

Kaleidoscope

Derek K. Tracy, Dan W. Joyce,
Sukhwinder S. Shergill

How much do different countries invest in mental health research compared with other branches of healthcare? As part of the ROAMER project, Hazo *et al*¹ compared four European nations: the UK, France, Spain and Finland. Using 2011 data, public and private (not-for-profit) annual spends were calculated, respectively, at €127.6, €84.8, €16.8 and €10.2 million. To look on it another way, that equates to a national spend per disability-adjusted life year (DALY) of €48.7, €31.2, €39.5 and €12.5. How does this relate to wider research spending? In the UK, just 4% of health research funding goes on mental health – given that it accounts for 12% of total DALYs, that's an enormous underspend (the Finns do better at almost 10%). A recent paper in the *BJPsych* confirmed² that greater national investment in mental health services produces better clinical outcomes, but the burden remains enormous and we need more research into prevention, intervention and treatment. We can all play a positive role: only 1.7% of charity research spend went to mental health – time to put your hands into your pockets.

A new treatment for postnatal depression? Brexanolone is an intravenous form of the progesterone metabolite allopregnanolone. Following gradual rise in concentration during pregnancy, this neuroactive GABA_A positive allosteric modulator has been shown to acutely decrease after giving birth, and has been strongly linked with animal models of depression and anxiety. Kanes and colleagues³ randomised 21 women less than 6 months postpartum with severe depression to receive either a continuous injection of this compound, or placebo, over 60 hours. Those in the active group showed significantly greater improvements at the infusion end-point – a very rapid onset of action. The numbers are clearly low, rates of adverse events were relatively high in both groups, and long-term sustainability of therapeutic gains uncertain. Intravenous interventions are also usually less acceptable to patients, but oral forms of this compound have low aqueous solubility and bioavailability. Nonetheless, this phase 2 study supports targeting of synaptic and extra-synaptic GABA_A, and certainly further such work in a condition that affects 10–20% of mothers.

Charles Bukowski once said 'I don't like the clean-shaven boy with the necktie and the good job. I like desperate men, men with broken teeth and broken minds and broken ways'. The question of what determines people's social mobility, career and prospects is hotly debated across psychology, sociology and economics. Labour economists – those who study employment, not those who follow Jeremy Corbyn – often argue that inter-generational mobility *increases* as inequality increases; this argument leverages the hypothesis that, as working-class people cannot follow their parents into ever decreasing amounts of work in factories and manufacturing, more of them will proceed to higher education. It's certainly true in the UK that more people are proceeding to higher education. However, Ananat and colleagues challenge this,⁴ putting forth that local job losses lead to lower educational mobility. They found that for a cohort of adolescents exposed to job losses in a given US state, an increase in job losses of 1 s.d. yields a 0.16 s.d. increase in college applicant

inequality; effectively, the more exposure to unemployment, the wider the gap between the proportion of wealthy and poor students attending university from that state. In numbers, exposure to a 7% cumulative increase in job losses leads to a 20% reduction in the probability a young person will attend university. This figure is unaffected by student financial aid or tuition costs for university attendance.

During economic downturns, mental health deteriorates at the population level. In this work, the link to mental health is provided by an analysis of the Youth Risk Behaviour Surveillance Survey that revealed suicidal ideation increases by 2.33% in response to state-wide increase in unemployment. Ananat and colleagues characterise this effect of unemployment as a community-level trauma harming both parents' and children's mental health in families that either have direct experience or even just witness community job losses. They propose looking to Denmark for examples of policies which emphasise re-employment for affected individuals, taking into account specific communities' skills in retraining them for new roles (rather than wholesale redeployment to just 'another job' that is compatible).

Here's a conundrum – how to treat hypochondriasis? It can feel oxymoronic, but of course it's a very real clinical challenge. Affected individuals can have functional impairment and resource utilisation comparable to major psychiatric and medical illnesses. Fallon *et al*⁵ report on the first large randomised controlled trial comparing psychological and pharmacological treatment, randomising almost 200 participants into one of four groups: fluoxetine, placebo, cognitive-behavioural therapy (CBT), or CBT and fluoxetine. Assessing symptoms, adverse events, functional status and quality of life, combination treatment was superior to either monotherapy, which in turn had significantly better outcomes than placebo at week 24. There were no differences in responder rates between the two active treatments, though medication was more effective than CBT over placebo at week 24 and showed a faster rate of improvement during treatment. Dropout rates and adverse incidents were similar across the groups. Although statistically significant, the relatively small advantage in response rates from combination treatment (47.2%) over either monotherapy (41.8%), and the practical realities of such interventions, mean that fluoxetine looks a particularly attractive intervention, though of course, this also highlights that over half showed no response. Of note, the effect size and number needed to treat were similar to those typically seen in pharmacological treatment of depression; importantly, there were no significant changes in depression scores, ruling out this as a potential confounder.

Going smoke-free on in-patient wards: good for physical health, but what's your prediction for the impact on rates of violence? Although we call for parity with physical health services, some within mental healthcare have argued, in the face of ubiquitous smoking bans elsewhere, for an exemption for in-patient wards. Allowing individuals to smoke during a time of intense distress was proposed to be reasonable, even if it might have added to their physical health burden, and there were undercurrent arguments that smoking helped 'calm people down'. Robson *et al*⁶ decided to replace speculation with science, undertaking an interrupted time series analysis of incident reports 30 months before, and 12 months after, the smoking ban implementation across an NHS Trust. In the first 30 months, 4550 physical assaults took place – which is representative for the organisation's size, if still shocking when viewed so starkly – of which about 5% were deemed smoking related. After adjusting

for confounders including age, gender, diagnosis, and detentions under the Mental Health Act, there was a 39% reduction in physical assaults after the smoking ban. The study design did not allow causality to be determined, though there were no other analogous Trust-wide initiatives during the study. The authors note how there were over 45 000 physical assaults against all UK NHS mental health professionals in 2014–15, with staff almost *nine times* more likely to be assaulted than those in general hospital acute settings. The negative impacts from these can be enormous: it looks like we can mitigate against them and improve patient health at the same time. An important message to pass to all in-patient colleagues.

Rodent Fight Club may help explain what it takes to ‘be a winner’ and climb the social ladder. Zhou *et al*⁷ show how mice placed in a tube – the social dominance tube test – can be assigned a dominance ‘rank’ based on how much they initiate pushing, push-back, resistance and retreat behaviours. More dominant mice exhibit higher frequency (and durations) of initiation, push-back and resistance but less retreat behaviours. In single-cell recordings, firing rates of putative pyramidal (pPyr) neurons in the dorsomedial prefrontal cortex (dmPFC) correlated with push and resistance behaviours, whereas putative fast-spiking interneurons (pIN) correlated more with retreat behaviours. Further *in vitro* experiments confirmed that clozapine-*N*-oxide (CNO) suppressed firing in dmPFC neurons and the authors translated this finding by injecting mice with CNO and these mice showed less pushing and push-back behaviours but more retreat behaviours, lowering their dominance rank scores: the effect washed out after 24 hours. To directly study the effects of acute activation of dmPFC neurons, Zhou *et al* then took pairs of mice (with unequal dominance ranks) and optogenetically photostimulated dmPFC neurons in the less dominant mouse. This instantly produced winning in the non-dominant mouse in 90% of trials against the dominant opponent and the rank change observed was proportional to the intensity of the stimulation. Testosterone levels measured 1.5 h later showed no change from baseline, suggesting the effect was not attributable to slow hormonal regulation in the central nervous system of the mice. On the second day after photostimulation, they noted that some mice (with enhanced dominance rank) returned to baseline, but this was proportional to the number of photostimulation exposures with those having more than 6 stimulations maintaining their rank. However, injections of MK801 (an NMDA receptor antagonist) eliminated the gain in rank, suggesting that long-term potentiation and synaptic plasticity in this dmPFC pathway plays a role in coding experience of winning and reinforcing future behaviour. They conclude by suggesting rather broadly that ‘an excess or lack of dominance drive is associated with many personality disorders and mental problems, our results shed light on the treatment of these psychiatric disorders’.

Tourette’s disorder (TD) and chronic tic disorder (CTD) are not uncommon, and frequently very distressing, but we know remarkably little about suicidality in this group. The incidence of TD/CTD peaks in early adolescence, impacting boys:girls in a ratio of about 3:1, persisting to adulthood in a fifth of these, and they form an overall prevalence of about 1% of the general population. The lack of data on intentional harm is more astonishing when one considers that over 80% will have at least one other comorbidity. Fernández de la Cruz *et al*⁸ matched

almost 8000 individuals with TD/CTD on a national patient register to unaffected controls. The odds ratios for attempting (3.86) and dying by suicide (4.39) were considerably above those for the general population, even after adjusting for psychiatric comorbidities. Of those who died by suicide, the methods did not differ significantly from those of the wider population, though hanging, strangulation, and suffocation were more common in the TD/CTD group who attempted suicide. The authors propose that inadequate attention has been paid to risk in these groups.

Finally, many of us have looked back on a past relationship and wondered if we were deluded by love. Writing in *Medical Humanities*, a delightful piece by Brendan Kelly⁹ of Trinity College Dublin explores the truly pathological variant of De Clerambault’s syndrome, or erotomania, where the sufferer falsely believes they are loved from afar by another. Professor Kelly notes a wider social fascination with the topic, which has found its way into representation in the arts and science as far back as the work of Hippocrates, but which has a very serious element that can require active management and be associated with significant forensic behaviour such as stalking, with rejection being taken as paradoxical ‘proof’ of love. He notes that it can be impacted by individual factors such as disappointment, shame, and narcissism – with delusions putatively protecting sufferers from low self-esteem – and presents a fascinating post-war case history based around an individual’s infatuation with the economist John Maynard Keynes (‘Love Island’ not being a thing in the 1940s). The argument is also put forth that not only may ‘lesser forms’ of delusional exaggeration form part of normal stable relationships, but that these might be ‘essential for their continued existence’. We leave the last word to the author, who surmises that any distinction between true and delusional love may not be so great, except to conclude ‘delusions persist; love dies’.

- Hazo J-B, Gandré C, Leboyer M, Obradors-Tarragó C, Belli S, McDavid D, et al. National funding for mental health research in Finland, France, Spain and the United Kingdom. *Eur Neuropsychopharmacol* 21 Jun 2017 (<https://dx.doi.org/10.1016/j.euroneuro.2017.06.008>).
- Taylor Salisbury T, Killaspy H, King M. Relationship between national mental health expenditure and quality of care in longer-term psychiatric and social care facilities in Europe: cross-sectional study. *Br J Psychiatry* 2017; **211**: 45–9.
- Kanes S, Colquhoun H, Gunduz-Bruce H, Raines S, Arnold R, Schacterle A, et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. *Lancet* 2017; **390**: 480–9.
- Ananat EO, Gassman-Pines A, Francis DV, Gibson-Davis CM. Linking job loss, inequality, mental health, and education. *Science* 2017; **356**: 1127–8.
- Fallon BA, Ahern DK, Pavlicova M, Slavov I, Skritskya N, Barsky AJ. A randomized controlled trial of medication and cognitive-behavioral therapy for hypochondriasis. *Am J Psychiatry* 29 Jun 2017 (<https://dx.doi.org/10.1176/appi.ajp.2017.16020189>).
- Robson D, Spaducci G, McNeill A, Stewart D, Craig TJK, Yates M, et al. Effect of implementation of a smoke-free policy on physical violence in a psychiatric inpatient setting: an interrupted time series analysis. *Lancet Psychiatry* 2017; **4**: 540–6.
- Zhou T, Zhu H, Fan Z, Wang F, Chen Y, Liang H, et al. History of winning remodels thalamo-PFC circuit to reinforce social dominance. *Science* 2017; **357**: 162–8.
- Fernández de la Cruz L, Rydell M, Runeson B, Brander G, Rück V, D’Onofrio BM, et al. Suicide in Tourette’s and chronic tic disorders. *Biol Psychiatry* 2017; **82**: 111–8.
- Kelly BD. Love as delusion, delusions of love: erotomania, narcissism and shame. *Med Humanit* 8 Jul 2017 (<https://dx.doi.org/10.1136/medhum-2017-011198>).