Moving light–dark exposure could reduce disruption faced by night shift workers

New research aims to understand the relationship between light exposure and how an individual's circadian rhythm is affected across a transition from day to night shift schedules (Stone et al, 2018).

This study was led by the Cooperative Research Centre for Alertness, Safety and Productivity and saw 21 participants (nursing and medical staff) recruited from an intensive care unit at a major hospital in Melbourne, Australia. Staff members were enrolled into the study when working a schedule of day or evening shifts, or days off, followed by at least 3 or 4 consecutive night shifts.

Professor Shantha Rajaratnam, Professor, Deputy Head of School, Monash Institute of Cognitive and Clinical Neurosciences, School of Psychological Sciences, Monash University, Victoria, Australia

To examine how the sleep–wake cycle responds to the shift schedule, the timing of the brain clock was measured on the day schedule, and at the end of the night shifts by monitoring urinary concentration of the major metabolite of melatonin. Individual light exposure was measured using wrist actigraphs, worn for the duration of the study.

This study demonstrated significant inter-individual variability in the direction and magnitude of circadian phase shift in response to multiple consecutive night shifts in nursing and medical staff working rotating shift schedules in the intensive care unit. No participants met the criteria for partial adaptation to night work after three or four consecutive night shifts.

The results showed that this variability can largely be explained by individual differences in the amount of light exposure in key phase shifting times, predicted by the human phase response curve to light.

The researchers found that 71% of the observed variability in the phase shift response to night shift work can be explained by a combination of the distribution of light exposure relative to individual circadian phase and diurnal preference. Using these variables, they were able to predict the magnitude of phase shift to within ±60 minutes in 85% of individuals (which is substantial given the 6.5 hour range in phase shifts observed). These findings support the concept that differences in light exposure relative to circadian phase strongly contribute to inter-individual variability in circadian response to night shift work.

The researchers found that the extent to which an individual is a 'morning' or 'evening' type (their diurnal preference) affects how the body responds. A personalised approach to managing these issues, with light–dark exposure scheduled and taking diurnal preferences into account, could reduce the increased risk of health problems in shift workers.

Professor Shantha Rajaratnam, from the Monash Institute of Cognitive and Clinical Neurosciences, Monash University, Victoria, Australia and the Cooperative Research Centre for Alertness, Safety and Productivity, corresponding author for the study, said: 'We know that night time shift workers are more likely to suffer health problems as a result of disruption of their circadian clock, and the mismatch between the timing of the clock and their sleep–wake cycle. This research is important because if we can realign a person's clock to fit their shift pattern, then they will sleep better and this may result in improved health, safety and productivity.

He added: 'These results will drive development of personalised approaches to improve sleep–wake cycles of shift workers and other vulnerable people, and could potentially reduce the increased risk of disease caused by circadian disruption.'

Stone JE, Sletten TL, Magee M et al (2018) Temporal dynamics of circadian phase shifting response to consecutive night shifts in healthcare workers: role of light-dark exposure. *J Physiol* https://doi.org/10.1113/JP275589

Updated guidelines for diagnosing and managing syncope

The European Society of Cardiology 2018 guidelines on syncope (https://doi.org/10.1093/eurheartj/ehy037) also include a supplementary data document giving further explanation on specific points and practical instructions. Advice is given on how to evaluate patients with loss of consciousness and how to perform and interpret tests properly; tracings, videos, flow charts and checklists are provided.

While the full text is mainly intended to give formal evidence-based recommendations, the supplementary data document allows expansion of the content to practical issues and aims to fill the gap between the best available scientific evidence and the need for dissemination of these concepts into clinical practice.

Estimating tuberculosis mortality accurately in England and Wales

Accurate estimates of tuberculosis mortality are required to monitor progress towards the World Health Organization goal of reducing tuberculosis deaths by 95% by 2035. Tuberculosis death data were compared for England and Wales from the national surveillance system (Enhanced Tuberculosis Surveillance System) and the vital registration system from the Office for National Statistics (https://doi.org/10.5588/ijtld.17.0695).

Tuberculosis cases notified in Enhanced Tuberculosis Surveillance System were matched to deaths in Office for National Statistics data. Deaths were stratified into active tuberculosis, tuberculosis sequelae, incidental deaths and not tuberculosis.

Between 2005 and 2015, deaths from tuberculosis recorded in the Enhanced Tuberculosis Surveillance System and Office for National Statistics data differed substantially. Almost one third of tuberculosis deaths recorded by Office for National Statistics were not the result of active tuberculosis; this can be amended through coding changes.

Socioeconomic disadvantages reduce physical function in old age

A global study of over 109 000 people found that 60-year-old individuals living in disadvantaged socioeconomic conditions lost up to 7 years of good physical function – more than those lost as a result of hypertension or smoking tobacco (https://doi.org/10.1136/bmj.k1046).

Detecting diminished dopaminergic cells in the brain could reveal earliest signs of Alzheimer's disease

A loss of dopaminergic cells may cause the ventral tegmental area (responsible for forming new memories) to function less effectively (https://doi.org/10.3233/JAD-171018). This could revolutionize screening for early signs of Alzheimer's disease, changing the way brain scans are acquired and interpreted as well as allowing use of different memory tests.

More than half of heart patients continue smoking after hospitalization

More than half of patients continue smoking and nearly half of obese patients have no plans to lose weight according to results of the EUROASPIRE V survey. The survey examined cardiovascular risk factors in 8261 patients with established coronary heart disease from 27 countries who had been hospitalized for coronary revascularization or an acute coronary event.

Tiny differences in patient's position for radiotherapy treatments could increase survival chances

Very small differences in the way a patient lies during radiotherapy treatment for lung or oesophageal cancer can have an impact on how likely they are to survive, according to research presented at the ESTRO 37 conference (Johnson et al, 2018).

Corinne Johnson, a medical physics PhD student at the Manchester Cancer Research Centre, part of the Christie NHS Foundation Trust and the University of Manchester, Manchester and her colleagues studied a group of 780 patients with non-small cell lung cancer who were treated with radiotherapy. For each treatment, patients were positioned on the treatment machine and an image was taken to confirm that they were lying within 5 mm of their original position. The data from these images were used to gauge how accurately the radiotherapy dose was delivered over the course of treatment, and whether it was shifted slightly closer or slightly further away from the patient's heart.

Comparing these data with how likely patients were to survive, they found that patients with slight shifts towards their hearts were around 30% more likely to die than those with similar-sized shifts away from their hearts.

Corinne Johnson, PhD Student, Manchester Cancer Research Centre, Manchester

When the research was repeated in 177 patients with oesophageal cancer, they found an even greater difference of around 50%. In both groups the pattern of survival remained even when other factors such as the patient's age were taken into account.

These differences of only a few millimetres can mean that the radiation treatment designed to target patients' tumours can move fractionally closer to the heart, where it can cause unintentional damage and reduce survival chances.

The findings suggest that survival could be improved by tightening up treatment guidelines to ensure patients are positioned more accurately.

Johnson C, Price G, Faivre-Finn C, van Herk M (2018) Residual setup errors after IGRT are linked to overall survival in lung and oesophageal cancers. Abstract no E37-0608. ESTRO, Barcelona, Spain: 20–24 April

Gastrointestinal events in patients with arthritis treated with non-steroidal anti-inflammatory drugs

A randomized, double-blind controlled trial analysed 24 081 patients (https://doi.org/10.1111/apt.14610), evaluating the gastrointestinal safety of celecoxib compared with ibuprofen or naproxen as a secondary objective of a trial looking at multiorgan safety.

Patients with osteoarthritis or rheumatoid arthritis, needing ongoing treatment with non-steroidal anti-inflammatory drugs, were randomized to receive celecoxib 100–200 mg twice daily, ibuprofen 600–800 mg three times daily or naproxen 375–500 mg twice daily plus esomeprazole, and low-dose aspirin or corticosteroids if already prescribed.

Clinically significant gastrointestinal events (bleeding, obstruction, perforation events from the stomach downwards or symptomatic ulcers) and iron deficiency anaemia were adjudicated blindly. Mean treatment and follow-up durations were 20.3 and 34.1 months.

While on treatment or 30 days after, gastrointestinal events occurred in 0.34%, 0.74% and 0.66% taking celecoxib, ibuprofen and naproxen. There was less iron deficiency anaemia in patients taking celecoxib. Even taken with low-dose aspirin, fewer gastrointestinal events occurred in those taking celecoxib than those taking ibuprofen, and less iron deficiency anaemia *vs* naproxen. *Helicobacter pylori* serological status had no influence.

Arthritis patients taking non-steroidal anti-inflammatory drugs plus esomeprazole have infrequent clinically significant gastrointestinal events. Co-prescribed with esomeprazole, celecoxib has better overall gastrointestinal safety than ibuprofen or naproxen at these doses, despite treatment with low-dose aspirin or corticosteroids.

Brief exposure to tiny air pollution particles triggers childhood lung infections

A team of American researchers has studied the association between ambient levels of fine particulate matter ($PM_{2.5}$) and health-care encounters for acute lower respiratory infection (Horne et al, 2018).

Using an observational case-crossover design, subjects (n=146 397) were studied if they had an acute lower respiratory infection diagnosis and lived in a metropolitan region. Odds ratios for acute lower respiratory infection health-care encounters were calculated after stratification by ages.

Dr Benjamin Horne, Director of Cardiovascular and Genetic Epidemiology, Intermountain Medical Center Heart Institute, Salt Lake City, Utah

Approximately 77% (n=112 467) of subjects were 0–2 years of age. The odds of acute lower respiratory infection encounter for young children increased within 1 week of elevated $PM_{2.5}$ and peaked after 3 weeks with a cumulative 28-day odds ratio of 1.15 per +10 µg/m^3 (95% confidence interval = 1.12–1.19). Acute lower respiratory infection encounters with diagnosed and laboratory-confirmed respiratory syncytial virus and influenza increased following elevated ambient $PM_{2.5}$ levels. Similar elevated odds for acute lower respiratory infection were also observed for older children, although the number of events and precision of estimates were much lower.

In this large sample of urban/suburban patients, short-term exposure to elevated $PM_{2.5}$ air pollution was associated with greater health-care utilization for acute lower respiratory infection in young children, older children and adults. Further exploration is needed of causal interactions between $PM_{2.5}$ and acute lower respiratory infection.

'The most important finding of this study is that infectious processes of respiratory disease may be influenced by particulate matter pollution at various levels,' emphasized lead author Dr Benjamin Horne, director of cardiovascular and genetic epidemiology at the Intermountain Medical Center Heart Institute in Salt Lake City, Utah.

Horne BD, Joy EA, Hofmann MG et al (2018) Short-term elevation of fine particulate matter air pollution and acute lower respiratory infection. *Am J Respir Crit Care Med* https://doi.org/10.1164/rccm.201709-1883OC

Orbital radiotherapy should not be used to treat thyroid eye disease

The first NHS-led clinical trial for thyroid eye disease, the CIRTED trial (https://doi.org/10.1016/S2213-8587(18)30021-4), has shown that currently widely used, expensive and time-consuming radiotherapy treatment does not help patients with thyroid eye disease who are also given steroids.

However, disease severity was reduced in patients who also received antiproliferative immunosuppressive drugs if they were able to tolerate these medications.

Joint senior author Dr Richard Lee, Consultant Senior Lecturer in the Bristol Medical School and deputy director, NIHR Moorfields Clinical Research Facility, said: 'Our research was jointly published with the MINGO trial (https://doi.org/10.1016/S2213-8587(18)30020-2), which both support the use of antiproliferative immunosuppressive drugs in patients with thyroid eye disease.'

The CIRTED and MINGO trials found that patients with thyroid eye disease treated with steroids would also benefit from an antiproliferative drug, such as mycophenolate, and they should not receive orbital radiotherapy.

Web-based decision aid may help with breast reconstruction decisions

A free web-based decision aid that helps women with breast cancer make decisions regarding reconstructive surgery after mastectomy is likely to be cost-effective (Parkinson et al, 2018).

The Australian study included women diagnosed with breast cancer or ductal carcinoma in situ and who were eligible for breast reconstruction following mastectomy. Of these, 106 accessed BRECONDA (Breast Reconstruction Decision Aid) for 6 months and received usual care and 116 women received usual care only.

Decisional conflict, satisfaction with information, decisional regret, and utilities were assessed by using maximum-likelihood linear mixed effects models. Costs included the fixed costs of BRECONDA, health-care provider time and health-care resource use.

BRECONDA resulted in significantly less decisional conflict and greater satisfaction with information over time. Quality-adjusted life years did not differ between participants who received the decision aid compared with usual care.

The cost of BRECONDA was estimated to be small (10 Australian dollars, or about US$7.40) relative to other health-care interventions, and resulted in decreased health-care costs overall (764 Australian dollars). Based on the point estimates, the decision aid was more effective and less costly for all measures of effectiveness. It was estimated that the decision aid has an 87% probability of being cost-effective.

'BRECONDA provides women considering breast reconstruction with much needed support in this important decision making. This public resource gives comprehensive and reliable information and helps women navigate the maze of breast reconstruction options,' said co-author Professor Kerry Sherman, of Macquarie University.

Parkinson B, Sherman KA, Brown P et al (2018) Cost-effectiveness of the BRECONDA decision aid for women with breast cancer: Results from a randomized controlled trial. *Psychooncology* https://doi.org/110.1002/pon.4698

Genetic scores can predict the risk of children developing type 1 diabetes

An international prospective study set out to determine to what extent genetic scores (two previous genetic scores and a merged genetic score) can improve the prediction of children developing type 1 diabetes (Bonifacio et al, 2018).

Genetically at-risk children were assessed at 3–6-monthly intervals from birth for the development of islet autoantibodies and type 1 diabetes.

Researchers determined risk scores derived from 41 gene loci associated with type 1 diabetes risk. They used data from more than 3000 children in the TEDDY study who have no relatives with type 1 diabetes.

Speaking about the findings, Professor Ezio Bonifacio of the DFG Center for Regenerative Therapies in Dresden said: 'With these risk scores, we can identify children who have a more than a 10% risk of developing presymptomatic type 1 diabetes by their sixth birthday'.

He continued: 'That means an at least 25-fold increased risk compared to the population average. The process is therefore significantly superior to previous methods.'

Limitations of the study include that the genetic scores were originally developed from case-control studies of clinical diabetes in individuals of mainly European decent, so they may not be applicable to all populations.

The type 1 diabetes genetic score identified infants without family history of type 1 diabetes who had a greater than 10% risk for pre-symptomatic type 1 diabetes, and a nearly 2-fold higher risk than children identified by high-risk HLA genotypes alone. This finding extends the possibilities for enrolling children into type 1 diabetes primary prevention trials.

Bonifacio E, Beyerlein A, Hippich M et al; TEDDY Study Group (2018) Genetic scores to stratify risk of developing multiple islet autoantibodies and type 1 diabetes: A prospective study in children. *PLoS Med* 15(4): e1002548. https://doi.org/10.1371/journal.pmed.1002548

Outpatient talc administration by indwelling pleural catheter effective in treating malignant effusion

Researchers have worked with patients with malignant pleural effusion in 18 UK hospitals to assess whether an alternative treatment approach, which combined talc with an indwelling pleural catheter, could be delivered to patients who preferred to remain at home rather than be admitted to hospital for treatment (Bhatnagar et al, 2018).

A total of 154 patients were randomly treated as outpatients with either an indwelling pleural catheter alone or with an indwelling pleural catheter in combination with talc.

At day 35, 30 of 69 patients (43%) in the talc group had successful pleurodesis, compared with 16 of 70 (23%) in the placebo group (hazard ratio 2.20; 95% confidence interval 1.23–3.92; P=0.008). No significant between-group differences in effusion size and complexity, number of inpatient days, mortality, or number of adverse events were identified.

Patients given talc through their indwelling pleural catheter were more than twice as likely to have their fluid dry up than those who were just treated as standard with an indwelling pleural catheter alone.

Dr Rahul Bhatnagar, Clinical Lecturer in Respiratory Medicine, University of Bristol, Bristol, who coordinated the trial, commented: 'This could change how malignant effusions are treated around the world ... those with cancer-related fluid around the lung can be more effectively managed at home than previously thought.

Dr Rahul Bhatnagar, Clinical Lecturer in Respiratory Medicine, Academic Respiratory Unit, University of Bristol, Bristol

He concluded: 'For those who would prefer not to spend any time in hospital, this combination is at least twice as good as any previous option. Most patients who are having an indwelling pleural catheter should now be considered for talc treatment as well.'

Bhatnagar R, Keenan EK, Morley AJ et al (2018) Outpatient talc administration by indwelling pleural catheter for malignant effusion. *N Engl J Med* **378**(14): 1313–1322. https://doi.org/10.1056/NEJMoa1716883

Large differences between neonatal intensive care units in drug prescriptions for newborns

A multicentre study has investigated the differences in currently prescribed drugs between neonatal intensive care units in the Netherlands (Flint et al, 2018).

The study included nearly 1500 newborns admitted during 12 months to four different neonatal intensive care units in The Netherlands. Drugs were classified in accordance with the Anatomical Therapeutic Chemical classification system and assessed for on/off-label status in relation to neonatal age. The treatment protocols for four common indications for drug use were compared: pain, intubation, convulsions and hypotension.

Drug use varied widely in neonatal clinical practice. Anti-infective drugs were most frequently used with a total of 3161 prescriptions, of which 4% were off-label in relation to neonatal age. Cardiovascular and nervous system drugs were most often prescribed off-label in relation to newborns' age, and their prescription was highly variable between neonatal intensive care units.

'These differences [in prescription] became larger with decreasing postmenstrual age although the proportion of off-label prescriptions in relation to neonatal age decreased,' said lead author Dr Robert Flint, of Erasmus Medical Center–Sophia Children's Hospital in The Netherlands.

The findings indicate that drug research in newborns should have high priority to ensure the use of safe and appropriate drug therapy in such young patients.

Flint RB, van Beek F, Andriessen P et al; DINO Research group (2018) Large differences in neonatal drug use between NICUs are common practice: time for consensus?. *Br J Clin Pharmacol* https://doi.org/10.1111/bcp.13563