CURRENT HEALTH LITERATURE AWARENESS SERVICES

COMPiled & Edited

By:

Meenakshi Bhatia
Librarian

With Best Complements:

Library Section
Central Council for Research in Homoeopathy
61-65, Institutional Area, Janakpuri, New Delhi
URL: www.ccrhindia.nic.in
E-mail: ccrhlibrary@gmail.com
PREFACE

Introduction

The library of the Central Council for Research in Homoeopathy has been circulating “Current Health Literature Awareness Service” (CHLAS). The main objective is to disseminate precise information/citation about scientific articles published in various journals/magazine subscribed by this Council.

Scope

This volume covers articles on AYUSH & other systems and Allied Sciences

Arrangement of Entries

The articles are indexed under the name of the authors, arranged in alphabetical order. The entries have been made in the following order:

Author
Title
Name of Journal
year of publication; Volume (issue no.): pagination
Abstract

Document Copy Service

This library can provide photocopies of the selected articles on specific request. The request can be send to:

Central Council for Research in Homoeopathy Library
61-65, Institutional Area, Janakpuri
New Delhi-110058, INDIA

e-mail: ccrhlibrary@gmail.com

Acknowledgement

We are grateful to Dr. R.K. Manchanda, Director General, CCRH for his encouragement and valuable suggestions from time to time. We sincere acknowledge the cooperation of Mrs. Nisha Adhikari, DEO in compiling this bulletin.

(Meenakshi Bhatia)
Librarian
AYUSH & Other Systems


Abstract:

Anxiety disorders are one of the most common mental health concerns with a major contribution to the global burden of disease. When not treated, anxiety can be aggravated to more serious and complicated health problems. Pharmacology and psychotherapy stand for the conventional treatment for anxiety disorders but these present limited efficacy, especially in the case of chronic anxiety, with high relapse rates and often causing adverse side effects. Clinical research studies render acupuncture as a valid treatment therapy for anxiety disorders without significant adverse effects.

The objective of this paper is to review the literature on the effectiveness of acupuncture and electroacupuncture for the treatment of patients with anxiety disorders in order to find strong scientific evidence for its regular practice in Western culture.

The systematic review of the clinical research was focused on published clinical trials (controlled, randomized and non-randomized) regarding the treatment of anxiety with acupuncture. Only clinical trials where anxiety was treated as the therapeutic target, and not as a secondary measurement or being associated with other health condition or disease, were considered. Two authors extracted the data independently and exclusion and inclusion criteria were set. The search rendered 1135 papers addressing anxiety as a primary therapeutic target. After review, 13 papers were identified to match exclusion and inclusion criteria and were selected for this analysis. Methodology, design, and quality of the research were highly variable and are discussed and compared.

Overall, there is good scientific evidence encouraging acupuncture therapy to treat anxiety disorders as it yields effective outcomes, with fewer side effects than conventional treatment. More research in this area is however needed.


Bhasin Manoj K, Denninger John W, Huffman Jeff C et al. Specific transcriptome changes associated with blood pressure reduction in hypertensive patients after

Abstract:

**Objective:** Mind–body practices that elicit the relaxation response (RR) have been demonstrated to reduce blood pressure (BP) in essential hypertension (HTN) and may be an adjunct to antihypertensive drug therapy. However, the molecular mechanisms by which the RR reduces BP remain undefined.

**Design:** Genomic determinants associated with responsiveness to an 8-week RR-based mind–body intervention for lowering HTN in 13 stage 1 hypertensive patients classified as BP responders and 11 as nonresponders were identified.

**Results:** Transcriptome analysis in peripheral blood mononuclear cells identified 1771 genes regulated by the RR in responders. Biological process- and pathway-based analysis of transcriptome data demonstrated enrichment in the following gene categories: immune regulatory pathways and metabolism (among downregulated genes); glucose metabolism, cardiovascular system development, and circadian rhythm (among upregulated genes). Further in silico estimation of cell abundance from the microarray data showed enrichment of the anti-inflammatory M2 subtype of macrophages in BP responders. Nuclear factor-κB, vascular endothelial growth factor, and insulin were critical molecules emerging from interactive network analysis.

**Conclusions:** These findings provide the first insights into the molecular mechanisms that are associated with the beneficial effects of the RR on HTN.


Abstract:

**Aim:** In the current study, we aimed to evaluate the relationship between life quality and use of complementary and alternative medicine (CAM) in patients with diabetes mellitus.

**Methods:** The Audit of Diabetes-Dependent Quality of Life (ADDQOL-19) scale was applied to 453 diabetic patients. Socio-demographic characteristics of the patients and their CAM usage were recorded.

**Results:** The rate of CAM use among diabetic patients was 46.1%. The most preferred practices were herbal medicine, including black cumin (26.6%), cinnamon (23.3%) and olive leaf (12.5%). 'Freedom to eat' (p = 0.002), 'drinking freedom' (p = 0.001) and 'physical health' (p = 0.001) were the most negatively affected items that may drive patients to use CAM.

**Conclusions:** In this sampling, the use of CAM among patients with diabetes mellitus is high. The association between CAM usage and eating and drinking freedom and physical health should be studied in detail in further studies.


Abstract:

Breast cancer is a hormonal genetic disease. The only treatment in conventional medicine is surgery i.e. lumpectomy with irradiation and chemotherapy which results in overall derangement in health. The case reported here is 63 years old lady, with cancer of breast with metastatic lesions in femur and spine which were successfully treated with Homoeopathic medicines. Diminution of mass in breast and spine in this with Homoeopathy can be considered gold-stone to explore the utility of alternative modes of treatment such as Homoeopathy, to give a better therapeutic option for irreversible and pseudo surgical conditions.


Abstract:

Background: Adventure therapy (AT) is a term that includes therapies such as wilderness therapy and adventure-based counseling. With growing empirical support for AT, the diversity of studies make it difficult to attribute outcomes to specific treatment factors.

Objectives: Researchers explored whether AT, often perceived as an alternative therapy, works because of AT's unique components, or whether factors shared by all therapies were responsible.

Methods: A scoping review was undertaken utilizing a search of major databases, unpublished dissertations, and a hand search for direct comparison trials matching AT with another therapeutic intervention.

Results: 881 publications were identified. 105 quantitative studies were included following a title and abstract review. Only 13 met the full inclusion criteria. Little to no differences were found to isolate specific therapeutic factors.

Conclusions: We discuss the implications of these results considering the movement toward evidence-based practice and recommend future research to eclipse our current understanding of AT.


Abstract:

Objective: Pain is one of the most common symptoms and may lead to important psychological, mental, and physiological problems in individuals. According to data by The Center for Reiki Research, Reiki is an effective approach to decrease the levels of pain, depression, and anxiety. Therefore, the aim of this meta-analysis was to investigate the effect of Reiki on pain level.
**Methods:** Randomized controlled clinical trials in databases of Pubmed, ISI Web of Sciences, and Google Scholar were investigated. 4 randomized controlled studies involving 212 participants were included in the meta-analysis.

**Results:** The result obtained after the final Reiki application was evaluated in VAS pain score. When Reiki (n = 104) group was compared with control group (n = 108), standardized mean difference was observed to be $-0.927$ (95% CI: $-1.867$ to $0.0124$). Reiki was observed to cause a statistically significant decrease in VAS score.

**Conclusion:** Consequently, this meta-analysis revealed that Reiki was an effective approach in relieving the pain.

**Fragile bones? Make them strong. Homoeopathy for All 2018; 20(5): 18-19p.**


**Abstract:**

**Background:** Conventional or homeopathic treatment of chronic immune thrombocytopenic purpura (ITP) is often difficult. The use of homeopathic dilutions of patient blood (HPB) for immunomodulation has been described, which inspired us to try the method in an ITP case.

**Case Report:** A 2-year-old girl with chronic ITP was treated with homeopathic dilutions of her own capillary blood, given rally over 5 months. Immediately after treatment onset there was a rapid normalization of the thrombocyte counts. Within 6 weeks, they rose from 15,000/μl to 254,000/μl. After treatment stop, they decreased to 155,000/μl, increased again spontaneously to 270,000/μl and remained within normal range for over 3 years.

**Conclusions:** Oral administration of homeopathic dilutions of capillary patient blood may possibly be an effective treatment in chronic ITP. If our results can be reproduced, this will revolutionize the treatment of ITP.


**Abstract:**

**Aim:** To assess the prevalence and prognostic factor of *Aranea diadema* in a population responding well to *Aranea diadema*.

**Material and Methods:** It was an open label, multicentric observational study wherein patients having minimum two known symptoms matching with the
pathogenesis of *Aranea diadema* were prescribed the remedy in 6C, 30C, 200C, and 1M potencies. The collected data were presented in terms of descriptive statistics.

**Results:** A total of 6806 cases were enrolled. Out of which a total of 172 cases were analysed, and demographic analysis shows male/female: 109/63; mean age 28.3 years. There were “clinical successes” in 115 cases (67.0%) and no response in 57 (33.1%) cases. The number of symptoms found prevalent in responders included proving (*n* = 13) and literature (*n* = 8). Symptoms coming from provings guide homoeopathic practitioners in prescribing their medicines, but should also be confirmed in patients responding well to these medicines. Significantly higher prevalence was observed among responders in respect of six tentatively confirmed symptoms (prevalence): Forgetfulness (0.11), white coated tongue (0.21), epistaxis (0.10), thirstlessness (0.13), seminal emissions (0.23), and fever (0.12).

**Conclusion:** This study was conducted to assess the prevalence of symptoms in a population responding well to *Aranea diadema* and to compare this with the prevalence of these symptoms in other populations. If a symptom has a higher prevalence in a population responding well to *Aranea* it indicates the increase of likelihood of a curative action of *Aranea* when that symptom is present. Our “test” is not meant to diagnose an illness but to increase the accuracy of prescribing *Aranea diadema*.

Hughes Ciara M, Liddle SD, Sinclair Marlene et al. Use of complementary and alternative medicine (CAM) for pregnancy related low back and/ or pelvic girdle pain: An online survey. *Complementary Therapies in Clinical Practice 2018; 31: 379-83p.*

**Abstract:**

Low back and pelvic girdle pain (LBPGP) is a common complaint among pregnant women, which increases throughout pregnancy and women use various complementary and alternative medicine (CAM) therapies to manage their pain. Using an online survey, CAM treatments used by pregnant women in the UK and their perceptions of these therapies to relieve LBPGP were investigated. 191 women completed the survey and 70% experienced LBPGP lasting more than one week. Over half of women who sought treatment from a GP or physiotherapist were dissatisfied. 25% of participants used CAM during pregnancy, the most popular being aromatherapy (21%), acupuncture (21%), and reflexology (15%). 81% of women used CAM to manage their LBPGP and 85% found it useful for pregnancy symptoms. Women experience high levels of pain during pregnancy with limited treatment options. Research into effective CAM treatments for LBPGP is required to allow women to make informed decisions regarding treatment options.


**Abstract:**

**Objective:** To study the effect of homeopathic medicines (in higher potencies) in normal subjects, Peripheral Pulse Analyzer (PPA) has been used to record physiologic
variability parameters before and after administration of the medicine/placebo in 210 normal subjects.

**Methods:** Data have been acquired in seven rounds; placebo was administered in rounds 1 and 2 and medicine in potencies 6, 30, 200, 1 M, and 10 M was administered in rounds 3 to 7, respectively. Five different medicines in the said potencies were given to a group of around 40 subjects each. Although processing of data required human intervention, a software application has been developed to analyze the processed data and detect the response to eliminate the undue delay as well as human bias in subjective analysis. This utility named Automatic Analysis of Intervention in the Field of Homeopathy is run on the processed PPA data and the outcome has been compared with the manual analysis. The application software uses adaptive threshold based on statistics for detecting responses in contrast to fixed threshold used in manual analysis.

**Results:** The automatic analysis has detected 12.96% higher responses than subjective analysis. Higher response rates have been manually verified to be true positive. This indicates robustness of the application software. The automatic analysis software was run on another set of pulse harmonic parameters derived from the same data set to study cardiovascular susceptibility and 385 responses were detected in contrast to 272 of variability parameters. It was observed that 65% of the subjects, eliciting response, were common.

**Conclusion:** This not only validates the software utility for giving consistent yield but also reveals the certainty of the response. This development may lead to electronic proving of homeopathic medicines (e-proving).

**James Peter Bai, Kamara Halimatu, Bah Abdulai Jawo et al. Herbal medicine use among hypertensive patients attending public and private health facilities in Freetown Sierra Leone. Complementary Therapies in Clinical Practice 2018; 31: 7-15p.**

**Abstract:**

**Objective:** This study aimed to determine the prevalence, determinants and pattern of herbal medicine use among hypertensive patients in Freetown.

**Methods and materials:** We conducted a cross-sectional study among hypertensive patients attending public and private health facilities in Freetown, Sierra Leone between August and October 2016. We analyzed the data using SPSS version 24. We used Chi-square, Fisher exact two-tailed test and regression analysis for data analysis. A p-value less than 0.05 was considered statistically significant.

**Results:** Out of 260 study participants, over half (n = 148, 56.9%) reported using herbal medicine for the treatment of hypertension alone or together with comorbid condition(s). The most commonly used herbal medicine among users were honey (n = 89, 33.3%), moringa (n = 80, 30.0%) and garlic (n = 73, 27.3%). No significant difference existed between users and non-users of herbal medicine with regards to socio-demographic and health-related factors. The majority (n = 241, 92.7%) of respondents considered herbal medicine beneficial if it was recommended by a
healthcare provider yet 85.1% (n = 126) did not disclose their herbal medicine use to their health care provider.

**Conclusion:** There is a high use of herbal medicines among hypertensive patients in Freetown, Sierra Leone. It is essential for healthcare providers to take heed of the findings of this study and routinely ask their patients about their herbal medicine use status. Such practice will provide the opportunity to discuss the benefits and risks of herbal medicine use with the aim of maximizing patient desired therapeutic outcomes.


**Abstract:**

Cancer is a group of disease involving abnormal cell growth with the potential to invade or spread to other parts of the body. It is one condition where disease may remain hidden until and unless it has spread extensively. There is a lot of anticipation regarding this disease among patients. Homoeopathy offers milder and gentle treatment for cancer. Understanding of clinical material medicas gives insight into the medicines and their indication for cancer.


**Abstract:**

**Objective:** To assess the effects of yogic exercise on nonspecific neck pain in university students.

**Methods:** This study is a pretest-posttest design with a non-equivalent control group. Thirty-eight university students were selected by convenience sampling, with 18 assigned to an exercise group and 20 assigned to a control group. The yoga group participated in one-hour sessions of yogic exercise two days a week for eight weeks. The exercise comprised eight stages: relaxation, flexion of neck, extension of neck, right lateral flexion of neck, left lateral flexion of neck, right rotation of neck, left rotation of neck, and relaxation. Neck pain intensity was measured using a 100 mm visual analogue scale.

**Results:** The yoga group showed significantly decreased neck pain scores compared with those of the control group.

**Conclusions:** These findings indicate that yogic exercises could reduce neck pain in university students.

**Kishore Lalit, Singh Randhir. Effect of cephalandra indica against advanced glycation end products, sorbitol accumulation and aldose reductase activity in homoeopathic formulation. Indian Journal Research in Homoeopathy 2018; 12(1): 11-19p.**

**Abstract:**
**Background:** Extreme generation of free radicals leads to oxidative stress which has been apprehensive in several disease processes such as diabetic complications and vascular and neurodegenerative diseases.

**Objective:** The present study was designed to evaluate the potential of homoeopathic preparations of *Cephalandra indica* L. against oxidative stress.

**Materials and Methods:** Potencies of *Cephalandra indica* (mother tincture, 6C and 30C) were procured from Dr. Willmar Schwabe India Pvt. Ltd. The antioxidant activity of *Cephalandra indica* was evaluated by employing various in vitro antioxidant methods.

**Results:** The total phenol content was found to be 1905, 849 and 495 mg/g gallic acid equivalents in mother tincture, 6C and 30C of *Cephalandra indica* and total antioxidant capacity was found to be 2710, 759 and 510 μM/g ascorbic acid equivalents, respectively. Mother tincture, 6C and 30C of *Cephalandra indica* was found to have strong reducing power, 2,2-diphenyl-1-picrylhydrazyl radical, hydrogen peroxide, nitric oxide and superoxide radical scavenging activity. Percentage inhibition of AGEs formation by mother tincture, 6C and 30C of *Cephalandra indica* (10–50 μl) was found to be 30.34%–91.77%, 29.98%–65.71% and 33.05%–57.75%, respectively. Mother tincture, 6C and 30C of *Cephalandra indica* showed inhibitory effect against sorbitol accumulation with IC_{50} value of 26.12 μl, 203.10 μl and 897.3 μl, respectively, whereas, in aldose reductase inhibition assay, the IC_{50} value was 32.54 μl, 175.02 μl and 834.34 μl, respectively.

**Conclusion:** The results revealed that homoeopathic preparations of *Cephalandra indica* exhibit protective effect against oxidative stress.


**Abstract:**

**Objectives:** The last systematic review of physicochemical research performed on homeopathic preparations was published in 2003. The aim of the study is to update and expand the current state of knowledge in the area of physicochemical properties of homeopathic preparations. In part 1 of the study, we aim to present an overview of the literature with respect to publication quality and methods used. In part 2, we aim to identify the most interesting experimental techniques. With this, we aim to be in a position to generate meaningful hypotheses regarding a possible mode of action of homeopathic preparations.

**Methods:** A two-step procedure was adopted: (1) an extensive literature search, followed by a bibliometric and quality analysis on the level of publications and (2) a thorough qualitative analysis of the individual physicochemical investigations found. In this publication, we report on step (1). We searched major scientific databases to find publications reporting physicochemical investigations of homeopathy from its origin to the end of 2015. Publications were assessed using a scoring scheme, the
Manuscript Information Score (MIS). Information regarding country of origin of the research and experimental techniques used was extracted.

**Results:** We identified 183 publications (compared to 44 in the last review), 122 of which had an MIS ≥5. The rate of publication in the field was ~2 per year from the 1970s until 2000. Afterward, it increased to over 5.5 publications per year. The quality of publications was seen to increase sharply from 2000 onward, whereas before 2000, only 12 (13%) publications were rated as “high quality” (MIS ≥7.5); 44 (48%) publications were rated as “high quality” from 2000 onward. Countries with most publications were Germany (n = 42, 23%), France (n = 29, 16%), India (n = 27, 15%), and Italy (n = 26, 14%). Techniques most frequently used were electrical impedance (26%), analytical methods (20%), spectroscopy (20%), and nuclear magnetic resonance (19%).

**Conclusions:** Physicochemical research into homeopathic preparations is increasing both in terms of quantity and quality of the publications.


**Abstract:**

**Objective:** To develop a policy, practice, education and research agenda for evidence-based practice (EBP) in traditional and complementary medicine (T&CM).

**Methods:** The study was a secondary analysis of qualitative data, using the method of roundtable discussion. The sample comprised seventeen experts in EBP and T&CM. The discussion was audio-recorded, and the transcript analysed using thematic analysis.

**Results:** Four central themes emerged from the data; understanding evidence and EBP, drivers of change, interpersonal interaction, and moving forward. Captured within these themes were fifteen sub-themes. These themes/sub-themes translated into three broad calls to action: (1) defining terminology, (2) defining the EBP approach, and (3) fostering social movement. These calls to action formed the framework of the agenda.

**Conclusions:** This analysis presents a potential framework for an agenda to improve EBP implementation in T&CM. The fundamental elements of this action plan seek clarification, leadership and unification on the issue of EBP in T&CM.


**Abstract:**
**Objective:** To investigate the relationships between the constitutions of Traditional Chinese Medicine (TCM) and patients with cerebral infarction (CI) in a Chinese sample.

**Methods:** A total of 3748 participants with complete data were available for data analysis. All study subjects underwent complete clinical baseline characteristics' evaluation, including a physical examination and response to a structured, nurse-assisted, self-administered questionnaire. A population of 2010 neutral participants were used as the control group. Multiple variable regression (MLR) were employed to estimate the relationship between constitutions of TCM and the outcome.

**Design:** A cross-sectional study was conducted to evaluate the association of body constitution of TCM and CI. Settings/Location: Communications and healthcare centers in Shanghai.

**Subjects:** A total of 3748 participants with complete data were available for data analysis. Outcome measures: All study subjects underwent complete clinical baseline characteristics' evaluation, including a physical examination and response to a structured, nurse-assisted, self-administered questionnaire. A population of 2010 neutral participants were used as the control group. MLR were employed to estimate the relationship between constitutions of TCM and the outcome.

**Result:** The prevalence of CI was 2.84% and 4.66% in neutral participants and yang-deficient participants ($p = 0.012$), respectively. Univariate analysis demonstrated a positive correlation between yang deficiency and CI. After adjustment for relevant potential confounding factors, the MLR detected significant associations between yang deficiency and CI (odds ratio = 1.44, $p = 0.093$). Conclusion: A yang-deficient constitution was significantly and independently associated with CI. A higher prevalence of CI was found in yang-deficient participants as compared with neutral participants.


**Abstract:**

**Background:** Embryonal carcinoma with immature teratoma is a cancer with poor prognosis if the expression levels of biological markers are very high. In such a case, after surgical removal of the tumor, homeopathic treatment resulted in maintenance of the cancer-free state for over 6 years.

**Case Report:** This is the case of a 3-year-old Indian girl diagnosed with embryonal carcinoma with immature teratoma (after surgery), treated and followed up for over 6 years. She was treated on the basis of the principles of classical homeopathy and has stayed free of cancer for 6 years now.

**Discussion:** The cancer marker expression levels dropped while the girl developed severe skin eruptions, which is in accordance with the laws of classical homeopathic
treatment. Although other examples of successful homeopathic treatment in severe pathologies exist, further confirmatory studies are needed on a large scale.


**Abstract:**

The aim of this study was to investigate the effectiveness of two different interventions on pain and disability in patients with knee osteoarthritis (KOA). Forty-one individuals (Mean ± SD: Age 52.1 ± 8.9 years, Height 172.8 ± 6.6 cm, Weight 80.2 ± 6.9 kg) with KOA were randomly allocated into Pilates (N = 14), conventional therapeutic exercise (CTE) (N = 14), and control (N = 13) groups. Joint position sense (JPS), functional performance, pain, and disability were examined using Biodex system, aggregate time of four daily activities, and Lequesne Index. One-Way ANOVA, and Post Hoc Scheffe test were administrated to analyze the data (P < 0.05). There was a significant (P < 0.001) difference between the experimental groups in all measured outcomes compared to the control. While, regarding pain and disability, more significant (P = 0.003) improvement was observed in participants following Pilates training compared to CTE. It seemed that Pilates training was more effective than the CTE to improve pain and disability in individuals with KOA.


**Abstract:**

Adequate oxidation catalysis prevents oxygen deficiency in any tissue. Many departures if not all from normal physiology are believed primarily to be due to a deficiency in the oxidation process of the body; cancer being one of them. Carbon group of homoeopathic medicines in potentized state is a good catalyst. In any case, Homeopathic exercise has steadily treasured carbon group as a worthwhile cancer remedy.


**Melchart D. From complementary to integrative medicine and health: Do we need a change in nomenclature? Complementary Medicine Research 2018; 25(2): 76-78p.**

**Miranda Ia Ferreira, Souza Catiane, Schneider Alexandre Tavares et al. Comparison of low back mobility and stability exercises from Pilates in non-specific low back pain: A study protocol of a randomized controlled trial. Complementary Therapies in Clinical Practice 2018; 31: 360-68p.**
Abstract:

Background: There is some evidence in the literature about the effectiveness of the Pilates methods in the low back pain. Moreover, Pilates focus on exercises that empathizes the stability and/or mobility of the spine. Therefore, it is discussed in the literature whether higher levels of stability or mobility of the lumbar spine generates better results, both in performance and rehabilitation for low back pain.

Objectives: Compare the effects of the low back mobility and stability exercises from Pilates Method on low back pain, disability and movement functionality in individuals with non-specific chronic low back pain.

Methods: 28 participants will be randomized into two exercise protocol from Pilates methods, one focusing on low back stability and other on low back mobility. Low back pain (visual analogic scale), low back disability (Oswestry) and movement functionality (7 functional movement tasks) will be evaluated before and after 10 sessions of Pilates exercise by the same trained assessor. A mixed designed ANOVA with two factors will be used. This study is the first to compare these outcomes for chronic low back pain participants with two exercises protocol focusing on low back mobility and stability and the results will evaluate what to prioritize with Pilates exercises to give better results for that population.


Abstract:

Background: *Polygala senega* L. is a small perennial herb belonging to the family Polygalaceae. The roots are used as stimulant and expectorant in bronchitis. In Homoeopathy, it is used for hypopyon, paresis of oculomotor nerve, catarrh of pharynx, sore throat, catarrh of bladder, influenza, asthma, whooping cough, soreness in chest, pleurisy, pneumonia, hydrothorax, pleuropneumonia, pneumonia, hydrothorax and ascites.

Objective: The objective of the present study deals with morpho-anatomical, powder and physicochemical characteristics of the root of *P. senega* for developing standards for authentication of drug.

Materials and Methods: The current study includes morpho-anatomical, powder and physicochemical studies of the root of *P. senega*. Physicochemical studies comprise extractive values, ash values, chemical tests, weight/millilitre, total solids, alcohol content and loss on drying.

Results: The root are yellowish brown to light brown and has as its unique mark a projecting line on its down side. The distinguishing microscopic characteristics of the
root included the presence of multilayered phellem, abundant phelloderm interrupted by tracheary elements, acicular crystals, abnormal development of phloem and V-shaped medullary rays. Physicochemical studies of the raw drug and mother tincture are standardised and depicted.

**Conclusion:** The pharmacognostic and physicochemical data depicted in this study may serve as pharmacopoeial standards for identification and authentication of the homoeopathic drug *P. senega*.


**Abstract:**

**Background:** The purpose of this study was to compare the efficacy of ibuprofen and *Belladonna* in the control of orthodontic pain and to ascertain the pain relief by *Belladonna* in comparison with ibuprofen during orthodontic separation.

**Materials and Methods:** Patients, between 20 and 35 years of age, 51 females and 21 males, were included in this study. Patients were randomly divided into two groups; one group was assigned to ibuprofen 400 mg and second group was allocated to *Belladonna* 6C group. Patients were given two doses of medication of their respective groups, 1 h before placement of elastomeric separators (Ormco Separators, Ormco Corporation, CA, USA) which was administered in the department and one dose 6 h after the placement. Pain scores recorded on visual analogue scale (VAS). VAS was a 10 cm scale with millimetre calibration to record their pain at the following intervals, 2 h after placement, 6 h after placement, bedtime, day 1 morning, day 2 morning, day 3 morning and day 5 morning.

**Results:** *Post hoc* comparisons indicated that there was no difference between the two groups at 2 h (*P* = 0.77), 6 h (0.073), 1 day (*P* = 0.120), 2 days (*P* = 0.283), 3 days (*P* = 0.363), 5 days (*P* = 0.622) and 7 days.

**Conclusion:** Ibuprofen and *Belladonna* 6C are effective and provide adequate analgesia with no statistically significant difference. Lack of adverse effects with *Belladonna* 6C makes it an effective and viable alternative.


**Abstract:**

Psoriasis is a chronic skin disorder that speeds up the life cycle of skin cells, typically on the surface of the skin. Additional skin cells form thick scales and red fixes which are awfully itchy and sometimes painful. Although there are many therapeutic systems available to get symptomatic relief, unfortunately replete cure for psoriasis is not yet reported. Moreover, poor treatment outcomes as well as high toxicity profile of drugs makes these therapies more inconvenient to treat psoriasis. In search of alternative and complementary therapy for this disease, the focus has been shifted to nutraceuticals, few of them were reported since ages. It includes vitamins, herbal extracts, phytochemicals and dietary supplements. In this review, the attempt has
been made to highlight key nutraceuticals for better management of psoriasis. Supplementation of appropriate nutraceutical may improve the quality of patient’s life and have positive impact on overall state of disease.


Abstract:

**Background:** In recent decades the concept of integrative medicine has attracted growing interest in patients and professionals. At the Gemeinschaftskrankenhaus Havelhöhe (GKH), a hospital specialized in anthroposophical medicine, a breast cancer center (BCC) has been successfully certified for more than 5 years. The objective of the present study was to analyze how integrative strategies were implemented in the daily care of primary breast cancer patients.

**Methods:** Clinical, demographic, and follow-up data as well as information on non-pharmacological interventions were analyzed. In addition, BCC quality measures were compared with data of the National Breast Cancer Benchmarking Report 2016.

**Results:** Between 2011 and 2016, 741 primary breast cancer patients (median age 57.4 years) were treated at the GKH BCC. 91.5% of the patients showed Union for International Cancer Control (UICC) stage 0, I, II, or III and 8.2% were in UICC stage IV. 97% of the patients underwent surgery, 53% radiation, 38% had hormone therapy, and 25% received cytostatic drugs. 96% of the patients received non-pharmacological interventions and 32% received Viscum album L. therapy. Follow-up was performed in up to 93% of the patients 2 years after first diagnosis. Compared to nationwide benchmarking BCCs, the GKH BCC met the requirements in central items.

**Conclusions:** The results of the present study show that integrative therapies offered by the concept of anthroposophical medicine can be implemented in the daily care and treatment of a certified BCC. However, as national guidelines on integrative concepts in oncology are missing, further studies are needed for a systematic evaluation of integrative treatment and care concepts in this field.


**Abstract:**

**Objective:** Assess pre to-post outcomes for people with chronic pain and Type 2 Diabetes Mellitus (T2DM) randomized to an 8-week yoga intervention or usual care.

**Methods:** Participants were included if they self-reported: chronic pain; T2DM; >18 years old; no exercise restrictions or consistent yoga; and consented to the study.

**Results:** After yoga, there were significant improvements in: Brief Pain Inventory pain interference (49 ± 15.00 vs. 41.25 ± 19.46, p = .034); Fullerton Advanced Balance scale (14.2 ± 14.1 vs. 20.4 ± 13.5, p = .03); upper extremity strength (7.7 ± 6.3 vs.10.8 ± 6.5,
lower extremity strength (4.1 ± 3.8 vs. 6.7 ± 4.8, p = .02); and RAND 36-item Health Survey quality of life scores (81.1 ± 7.7 vs. 91.9 ± 8.9, p = .04). Balance scores became significantly worse during the 8 weeks for people randomized to the control (27.1 ± 9.9 vs. 21.7 ± 13.4, = p.01).

**Conclusion:** Data from this small RCT indicates yoga may be therapeutic and may improve multiple outcomes in this seemingly at-risk population.


**Abstract:**

**Objectives:** Mind and Body Practice (MBP) use (e.g., chiropractic, acupuncture, meditation) among Emergency Department (ED) patients is largely unknown. We aimed to determine the period prevalence, nature of MBP use, and perceptions of MBP among adult ED patients.

**Design and Setting:** We undertook a cross-sectional survey of a convenience sample of patients presenting to three EDs between February and June 2016. Subjects: Patients were eligible for inclusion if they were aged 18 years or more and had presented for medical treatment. Intervention: An anonymous, self-administered questionnaire, based upon a validated pediatric questionnaire, was completed by the patient, with assistance if required.

**Outcome measures:** The primary outcome was the nature and 12 month period prevalence of MBP use. Secondary outcomes were variables associated with use and patient perceptions of MBP.

**Results:** 674 patients were enrolled. In the previous 12 months, 500 (74.2%) patients had used at least one MBP. MBP users and nonusers did not differ in gender, ancestry, or chronic illness status (p > 0.05). However, users were significantly younger and more likely to have private health insurance (p < 0.001). A total of 2094 courses of 68 different MBP had been used including massage (75.0% of users), meditation (35.2%), chiropractic (32.6%), acupuncture (32.0%), and yoga (30.6%). Users were significantly more likely (p < 0.01) to believe that MBP prevented illness, treated illness, were more effective than prescription medicines, assisted prescription medications, and were safe and provided a more holistic approach. Forty-one (6.1%) patients used MBP for their ED presenting complaint. However, only 14 (34.1%) advised their ED physician of this.

**Conclusion:** The period prevalence of MBP use among ED patients is high. Knowledge of the MBP used for a patient’s presenting complaint may better inform the ED physician when making management decisions.

Abstract:
Apitherapy is the medical use and the application of honey bee products and in recent years there has been a growing interest in studies of this field. We aimed to perform a bibliometric study in the apitherapy literature. We used Web of Science database in this study and our search retrieved a total of 6917 documents of which great majority (82.4%) was original articles. Brazil was found to ranked first on the publication number with 889 papers followed by the USA, China, Japan and Turkey. We measured a productivity score for each country and the most productive countries in apitherapy field were Switzerland (2.978), Croatia (2.074), and Bulgaria (1.840). Propolis was the most used keyword followed by bee venom, flavonoids, apis mellifera and apoptosis. A moderate correlation was detected between number of publications and GDP. To the best of our knowledge our study was the first in this area and we proposed that further studies should be supported in this field.


Abstract:
Role of homoeopathy varies in cancer cases depending on the progress of pathology, patient’s general vitality and immunity level. If patient comes to us in very early stage, cure is possible. If patient comes in later stage, then also we can give palliation, relief from mental and physical agony. Homoeopathic medicines also have definite role in relieving side effects of chemo and radiotherapy.

Homoeopathic prescription will vary from case to case depending on what characteristics are available in patient! It can be organ-specific remedy (Remedy that has affinity for that organ and power to produce cancerous pathology, or it can be a deeper acting similimum if presenting like that: It can be cancer nosodes like Carcinosin or Scirrhinum if its indications are present.


Abstract:
While treating a cancer patient, if we can find out the emotional causative conflict patient suffered during the period of getting cancer, it takes us directly to the core of the problem. We can use this knowledge in our case taking and this makes it easier to reach similimum.


Abstract:
Leech saliva extract (LSE) in the liposome-based gel was used as a supplementary treatment to relief the signs and symptoms of osteoarthritis (OA). The saliva of medical leech was extracted and nano liposomes were used to formulate the supplement to enhance skin absorption. A clinical trial was designed to evaluate the therapeutic effects of LSE liposomal gel. Lenquesne and VAS questionnaires were used as indexes of this supplement therapy efficacy for 30 days. Questionnaires analysis showed that after one-month administration of LSE liposomal gel, patients' pain was relieved approximately up to 50%; also, due to reduction in joint inflammation and stiffness, the range of motion was increased and the patients' quality of life was enhanced (p < 0.001). LSE nano scaled liposomal gel as an innovative supplement therapy in OA patients, makes desirable therapeutic approach, which seems to make a significant impact on patient's quality of life and self-care capability.


Abstract:

Cancer is the most deadly disease of present era. It involves abnormal cell growth with the potential to invade or spread to other parts of the body. Hahnemann is his writings protested against the harsh, barbaric medical practices of the time, especially bloodletting, purging and drastic doses of medicines often with terrible side effects. Homoeopathy is based on principle Similia Similibus curentur let likes be treated by likes. The curative principle being a weaker dynaix affection is permanently extinguished by a stronger one, if the latter whilst differing in kind is very similar to the former in its manifestations. This holistic approach treats the disturbance on the mental, physical and emotional level, to bring back the lost equilibrium by stimulating and strengthening body defence mechanism.


Abstract:

Background: Elaborate consultations and life review (ECLR) has been regularly applied in patients of various cancer entities and stages within Anthroposophic-integrative oncology concepts. However, a lack of systematic research in this field has been detected. To close this gap of knowledge, we evaluated the impact of ECLR in patients with non-metastasized breast cancer before, during, and after primary oncological treatment.

Methods: Patient-reported outcome measures were evaluated by analyzing European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30) in patients with non-metastasized breast cancer who had received either oncological standard therapy alone or in combination with ECLR.

Results: 95 female patients were eligible for questionnaire analysis (median age 58 years). Adjusted multivariable linear regression analysis revealed that ECLR was associated with significant improvements in medium-term global health/quality of life and emotional, social, and cognitive functioning. Furthermore, ECLR was associated with significant reductions of short-term appetite loss burden, pain, and short and
medium-term financial difficulties. Subgroup analyses revealed significant improvements in pivotal quality-of-life aspects including fatigue (p = 0.002) in chemotherapy-treated patients after ECLR.

**Conclusions:** 12 months of surveillance of breast cancer patients reveals medium-term recovery of the global health status/quality of life and cognitive and psychosocial well-being associated with ECLR. In addition, our data indicate a possible association between ECLR and reduced short-term fatigue burden, which has to be re-confirmed prospectively in a larger study cohort. As long-term cancer survivors develop psychological symptoms similar to patients with chronic diseases, prospective studies should evaluate the impact of ECLR on the psychosocial well-being in these patients.


**Abstract:**

**Objective:** Research pertaining to yoga and children with cerebral palsy (CP) is negligible. The primary purpose of this study was to determine the domains of the International Classification of Functioning, Disability, and Health (ICF) model and levels of evidence for yoga and adults with stroke and multiple sclerosis (MS), and children. A secondary purpose was to decide whether any inferences could be made for children with CP.

**Design:** This study included a meta-analysis.

**Interventions:** A systematic review was performed of yoga and said populations. Outcome measures were categorized according to the ICF model domains of body structures and function, activity, and quality of life. Effect sizes (ESs) were calculated by using Cohen's d. Since there were few commonalities among outcome measures and reporting of outcomes within and among diagnostic groups, direct comparisons of ESs were difficult. Hence, we chose to evaluate the impact of yoga as compared with the control group or other physical exercise by using a General Linear Mixed Model.

**Results:** There were 5 yoga studies with stroke, 15 with MS, and 12 with children. Studies with children used outcomes related to body structure and function, whereas those with stroke and MS used outcomes across all three domains of the ICF. ESs varied from negligible to medium for stroke, from negligible to large for MS and children.

**Conclusions:** The findings of this meta-analysis indicate that yoga is no better or worse than other exercise modalities as a treatment intervention for adults with stroke and MS, and children. Group yoga classes are typically social environments that can contribute to increased physical progress and feelings that contribute to quality of life, which may benefit individuals with CP. More research on yoga and particularly in children and adults with CP would yield valuable information for creating effective and safe yoga programs with a rich array of benefits.


**Abstract:**

**Purpose:** This study is aimed to explore the combined use of goiter dispersion formula and antithyroid drugs in the treatment of patients with neurologic manifestations of Graves' disease by examining its modulating effects on patients' cytokines.

**Methods:** A total of 80 patients with Graves' disease were randomly divided into treatment and control groups. Patients of the treatment group received goiter dispersion formula and antithyroid drugs (methimazole or propylthiouracil), whereas those of the control group received antithyroid drug alone. FT3, FT4, and TSH contents were detected by chemiluminescence immunoassay at pre- and post-treatment; interleukin (IL)-2, IL-8, and IL-17 serum levels before and after the treatment were detected by radioimmunoassay; thyroid B-mode ultrasound and liver and renal function tests were performed in all patients of both groups. An additional cohort of 40 healthy subjects was recruited for baseline measurement.

**Results:** All the enrolled patients completed the trial. The effective treatment rate was higher in the treatment group than in the control group, of which the difference was statistically significant (treatment group, 95%; control group, 75%, p < 0.01). For blood cytokine, before treatment, IL-2 was reduced whereas IL-8 and IL-17 were increased significantly in both groups of patients with Graves' disease comparing with those in healthy subjects (p < 0.01). For patients of the treatment group, after treatment, their IL-2 levels were increased (p < 0.01) with concomitant decreases in IL-8 and IL-17 levels (p < 0.05). There were no significant changes in blood cytokine levels before and after treatment in the control group.

**Conclusions:** Goiter dispersion formula significantly improved the treatment outcomes of antithyroid drug in hyperthyroidism patients with neurologic manifestations of Graves' disease by modulating IL-2, IL-8, and IL-17. The data supported the rationale for the use of goiter dispersion formula in Graves' disease treatment.


**Abstract:**

**Purpose:** Medical students have higher rates of depression and psychologic distress than the general population, which may negatively impact academic performance and professional conduct. This study assessed whether 10–20 min of daily mindfulness meditation for 30 days, using a mobile phone application, could decrease perceived stress and improve well-being for medical students.

**Methods:** Eighty-eight medical students were stratified by class year and randomized to either intervention or control groups to use the mobile application Headspace, an audio-guided mindfulness meditation program, for 30 days. All participants completed the Perceived Stress Scale (PSS), Five-Facet Mindfulness Questionnaire (FFMQ), and General Well-Being Schedule (GWBS) at baseline (T1), 30 days (T2), and 60 days (T3). Repeated measures analysis of variance (rANOVA) was conducted for intervention versus control groups across T1, T2, and T3 to examine differences in stress, mindfulness, and well-being.

**Results:** There was a significant interaction between time and treatment group for perceived stress and well-being. Perceived stress significantly decreased for the intervention group from T1 to T3 ($F[2,142] = 3.98$, $p < 0.05$). General well-being significantly increased for the intervention group compared to the control group from T1 to T2, and the increase was sustained through T3 ($F[2,144] = 3.36$, $p < 0.05$).

**Conclusions:** These results highlight that a mobile audio-guided mindfulness meditation program is an effective means to decrease perceived stress in medical students, which may have implications on patient care. Integrating mindfulness training into medical school curricula for management of school- and work-related stress may lead to fewer negative physician outcomes (e.g., burnout, anxiety, and depression) and improved physician and patient outcomes. This has implications for a broad group of therapists and healthcare providers, ultimately improving quality of healing and patient care.


**Abstract:**

**Objectives:** Pharmacotherapy among children with attention-deficit/hyperactivity disorder (ADHD) is effective, but many patients suffer from secondary psychiatric problems even after improvement of ADHD core symptoms. Hippotherapy have been used as adjunct treatment options for physical and psychosocial rehabilitation as well as to ameliorate core symptoms. The aim of this study was to investigate the effects of Hippotherapy versus pharmacotherapy for children with ADHD.
**Design:** Thirty-four participants with ADHD were randomly assigned at a 1:1 ratio to either 24 sessions of a twice-weekly hippotherapy or pharmacotherapy. To assess therapeutic effects, the ADHD Rating Scale (ARS) was used pretreatment and posttreatment as the primary outcome measure. Secondary outcomes included the Child Behavior Checklist (CBCL), Self-Esteem Scale (SES), Pediatric Quality of Life Inventory (PedsQL) child and parent report version, Developmental Coordination Disorder Questionnaire (DCDQ), Clinical Global Impressions-Severity (CGI-S), and quantitative electroencephalography.

**Results:** Both groups showed marked improvements in ADHD symptoms, CGI-S. No significant differences between groups were detected regarding treatment outcome except thought problem subscales of CBCL. Twelve weeks of hippotherapy improved attention, impulsivity/hyperactivity, and quality of life.

**Conclusion:** This trial is promising, but further studies are required to evaluate the long-term clinical effectiveness of hippotherapy. The study is registered with ClinicalTrials.gov, number NCT 02482649.

**Zhao Dong, Zhao Jing-Bo. Comparison of Chang Run Tong and Forlaxin treatment of constipation in elderly diabetic patients. Journal of Alternative and Complementary Medicine 2018; 24(5): 472-80p.**

**Abstract:**

**Objective:** Constipation is quite common and has impact on life quality in the elderly diabetic patients; therefore it is important to seek better treatments. The aim of this study is to evaluate the effect of Chang Run Tong (CRT) decoction on constipation in elderly diabetic patients in comparison with the effect of Macrogol 4000 powder (Forlax).

**Design:** This study was designed as a prospective study consisting of two parallel arms: CRT group and Forlax group. Settings/Location: The study was conducted in China-Japan Hospital. Subject interventions: Eighty elderly diabetic patients with constipation were evaluated, among them 52 patients were treated with CRT and 28 patients were treated with Forlax.

**Outcome measures:** The patients were interviewed for Bristol stool scale, spontaneous complete bowel movements (SCBM) and symptoms of defecation feeling, defecation weakness, feeling of incomplete evacuation, bloating, and flatulence at different time points. The changes of all above parameters from treatment for 2 and 4 weeks and follow-up for 1 and 2 months with reference to the baseline (before treatment) were compared between CRT and Forlax treatments. The treatment efficiency was evaluated and compared between two different treatments.

**Results:** For the improvement of Bristol stool scale, SCBM and feeling of incomplete evacuation, CRT was significantly better than Forlax at different time points (p < 0.01, p < 0.001). For the symptoms of defecation feeling, defecation weakness, bloating, and flatulence, CRT was significantly better than Forlax for follow-up improvement (p < 0.01, p < 0.001); whereas no difference was found at other time points of the
treatment (p > 0.05). Furthermore, CRT had a significantly better treatment efficiency than Forlax (p < 0.001).

**Conclusions:** Both CRT and Forlax treatment could effectively improve bowel habits and symptoms of constipation in elderly diabetic patients. CRT was better than Forlax to treat constipation in elderly diabetic patients and had better follow-up improvement after stopping drugs.

**Abstract:**

**Objective:** To assess the effectiveness of osteopathic intervention (OI) and general osteopathic treatment (GOT) in individuals with fibromyalgia syndrome (FMS).

**Methods:** The trial was designed as a randomized controlled trial with 2 osteopathic interventions and 1 untreated control group. The patients in the two osteopathic groups received 10 osteopathic treatments (OI or GOT) within a time period of 12 weeks. The control group did not receive any osteopathic treatment. The primary outcome was the average pain intensity (API) assessed by visual analog scale (VAS). Secondary outcomes were the pressure-pain threshold rated by means of a tender point score, and disease severity, assessed by the Fibromyalgia Impact Questionnaire (FIQ).

**Results:** 50 patients were randomized. The primary outcome parameter API decreased from 7.2 to 4.7 in the OI group, from 6.3 to 4.3 in the GOT group, and increased slightly in the control group from 6.2 to 6.6. There were significant differences for the change in API between the OI group and the control group (VAS: 2.9, 95% confidence interval (CI) = 1.12–4.52), and between the GOT group and the control group (VAS: 2.4, 95% CI = 0.65–4.11), but no significant differences between the OI group and the GOT group.
There were no significant differences for the secondary outcome parameters between the groups.

**Conclusion:** A series of osteopathic treatments might be beneficial for patients suffering from FMS.


**Abstract:**

The global burden of non-communicable diseases (NCDs) is growing, and there is an urgent need to estimate the costs and benefits of an investment strategy to prevent and control NCDs. Results from an investment-case analysis can provide important new evidence to inform decision making by governments and donors. We propose a methodology for calculating the economic benefits of investing in NCDs during the Sustainable Development Goals (SDGs) era, and we applied this methodology to cardiovascular disease prevention in 20 countries with the highest NCD burden. For a limited set of prevention interventions, we estimated that US$120 billion must be invested in these countries between 2015 and 2030. This investment represents an additional $1.50 per capita per year and would avert 15 million deaths, 8 million incidents of ischaemic heart disease, and 13 million incidents of stroke in the 20 countries. Benefit–cost ratios varied between interventions and country-income levels, with an average ratio of 5.6 for economic returns but a ratio of 10.9 if social returns are included. Investing in cardiovascular disease prevention is integral to achieving SDG target 3.4 (reducing premature mortality from NCDs by a third) and to progress towards SDG target 3.8 (the realisation of universal health coverage). Many countries have implemented cost-effective interventions at low levels, so the potential to achieve these targets and strengthen national income by scaling up these interventions is enormous.


**Abstract:**

**Background:** Few studies have examined the efficacy of drug-eluting stents (DES) for reducing aortocoronary saphenous vein bypass graft (SVG) failure compared with bare-metal stents (BMS) in patients undergoing stenting of de-novo SVG lesions. We assessed the risks and benefits of the use of DES versus BMS in de-novo SVG lesions.
Methods: Patients were recruited to our double-blind, randomised controlled trial from 25 US Department of Veterans Affairs centres. Eligible participants were aged at least 18 years and had at least one significant de-novo SVG lesion (50–99% stenosis of a 2·25–4·5 mm diameter SVG) requiring percutaneous coronary intervention with intent to use embolic protection devices. Enrolled patients were randomly assigned, in a 1:1 ratio, by phone randomisation system to receive a DES or BMS. Randomisation was stratified by presence or absence of diabetes and number of target SVG lesions requiring percutaneous coronary intervention (one or two or more) within each participating site by use of an adaptive scheme intended to balance the two stent type groups on marginal totals for the stratification factors. Patients, referring physicians, study coordinators, and outcome assessors were masked to group allocation. The primary endpoint was the 12-month incidence of target vessel failure, defined as the composite of cardiac death, target vessel myocardial infarction, or target vessel revascularisation. The DIVA trial is registered with ClinicalTrials.gov, number NCT01121224.

Findings: Between Jan 1, 2012, and Dec 31, 2015, 599 patients were randomly assigned to the stent groups, and the data for 597 patients were used. The patients’ mean age was 68·6 (SD 7·6) years, and 595 (>99%) patients were men. The two stent groups were similar for most baseline characteristics. At 12 months, the incidence of target vessel failure was 17% (51 of 292) in the DES group versus 19% (58 of 305) in the BMS group (adjusted hazard ratio 0·92, 95% CI 0·63–1·34, p=0·70). Between-group differences in the components of the primary endpoint, serious adverse events, or stent thrombosis were not significant. Enrolment was stopped before the revised target sample size of 762 patients was reached.

Interpretation: In patients undergoing stenting of de-novo SVG lesions, no significant differences in outcomes between those receiving DES and BMS during 12 months of follow-up were found. The study results have important economic implications in countries with high DES prices such as the USA, because they suggest that the lower-cost BMS can be used in SVG lesions without compromising either safety or efficacy.

Funding: US Department of Veterans Affairs Cooperative Studies Program.


Abstract:

Background: Recipients of autologous haemopoietic stem-cell transplants (auto-HSCT) have an increased risk of herpes zoster and herpes zoster-related complications. The aim of this study was to establish the efficacy and safety of an inactivated varicella zoster vaccine for the prevention of herpes zoster after auto-HSCT.

Methods: In this randomised, double-blind, placebo-controlled phase 3 trial, participants were recruited from 135 medical centres (ie, stem-cell transplant centres and hospitals) in North America, South America, Europe, and Asia. Patients were eligible if they were aged 18 years or older, scheduled to receive an auto-HSCT within 60 days of enrolment, and had a history of varicella infection or were seropositive for antibodies to varicella zoster virus, or both. Exclusion criteria included a history of herpes zoster within the previous year of enrolment, and intended antiviral prophylaxis for longer than 6 months after transplantation. Participants were randomly assigned according to a central randomisation schedule generated by the trial statistician, to receive either the inactivated-virus vaccine from one of three consistency lots, a high-antigen lot, or placebo, stratified by age (<50 vs ≥50 years) and intended duration of antiviral prophylaxis after transplant (≤3 months vs >3 to ≤6 months). Participants, investigators, trial staff, and the funder’s clinical and laboratory personnel were masked to group assignment. Participants were given four doses of inactivated vaccine or placebo, with the first dose 5–60 days before auto-HSCT, and the second, third, and fourth doses at about 30, 60, and 90 days after transplantation. The primary efficacy endpoint was the incidence of herpes zoster, confirmed by PCR or adjudication by a masked clinical committee, or both, assessed in all participants randomly assigned to the vaccine consistency lot group or placebo group who received at least one dose of vaccine and had auto-HSCT. Safety was assessed in all randomised participants who received at least one dose of vaccine and had follow-up data. A prespecified vaccine efficacy success criterion required the lower bound of the 95% CI be higher than 25% for the relative reduction of the hazard ratio of herpes zoster infection in participants given the vaccine from one of the consistency lots compared with those given placebo. This trial is registered on ClinicalTrials.gov (NCT01229267) and EudraCT (2010–020150–34).

Findings: Between Dec 7, 2010, and April 25, 2013, 560 participants were randomly assigned to the vaccine consistency lot group, 106 to the high-antigen lot group, and 564 to the placebo group. 249 (44%) of patients in the vaccine consistency lot group, 35 (33%) in the high-antigen lot group, and 220 (39%) in the placebo group discontinued before study end, mostly because of death or withdrawal. 51 participants were excluded from the primary efficacy endpoint analyses because they did not undergo auto-HSCT or were not vaccinated, or both (22 [4%] in the vaccine consistency lot group, and 29 [5%] in the placebo group). Mean follow-up for efficacy was 2·4 years (SD 1·3) in the vaccine consistency lot group and 2·3 years (SD 1·3) in the placebo group. 42 (8%) of 538 participants in the vaccine consistency lot group (32·9 per 1000 person-years) and 113 (21%) of 535 in the placebo group (91·9 per 1000 person-years) had a confirmed case of herpes zoster. The estimated vaccine efficacy was 63·8% (95% CI 48·4–74·6), meeting the pre-specified success criterion. For the combined vaccine groups versus the placebo group, the proportion of patients with serious adverse events [216 [33%] of 657 vs 181 [33%] of 554; risk difference 0·2%, 95% CI −5·1 to 5·5] and serious vaccine-
related adverse events (five [1%] vs five [1%]; risk difference 0.1%, −1.4 to 1.1) were similar. Vaccine-related injection-site adverse events occurred more frequently in participants given vaccine than those given placebo (191 [29%] vs 36 [7%]; risk difference 22.6%, 95% CI 18.5–26.6; p<0.0001).

**Interpretation:** This study shows for the first time in a large phase 3 trial that early vaccination of auto-HSCT recipients during the peri-transplant period can be effective for the prevention of an opportunistic infection like herpes zoster and that the vaccine is well tolerated.

**Funding:** Merck & Co., Inc.


**Abstract:**

Modern, affordable pathology and laboratory medicine (PALM) systems are essential to achieve the 2030 Sustainable Development Goals for health in low-income and middle-income countries (LMICs). In this last in a Series of three papers about PALM in LMICs, we discuss the policy environment and emphasise three crucial high-level actions that are needed to deliver universal health coverage. First, nations need national strategic laboratory plans; second, these plans require adequate financing for implementation; and last, pathologists themselves need to take on leadership roles to advocate for the centrality of PALM to achieve the Sustainable Development Goals for health. The national strategic laboratory plan should deliver a tiered, networked laboratory system as a central element. Appropriate financing should be provided, at a level of at least 4% of health expenditure. Financing of new technologies such as molecular diagnostics is challenging for LMICs, even though many of these tests are cost-effective. Point-of-care testing can substantially reduce test-reporting time, but this benefit must be balanced with higher costs. Our research analysis highlights a considerable deficiency in advocacy for PALM; pathologists have been invisible in national and international health discourse and leadership. Embedding PALM in LMICs can only be achieved if pathologists advocate for these services, and undertake leadership roles, both nationally and internationally. We articulate eight key recommendations to address the current barriers identified in this Series and issue a call to action for all stakeholders to come together in a global alliance to ensure the effective provision of PALM services in resource-limited settings.


**Abstract:**
The economic burden on households of non-communicable diseases (NCDs), including cardiovascular diseases, cancer, respiratory diseases, and diabetes, poses major challenges to global poverty alleviation efforts. For patients with NCDs, being uninsured is associated with 2–7-fold higher odds of catastrophic levels of out-of-pocket costs; however, the protection offered by health insurance is often incomplete. To enable coverage of the predictable and long-term costs of treatment, national programmes to extend financial protection should be based on schemes that entail compulsory enrolment or be financed through taxation. Priority should be given to eliminating financial barriers to the uptake of and adherence to interventions that are cost-effective and are designed to help the poor. In concert with programmes to strengthen national health systems and governance arrangements, comprehensive financial protection against the growing burden of NCDs is crucial in meeting the UN’s Sustainable Development Goals.


Abstract:

Background: Potentially untreatable Plasmodium falciparum malaria threatens the Greater Mekong subregion. A previous series of pilot projects in Myanmar, Laos, Cambodia, and Vietnam suggested that mass drug administration was safe, and when added to provision of early diagnosis and treatment, could reduce the reservoir of P falciparum and interrupts transmission. We examined the effects of a scaled-up programme of this strategy in four townships of eastern Myanmar on the incidence of P falciparum malaria.

Methods: The programme was implemented in the four townships of Myawaddy, Kawkareik, Hlaingbwe, and Hpapun in Kayin state, Myanmar. Increased access to early diagnosis and treatment of malaria was provided to all villages through community-based malaria posts equipped with rapid diagnostic tests, and treatment with artemether–lumefantrine plus single low-dose primaquine. Villages were identified as malarial hotspots (operationally defined as >40% malaria, of which 20% was P falciparum) with surveys using ultrasensitive quantitative PCR either randomly or targeted at villages where the incidence of clinical cases of P falciparum malaria remained high (ie, >100 cases per 1000 individuals per year) despite a functioning malaria post. During each survey, a 2 mL sample of venous blood was obtained from randomly selected adults. Hotspots received targeted mass drug administration with dihydroartemisinin–piperaquine plus single-dose primaquine once per month for 3 consecutive months in addition to the malaria posts. The main outcome was the change in village incidence of clinical P falciparum malaria, quantified using a multivariate, generalised, additive multilevel model. Malaria prevalence was measured in the hotspots 12 months after mass drug administration.

Findings: Between May 1, 2014, and April 30, 2017, 1222 malarial posts were opened, providing early diagnosis and treatment to an estimated 365 000 individuals. Incidence of P falciparum malaria decreased by 60 to 98% in the four townships. 272 prevalence surveys were undertaken and 69 hotspot villages were identified. By April 2017, 50
hotspots were treated with mass drug administration. Hotspot villages had a three times higher incidence of P. falciparum at malarial posts than neighbouring villages (adjusted incidence rate ratio [IRR] 2·7, 95% CI 1·8–4·4). Early diagnosis and treatment was associated with a significant decrease in P. falciparum incidence in hotspots (IRR 0·82, 95% CI 0·76–0·88 per quarter) and in other villages (0·75, 0·73–0·78 per quarter). Mass drug administration was associated with a five-times decrease in P. falciparum incidence within hotspot villages (IRR 0·19, 95% CI 0·13–0·26). By April, 2017, 965 villages (79%) of 1222 corresponding to 104 village tracts were free from P. falciparum malaria for at least 6 months. The prevalence of wild-type genotype for K13 molecular markers of artemisinin resistance was stable over the three years (39%; 249/631).

**Interpretation:** Providing early diagnosis and effective treatment substantially decreased village-level incidence of artemisinin-resistant P. falciparum malaria in hard-to-reach, politically sensitive regions of eastern Myanmar. Targeted mass drug administration significantly reduced malaria incidence in hotspots. If these activities could proceed in all contiguous endemic areas in addition to standard control programmes already implemented, there is a possibility of subnational elimination of P. falciparum.

**Funding:** The Bill & Melinda Gates Foundation, the Regional Artemisinin Initiative (Global Fund against AIDS, Tuberculosis and Malaria), and the Wellcome Trust.

---


**Abstract:**

**Background:** Stroke disproportionately affects people in low-income and middle-income countries. Although improvements in stroke care and outcomes have been reported in high-income countries, little is known about practice and outcomes in low and middle-income countries. We aimed to compare patterns of care available and their association with patient outcomes across countries at different economic levels.

**Methods:** We studied the patterns and effect of practice variations (ie, treatments used and access to services) among participants in the INTERSTROKE study, an international observational study that enrolled 13 447 stroke patients from 142 clinical sites in 32 countries between Jan 11, 2007, and Aug 8, 2015. We supplemented patient data with a questionnaire about health-care and stroke service facilities at all participating hospitals. Using univariate and multivariate regression analyses to account for patient casemix and service clustering, we estimated the association between services available, treatments given, and patient outcomes (death or dependency) at 1 month.
**Findings:** We obtained full information for 12,342 (92%) of 13,447 INTERSTROKE patients, from 108 hospitals in 28 countries; 2,576 from 38 hospitals in ten high-income countries and 9,766 from 70 hospitals in 18 low and middle-income countries. Patients in low-income and middle-income countries more often had severe strokes, intracerebral haemorrhage, poorer access to services, and used fewer investigations and treatments (p<0·0001) than those in high-income countries, although only differences in patient characteristics explained the poorer clinical outcomes in low and middle-income countries. However across all countries, irrespective of economic level, access to a stroke unit was associated with improved use of investigations and treatments, access to other rehabilitation services, and improved survival without severe dependency (odds ratio [OR] 1·29; 95% CI 1·14–1·44; all p<0·0001), which was independent of patient casemix characteristics and other measures of care. Use of acute antiplatelet treatment was associated with improved survival (1·39; 1·12–1·72) irrespective of other patient and service characteristics.

**Interpretation:** Evidence-based treatments, diagnostics, and stroke units were less commonly available or used in low and middle-income countries. Access to stroke units and appropriate use of antiplatelet treatment were associated with improved recovery. Improved care and facilities in low-income and middle-income countries are essential to improve outcomes.

**Funding:** Chest, Heart and Stroke Scotland.


**Abstract:**

**Background:** Cholera remains a persistent health problem in sub-Saharan Africa and worldwide. Cholera can be controlled through appropriate water and sanitation, or by oral cholera vaccination, which provides transient (~3 years) protection, although vaccine supplies remain scarce. We aimed to map cholera burden in sub-Saharan Africa and assess how geographical targeting could lead to more efficient interventions.

**Methods:** We combined information on cholera incidence in sub-Saharan Africa (excluding Djibouti and Eritrea) from 2010 to 2016 from datasets from WHO, Médecins Sans Frontières, ProMED, ReliefWeb, ministries of health, and the scientific literature. We divided the study region into 20 km × 20 km grid cells and modelled annual cholera incidence in each grid cell assuming a Poisson process adjusted for covariates and spatially correlated random effects. We combined these findings with data on population distribution to estimate the number of people living in areas of high cholera incidence (>1 case per 1000 people per year). We further estimated the reduction in cholera incidence that could be achieved by targeting cholera prevention and control interventions at areas of high cholera incidence.

**Findings:** We included 279 datasets covering 2,283 locations in our analyses. In sub-Saharan Africa (excluding Djibouti and Eritrea), a mean of 141,918 cholera cases (95% credible interval [CrI] 141,538–146,505) were reported per year. 4·0% (95% CrI 1·7–16·8) of districts, home to 87·2 million people (95% CrI 60·3 million to 118·9 million), have high cholera incidence. By focusing on the highest incidence districts first, effective
targeted interventions could eliminate 50% of the region's cholera by covering 35·3 million people (95% CrI 26·3 million to 62·0 million), which is less than 4% of the total population.

**Interpretation:** Although cholera occurs throughout sub-Saharan Africa, its highest incidence is concentrated in a small proportion of the continent. Prioritising high-risk areas could substantially increase the efficiency of cholera control programmes.

**Funding:** The Bill & Melinda Gates Foundation.


**Abstract:**

Five Sustainable Development Goals (SDGs) set targets that relate to the reduction of health inequalities nationally and worldwide. These targets are poverty reduction, health and wellbeing for all, equitable education, gender equality, and reduction of inequalities within and between countries. The interaction between inequalities and health is complex: better economic and educational outcomes for households enhance health, low socioeconomic status leads to chronic ill health, and non-communicable diseases (NCDs) reduce income status of households. NCDs account for most causes of early death and disability worldwide, so it is alarming that strong scientific evidence suggests an increase in the clustering of non-communicable conditions with low socioeconomic status in low-income and middle-income countries since 2000, as previously seen in high-income settings. These conditions include tobacco use, obesity, hypertension, cancer, and diabetes. Strong evidence from 283 studies overwhelmingly supports a positive association between low-income, low socioeconomic status, or low educational status and NCDs. The associations have been differentiated by sex in only four studies. Health is a key driver in the SDGs, and reduction of health inequalities and NCDs should become key in the promotion of the overall SDG agenda. A sustained reduction of general inequalities in income status, education, and gender within and between countries would enhance worldwide equality in health. To end poverty through elimination of its causes, NCD programmes should be included in the development agenda. National programmes should mitigate social and health shocks to protect the poor from events that worsen their frail socioeconomic condition and health status. Programmes related to universal health coverage of NCDs should specifically target susceptible populations, such as elderly people, who are most at risk. Growing inequalities in access to resources for prevention and treatment need to be addressed through improved international regulations across jurisdictions that eliminate the legal and practical barriers in the implementation of non-communicable disease control.


**Abstract:**

Reduction of the non-communicable disease (NCD) burden is a global development imperative. Sustainable Development Goal (SDG) 3 includes target 3.4 to reduce
premature NCD mortality by a third by 2030. Progress on SDG target 3·4 will have a central role in determining the success of at least nine SDGs. A strengthened effort across multiple sectors with effective economic tools, such as price policies and insurance, is necessary. NCDs are heavily clustered in people with low socioeconomic status and are an important cause of medical impoverishment. They thereby exacerbate economic inequities within societies. As such, NCDs are a barrier to achieving SDG 1, SDG 2, SDG 4, SDG 5, and SDG 10. Productivity gains from preventing and managing NCDs will contribute to SDG 8. SDG 11 and SDG 12 offer clear opportunities to reduce the NCD burden and to create sustainable and healthy cities.


Abstract:

**Background:** Most cardiovascular disease risk prediction equations in use today were derived from cohorts established last century and with participants at higher risk but less socioeconomically and ethnically diverse than patients they are now applied to. We recruited a nationally representative cohort in New Zealand to develop equations relevant to patients in contemporary primary care and compared the performance of these new equations to equations that are recommended in the USA.

**Methods:** The PREDICT study automatically recruits participants in routine primary care when general practitioners in New Zealand use PREDICT software to assess their patients' risk profiles for cardiovascular disease, which are prospectively linked to national ICD-coded hospitalisation and mortality databases. The study population included male and female patients in primary care who had no prior cardiovascular disease, renal disease, or congestive heart failure. New equations predicting total cardiovascular disease risk were developed using Cox regression models, which included clinical predictors plus an area-based deprivation index and self-identified ethnicity. Calibration and discrimination performance of the equations were assessed and compared with 2013 American College of Cardiology/American Heart Association Pooled Cohort Equations (PCEs). The additional predictors included in new PREDICT equations were also appended to the PCEs to determine whether they were independent predictors in the equations from the USA.

**Findings:** Outcome events were derived for 401,752 people aged 30–74 years at the time of their first PREDICT risk assessment between Aug 27, 2002, and Oct 12, 2015, representing about 90% of the eligible population. The mean follow-up was 4·2 years, and a third of participants were followed for 5 years or more. 15,386 (4%) people had cardiovascular disease events (1507 [10%] were fatal, and 8549 [56%] met the PCEs definition of hard atherosclerotic cardiovascular disease) during 1,685,521 person-years follow-up. The median 5-year risk of total cardiovascular disease events predicted by the new equations was 2·3% in women and 3·2% in men. Multivariable adjusted risk increased by about 10% per quintile of socioeconomic deprivation. Māori, Pacific, and Indian patients were at 13–48% higher risk of cardiovascular disease than Europeans, and Chinese or other Asians were at 25–33% lower risk of cardiovascular disease than Europeans. The PCEs overestimated of hard atherosclerotic cardiovascular disease by about 40% in men and by 60% in women, and the additional predictors in the new
equations were also independent predictors in the PCEs. The new equations were significantly better than PCEs on all performance metrics.

**Interpretation:** We constructed a large prospective cohort study representing typical patients in primary care in New Zealand who were recommended for cardiovascular disease risk assessment. Most patients are now at low risk of cardiovascular disease, which explains why the PCEs based mainly on old cohorts substantially overestimate risk. Although the PCEs and many other equations will need to be recalibrated to mitigate overtreatment of the healthy majority, they also need new predictors that include measures of socioeconomic deprivation and multiple ethnicities to identify vulnerable high-risk subpopulations that might otherwise be undertreated.

**Funding:** Health Research Council of New Zealand, Heart Foundation of New Zealand, and Healthier Lives National Science Challenge.


**Abstract:**

**Objectives:** The aim of this study was to assess the possibility of transmitting the “ampicillin” growth inhibitory property to pure sterile water.

**Design:** Three control groups were designed as references of bacterial maximal growth (MG). Different concentrations of ampicillin and pure sterile water used as “positive” and “negative” controls, respectively, and the bacterial cultures supplemented with water that merely exposed to the background carrier waves were set as “sham control.”

**Settings:** The electronic characteristic of the ampicillin solution relayed to the water and then it was added to the bacterial culture medium. By this treatment, water received both the carrier wave and ampicillin electronic properties at 1–10^5 Hz range.

**Results:** When the MG of the “treated water” and “positive control” dilutions is getting normalized against either sham or negative control, the treated water competently imitates ampicillin in a way that there is no significant difference with the positive control. These results will be affected to some extent by the time of electronic transmission and the inoculation concentration of bacterial culture. Comparison of electromagnetic signal patterns of “treated water” with the “positive control” shows that they are more similar to each other rather than negative control.

**Conclusion:** It is believed that the extremely low frequencies can facilitate electronic transmission of ampicillin supramolecular chemistry into water. Imprinting such a property in water could be the result of durable structural configuration in treated water.

**Sassi Franco, Belloni Annalisa, Mirelman Andrew J et al.** Equity impacts of price policies to promote healthy behaviours. *Lancet 2018: 391(10134); 2059-70p.*

**Abstract:**

Governments can use fiscal policies to regulate the prices and consumption of potentially unhealthy products. However, policies aimed at reducing consumption by increasing prices, for example by taxation, might impose an unfair financial burden on
low-income households. We used data from household expenditure surveys to estimate patterns of expenditure on potentially unhealthy products by socioeconomic status, with a primary focus on low-income and middle-income countries. Price policies affect the consumption and expenditure of a larger number of high-income households than low-income households, and any resulting price increases tend to be financed disproportionately by high-income households. As a share of all household consumption, however, price increases are often a larger financial burden for low-income households than for high-income households, most consistently in the case of tobacco, depending on how much consumption decreases in response to increased prices. Large health benefits often accrue to individual low-income consumers because of their strong response to price changes. The potentially larger financial burden on low-income households created by taxation could be mitigated by a pro-poor use of the generated tax revenues.


Abstract:

Insufficient awareness of the centrality of pathology and laboratory medicine (PALM) to a functioning health-care system at policy and governmental level, with the resultant inadequate investment, has meant that efforts to enhance PALM in low-income and middle-income countries have been local, fragmented, and mostly unsustainable. Responding to the four major barriers in PALM service delivery that were identified in the first paper of this Series (workforce, infrastructure, education and training, and quality assurance), this second paper identifies potential solutions that can be applied in low-income and middle-income countries (LMICs). Increasing and retaining a quality PALM workforce requires access to mentorship and continuing professional development, task sharing, and the development of short-term visitor programmes. Opportunities to enhance the training of pathologists and allied PALM personnel by increasing and improving education provision must be explored and implemented. PALM infrastructure must be strengthened by addressing supply chain barriers, and ensuring laboratory information systems are in place. New technologies, including telepathology and point-of-care testing, can have a substantial role in PALM service delivery, if used appropriately. We emphasise the crucial importance of maintaining PALM quality and posit that all laboratories in LMICs should participate in quality assurance and accreditation programmes. A potential role for public-private partnerships in filling PALM services gaps should also be investigated. Finally, to deliver these solutions and ensure equitable access to essential services in LMICs, we propose a PALM package focused on these countries, integrated within a nationally tiered laboratory system, as part of an overarching national laboratory strategic plan.


Abstract:
As global efforts accelerate to implement the Sustainable Development Goals and, in particular, universal health coverage, access to high-quality and timely pathology and laboratory medicine (PALM) services will be needed to support health-care systems that are tasked with achieving these goals. This access will be most challenging to achieve in low-income and middle-income countries (LMICs), which have a disproportionately large share of the global burden of disease but a disproportionately low share of global health-care resources, particularly PALM services. In this first in a Series of three papers on PALM in LMICs, we describe the crucial and central roles of PALM services in the accurate diagnosis and detection of disease, informing prognosis and guiding treatment, contributing to disease screening, public health surveillance and disease registries, and supporting medical-legal systems. We also describe how, even though data are sparse, these services are of both insufficient scope and inadequate quality to play their key role in health-care systems in LMICs. Lastly, we identify four key barriers to the provision of optimal PALM services in resource-limited settings: insufficient human resources or workforce capacity, inadequate education and training, inadequate infrastructure, and insufficient quality, standards, and accreditation.


Abstract:
Background: Child mortality is almost twice as high in England compared with Sweden. We aimed to establish the extent to which adverse birth characteristics and socioeconomic factors explain this difference.

Methods: We developed nationally representative cohorts of singleton livebirths between Jan 1, 2003, and Dec 31, 2012, using the Hospital Episode Statistics in England, and the Swedish Medical Birth Register in Sweden, with longitudinal follow-up from linked hospital admissions and mortality records. We analysed mortality as the outcome, based on deaths from any cause at age 2–27 days, 28–364 days, and 1–4 years. We fitted Cox proportional hazard regression models to estimate the hazard ratios (HRs) for England compared with Sweden in all three age groups. The models were adjusted for birth characteristics (gestational age, birthweight, sex, and congenital anomalies), and for socioeconomic factors (maternal age and socioeconomic status).

Findings: The English cohort comprised 3 932 886 births and 11 392 deaths and the Swedish cohort comprised 1 013 360 births and 1927 deaths. The unadjusted HRs for England compared with Sweden were 1·66 (95% CI 1·53–1·81) at 2–27 days, 1·59 (1·47–1·71) at 28–364 days, and 1·27 (1·15–1·40) at 1–4 years. At 2–27 days, 77% of the excess risk of death in England was explained by birth characteristics and a further 3% by socioeconomic factors. At 28–364 days, 68% of the excess risk of death in England was explained by birth characteristics and a further 11% by socioeconomic factors. At 1–4 years, the adjusted HR did not indicate a significant difference between countries.

Interpretation: Excess child mortality in England compared with Sweden was largely explained by the unfavourable distribution of birth characteristics in England.
Socioeconomic factors contributed to these differences through associations with adverse birth characteristics and increased mortality after 1 month of age. Policies to reduce child mortality in England could have most impact by reducing adverse birth characteristics through improving the health of women before and during pregnancy and reducing socioeconomic disadvantage.

**Funding:** The Farr Institute of Health Informatics Research (through the Medical Research Council, Arthritis Research UK, British Heart Foundation, Cancer Research UK, Chief Scientist Office, Economic and Social Research Council, Engineering and Physical Sciences Research Council, National Institute for Health Research, National Institute for Social Care and Health Research, and the Wellcome Trust).