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# Kaleidoscope

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**Starting antidepressants – monitor over a fortnight, and if well-tolerated but unclear efficacy, consider increasing the dosage.** Except that we have never been so sure about that last bit – neither clinicians nor guidelines – and anecdotally some divide individuals in a binary way into 'responders' and 'non-responders' to a given drug. We previously reported on a patient-level mega-analysis showing greater gains at higher dose ranges,[1] although the inclusion of subtherapeutic doses might have skewed those results. Furukawa *et al* update us with a dose–response meta-analysis of five selective serotonin reuptake inhibitors (SSRIs), venlafaxine and mirtazapine in the acute management of major depressive disorders.[2] Their analysis included 77 double-blind randomised controlled trials, covering almost 20 000 participants. For SSRIs, the dose–efficacy curve, demonstrating the probability of response, gradually increased up to a dose equivalent between 20 and 40 mg of fluoxetine, and thereafter showed a flat to decreasing effect up to 80 mg. The authors note how this fits with positron emission tomography data that show about 80% serotonin receptor occupancy at low doses, with only small subsequent increases as doses rise. For venlafaxine there was an increasing gain through 75–150 mg, the higher doses potentially required to attain noradrenergic activity, with fewer gains at doses beyond this. For mirtazapine, there were improvements through to 30 mg, and decreased gains above that. Contrary to the efficacy, side-effects went up pretty much in a linear fashion with dose. As ever, treat the person in front of you, but these results support antidepressant sweet-spots being at the lower end of the dose range for most.

**Stopping antidepressants – monitor slowly over several weeks keeping an eye on mental state and discontinuation symptoms as the dose is reduced.** Except that there has been growing anxiety and public calls that this can be very difficult for some. Indeed, in the UK the Royal College of Psychiatrists has joined other bodies urging the National Institute for Health and Care Excellence to review this evidence, and some have argued that antidepressants are actually addictive for some people. Jauhar *et al* explore the evidence and argue that it is very difficult to assign 'addiction' as a label to these medications, not least as their use lacks the core concept of compulsion and voluntary drug-seeking.[3] Nevertheless, withdrawal effects are more clearly problematic, although the authors note the challenge of getting good quantitative date on their incidence, with the inevitable problem and biases of surveys. They cite work showing a range of such discontinuation symptoms, varying between drugs, but hovering close to 30%. However, notably, this is much lower (1.9–12.2%) in trials that had medication replaced by placebo (where individuals 'should' get discontinuation symptoms as the drug is stopped, but they do not realise this as they are switched to placebo); and the much discussed 'nocebo' effect also occurs for withdrawals, with high rates of discontinuation symptoms reported where individuals had their placebo stopped. A further problem is the challenge of how to disentangle symptom relapse in those stopping treatment. There is no doubt that the withdrawal problem is a real and significant one for many, and key missing data include the lack of adequate long-term follow-up of most research, and understanding the pharmacological mechanisms underpinning such symptoms, for example drug half-life or changes over time in specific receptor affinity.

**In psychiatry, you simply cannot ignore dopamine, a monoamine implicated in reinforcement learning, operant conditioning, mood, delusions, hallucinations, movement, motivation, compulsive behaviour, and Brexit (probably).** The origin of dopamine cell bodies for the mesocorticolimbic pathway are in the ventral tegmental area (VTA), implicated in motivation, that projects to the more anterior nucleus accumbens (NAc, implicated in motor programming, reward and reinforcement learning), receiving input from frontal lobe structures. After a rewarded action, dopamine cell firing correlates to the discrepancy between actual (received) and expected reward, the so-called reward prediction error. However, before taking an action – i.e. in a motivated approach – dopamine firing in the NAc ramps up in expectation of reward to signal the value of an activity (in advance of its execution). The temporal and regional specificity of changes in dopamine activity are unclear.

Mohebi *et al* recorded rat neurons in the VTA and NAc using microdialysis/spectroscopy to look at concentrations of neurotransmitters over 1 min intervals, as well as using a fluorescence method that reflected dopamine binding (which is proportional to dopamine release, rather than dopamine cell firing) with high specificity at much shorter timescales (the so-called dLight1 suite of genetically encoded optical dopamine indicators).[4] Rats were trained on a 'bandit task' that works as follows: the rat has to decide between a left or right 'port' that dispenses a sugar pellet with probabilities that change unpredictably. First, the rat is presented with a light that prompts the rat to approach and enter a central nose-poke port; after a short, variable time interval an auditory 'go' cue leads the rat to withdraw and nose-poke the left or right adjacent port. On some trials there is an audible 'click' that then prompts the rat to approach a food-port to collect a sugar pellet. The task is to learn the environmental stimuli that signal release of a sugar pellet. Importantly, the experimental design provides the rat with motivation to expend time and effort to act on some trials (leading to reward) but not others.

They found that the dLight1 method over 1 min to be consistent with previous studies with the NAc dopamine neurons clearly signalling reward-predicting cues in the environment similarly to those in the VTA. However, when looking at the dLight1-labelled NAc neurons at much shorted timescales there was a dynamic pattern within and between trials. They found that NAc dopamine correlated with state value – which is to say, there is a ramping up within trials prior to an expected rewarding outcome These cell's 'ramping up' behaviour was more prevalent than either reward prediction errors or the rate at which rewards were delivered, further supporting their role in signalling expected value.

In summary, the VTA consistently display burst firing activity that codes for reward prediction error and this drives activity in the NAc. The novel finding was that NAc neurons release dopamine in response to state value independently of the VTA. They suggest that dopamine cell firing alone is insufficient to understand the range of signals across different functions and timescales – and it is the dopamine release (and binding) that might be responsible for these differential functions. Given the propensity of most antipsychotics to blockade striatal dopamine, there has been some debate about antipsychotic-induced amotivation either mimicking or inducing the negative syndrome features of schizophrenia. A 2015 study by Fervaha *et al* in 121 patients who were antipsychotic naive (from the CATIE trial) examined medication and motivation at 6 months; interestingly, they found that neither the level of sedation or drug treatment (olanzapine, perphenazine, quetiapine, risperidone or ziprasidone) was associated with amotivation.[5]

**When first working to uncover brain mechanism, deletion can be a useful, if blunt, tool; remove a part of the brain, knockout a**



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**gene or deplete a neurotransmitter and observe the effect on function.** It is correlational at best, but has historically proven helpful in pointing us in the right direction. However, eliminating or having an impact on a function is not enough. To demonstrate true understanding of a process, it could be argued one must also be able to orchestrate its recreation. In an elegant series of experiments, Vetere and colleagues have done just that and claim to be the first to implant a true artificial memory.[6]

They focused on mice and an odour (acetophenone), which activates a specific receptor M72 OR, coded by a known gene *Olfr160* that can be precisely targeted. They began with the basics by proving that the odour, when paired with an unpleasant foot shock, would produce aversion to the scent. Next, they paired direct stimulation of the receptor with foot shock. When these mice were subsequently exposed to the odour for the first time, they too showed aversion. Finally, they eliminated all external sensory experience in the training by replacing the foot shock with direct activation of a projection that mediates aversion and found these mice were also motivated to avoid the smell they had never before encountered. The authors focused next on producing odour attraction, replacing foot shock with a food reward, and the aversive projection with one known to mediate reward. They found the same neural circuits to be active in both real and artificial memories, identifying the basolateral amygdala as the learning-specific site where all associations were formed. Collectively, these data show that it is possible to artificially circumvent experience and implant a specific memory in mice that can be retrieved with a never before seen external stimulus.

**We have all looked at some psychiatric facilities and wondered how the physical environment helps or hinders care.** Jovanović *et al* systemically reviewed the evidence for nidotherapy, noting how poorly designed facilities can appear custodial and repressive, and are blamed for contributing to boredom, reduced meaningful therapeutic engagement and even increased levels of violence.[7] They found that positive factors contributing to improved social interactions included having a community location, being smaller and more 'homelike' (up to 20 beds) and offering a wide range of communal areas and open nursing stations. In terms of interior design, plants were valued and furniture was preferred in small groupings, with secluded areas for conversations. Attaining the right balance between private and shared areas was a critical theme: having staff accessible, yet being able to have one's own space to 'retreat when feeling overwhelmed'. Clearly these factors vary in cost, and while some alterations can be retrofitted to existing space, others require bespoke or new builds. It comes back to the fact that the lived space matters to people, perhaps more so, when they are staying in hospital.

**Finally, it is been said that alcohol is a perfect solvent – it dissolves marriages, families and careers – and so to two papers that we think many of you will relate to, on doctors, stress and booze**. Ridout *et al* assayed saliva samples from 250 first-year junior doctors across 55 US hospitals.[8] They examined the associations between doctors' experiences and saliva-measured telomere attrition. Telomeres are tandem DNA nucleotide repeats found at the end of chromosomes, maintaining the stability and integrity of the genome. They decrease with cell replication, and below a certain level a cell will stop replicating. Stress has been shown to exacerbate this attrition and is linked to a number of health conditions including heart disease and increased premature mortality. Surveys were completed every 3 months during this year, exploring well-being, working hours and sleep, outside stressful events; saliva samples were taken at the start and end of the year. Longer working hours were associated with significantly greater telomere loss across the year. Shockingly, the mean attrition was six times greater than that seen in the general population across a similar time frame.

Medisauskaite & Kamau report on that dubious 'cure' for stress – alcohol – in the first study to explore a wide range of health problems and work risk factors in UK medics.[9] A total of 417 doctors completed the survey; 52% were women, and 49% were consultants. Of these, 44% binge-drank alcohol, with 5% meeting criteria for alcohol dependency. Sleep problems were reported in 20–61% (12% moderate–severe insomnia) and 69% experienced fatigue. The results are concordant with the fact that 55% of doctors report suffering from burnout or emotional exhaustion: a clarion call for nidotherapy and support for doctors as well as patients.

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