

Kaleidoscope

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‘Herb is the healing of a nation, alcohol is the destruction’ taught Bob Marley; should cannabis be legal? There are reasoned calls to decriminalise its use, and – in the UK – a rescheduling and easing of restrictions on medicinal prescribing and research, but is the rising potency of street cannabis increasing adverse outcomes? There are very many intermediate variables between drug consumption and any impact on health, making it difficult to determine if higher-levels of δ -9-tetrahydrocannabinol (THC) have altered presentations for treatment. Nevertheless, prevalence-of-use estimates show cannabis consumption to be stable or falling, while cannabis-related hospital admissions have been rising. Tom Freeman and colleagues¹ analysed THC concentrations from popular herbal cannabis brands sold in the Netherlands, and, using mixed-effects linear regression models, explored time-dependent associations between these and first-time admissions to specialist drug treatment. Mean THC levels were 8.62 in the year 2000, rising rapidly to 20.38 by 2004, then dropping back to 15.31 by 2015. And the clinical admissions tracked this: they went from 7.08 per 100 000 inhabitants in 2000, to 26.36 by 2010, falling to 19.82 by 2015. The strongest association was 5-years post-initiation. The study was not designed to determine causality, and there were some changes to the results after adjusting for age, gender and other factors (though the figures remained significant). The authors remind us of the lack of effective interventions, both pharmacological and psychosocial, for this cohort, and highlight that cannabis has replaced opioids as the primary drug problem facing Europe. Carl Sagan went further than Marley, contending that ‘the illegality of cannabis is outrageous, an impediment to full utilization of a drug which helps produce the serenity and insight, sensitivity and fellowship so desperately needed in this increasingly mad and dangerous world’. That might have legitimacy for many people, in both recreational and medicinal use, yet in parallel it clearly also causes harms for others. How we as a society manage and hold these simultaneously conflicting yet accurate truths remains a question of our time. If the current study follows the more general trend of work discussing cannabis, the findings will be hugely debated.

Kaleidoscope previously described² an early phase 2 study on brexanolone for postpartum depression. Writing in the *Lancet*, Meltzer-Brody *et al*³ update us with the results of their follow-up large phase 3 double-blind randomised, placebo-controlled trial. The principle is that the progesterone metabolite allopregnanolone drops precipitously after giving birth, and animal model data strongly link this to psychiatric symptomatology. Brexanolone is an intravenous form of this GABA_A (γ -aminobutyric-acid type A)-positive allosteric modulator, and therefore can be used to replace naturally falling levels. Across 30 specialist units in the USA, 246 women with 6 months or less moderate-to-severe postpartum depression were randomised to receive either this active compound or placebo. Two different dosing regimens were tested: 90 μ g/kg/h and 60 μ g/kg/h, and in both cases (and placebo), this was continuously infused over 60 h. Brexanolone resulted in significant and clinically meaningful improvement in depressive symptomatology at the infusion end-point – a very rapid response; in those that responded, 94% had not relapsed by the 30-day follow-up point. Most participants were not on antidepressants concomitantly, so therapeutic actions appear primary as opposed to pharmacologically augmenting. There are considerable challenges in mental

health units setting up intravenous infusions, but absolutely no fundamental reason that this cannot occur. It might not always be recognised as such, but the authors remind us that postnatal depression is the most common complication of childbirth. In the UK there is a rightful push to enhance our perinatal services and recognise the distinct difficulties this cohort can face – they might just have a new weapon in their armamentarium.

How effective are talking therapies in treatment-resistant depression (TRD) and which factors mediate outcome? It is an area that has received less attention than mild and moderate depressive episodes; indeed a rigorous literature than TRD really only began about 15 years ago. van Bronswijk *et al*⁴ meta-analysed 21 TRD trials that encompassed seven different psychotherapy types and 25 comparisons against treatment as usual. The most frequently evaluated interventions were cognitive-behavioural therapy, interpersonal psychotherapy, mindfulness-based cognitive therapy and the cognitive-behavioural analysis system of psychotherapy. Of the 25, 22 found in favour of augmentation, with a moderate general effect size of 0.42. Meta-regression of the data found that baseline severity and setting (group versus individual) were moderators. Perhaps contrary to many clinicians’ expectations, group interventions were more effective; it is not clear why this is the case, although an argument can be made for both peer-support and often longer session durations. Helpful findings for instilling hope in both patients and clinicians, and reminding us all of the breadth of therapeutic options, especially when data suggest some time-pressured professionals move to a primarily or solely pharmacological approach in TRD.

Perhaps surprisingly, despite their long existence and solid evidence base, it remains unclear what determines change in talking therapies (so it is not just medication where we are not entirely sure what is happening). Although his name is generally *verboden* in the *BJPsych*, the idea of insight being key harks back to Freud, but empirical evidence was never his strong point, and data backing this (perhaps appositely) are ambivalent. The problem is not eased by a lack of a consensus definition of a term we think we all understand. Writing in the *American Journal of Psychiatry*, Jennissen *et al*⁵ defined insight as ‘patients’ understanding of associations between past and present experiences, typical relationship patterns and the relation between interpersonal challenges, emotional experience, and psychological symptoms’, and tested its impact by meta-analysing effect sizes from 23 relevant trials. They confirmed what Freud taught us: insight is significantly linked with better treatment outcomes, and in this work it had an effect magnitude equivalent to therapeutic alliance, positive regard and empathy. Forgive us father for doubting.

We previously highlighted⁶ that even chicks – that is baby chickens, folks – understand the number line, with smaller quantities to the left of larger quantities. A related principle is ‘categorical perception’, where for a continuous stimulus, our brains divide it up into ordered chunks. This helps extract patterns and regularities that are meaningful for survival. An example is that we perceive a rainbow as discrete ‘bands’ of colour (red, orange, yellow, green etc.) despite the continuous nature of the wavelengths of light – our brain’s construction of the rainbow percept supervenes on its wiring. So, *categorisation* is the brain’s ability to group similar stimuli together – based on some similarity for example, ‘red’ represents a group of wavelengths close to each other – and *discrimination* is the ability to tell two stimuli apart.

In evolution, phenotypes are often continuous, and Caves *et al* report⁷ on female zebra finches’ ability to categorise and discriminate the beak colours of potential mates – colours varying from yellow through orange to red. This is important to zebra finches:

beak redness is proportional to variation in cell-mediated immunity, and female finches prefer red over orange beaks for selective advantage. The researchers constructed eight discrete colours ranging chromatically from orange to red; they then coloured discs either one of the eight colours ('solid colour') or half-and-half with two colours ('bicolour'). The female finches were then trained to flip over the bicolour discs before solid colour discs for food rewards. In the experiment, finches were presented with 12 'food wells' covered by either solid or bicolour discs. For the bicolour discs, the chromatic difference between the two-coloured halves were varied so that they were similar or different (for example one-half dark red, one-half bright orange being the most extreme with subtly different red–orange halves for practically indistinguishable). They discovered that there was a 'boundary' in the chromatic space of orange–red that provides a sharp boundary for the probability of success in getting a food reward across 26 birds. The authors propose that this is unlikely to be a function of just the retinal system and reflects a higher cognitive function. Chunking complex information into larger groups is helpful, and allows useful generalisations and rapid separation of useful information from the extraneous in a world overflowing with sensory input. Humans also categorise colours and this work demonstrates that this is an ancient hard-wired brain function preserved across several species. It supports the argument that colour perception is biologically inbuilt, not, as is also argued, a cultural vagary dependent upon the language a given group uses.

Kamaal Ibn John Fareed – that is the musician Q-Tip to you – cautioned that 'If there's a "Cruel Summer" then there's got to be a "Cruel Winter," right?' The UK is at that time of year where trains are cancelled because of our misunderstanding of deciduous trees (leaves, apparently, shed at this time of year) and we pine for the Spring, when cancellations will be driven by our misunderstanding of heat (metal, it turns out, expands and contracts depending on the temperature). Following the seasons, Lim *et al* present⁸ the interesting hypothesis that cognition and biomarkers of 'brain health' also fluctuate with the season and they use three observational cohort studies of a total of 3353 older people (aged 70 to late 80s, with and without dementia) to establish this relationship. Cohorts had different data available: some participants had sampled cerebrospinal fluid markers (such as A β 40 and 42, tau and phosphorylated tau) whereas in those who had died, post-mortem diagnoses of Alzheimer's disease were recorded, as well as post-mortem tissue RNA sampling from the dorsolateral prefrontal cortex. All included participants had cognitive testing and could be classified as having: no impairment, being mildly cognitively impaired or having clinical threshold dementia. In total, 2761 participants were free of a dementia diagnosis at the start of the sampling periods over all three studies. When modelling effects of season, the authors covaried for comorbid mood disorders, sleep, thyroid function and time-of-day on cognitive testing data. In those participants with or without cognitive impairment, the average composite measure of cognitive performance varied over the year, with it being the highest in the summer/autumn period

compared with winter/spring. The authors interpreted the effect with respect to population norms for cognition by age, showing that the effect of season amounts to a 4.8 years difference in age (95% CI 2.1–8.4), and they noted that working memory was the domain most affected by the winter/spring season. Interestingly, the A β 42 CSF level fluctuated by season peaking in the summer and the odds of meeting threshold for mild cognitive impairment or dementia were around 30% higher in the winter/spring seasons. The authors argue that their studies differ from previous findings (where no association of season was found, but in younger people) because cognitive reserve decreases as we age.

Finally, heartening evidence from the Eurovision Song Contest (ESC) that taking part is more important than winning. It is intuitive that the ESC adds to the karmic happiness and well-being of the universe, but it is good to see that science is trying to map this. Filippidis & Lavery⁹ analysed life satisfaction data from 33 European countries from 2009 to 2015, covering over 160 000 individuals, and correlated it with national ESC performance. Actually winning the ESC was not associated with greater national life satisfaction, but every ten-place increase in the rankings did produce a significant gain. However, crucially, even terrible performances – something many cynics might argue is the hallmark of the ESC – were associated with greater life satisfaction than not competing. So it is taking part in this annual festival of schmaltz and sequins that brings happiness, something that should prove of particular comfort to those of us living in the UK as we endure our annual pasting of 'nul points'.

References

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