Kaleidoscope

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How has the covid-19 pandemic affected individuals with pre-existing mental illnesses? An estimated 200 000 scientific papers on covid-19 had been published by December 2020, but some studies were clearly more important and better designed than others. Pan et al\(^3\) assayed the effects of the pandemic on three existing longitudinal case–control cohort studies of over 1000 individuals with pre-existing depressive, anxiety or obsessive–compulsive (OCD) disorders. This was helpful as, to date, among the 200 000 papers, the significant number looking at mental health have often been based on convenience samples and self-selecting survey participants without pre-pandemic comparator data. Such studies have typically reported alarming rises in psychological distress, but their methodological limitations compromise the validity of the findings. Here, online questionnaires asked about perceived effect on mental health, fear of the virus and coping; and, crucially, repeated previously collected scales assessing various symptom domains including worry and loneliness. Fascinatingly, the control group without any pre-existing problems showed a greater increase in symptoms during the pandemic than those who already had such difficulties. Those with depression, anxiety and OCD remained unwell, with considerable illness burden – and they had considerable concerns about the virus and its potential effects – but overall this did not increase. Indeed, those who had the greatest prior illness burden actually showed a modest symptom decrease. There is no clear explanation for this latter finding, although the authors suggest that societal lockdowns might make the wider world more ‘in sync’ with those who have mental illnesses, staying at home might help some with structure and daily routine, and there might be some regression to the mean in this most unwell group.

Vaccinating individuals with severe mental illness (SMI) against covid-19 is a public health priority. Those with an SMI are at greater risk of catching the virus and have worse subsequent outcomes for a range of reasons, including pre-existing physical comorbidities, lifestyles and environments that are often less healthy, and poorer advocacy. Warren et al\(^1\) note that past experience from vaccination and public health programmes shows that it can be harder to make inroads and address the individual- and system-level barriers in this group. They propose that mental health professionals are uniquely positioned both to broadly educate and to deal with any specific issues that might arise from a mental illness. There is evidence that running vaccine clinics alongside standard mental health out-patient services removes some access and transport barriers, and increases uptake. What is clear from their thoughtful piece is that ‘business as usual’ and expecting some of our most vulnerable patients to turn up for vaccination, much as everyone else does, is liable to lead to many missing this critical health intervention. Mental health services will need to advocate for and proactively assist those who need it.

This takes us to a related and important wider phenomenon: public health messaging in the era of social media and #FakeNews. It would appear that broad public platforms give an opportunity for those with alternative medical views – such as anti-vaxxers – to find, reinforce and amplify each other’s opinions. Crude responses of dismissal or mocking by professionals – as does occur – is unlikely to help. Merchant et al\(^2\) discuss approaches in the noisy and often confrontational online world, breaking this down to four main strategies: deploying countermeasures to misinformation; surveillance of digital data to help inform messaging; partnering with trusted messengers; and promoting equality. There is evidence for ‘find and replace’ of false information (for example, drinking bleach being helpful!), but it is not always so easy to find, and whose role is it to replace? The authors call for public health organisations to work with major tech companies such as Twitter, and indeed these can be a source of information on the type of (erroneous) messaging that is occurring. There is clearly a need for various organisations to try to act as trusted resources, and this is likely to be multipronged, from healthcare trusts, through academic departments, to scientific journals. The BJPsych remains active on Twitter – the open question to you is what we should be doing at this time.

Thankfully we have discovered it takes exactly either 12 or 18 sessions of cognitive-behavioural therapy to fix depression. This is just as fortunate as the finding that transcranial magnetic stimulation need only be given Monday to Friday, with no rationale for weekend application. Obviously, we have pragmatic models of care (and in reality therapists will of course individualise their inputs), but how long should psychotherapy last? It would be good to have evidence of any differential effects of duration. Nordmo et al\(^5\) report on open-ended psychotherapy in a representative sample of 362 patients, some of whom were quite unwell. Mean attendance was 52 sessions, but it’s what lies beneath that is interesting, and the degree of improvement had a linear association with initial symptom severity and duration of therapy. Those with the mildest difficulties showed the most rapid change, although this was of smaller magnitude, and they received the shortest duration of treatment. Those with the greatest difficulties stayed in therapy the longest: their improvements were slower, but they were the ones who generally showed the greatest gains with time. Of course, the nature of the design means one cannot argue causality: rather than ‘longer treatment’ being ‘better’ for more severe illness, it is likely that this is what was needed to effect change. What the findings support are the principles – which every therapist will feel, but which it’s good to evidence – that one should tailor duration to individuals’ needs, not protocol recommendations, and that for some, gains may well take time to accrue and embed.

The predominant academic publishing model to disseminate novel research data is perverse; crudely, a publisher’s business model is to sell this knowledge at a profit through inducing an intersecting set of producers and consumers of knowledge to format and quality control their work. Or, as Montgomery et al\(^6\) put it, ‘The current system is built upon a set of closed transactions that imagine knowledge as a private good that is commodified through corporate publishing’. For an example of the success of publishing empires, read the brief history of Pergamon Press (https://en.wikipedia.org/wiki/Pergamon_Press). At the start of 2021, the Plan S/Coalition S implementation was initiated to resolve some of these access issues (https://www.coalition-s.org/), requiring the output of publicly funded research to be made free through enforced open access. It is unclear where this leaves the subscription service journal. Given the current publishing model, there are broadly three ways this is happening: (a) the journal publishes work at no cost to the producer, charges consumers for the journal (the traditional paywall model) but allows authors to pay a fee for an open access version to be available; (b) the journal only charges the author to publish, and all consumers have access for free; and (c) the journal doesn’t charge producers to publish, is accessible by subscription (paywalled), but allows work it has published to be made available in open-access repositories after an ‘embargo’ period to retain added value for paying subscribers.
Brainard² analysed the frictions, effects and unintended consequences of the Plan S model. The most obvious tension is that publishers want to generate revenue, and it transpires that although 30% of papers published in 2019 were paid-for open access, 90% of publisher’s revenues (totalling 10 billion USD worldwide) were from subscriptions. The current model is transitional, presumably with the hope that the costs of subscriptions to journals will be slowly diverted into per-article publishing fees. However, this doesn’t balance financially: the cost of publishing a university’s total output by upfront per-article fees exceeds the university library’s total journal subscription budget. Paying to make one’s work visible in a journal pushes the cost burden to the author, disadvantaging researchers with lower funding. Brainard highlights that the median fee for an article to be made open access is 2600 USD, with a handful of prestige journals charging as much as 11 000 USD. Further, it is suggested that in the biological, physical and mathematical sciences, those opting to pay for open access visibility for their work were more likely to be senior academics in leading research institutions. This could lead to an arms race where only wealthy groups can publish high visibility work, which, in turn, makes them more competitive (at least, by current metrics) to attract further funding. Early-career researchers are encouraged to publish their work in high-prestige (mostly paywalled) journals to attract peer esteem and increase their academic market value – so there is less incentive for the vast majority of emerging academic experts to make their knowledge an open public good, even less so if they have to find funding to make it open access.

The Open Knowledge Initiative (https://ccat.curtin.edu.au/programs/innovation-knowledge-communication/curtin-open-knowledge-initiative-coki/) takes a more polemic and systemic view – in their book (Montgomery et al, 2018), they argue that universities need to fundamentally alter their relationship with knowledge production and society. To do this, universities must move away from what they call the closed-knowledge systems that enabled the very academic publishing empires whose terms and relationships with knowledge production we are now trying to renegotiate.

Finally, ketamine remains a hot point of debate on effectiveness versus harm. Its antidepressant actions have been proposed to occur via a metabolite, (2R,6R)-hydroxynorketamine ((2R,6R)-HNK), and although the quick effects point toward cellular signalling and gene expression, the specific mechanism of action is unknown. Human post-mortem studies have identified reduced activity in the mTORC1 signalling pathway in the brains of individuals with major depressive disorder, and laboratory studies have shown mTORC1 kinase activation in the prefrontal cortex (PFC) and hippocampus to be necessary for ketamine’s antidepressant effects; however, it controls a host of varied neuronal functions, so the mechanism mystery has, until now, remained unsolved.

A recent study in Nature⁸ used a triangulation of techniques in mice to pinpoint the cause of the effects of mTORC1 to downstream eukaryotic initiation factor 4E-binding proteins (4E-BPs), which are known to be important for neurotransmission and structural plasticity. Within the hippocampus, immunohistochemistry confirmed the presence of 4E-BP2 in excitatory and inhibitory neurons, while expression of both 4E-BP1 and 4E-BP2 was seen in the PFC. Using multiple behavioural models of depression with wild-type, 4E-BP1 and 4E-BP2 knockout rodents, administration of ketamine and its metabolite led to behavioural recovery within 1 h in wild-type animals but not in knockout animals. By contrast, fluoxetine was effective for all mice. This effect was also seen in the neural activity associated with ketamine’s ability to induce synaptic plasticity. Electrophysiological investigation of CA1 hippocampal tissue slices confirmed the role of the binding proteins in the ketamine-induced influence on field excitatory postsynaptic potentials. Finally, cell-specific deletions were used to confirm the necessity of 4E-BP2 in excitatory neurons and of both 4E-BP1 and 4E-BP2 in inhibitory neurons for antidepressant effects. Rarely does the basic science of protein synthesis feel so directly relevant, but by understanding the very specific mechanism by which ketamine rapidly induces sustained changes in excitatory neural transmission, and its corresponding antidepressant effects, we now have a novel focal point in our search for safer, targeted treatments for depression.

References