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Kaleidoscope

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February's Kaleidoscope explored the 'iceberg model' of self-harm; March's copy reported several negative-outcome trials; and April is the cruellest month, sadly joining these issues. Cottrell *et al*[1] report on a multicentre, randomised controlled trial of manualised family therapy compared with treatment as usual in young people (11–17 years old) who had self-harmed at least twice and were under the care of secondary mental health services. Over 800 individuals were randomised, and the primary outcome was hospital attendance with self-harm in the year-and-a-half following the intervention. Disappointingly, there were no significant differences between the groups, with approximately a quarter re-attending in this way. However, there were gains in terms of secondary outcomes of reducing emotional and other behavioural problems. This obliges a reminder of the scale of the problem: for every adolescent death through suicide, there are 370 hospital presentations with self-harm; for each of these, there are 3900 adolescents self-harming but unseen in the community. As the authors state, scarce evidence exists in this area, and indeed they highlight how we are lacking a single effective intervention to reduce self-harm. The paper notes that this is a final common pathway for a multitude of problems in a very heterogeneous population, invoking Melville – 'it's not down in any map; true places never are'.

'Swallowing a spy' is a wonderfully entitled editorial[2] on the brave new world of digital adherence monitoring. In late 2017, Abilify MyCite was licensed for use in the USA. This combines the antipsychotic aripiprazole with an ingestible event marker that is activated by gastrointestinal fluids; transmitting a signal to an abdominal cutaneous patch, in turn contacting a mobile phone. All at once it combines a sensible principle and a remarkable technological achievement with the worst of psychiatry's legacies as societal controllers and a cohort of individuals typically defined by paranoia. As the worst tabloid journalism puts it: you couldn't make this stuff up. Taking an optimistic tack, John Kane, who is leading early trials on MyCite, argues that patients can delineate illness-based paranoid delusions from engaging with their doctor, and, further, that it is perpetuating stigma to say that those with psychoses cannot engage with or should not receive frontline novel interventions. Rosenbaum's piece in the *New England Journal of Medicine* talks thoughtfully of why people commonly don't take medication, an issue that pervades medicine and not just the realm of psychiatry. She notes how 'forgetting' may be sublimated from a desire to forget an illness, a sense of mortality and feeling defined by something that distresses us. The proposed issue is argued to be understanding and discussing non-adherence, rather than just reminding people to take medication.

'The depressions' continue to be slowly scientifically unravelled, even if no one else seems to be picking up on our proposed spectrum term. The 'transcriptome' is a summary of all RNA molecules in a cell and, as such, captures patterns of transcription of DNA. The transcriptome also reflects concentrations (or levels of expression) of RNA, so it is a candidate for studying the dynamic processes (e.g. gene–environment interactions) affecting the phenotype, in contrast to seeking the presence or absence of disease–gene associations in genome-wide association studies (GWAS). MicroRNAs (miRNAs) are epigenetic regulators of over half of our genes and miR-132 has attracted attention, with roles in cell proliferation, differentiation and synaptic plasticity; further, miR-132 has posited roles in complex neuronal processes, including longterm depression. Several genes associated with major depressive disorders (MDD) have been shown to be epigenetic targets of miR-132, and elevated serum levels have been demonstrated in individuals with MDD. Qi *et al*[3] explored the association between miR-132 levels and brain imaging in unmedicated patients with MDD. Compared with controls, greater levels were associated with reduced grey matter volumes in fronto-limbic networks and poorer cognitive functioning. Determining causality requires further work, but this opens up a putative mechanism for some of the brain changes seen in MDD.

Gandal *et al*[4] describe an analysis of the transcriptomes for schizophrenia (SCZ; $n = 159$), autism (ASD; $n = 50$), bipolar affective disorder ($n = 94$), depression (MDD; $n = 87$) and alcohol dependence (AAD; $n = 17$) alongside 293 matched controls. Complement component 4A (C4A) – previously implicated in GWAS of schizophrenia – was upregulated in the SCZ and ASD groups, but not in bipolar affective disorder, MDD or AAD. As the transcriptome may be modulated by use of psychotropics, the researchers also analysed the transcriptome signatures of primates treated with antipsychotics and showed a negative overlap with the SCZ group, which they suggests demonstrates that antipsychotic treatment moves the signatures closer to the normative levels of healthy controls. They then ran a replication for three of the disorder groups – ASD, SCZ and bipolar affective disorder – and found similar overlapping signatures. Transcriptomes may be an epiphenomenon of the disorder, rather than a component in a causal pathway from gene through to expressed phenotype. To test this, they compared disease-paired single-nucleotide polymorphism correlations (from published GWAS) with their transcriptome signature overlap data, finding a significant correlation that suggests the gene–transcriptome association is robust for each disorder. To identify common and distinct networks in transcriptome signatures, they ran a network analysis that clustered together common gene expressions across tissue types. For genes involved in synaptic regulation, there was a gradient of downregulated expression in the transcriptomes of ASD > SCZ. The SCZ group was approximately the same as the bipolar affective disorder group, which was in turn absent for the MDD and AAD groups. The MDD group showed a distinct pattern of dysregulated expression for genes associated with the hypothalamic–pituitary axis and hormonal signalling. The ASD group showed a distinct signature of upregulated microglia-associated genes that – given ASD's earlier onset in neurodevelopment – might represent a regulating role for microglia in early synaptic connectivity. Together, these results suggest that both genes and their expression share common pathways to the expression of phenotype in affected people.

Ketamine is the glamour child of psychopharmacology, stealing all the limelight, even if closer inspection of the data often fails to really impress; it has certainly opened up new avenues of research into glutamatergic and rapid-acting antidepressants. Yang *et al*[5] investigated its mechanism of action in a model whereby rats with congenitally learned helplessness (cLH) display a change in behaviour on the forced swim test (FST) when injected with ketamine. After infusion with 25 micrograms bilaterally into the lateral habenula (LHb), the rats displayed 'recovery' of behavioural despair and anhedonia (measured as immobile time in the FST and increased consumption of sucrose over saline in a preference test). The LHb is proposed to be an 'anti-reward' centre, with largely glutamatergic neurons sending inhibitory connections to the ventral tegmental area (VTA) – the midbrain origin of dopaminergic neurons for the mesocorticolimbic 'reward' pathway – and the dorsal raphe nucleus (DRN) – the serotonergic centre projecting

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to the forebrain. LHb neurons exhibit a burst-firing rather than tonic-firing pattern that activates inhibitory interneurons in the VTA and DRN, subsequently reducing their respective dopaminergic and serotonergic activity. This burst firing appears to be dependent on calcium influx mediated via the *N*-methyl-D-aspartate receptor, and ketamine is a potent antagonist of this receptor. Application of ketamine in the LHb reduced the burst-firing output to the VTA and DRN, but the selective serotonin reuptake inhibitor fluoxetine did not. Yang *et al* propose that the burst-firing behaviours in the LHb are key to both the biological symptoms of the depressions (essentially by applying a 'brake' to the VTA and DRN) and the mechanism by which ketamine exerts its rapid antidepressant effects. In cLH depressed animals (versus controls), the resting membrane potentials in LHb neurons were more hyperpolarised – although that might suggest these neurons are more likely to be silent, in fact, Yang *et al* suggest that a hyperpolarised neuron in the LHb is easier to 'switch' to a bursting pattern (rather than to a tonic, more constant background firing rate).

McMurray *et al*[6] bring forth an alternative pharmacological contender: a fast-acting GABAergic class, GLO1 inhibitors. Animal data have shown that increased levels of the ubiquitous cellular GLO1 are associated with depression and anxiety behaviours. This opens up testing the effect of pharmacotherapeutic intervention: reducing GLO1 levels. GLO1 catalyses and detoxifies the intracellular metabolic by-product methylglyoxal, which is a competitive partial agonist at $GABA_A$ receptors. In other words, a GLO1 inhibitor would lead in turn to an increase in $GABA_A$ receptor activity. Two novel compounds both showed rapid positive effects on the mice, with improvements by day 5 (compared with day 14 in those given fluoxetine), with concurrent enhancement of molecular markers of depression response, including brain-derived neurotrophic factor. Methylglyoxal crosses cell membranes easily, and its competitive partial agonist actions appear to offer benefits over direct $GABA_A$ modulators – none of the classical sedation and ataxia typically seen with such agents was shown here.

The dopamine D_2 receptor (DRD2) is psychiatry's white whale. So central to psychosis studies, yet only now is its structure when bound to an antipsychotic being revealed. In a magisterial piece of work in *Nature*, Wang *et al*[7] report on a structural study of an engineered human DRD2 crystallised in complex with the atypical antipsychotic risperidone at 2.9 Å resolution. It showed substantial differences from D_3 and D_4 receptors in extracellular loops and transmembrane helices. As would be expected, the complex with the drug shows the receptor in an inactive conformation, with a benzisoxazole component of risperidone extending into a deep extended binding pocket, while its tetrahydropyridopyrimidinone ring is rotated 90°. This binding was most noteworthy by the degree to which the cytoplasmic tip of transmembrane helix VI was separate from the transmembrane helical bundle, with a salt-bridge interaction acting as an 'ionic lock' during such binding. Differential side-effects, especially extrapyramidal ones, of typical and atypical antipsychotics have been proposed to be due to varying drug kinetics and serotonergic receptor binding affinities; the authors explain how the key pocket residue $Trp100^{EL1}$ controls risperidone's association and dissociation kinetics, and that this and other residues are shared with the $5HT_{2A}$ receptor.

Antipsychotics' relative inefficacy at treating negative symptoms is linked with their general inability to enhance mesocortical dopaminergic functioning, and the fact that in the prefrontal cortex, there is life beyond dopamine. Davidson *et al*[8] report on a double-blind randomised controlled trial of a novel compound MIN-101 that has affinity for sigma-2 and $5HT_{2A}$ receptors, but none for dopamine. A total of 244 stable patients were withdrawn off all antipsychotic medication and after 5 days given either the novel compound or placebo. By the 12-week end point, those on MIN-101 showed significant improvement on several negative symptom scales. Activation of sigma receptors leads to complex and as yet incompletely understood changes; they appear to indirectly modulate glutamate and dopamine pathways, as well as neuronal calcium. Quite how this might act therapeutically remains speculative.

Finally, 'preprint' is a common mechanism for early dissemination of findings in the physical sciences: should medicine follow suit? ArXiv is the largest such database, with over a million papers, mostly in the fields of physics and maths, and the principle is well embraced there. This is far less established in biological sciences, although the sharpest-eyed among you may have noticed that we included such a preprint paper in February's Kaleidoscope. 'MedArXiv' has been proposed, and, writing in *JAMA*, David Maslove[9] says it's time for us to debate this. There are the obvious problems in accessing early-stage data that have not been peer-reviewed and that may never make it through to being published, but also the seduction of very rapid open-access communication of findings that are archived and can be cited. Maslove says that clinical practice faces challenges not seen by the oft-compared early-adopter physicists and mathematicians: our data are typically of more interest to the public and media, with dangers of misinterpretation, unwarranted hype and expectation, especially as they typically 'look' very like standard peer-reviewed papers. They present a challenge to professionals, too, as we are less used to seeing them: if you read the aforementioned piece in February's Kaleidoscope, we suspect you missed that it was a preprint and probably just assumed it had been peer-reviewed and was reliable. As these papers are 'citable', we will see more journals referencing them; this will force reviewers and readers to pay more attention to reference lists, as such data must inevitably be treated with more circumspection. An exciting but testing development – we love to sail forbidden seas and land on barbarous coasts.

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