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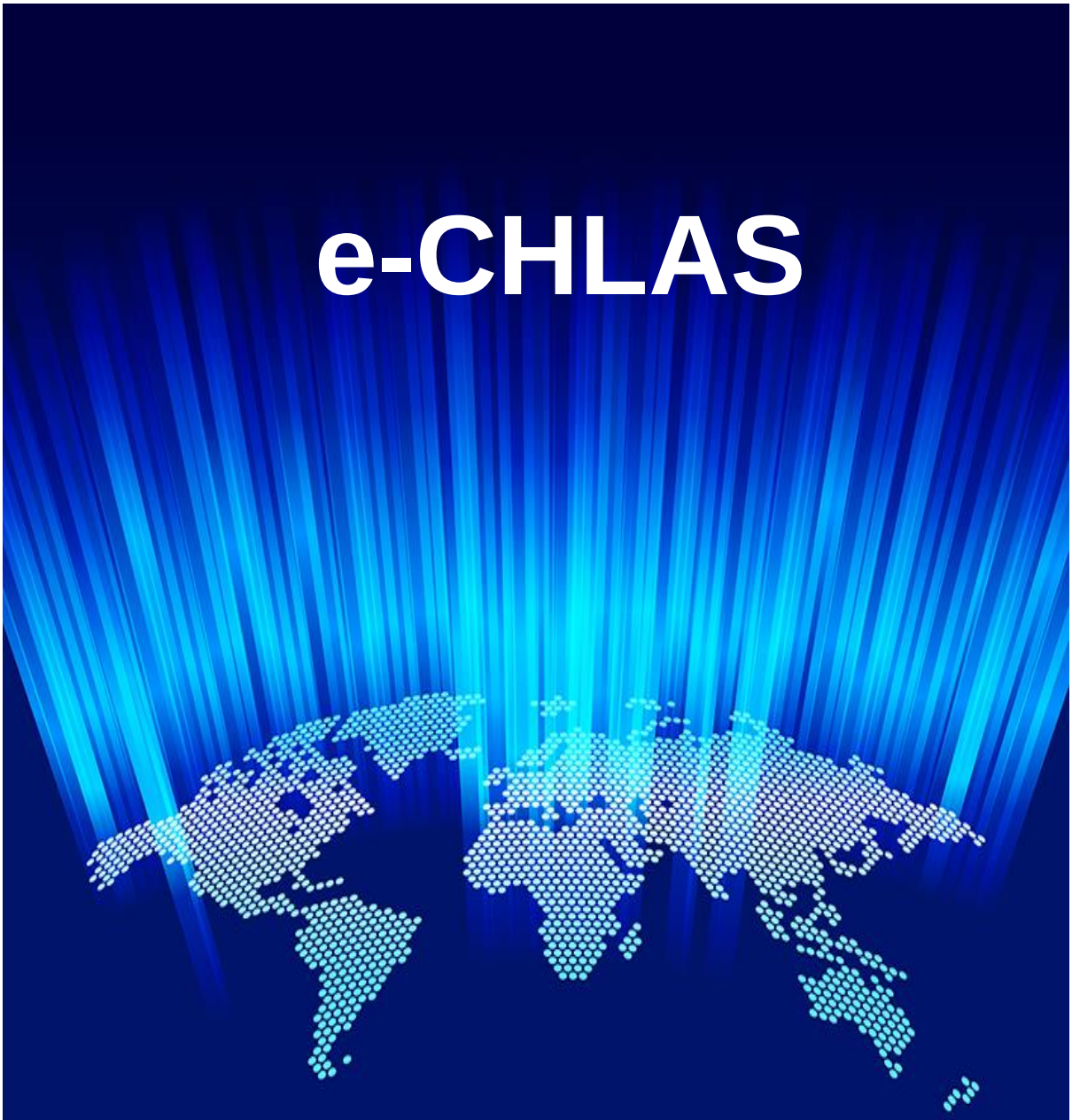

JANUARY 2022

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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 enteries have been made in the following order:

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

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Acknowledgement

We are grateful to Dr. Anil Khurana, Director General Incharge, CCRH for his encouragement and valuable suggestions from time to time. We sincere acknowledge the cooperation of Mrs. Nisha Adhikari, Office Assistant in compiling this bulletin.

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AYUSH & Other System

Anama-Green Chris. Intrapersonal mindfulness is associated with reduced risk of burnout among Central Appalachian educators. *Explore 2022;* 18(1): 64-69p

Abstract:

Background: National statistics suggest that up to 40% of new teachers will leave their school or the teaching profession within their first five years of teaching. Much of this attrition is associated with work-related burnout, some of which may be preventable with targeted worksite health interventions. Previous research suggests that mindfulness skills may be protective from burnout, ultimately reducing the likelihood of attrition from the profession.

Methods: This study compared the self-reported levels of burnout and secondary traumatic stress with participants' levels of interpersonal and intrapersonal mindfulness. A total of 144 participants completed the Professional Quality of Life Inventory and the Mindfulness in Teaching Inventory. Study participants included K-12 teachers in Eastern Kentucky. Odds Ratios and Relative Risks were calculated using Epi Info. Pearson correlations, linear regression, and ANOVA analyses were completed using SPSS. Chronbach's alpha values were also calculated to evaluate score reliability of the five constructs.

Results: Relative Risks and Odds Ratios of having secondary traumatic stress scores of "average/high" were significantly lower for those with high intrapersonal mindfulness scores (OR = 0.12, CI: 0.05–0.30; RR = 0.21, CI: 0.10–0.44). Those who reported high intrapersonal mindfulness scores were up to 11 times more likely to report "low" burnout than those who reported low intrapersonal mindfulness scores (OR = 11.58, CI: 5.06–26.52). Burnout neg- atively correlated with intrapersonal mindfulness ($r = -0.616$, $p < .05$) suggesting that as intrapersonal mindfulness level decreases, burnout increases. ANOVA testing identified significant differences in burnout based on intrapersonal mindfulness level ($F = 8.928$, $p < .05$).

Conclusion: Those who reported high levels of intrapersonal mindfulness had significantly reduced risk of burnout. These results will inform further research in the region regarding mindfulness practice and the experience of burnout among teachers in the region. Thus, mindfulness may be protective from occupation-related burnout for this population. Interventions informed by additional research could reduce the burden of occupation-related burnout and may ultimately contribute toward reduced attrition in the teaching profession.

Anheyer Dennis, Leach Matthew J, Zhang Yan, Cramer Holger. Predictors of Headache/Migraine and the Use of Complementary Medicine in U.S. Children: A Population-Based Analysis of 2017

National Health Interview Survey Data. ***Journal of Integrative and Complementary Medicine 2022;*** **28(1): 60-66p.**

Abstract:

Background: This study set out to determine the prevalence and possible risk factors of headache and/or migraine in U.S. children, as well as the prevalence of complementary medicine use in this population.

Methods: This is a secondary analysis of data from the 2017 U.S. National Health Interview Survey. Sociodemographic and clinical characteristics were compared between individuals with and without headaches. A backward stepwise procedure with a logistic regression statistic was used to test for potential predictors.

Results: Six percent of children reported headaches and/or migraine within the past 12 months. Headaches were predicted by older age, female sex, non-Hispanic white ethnicity, and living in the southern United States. Inability to afford balanced meals and feeling sad or depressed in the past 6 months were also associated with higher odds of headache. A total of 19.2% of children with headaches reported using mind–body medicine, compared with 12.2% of children without headaches. Most frequently used therapy was yoga (57.2%), followed by spiritual meditation (31.1%) and mindfulness meditation (24.0%). The prevalence of visits to a complementary medicine practitioner or healer was 12.5%. Most frequently seen practitioners were chiropractors (62.1%), followed by naturopaths (21.2%), homeopaths (14.1%), and traditional healers (2.5%).

Conclusions: The common use of complementary medicine among children suffering from headaches is worth noting. Understanding the motivation for using complementary medicine, as well as the choice of different forms of such therapy, may shed further light on the health-seeking behavior of this population.

Boehnke Kevin F, LaMore Cheryl, Hart Patty, Zick Suzanna M. Feasibility study of a modified yoga program for chronic pain among elderly adults in assisted and independent living. ***Explore 2022;*** **18(1): 104-107p.**

Abstract:

Context: Yoga improves quality of life in elders ≥65 years, but studies among elders with chronic pain are limited.

Objective: Conduct a feasibility study of gentle yoga among elders in assisted and independent living.

Design: Single arm pre/post clinical trial.

Subjects: Adults (≥65 years of age) with self-identified chronic pain (≥3 on a 10-point scale, lasting for ≥3 months) and no current yoga practice.

Intervention: Ten weekly 60-min gentle yoga classes tailored to elderly adults.

Outcome measures: At baseline, weeks 5, 10 (end of intervention), and 20 (follow-up), we collected data on feasibility (adherence, retention, safety), pain, anxiety, depression, fatigue, sleep disturbance, and physical function.

Results: Twenty-six participants enrolled (88% women, 77% white, 58% in assisted living) with average age of 86.6 ± 4.4 (Mean, STD). Twenty participants completed the intervention, with 90% adhering (completing ≥6 classes). Nine participants (45% of completers) experienced adverse events, which were non-serious and related to transient musculoskeletal pain. No adverse events resulted in study withdrawal. Participants reported being somewhat likely to recommend yoga to a friend, and quite a bit likely to do yoga again. At the end of the intervention, four of twenty participants reported practicing yoga outside of class. Anxiety significantly decreased from 5.80 (SE=0.90) to 4.44 (SE=0.74) ($p = 0.014$), but there were no changes in other measures.

Conclusions: Our pilot 10-week yoga study was generally safe for and suitable to assisted and independent living elderly adults. Future studies are needed to examine other effects of yoga in assisted/independent living adults with chronic pain.

Brambila Tapia Aniel Jessica Leticia, Gutiérrez Garcia Maria Margarita, Ruiz Sandoval Jose Luis, Vazquez Vazquez David, Lara Rosa Martha Meda. Using hypnoanalysis and guided imagery to identify and manage emotional aspects of multiple sclerosis. *Explore 2022;* 18(1): 88-95p

Abstract:

Background: To date, no studies have used hypnosis to examine and manage the potential emotional causes of multiple sclerosis (MS) in the scientific field; therefore, we decided to compare the effectiveness of hypnoanalysis and guided imagery for determining and manage these emotional causes.

Methods: Fifteen participants with severe MS were included and assigned into 2 groups: hypnoanalysis and guided imagery. In the hypnoanalysis group, the participants underwent 10 hypnotic sessions to understand events related to the cause of the disease, which were restructured (the events were modified by adding the psychological resources that each involved person needed); in addition, other techniques were used to investigate the causes and solutions according to the participants' unconscious. The guided imagery group received 10 group sessions of body relaxation and guided imagery, which were recorded for practice at home. Outcome measures, namely, disability (the Expanded Disability Status

Scale, EDSS), quality of life (QoL, measured with the SF-36) and number of relapses, were evaluated 4 months previous the intervention, at baseline, post-intervention, and 3 months later.

Results: Hypnoanalysis revealed that stressful events and psycho-emotional maladaptive patterns acted as causal, detonating, or aggravating factors of disease, and psycho-emotional changes were the most frequent and varied solutions. No changes were observed in disability between the two groups. The guided imagery group showed an improvement in 2 subscales of QoL when compared with the hypnoanalysis group (which disappeared at the follow-up); this difference is probably due to the increased number of sessions and probably due to psycho-emotional maladaptive patterns being more frequently mentioned than difficult circumstances in life and/or unsolved past events. However, the techniques used in hypnoanalysis were effective in understanding the potential emotional causes of MS, which showed high intra- and inter-participant consistency.

Conclusions: The daily use of guided imagery overcame the restructuring of negative past events to improve QoL in patients with MS.

Chen Su Ru, Hou Wen Hsuan, Lai Jung Nien, Kwong Joey SW, Lin Pi Chu. Effects of Acupressure on Anxiety: A Systematic Review and Meta-Analysis. *Journal of Integrative and Complementary Medicine 2022;* 28(1): 25-35p.

Abstract:

Objectives: The research aim was to perform a systematic review and meta-analysis evaluating the ability of acupressure to reduce anxiety.

Design: Randomized controlled trials were obtained through a search of electronic medical databases (four in English and one in Chinese) from inception to October 5, 2020. Two authors searched the databases, evaluated studies' methodological quality, and performed data extraction independently. The final studies for analysis were identified after discussion with the third author.

Results: We obtained 27 studies for our systematic review and meta-analysis. Eight studies had a low overall risk of bias, and 13 had some bias concerns with methodological quality. According to the results, acupressure significantly reduced patient anxiety (standardized mean difference = 1.152; 95% confidence interval: 0.847–1.459, $p < 0.001$), and the study heterogeneity was high ($Q = 299.74$, $p < 0.001$, $I2 = 91.333\%$). Two studies reported acupressure-associated adverse events. We also performed a sensitivity analysis by omitting one outlier study, which had the largest effect size; however, high heterogeneity remained ($I2 = 87.816\%$). A subgroup analysis revealed significant differences between participant types ($Q = 46.573$, $p < 0.001$), levels of methodological quality ($Q = 6.228$, $p = 0.044$), and massage equipment ($Q = 4.642$, $p = 0.031$).

Conclusions: Our meta-analysis suggests that acupressure can alleviate anxiety. Acupressure was more effective for inpatients and preoperative patients when finger massage was applied. In individuals with anxiety and a stable hemodynamic status, acupressure could be a promising treatment option. However, the substantial heterogeneity across studies means that any inference from the results should be performed cautiously.

Choi Suvin, Park Sang-Gue. Effects of anxiety-related psychological states on music-induced analgesia in cold pressor pain responses. ***Explore 2022;*** **18(1): 25-30p**

Abstract:

Context: The analgesic effect of music has long been reported.

Objective: To assess how anxiety-related psychological states affect the analgesic effect of music using the cold pressor task (CPT).

Design: A 3-period × 3-sequence crossover design was adopted; three conditions were used: “no sound,” “music-listening,” and “news-listening.”

Setting: Participants Forty-nine participants were included.

Interventions: After completing five anxiety-related psychological instruments (Anxiety Sensitivity Index [ASI]-16, ASI-Revised, State-Trait Anxiety Inventory [STAI]-S, STAI-T, and Pain Anxiety Symptoms Scale-20), the participants were allocated to the low- or high-anxiety group. The high- and low-anxiety groups were defined based on cutoff points according to the distributions and characteristics of the five instruments.

Main outcome measures: Pain responses, such as pain tolerance time, pain intensity, and pain unpleasantness, were measured on the CPT. Pain responses in the music-listening condition were also compared to those in the other two conditions via pairwise comparisons within each anxiety group.

Results: The Cronbach alpha of the five instruments ranged from 0.866 to 0.95, indicating that they were reliable. Pain responses in the music-listening condition in the low-anxiety groups based on any of the five scales were significantly different from those in the other conditions, but this effect was not found in the high-anxiety groups. This study demonstrates that anxiety-related psychological states can predict the analgesic effect of music on pain responses measured by the CPT and suggests that music may be beneficial as a pain management tool in low-anxiety groups.

DUMAN Mesude, Ozan Yeter Durgun, Derya Yeşim Aksoy, Taşhan Sermin Timur. Effect of relaxation exercises training on pregnancy-related anxiety after perinatal loss: A pilot randomized control trial. ***Explore 2022;*** **18(1): 44-50p**

Abstract:

Background: Pregnancy-related anxiety is quite frequent during pregnancy after perinatal loss, and it is likely to cause negative effects on the mother and the foetus. amongst independent nursing practices, progressive muscle relaxation exercises are considered to be one of alternative treatment methods to relax pregnant women physically and psychologically.

Purpose: The aim of this study is to examine the effect of progressive muscle relaxation exercises on the pregnancy-related anxiety levels of pregnant women who have experienced a perinatal loss.

Methods: One hundred and four pregnant women who had experienced a perinatal loss were randomly assigned to an intervention group (n = 31) or a control group (n = 33) and participated in a 12-week trial. The intervention group received training on progressive muscle relaxation exercises, while the control group was provided only with routine healthcare services. The Pregnancy-Related Anxiety Questionnaire-R2 was used to evaluate the level of pregnancy-related anxiety.

Results: The intervention group showed improvement in comparison to the control group at the end of the intervention. After the intervention, the measured levels of “pregnancy related anxiety”, “fear of giving birth”, and “worries about bearing a handicapped child” significantly decreased in the intervention group compared to the pre-intervention levels and the control group, and the difference between the groups was statistically significant ($p<0.001$, $p<0.001$, and $p<0.001$, respectively). However, there were no significant differences in the levels of concern about own appearance between the groups after the intervention ($p>0.05$).

Conclusion: According to the results of the study, progressive muscle relaxation led to a decrease in the pregnancy-related anxiety levels of the pregnant women who had experienced a perinatal loss.

Hung Jui Hung, Chen Wei Chieh, Lin Mei Chen, Chuang Hsiao Mei, Wang Jiun Long, Fu Pin Kuei et al. Associations of Chinese Herbal Medicine Use with the Risks of Acute Exacerbation and Mortality in Patients with Chronic Obstructive Pulmonary Disease: A Nationwide Retrospective Cohort Study. *Journal of Integrative and Complementary Medicine 2022;* 28(1): 77-86p.

Abstract:

Objectives: This study aimed to assess the correlation of exacerbation and the mortality rate in patients with chronic obstructive pulmonary disease (COPD) between biomedical treatments with or without Chinese herbal medicine (CHM) as an adjunct.

Design: A total of 81,261 COPD patients were identified from the National Health Insurance Research Database in Taiwan between 2001 and 2012. After screening and matching, 3176 COPD patients were included in the study. Statistical analyses were performed to assess the differences in the baseline characteristics. The authors used the Cox proportional hazard regression analysis to calculate the risks of mortality and hospitalization due to acute exacerbation of COPD within 1 year between a CHM user cohort and non-CHM user cohort. The cumulative incidence of mortality in COPD patients with or without CHM treatment was calculated by the Kaplan–Meier method.

Results: COPD patients in the CHM user cohort demonstrated a significantly lower risk of mortality ($p < 0.001$) and acute exacerbation ($p < 0.05$), compared with the non-CHM user cohort. In addition, the CHM users exhibited a reduced cumulative incidence of mortality compared with the non-CHM user cohort ($p < 0.001$). Xiao Qing Long Tang and Fritillariae thunbergii were the most common Chinese herbal formula and single Chinese herb prescribed for COPD patients.

Conclusion: Combining CHM with biomedical treatment might reduce the risk of acute exacerbation and incidence of mortality in patients with COPD.

Jung Hsuan Kuang, Lai Jung Nien, Lin Jaung Geng, Chiang Huo Ju, Kao Shung Te. Intradialytic hypotension: Is intradialytic acupuncture a complementary option? A case report. ***Explore 2022;*** **18(1): 31-35p**

Abstract:

Background: Intradialytic hypotension (IDH) is a common complication during hemodialysis (HD) and is positively associated with either poor quality of life or mortality. The present case report described the effect of intradialytic acupuncture (IA) in decreasing the occurrence of IDH.

Methods: A 70-year-old female with diabetic nephropathy had been receiving regular dialysis twice weekly since end-stage renal disease was diagnosed. She had several episodes of intradialytic systolic blood pressure (iSBP) drop accompanied with severe complications within one month. In the 10 dialysis sessions prior to IA intervention, the case patient experienced two episodes of nadir iSBP < 90 mmHg, seven episodes of iSBP drop ≥ 20 mmHg, among which two episodes occurred with symptoms; and three episodes of iSBP drop required nursing intervention.

Interventions: Dialysis sessions proceeded as usual with the patient receiving five sessions of 30-min IA as an add-on therapy starting from the second hour of dialysis.

Results: In the 10 sessions with IA administered alternately, she experienced one episode of nadir iSBP < 90 mmHg and three episodes of iSBP drop ≥ 20 mmHg, among which two episodes occurred with symptoms.

Occurrence of IDH reduced and no IDH necessitating nursing intervention occurred during IA-HD sessions.

Conclusions: The administration of IA showed potential effect in decreasing the occurrence of IDH.

Karuppusamy Avaranjika, Paul Swapan, Chattopadhyay Abhijit, Balamurugan Dharshna, Malathi Maria, Kumar Ashwani et al. Individualized Homeopathic Medicines in Treatment of Vitiligo: Double-Blind, Randomized, Placebo-Controlled Pilot Trial. *Journal of Integrative and Complementary Medicine 2022;* 28(1): 96-102p.

Abstract:

Objective: The feasibility of a definitive trial was tested to evaluate individualized homeopathic medicines (IHMs) for the treatment of vitiligo.

Design: This was a double-blind randomized (1:1) placebo-controlled pilot trial conducted at the National Institute Homeopathy, India. Sixty patients with vitiligo were included in the study.

Interventions: IHMs and identical-looking placebos at 50-millesimal (LM) potencies.

Outcome measures: Feasibility issues and scores from the Vitiligo Area Scoring Index (VASI), Vitiligo-specific Quality-of-life instrument (VitiQoL), and Dermatology Life Quality Index (DLQI) were measured at baseline and after 3 and 6 months.

Results: The recruitment and retention rates were satisfactory. Mean reductions in the outcome measures were higher in the IHM group than placebo.

Conclusions: Definitive efficacy trials are warranted.

Khodarahimi Siamak, Mirderikvand Fazlolah, Amraei Kourosh. Efficacy of affective and sensory psychotherapy module for sleep disturbances in generalized anxiety disorder. *Explore 2022;* 18(1): 17-24p

Abstract:

Objective: This study was aimed to examine the effectiveness of a newly developed therapeutic method focusing on affective and sensory processes in the treatment of sleep problems in outpatients with Generalized Anxiety Disorder (GAD), called the 'Affective and Sensory Psychotherapy Module' (ASPM).

Method: A randomised controlled trial was conducted, there were 60 outpatient participants. The Generalized Anxiety Disorder 7-Item Scale

(GAD-7) and the Pittsburgh Sleep Quality Index (PSQI) were used at baseline, post-treatment, and 3 month follow-up.

Results: There were no significant differences between the therapeutic and control groups at baseline. The therapeutic group showed a significant improvement in sleep quality and anxiety decrease compared to the control group. Sex differences did not occur in the results for within-subjects and between-group effects in this study.

Conclusions: The present study supported the efficacy of ASPM in the treatment of sleep problems in adult outpatients with GAD.

Lee Tamsin L, Langley Blake O, Noborikawa Jennifer, Skye-Babbott Ariana, Booth LaForce Cathryn. Acupuncture and Telehealth Survey: A Cross-Sectional Survey Exploring Early COVID-19 Impacts on the Acupuncture Profession. *Journal of Integrative and Complementary Medicine 2022;* 28(1): 36-44p.

Abstract:

Introduction: As the COVID-19 pandemic continues to impact workforces in the United States, the Acupuncture and Telehealth Survey was released to assess the acupuncture profession's use of telehealth and workforce response to a changing regulatory landscape.

Methods: An online cross-sectional survey of licensed acupuncturists in the United States was conducted in May 2020 for 4 weeks. Novel online recruitment strategies were successfully implemented including social media pages, digital media marketing, and webinar presentations. Statistical analyses were used to ascertain varying impacts on acupuncturists with telehealth training, and the use of online health care platforms, stratified by age, and history of licensure.

Results: One thousand forty-five respondents from 46 states completed the survey. The majority of respondents noted a significant reduction in working hours regardless of telehealth training history (mean −18.7 h/week, $p < 0.001$, 95% confidence interval [−19.5 to −18.0]); however, acupuncturists managing patients online reported a lesser magnitude of impact (mean −17.3, $p = 0.004$). Respondents noted stress, immune support, and pain as the most common conditions managed through telehealth. Acupuncturists using telehealth primarily educated patients on nutrition- or herbal-based therapies and acupressure techniques, similar to acupuncturists managing suspected or confirmed COVID-19 cases. Although only 21% of acupuncturists reported receiving telehealth training, 38% were providing telehealth, and 13% were considering it in the future with concerns for quality patient care.

Discussion: Acupuncturists' working hours were significantly reduced during the COVID-19 pandemic although many pivoted to a variety of online health care techniques and profession-specific modalities for continued

patient care. This effect could be minimized by the use of telehealth platforms, necessitating adequate training on telehealth in the acupuncture profession.

Milewska Wrobel Dorota, Lis Swięty Anna. Does antioxidant-rich diet during pregnancy protect against atopic multimorbidity in children? *Explore 2022;* 18(1): 96-99p.

Abstract:

Background: Genetics and prenatal environmental exposures are indicated in the complex etiopathogenesis and clinical expression of atopic diseases. This study examined the clinical features of infantile-onset atopic dermatitis (AD) in relation to maternal diet during pregnancy.

Methods: Maternal dietary habits were evaluated in terms of the frequency of intake of six different food categories rich in antioxidants or omega-3 fatty acids.

Results: One hundred mother–child pairs were recruited, 47 infants (<12 months) and 53 children aged 12–36 months. Forty-six of the children had mild, 41 moderate and 13 severe AD. The other atopic manifestations (alone or associated) included: asthma in 9 cases, allergic rhinitis in 22 cases and food allergy in 33 cases. The presence of asthma in children was significantly associated with a lower level of maternal dietary intake of fruits and vegetables as well as chocolate confectionery, while associations with whole grain breakfast cereals, nuts and seeds, non-alcoholic beverages (coffee, tea, fruit juices) and fish and fish products, were not statistically significant. The age of onset and severity of infantile-onset AD were not linked to any of the food categories considered for analyses.

Conclusions: Healthy diet in pregnant women that is rich especially in antioxidants may provide protection against atopic comorbidities of AD. Further prospective reasearch on the role of maternal diet in primary prevention of atopic diseases is warranted.

Polykarpos C Patsalis, Malik Patsalis Amena B, Rauscher Helen Gwendolin, Schaefers Christian, Useini Dritan, Strauch Justus Thomas et al. Efficacy of Auricular Acupuncture and Lavender Oil Aromatherapy in Reducing Preinterventional Anxiety in Cardiovascular Patients: A Randomized Single-Blind Placebo-Controlled Trial. *Journal of Integrative and Complementary Medicine 2022;* 28(1): 45-50p.

Abstract:

Introduction: Auricular acupuncture at the “relaxation point” and lavender oil aromatherapy can reduce preoperative anxiety associated with increased mortality and morbidity. Data on the effect of combined auricular acupuncture and lavender oil aromatherapy in patients undergoing

cardiovascular interventions with the use of local anesthesia or under conscious sedation are sparse. The authors sought to evaluate the efficacy of auricular acupuncture and lavender oil aromatherapy in reducing preinterventional anxiety in cardiovascular patients.

Materials and Methods: Data of 80 consecutive patients undergoing diagnostic coronary angiography (n = 56) with or without percutaneous coronary intervention (n = 9) and right heart catheterization (n = 6), transcatheter aortic valve replacement (n = 17) and percutaneous mitral valve repair (MitraClip; n = 2) were analyzed. Patients were prospectively randomized to receive either preinterventional auricular acupuncture and lavender oil (Lavandula angustifolia) aromatherapy (verum group, n = 39) or combined sham auricular acupuncture and placebo oil aromatherapy (placebo group, n = 41). For the verum group bilateral auricular acupuncture was performed at the "relaxation point." State anxiety and blood pressure were assessed before and at 30 min after acupuncture and presternal oil application. State anxiety was defined as primary outcome measure and assessed using the Spielberger State Anxiety Inventory (STAI) for Adults form Y6. Intervention-specific anxiety was assessed by a 10-point numerical rating scale, and perceived treatment success by a single dichotomous question. Clinical blood pressure was further assessed.

Results: After the intervention, the verum group had significantly decreased anxiety on the STAI compared with the placebo group (Δ = −4.18; 95% confidence interval = −8.31 to −0.05; p = 0.047). Significantly more patients reported subjective treatment success in the verum group (87.2%) than in the placebo group (65.9%, p = 0.035). No significant differences were observed regarding intervention-specific anxiety and blood pressure between the two groups. No serious adverse events occurred in any group.

Conclusions: Combined auricular acupuncture and lavender oil aromatherapy can decrease preinterventional anxiety in cardiovascular patients and requires further investigation.

Pupysheva Natalia V, Boronoev Vitaly V. Tibetan pulse diagnostics and attempts to computerize it. *Explore 2022;* 18(1): 51-56p

Abstract:

Study Subject: The research concerns attempts to computerize the foundations of pulse diagnostics of Tibetan medicine. An expert in Tibetan pulse diagnostics can evaluate the functioning of an organism (twelve internal organs and three psychophysiological systems) by feeling the pulse in six palpation points on the radial arteries of both wrists of a patient. Nowadays many physicists make attempts to computerize this method. The paper shows a few tests that are intended to «teach» a pulse diagnostics device to identify the diagnostically relevant characteristics of pulse waves.

Objective of the Research: This investigation is an attempt to objectify basic characteristics of pulse diagnostics. Though pulse diagnostics has

always been a subjective art of an experienced doctor, it may also become part of an objective science due to the physical basis that underlies it.

Method: The paper presents tests of pulse measurements by a pulse diagnostics device in conditions that create certain predictable responses of an organism to outer stimuli. A group of volunteers were exposed to certain stimuli that can bring about predictable responses of the organism to be detected, processed and analyzed by the pulse diagnostics equipment.

Conclusion: Experiments of this kind give practical material for the analysis of the pulse waves obtained under special conditions, which provides the development of the software for the pulse diagnostic equipment and confirms that objectifying basic characteristics of pulse diagnostics of Tibetan medicine is possible, though in a limited scope.

Rasoul Goli, Mansour Arad, Mam Qaderi Mohsen, Parizad Naser. Comparing the effects of geranium aromatherapy and music therapy on the anxiety level of patients undergoing inguinal hernia surgery: A clinical trial. *Explore 2022;* 18(1): 57-63p

Abstract:

Introduction: Anxiety may lead to negative post-surgery outcomes in patients. It is essential to find strategies to manage pre-surgery anxiety and prevent unwanted consequences in patients. Aromatherapy and music therapy can be used to help patients managing their pre-surgery anxiety.

Objective: To compare the effects of Geranium aromatherapy and music therapy on the anxiety level of patients undergoing inguinal hernia surgery.

Methods: This randomized clinical trial was conducted in Imam Educational Hospital in Mahabad, Iran. One hundred and fifty patients were recruited and randomly allocated to aromatherapy, music therapy, and control groups. The Spielberger State-Trait Anxiety Inventory was used to measure the patients' pre-surgery anxiety (primary outcome) before and after the intervention. Geranium essential oil and instrumental music were used in aromatherapy and music therapy groups respectively. The patients in the control group received no intervention. The data were analyzed with SPSS version 25.0.
Results: The results showed significant differences in the mean anxiety score of aromatherapy, music therapy, and control groups (P=0.011). Inhalation Geranium aromatherapy and music therapy groups had significantly lower mean anxiety scores compared with the control group after the intervention (P<0.001). Moreover, the value of decrease in the mean anxiety score was greater in the aromatherapy group compared to the music therapy group.

Conclusions: Music therapy and aromatherapy are recommended as inexpensive and safe complementary medicine. These methods are effective strategies to assist patients with managing their pre-surgery anxiety, which

results in reduced patient post-surgery complications and shorter surgery recovery time.

Reangsing Chuntana, Lauderman Christina, Schneider Joanne Kraenzle. Effects of Mindfulness Meditation Intervention on Depressive Symptoms in Emerging Adults: A Systematic Review and Meta-Analysis. *Journal of Integrative and Complementary Medicine 2022;* 28(1): 6-24p.

Abstract:

Introduction: Depression in emerging adults (20–29 years of age), a transition from adolescence to adulthood, is a mental health problem globally. Antidepressants and psychotherapy have limited effectiveness and might not be available worldwide. Alternative and complementary treatments, such as mindfulness meditation, are growing.

Objective: We examined the effects of mindfulness interventions on depression in emerging adults and explored the moderating effects of participants, methods, and intervention characteristics.

Design: Systematic review and meta-analysis.

Subjects: Emerging adults.

Interventions: Mindfulness meditation interventions versus control groups.

Outcomes measures: depressive symptoms.

Results: Forty-five studies resulted in 49 comparisons, including 3479 participants (23.0–2.7 years old); 1826 participants practiced mindfulness and 1653 served as controls. Overall, mindfulness interventions showed significant reduction in depression compared with controls ($g = 0.44$, 95% confidence interval: 0.33–0.55). Mindfulness interventions conducted in Asian countries had a greater decrease in depression ($g = 0.69$) than studies conducted in North America ($g = 0.44$) or Europe ($g = 0.23$). Mindfulness interventions showed greater reductions in depression in studies with higher proportion of females (Slope = 0.010, $\tau 2 = 0.07$, Q between = 7.10, $p = 0.008$). Mindfulness interventions conducted in emerging adults with depressive disorders reduced depression more ($g = 1.12$) than in emerging adults without ($g = 0.40$). Providing mindfulness intervention in a group setting had a greater reduction of depression ($g = 0.54$) than on an individual basis ($g = 0.30$). More minutes of unstructured mindfulness practice per session showed a greater reduction in depressive symptoms (Slope = 0.016, Q between = 1.34, $p = 0.035$). Using intention-to-treat analyses showed a lower ES ($g = 0.14$) than not using it ($g = 0.55$). Other quality indicators were not significant moderators. Primary researchers did not report the adverse effects of mindfulness interventions.

Conclusion: Mindfulness interventions somewhat improved depression in emerging adults. Because primary researchers did not report the adverse effects, mindfulness interventions should be used with caution. Future researchers might study the adverse effects of mindfulness interventions as well as the long-term effects.

Schwartz Stephan A. America's desperate need for wellbeing. *Explore 2022;* 18(1): 5-9p

Shathirapathiy G, Mooventhan A, Mangaiarkarasi N, Sangavi SA, Gayathri A. Effect of trataka (yogic gazing) on insomnia severity and quality of sleep in people with insomnia. *Explore 2022;* 18(1): 100-103p.

Abstract:

Introduction: Insomnia or sleeplessness is a common disorder associated with morbidity and poor quality of life. Trataka is one of the six cleansing techniques of yoga. Literature suggests that trataka could help in relieving insomnia. A study was conducted to evaluate the effect of trataka on insomnia severity and quality of sleep (QoS) in people with insomnia.

Materials and Methods: Twenty-nine participants with insomnia were recruited, who underwent trataka (45 minutes per day daily) for a period of 10 days. Insomnia severity and QoS were assessed before and after the intervention using the Insomnia Severity Index (ISI) and The Pittsburgh Sleep Quality Index (PSQI), respectively.

Results: This study showed a significant reduction in ISI score and PSQI global score and its associated subscale scores except sleep medication scores after the intervention.

Conclusion: Trataka may be considered as a treatment modality in reducing insomnia severity and in improving QoS in people with insomnia.

Souza Laura Alves Cota e, Reis Ilka Afonso, Lima Angelica Alves. Climacteric symptoms and quality of life in yoga practitioners. *Explore 2022;* 18(1): 70-75p

Abstract:

Background: Yoga is among the most commonly studied complementary therapies for managing climacteric symptoms. However, it is unclear whether yoga practices in premenopause can affect the occurrence of symptoms when women reach menopause.

Objective: To assess climacteric symptoms and quality of life in regular yoga practitioners and to determine whether yoga practices before menopause may avoid or mitigate climacteric-related symptoms.

Design: This study of 108 women between 40 and 65 years old included 28 women who started to practice yoga in premenopause and had already practiced for at least five years, and as controls 30 physical activity practitioners (PA) who had practiced for at least five years, and 50 sedentary women.

Main outcome measures: Climacteric symptoms were evaluated with the Kupperman Menopausal Index (KMI) and the Women's Health Questionnaire (WHQ). Moreover, we measured the quality of life with the WHQ.

Stub Trine, Kristoffersen Agnete E, Overvag Grete, Jong Miek C, Liu Jianping. Adverse effects in homeopathy. A systematic review and meta-analysis of observational studies. *Explore 2022;* 18(1): 114-28p.

Abstract:

Background: Almost all health care interventions have the potential to be associated with risk to patient safety. Different terminologies are used to define treatment induced risk to patient safety and a common definition is the term adverse effect. Beyond the concept of adverse effect and specific to homeopathy is the concept of homeopathic aggravation. Homeopathic aggravation describes a transient worsening of the patients' symptoms, which is not understood as an adverse effect. In order to ensure patient safety within a homeopathic treatment setting, it is important to identify adverse effects, as well as homeopathic aggravations, even though it may be challenging to distinguish between these two concepts. To date there is an obvious lack of systematic information on how adverse effects and homeopathic aggravations are reported in studies. This systematic review and meta-analysis focuses on observational studies, as a substantial amount of the research base for homeopathy are observational.

Method: Eight electronic databases, central webpages and journals were searched for eligible studies. The searches were limited from the year 1995 to January 2020. The filters used were observational studies, human, English and German language. Adverse effects and homeopathic aggravations were identified and graded according to The Common Terminology Criteria for Adverse Effects (CTCAE). Meta-analysis was performed separately for adverse effects and homeopathic aggravations.

Results: A total of 1,169 studies were identified, 41 were included in this review. Eighteen studies were included in a meta-analysis that made an overall comparison between homeopathy and control (conventional medicine and herbs). Eighty-seven percent (n = 35) of the studies reported adverse effects. They were graded as CTCAE 1, 2 or 3 and equally distributed between the intervention and control groups. Homeopathic aggravations were reported in 22,5% (n = 9) of the studies and graded as CTCAE 1 or 2.

The frequency of adverse effects for control versus homeopathy was statistically significant (P < 0.0001). Analysis of sub-groups indicated that, compared to homeopathy, the number of adverse effects was significantly higher for conventional medicine (P = 0.0001), as well as other complementary therapies (P = 0.05).

Conclusion: Adverse effects of homeopathic remedies are consistently reported in observational studies, while homeopathic aggravations are less documented. This meta-analysis revealed that the proportion of patients experiencing adverse effects was significantly higher when receiving conventional medicine and herbs, compared to patients receiving homeopathy. Nonetheless, the development and implementation of a standardized reporting system of adverse effects in homeopathic studies is warranted in order to facilitate future risk assessments.

Suk Min Hwa, Kwon Jeong Yi. Effect of Equine-Assisted Activities and Therapies on Cardiorespiratory Fitness in Children with Cerebral Palsy: A Randomized Controlled Trial. *Journal of Integrative and Complementary Medicine 2022;* 28(1): 51-59p.

Abstract:

Objectives: To determine the effects of an equine-assisted activities and therapies (EAAT) program on cardiorespiratory fitness (CRF) in children with cerebral palsy (CP).

Design: An evaluator-blinded, parallel, two-arm, randomized controlled clinical trial with 1:1 randomization.

Settings/Location: A tertiary university hospital and a local arena.

Subjects: Forty-six children with CP (24 boys and 22 girls) classified as Gross Motor Function Classification System levels I, II, or III were included.

Interventions: The EAAT program was conducted for 40 min twice a week for 16 weeks (32 lessons).

Outcome measures: Clinical global impression scales, motor capacity, cardiopulmonary fitness, and habitual physical activity was measured on both groups before and after the 16-week period.

Results: Changes in the Clinical Global Impression–Severity scale and Clinical Global Impression–Improvement scale scores were not different between the groups after the intervention. Analysis of covariance revealed statistically significant differences in Gross Motor Function Measure 66 (GMFM 66) ($p < 0.05$) and Pediatric Balance Scale ($p < 0.001$) in motor capacity and resting heart rate (HRrest) ($p < 0.001$) in CRF, between the EAAT group and the control group. Subgroup analysis using multiple linear regression analysis revealed that the GMFM 66 changes had a statistically significant effect on the HRrest changes in the EAAT group ($p < 0.05$).

Conclusions: The present study showed decreased HRrest in children with CP after completing the 16-week EAAT program. This improvement was explained by the improvement of GMFM 66 in the EAAT group. Thus, EAAT may be among the endurance training programs that could be offered to children with CP to improve their CRF.

Torlak Mustafa S, Bagcaci Sinan, Akpinar Elif, Okutan Ozerk, Kuccukturk Serkan. Effect of intermittent diet and/or physical therapy in patients with chronic low back pain: A single-blinded randomized controlled trial. *Explore 2022;* 18(1): 76-81p

Abstract:

Background and purpose: This study aimed to investigate the effect of intermittent diet and/or physical therapy in patients with chronic low back pain.

Materials and methods: Sixty sedentary volunteers with chronic low back pain participated in the study. Body weight and body mass index (BMI) were measured. Pain severity was assessed using Visual Analogue Scale (VAS) and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), while assessment of disability was done using Barthel Index (BI).

Results: The weight and BMI were reduced after treatment with diet only and diet plus physical therapy ($p < 0.001$). The pain severity was reduced in all the treated groups ($p < 0.001$), while BI was increased in the group treated with only physical therapy ($p < 0.001$).

Conclusion: The present study indicated that intermittent diet and/or physical therapy are beneficial to patients with chronic low back pain in terms of pain sensation and daily activities.

Vardanjani Hossein Molavi, Salehi Zahra, Alembizar Faranak, Cramer Holger, Pasalar Mehdi. Prevalence and the Determinants of Traditional, Complementary, and Integrative Medicine Use Among Breastfeeding Mothers: A Cross-Sectional Study. *Journal of Integrative and Complementary Medicine 2022;* 28(1): 67-76p.

Abstract:

Objectives: Breastfeeding is highly important for a child's health, and the widespread use of herbal medicines as galactagogues has been reported. The present study was conducted to evaluate the use of traditional, complementary, and integrative medicine (TCIM) and its determinants among breastfeeding mothers in Shiraz, Iran.

Design: Cross-sectional study.

Setting/Location: Neonatal clinics affiliated to Shiraz University of Medical Sciences.

Subjects: Mothers elder than 18 years old.

Interventions: Nothing.

Outcome Measures: Prevalence and of the use of TCIM products and its associated factors.

Methods: In this cross-sectional study, mothers older than 18 years who referred to neonatal clinics affiliated to Shiraz University of Medical Sciences were enrolled. Using a structured interview, the authors explored the prevalence and of the use of TCIM products and its associated factors.

Results: Of 625 mothers who were approached, 483 agreed to participate (response rate: 77.3%). The average age was 27.3 ± 5.9 years. The prevalence of using TCIM products during current breastfeeding was 97.1%. There were 168 working mothers (44.9%); 163 mothers (34.1%) complaining of postpartum breastfeeding problems, and 327 mothers (68%) had no history of breastfeeding. Recommendations of medical staff or relatives were the most frequent reasons for the consumption of TCIM products (64.9%). Only 27% of mothers disclosed the use of TCIM products to their doctor or health care provider, although 62% of mothers were asked about the use of such products. Notably, 438 mothers (95.8%) considered TCIM to increase their milk. Based on multivariable logistic regression, literacy and past use of TCIM galactagogues were independently associated with TCIM products use.

Conclusions: The use of TCIM galactagogues is highly common among breastfeeding mothers in south of Iran, showing a diverse range of determinants. It is necessary to evaluate the safety and efficacy of common herbal galactagogues, and evidence-based studies must be designed to achieve standardized complementary medicine approaches in this regard.

Wahbeh Helane, Yount Garret, Vieten Cassandra, Radin Dean, Delorme Arnaud. Exploring Personal Development Workshops' Effect on Well-Being and Interconnectedness. *Journal of Integrative and Complementary Medicine 2022;* 28(1): 87-95p.

Abstract:

Introduction: Personal development workshops are increasingly popular. This study evaluated the relationships between the measures of well-being, interconnectedness, and extended perception in various workshops and explored which kinds of workshops and individual characteristics predicted changes in these outcomes.

Materials and Methods: In a prospective, uncontrolled, within-participant design study, adult participants completed questionnaires and online tasks

before and after personal development workshops. Three analyses were conducted: (1) examining the relationships between measures by using only pre-workshop measures using Spearman correlations; (2) exploring change scores pre- to post-workshop and workshop using Wilcoxon signed-rank test; (3) assessing workshop format and content, and individual characteristics as predictors of those change scores multivariate nonparametric regression. The following outcomes were collected: Well-being—Arizona Integrative Outcomes Scale, positive and negative affect, Dispositional Positive Emotions Scale—Compassion subscale, Sleep Quality Scale, Numeric Pain Rating Scale; Interconnectedness—Cloninger Self-Transcendence Scale, Inclusion of Nature in Self and Inclusion of the Other in Self; and Extended perception tasks—Intuition Jar, Quick Remote Viewing, Psychokinesis Bubble, and Time Estimation. The following potential predictor variables were collected: demographic, mental health, psychiatric and meditation history, Single General Self-Rated Health Question, Brief Five-Factor Inventory-10, and the Noetic Experience and Belief Scale. Workshop leaders also selected which format and content characteristics applied to their workshop.

Results: Interconnectedness measures were significantly and positively correlated with well-being (ρ: 0.27 to 0.33), positive affect (ρ: 0.20 to 0.27), and compassion (ρ: 0.21 to 0.32), and they were negatively correlated with sleep disturbance (ρ: −0.13 to −0.16) and pain (ρ: −0.11 to −0.16). Extended perception task performance was not correlated with interconnectedness or well-being. General personal development workshops improved subjective interconnectedness, well-being, positive emotion, and compassion, and they reduced sleep disturbances, negative emotion, and pain (all p's < 0.00005). The lecture ($p = 0.03$), small groups ($p = 0.001$), pairs ($p = 0.01$), and discussion ($p = 0.03$) workshop formats were significant predictors of well-being outcomes. The workshop content categories of meditation ($p = 0.0002$) and technology tools ($p = 0.01$) were also predictive of well-being outcomes, with meditation being the most consistent predictor of positive well-being changes. Conscientiousness was the only significant individual characteristic predictor ($p = 0.002$), although it was associated with increases in some well-being measures and decreases in others.

Conclusions: This study provides preliminary evidence for the positive relationship between the subjective sense of interconnectedness and multiple well-being measures and the beneficial effects of some personal development workshops.

Wang Karen. Expanding the definition of healthy eating: Incorporating food packaging, kitchen equipment, and food storage. *Explore 2022;* 18(1): 129-30p.

Wang Xiao Qing, Xiao Lei, Duan Pei Bei, Xu Qian, Wang Yan. Feasibility and efficacy of perioperative auricular acupuncture technique via intradermal needle buried for postoperative movement-evoked pain after open radical gastrectomy: A randomized controlled pilot trial. *Explore 2022;* 18(1): 36-43p

Abstract:

Introduction: Auricular acupuncture is widely used in the treatment of pain. Recently, the most commonly used method of auricular acupuncture is to embed an intradermal needle into the skin to enhance analgesia through continuous stimulation. We aimed to explore the efficacy and feasibility of this form of auricular acupuncture in the treatment of postoperative movement-evoked pain.

Methods: This single-blind randomized controlled pilot trial was conducted between 23/8/2019 and 10/1/2020. Forty patients were recruited and randomised to either the control group (n = 20) or the experimental group (n = 20). Patients in the control group received sham auricular acupuncture, while patients in the experimental group received auricular acupuncture. A standard routine analgesia was performed in both groups. The patients with NRS score≥4 were given rescue analgesia. Postoperative pain, use of opioids and other analgesics, postoperative recovery and patient's satisfaction were recorded.

Results: The credibility and feasibility of auricular acupuncture for postoperative pain were high in both groups. After auricular acupuncture, the scores of the postoperative movement-evoked pain had a tendency to decrease, but no significant difference was observed between two groups at any time point (P = 0.234~0.888). The data on postoperative pain at rest confirmed that no significant difference was observed between two groups within 48 h of surgery (P = 0.134~0.520), and the postoperative pain at rest scores decreased over time; however, from the third day, the pain at rest scores of the experimental group were decreased, and significant differences were observed between the two groups (P = 0.039~0.047). As for use of rescue analgesic, total opioid consumption and the incidence of postoperative nausea and vomiting, there were no significant differences between the two groups (P = 0.311, P = 0.101, P = 0.661) . In terms of patients' satisfaction, the score of the experimental group was higher than that of the control group, and a significant difference was observed between the two groups (P = 0.000). As for adverse events, two participants reported pain and one patient reported discomfort at the insertion sites during the process of auricular acupuncture intervention, but they both were minor and tolerable.

Conclusion: Auricular acupuncture may have a relief effect on mild postoperative pain at rest with pain score below 3, suggesting that it may be a feasible adjuvant method to relieve mild pain at rest. However, more multi-centre and large-sample studies are needed to verify this result.

Allied System of Medicine

Arik Meltem Isintas, Kiloatar Humeyra, Aslan Burak, Icelli Muge. Effect of TENS for pain relief in women with primary dysmenorrhea: A systematic review and meta-analysis. *Explore 2022;* 18(1): 108-113p.

Abstract:

Objective: Primary dysmenorrhea (PD) is a chronic health condition that affects primarily young women and interferes with daily activities, causes loss of work productivity, and reduces quality of life. Transcutaneous electrical nerve stimulation (TENS) is a complementary and alternative therapy used to reduce pain related to PD. The purpose of this meta-analysis study was to evaluate the effectiveness of TENS in the treatment of pain in women with PD.

Methods: A search of the English literature in the Cochrane Library, MEDLINE (EBSCO), Physiotherapy Evidence Database (PEDro), CINAHL (EBSCO), PUBMED, OVID, Science Direct, Scopus, Academic Search Complete databases was conducted using combinations of the following search terms: 'primary dysmenorrhea', 'pain', 'transcutaneous electrical nerve stimulation', 'TENS', and 'electrical stimulation'. All content from database inception through April 2020 was included in the search.

Results: The initial search strategy based on date range and language yielded 571 relevant records and 4 of them were about both TENS and PD. A total of 260 patients were enrolled in the included studies. In all of the included studies, the comparison intervention consisted of sham TENS. The primary outcome of interest was pain intensity. Our analysis indicated that TENS was statistically more effective than sham TENS in reducing PD-related pain (SMD=1.384; 95% CI=0.505, 2.262; p = 0.002).

Conclusion: TENS is a safe and well-tolerated electrophysical therapy that may be effective for relieving pain in PD.

Attard Gerhardt, Murphy Laura, Clarke Noel W, Cross William, Donat Durr. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: A meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet 2022;* 399(10323): 447-60p.

Abstract:

Background: Men with high-risk non-metastatic prostate cancer are treated with androgen-deprivation therapy (ADT) for 3 years, often combined

with radiotherapy. We analysed new data from two randomised controlled phase 3 trials done in a multiarm, multistage platform protocol to assess the efficacy of adding abiraterone and prednisolone alone or with enzalutamide to ADT in this patient population.

Methods: These open-label, phase 3 trials were done at 113 sites in the UK and Switzerland. Eligible patients (no age restrictions) had high-risk (defined as node positive or, if node negative, having at least two of the following: tumour stage T3 or T4, Gleason sum score of 8–10, and prostate-specific antigen [PSA] concentration ≥40 ng/mL) or relapsing with high-risk features (≤12 months of total ADT with an interval of ≥12 months without treatment and PSA concentration ≥4 ng/mL with a doubling time of <6 months, or a PSA concentration ≥20 ng/mL, or nodal relapse) non-metastatic prostate cancer, and a WHO performance status of 0–2. Local radiotherapy (as per local guidelines, 74 Gy in 37 fractions to the prostate and seminal vesicles or the equivalent using hypofractionated schedules) was mandated for node negative and encouraged for node positive disease. In both trials, patients were randomly assigned (1:1), by use of a computerised algorithm, to ADT alone (control group), which could include surgery and luteinising-hormone-releasing hormone agonists and antagonists, or with oral abiraterone acetate (1000 mg daily) and oral prednisolone (5 mg daily; combination-therapy group). In the second trial with no overlapping controls, the combination-therapy group also received enzalutamide (160 mg daily orally). ADT was given for 3 years and combination therapy for 2 years, except if local radiotherapy was omitted when treatment could be delivered until progression. In this primary analysis, we used meta-analysis methods to pool events from both trials. The primary endpoint of this meta-analysis was metastasis-free survival. Secondary endpoints were overall survival, prostate cancer-specific survival, biochemical failure-free survival, progression-free survival, and toxicity and adverse events. For 90% power and a one-sided type 1 error rate set to 1·25% to detect a target hazard ratio for improvement in metastasis-free survival of 0·75, approximately 315 metastasis-free survival events in the control groups was required. Efficacy was assessed in the intention-to-treat population and safety according to the treatment started within randomised allocation. STAMPEDE is registered with ClinicalTrials.gov, NCT00268476, and with the ISRCTN registry, ISRCTN78818544.

Findings: Between Nov 15, 2011, and March 31, 2016, 1974 patients were randomly assigned to treatment. The first trial allocated 455 to the control group and 459 to combination therapy, and the second trial, which included enzalutamide, allocated 533 to the control group and 527 to combination

therapy. Median age across all groups was 68 years (IQR 63–73) and median PSA 34 ng/ml (14·7–47); 774 (39%) of 1974 patients were node positive, and 1684 (85%) were planned to receive radiotherapy. With median follow-up of 72 months (60–84), there were 180 metastasis-free survival events in the combination-therapy groups and 306 in the control groups. Metastasis-free survival was significantly longer in the combination-therapy groups (median not reached, IQR not evaluable [NE]–NE) than in the control groups (not reached, 97–NE; hazard ratio [HR] 0·53, 95% CI 0·44–0·64, p<0·0001). 6-year metastasis-free survival was 82% (95% CI 79–85) in the combination-therapy group and 69% (66–72) in the control group. There was no evidence of a difference in metatasis-free survival when enzalutamide and abiraterone acetate were administered concurrently compared with abiraterone acetate alone (interaction HR 1·02, 0·70–1·50, p=0·91) and no evidence of between-trial heterogeneity (I2 p=0·90). Overall survival (median not reached [IQR NE–NE] in the combination-therapy groups vs not reached [103–NE] in the control groups; HR 0·60, 95% CI 0·48–0·73, p<0·0001), prostate cancer-specific survival (not reached [NE–NE] vs not reached [NE–NE]; 0·49, 0·37–0·65, p<0·0001), biochemical failure-free-survival (not reached [NE–NE] vs 86 months [83–NE]; 0·39, 0·33–0·47, p<0·0001), and progression-free-survival (not reached [NE–NE] vs not reached [103–NE]; 0·44, 0·36–0·54, p<0·0001) were also significantly longer in the combination-therapy groups than in the control groups. Adverse events grade 3 or higher during the first 24 months were, respectively, reported in 169 (37%) of 451 patients and 130 (29%) of 455 patients in the combination-therapy and control groups of the abiraterone trial, respectively, and 298 (58%) of 513 patients and 172 (32%) of 533 patients of the combination-therapy and control groups of the abiraterone and enzalutamide trial, respectively. The two most common events more frequent in the combination-therapy groups were hypertension (abiraterone trial: 23 (5%) in the combination-therapy group and six (1%) in control group; abiraterone and enzalutamide trial: 73 (14%) and eight (2%), respectively) and alanine transaminitis (abiraterone trial: 25 (6%) in the combination-therapy group and one (<1%) in control group; abiraterone and enzalutamide trial: 69 (13%) and four (1%), respectively). Seven grade 5 adverse events were reported: none in the control groups, three in the abiraterone acetate and prednisolone group (one event each of rectal adenocarcinoma, pulmonary haemorrhage, and a respiratory disorder), and four in the abiraterone acetate and prednisolone with enzalutamide group (two events each of septic shock and sudden death).

Interpretation: Among men with high-risk non-metastatic prostate cancer, combination therapy is associated with significantly higher rates of metastasis-free survival compared with ADT alone. Abiraterone acetate with

prednisolone should be considered a new standard treatment for this population.

Funding: Cancer Research UK, UK Medical Research Council, Swiss Group for Clinical Cancer Research, Janssen, and Astellas.

Bowman Simon J, Fox Robert, Dorner Thomas, Mariette Xavier, Hueber Wolfgang. Safety and efficacy of subcutaneous ianalumab (VAY736) in patients with primary Sjogren's syndrome: A randomised, double-blind, placebo-controlled, phase 2b dose-finding trial. *Lancet 2022;* 399(10320): 161-71p.

Abstract:

Background: Sjogren's syndrome is an autoimmune disease characterised by dry eyes and mouth, systemic features, and reduced quality of life. There are no disease-modifying treatments. A new biologic, ianalumab (VAY736), with two modes of suppressing B cells, has previously shown preliminary efficacy. This dose-finding trial aimed to assess the safety and efficacy of different subcutaneous doses of ianalumab in patients with moderate to severe primary Sjogren's syndrome.

Methods: VAY736A2201 was a randomised, parallel, double-blind, placebo-controlled, phase 2b dose-finding study done in 56 centres in 19 countries. Patients aged 18–75 years with primary Sjögren's syndrome with moderate to severe disease activity (European Alliance of Associations for Rheumatology [EULAR] Sjögren's Syndrome Disease Activity Index [ESSDAI] score ≥6) and symptom severity (EULAR Sjögren's Syndrome Patient Reported Index score ≥5) were eligible. Participants were randomly assigned (1:1:1:1) to receive subcutaneous placebo or ianalumab (5 mg, 50 mg, or 300 mg) every 4 weeks for 24 weeks using a secure, online randomisation system. Randomisation was stratified by the ESSDAI score at baseline (≥10 or <10). Study personnel and patients were masked to treatment assignment. The primary outcome was the change in ESSDAI score from baseline to 24 weeks in all randomly assigned patients. Dose-related change in disease activity (ESSDAI) from baseline at week 24 was assessed by multiple comparison procedure with modelling analysis. Safety was measured in all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT02962895.

Findings: Between June 27, 2017, and Dec 06, 2018, 293 patients were screened, 190 of whom were randomly assigned (placebo n=49, ianalumab 5 mg n=47, ianalumab 50 mg n=47, ianalumab 300 mg n=47). Statistically

significant dose-responses were seen for overall disease activity (ESSDAI score) in four of the five dose-response models tested (p<0·025 in four models, p=0·060 in one model). The ESSDAI score decreased from baseline in all ianalumab groups, with the maximal ESSDAI score change from baseline observed in the ianalumab 300 mg group: placebo-adjusted least-squares mean change from baseline −1·92 points (95% CI −4·15 to 0·32; p=0·092). There were four serious adverse events in three patients considered treatment-related (pneumonia [n=1] and gastroenteritis [n=1] in the placebo group; appendicitis plus tubo-ovarian abscess in the same patient in the ianalumab 50 mg group).

Interpretation: The study met its primary objective, showing a dose-related decrease in disease activity as measured by ESSDAI at week 24. Overall, ianalumab was well tolerated and safe, with no increase in infections. To our knowledge, this is the first large, randomised, controlled trial in primary Sjogren's syndrome that met its primary endpoint, and its results mean there is potential for more studies of this mechanism in the future.

Funding: Novartis.

Bravo Lulu, Smolenov Igor, Han Htay Htay, Li Ping, Clemens Ralf. Efficacy of the adjuvanted subunit protein COVID-19 vaccine, SCB-2019: A phase 2 and 3 multicentre, double-blind, randomised, placebo-controlled trial. *Lancet 2022;* 399(10323): 461-72p.

Abstract:

Background: A range of safe and effective vaccines against SARS CoV 2 are needed to address the COVID 19 pandemic. We aimed to assess the safety and efficacy of the COVID-19 vaccine SCB-2019.

Methods: This ongoing phase 2 and 3 double-blind, placebo-controlled trial was done in adults aged 18 years and older who were in good health or with a stable chronic health condition, at 31 sites in five countries (Belgium, Brazil, Colombia, Philippines, and South Africa). The participants were randomly assigned 1:1 using a centralised internet randomisation system to receive two 0·5 mL intramuscular doses of SCB-2019 (30 µg, adjuvanted with 1·50 mg CpG-1018 and 0·75 mg alum) or placebo (0·9% sodium chloride for injection supplied in 10 mL ampoules) 21 days apart. All study staff and participants were masked, but vaccine administrators were not. Primary endpoints were vaccine efficacy, measured by RT-PCR-confirmed COVID-19 of any severity with onset from 14 days after the second dose in baseline SARS-CoV-2 seronegative participants (the per-protocol

population), and the safety and solicited local and systemic adverse events in the phase 2 subset. This study is registered on EudraCT (2020–004272–17) and ClinicalTrials.gov (NCT04672395).

Findings: 30 174 participants were enrolled from March 24, 2021, until the cutoff date of Aug 10, 2021, of whom 30 128 received their first assigned vaccine (n=15 064) or a placebo injection (n=15 064). The per-protocol population consisted of 12 355 baseline SARS-CoV-2-naive participants (6251 vaccinees and 6104 placebo recipients). Most exclusions (13 389 [44·4%]) were because of seropositivity at baseline. There were 207 confirmed per-protocol cases of COVID-19 at 14 days after the second dose, 52 vaccinees versus 155 placebo recipients, and an overall vaccine efficacy against any severity COVID-19 of 67·2% (95·72% CI 54·3–76·8), 83·7% (97·86% CI 55·9–95·4) against moderate-to-severe COVID-19, and 100% (97·86% CI 25·3–100·0) against severe COVID-19. All COVID-19 cases were due to virus variants; vaccine efficacy against any severity COVID-19 due to the three predominant variants was 78·7% (95% CI 57·3–90·4) for delta, 91·8% (44·9–99·8) for gamma, and 58·6% (13·3–81·5) for mu. No safety issues emerged in the follow-up period for the efficacy analysis (median of 82 days [IQR 63–103]). The vaccine elicited higher rates of mainly mild-to-moderate injection site pain than the placebo after the first (35·7% [287 of 803] vs 10·3% [81 of 786]) and second (26·9% [189 of 702] vs 7·4% [52 of 699]) doses, but the rates of other solicited local and systemic adverse events were similar between the groups.

Interpretation: Two doses of SCB-2019 vaccine plus CpG and alum provides notable protection against the entire severity spectrum of COVID-19 caused by circulating SAR-CoV-2 viruses, including the predominating delta variant.

Funding: Clover Biopharmaceuticals and the Coalition for Epidemic Preparedness Innovations.

Caeymaex Laurence, Astruc Dominique, Biran Valerie, Marcus Leila, Audureau Etienne. Educational programme in neonatal intensive care units (SEPREVEN): A stepped-wedge, cluster-randomised controlled trial. *Lancet 2022;* 399(10322): 384-92p.

Abstract:

Background: Patients in neonatal intensive care units (NICUs) are at high risk of adverse events. The effects of medical and paramedical education programmes to reduce these have not yet been assessed.

Methods: In this multicentre, stepped-wedge, cluster-randomised controlled trial done in France, we randomly assigned 12 NICUs to three clusters of four units. Eligible neonates were inpatients in a participating unit for at least 2 days, with a postmenstrual age of 42 weeks or less on admission. Each cluster followed a 4-month multifaceted programme including education about root-cause analysis and care bundles. The primary outcome was the rate of adverse events per 1000 patient-days, measured with a retrospective trigger-tool based chart review masked to allocation of randomly selected files. Analyses used mixed-effects Poisson modelling that adjusted for time. This trial is registered with ClinicalTrials.gov, NCT02598609.

Findings: Between Nov 23, 2015, and Nov 2, 2017, event rates were analysed for 3454 patients of these 12 NICUs for 65 830 patient-days. The event rate per 1000 patient-days reduced significantly from the control to the intervention period (33·9 vs 22·6; incidence rate ratio 0·67; 95% CI 0·50–0·88; p=0·0048).

Interpretation: A multiprofessional safety-promoting programme in NICUs reduced the rate of adverse events and severe and preventable adverse events in highly vulnerable patients. This programme could significantly improve care offered to critically ill neonates.

Funding: Solidarity and Health Ministry, France

Children and adolescents deserve a better future. *Lancet 2021;* 399(10320): 117p.

Cramer Holger. Of Gifts and Ghosts: Why Common Authorship Practices in Science Need to Be Reconsidered. *Journal of Integrative and Complementary Medicine 2022;* 28(1): 1-2p.

Demarinis Susie. Modified mosquitoes result in 77% fewer Indonesian dengue cases. *Explore 2022;* 18(1): 3-4p.

Dossey Larry. Coronavirus pandemic. *Explore 2022;* 18(1): 1-2p.

Fumagalli Francesca, Calbi Valeria, Sora Maria Grazia Natali, Sessa Maria, Aiuti Alessandro. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: Long-term

results from a non-randomised, open-label, phase 1/2 trial and expanded access. *Lancet 2022;* 399(10322): 372-83p.

Abstract:

Background: Effective treatment for metachromatic leukodystrophy (MLD) remains a substantial unmet medical need. In this study we investigated the safety and efficacy of atidarsagene autotemcel (arsa-cel) in patients with MLD.

Methods: This study is an integrated analysis of results from a prospective, non-randomised, phase 1/2 clinical study and expanded-access frameworks. 29 paediatric patients with pre-symptomatic or early-symptomatic early-onset MLD with biochemical and molecular confirmation of diagnosis were treated with arsa-cel, a gene therapy containing an autologous haematopoietic stem and progenitor cell (HSPC) population transduced ex vivo with a lentiviral vector encoding human arylsulfatase A (ARSA) cDNA, and compared with an untreated natural history (NHx) cohort of 31 patients with early-onset MLD, matched by age and disease subtype. Patients were treated and followed up at Ospedale San Raffaele, Milan, Italy. The coprimary efficacy endpoints were an improvement of more than 10% in total gross motor function measure score at 2 years after treatment in treated patients compared with controls, and change from baseline of total peripheral blood mononuclear cell (PBMC) ARSA activity at 2 years after treatment compared with values before treatment. This phase 1/2 study is registered with ClinicalTrials.gov, NCT01560182.

Findings: At the time of analyses, 26 patients treated with arsa-cel were alive with median follow-up of 3·16 years (range 0·64–7·51). Two patients died due to disease progression and one due to a sudden event deemed unlikely to be related to treatment. After busulfan conditioning, all arsa-cel treated patients showed sustained multilineage engraftment of genetically modified HSPCs. ARSA activity in PBMCs was significantly increased above baseline 2 years after treatment by a mean 18·7-fold (95% CI 8·3–42·2; p<0·0001) in patients with the late-infantile variant and 5·7-fold (2·6–12·4; p<0·0001) in patients with the early-juvenile variant. Mean differences in total scores for gross motor function measure between treated patients and age-matched and disease subtype-matched NHx patients 2 years after treatment were significant for both patients with late-infantile MLD (66% [95% CI 48·9–82·3]) and early-juvenile MLD (42% [12·3–71·8]). Most treated patients progressively acquired motor skills within the predicted range of healthy children or had stabilised motor performance (maintaining the ability to walk). Further, most displayed normal cognitive development and

prevention or delay of central and peripheral demyelination and brain atrophy throughout follow-up; treatment benefits were particularly apparent in patients treated before symptom onset. The infusion was well tolerated and there was no evidence of abnormal clonal proliferation or replication-competent lentivirus. All patients had at least one grade 3 or higher adverse event; most were related to conditioning or to background disease. The only adverse event related to arsa-cel was the transient development of anti-ARSA antibodies in four patients, which did not affect clinical outcomes.

Interpretation: Treatment with arsa-cel resulted in sustained, clinically relevant benefits in children with early-onset MLD by preserving cognitive function and motor development in most patients, and slowing demyelination and brain atrophy.

Funding: Orchard Therapeutics, Fondazione Telethon, and GlaxoSmithKline.

Halperin Scott A, Ye Lingyun, MacKinnon Cameron Donna, Smith Bruce, Zubkova Tatyana. Final efficacy analysis, interim safety analysis, and immunogenicity of a single dose of recombinant novel coronavirus vaccine (adenovirus type 5 vector) in adults 18 years and older: An international, multicentre, randomised, double-blinded, placebo-controlled phase 3 trial. *Lancet 2022;* 399(10321): 237-48p.

Abstract:

Background: The Ad5-nCoV vaccine is a single-dose adenovirus type 5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike protein that was well-tolerated and immunogenic in phase 1 and 2 studies. In this study, we report results on the final efficacy and interim safety analyses of the phase 3 trial.

Methods: This double-blind, randomised, international, placebo-controlled, endpoint-case driven, phase 3, clinical trial enrolled adults aged 18 years older at study centres in Argentina, Chile, Mexico, Pakistan, and Russia. Participants were eligible for the study if they had no unstable or severe underlying medical or psychiatric conditions; had no history of a laboratory-confirmed SARS-CoV-2 infection; were not pregnant or breastfeeding; and had no previous receipt of an adenovirus-vectored, coronavirus, or SARS-CoV-2 vaccine. After informed consent was obtained, 25 mL of whole blood was withdrawn from all eligible participants who were randomised in a 1:1 ratio to receive a single intramuscular dose of 0·5 mL placebo or a 0·5 mL

dose of 5 × 1010 viral particle (vp)/mL Ad5-nCoV vaccine; study staff and participants were blinded to treatment allocation. All participants were contacted weekly by email, telephone, or text message to self-report any symptoms of COVID-19 illness, and laboratory testing for SARS-CoV-2 was done for all participants with any symptoms. The primary efficacy objective evaluated Ad5-nCoV in preventing symptomatic, PCR-confirmed COVID-19 infection occurring at least 28 days after vaccination in all participants who were at least 28 days postvaccination on Jan 15, 2021. The primary safety objective evaluated the incidence of any serious adverse events or medically attended adverse events postvaccination in all participants who received a study injection. This trial is closed for enrolment and is registered with ClinicalTrials.gov (NCT04526990).

Findings: Study enrolment began on Sept 22, 2020, in Pakistan, Nov 6, 2020, in Mexico, Dec 2, 2020, in Russia and Chile, and Dec 17, 2020, in Argentina; 150 endpoint cases were reached on Jan 15, 2021, triggering the final primary efficacy analysis. One dose of Ad5-nCoV showed a 57·5% (95% CI 39·7–70·0, p=0·0026) efficacy against symptomatic, PCR-confirmed, COVID-19 infection at 28 days or more postvaccination (21 250 participants; 45 days median duration of follow-up [IQR 36–58]). In the primary safety analysis undertaken at the time of the efficacy analysis (36 717 participants), there was no significant difference in the incidence of serious adverse events (14 [0·1%] of 18 363 Ad5-nCoV recipients and 10 [0·1%] of 18 354 placebo recipients, p=0·54) or medically attended adverse events (442 [2·4%] of 18 363 Ad5-nCoV recipients and 411 [2·2%] of 18 354 placebo recipients, p=0·30) between the Ad5-nCoV or placebo groups, or any serious adverse events considered related to the study product (none in both Ad5-nCoV and placebo recipients). In the extended safety cohort, 1004 (63·5%) of 1582 of Ad5-nCoV recipients and 729 (46·4%) of 1572 placebo recipients reported a solicited systemic adverse event (p<0·0001), of which headache was the most common (699 [44%] of Ad5-nCoV recipients and 481 [30·6%] of placebo recipients; p<0·0001). 971 (61·3%) of 1584 Ad5-nCoV recipients and 314 (20·0%) of 1573 placebo recipients reported an injection-site adverse event (p<0·0001), of which pain at the injection site was the most frequent; reported by 939 (59%) Ad5-nCoV recipients and 303 (19%) placebo recipients.

Interpretation: One dose of Ad5-nCoV is efficacious and safe in healthy adults aged 18 years and older.

Funding: CanSino Biologics and the Beijing Institute of Biotechnology.

Hargreaves Dougal, Mates Emily, Menon Purnima, Alderman Harold, Patton George C. Strategies and interventions for healthy adolescent growth, nutrition, and development. ***Lancet 2022;*** **399(10320): 198-210p.**

Abstract:

Adolescence is a pivotal point in the life course, characterised by transformative physical, cognitive, and emotional growth, an openness to change, and a drive to reshape the social environment. It offers unique opportunities to adopt changes in diet and physical activity that can persist into later life. Yet pre-existing nutritional problems, including micronutrient deficiencies, food insecurity, and poor-quality diets, persist at the same time as adolescents face the rapid emergence of an obesity epidemic. Adolescent growth and nutrition has been largely overlooked in intervention and policy research. Most intervention studies have emphasised micronutrient supplementation, with few taking into account the multiple drivers of adolescent diets. This Series paper highlights that effective interventions and policies will need to cut across sectors; be supported by multifaceted and multilevel policy; and extend across education, health, food systems, social protection, and digital media. Better data standardisation and systems will be essential in coordinating and monitoring these responses. In a context of shifts in planetary ecosystems and commercial drivers, resilient food systems will need to both ensure access to healthy and affordable foods and provide the infrastructure and incentives for continuing physical activity. Intergenerational partnerships with young people will be essential in bringing about transformative change and ensuring that food policies reflect their needs and aspirations.

Hicks Scott Rory, O'Dempsey Tim, Khoyratty Fadil, Gupta Abha, Slack Iain. Cause of hypereosinophilia shows itself after 6 years: Loa loa. ***Lancet 2022;*** **399(10323): e2**

Jauhar Sameer, Johnstone Mandy, McKenna Peter J. Schizophrenia. ***Lancet 2022;*** **399(10323): 473-486p.**

Abstract:

Schizophrenia, characterised by psychotic symptoms and in many cases social and occupational decline, remains an aetiological and therapeutic challenge. Contrary to popular belief, the disorder is modestly more common in men than in women. Nor is the outcome uniformly poor. A division of symptoms into positive, negative, and disorganisation syndromes

is supported by factor analysis. Catatonic symptoms are not specific to schizophrenia and so-called first rank symptoms are no longer considered diagnostically important. Cognitive impairment is now recognised as a further clinical feature of the disorder. Lateral ventricular enlargement and brain volume reductions of around 2% are established findings. Brain functional changes occur in different subregions of the frontal cortex and might ultimately be understandable in terms of disturbed interaction among large-scale brain networks. Neurochemical disturbance, involving dopamine function and glutamatergic N-methyl-D-aspartate receptor function, is supported by indirect and direct evidence. The genetic contribution to schizophrenia is now recognised to be largely polygenic. Birth and early life factors also have an important aetiological role. The mainstay of treatment remains dopamine receptor-blocking drugs; a psychological intervention, cognitive behavioural therapy, has relatively small effects on symptoms. The idea that schizophrenia is better regarded as the extreme end of a continuum of psychotic symptoms is currently influential. Other areas of debate include cannabis and childhood adversity as causative factors, whether there is progressive brain change after onset, and the long-term success of early intervention initiatives.

Jones Stacie M, Kim Edwin H, Nadeau Kari C, Nowak-Wegrzyn Anna, Burks A Wesley. Efficacy and safety of oral immunotherapy in children aged 1–3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): A randomised placebo-controlled study. *Lancet 2022;* 399(10322): 359-71p.

Abstract:

Background: For young children with peanut allergy, dietary avoidance is the current standard of care. We aimed to assess whether peanut oral immunotherapy can induce desensitisation (an increased allergic reaction threshold while on therapy) or remission (a state of non-responsiveness after discontinuation of immunotherapy) in this population.

Methods: We did a randomised, double-blind, placebo-controlled study in five US academic medical centres. Eligible participants were children aged 12 to younger than 48 months who were reactive to 500 mg or less of peanut protein during a double-blind, placebo-controlled food challenge (DBPCFC). Participants were randomly assigned by use of a computer, in a 2:1 allocation ratio, to receive peanut oral immunotherapy or placebo for 134 weeks (2000 mg peanut protein per day) followed by 26 weeks of avoidance, with participants and study staff and investigators masked to group treatment assignment. The primary outcome was desensitisation at the end

of treatment (week 134), and remission after avoidance (week 160), as the key secondary outcome, were assessed by DBPCFC to 5000 mg in the intention-to-treat population. Safety and immunological parameters were assessed in the same population. This trial is registered on ClinicalTrials.gov, NCT03345160.

Findings: Between Aug 13, 2013, and Oct 1, 2015, 146 children, with a median age of 39·3 months (IQR 30·8–44·7), were randomly assigned to receive peanut oral immunotherapy (96 participants) or placebo (50 participants). At week 134, 68 (71%, 95% CI 61–80) of 96 participants who received peanut oral immunotherapy compared with one (2%, 0·05–11) of 50 who received placebo met the primary outcome of desensitisation (risk difference [RD] 69%, 95% CI 59–79; p<0·0001). The median cumulative tolerated dose during the week 134 DBPCFC was 5005 mg (IQR 3755–5005) for peanut oral immunotherapy versus 5 mg (0–105) for placebo (p<0·0001). After avoidance, 20 (21%, 95% CI 13–30) of 96 participants receiving peanut oral immunotherapy compared with one (2%, 0·05–11) of 50 receiving placebo met remission criteria (RD 19%, 95% CI 10–28; p=0·0021). The median cumulative tolerated dose during the week 160 DBPCFC was 755 mg (IQR 0–2755) for peanut oral immunotherapy and 0 mg (0–55) for placebo (p<0·0001). A significant proportion of participants receiving peanut oral immunotherapy who passed the 5000 mg DBPCFC at week 134 could no longer tolerate 5000 mg at week 160 (p<0·001). The participant receiving placebo who was desensitised at week 134 also achieved remission at week 160. Compared with placebo, peanut oral immunotherapy decreased peanut-specific and Ara h2-specific IgE, skin prick test, and basophil activation, and increased peanut-specific and Ara h2-specific IgG4 at weeks 134 and 160. By use of multivariable regression analysis of participants receiving peanut oral immunotherapy, younger age and lower baseline peanut-specific IgE was predictive of remission. Most participants (98% with peanut oral immunotherapy vs 80% with placebo) had at least one oral immunotherapy dosing reaction, predominantly mild to moderate and occurring more frequently in participants receiving peanut oral immunotherapy. 35 oral immunotherapy dosing events with moderate symptoms were treated with epinephrine in 21 participants receiving peanut oral immunotherapy.

Interpretation: In children with a peanut allergy, initiation of peanut oral immunotherapy before age 4 years was associated with an increase in both desensitisation and remission. Development of remission correlated with immunological biomarkers. The outcomes suggest a window of opportunity at a young age for intervention to induce remission of peanut allergy.

Funding: National Institute of Allergy and Infectious Disease, Immune Tolerance Network.

Jovin Tudor G, Nogueira Raul G, Lansberg Maarten G, Demchuk Andrew M, Albers Gregory W. Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA): A systematic review and individual patient data meta-analysis. ***Lancet 2022;*** **399(10321): 249-58p.**

Abstract:

Background: Trials examining the benefit of thrombectomy in anterior circulation proximal large vessel occlusion stroke have enrolled patients considered to have salvageable brain tissue, who were randomly assigned beyond 6 h and (depending on study protocol) up to 24 h from time last seen well. We aimed to estimate the benefit of thrombectomy overall and in prespecified subgroups through individual patient data meta-analysis.

Methods: We did a systematic review and individual patient data meta-analysis between Jan 1, 2010, and March 1, 2021, of randomised controlled trials of endovascular stroke therapy. In the Analysis of Pooled Data From Randomized Studies Of Thrombectomy More Than 6 Hours After Last Known Well (AURORA) collaboration, the primary outcome was disability on the modified Rankin Scale (mRS) at 90 days, analysed by ordinal logistic regression. Key safety outcomes were symptomatic intracerebral haemorrhage and mortality within 90 days.

Findings: Patient level data from 505 individuals (n=266 intervention, n=239 control; mean age 68·6 years [SD 13·7], 259 [51·3%] women) were included from six trials that met inclusion criteria of 17 screened published randomised trials. Primary outcome analysis showed a benefit of thrombectomy with an unadjusted common odds ratio (OR) of 2·42 (95% CI 1·76–3·33; p<0·0001) and an adjusted common OR (for age, gender, baseline stroke severity, extent of infarction on baseline head CT, and time from onset to random assignment) of 2·54 (1·83–3·54; p<0·0001). Thrombectomy was associated with higher rates of independence in activities of daily living (mRS 0–2) than best medical therapy alone (122 [45·9%] of 266 vs 46 [19·3%] of 238; p<0·0001). No significant difference between intervention and control groups was found when analysing either 90-day mortality (44 [16·5%] of 266 vs 46 [19·3%] of 238) or symptomatic intracerebral haemorrhage (14 [5·3%] of 266 vs eight [3·3%] of 239). No heterogeneity of treatment effect was noted across subgroups defined by age, gender, baseline stroke severity, vessel occlusion site, baseline Alberta Stroke

Program Early CT Score, and mode of presentation; treatment effect was stronger in patients randomly assigned within 12–24 h (common OR 5·86 [95% CI 3·14–10·94]) than those randomly assigned within 6–12 h (1·76 [1·18–2·62]; pinteraction=0·0087).

Interpretation: These findings strengthen the evidence for benefit of endovascular thrombectomy in patients with evidence of reversible cerebral ischaemia across the 6–24 h time window and are relevant to clinical practice. Our findings suggest that in these patients, thrombectomy should not be withheld on the basis of mode of presentation or of the point in time of presentation within the 6–24 h time window.

Funding: Stryker Neurovascular.

Kamoi Koju, Uchimaru Kaoru, Tojo Arinobu, Watanabe Toshiki, Ohno Matsui Kyoko. HTLV-1 uveitis and Graves' disease presenting with sudden onset of blurred vision. ***Lancet 2022;*** **399(10319): 60p.**

Karlsen Tom H, Sheron Nick, Zelber Sagi Shira, Carrieri Patrizia, Manns Michael P. EASL–Lancet Liver Commission: Protecting the next generation of Europeans against liver disease complications and premature mortality. ***Lancet 2022;*** **399(10319): 61-116p.**

Katikireddi Srinivasa Vittal, Cerqueira Silva Thiago, Vasileiou Eleftheria, Robertson Chris, Sheikh Aziz. Two-dose ChAdOx1 nCoV-19 vaccine protection against COVID-19 hospital admissions and deaths over time: A retrospective, population-based cohort study in Scotland and Brazil. ***Lancet 2022;*** **399(10319): 25-35p.**

Abstract:

Background: Reports suggest that COVID-19 vaccine effectiveness is decreasing, but whether this reflects waning or new SARS-CoV-2 variants—especially delta (B.1.617.2)—is unclear. We investigated the association between time since two doses of ChAdOx1 nCoV-19 vaccine and risk of severe COVID-19 outcomes in Scotland (where delta was dominant), with comparative analyses in Brazil (where delta was uncommon).

Methods: In this retrospective, population-based cohort study in Brazil and Scotland, we linked national databases from the EAVE II study in Scotland; and the COVID-19 Vaccination Campaign, Acute Respiratory Infection Suspected Cases, and Severe Acute Respiratory Infection/Illness datasets in Brazil) for vaccination, laboratory testing, clinical, and mortality data. We

defined cohorts of adults (aged ≥18 years) who received two doses of ChAdOx1 nCoV-19 and compared rates of severe COVID-19 outcomes (ie, COVID-19 hospital admission or death) across fortnightly periods, relative to 2–3 weeks after the second dose. Entry to the Scotland cohort started from May 19, 2021, and entry to the Brazil cohort started from Jan 18, 2021. Follow-up in both cohorts was until Oct 25, 2021. Poisson regression was used to estimate rate ratios (RRs) and vaccine effectiveness, with 95% CIs.

Findings: 1 972 454 adults received two doses of ChAdOx1 nCoV-19 in Scotland and 42 558 839 in Brazil, with longer follow-up in Scotland because two-dose vaccination began earlier in Scotland than in Brazil. In Scotland, RRs for severe COVID-19 increased to 2·01 (95% CI 1·54–2·62) at 10–11 weeks, 3·01 (2·26–3·99) at 14–15 weeks, and 5·43 (4·00–7·38) at 18–19 weeks after the second dose. The pattern of results was similar in Brazil, with RRs of 2·29 (2·01–2·61) at 10–11 weeks, 3·10 (2·63–3·64) at 14–15 weeks, and 4·71 (3·83–5·78) at 18–19 weeks after the second dose. In Scotland, vaccine effectiveness decreased from 83·7% (95% CI 79·7–87·0) at 2–3 weeks, to 75·9% (72·9–78·6) at 14–15 weeks, and 63·7% (59·6–67·4) at 18–19 weeks after the second dose. In Brazil, vaccine effectiveness decreased from 86·4% (85·4–87·3) at 2–3 weeks, to 59·7% (54·6–64·2) at 14–15 weeks, and 42·2% (32·4–50·6) at 18–19 weeks.

Interpretation: We found waning vaccine protection of ChAdOx1 nCoV-19 against COVID-19 hospital admissions and deaths in both Scotland and Brazil, this becoming evident within three months of the second vaccine dose. Consideration needs to be given to providing booster vaccine doses for people who have received ChAdOx1 nCoV-19.

Funding: UK Research and Innovation (Medical Research Council), Scottish Government, Research and Innovation Industrial Strategy Challenge Fund, Health Data Research UK, Fiocruz, Fazer o Bem Faz Bem Programme; Conselho Nacional de Desenvolvimento Científico e Tecnológico, Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro.

Translation: For the Portuguese translation of the abstract see Supplementary Materials section.

Lingvay Ildiko, Sumithran Priya, Cohen Ricardo V, Roux Carel W le. Obesity management as a primary treatment goal for type 2 diabetes: Time to reframe the conversation. *Lancet 2022;* 399(10322): 394-405p.

Abstract:

Obesity is now recognised as a disease that is associated with serious morbidity and increased mortality. One of its main metabolic complications is type 2 diabetes, as the two conditions share key pathophysiological mechanisms. Weight loss is known to reverse the underlying metabolic abnormalities of type 2 diabetes and, as such, improve glucose control; loss of 15% or more of bodyweight can have a disease-modifying effect in people with type 2 diabetes, an outcome that is not attainable by any other glucose-lowering intervention. Furthermore, weight loss in this population exerts benefits that extend beyond glycaemic control to improve risk factors for cardiometabolic disease and quality of life. We review the evidence supporting the role of weight loss in the management of type 2 diabetes and propose that many patients with type 2 diabetes would benefit from having a primary weight-centric approach to diabetes treatment. We discuss the logistical challenges to implementing a new weight-centric primary treatment goal in people with type 2 diabetes.

Lord Catherine, Charman Tony, Havdahl Alexandra, Carbone Paul, McCauley James B. The Lancet Commission on the future of care and clinical research in autism. ***Lancet 2022;*** **399(10321): 271-334p.**

McCall Chris. Disrupted care in Papua New Guinea: the harms of COVID-19. ***Lancet 2022;*** **399(10321): 226-27p.**

McIntyre Peter B, Aggarwal Rakesh, Jani Ilesh, Jaleela Jawad, Cravioto Alejandro. COVID-19 vaccine strategies must focus on severe disease and global equity. ***Lancet 2022;*** **399(10322): 406-410p.**

McNamara Lucy A, Wiegand Ryan E, Burke Rachel M, Sharma Andrea J, Schrag Stephanie J. Estimating the early impact of the US COVID-19 vaccination programme on COVID-19 cases, emergency department visits, hospital admissions, and deaths among adults aged 65 years and older: an ecological analysis of national surveillance data. ***Lancet 2022;*** **399(10320): 152-60p.**

Abstract:

Background: In the USA, COVID-19 vaccines became available in mid-December, 2020, with adults aged 65 years and older among the first groups prioritised for vaccination. We estimated the national-level impact of the initial phases of the US COVID-19 vaccination programme on COVID-19

cases, emergency department visits, hospital admissions, and deaths among adults aged 65 years and older.

Methods: We analysed population-based data reported to US federal agencies on COVID-19 cases, emergency department visits, hospital admissions, and deaths among adults aged 50 years and older during the period Nov 1, 2020, to April 10, 2021. We calculated the relative change in incidence among older age groups compared with a younger reference group for pre-vaccination and post-vaccination periods, defined by the week when vaccination coverage in a given age group first exceeded coverage in the reference age group by at least 1%; time lags for immune response and time to outcome were incorporated. We assessed whether the ratio of these relative changes differed when comparing the pre-vaccination and post-vaccination periods.

Findings: The ratio of relative changes comparing the change in the COVID-19 case incidence ratio over the post-vaccine versus pre-vaccine periods showed relative decreases of 53% (95% CI 50 to 55) and 62% (59 to 64) among adults aged 65 to 74 years and 75 years and older, respectively, compared with those aged 50 to 64 years. We found similar results for emergency department visits with relative decreases of 61% (52 to 68) for adults aged 65 to 74 years and 77% (71 to 78) for those aged 75 years and older compared with adults aged 50 to 64 years. Hospital admissions declined by 39% (29 to 48) among those aged 60 to 69 years, 60% (54 to 66) among those aged 70 to 79 years, and 68% (62 to 73), among those aged 80 years and older, compared with adults aged 50 to 59 years. COVID-19 deaths also declined (by 41%, 95% CI –14 to 69 among adults aged 65–74 years and by 30%, –47 to 66 among those aged ≥75 years, compared with adults aged 50 to 64 years), but the magnitude of the impact of vaccination roll-out on deaths was unclear.

Interpretation: The initial roll-out of the US COVID-19 vaccination programme was associated with reductions in COVID-19 cases, emergency department visits, and hospital admissions among older adults.

Funding: None.

Moon Suerie, Armstrong Jana, Hutler Brian, Upshur Ross, Wolff Jonathan. Governing the Access to COVID-19 Tools Accelerator: Towards greater participation, transparency, and accountability. ***Lancet 2022;*** **399(10323): 487-94p.**

Abstract:

The Access to COVID-19 Tools Accelerator (ACT-A) is a multistakeholder initiative quickly constructed in the early months of the COVID-19 pandemic to respond to a catastrophic breakdown in global cooperation. ACT-A is now the largest international effort to achieve equitable access to COVID-19 health technologies, and its governance is a matter of broad public importance. We traced the evolution of ACT-A's governance through publicly available documents and analysed it against three principles embedded in the founding mission statement of ACT-A: participation, transparency, and accountability. We found three challenges to realising these principles. First, the roles of the various organisations in ACT-A decision making are unclear, obscuring who might be accountable to whom and for what. Second, the absence of a clearly defined decision making body; ACT-A instead has multiple centres of legally binding decision making and uneven arrangements for information transparency, inhibiting meaningful participation. Third, the nearly indiscernible role of governments in ACT-A, raising key questions about political legitimacy and channels for public accountability. With global public health and billions in public funding at stake, short-term improvements to governance arrangements can and should now be made. Efforts to strengthen pandemic preparedness for the future require attention to ethical, legitimate arrangements for governance.

Neglected tropical diseases: Ending the neglect of populations. *Lancet 2021;* 399(10323): 411p.

Neufeld Lynnette M, Andrade Eduardo B, Suleiman Ahna Ballonoff, Barker Mary, Zou Zhiyong. Food choice in transition: Adolescent autonomy, agency, and the food environment. *Lancet 2022;* 399(10320): 185-97p.

Abstract:

Dietary intake during adolescence sets the foundation for a healthy life, but adolescents are diverse in their dietary patterns and in factors that influence food choice. More evidence to understand the key diet-related issues and the meaning and context of food choices for adolescents is needed to increase the potential for impactful actions. The aim of this second Series paper is to elevate the importance given to adolescent dietary intake and food choice, bringing a developmental perspective to inform policy and programmatic actions to improve diets. We describe patterns of dietary intake, then draw on existing literature to map how food choice can be influenced by unique features of adolescent development. Pooled qualitative

data is then combined with evidence from the literature to explore ways in which adolescent development can interact with sociocultural context and the food environment to influence food choice. Irrespective of context, adolescents have a lot to say about why they eat what they eat, and insights into factors that might motivate them to change. Adolescents must be active partners in shaping local and global actions that support healthy eating patterns. Efforts to improve food environments and ultimately adolescent food choice should harness widely shared adolescent values beyond nutrition or health.

Norris Shane A, Frongillo Edward A, Black Maureen M, Dong Yanhui, Patton George C. Nutrition in adolescent growth and development. *Lancet 2022;* 399(10320): 172-84p.

Abstract:

During adolescence, growth and development are transformative and have profound consequences on an individual's health in later life, as well as the health of any potential children. The current generation of adolescents is growing up at a time of unprecedented change in food environments, whereby nutritional problems of micronutrient deficiency and food insecurity persist, and overweight and obesity are burgeoning. In a context of pervasive policy neglect, research on nutrition during adolescence specifically has been underinvested, compared with such research in other age groups, which has inhibited the development of adolescent-responsive nutritional policies. One consequence has been the absence of an integrated perspective on adolescent growth and development, and the role that nutrition plays. Through late childhood and early adolescence, nutrition has a formative role in the timing and pattern of puberty, with consequences for adult height, muscle, and fat mass accrual, as well as risk of non-communicable diseases in later life. Nutritional effects in adolescent development extend beyond musculoskeletal growth, to cardiorespiratory fitness, neurodevelopment, and immunity. High rates of early adolescent pregnancy in many countries continue to jeopardise the growth and nutrition of female adolescents, with consequences that extend to the next generation. Adolescence is a nutrition-sensitive phase for growth, in which the benefits of good nutrition extend to many other physiological systems.

Ramacciotti Eduardo, Agati Leandro Barile, Calderaro Daniela, Aguiar Valeria Cristina Resende, Santos Marcus Vinicius Barbosa. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): An open-label, multicentre, randomised, controlled trial. *Lancet 2022;* 399(10319): 50-59p.

Abstract:

Background: Patients hospitalised with COVID-19 are at risk for thrombotic events after discharge; the role of extended thromboprophylaxis in this population is unknown.

Methods: In this open-label, multicentre, randomised trial conducted at 14 centres in Brazil, patients hospitalised with COVID-19 at increased risk for venous thromboembolism (International Medical Prevention Registry on Venous Thromboembolism [IMPROVE] venous thromboembolism [VTE] score of ≥4 or 2–3 with a D-dimer >500 ng/mL) were randomly assigned (1:1) to receive, at hospital discharge, rivaroxaban 10 mg/day or no anticoagulation for 35 days. The primary efficacy outcome in an intention-to-treat analysis was a composite of symptomatic or fatal venous thromboembolism, asymptomatic venous thromboembolism on bilateral lower-limb venous ultrasound and CT pulmonary angiogram, symptomatic arterial thromboembolism, and cardiovascular death at day 35. Adjudication was blinded. The primary safety outcome was major bleeding. The primary and safety analyses were carried out in the intention-to-treat population. This trial is registered at ClinicalTrials.gov, NCT04662684.

Findings: From Oct 8, 2020, to June 29, 2021, 997 patients were screened. Of these patients, 677 did not meet eligibility criteria; the remaining 320 patients were enrolled and randomly assigned to receive rivaroxaban (n=160 [50%]) or no anticoagulation (n=160 [50%]). All patients received thromboprophylaxis with standard doses of heparin during hospitalisation. 165 (52%) patients were in the intensive care unit while hospitalised. 197 (62%) patients had an IMPROVE score of 2–3 and elevated D-dimer levels and 121 (38%) had a score of 4 or more. Two patients (one in each group) were lost to follow-up due to withdrawal of consent and not included in the intention-to-treat primary analysis. The primary efficacy outcome occurred in five (3%) of 159 patients assigned to rivaroxaban and 15 (9%) of 159 patients assigned to no anticoagulation (relative risk 0·33, 95% CI 0·12–0·90; p=0·0293). No major bleeding occurred in either study group. Allergic reactions occurred in two (1%) patients in the rivaroxaban group.

Interpretation: In patients at high risk discharged after hospitalisation due to COVID-19, thromboprophylaxis with rivaroxaban 10 mg/day for 35 days improved clinical outcomes compared with no extended thromboprophylaxis.

Funding: Bayer.

RECOVERY Collaborative Group. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. ***Lancet 2022;*** **399(10320): 143-51p.**

Abstract:

Background: Aspirin has been proposed as a treatment for COVID-19 on the basis of its anti-thrombotic properties. We aimed to evaluate the efficacy and safety of aspirin in patients admitted to hospital with COVID-19.

Methods: In this randomised, controlled, open-label, platform trial, several possible treatments were compared with usual care in patients hospitalised with COVID-19. The trial took place at 177 hospitals in the UK, two hospitals in Indonesia, and two hospitals in Nepal. Eligible and consenting adults were randomly allocated in a 1:1 ratio to either usual standard of care plus 150 mg aspirin once per day until discharge or usual standard of care alone using web-based simple (unstratified) randomisation with allocation concealment. The primary outcome was 28 day mortality. All analyses were done by intention to treat. The trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936).

Findings: Between Nov 1, 2020, and March 21, 2021, 14 892 (66%) of 22 560 patients enrolled into the RECOVERY trial were eligible to be randomly allocated to aspirin. 7351 patients were randomly allocated (1:1) to receive aspirin and 7541 patients to receive usual care alone. Overall, 1222 (17%) of 7351 patients allocated to aspirin and 1299 (17%) of 7541 patients allocated to usual care died within 28 days (rate ratio 0·96, 95% CI 0·89–1·04; p=0·35). Consistent results were seen in all prespecified subgroups of patients. Patients allocated to aspirin had a slightly shorter duration of hospitalisation (median 8 days, IQR 5 to >28, vs 9 days, IQR 5 to >28) and a higher proportion were discharged from hospital alive within 28 days (75% vs 74%; rate ratio 1·06, 95% CI 1·02–1·10; p=0·0062). Among patients not on invasive mechanical ventilation at baseline, there was no significant difference in the proportion meeting the composite endpoint of invasive mechanical ventilation or death (21% vs 22%; risk ratio 0·96, 95% CI 0·90–1·03; p=0·23). Aspirin use was associated with a reduction in thrombotic events (4·6% vs 5·3%; absolute reduction 0·6%, SE 0·4%) and an increase in major bleeding events (1·6% vs 1·0%; absolute increase 0·6%, SE 0·2%).

Interpretation: In patients hospitalised with COVID-19, aspirin was not associated with reductions in 28 day mortality or in the risk of progressing

to invasive mechanical ventilation or death, but was associated with a small increase in the rate of being discharged alive within 28 days.

Funding: UK Research and Innovation (Medical Research Council), National Institute of Health Research, and the Wellcome Trust through the COVID-19 Therapeutics Accelerator.

Shi Qingyang, Wang Yang, Hao Qiukui, Vandvik Per Olav, Li Sheyu. Pharmacotherapy for adults with overweight and obesity: A systematic review and network meta-analysis of randomised controlled trials. ***Lancet 2021;*** **399(10322): 259-69p.**

Abstract:

Background: Pharmacotherapy provides an option for adults with overweight and obesity to reduce their bodyweight if lifestyle modifications fail. We summarised the latest evidence for the benefits and harms of weight-lowering drugs.

Methods: This systematic review and network meta-analysis included searches of PubMed, Embase, and Cochrane Library (CENTRAL) from inception to March 23, 2021, for randomised controlled trials of weight-lowering drugs in adults with overweight and obesity. We performed frequentist random-effect network meta-analyses to summarise the evidence and applied the Grading of Recommendations Assessment, Development, and Evaluation frameworks to rate the certainty of evidence, calculate the absolute effects, categorise interventions, and present the findings. The study was registered with PROSPERO, CRD 42021245678.

Findings: 14 605 citations were identified by our search, of which 143 eligible trials enrolled 49 810 participants. Except for levocarnitine, all drugs lowered bodyweight compared with lifestyle modification alone; all subsequent numbers refer to comparisons with lifestyle modification. High to moderate certainty evidence established phentermine–topiramate as the most effective in lowering weight (odds ratio [OR] of ≥5% weight reduction 8·02, 95% CI 5·24 to 12·27; mean difference [MD] of percentage bodyweight change −7·97, 95% CI −9·28 to −6·66) followed by GLP-1 receptor agonists (OR 6·33, 95% CI 5·00 to 8·00; MD −5·76, 95% CI −6·30 to −5·21). Naltrexone–bupropion (OR 2·69, 95% CI 2·11 to 3·43), phentermine–topiramate (2·40, 1·69 to 3·42), GLP-1 receptor agonists (2·17, 1·71 to 2·77), and orlistat (1·72, 1·44 to 2·05) were associated with increased adverse events leading to drug discontinuation. In a post-hoc analysis, semaglutide, a GLP-1 receptor agonist, showed substantially larger benefits than other

drugs with a similar risk of adverse events as other drugs for both likelihood of weight loss of 5% or more (OR 9·82, 95% CI 7·09 to 13·61) and percentage bodyweight change (MD −11·41, 95% CI −12·54 to −10·27).

Interpretation: In adults with overweight and obesity, phentermine–topiramate and GLP-1 receptor agonists proved the best drugs in reducing weight; of the GLP-1 agonists, semaglutide might be the most effective.

Funding: 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University.

Stuart Arabella S V, Shaw Robert H, Liu Xinxue, Greenland Melanie, Snape Matthew D. Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial. *Lancet 2022;* 399(10319): 36-49p.

Abstract:

Background: Given the importance of flexible use of different COVID-19 vaccines within the same schedule to facilitate rapid deployment, we studied mixed priming schedules incorporating an adenoviral-vectored vaccine (ChAdOx1 nCoV-19 [ChAd], AstraZeneca), two mRNA vaccines (BNT162b2 [BNT], Pfizer–BioNTech, and mRNA-1273 [m1273], Moderna) and a nanoparticle vaccine containing SARS-CoV-2 spike glycoprotein and Matrix-M adjuvant (NVX-CoV2373 [NVX], Novavax).

Methods: Com-COV2 is a single-blind, randomised, non-inferiority trial in which adults aged 50 years and older, previously immunised with a single dose of ChAd or BNT in the community, were randomly assigned (in random blocks of three and six) within these cohorts in a 1:1:1 ratio to receive a second dose intramuscularly (8–12 weeks after the first dose) with the homologous vaccine, m1273, or NVX. The primary endpoint was the geometric mean ratio (GMR) of serum SARS-CoV-2 anti-spike IgG concentrations measured by ELISA in heterologous versus homologous schedules at 28 days after the second dose, with a non-inferiority criterion of the GMR above 0·63 for the one-sided 98·75% CI. The primary analysis was on the per-protocol population, who were seronegative at baseline. Safety analyses were done for all participants who received a dose of study vaccine. The trial is registered with ISRCTN, number 27841311.

Findings: Between April 19 and May 14, 2021, 1072 participants were enrolled at a median of 9·4 weeks after receipt of a single dose of ChAd (n=540, 47% female) or BNT (n=532, 40% female). In ChAd-primed participants, geometric mean concentration (GMC) 28 days after a boost of SARS-CoV-2 anti-spike IgG in recipients of ChAd/m1273 (20 114 ELISA laboratory units [ELU]/mL [95% CI 18 160 to 22 279]) and ChAd/NVX (5597 ELU/mL [4756 to 6586]) was non-inferior to that of ChAd/ChAd recipients (1971 ELU/mL [1718 to 2262]) with a GMR of 10·2 (one-sided 98·75% CI 8·4 to ∞) for ChAd/m1273 and 2·8 (2·2 to ∞) for ChAd/NVX, compared with ChAd/ChAd. In BNT-primed participants, non-inferiority was shown for BNT/m1273 (GMC 22 978 ELU/mL [95% CI 20 597 to 25 636]) but not for BNT/NVX (8874 ELU/mL [7391 to 10 654]), compared with BNT/BNT (16 929 ELU/mL [15 025 to 19 075]) with a GMR of 1·3 (one-sided 98·75% CI 1·1 to ∞) for BNT/m1273 and 0·5 (0·4 to ∞) for BNT/NVX, compared with BNT/BNT; however, NVX still induced an 18-fold rise in GMC 28 days after vaccination. There were 15 serious adverse events, none considered related to immunisation.

Interpretation: Heterologous second dosing with m1273, but not NVX, increased transient systemic reactogenicity compared with homologous schedules. Multiple vaccines are appropriate to complete primary immunisation following priming with BNT or ChAd, facilitating rapid vaccine deployment globally and supporting recognition of such schedules for vaccine certification.

Funding: UK Vaccine Task Force, Coalition for Epidemic Preparedness Innovations (CEPI), and National Institute for Health Research. NVX vaccine was supplied for use in the trial by Novavax.

Theranos and the scientific community: At the bleeding edge. *Lancet 2022;* 399(10321): 211p.

Valaiyapathi Rajalakshmi, Wu Meng-San, McGregor Alastair. Ground glass opacities are not always COVID-19: A case of acute eosinophilic pneumonitis caused by daptomycin. *Lancet 2022;* 399(10321): 270p.

Wolter Nicole, Jassat Waasila, Walaza Sibongile, Welch Richard, Cohen Cheryl. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: A data linkage study. *Lancet 2022;* 399(10323): 437-46p.

Abstract:

Background: The SARS-CoV-2 omicron variant of concern was identified in South Africa in November, 2021, and was associated with an increase in COVID-19 cases. We aimed to assess the clinical severity of infections with the omicron variant using S gene target failure (SGTF) on the Thermo Fisher Scientific TaqPath COVID-19 PCR test as a proxy.

Methods: We did data linkages for national, South African COVID-19 case data, SARS-CoV-2 laboratory test data, SARS-CoV-2 genome data, and COVID-19 hospital admissions data. For individuals diagnosed with COVID-19 via TaqPath PCR tests, infections were designated as either SGTF or non-SGTF. The delta variant was identified by genome sequencing. Using multivariable logistic regression models, we assessed disease severity and hospitalisations by comparing individuals with SGTF versus non-SGTF infections diagnosed between Oct 1 and Nov 30, 2021, and we further assessed disease severity by comparing SGTF-infected individuals diagnosed between Oct 1 and Nov 30, 2021, with delta variant-infected individuals diagnosed between April 1 and Nov 9, 2021.

Findings: From Oct 1 (week 39), 2021, to Dec 6 (week 49), 2021, 161 328 cases of COVID-19 were reported in South Africa. 38 282 people were diagnosed via TaqPath PCR tests and 29 721 SGTF infections and 1412 non-SGTF infections were identified. The proportion of SGTF infections increased from two (3·2%) of 63 in week 39 to 21 978 (97·9%) of 22 455 in week 48. After controlling for factors associated with hospitalisation, individuals with SGTF infections had significantly lower odds of admission than did those with non-SGTF infections (256 [2·4%] of 10 547 vs 121 [12·8%] of 948; adjusted odds ratio [aOR] 0·2, 95% CI 0·1–0·3). After controlling for factors associated with disease severity, the odds of severe disease were similar between hospitalised individuals with SGTF versus non-SGTF infections (42 [21%] of 204 vs 45 [40%] of 113; aOR 0·7, 95% CI 0·3–1·4). Compared with individuals with earlier delta variant infections, SGTF-infected individuals had a significantly lower odds of severe disease (496 [62·5%] of 793 vs 57 [23·4%] of 244; aOR 0·3, 95% CI 0·2–0·5), after controlling for factors associated with disease severity.

Interpretation: Our early analyses suggest a significantly reduced odds of hospitalisation among individuals with SGTF versus non-SGTF infections diagnosed during the same time period. SGTF-infected individuals had a significantly reduced odds of severe disease compared with individuals infected earlier with the delta variant. Some of this reduced severity is probably a result of previous immunity.

Funding: The South African Medical Research Council, the South African National Department of Health, US Centers for Disease Control and Prevention, the African Society of Laboratory Medicine, Africa Centers for Disease Control and Prevention, the Bill & Melinda Gates Foundation, the Wellcome Trust, and the Fleming Fund.