

Kaleidoscope

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

Early stage research has shown cannabidiol (CBD) to have therapeutic potential for psychoses, but robust patient data are still needed. The cannabis plant, *Cannabis sativa*, contains dozens of psychoactive components: Δ -9-tetrahydrocannabinol (THC) is the most notorious, with pro-psychotic properties; CBD is the next most abundant, and seemingly exerting an opposing effect. The ratio of THC/CBD is important in determining the strength of smoked cannabis, with recent well-publicised concerns about the emergence of increasingly potent varieties. Interestingly, CBD does not appear to directly antagonise dopamine receptors, although its precise mechanism of action has yet to be determined.

In the first double-blind randomised parallel-group trial of CBD in schizophrenia, McGuire *et al*¹ compared its effectiveness over placebo, as an adjunct to regular antipsychotic medication in just under 100 patients. After 6 weeks of treatment those in the active arm showed significantly fewer positive symptoms and were more likely to be rated as improved; there was also a non-significant trend to improved cognitive performance. The overall effect size was modest – although the authors remind us that this was in a cohort where all were already on treatment – and CBD was well-tolerated, with similar rates of adverse events to placebo. The results are doubly encouraging as CBD's unique mechanism of action may represent a new pharmacological class of novel antipsychotics.

Returning to THC, it is estimated that about 10% of regular smokers will develop cannabis use disorder, accounting for around one in six of those admitted for drug dependency treatment. Simple discontinuation strategies and psychological interventions show only modest benefit, but there is an increasing interest in effective pharmacological treatments. Brezing & Levin update us² on the state of play with drugs that act at the cannabinoid-1 (CB-1) receptor. Replacing cannabis with a controlled receptor agonist would model nicotine, alcohol and opioid replacement/reduction treatment. Early positive laboratory data on oral THC (dronabinol) has not translated to real-world settings, potentially because of its lack of bioavailability, but the synthetic cannabinoid nabilone and nabiximols (which contains THC and CBD extracts from the cannabis plant) are showing some promise. Rounding off the nascent research, a CB-1 receptor antagonist might decrease the subjective drug-reinforcing effects, again akin to other dependency models, but the initial exemplar, rimonabant, showed serious adverse events. Rimonabant may actually be producing these via inverse agonist effects, and work continues on a more benign version. The field is progressing, albeit more slowly than one might wish.

'Social isolation' is a common descriptor in mental health, but typically ill-defined. This is problematic when we consider the frequency of occurrence and its impact. Wang *et al*³ undertook a narrative synthesis and systematic review of this area, including a multidisciplinary panel of senior academics considering conceptual papers and making expert recommendations. This led the authors to propose a 'conceptual framework' of five subdomains: social network – quantity; social network – structure; social network – quality; appraisal of relationships – emotional; and appraisal of relationships – resources. This structure identified validated measures for each subdomain and facilitates a more rigorous approach to future research on the topic. This acts as a reminder for everyone to be more specific in our own documentation, ensuring that we do not incorrectly use 'social isolation' as a synonym for 'loneliness'.

This leads directly to assessment of interventions; Fowler *et al*⁴ report on a single-blind randomised controlled trial of social recovery therapy (SRT) in individuals with a first-episode non-affective psychosis. The authors note that before the development of early intervention services (EIS), only one in seven people had a partial or full social recovery by 2 years, but their wide-spread implementation increased this figure to 40–60%. This particular sample included participants who had persistent and severe social disability (i.e. a more complex EIS case-load) and the primary outcome was time spent in structured activity at 9 months. SRT led to clinically important benefits at 9 months in this cohort, although loss of participant follow-up left it underpowered to test the 15-month endpoint. Social functioning is a strong prognostic factor in psychoses, and the paper proposes SRT might have a particular role in those seeming less motivated to engage or who have comorbidities that limit their ability to do so.

The 'iceberg model' places fatal self-harm (suicide) as the highly visible tip overlaying the more frequent non-fatal self-harm seen by clinical services, which lies atop of an even larger base never contacting services. Although accepted in principle, few data have shown the relative sizes of these three groups, hampering potential preventative and educative programmes. Geulayov *et al*⁵ explored this in young people using national mortality and hospital monitoring self-harm data, and a schools' survey. The data are harrowing: 171 adolescents (aged 12–17) died by suicide in England between 2011 and 2013; for each of these deaths there were about 370 hospital presentations with self-harm and 3900 adolescents self-harming but unseen in the community. Ratios of non-fatal/fatal self-harm varied between genders – the former far higher in females, with males accounting for 70% of suicides. Hanging or asphyxiation were the most common cause of death, self-poisoning the most common hospital presentation and self-cutting the most common form of self-harm in the community.

These figures are difficult to ignore, suicide is the leading cause of adolescent death in the UK. Every year an estimated 200 000 young people self-harm in England and are not seen; this suggests that out-reach of our services must be developed and the authors propose schools-based programmes as a key target.

On the topic of mass firearm killings, the geneticist Adam Rutherford wrote 'We look to statistics for reassurance in these types of situations. Here is one: 100% of mass shootings have been enabled by access to guns. I can guarantee that even if there were a genotype shared by the mass shooters, which there will not be, none of the killings would have happened if they did not have guns'. Those opposing gun control recite the mantra that guns do not kill, people do. After the Sandy Hook shootings in 2012, President Obama called for a revision of gun control law and Levine & McKnight⁶ have analysed the impact of these two events on the consequent number of attributable accidental firearm deaths in the period 2012–2014.

Their logic proceeds as follows: increased focus on gun control law made the American public more interested in guns, measured as an increase in Google searches for 'buy gun' (signalling the intent to purchase) and 'clean gun' (signalling the intent to retrieve and make available a stored weapon); this may have led to more accidental firearm incidents. The Google search frequency increased in the short period after the Sandy Hook incident, and again in early 2013 when the President's state of the union address mentioned gun control.

Similarly, using a national database, there was a correlated increase in background checks for people seeking to buy guns (correlation coefficient of 0.71). In one state (California) the number of handgun sales increased by an additional 26 000 in the 6 weeks after the Sandy Hook incident (of which 59% were first-time buyers). Total US gun sales in

the 4 months or so after Sandy Hook increased by three million. Controlling for seasonal and long-term trend effects, a regression model showed an additional 0.0036 deaths per 100 000 people ($P < 0.01$) in this period: 57 people of whom 18 were likely to be children. Is this an example of the impact of the law of unintended consequences on conveying messages on gun safety?

Resonating in the era of #fakenews, Mark Twain's asserted that 'Facts are stubborn things, but statistics are pliable'. An ongoing furor about statistical practices has led to attempts to build consensus on methodology and reporting in science and medicine. *Nature* asked six eminent statisticians to describe the root cause problems with current practices.⁷ Leek describes how methods designed for simple, multiple variables and small expensive-to-collect data have been 'jury rigged' to be applied to massive sets of variables with orders-of-magnitude greater samples, but our understanding of how human cognitive processes cope with such data (and analysis) has not kept pace.

McShane & Gelman highlight the fallacy of continuing to blindly obey (and report the outcome of) null hypothesis significance testing – where we force data to speak to either an 'effect' (reject the null hypothesis) or 'no effect' (accept the null hypothesis). They suggest that when there is no account of how noisy the data are, no assessment of the plausibility of effect size and no accounting for the quality of experimental design, the likelihood of a false positive is high – and P -values alone are therefore meaningless in discriminating a real result from one attributable to chance.

Colquhoun argues it is the risk of finding a false positive that needs controlling. Instead of the absolute P -value, Colquhoun suggests we report the false-positive risk, where the prior probability of a true effect is combined with the desired significance level – for example a moon-shot hypothesis with only a 10% chance of a true effect yields a 76% false-positive risk if the significance level is 0.05. To achieve a false-positive risk of 5% under the same hypothesis (which he argues is what people commonly and incorrectly understand $P < 0.05$ to mean) really requires a $P < 0.00045$.

Nuijten argues that defining more hard rules for researchers to follow is impossible – because there are too many contingencies to account for. The solution? Openness – everyone publishes the data and the code that yield the reported results so others can interrogate them. Finally, Goodman suggests that the problem is with norms of practice in different disciplines. He states that when we teach statistics, we are compelled to instruct on methods with which journals and peer scientists feel familiar (rather than advocating for methods that really expose the conclusions the data speak to). He argues that the obligation to $P < 0.05$ is because no one feels confident making a case for anything else – be it more liberal thresholds where there is, for example, a strong and clearly directional *a priori* hypothesis; or admitting to the possibility that a default $P < 0.05$ claim might be a false positive because of experimental design. He argues that when some journals, funding bodies or eminent research leaders start promoting this idea, it becomes self-reinforcing. To conclude: statistics do not make false positives, people do.

Finally, #MeToo was a defining cultural shift from 2017, and with multiple levels of irony the movement trumped Trump to *Time* magazine's Person of the Year. We have seen politicians, film directors, actors and many others exposed for grossly unacceptable behaviour – does it happen in medicine too? Writing in *The New England Journal of Medicine*,⁸ Reshma Jaggi stands up to say yes, it does. Her research has shown that about 30% of women in medicine have been sexually harassed, and she notes how what she labels as the 'normally highly articulate men' in our profession are often astonished that they are surrounded by women who have suffered such egregious behaviour. In a very personal and moving editorial, she

also notes the fear of women in academic medicine of being 'cast as a victim' and the impact that this could have on their careers, leading to very few reporting such experiences, compounded by the observation that many institutions allegedly discouraged complaints against their star academics. Dr Jaggi comments on how the media often expect medicine to be better than other fields of endeavour, filled with presumably altruistic and highly educated professionals; she counsels that it is just as bad as everywhere else.

There is a recognised attrition of senior female representation in academic careers across medical specialties, and observed in the sciences more generally, with 59% of European undergraduate degrees going to women yet the comparable figure for senior faculty being only 21%. Although the aforementioned issue of sexual harassment must be a factor for some there are also too few role models for early stage academics.

Carter *et al*⁹ explored women's visibility at academic seminars, looking specifically at how those in the audience asked questions. From survey and observation data women asked proportionally fewer questions, on average being two and a half times less likely than men when audience gender ratios were equal. The genders differed in the factors they attributed to preventing them from doing so – internal factors ('not working up the nerve') being more common in women. Interestingly, the gender of the first question asker was crucial: when a man asked this, fewer women followed, with the authors suggesting this was because of problematically reinforced gender stereotypes of assertive, confident men. Women are literally less visible at talks, and the authors propose this has an iteratively negative impact on the other junior women academics; they call it both a symptom and a cause of the problem. We spoke with science journalist Mika McKinnon who noted how challenging she can find it to get women scientists to comment: in one instance of reaching out to experts and specifically looking for diversity of opinion, all 75 women approached declined, whereas 11 of 15 men agreed, including a couple who said it wasn't specifically their area. It is 2018 folks; all of this has to improve. Helpfully, some suggestions are put forth, including for seminar chairs to actively moderate audience members – especially those who are showing off. We'll be podcasting about this with the Mental Health Foundation in the near future.

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