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Ann Robinson's research reviews—24 February 2022

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Ivermectin to prevent severe covid-19?

In wealthier countries there is now a range of drugs to treat high risk individuals who get covid-19, including antivirals such as nirmatrelvir-ritonavir, remdesivir, and molnupiravir and the neutralising monoclonal antibody sotrovimab. But is there a place for the cheap and widely available antiparasitic drug ivermectin? This open-label, randomised trial from Malaysia found that a five day course of oral ivermectin given during the first week of illness didn't reduce the risk of developing severe disease (requiring supplemental oxygen to maintain saturation of 95%) compared with standard care of symptomatic treatment and monitoring for signs of deterioration (21.6% *v* 17.3%). There was no difference in other outcomes such as rates of mechanical ventilation (1.7% *v* 4%), admission to intensive care (2.4% *v* 3.2%), or 28-day inpatient deaths (1.2% *v* 4%). The mean age of patients was 62 years; in a younger, healthier population ivermectin is even less likely to be beneficial.

JAMA Intern Med doi:10.1001/jamainternmed.2022.0189

Relative distress from "closed" ICUs

Seeing a family member in an intensive care unit is extremely distressing even if the outcome is good. But this interesting French prospective cohort study found that, three months after ICU discharge, post-traumatic stress disorder (PTSD) symptoms, anxiety, and depression were significantly more common in family members of ICU patients with acute respiratory distress syndrome due to covid-19 than relatives of patients with non-covid acute respiratory distress syndrome (35% *v* 19%).

The key difference was that, before covid-19, participating ICUs generally allowed unrestricted family visits and offered a meeting with the family soon after admission and if death was expected. During the pandemic, all family visits were banned unless death was imminent, family members were typically younger (average age 50 *v* 55 years), there were staff shortages, and information was more often relayed by phone rather than face to face (84% *v* 20%.) Overall, about a quarter of the ICU patients with covid or non-covid acute respiratory distress syndrome died before the 90 day phone interviews with relatives. However, the prevalence of PTSD was much higher among people whose relatives died of covid-19 acute respiratory distress syndrome (63% *v* 39%.) The inference is that the very restricted access to ICU during covid-19 was associated with much higher degrees of lasting psychological distress in relatives.

JAMA doi:10.1001/jama.2022.2017

Suicide prevention: does it need a human face?

We're much better at identifying people at risk of self harm and suicidal behaviour than we are at preventing it. Effective interventions that can be provided at scale are sorely needed. This US based pragmatic randomised trial of nearly 19 000 outpatients who reported frequent suicidal thoughts compared usual care against two low-intensity outreach programmes. These consisted of up to a year of online messaging of an outreach and care package or dialectical behavioural therapy (DBT) skills including mindfulness, paced breathing, and opposite action in which you do exactly the opposite of what your emotions tell you to do.

Overall, there were 45 deaths from self harm and 495 non-fatal injuries or poisonings, equivalent to event rates of 3-4%. Neither programme reduced the outcome events over 18 months, and the risk of self harm was actually 30% higher among those offered DBT skills than those receiving usual care. Previous studies have shown positive results for traditional DBT, but in this study, DBT skills were demonstrated in a brief online presentation and there was no real human contact such as face to face meetings or group therapy. Support consisted of reminders and encouragement via the electronic patient portal. I don't think this study helps us much; was it the message or the medium that failed?

JAMA doi:10.1001/jama.2022.0423

Metastatic prostate cancer: promising results

The old adage that more men die with prostate cancer than because of it is still true. But that's not much comfort for those who develop metastatic disease and die prematurely as a result. This international, randomised phase 3 trial showed that men with metastatic, hormone-sensitive prostate cancer who received the androgen receptor inhibitor darolutamide in addition to androgen deprivation therapy (ADT) and docetaxel survived significantly longer than those who only received ADT and docetaxel (overall survival at 4 years 62.7% *v* 50.4%), with no increase in adverse events. Adding darolutamide was also associated with a slower rate of progression of pain, bone symptoms, and "castration-resistant disease" (cancer that doesn't respond to ADT). Most of the patients had widespread, advanced disease, and the results may not be applicable to men with a better prognosis, but these results look promising.

N Engl J Med doi:10.1056/NEJMoa2119115

Homozygous familial hypercholesterolaemia

Homozygous familial hypercholesterolaemia may be very rare (around 1 in 300 000), but it causes such high LDL cholesterol levels that early death from atherosclerotic cardiovascular disease or aortic stenosis is the norm unless it is diagnosed early and treated aggressively. Management guidelines are mostly derived from small studies in high income countries, so this global retrospective cohort study is important. It used genetic or clinical diagnostic criteria, including LDL cholesterol levels >13 mmol/L (untreated) or ≥8 mmol/L (on conventional lipid-lowering drugs), xanthomas in children under 10 years, or a history of heterozygous familial hypercholesterolaemia in both parents.

The authors found that patients in low income countries were diagnosed later than in high income countries (16 *v* 10 years old) and were less likely to achieve target LDL levels with lipid lowering treatment (3% *v* 21%). The effects of the condition are savage; the youngest case of angina was in a 4 year old, and the median age for a major cardiovascular event was 31. This impressive collaborative project, resulting in the first ever global homozygous familial hypercholesterolaemia registry, represents an important step towards improving outcomes for everyone.

Lancet doi:10.1016/S0140-6736(21)02001-8