BJPsych The British Journal of Psychiatry (2023)
222, 224–225. doi: 10.1192/bjp.2023.38

Kaleidoscope

Derek K. Tracy, Dawn N. Albertson,
Emmeline Lagunes Cordoba,
Sukhwinder S. Shergill

'A glass of wine to help my heart!' is – in the K Team's experience – the most optimistically overused health cry at parties. How strong are the data that suggest moderate alcohol also decreases the risk of depression? A challenge has been the inability to robustly determine causality, with much of the existing research on the topic favouring this risk reduction. Writing in the *American Journal of Psychiatry*, Visontay et al[1] explored a national longitudinal cohort to contrast abstinence and occasional, moderate and above-guidelines alcohol consumption through adulthood (baseline measurements at ages 29–37 years) and any depression at age 50. Valid data were obtained from over 3500 individuals, and a J-curve relationship emerged. When various confounders were accounted for, marginal structural models for causal inference showed that consistent occasional and moderate drinkers had reduced depression scores and reduced rates of probable depression by age 50 compared with those who abstained completely. Those with consistent above-guidelines consumption had a greater risk of depression, though not at a statistically significant level. There were no differences between genders. The results are fascinating and perhaps contrary to what most of us might have predicted, not least as alcohol use disorders have well-established comorbid links with depression. They show that the previously found J-curve appears to be a true finding when modern statistical methods and careful controlling of confounders are applied. The authors note that moderate alcohol consumption increases brain-derived neurotrophic factor and lowers inflammatory biomarkers, both of which are associated with depression. Perhaps more parsimoniously, modest consumption might reflect better social connections. The clinicians in the room will also instinctively feel the tension of how this could be misinterpreted, not least as increasingly we seem to be moving socially to a 'no safe limit' culture.

The placebo response in antidepressant trials remains fascinating and incompletely understood. It's an important area: *something* is improving individuals' moods, often for months, which feels important to elucidate, and it's the primary comparator group in frequently criticised randomised controlled trials of antidepressants. Several mechanisms have been suggested, including setting expectancies, Pavlovian conditioning and, more recently, reinforcement learning. Reinforcement learning is interesting, as it offers a computational approach, but one might anticipate that as prior expectancies (getting better) are not met by experience, they are eliminated. There is active debate about whether there is an issue of impaired extinction learning and confirmation biases that seek reinforcing (false) experience and discard evidence to the contrary. Peciña et al[2] recruited 60 individuals with major depressive disorders not receiving medication in a within-participant cross-sectional study of placebo response. Individuals, who were deceived about the true nature of the study, were advised that it was testing the brain effects of a fast-acting antidepressant compared with a standard tablet version (setting the prior expectation, whereas the intervention was actually placebo) and scanned with functional magnetic resonance imaging while undertaking a neurofeedback reinforcement condition. They were told that neurofeedback of the positive signal post-infusion would be associated with rapid improvement in mood, but that a baseline feedback signal would see no change. Sham positive neurofeedback was provided in 75% of trials and sham negative in 25%, with participants thereafter rating their expected and actual change in mood. As participants anticipated infusions, learned placebo expectancies modulated the salience network. Within minutes, antidepressant placebo effects were maintained by positive feedback loops and reinforcement learning between expectancies and mood improvement. During learning, representations of the infusions and their (perceived) effects were enhanced in the primary and secondary sensory cortices. This rather clever study design enables the inference that placebos are definitely not inert but set off positive feedback loops between expectancies and learning, and that it is this that leads to mood improvement.

Continuing the theme of understanding depression, whereas trials of psychedelics are simultaneously intriguing and heavily critiqued, we really need to get under the bonnet and better understand any putative therapeutic mechanisms. It's known that they activate the serotonin 2A receptor (5HT2AR), but, thereafter, effects are less clear, and only some 5HT2AR agonists appear to induce the cortical plasticity put forth as one psychotherapeutic effect. Writing in *Science*, Vargas et al[3] provide a *tour de force* that not only better explains this but shifts our understanding in the broader neurobiology of depression. Serotonin activates neuronal membrane 5HT2ARs, but its unmethylated amino group means it cannot permeate to the inner cell, which is the primary site for these receptors in the brain. That functional group is methylated in classic psychedelics, which allows them to enter the cell and activate intracellular 5HT2ARs that occur across a range of organelles such as the Golgi apparatus and endosomes. Localisation here is interesting as, inferentially, binding might be able to produce more sustained responses. Neuronal signalling is affected by the distinct localisation of these receptors, and the authors demonstrated in cultured cells that the psychedelic moiety DMT binds to them, producing rapid changes in dendrite growth and spine density. Binding to surface 5HT2ARs, which serotonin will do, does not appear to produce similar changes.

The authors were able to produce a parallel response in cells altered with serotonin transporters to allow serotonin into the cell body, mimicking the binding actions of DMT. Behavioural analogue responses were produced in rodents via the forced swim test model of depression, which were reversed by serotonin enabled to act on the intracellular 5HT2ARs. This is all fascinating, but in 'real life' serotonin cannot get inside the cells in this way. DMT, which in psychedelics work comes from the ayahuasca plant, also occurs endogenously in mammalian brains synthesised from tryptophan, but its normal physiological roles have not been well understood. Vargas et al show that exogenous psychedelics might therapeutically act via rapid intracellular binding to 5HT2ARs, though the precise subsequent cascades that induce the dendritic changes are still to be fully determined. Not only does this further open up areas for future targeted pharmacological developments, it raises the seemingly heretical proposition that serotonin is not the endogenous ligand for cortical intracellular 5HT2ARs. We need to better understand the functioning of endogenous DMT and whether 'standard' antidepressants might produce their effects by means other than the observed rise in synaptic serotonin – other contemporary literature suggests that activation of tropomyosin receptor kinase B might be one such candidate.

Sticking with serotonin but changing gear: premenstrual dysphoric disorder (PMDD) is a cyclical dance of emerging and remitting symptoms of a physical and psychological nature experienced by 3–8% of people who menstruate. Despite a total illness time across the lifespan that rivals major depressive disorder, research focusing on the underlying mechanisms of PMDD has only

recently picked up speed. Although there is no difference in peripheral hormone fluctuations, the central nervous systems of those with PMDD appear sensitive to the hormonal level drops in the premenstrual phase. Some PMDD patients have been shown to experience symptom relief within mere hours of taking a selective serotonin reuptake inhibitor (SSRI), rather than the weeks required for major depression. This, along with the significant expression of serotonin and oestrogen receptors within the midbrain, have made the neurotransmitter a focus of enquiry. A team led by Julia Sacher at the Max Planck Institute for Human and Cognitive Brain Sciences investigated the role of the serotonin transporter in PMDD.[4] The team used positron emission tomography scans to measure estimates of 5-HTT expression and density within the midbrain and prefrontal cortex at key points across two menstrual cycles in 30 participants with PMDD and matched controls. Menstrual cycle monitoring allowed for scans targeted within 24 h of confirmed ovulation (e.g. the periovulatory phase) and a premenstrual assessment within 3 days of next period onset. Shortly prior to the scans, participants were measured with the Hamilton Rating Scale for Depression and other mood assessments. Blood samples were used to assay hormone levels at every scan. Significantly elevated 5-HTT availability was seen within the symptomatic premenstrual phase in those with PMDD as compared with their own levels during the periovulatory phase, with an 18% increase noted within the midbrain. This cyclical increase in transporter availability was associated with the severity of depressed mood and provides evidence of a rapid and dynamic mechanism that could explain the quick relief seen with SSRIs. Within the controls, a decrease in midbrain transporter availability was seen and was hypothesised to act as a protective mechanism. Although serotonin transporter levels are generally considered to be stable in individuals, a correlation between fluctuating 5-HTT availability and depressed mood is also seen in seasonal affective disorder (SAD). Although it may simply be that increased 5-HTT availability is a marker of low mood vulnerability, it is intriguing to imagine the possibility of non-pharmacological interventions to support those with PMDD as we see with SAD.

Finally, are violence encounters risks for suicidal ideation in teenagers with depression? The prevalence of depression in adolescents has been reported to be as high as 34%, and it's a disorder with strong associations with developing suicidal ideation. Similarly, being a victim of violence has been associated with higher risk of developing depression and suicidal thoughts. However, the real impact of a recent violence encounter on developing suicidal ideation in teenagers with depression has not been assessed. Wang et al[5] conducted a retrospective cohort study in which they analysed electronic data from 24 047 adolescents (10 to 19 years old) in the USA between 2016 and 2019, to identify the risk of developing suicidal ideation in teenagers with depression within a year of having been a victim of some form of violence (child maltreatment, physical assault, sexual abuse, psychological abuse or neglect) compared with those with depression but without the violence encounters. The authors identified 378 depressed adolescents who had experienced some form of violence, of whom 27.5% reported suicidal ideation within the following year, contrasted with 13.5% in the comparator group. After adjusting for covariates, adolescents who experienced a violence encounter were 1.7 times more at risk of developing suicidal ideation. Drilling into this, sexual abuse and physical assault were the events most likely to increase suicidal ideation, followed by having a history of substance use, being younger in age (10–14 years old), being of Black or Hispanic ethnicity, and having public insurance. This study highlights the need for identifying violence encounters not only in teenagers recently diagnosed with depression but also in anyone known to have been a victim of some form of violence. It is an issue particularly pertinent during the period of adolescence, with potential vulnerabilities to violence from carers, seniors and peers, and bullying – a common form of violence – feels sadly ubiquitous at this phase. These data show that victims of violence are at higher risk of suicidal ideation, even a year or more down then line, so there is an urgent need to provide timely support to young people who we know are at higher risk.

References

1 Visontay R, Mewton L, Slade T, Aris IM, Sunderland M. Moderate alcohol consumption and depression: a marginal structural model approach promoting causal inference. *Am J Psychiatry* 2023; **180**(3): 209–17.

2 Pecina M, Chen J, Karp JF, Dombrovski AY. Dynamic feedback between antidepressant placebo expectancies and mood. *JAMA Psychiatry* [Epub ahead of print] 1 Mar 2023. Available from: https://doi.org/10.1001/jamapsychiatry.2023.0010.

3 Vargas MV, Dunlap LE, Dong C, Carter SJ, Tombari RJ, Jami SA, et al. Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors. *Science* 2023; **379**(6633): 700–6.

4 Sacher J, Zsido RG, Barth C, Zientek F, Rullmann M, Luthardt J, et al. Increase in serotonin transporter binding in patients with premenstrual dysphoric disorder across the menstrual cycle: a case-control longitudinal neuroreceptor ligand PET imaging study. *Biological Psychiatry* [Epub ahead of print] 18 Jan 2023. Available from: https://doi.org/10.1016/j.biopsych.2022.12.023.

5 Wang J, Harrer S, Zwald ML, Leemis RW, Holland KM, Stone DM, et al. Association of recent violence encounters with suicidal ideation among adolescents with depression. *JAMA Netw Open* 2023; **6**(3): e231190.

https://doi.org/10.1192/bjp.2023.38 Published online by Cambridge University Press