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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/magazines 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:

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

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ACKNOWLEDGEMENT

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

(Meenakshi Bhatia)
Librarian
AYUSH & Other Systems


Abstract:

The idea behind the doctrine of signature advocated by Paracelsus is to infer the nature of action of a substance from its physical appearance and properties especially color and form. Nature always presents healing substance with some signs indicating their use against diseases. The idea of application of doctrine of signature is a very old one and was one of the prime sources of materia medica before Dr. Hahnemann. Studying the physical properties of the drug substance was of great importance for understanding constitution of materia medica of the same drug.

Arora Mudita, Maurya Pooja. Relieving constipation with homoeopathy. Homoeopathy for All 2019; 21(1) 228: 54-59p.


Abstract:

Objective: The overuse of prescription opioids for chronic pain is recognized as a public health crisis. Yet, poor access to nonpharmacologic treatments is the norm in low-income, racially and ethnically diverse patients with chronic pain. The main objective of this study was to understand how chronic pain impacts low-income individuals with chronic pain and their communities from multiple perspectives.

Design: This was a qualitative study using a Science Café methodology.

Setting: The Science Café event was held at an urban community center in Boston, MA.

Subjects: Inclusion criteria included the following: having the ability to attend the event, being at least 18 years of age or older, and participating in English.
Methods: Data were collected through self-reported questionnaires and audio or video recordings of two focus groups. Quantitative and qualitative data were analyzed with SAS 9.3 and NVivo 10.

Results: Thirty participants attended the Science Café event. The average age was 45 years, 77% reported as female, 42% identified as black, and 19% as Hispanic. Participants identified themselves as either patients (46%) or providers (54%) to the chronic pain community. Our forum revealed three major themes: (1) nonpharmacologic options for chronic pain management are warranted, (2) larger sociodemographic and contextual factors influence management of chronic pain, and (3) both patients and providers value the patient-provider relationship and acknowledge the need for better communication for patients with chronic pain.

Conclusions: Future research should consider identifying and addressing disparities in access to nonpharmacologic treatments for chronic pain in relation to underlying social determinants of health, particularly for racially and ethnically diverse patients.


Abstract:
Indolence in thoughts and action always leads to stagnation. This case depicts it clearly!


Abstract:
The best way to treat corn is by homeopathy, because surgery can cauterize it, but can’t remove the predisposing factors. This is a case of corn completely treated by taking only mental symptoms into consideration.


Gohel Rakesh. And the scalpel was made useless. National Journal of Homoeopathy 2019; 21(1) 232: 14-16p.

Abstract:
Homoeopathy plays an important role in so called surgical cases. Incision and drainage sometimes becomes an essential part of the treatment. Homeopathy has many medicines which are helpful in septic conditions. Medicines can abort as well as promote suppurative processes in order to
hasten cure. So here I want to focus on utility of homoeopathic medicines which can abort minor surgical interventions.

**Hak. Cancer ki chikitsa mein prabhvi homoeopathic davae. Homoeo Gagan 2019; 43p.**


**Abstract:**

**Introduction:** Several studies have shown intra-ocular pressure (IOP) reductions following lifestyle and behavior changes in primary open-angled glaucoma (POAG) in the short term. Our aim in this study was to examine the potential of such interventions as an adjunct treatment and assess their cumulative short-term effect on IOP and illness perception in patients with POAG.

**Methods:** In this randomized, parallel-arm, single blind controlled trial, POAG patients were randomized in a 1:1 ratio to either a treatment group which received instructions on dietary and lifestyle changes in addition to their standard therapy or to a control group which continued their standard therapy. Recommendations were selected to include those previously reported to reduce IOP; including: Saffron spice supplementation, high fiber diet, avoidance of caffeine, aerobic exercise, head elevation during sleep and others. Illness perception was assessed using the Brief IPQ questionnaire.

**Results:** 22 participants were enrolled, 3 were lost to follow-up and 19 entered analysis. Mean age was 69 ± 12 and 12 (63%) were female. Concerns about the illness, symptoms, and feelings of control were significantly improved in the treatment group compared with controls (all P < 0.05). Mean IOP reduced in the treatment group by 1.0 ± 3.1 mmHg (17.5 ± 4.3–16.5 ± 4.7) and by 0.7 ± 4.1 mmHg in the controls (16.8 ± 4.7–16.1 ± 6.2) with no significant difference between them (P = 0.866).

**Conclusions:** Dietary and lifestyle changes may improve illness perception and patient well-being, however they do not appear to affect IOP in the short term among patients with POAG.


**Abstract:**
**Introduction:** The diagnostic categories used in Traditional Medicine (TM) that originated in China and are now used around the world have been classified for inclusion as a chapter within the World Health Organization’s International Classification of Diseases (ICD). As a new chapter in ICD, the TM ICD codes were subject to international field testing. A pilot field test of the TM ICD codes was conducted to investigate their clinical utility in the European context.

**Design:** A mixed methods approach, including a Europe wide survey of practitioner views on TM ICD codes; and investigating the coding process of case study vignettes to explore coders’ experiences of using TM ICD codes.

**Results:** Survey: The majority of participants felt TM ICD codes provide a meaningful way to classify TM disorders and patterns; felt their patients’ diagnoses could be represented within the codes; and felt the codes would be important in their clinical practice.

**Coding of vignettes:** In 60.7% of cases the specificity of the assigned code was perceived as ‘just right’. Participants experienced difficulties assigning a single TM ICD disorder and pattern code, due to multiple codes being viewed as appropriate for the case.

**Conclusions:** The European TM practitioners who participated in this study largely perceive the TM ICD codes as valuable, conceptually accurate, and incorporating the range of TM diagnoses utilized within clinical practice. The TM ICD codes could be improved for European TM practitioners by expanding the scope of TM ICD codes, and adopting a multidimensional approach whereby more than one disorder and/or pattern code can be applied to single patients.


**Abstract:**

**Introduction:** This study was conducted to analyze the factors associated with the concurrent use of biomedicine and Korean Medicine (KM) in an outpatient medical service using data from the Korean Health Panel (KHP) 2008–2014.

**Method:** Using the KHP, which is an ongoing longitudinal survey of a nationally representative Korean population, descriptive analysis was employed to present the frequency and percentage of concurrent use of biomedicine and KM with those who only used biomedicine. In addition, factors associated with the types of medical institutions receiving outpatient
medical services were analyzed using the random effects panel probit model and the random effects panel logit model.

**Results:** Analysis of the KHP data from 2008 to 2014 revealed that 16–18% of the population used both biomedicine and KM services concurrently. Moreover, concurrent users were more likely to be female, over 40 years old, have a lower confidence in healthcare services quality, have chronic disease, have used medication for more than three months and to have a high mean frequency of medical services use.

**Conclusion:** Identifying determinants associated with concurrent use of biomedicine and KM might help medical professionals and policy makers to make wise judgments, plan treatments successfully and allocate resources efficiently.


**Abstract:**
A 5 days old neonate, was brought with the chief complaint to right sided bell’s palsy wherein homoeopathy paved the way to gentle and speedy cure of the case.


**Abstract:**
A thoughtful, homoeopathic intervention helps the patient to encounter a confident, hassel free event which would otherwise be a physically mentally traumatic and financially draining experience.


**Abstract:**
**Introduction:** Historically, medicinal plants and natural products have been used to treat a variety of human health issues and there has been renewed interest in their use for integrated cancer management. The present investigation was aimed to evaluate the anti-breast cancer, anti-angiogenic and antioxidant potential of selected local botanicals.

**Methods:** The methanolic extracts of Cassia occidentalis, Callistemon viminalis, Cleome viscosa and Mimosa hamata were assessed for their
Cytotoxic properties against a human breast cancer cell line MCF-7 by using the Sulforhodamine B (SRB) assay. The anti-angiogenic potential of all plant extracts was assessed by using an in vivo chorioallantoic membrane (CAM) model. Furthermore, the antioxidant potential of plant samples was evaluated using 2, 2-diphenyl-1-picryl hydrazine (DPPH), hydroxyl (OH) and superoxide radical (SOR) scavenging assays.

**Results:** The results of the present investigation revealed that all the selected plant extracts: C. occidentalis (IC50 = 70 ± 0.11 μg/ml), C. viminalis (IC50 = 44 ± 0.19 μg/ml), C. viscosa leaves (IC50 = 70 ± 0.22 μg/ml), C. viscosa root (IC50 = 73.2 ± 0.36 μg/ml) and M. hamata (IC50 = 65.8 ± 0.25 μg/ml) demonstrated an effective cytotoxic effect against MCF-7 cells. In the CAM model, the plant extracts exhibited significant anti-angiogenic activity by inhibiting the blood vessels density. Amongst the tested samples, the most efficient anti-angiogenic effect was demonstrated by extract of C. viminalis (67.76 ± 0.77%). Additionally, all the studied plant extracts were found to possess considerable antioxidant activity.

**Conclusion:** The selected botanicals with their anti-angiogenic and antioxidant potential could be considered as natural resources in the identification of possible therapeutic agents for breast cancer.


**Abstract:**

Case of a dengue with severe thrombocytopenia and high grade fever not recovering even by blood transfusion as it wasn’t because transfusion cannot fix the injured dignity but our homoeopathy can. It has to be a sensitive personality with the deep grief hitting the bone marrow physiology.


**Abstract:**

**Introduction:** College musicians preparing for performing careers must sustain physical-mental fitness as deficiencies can cause pain and injury and compound stress and anxiety. An integrative intervention program was embedded in a college music course.
**Methods:** The program included yoga, physical therapy exercises, and mental fitness & improvisation practices. Data were collected from a purposive sample of 34 over six semesters. We assessed the effects of the program by comparing pre-post data of (1) physical strength-flexibility-endurance tests and (2) psychometrics containing health-practice inventory (HPI), physical-musical efficacy (PME), and mental fitness and improvisation (MFI). Nonparametric Paired Sample Wilcoxon Signed Rank Tests were used to assess statistical significance of pre-post changes and Matched Pair Rank Biserial Correlation r was applied to demonstrate the effect size. (3) We observed kinematics of string players by plotting pre-post motion capture.

**Results:** Physical strength showed significant changes with left pectoral minor length (p = .01, r = .64) and deep neck flexor strength/endurance (p < .001, r = .92). HPI revealed healthy practice habits and lifestyle in our collegiate musicians. Survey results showed significant changes in all PME and MFI composite indices: physical awareness (p = .002, r = .66) and comfort (p = .004, r = .60), musical awareness (p = .01, r = .68) and comfort (p = .001, r = .74), calm mind (p = .043, r = .49), mental practice (p = .028, r = .51), calm recital (p = .002, r = .74), recall recital (p = .022, r = .53), comfort improvisation (p = .001, r = .78), in-the-moment improvisation (p = .004, r = .72), and satisfaction improvisation (p < .001, r = .85). Kinematics showed positive changes in range of motion and fluency.

**Conclusion:** College musicians’ integrative intervention program was effective with a modest postural change in our purposive sample (250).

Luthra Nidhi. Anxiety growing problem in the youth and young children. *Homoeopathy for All 2019; 21(1) 228: 24-26p.*


**Abstract:**

**Introduction:** *Carthamus tinctorius* L. (safflower) is a traditional Chinese medicine, the active ingredient of which is hydroxysafflor yellow A (HSYA). HSYA has been shown to have the potential to inhibit tumor growth. However, the molecular mechanisms whereby HSYA exerts its antitumor functions remain largely unclear. In this study, we investigated the antitumor mechanisms of HSYA in ovarian cancer cell line Skov3.
Methods: The cell proliferation assay was conducted using a Cell Proliferation Assay kit. The cell viability assay was performed using the CellTiter-Blue Cell Viability kit. Microarray was conducted to identify the global gene expression change of ovarian cancer cells caused by HSYA treatment. Small interfering RNA (siRNA) transfection was conducted to knock down WD repeat and SOCS box-containing protein 1 (WSB1). WSB1 expression was detected by quantitative reverse transcription-quantitative polymerase chain reaction (qRT-PCR). The protein expression of extracellular signal-related kinase (Erk) and phosphorylation-Erk1/2 was detected by western blot.

Results: HSYA inhibited Skov3 cell proliferation in a dose-dependent manner (P < 0.05). When cells were cultured with HSYA and doxorubicin, cell viability was further reduced (P < 0.05). HSYA could decrease the expression of WSB1. Through knocking down of WSB1, ovarian cancer cell proliferation was inhibited and further reduced by treating with doxorubicin (P < 0.05), the expression of Erk1/2 and Erk phosphorylation were downregulated.

Conclusion: HSYA may inhibit ovarian cancer cell line Skov3 proliferation and sensitize Skov3 cells to chemotherapeutic agents through the reduction of WSB1 expression.

Nagar Gaurav, Bishnoi Anju. Doctrine of signature; an easy way to understand the remedy. *Homoeopathy for All 2019; 21(1) 228: 29-31p.*

Abstract:

The doctrine of signatures is an ancient concept which assume that a plant was good for healing that which it looked like. The nature itself will tell you what they are used for and its well stocked medicine cabinet is right in front of us every day. This is an attempt to understand the views of Hahnemann and various stalwarts.


Abstract:

**Objectives:** To evaluate the traditional use of Chinese herbal medicine (CHM) for insomnia in pre-contemporary times.

**Materials and methods:** The Encyclopedia of Traditional Chinese Medicine (fifth edition) was systematically searched using seven Chinese medicine
disease nomenclatures to identify insomnia citations. Citations were coded, and frequently used herbal formulae specific for insomnia were analyzed.

**Results:** Insomnia treatments were mentioned in 940 citations, and insomnia diagnosis treated with Chinese herbal formulae was specifically described in 800 citations. The traditional use of CHM appeared to be individualized based on the cause, pathogenesis, phase, phenotype, demographics, and concurrent medical conditions of insomnia. The most common herbal formulae for insomnia included Wen dan tang, Suan zao ren tang, Ban xia shu mi tang, and Gui pi tang. The most frequently cited herb was suan zao ren (Ziziphi spinosae semen).

**Conclusions:** A number of herbal formulae for insomnia were cited in the historical literature. The commonly cited formulae such as Wen dan tang and Suan zao ren tang are consistent with current clinical practice and are good prospects for further therapeutic development.


**Abstract:**

**Purpose:** The current investigation assessed the feasibility, acceptability, and efficacy of the Cooking Up Health (CUH) culinary medicine elective that was offered to medical students at Northwestern University's Feinberg School of Medicine. The elective included a combination of didactics, plant-based culinary sessions, and service learning, in which students translated nutrition and health connections to elementary school children in at-risk communities.

**Method:** Nine medical students enrolled in cohort 1 and 12 in cohort 2. Students completed assessments before and after the course measuring confidence in nutrition and obesity counseling, attitudes toward nutrition counseling, personal dietary intake, and cooking confidence and behaviors.

**Results:** The elective showed high feasibility and acceptability with strong class attendance (96%–99%) and retention (89%–100%). Over the course of the elective, students across both cohorts showed increased confidence in nutrition and obesity counseling (ps < 0.001), cooking abilities (ps < 0.01),
and food preparation practices (ps < 0.04). Cohort 1 reported decreased meat consumption (p = 0.045), and cohort 2 showed increased fruit and vegetable intake (p = 0.04). Finally, cohort 2 showed increased knowledge and confidence regarding consuming a plant-based diet (ps < 0.002). Students reported an increased appreciation for the role of nutrition in health promotion and disease prevention and an intention to incorporate nutrition into patient care.

Conclusion: This study provided preliminary evidence demonstrating feasibility, acceptability, and efficacy of the CUH culinary medicine elective for increasing medical students' confidence in nutrition and obesity counseling of patients and in their ability to use nutrition and cooking for personal self-care. Ultimately, this program of research may provide evidence to support widespread integration of CUH into medical education and has the potential to prepare medical students to properly advise patients on nutrition to combat the rising rates of obesity, diabetes, and preventable diseases related to nutrition.


Abstract:

Objectives: Poor lifestyle choices play a significant role in the development and progression of preventable chronic diseases, including cancer. In this study, we evaluate the effectiveness of a comprehensive lifestyle medicine intervention on chronic disease risk factors and quality of life in breast cancer survivors.

Design: This is a retrospective review of a clinical program from January 2016 to July 2017.

Settings/Location: It includes seven 2-h group medical visits held every other week at an outpatient wellness facility.

Subjects: Eligible participants are breast cancer survivors who have completed treatment, including those who remain on hormonal therapy.

Intervention: Patients receive education and experience in nutrition, culinary medicine, physical activity, and stress relief practices.

Outcome measures: Participants' weight, body mass index (BMI), body fat mass, lean body mass, and percent body fat were measured at visit 1 and visit 7. Standard validated questionnaires were used to measure perceived stress, depression, patient activation, physical and mental quality of life, dietary fat consumption, and dietary fruit, vegetable, and fiber consumption.

Results: A total of 31 patients participated in the group visits. Pre–post comparison data were not available for 10 patients. More than three-
quarters of the 21 breast cancer survivors who attended 5 or more of the 7 group visits and provided data at the first and the last group visit decreased their body weight. On average, patients lost 4.9 pounds (−2.6%, p < 0.01), and their BMI decreased by 0.8 kg/m² (−2.5%, p < 0.01). Changes in psychosocial variables of perceived stress, depression, patient activation, and quality of life trended in a positive direction, but did not reach statistical significance. Patients reported a significant decrease in average weekly fat consumption (−31.5%, p < 0.01). Most patients found the program educational and enjoyable, and nearly half of them described it as life changing.

Conclusions: Breast cancer survivors could employ the prescribed lifestyle modifications to produce clinically relevant health benefits. Interdisciplinary teams of health care professionals may help breast cancer survivors with chronic diseases implement evidence-based, individualized, and effective lifestyle prescription through group medical visits.


Abstract:

I learnt two new mind rubrics while understanding some peculiar behavior of this pt. So, thought of sharing the case with our readers. Whenever we come across some strange behavior or gesture in patient, please don’t just ignore it. Try to understand the WHY behind it and that will lead to rub National Journal of Homoeopathy 2019; 21(1) 232: 28-33p.vrics and give your fantastic result in patients.


Abstract:

This is a case of a 22 yrs unmarried nurse in a hospital where I was practicing as a RMO 3yrs back. She was admitted with C/o severe nausea and vomiting. Sips of water too came out in 5min since 3-4 days. This type of episodes happens monthly or bimonthly and she was admitted 1 or 2 times for the same. She likes to eat spicy, fast food and outside food. For the present complaint she was on antiemetics, injections and saline. But this time around antiemetics were not working at all. H/o insomnia since 1 1/2 yr, on medication tab anzol/tab cetriz, but it did not give any result.

Shou Xiao-Ling, Wang Lei, Jin Xiao-Qing et al. Effect of T’ai Chi Exercise on Hypertension in Young and Middle-Aged In-Service Staff.
Abstract:

**Objective:** This study aims to investigate the effect of T'ai chi exercise on hypertension in young and middle-aged in-service staff.

**Methods:** A total of 208 subjects with grade 1 hypertension were enrolled into this study. These subjects were randomly divided into two groups: research group and control group (n = 104, each). On the basis of general daily lifestyle intervention, subjects in the research group underwent 24-Style Simplified t'ai chi exercise for 3 months, whereas subjects in the control group underwent general daily lifestyle intervention. All subjects were followed up at the first and third month of intervention. The body mass index (BMI), blood pressure, blood lipid, and other indexes were measured before and after the intervention, and quality of life was evaluated.

**Results:** (1) In the research group, after 1 month of exercise, systolic blood pressure (SBP), heart rate (HR), triglyceride (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) significantly decreased (p < 0.05), while BMI, blood glucose (Glu), diastolic blood pressure (DBP), and pulse pressure (PP) did not significantly change. Furthermore, after 3 months of exercise, BMI, HR, SBP, DBP, PP, TG, TC, LDL-C, and Glu all significantly decreased (p < 0.05). (2) Moreover, the quality of life of subjects in the research group obviously improved after 3 months of t’ai chi exercise (p < 0.05).

**Conclusions:** T’ai chi exercise can reduce the level of blood pressure in young and middle-aged in-service staff with grade 1 hypertension, control weight, slow down the HR, improve metabolism, and improve quality of life. T’ai chi is an exercise suitable for in-service hypertension subjects.


Abstract:

Autism is a neuro developmental disorder, accompanied by intellectual and social behavioural deficits; the child exhibits peculiar and bizarre characteristics with social interactions, communications and behaviours. Homoeopathic intervention is found to held well. This patient attended out patient department chiefly for complaints of abnormal behavior and running nose. Child had a history of delayed milestones. After detailed case taking and repertorization stramonium was given in 200 potency and gradually the potency was raised as per the response. Within 8 months of homoeopathic treatment the patient started improving.

Abstract:

The case of a woman’s insecurity. The patients reaction and adaptation to things is the root cause and awareness is the key. The case shows how interpersonal relationship (IPR) and the patient’s adaptation in the family plays a vital role in the case.

Allied System


Abstract:

Indonesia is a rapidly growing middle-income country with 262 million inhabitants from more than 300 ethnic and 730 language groups spread over 17 744 islands, and presents unique challenges for health systems and universal health coverage (UHC). From 1960 to 2001, the centralised health system of Indonesia made gains as medical care infrastructure grew from virtually no primary health centres to 20 900 centres. Life expectancy improved from 48 to 69 years, infant mortality decreased from 76 deaths per 1000 livebirths to 23 per 1000, and the total fertility rate decreased from 5·61 to 2·11. However, gains across the country were starkly uneven with major health gaps, such as the stagnant maternal mortality of around 300 deaths per 100 000 livebirths, and minimal change in neonatal mortality. The centralised one size fits all approach did not address the complexity and diversity in population density and dispersion across islands, diets, diseases, local living styles, health beliefs, human development, and community participation. Decentralisation of governance to 354 districts in 2001, and currently 514 districts, further increased health system heterogeneity and exacerbated equity gaps. The novel UHC system introduced in 2014 focused on accommodating diversity with flexible and adaptive implementation features and quick evidence-driven decisions based on changing needs. The UHC system grew rapidly and covers 203 million people, the largest single-payer scheme in the world, and has
improved health equity and service access. With early success, challenges have emerged, such as the so-called missing-middle group, a term used to designate the smaller number of people who have enrolled in UHC in wealth quintiles Q2–Q3 than in other quintiles, and the low UHC coverage of children from birth to age 4 years. Moreover, high costs for non-communicable diseases warrant new features for prevention and promotion of healthy lifestyles, and investment in a robust integrated digital health-information system for front-line health workers is crucial for impact and sustainability. This Review describes the innovative UHC initiative of Indonesia along with the future roadmap required to meet sustainable development goals by 2030.


Abstract:

Background: There is an ongoing debate concerning which guidelines and monitoring tools are most beneficial for assessing labour progression, to help prevent use of intrapartum caesarean section (ICS). The WHO partograph has been used for decades with the assumption of a linear labour progression; however, in 2010, Zhang introduced a new guideline suggesting a more dynamic labour progression. We aimed to investigate whether the frequency of ICS use differed when adhering to the WHO partograph versus Zhang's guideline for labour progression.

Methods: We did a multicentre, cluster-randomised controlled trial at obstetric units in Norway, and each site was required to deliver more than 500 fetuses per year to be eligible for inclusion. The participants were nulliparous women who had a singleton, full-term fetus with cephalic presentation, and who entered spontaneous active labour. The obstetric units were treated as clusters, and women treated within these clusters were all given the same treatment. We stratified these clusters by size and number of previous caesarean sections. The clusters containing the obstetric units were then randomly assigned (1:1) to the control group, which adhered to the WHO partograph, or to the intervention group, which adhered to Zhang's guideline. The randomisation was computer-generated and was done in the Unit of Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway, and investigators in this unit had no further involvement in the trial. Our study design did not enable masking of participants or health-care providers, but the investigators who were analysing the data were masked to group allocation. The primary outcome was use of ICS during active labour (cervical dilatation of 4–10 cm) in all
participating women. The Labour Progression Study (LaPS) is registered with ClinicalTrials.gov, number NCT02221427.

**Findings:** Between Aug 1, 2014, and Sept 1, 2014, 14 clusters were enrolled in the LaPS trial, and on Sept 11, 2014, seven obstetric units were randomly assigned to the control group (adhering to the WHO partograph) and seven obstetric units were randomly assigned to the intervention group (adhering to Zhang’s guideline). Between Dec 1, 2014, and Jan 31, 2017, 11,615 women were judged to be eligible for recruitment in the trial, which comprised 5421 (46·7%) women in the control group units and 6194 (53·3%) women in the intervention group units. In the control group, 2100 (38·7%) of 5421 women did not give signed consent to participate and 16 (0·3%) women abstained from participation. In the intervention group, 2181 (35·2%) of 6194 women did not give signed consent to participate and 41 (0·7%) women abstained from participation. 7277 (62·7%) of 11,615 eligible women were therefore included in the analysis of the primary endpoint. Of these women, 3305 (45·4%) participants were in an obstetric unit that was randomly assigned to the control group (adhering to the WHO partograph) and 3972 (54·6%) participants were in an obstetric unit that was randomly assigned to the intervention group (adhering to Zhang’s guideline). No women dropped out during the trial. Before the start of the trial, ICS was used in 9·5% of deliveries in the control group obstetric units and in 9·3% of intervention group obstetric units. During our trial, there were 196 (5·9%) ICS deliveries in women in the control group (WHO partograph) and 271 (6·8%) ICS deliveries in women in the intervention group (Zhang’s guideline), and the frequency of ICS use did not differ between the groups (adjusted relative risk 1·17, 95% CI 0·98–1·40; p=0·08; adjusted risk difference 1·00%, 95% CI −0·1 to 2·1). We identified no maternal or neonatal deaths during our study.

**Interpretation:** We did not find any significant difference in the frequency of ICS use between the obstetric units assigned to adhere to the WHO partograph and those assigned to adhere to Zhang’s guideline. The overall decrease in ICS use that we observed relative to the previous frequency of ICS use noted in these obstetric units might be explained by the close focus on assessing labour progression more than use of the guidelines. Our results represent an important contribution to the discussion on implementation of the new guideline.

**Funding:** Østfold Hospital Trust.


**Abstract:**

Antibiotics are the commonest cause of life-threatening immune-mediated drug reactions that are considered off-target, including anaphylaxis, and organ-specific and severe cutaneous adverse reactions. However, many antibiotic reactions documented as allergies were unknown or not remembered by the patient, cutaneous reactions unrelated to drug
hypersensitivity, drug-infection interactions, or drug intolerances. Although such reactions pose negligible risk to patients, they currently represent a global threat to public health. Antibiotic allergy labels result in displacement of first-line therapies for antibiotic prophylaxis and treatment. A penicillin allergy label, in particular, is associated with increased use of broad-spectrum and non-β-lactam antibiotics, which results in increased adverse events and antibiotic resistance. Most patients labelled as allergic to penicillins are not allergic when appropriately stratified for risk, tested, and re-challenged. Given the public health importance of penicillin allergy, this Review provides a global update on antibiotic allergy epidemiology, classification, mechanisms, and management.


Abstract:

**Background:** Effective two-drug regimens could decrease long-term drug exposure and toxicity with HIV-1 antiretroviral therapy (ART). We therefore aimed to evaluate the efficacy and safety of a two-drug regimen compared with a three-drug regimen for the treatment of HIV-1 infection in ART-naive adults.

**Methods:** We conducted two identically designed, multicentre, double-blind, randomised, non-inferiority, phase 3 trials: GEMINI-1 and GEMINI-2. Both studies were done at 192 centres in 21 countries. We included participants (≥18 years) with HIV-1 infection and a screening HIV-1 RNA of 500 000 copies per mL or less, and who were naive to ART. We randomly assigned participants (1:1) to receive a once-daily two-drug regimen of dolutegravir (50 mg) plus lamivudine (300 mg) or a once-daily three-drug regimen of dolutegravir (50 mg) plus tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg). Both drug regimens were administered orally. We masked participants and investigators to treatment assignment: dolutegravir was administered as single-entity tablets (similar to its commercial formulation, except with a different film colour), and lamivudine tablets and tenofovir disoproxil fumarate and emtricitabine tablets were over-encapsulated to visually match each other. Primary endpoint was the proportion of participants with HIV-1 RNA of less than 50 copies per mL at week 48 in the intention-to-treat-exposed population, using the Snapshot algorithm and a non-inferiority margin of −10%. Safety analyses were done
on the safety population. GEMINI-1 and GEMINI-2 are registered with ClinicalTrials.gov, numbers NCT02831673 and NCT02831764, respectively.

**Findings:** Between July 18, 2016, and March 31, 2017, 1441 participants across both studies were randomly assigned to receive either the two-drug regimen (n=719) or three-drug regimen (n=722). At week 48 in the GEMINI-1 intention-to-treat-exposed population, 320 (90%) of 356 participants receiving the two-drug regimen and 332 (93%) of 358 receiving the three-drug regimen achieved plasma HIV-1 RNA of less than 50 copies per mL (adjusted treatment difference −2·6%, 95% CI −6·7 to 1·5); in GEMINI-2, 335 (93%) of 360 in the two-drug regimen and 337 (94%) of 359 in the three-drug regimen achieved HIV-1 RNA of less than 50 copies per mL (adjusted treatment difference −0·7%, 95% CI −4·3 to 2·9), showing non-inferiority at a −10% margin in both studies (pooled analysis: 655 [91%] of 716 in the two-drug regimen vs 669 [93%] of 717 in the three-drug regimen; adjusted treatment difference −1·7%, 95% CI −4·4 to 1·1). Numerically, more drug-related adverse events occurred with the three-drug regimen than with the two-drug regimen (169 [24%] of 717 vs 126 [18%] of 716); few participants discontinued because of adverse events (16 [2%] in the three-drug regimen and 15 [2%] in the two-drug regimen). Two deaths were reported in the two-drug regimen group of GEMINI-2, but neither was considered to be related to the study medication.

**Interpretation:** The non-inferior efficacy and similar tolerability profile of dolutegravir plus lamivudine to a guideline-recommended three-drug regimen at 48 weeks in ART-naive adults supports its use as initial therapy for patients with HIV-1 infection.

**Funding:** ViiV Healthcare.

**Chekhchar Mariam, Hajji Ibtissam, Madiq Brahim et al. Mitral stenosis found after eye problem. Lancet 2019; 393(10168): 275p.**


**Abstract:**

**Background:** There are few effective treatment options for patients with recurrent or metastatic head-and-neck squamous cell carcinoma. Pembrolizumab showed antitumour activity and manageable toxicity in early-phase trials. We aimed to compare the efficacy and safety of pembrolizumab versus standard-of-care therapy for the treatment of head-and-neck squamous cell carcinoma.

**Methods:** We did a randomised, open-label, phase 3 study at 97 medical centres in 20 countries. Patients with head-and-neck squamous cell carcinoma that progressed during or after platinum-containing treatment for recurrent or metastatic disease (or both), or whose disease recurred or
progressed within 3–6 months of previous multimodal therapy containing platinum for locally advanced disease, were randomly assigned (1:1) in blocks of four per stratum with an interactive voice-response and integrated web-response system to receive pembrolizumab 200 mg every 3 weeks intravenously or investigator's choice of standard doses of methotrexate, docetaxel, or cetuximab intravenously (standard-of-care group). The primary endpoint was overall survival in the intention-to-treat population. Safety was analysed in the as-treated population. This trial is registered with ClinicalTrials.gov, number NCT02252042, and is no longer enrolling patients.

**Findings:** Between Dec 24, 2014, and May 13, 2016, 247 patients were randomly allocated to pembrolizumab and 248 were randomly allocated to standard of care. As of May 15, 2017, 181 (73%) of 247 patients in the pembrolizumab group and 207 (83%) of 248 patients in the standard-of-care group had died. Median overall survival in the intention-to-treat population was 8.4 months (95% CI 6.4–9.4) with pembrolizumab and 6.9 months (5.9–8.0) with standard of care (hazard ratio 0.80, 0.65–0.98; nominal p=0.0161). Fewer patients treated with pembrolizumab than with standard of care had grade 3 or worse treatment-related adverse events (33 [13%] of 246 vs 85 [36%] of 234). The most common treatment-related adverse event was hypothyroidism with pembrolizumab (in 33 [13%] patients) and fatigue with standard of care (in 43 [18%]). Treatment-related death occurred in four patients treated with pembrolizumab (unspecified cause, large intestine perforation, malignant neoplasm progression, and Stevens-Johnson syndrome) and two patients treated with standard of care (malignant neoplasm progression and pneumonia).

**Interpretation:** The clinically meaningful prolongation of overall survival and favourable safety profile of pembrolizumab in patients with recurrent or metastatic head and neck squamous cell carcinoma support the further evaluation of pembrolizumab as a monotherapy and as part of combination therapy in earlier stages of disease.

**Funding:** Merck Sharp & Dohme, a subsidiary of Merck & Co.


**Abstract:**

Each year, more than half a million women are diagnosed with cervical cancer and the disease results in over 300 000 deaths worldwide. High-risk subtypes of the human papilloma virus (HPV) are the cause of the disease in most cases. The disease is largely preventable. Approximately 90% of cervical cancers occur in low-income and middle-income countries that lack organised screening and HPV vaccination programmes. In high-income countries, cervical cancer incidence and mortality have more than halved over the past 30 years since the introduction of formal screening programmes. Treatment depends on disease extent at diagnosis and locally available resources, and might involve radical hysterectomy or
chemoradiation, or a combination of both. Conservative, fertility-preserving surgical procedures have become standard of care for women with low-risk, early-stage disease. Advances in radiotherapy technology, such as intensity-modulated radiotherapy, have resulted in less treatment-related toxicity for women with locally-advanced disease. For women with metastatic or recurrent disease, the overall prognosis remains poor; nevertheless, the incorporation of the anti-VEGF agent bevacizumab has been able to extend overall survival beyond 12 months. Preliminary results of novel immunotherapeutic approaches, similarly to other solid tumours, have shown promising results so far.


**Abstract:**

**Background:** Results of small trials indicate that fluoxetine might improve functional outcomes after stroke. The FOCUS trial aimed to provide a precise estimate of these effects.

**Methods:** FOCUS was a pragmatic, multicentre, parallel group, double-blind, randomised, placebo-controlled trial done at 103 hospitals in the UK. Patients were eligible if they were aged 18 years or older, had a clinical stroke diagnosis, were enrolled and randomly assigned between 2 days and 15 days after onset, and had focal neurological deficits. Patients were randomly allocated fluoxetine 20 mg or matching placebo orally once daily for 6 months via a web-based system by use of a minimisation algorithm. The primary outcome was functional status, measured with the modified Rankin Scale (mRS), at 6 months. Patients, carers, health-care staff, and the trial team were masked to treatment allocation. Functional status was assessed at 6 months and 12 months after randomisation. Patients were analysed according to their treatment allocation. This trial is registered with the ISRCTN registry, number ISRCTN83290762.

**Findings:** Between Sept 10, 2012, and March 31, 2017, 3127 patients were recruited. 1564 patients were allocated fluoxetine and 1563 allocated placebo. mRS data at 6 months were available for 1553 (99·3%) patients in each treatment group. The distribution across mRS categories at 6 months was similar in the fluoxetine and placebo groups (common odds ratio adjusted for minimisation variables 0·951 [95% CI 0·839–1·079]; p=0·439). Patients allocated fluoxetine were less likely than those allocated placebo to develop new depression by 6 months (210 [13·43%] patients vs 269 [17·21%]; difference 3·78% [95% CI 1·26–6·30]; p=0·0033), but they had more bone fractures (45 [2·88%] vs 23 [1·47%]; difference 1·41% [95% CI 0·38–2·43]; p=0·0070). There were no significant differences in any other event at 6 or 12 months.

**Interpretation:** Fluoxetine 20 mg given daily for 6 months after acute stroke does not seem to improve functional outcomes. Although the treatment reduced the occurrence of depression, it increased the frequency
of bone fractures. These results do not support the routine use of fluoxetine either for the prevention of post-stroke depression or to promote recovery of function.

**Funding:** UK Stroke Association and NIHR Health Technology Assessment Programme.


**Abstract:**

Public security and law enforcement have a crucial but often largely unacknowledged role in protecting and promoting public health. Although the security sector is a key partner in many specific public health programmes, its identity as an important part of the public health endeavour is rarely recognised. This absence of recognition has resulted in a generally inadequate approach to research and investigation of ways in which law enforcement, especially police at both operational and strategic levels, can be effectively engaged to actively promote and protect public health as part of a broader multisectoral public health effort. However, the challenge remains to engage police to consider their role as one that serves a public health function. The challenge consists of overcoming the continuous and competitive demand for police to do so-called policing, rather than serve a broader public health function—often derogatively referred to as social work. This Series paper explores the intersect between law enforcement and public health at the global and local levels and argues that public health is an integral aspect of public safety and security. Recognition of this role of public health is the first step towards encouraging a joined-up approach to dealing with entrenched social, security, and health issues.


**Abstract:**

**Background:** Maintenance therapy following autologous stem cell transplantation (ASCT) can delay disease progression and prolong survival in patients with multiple myeloma. Ixazomib is ideally suited for maintenance therapy given its convenient once-weekly oral dosing and low toxicity profile. In this study, we aimed to determine the safety and efficacy of ixazomib as maintenance therapy following ASCT.

**Methods:** The phase 3, double-blind, placebo-controlled TOURMALINE-MM3 study took place in 167 clinical or hospital sites in 30 countries in
Europe, the Middle East, Africa, Asia, and North and South America. Eligible participants were adults with a confirmed diagnosis of symptomatic multiple myeloma according to International Myeloma Working Group criteria who had achieved at least a partial response after undergoing standard-of-care induction therapy followed by high-dose melphalan (200 mg/m2) conditioning and single ASCT within 12 months of diagnosis. Patients were randomly assigned in a 3:2 ratio to oral ixazomib or matching placebo on days 1, 8, and 15 in 28-day cycles for 2 years following induction, high-dose therapy, and transplantation. The initial 3 mg dose was increased to 4 mg from cycle 5 if tolerated during cycles 1–4. Randomisation was stratified by induction regimen, pre-induction disease stage, and response post-transplantation. The primary endpoint was progression-free survival (PFS) by intention-to-treat analysis. Safety was assessed in all patients who received at least one dose of ixazomib or placebo, according to treatment actually received. This trial is registered with ClinicalTrials.gov, number NCT02181413, and follow-up is ongoing.

**Findings:** Between July 31, 2014, and March 14, 2016, 656 patients were enrolled and randomly assigned to receive ixazomib maintenance therapy (n=395) or placebo (n=261). With a median follow-up of 31 months (IQR 27·3–35·7), we observed a 28% reduction in the risk of progression or death with ixazomib versus placebo (median PFS 26·5 months [95% CI 23·7–33·8] vs 21·3 months [18·0–24·7]; hazard ratio 0·72, 95% CI 0·58–0·89; p=0·0023). No increase in second malignancies was noted with ixazomib therapy (12 [3%] patients) compared with placebo (eight [3%] patients) at the time of this analysis. 108 (27%) of 394 patients in the ixazomib group and 51 (20%) of 259 patients in the placebo group experienced serious adverse events. During the treatment period, one patient died in the ixazomib group and none died in the placebo group.

**Interpretation:** Ixazomib maintenance prolongs PFS and represents an additional option for post-transplant maintenance therapy in patients with newly diagnosed multiple myeloma.

**Funding:** Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceutical Company.


**Abstract:**

**Objective:** To evaluate the incidence rate of nephrotoxicity in Tripterygium wilfordii Hook. f (TwHF) preparations approved by the China Food and Drug Administration and the potential risk factors.

**Methods:** CENTRAL, PubMed, Sinomed, Chinese National Knowledge Infrastructure, VIP, China Important Conference Papers Database, China Dissertation Database, and online clinical trial registry websites were
searched for articles that reported on nephrotoxicity of TwHF preparations until November 23, 2017. There was no limitation for study design.

**Results:** A total of 36 articles involving 2,017 participants were included. Results showed that the incidence of nephrotoxicity associated with TwHF preparations was 5.81% (95% confidence interval: 4.43–7.57). Subgroup analysis showed that the disease type, combined medication, duration, and study design were not correlated with the incidence of nephrotoxicity.

**Conclusion:** The incidence rate of nephrotoxicity in TwHF preparations was 5.81%. The possible risk factors, such as disease type, the combination with other drugs, medication time, and study design, were not found to be correlated with the incidence of nephrotoxicity. However, due to the limited number of included articles, the limited sample size, and the poor methodology quality, the incidence rate of nephrotoxicity of TwHF preparations might be overestimated, and more prospective articles are needed to explore the potential influence factor.


**Abstract:**

**Background:** Patients with human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma have high survival when treated with radiotherapy plus cisplatin. Whether replacement of cisplatin with cetuximab—an antibody against the epidermal growth factor receptor—can preserve high survival and reduce treatment toxicity is unknown. We investigated whether cetuximab would maintain a high proportion of patient survival and reduce acute and late toxicity.

**Methods:** RTOG 1016 was a randomised, multicentre, non-inferiority trial at 182 health-care centres in the USA and Canada. Eligibility criteria included histologically confirmed HPV-positive oropharyngeal carcinoma; American Joint Committee on Cancer 7th edition clinical categories T1–T2, N2a–N3 M0 or T3–T4, N0–N3 M0; Zubrod performance status 0 or 1; age at least 18 years; and adequate bone marrow, hepatic, and renal function. We randomly assigned patients (1:1) to receive either radiotherapy plus cetuximab or radiotherapy plus cisplatin. Randomisation was balanced by using randomly permuted blocks, and patients were stratified by T category (T1–T2 vs T3–T4), N category (N0–N2a vs N2b–N3), Zubrod performance status (0 vs 1), and tobacco smoking history (<10 pack-years vs >10 pack-years). Patients were assigned to receive either intravenous cetuximab at a loading dose of 400 mg/m2 5–7 days before radiotherapy initiation, followed by cetuximab 250 mg/m2 weekly for seven doses (total 2150 mg/m2), or cisplatin 100 mg/m2 on days 1 and 22 of radiotherapy (total 200 mg/m2). All patients received accelerated intensity-modulated radiotherapy delivered at 70 Gy in 35 fractions over 6 weeks at six fractions per week (with two fractions given on one day, at least 6 h apart). The primary endpoint was
overall survival, defined as time from randomisation to death from any cause, with non-inferiority margin 1.45. Primary analysis was based on the modified intention-to-treat approach, whereby all patients meeting eligibility criteria are included. This study is registered with ClinicalTrials.gov, number NCT01302834.

Findings: Between June 9, 2011, and July 31, 2014, 987 patients were enrolled, of whom 849 were randomly assigned to receive radiotherapy plus cetuximab (n=425) or radiotherapy plus cisplatin (n=424). 399 patients assigned to receive cetuximab and 406 patients assigned to receive cisplatin were subsequently eligible. After median follow-up duration of 4.5 years, radiotherapy plus cetuximab did not meet the non-inferiority criteria for overall survival (hazard ratio [HR] 1.45, one-sided 95% upper CI 1.94; p=0.5056 for non-inferiority; one-sided log-rank p=0.0163). Estimated 5-year overall survival was 77.9% (95% CI 73.4–82.5) in the cetuximab group versus 84.6% (80.6–88.6) in the cisplatin group. Progression-free survival was significantly lower in the cetuximab group compared with the cisplatin group (HR 1.72, 95% CI 1.29–2.29; p=0.0002; 5-year progression-free survival 67.3%, 95% CI 62.4–72.2 vs 78.4%, 73.8–83.0), and locoregional failure was significantly higher in the cetuximab group compared with the cisplatin group (HR 2.05, 95% CI 1.35–3.10; 5-year proportions 17.3%, 95% CI 13.7–21.4 vs 9.9%, 6.9–13.6). Proportions of acute moderate to severe toxicity (77.4%, 95% CI 73.0–81.5 vs 81.7%, 77.5–85.3; p=0.1586) and late moderate to severe toxicity (16.5%, 95% CI 12.9–20.7 vs 20.4%, 16.4–24.8; p=0.1904) were similar between the cetuximab and cisplatin groups.

Interpretation: For patients with HPV-positive oropharyngeal carcinoma, radiotherapy plus cetuximab showed inferior overall survival and progression-free survival compared with radiotherapy plus cisplatin. Radiotherapy plus cisplatin is the standard of care for eligible patients with HPV-positive oropharyngeal carcinoma.

Funding: National Cancer Institute USA, Eli Lilly, and The Oral Cancer Foundation.


Abstract:

Background: Drink driving is an important risk factor for road traffic accidents (RTAs), which cause high levels of morbidity and mortality globally. Lowering the permitted blood alcohol concentration (BAC) for drivers is a common public health intervention that is enacted in countries and jurisdictions across the world. In Scotland, on Dec 5, 2014, the BAC limit for drivers was reduced from 0.08 g/dL to 0.05 g/dL. We therefore aimed to evaluate the effects of this change on RTAs and alcohol consumption.
**Methods:** In this natural experiment, we used an observational, comparative interrupted time-series design by use of data on RTAs and alcohol consumption in Scotland (the interventional group) and England and Wales (the control group). We obtained weekly counts of RTAs from police accident records and we estimated weekly off-trade (eg, in supermarkets and convenience stores) and 4-weekly on-trade (eg, in bars and restaurants) alcohol consumption from market research data. We also used data from automated traffic counters as denominators to calculate RTA rates. We estimated the effect of the intervention on RTAs by use of negative binomial panel regression and on alcohol consumption outcomes by use of seasonal autoregressive integrated moving average models. Our primary outcome was weekly rates of RTAs in Scotland, England, and Wales. This study is registered with ISRCTN, number ISRCTN38602189.

**Findings:** We assessed the weekly rate of RTAs and alcohol consumption between Jan 1, 2013, and Dec 31, 2016, before and after the BAC limit came into effect on Dec 5, 2014. After the reduction in BAC limits for drivers in Scotland, we found no significant change in weekly RTA rates after adjustment for seasonality and underlying temporal trend (rate ratio 1·01, 95% CI 0·94–1·08; p=0.77) or after adjustment for seasonality, the underlying temporal trend, and the driver characteristics of age, sex, and socioeconomic deprivation (1·00, 0·96–1·06; p=0.73). Relative to RTAs in England and Wales, where the reduction in BAC limit for drivers did not occur, we found a 7% increase in weekly RTA rates in Scotland after this reduction in BAC limit for drivers (1·07, 1·02–1·13; p=0·007 in the fully-adjusted model). Similar findings were observed for serious or fatal RTAs and single-vehicle night-time RTAs. The change in legislation in Scotland was associated with no change in alcohol consumption, measured by per-capita off-trade sales (−0·3%, −1·7 to 1·1; p=0·71), but a 0·7% decrease in alcohol consumption measured by per-capita on-trade sales (−0·7%, −0·8 to −0·5; p<0·0001).

**Interpretation:** Lowering the driving BAC limit to 0·05 g/dL from 0·08 g/dL in Scotland was not associated with a reduction in RTAs, but this change was associated with a small reduction in per-capita alcohol consumption from on-trade alcohol sales. One plausible explanation is that the legislative change was not suitably enforced—for example with random breath testing measures. Our findings suggest that changing the legal BAC limit for drivers in isolation does not improve RTA outcomes. These findings have significant policy implications internationally as several countries and jurisdictions consider a similar reduction in the BAC limit for drivers.

**Funding:** National Institute for Health Research Public Health Research Programme.

**Abstract:**

**Background:** Patients with dilated cardiomyopathy whose symptoms and cardiac function have recovered often ask whether their medications can be stopped. The safety of withdrawing treatment in this situation is unknown.

**Methods:** We did an open-label, pilot, randomised trial to examine the effect of phased withdrawal of heart failure medications in patients with previous dilated cardiomyopathy who were now asymptomatic, whose left ventricular ejection fraction (LVEF) had improved from less than 40% to 50% or greater, whose left ventricular end-diastolic volume (LVEDV) had normalised, and who had an N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) concentration less than 250 ng/L. Patients were recruited from a network of hospitals in the UK, assessed at one centre (Royal Brompton and Harefield NHS Foundation Trust, London, UK), and randomly assigned (1:1) to phased withdrawal or continuation of treatment. After 6 months, patients in the continued treatment group had treatment withdrawn by the same method. The primary endpoint was a relapse of dilated cardiomyopathy within 6 months, defined by a reduction in LVEF of more than 10% and to less than 50%, an increase in LVEDV by more than 10% and to higher than the normal range, a two-fold rise in NT-pro-BNP concentration and to more than 400 ng/L, or clinical evidence of heart failure, at which point treatments were re-established. The primary analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT02859311.

**Findings:** Between April 21, 2016, and Aug 22, 2017, 51 patients were enrolled. 25 were randomly assigned to the treatment withdrawal group and 26 to continue treatment. Over the first 6 months, 11 (44%) patients randomly assigned to treatment withdrawal met the primary endpoint of relapse compared with none of those assigned to continue treatment (Kaplan-Meier estimate of event rate 45.7% [95% CI 28.5–67.2]; p=0.0001). After 6 months, 25 (96%) of 26 patients assigned initially to continue treatment attempted its withdrawal. During the following 6 months, nine patients met the primary endpoint of relapse (Kaplan-Meier estimate of event rate 36.0% [95% CI 20.6–57.8]). No deaths were reported in either group and three serious adverse events were reported in the treatment withdrawal group: hospital admissions for non-cardiac chest pain, sepsis, and an elective procedure.

**Interpretation:** Many patients deemed to have recovered from dilated cardiomyopathy will relapse following treatment withdrawal. Until robust predictors of relapse are defined, treatment should continue indefinitely.

**Funding:** British Heart Foundation, Alexander Jansons Foundation, Royal Brompton Hospital and Imperial College London, Imperial College Biomedical Research Centre, Wellcome Trust, and Rosetrees Trust.

**Hofmeyr G Justus, Betran Ana Pilar, Singata Madliki Mandisa et al.** Pre-pregnancy and early pregnancy calcium supplementation among women at high risk of pre-eclampsia: A multicentre, double-blind,

**Abstract:**

**Background:** Reducing deaths from hypertensive disorders of pregnancy is a global priority. Low dietary calcium might account for the high prevalence of pre-eclampsia and eclampsia in low-income countries. Calcium supplementation in the second half of pregnancy is known to reduce the serious consequences of pre-eclampsia; however, the effect of calcium supplementation during placentation is not known. We aimed to test the hypothesis that calcium supplementation before and in early pregnancy (up to 20 weeks’ gestation) prevents the development of pre-eclampsia

**Methods:** We did a multicountry, parallel arm, double-blind, randomised, placebo-controlled trial in South Africa, Zimbabwe, and Argentina. Participants with previous pre-eclampsia and eclampsia received 500 mg calcium or placebo daily from enrolment prepregnancy until 20 weeks' gestation. Participants were parous women whose most recent pregnancy had been complicated by pre-eclampsia or eclampsia and who were intending to become pregnant. All participants received unblinded calcium 1.5 g daily after 20 weeks' gestation. The allocation sequence (1:1 ratio) used computer-generated random numbers in balanced blocks of variable size. The primary outcome was pre-eclampsia, defined as gestational hypertension and proteinuria. The trial is registered with the Pan-African Clinical Trials Registry, number PACTR201105000267371. The trial closed on Oct 31, 2017.

**Findings:** Between July 12, 2011, and Sept 8, 2016, we randomly allocated 1355 women to receive calcium or placebo; 331 of 678 participants in the calcium group versus 320 of 677 in the placebo group became pregnant, and 298 of 678 versus 283 of 677 had pregnancies beyond 20 weeks' gestation. Pre-eclampsia occurred in 69 (23%) of 296 participants in the calcium group versus 82 (29%) of 283 participants in the placebo group with pregnancies beyond 20 weeks' gestation (risk ratio [RR] 0·80, 95% CI 0·61–1·06; p=0·121). For participants with compliance of more than 80% from the last visit before pregnancy to 20 weeks' gestation, the pre-eclampsia risk was 30 (21%) of 144 versus 47 (32%) of 149 (RR 0·66, CI 0·44–0·98; p=0·037). There were no serious adverse effects of calcium reported.

**Interpretation:** Calcium supplementation that commenced before pregnancy until 20 weeks' gestation, compared with placebo, did not show a significant reduction in recurrent pre-eclampsia. As the trial was powered to detect a large effect size, we cannot rule out a small to moderate effect of this intervention.

**Funding:** The University of British Columbia, a grantee of the Bill & Melinda Gates Foundation; UNDP–UNFPA–UNICEF–WHO–World Bank Special Programme of Research, Development and Research Training in Human Reproduction, WHO; the Argentina Fund for Horizontal Cooperation of the

Abstract:

Background: Based on the encouraging activity and manageable safety profile observed in a phase 1 study, the ECHELON-2 trial was initiated to compare the efficacy and safety of brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone (A+CHP) versus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for the treatment of CD30-positive peripheral T-cell lymphomas.

Methods: ECHELON-2 is a double-blind, double-dummy, randomised, placebo-controlled, active-comparator phase 3 study. Eligible adults from 132 sites in 17 countries with previously untreated CD30-positive peripheral T-cell lymphomas (targeting 75% with systemic anaplastic large cell lymphoma) were randomly assigned 1:1 to receive either A+CHP or CHOP for six or eight 21-day cycles. Randomisation was stratified by histological subtype according to local pathology assessment and by international prognostic index score. All patients received cyclophosphamide 750 mg/m² and doxorubicin 50 mg/m² on day 1 of each cycle intravenously and prednisone 100 mg once daily on days 1 to 5 of each cycle orally, followed by either brentuximab vedotin 1·8 mg/kg and a placebo form of vincristine intravenously (A+CHP group) or vincristine 1·4 mg/m² and a placebo form of brentuximab vedotin intravenously (CHOP group) on day 1 of each cycle. The primary endpoint, progression-free survival according to blinded independent central review, was analysed by intent-to-treat. This trial is registered with ClinicalTrials.gov, number NCT01777152.

Findings: Between Jan 24, 2013, and Nov 7, 2016, 601 patients assessed for eligibility, of whom 452 patients were enrolled and 226 were randomly assigned to both the A+CHP group and the CHOP group. Median progression-free survival was 48·2 months (95% CI 35·2–not evaluable) in the A+CHP group and 20·8 months (12·7–47·6) in the CHOP group (hazard ratio 0·71 [95% CI 0·54–0·93], p=0·0110). Adverse events, including incidence and severity of febrile neutropenia (41 [18%] patients in the A+CHP group and 33 [15%] in the CHOP group) and peripheral neuropathy (117 [52%] in the A+CHP group and 124 [55%] in the CHOP group), were similar between groups. Fatal adverse events occurred in seven (3%) patients in the A+CHP group and nine (4%) in the CHOP group.

Interpretation: Front-line treatment with A+CHP is superior to CHOP for patients with CD30-positive peripheral T-cell lymphomas as shown by a
significant improvement in progression-free survival and overall survival with a manageable safety profile.

**Funding:** Seattle Genetics Inc, Millennium Pharmaceuticals Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and National Institutes of Health National Cancer Institute Cancer Center.


**Abstract:**

Fractures resulting from osteoporosis become increasingly common in women after age 55 years and men after age 65 years, resulting in substantial bone-associated morbidities, and increased mortality and health-care costs. Research advances have led to a more accurate assessment of fracture risk and have increased the range of therapeutic options available to prevent fractures. Fracture risk algorithms that combine clinical risk factors and bone mineral density are now widely used in clinical practice to target high-risk individuals for treatment. The discovery of key pathways regulating bone resorption and formation has identified new approaches to treatment with distinctive mechanisms of action. Osteoporosis is a chronic condition and long-term, sometimes lifelong, management is required. In individuals at high risk of fracture, the benefit versus risk profile is likely to be favourable for up to 10 years of treatment with bisphosphonates or denosumab. In people at a very high or imminent risk of fracture, therapy with teriparatide or abaloparatide should be considered; however, since treatment duration with these drugs is restricted to 18–24 months, treatment should be continued with an antiresorptive drug. Individuals at high risk of fractures do not receive adequate treatment and strategies to address this treatment gap—eg, widespread implementation of Fracture Liaison Services and improvement of adherence to therapy—are important challenges for the future.


**Abstract:**

**Introduction:** Decanal (C10) is an important aldehyde, extensively used to enhance floral and citrus notes in various perfumery products. It is well-known that the human electroencephalographic (EEG) activity is highly susceptible to change due to the exposure of fragrances. However, the EEG findings exhibit non-stationary behavior in terms of analysis and recording time. Hence, the present study aimed to investigate the effect of inhalation
Methods: Twenty healthy volunteers (10 men and 10 women) participated in the EEG study. The EEG data were recorded from 8 channels according to the International 10–20 System. The EEG readings were analyzed for every second by splitting the total 30s data during the no odor and C10 odor exposures.

Results: The exposure of C10 odor produced significant changes ($p < 0.05$) in all the absolute waves at a certain time during the time series analysis. The results revealed that all absolute waves significantly decreased during the first 13s period of time due to the exposure of C10 odor. After that, absolute alpha, absolute slow alpha, and absolute fast alpha markedly increased. Furthermore, the exposure to C10 appears to mainly affect the frontal regions, especially the left frontal region (F3) compared with other regions.

Conclusion: Our data suggest that the EEG activity of C10 odor is highly unstable in the time series analysis, thereby analysis time could play a key role in the EEG response to olfactory stimulation.


Abstract:

Introduction: Gender differences are important intrinsic factors in wrist arterial pulse assessment in traditional Chinese and Korean medicine. The current study aimed to examine gender differences in wrist pulse waves at the Cun, Guan, and Chi positions of the wrist and to identify associations between physical indices and anatomical properties at all three positions.

Methods: One hundred thirty-nine middle-aged Korean men and women participated in this cross-sectional study. A blood analysis was performed, and blood pressure and medical history were recorded. Artery diameter and depth, blood flow velocity, and pulse wave were measured.

Results: The pulse power index (PPI), pulse depth index (PDI), and power spectrum density at the third harmonic frequency/first harmonic frequency (PSD_w3_w1) showed highly significant differences according to gender. Men exhibited larger PPI values than women at all three positions. The PDI and PSD_w3_w1 in men were higher at the Cun position than those in women, whereas the PDI at the Chi position was higher in women than in men. Gender differences in the spectral harmonic energy ratio were greater at the Guan and Chi positions than those at the Cun position. The subendocardial viability ratio differed significantly between genders. In
women, the PDI was highly positively correlated with radial artery depth at all positions; however, in men, the PDI was only marginally correlated with artery depth at the Guan and Chi positions.

**Conclusion:** We suggest that gender differences should be considered in wrist artery pulse diagnosis, including those related to pulse diagnostic positions and anatomical properties.


**Abstract:**

**Background:** As one of only a handful of countries that have achieved both Millennium Development Goals (MDGs) 4 and 5, China has substantially lowered maternal mortality in the past two decades. Little is known, however, about the levels and trends of maternal mortality at the county level in China.

**Methods:** Using a national registration system of maternal mortality at the county level, we estimated the maternal mortality ratios for 2852 counties in China between 1996 and 2015. We used a state-of-the-art Bayesian small-area estimation hierarchical model with latent Gaussian layers to account for space and time correlations among neighbouring counties. Estimates at the county level were then scaled to be consistent with country-level estimates of maternal mortality for China, which were separately estimated from multiple data sources. We also assessed maternal mortality ratios among ethnic minorities in China and computed Gini coefficients of inequality of maternal mortality ratios at the country and provincial levels.

**Findings:** China as a country has experienced fast decline in maternal mortality ratios, from 108.7 per 100,000 livebirths in 1996 to 21.8 per 100,000 livebirths in 2015, with an annualised rate of decline of 8.5% per year, which is much faster than the target pace in MDG 5. However, we found substantial heterogeneity in levels and trends at the county level. In 1996, the range of maternal mortality ratios by county was 16.8 per 100,000 livebirths in Shantou, Guangdong, to 3510.3 per 100,000 livebirths in Zanda County, Tibet. Almost all counties showed remarkable decline in maternal mortality ratios in the two decades regardless of those in 1996. The annualised rate of decline across counties from 1996 to 2015 ranges from 4.4% to 12.9%, and 2838 (99.5%) of the 2852 counties had achieved the MDG 5 pace of decline. Decline accelerated between 2005 and 2015 compared with between 1996 and 2005. In 2015, the lowest county-level maternal mortality ratio was 3.4 per 100,000 livebirths in Nanhu District, Zhejiang Province. The highest was still in Zanda County, Tibet, but the fall to 830.5 per 100,000 livebirths was only 76.3%. 26 ethnic groups had population majorities in at least one county in China, and all had achieved
declines in maternal mortality ratios in line with the pace of MDG 5. Intercounty Gini coefficients for maternal mortality ratio have declined at the national level in China, indicating improved equality, whereas trends in inequality at the provincial level varied.

**Interpretation:** In the past two decades, maternal mortality ratios have reduced rapidly and universally across China at the county level. Fast improvement in maternal mortality ratios is possible even in less economically developed places with resource constraints. This finding has important implications for improving maternal mortality ratios in developing countries in the Sustainable Development Goal era.

**Funding:** National Health and Family Planning Commission of the People's Republic of China, China Medical Board, WHO, University of Washington Center for Demography and Economics of Aging, Bill & Melinda Gates Foundation.


**McCall Becky.** *Sub-Saharan Africa leads the way in medical drones.* *Lancet* 2019; 393(10166): 17-18p.


**Abstract:**

**Background:** The incidence of human papillomavirus (HPV)-positive oropharyngeal cancer, a disease affecting younger patients, is rapidly increasing. Cetuximab, an epidermal growth factor receptor inhibitor, has been proposed for treatment de-escalation in this setting to reduce the toxicity of standard cisplatin treatment, but no randomised evidence exists for the efficacy of this strategy.

**Methods:** We did an open-label randomised controlled phase 3 trial at 32 head and neck treatment centres in Ireland, the Netherlands, and the UK, in patients aged 18 years or older with HPV-positive low-risk oropharyngeal cancer (non-smokers or lifetime smokers with a smoking history of <10 pack-years). Eligible patients were randomly assigned (1:1) to receive, in addition to radiotherapy (70 Gy in 35 fractions), either intravenous cisplatin (100 mg/m2 on days 1, 22, and 43 of radiotherapy) or intravenous cetuximab (400 mg/m2 loading dose followed by seven weekly infusions of 250 mg/m2). The primary outcome was overall severe (grade 3–5) toxicity events at 24 months from the end of treatment. The primary outcome was assessed by intention-to-treat and per-protocol analyses. This trial is registered with the ISRCTN registry, number ISRCTN33522080.

**Findings:** Between Nov 12, 2012, and Oct 1, 2016, 334 patients were recruited (166 in the cisplatin group and 168 in the cetuximab group).
Overall (acute and late) severe (grade 3–5) toxicity did not differ significantly between treatment groups at 24 months (mean number of events per patient 4·8 [95% CI 4·2–5·4] with cisplatin vs 4·8 [4·2–5·4] with cetuximab; p=0·98). At 24 months, overall all-grade toxicity did not differ significantly either (mean number of events per patient 29·2 [95% CI 27·3–31·0] with cisplatin vs 30·1 [28·3–31·9] with cetuximab; p=0·49). However, there was a significant difference between cisplatin and cetuximab in 2-year overall survival (97·5% vs 89·4%, hazard ratio 5·0 [95% CI 1·7–14·7]; p=0·001) and 2-year recurrence (6·0% vs 16·1%, 3·4 [1·6–7·2]; p=0·0007).

**Interpretation:** Compared with the standard cisplatin regimen, cetuximab showed no benefit in terms of reduced toxicity, but instead showed significant detriment in terms of tumour control. Cisplatin and radiotherapy should be used as the standard of care for HPV-positive low-risk patients who are able to tolerate cisplatin.

**Funding:** Cancer Research UK.


**Abstract:**

Many countries show a growing willingness to use militaries in support of global health efforts. This Series paper summarises the varied roles, responsibilities, and approaches of militaries in global health, drawing on examples and case studies across peacetime, conflict, and disaster response environments. Militaries have many capabilities applicable to global health, ranging from research, surveillance, and medical expertise to rapidly deployable, large-scale assets for logistics, transportation, and security. Despite this large range of capabilities, militaries also have limitations when engaging in global health activities. Militaries focus on strategic, operational, and tactical objectives that support their security and defence missions, which can conflict with humanitarian and global health equity objectives. Guidelines—both within and outside militaries—for military engagement in global health are often lacking, as are structured opportunities for military and civilian organisations to engage one another. We summarise policies that can help close the gap between military and civilian actors to catalyse the contributions of all participants to enhance global health.


**Abstract:**
**Introduction:** Attention Deficit Hyperactivity Disorder (ADHD) is a common mental disorder in children. Drug treatment is the most prevalent method used to control it; however, considering the low efficacy and frequent side effects of current drugs, more attempts are needed to replace them with safer agents. Several studies have shown the beneficial role of micronutrients such as vitamin D in development and improving the performance of neuronal system. This research intended to study the effects of vitamin D supplementation in 6–13 year-old students with ADHD.

**Methods:** 6–13 year-old students with ADHD diagnosed by a child psychiatry specialist. Vitamin D3 supplements (1000 IU) or placebo given daily to 70 subjects for three months. ADHD symptoms were evaluated before and after the intervention using Conners Parent Questionnaire (CPQ), the Strengths and Difficulties Questionnaire Teacher Version (SDQT), the Strengths and Difficulties Questionnaire Parent Version (SDQP) and Continuous performances Test (CPT) scores.

**Results:** The mean scores of the CPQ, SDQP and SDQT showed a significant difference in the two groups after intervention ($p < 0.05$). The impulsivity mean scores of the CPT after intervention showed statistical significance ($p = 0.002$), but the attention ($p = 0.11$) and mean reaction time ($p = 0.19$) mean scores did not.

**Conclusions:** Vitamin D supplementation not only improves some behavioral problems but may prevent exacerbation in some symptoms of the disorder and reduce impulsivity.


**Abstract:**

**Background:** Primary prevention of cardiovascular disease often fails because of poor adherence among practitioners and individuals to prevention guidelines. We aimed to investigate whether ultrasound-based pictorial information about subclinical carotid atherosclerosis, targeting both primary care physicians and individuals, improves prevention.

**Methods:** Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA) is a pragmatic, open-label, randomised controlled trial that was integrated within the Västerbotten Intervention Programme, an ongoing population-based cardiovascular disease prevention programme in northern Sweden. Individuals aged 40, 50, or 60 years with one or more conventional risk factors were eligible to participate. Participants underwent clinical examination, blood sampling,
and ultrasound assessment of carotid intima media wall thickness and plaque formation. Participants were randomly assigned 1:1 with a computer-generated randomisation list to an intervention group (pictorial representation of carotid ultrasound plus a nurse phone call to confirm understanding) or a control group (not informed). The primary outcomes, Framingham risk score (FRS) and European systematic coronary risk evaluation (SCORE), were assessed after 1 year among participants who were followed up. This study is registered with ClinicalTrials.gov, number NCT01849575.

**Findings:** 3532 individuals were enrolled between April 29, 2013, and June 7, 2016, of which 1783 were randomly assigned to the control group and 1749 were assigned to the intervention group. 3175 participants completed the 1-year follow-up. At the 1-year follow-up, FRS and SCORE differed significantly between groups (FRS 1·07 [95% CI 0·11 to 2·03, p=0·0017] and SCORE 0·16 [0·02 to 0·30, p=0·0010]). FRS decreased from baseline to the 1-year follow-up in the intervention group and increased in the control group (−0·58 [95% CI −0·86 to −0·30] vs 0·35 [0·08 to 0·63]). SCORE increased in both groups (0·13 [95% CI 0·09 to 0·18] vs 0·27 [0·23 to 0·30]).

**Interpretation:** This study provides evidence of the contributory role of pictorial presentation of silent atherosclerosis for prevention of cardiovascular disease. It supports further development of methods to reduce the major problem of low adherence to medication and lifestyle modification.

**Funding:** Vasterbotten County Council, the Swedish Research Council, the Heart and Lung Foundation, the Swedish Society of Medicine, and Carl Bennet Ltd, Sweden.


**Abstract:**

**Objective:** To partially address the opioid crisis, some complementary and integrative health (CIH) therapies are now recommended for chronic musculoskeletal pain, a common condition presented in primary care. As such, health care systems are increasingly offering CIH therapies, and the
Veterans Health Administration (VHA), the nation's largest integrated health care system, has been at the forefront of this movement. However, little is known about the uptake of CIH among patients with chronic musculoskeletal pain. As such, we conducted the first study of the use of a variety of nonherbal CIH therapies among a large patient population having chronic musculoskeletal pain.

**Materials and methods:** We examined the frequency and predictors of CIH therapy use using administrative data for a large retrospective cohort of younger veterans with chronic musculoskeletal pain using the VHA between 2010 and 2013 (n = 530,216). We conducted a 2-year effort to determine use of nine types of CIH by using both natural language processing data mining methods and administrative and CPT4 codes. We defined chronic musculoskeletal pain as: (1) having 2+ visits with musculoskeletal diagnosis codes likely to represent chronic pain separated by 30–365 days or (2) 2+ visits with musculoskeletal diagnosis codes within 90 days and with 2+ numeric rating scale pain scores ≥4 at 2+ visits within 90 days.

**Results:** More than a quarter (27%) of younger veterans with chronic musculoskeletal pain used any CIH therapy, 15% used meditation, 7% yoga, 6% acupuncture, 5% chiropractic, 4% guided imagery, 3% biofeedback, 2% t’ai chi, 2% massage, and 0.2% hypnosis. Use of any CIH therapy was more likely among women, single patients, patients with three of the six pain conditions, or patients with any of the six pain comorbid conditions.

**Conclusions:** Patients appear willing to use CIH approaches, given that 27% used some type. However, low rates of some specific CIH suggest the potential to augment CIH use.


**Abstract:**

This commentary describes the clinician experience of certifying patients for medical cannabis (MC) in a north suburban Chicago integrative family medicine practice. The physician and research assistant performed a comprehensive chart review of the first 166 MC patients certified in the practice. Based on this review, barriers and opportunities were elucidated to improve delivery of MC therapy in Illinois within the existing framework of regulation, licensing, certification, and distribution. The following factors have posed challenges for the Illinois Medical Cannabis Pilot Program. These factors are interrelated and include: (1) inadequate scientific knowledge regarding effectiveness, dosage, delivery mechanism, indications, and drug interactions in humans; (2) lack of educational standards for dispensary and medical staff training; (3) lack of communication and coordination of patient care; (4) complexity and inconsistent availability of dosing options; and (5) barriers to access for patients seeking this therapy.


Abstract:

Mortality from severe dengue is low, but the economic and resource burden on health services remains substantial in endemic settings. Unfortunately, progress towards development of effective therapeutics has been slow, despite notable advances in the understanding of disease pathogenesis and considerable investment in antiviral drug discovery. For decades antibody-dependent enhancement has been the prevalent model to explain dengue pathogenesis, but it was only recently demonstrated in vivo and in clinical studies. At present, the current mainstay of management for most symptomatic dengue patients remains careful observation and prompt but judicious use of intravenous hydration therapy for those with substantial vascular leakage. Various new promising technologies for diagnosis of dengue are currently in the pipeline. New sample-in, answer-out nucleic acid amplification technologies for point-of-care use are being developed to improve performance over current technologies, with the potential to test for multiple pathogens using a single specimen. The search for biomarkers that reliably predict development of severe dengue among symptomatic individuals is also a major focus of current research efforts. The first dengue vaccine was licensed in 2015 but its performance depends on serostatus. There is an urgent need to identify correlates of both vaccine protection and disease enhancement. A crucial assessment of vector control tools should guide a research agenda for determining the most effective interventions, and how to best combine state-of-the-art vector control with vaccination.


Abstract:

Introduction: The demand for treatment of hyperpigmentation disorders are on the rise. Artemisia capillaris is a traditional herbal plant widely used in skin protective remedies. In the present study, the inhibitory effect of
Artemisia capillaris ethanol extract on the production of melanin is examined, and the active compound was isolated from the crude extract and identified.

**Methods:** The structure of the purified active compound of A. capillaris ethanol extract (ACE) was elucidated by NMR spectroscopy. ACE at the concentration of 6.25, 12.5, 25, and 50 μg/ml and active compound at the concentration of 37.5, 75, and 150 μg/ml were treated alpha-melanocyte stimulating hormone (α-MSH) induced in B16F10 melanoma cells. Melanin contents, tyrosinase activity, and protein expression of melanogenesis-related proteins were analyzed in ACE or active compound treated or untreated control.

**Results:** ACE significantly inhibited melanogenesis induced by α-MSH and tyrosinase activity without cell cytotoxicity in a dose-dependent manner. Western blot demonstrated that ACE downregulated the expression of melanocyte-specific proteins such as tyrosinase, tyrosinase-related protein-1 (TRP-1), and tyrosinase-related protein-2, which catalyzes the rate-limiting oxidation of tyrosine to melanin. The active compound was finally identified as leukodin. It inhibited melanin pigment synthesis and tyrosinase activity in B16F10 melanoma cells without cytotoxicity. In addition, the leukodin decreased TRPs expression in a dose-dependent manner.

**Conclusions:** Bioactivity-guided fraction identified leukodin is the active compound in ACE extract. Leukodin suppressed melanin synthesis through inhibition of the expression of melanogenic enzymes.


**Abstract:**

**Background:** The magnitude of effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on specific cardiovascular and renal outcomes and whether heterogeneity is based on key baseline characteristics remains undefined.

**Methods:** We did a systematic review and meta-analysis of randomised, placebo-controlled, cardiovascular outcome trials of SGLT2i in patients with type 2 diabetes. We searched PubMed and Embase for trials published up to Sept 24, 2018. Data search and extraction were completed with a standardised data form and any discrepancies were resolved by consensus. Efficacy outcomes included major adverse cardiovascular events
(myocardial infarction, stroke, or cardiovascular death), the composite of cardiovascular death or hospitalisation for heart failure, and progression of renal disease. Hazard ratios (HRs) with 95% CIs were pooled across trials, and efficacy outcomes were stratified by baseline presence of atherosclerotic cardiovascular disease, heart failure, and degree of renal function.

**Findings:** We included data from three identified trials and 34,322 patients (60·2% with established atherosclerotic cardiovascular disease), with 3342 major adverse cardiovascular events, 2028 cardiovascular deaths or hospitalisation for heart failure events, and 766 renal composite outcomes. SGLT2i reduced major adverse cardiovascular events by 11% (HR 0·89 [95% CI 0·83–0·96], p=0·0014), with benefit only seen in patients with atherosclerotic cardiovascular disease (0·86 [0·80–0·93]) and not in those without (1·00 [0·87–1·16], p for interaction=0·0501). SGLT2i reduced the risk of cardiovascular death or hospitalisation for heart failure by 23% (0·77 [0·71–0·84], p<0·0001), with a similar benefit in patients with and without atherosclerotic cardiovascular disease and with and without a history of heart failure. SGLT2i reduced the risk of progression of renal disease by 45% (0·55 [0·48–0·64], p<0·0001), with a similar benefit in those with and without atherosclerotic cardiovascular disease. The magnitude of benefit of SGLT2i varied with baseline renal function, with greater reductions in hospitalisations for heart failure (p for interaction=0·0073) and lesser reductions in progression of renal disease (p for interaction=0·0258) in patients with more severe kidney disease at baseline.

**Interpretation:** SGLT2i have moderate benefits on atherosclerotic major adverse cardiovascular events that seem confined to patients with established atherosclerotic cardiovascular disease. However, they have robust benefits on reducing hospitalisation for heart failure and progression of renal disease regardless of existing atherosclerotic cardiovascular disease or a history of heart failure.

**Funding:** None.