficacy and safety of *Luffa comp.-Heel* nasal spray with cromolyn sodium spray in the treatment of seasonal allergic rhinitis. *Forschende Komplementärmedizin und Klassische Naturheilkunde*, 1999; 6: 142–148.
- 21) Friese K-H, Zabalotnyi DI. [Homeopathy in acute rhinosinusitis. A double-blind, placebo controlled study shows the effectiveness and tolerability of a homeopathic combination remedy]. *HNO*, 2007; 55: 271–277.
- 22) Weiser M, Clasen B. [Randomized, placebo-controlled, double-blind study of the clinical efficacy of the homeopathic *Euphorbium compositum-S* nasal spray in cases of chronic sinusitis]. *Forschende Komplementärmedizin*, 1994; 1: 251–259.
- 23) Wiesenauer M, Gaus W, Bohnacker U, Häussler S. [Effectiveness trial of homeopathic drug combinations for the treatment of sinusitis. Results of a randomized double-blind study in primary care]. *Arzneimittelforschung*, 1989; 39: 620–625.

24) Zabolotnyi DI, Kneis KC, Richardson A, et al. Efficacy of a complex homeopathic medication (Sinfrontal) in patients with acute maxillary sinusitis: a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial. *Explore (NY)*, 2007; 3: 98–109.

25) Issing W, Klein P, Weiser M. The homeopathic preparation Vertigoheel versus Ginkgo biloba in the treatment of vertigo in an elderly population: a double-blinded, randomized, controlled clinical trial. *Journal of Alternative and Complementary Medicine*, 2005; 11: 155–160.

26) Weiser M, Strösser W, Klein P. Homeopathic vs. conventional treatment of vertigo: a randomized double-blind controlled clinical study. *Archives of Otolaryngology – Head and Neck Surgery*, 1998; 124: 879–885.

#### **結果が出ていない主な論文あるいは negative な結果の主な論文**

1) Baker DG, Myers SP, Howden I, Brooks L. The effects of homeopathic Argentum nitricum on test anxiety. *Complementary Therapies in Medicine*, 2003; 11: 65–71.

2) Bonne O, Shemer Y, Goral Y, et al. A randomized, double-blind, placebo-controlled study of classical homeopathy in generalized anxiety disorder. *Journal of Clinical Psychiatry*, 2003; 64: 282–287.

3) White A, Slade P, Hunt C, et al. Individualised homeopathy as an adjunct in the treatment of childhood asthma: a randomized placebo controlled trial. *Thorax*, 2003; 58: 317–321.

4) Hill N, Stam C, Tuinder S, van Haselen RA. A placebo controlled clinical trial investigating the efficacy of a homeopathic after-bite gel in reducing mosquito bite induced erythema. *European Journal of Clinical Pharmacology*, 1995; 49: 103–108.

5) Jacobs J, Herman P, Heron K, et al. Homeopathy for menopausal symptoms in breast cancer survivors: a preliminary randomized controlled trial. *Journal of Alternative and Complementary Medicine*, 2005; 11: 21–27.

6) Thompson EA, Montgomery A, Douglas D, Reilly D. A pilot, randomized, double-blinded, placebo-controlled trial of individualized homeopathy for symptoms of estrogen withdrawal in breast-cancer survivors. *Journal of Alternative and Complementary Medicine*, 2005; 11: 13–20.

7) Brigo B, Serpelloni G. Homeopathic treatment of migraines: a randomized double-blind study of sixty cases (homeopathic remedy versus placebo). *Berlin Journal on Research in Homeopathy*, 1991; 1: 98–106.

8) Straumsheim P, Borchgrevink C, Mowinckel P, et al. Homeopathic treatment of migraine: a double blind, placebo controlled trial of 68 patients. *British Homeopathic Journal*, 2000; 89: 4–7.

9) Whitmarsh TE, Coleston-Shields DM, Steiner TJ. Double-blind randomized placebo-controlled study of homeopathic prophylaxis of migraine. *Cephalalgia*, 1997; 17: 600–604.

10) Jawara N, Lewith G, Mullee M, Smith C. Homeopathic Arnica and Rhus Toxicodendron for delayed onset muscle soreness: a randomized, double-blind, placebo-controlled trial. *British Homeopathic Journal*, 1997; 86: 10–15.

- 11) Tveiten D, Bruseth S, Borchgrevink CF, Løhne K. [Effect of Arnica D30 on hard physical exertion. A double-blind randomized trial during the 1990 Oslo Marathon]. *Tidsskrift for den Norske Lægeforening*, 1991; 111: 3630–3631.
- 12) Tveiten D, Bruseth S, Borchgrevink CF, Norseth J. Effects of the homeopathic remedy Arnica D30 on marathon runners: a randomized, double-blind study during the 1995 Oslo Marathon. *Complementary Therapies in Medicine*, 1998; 6: 71–74.
- 13) Vickers AJ, Fisher P, Smith C, et al. Homeopathy for delayed onset muscle soreness: a randomized double blind placebo controlled trial. *British Journal of Sports Medicine*, 1997; 31: 304–307.
- 14) Vickers AJ, Fisher P, Smith C, et al. Homeopathic Arnica 30X is ineffective for muscle soreness after long-distance running: a randomized, double-blind, placebo-controlled trial. *Clinical Journal of Pain*, 1998; 14: 227–231.
- 15) Hart O, Mullee MA, Lewith G, Miller J. Double-blind, placebo-controlled, randomized clinical trial of homeopathic arnica C30 for pain and infection after total abdominal hysterectomy. *Journal of the Royal Society of Medicine*, 1997; 90: 73–78.
- 16) Kaziro GS. Metronidazole (Flagyl) and Arnica montana in the prevention of post-surgical complications, a comparative placebo controlled clinical trial. *British Journal of Oral & Maxillofacial Surgery*, 1984; 22: 42–49.
- 17) Lökken P, Straumsheim PA, Tveiten D, et al. Effect of homeopathy on pain and other events after acute trauma; placebo controlled trial with bilateral oral surgery. *British Medical Journal*, 1995; 310: 1439–1442.
- 18) Seeley BM, Denton AB, Ahn MS, Maas CS. Effect of homeopathic Arnica montana on bruising in face-lifts: results of a randomized, double-blind, placebo-controlled clinical trial. *Archives of Facial Plastic Surgery*, 2006; 8: 54–59.
- 19) Stevinson C, Devaraj VS, Fountain-Barber A, et al. Homeopathic arnica for prevention of pain and bruising: randomized placebo-controlled trial in hand surgery. *Journal of the Royal Society of Medicine*, 2003; 96: 60–65.
- 20) Robertson A, Suryanarayanan R, Banerjee A. Homeopathic Arnica montana for post-tonsillectomy analgesia: a randomised placebo control trial. *Homeopathy*, 2007; 96: 17–21.
- 21) Wolf M, Tamaschke C, Mayer W, Heger M. [Efficacy of Arnica in varicose vein surgery: results of a randomized, double-blind, placebo-controlled pilot study]. *Forschende Komplementär-medicin und Klassische Naturheilkunde*, 2003; 10: 242–247.
- 22) Fisher P, Scott DL. A randomized controlled trial of homeopathy in rheumatoid arthritis. *Rheumatology*, 2001; 40: 1052–1055.
- 23) Wiesenauer M, Gaus W. [A randomized double-blind trial on the efficacy of a homeopathic drug for rheumatoid arthritis]. *Aktuelle Rheumatologie*, 1991; 16: 1–9.

- 24) Steinsbekk A, Bentzen N, Fønnebø V, Lewith G. Self treatment with one of three self selected, ultramolecular homeopathic medicines for the prevention of upper respiratory tract infections in children. A double-blind randomized placebo controlled trial. *British Journal of Clinical Pharmacology*, 2005; 59: 447–455.
- 26) Steinsbekk A, Fønnebø V, Lewith G, Bentzen N. Homeopathic care for the prevention of upper respiratory tract infections in children: a pragmatic, randomized, controlled trial comparing randomized homeopathic care and waiting-list controls. *Complementary Therapies in Medicine*, 2005; 13: 231–238.
- 27) Kainz JT, Kozel G, Haidvogel M, Smolle J. Homeopathic versus placebo therapy of children with warts on the hands: a randomized, double-blind clinical trial. *Dermatology*, 1996; 193: 318–320.
- 28) Labrecque M, Audet D, Latulippe LG, Drouin J. Homeopathic treatment of plantar warts. *Canadian Medical Association Journal*, 1992; 146: 1749–1753.
- 29) Weatherley-Jones E, Nicholl JP, Thomas KJ, et al. A randomized, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome. *Journal of Psychosomatic Research*, 2004; 56: 189–197.
- 30) Yakir M, Kreitler S, Brzezinski A, et al. Effects of homeopathic treatment in women with premenstrual syndrome: a pilot study. *British Homeopathic Journal*, 2001; 90: 148–153.
- 31) Oberbaum M, Galoyan N, Lerner-Geva L, et al. The effect of the homeopathic remedies *Arnica* and *Bellis perennis* on mild postpartum bleeding – a randomized, double-blind, placebo-controlled study – preliminary results. *Complementary Therapies in Medicine*, 2005; 13: 87–90.
- 32) Frass M, Linkesch M, Banyai S, et al. Adjunctive homeopathic treatment in patients with severe sepsis: a randomized, double-blind, placebo-controlled trial in an intensive care unit. *Homeopathy*, 2005; 94: 75–80.
- 33) Oberbaum M, Yaniv I, Ben-Gal Y, et al. A randomized, controlled clinical trial of the homeopathic medication *Traumeel S* in the treatment of chemotherapy-induced stomatitis in children undergoing stem cell transplantation. *Cancer*, 2001; 92: 684–690.