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Kaleidoscope

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'Special K' has had various connotations over the years, and with respect to depressive illness ketamine has most recently been mooted as a potential antidepressant. It is intriguing because of its almost immediate effects, and a pharmacology that has little connection with the predominant monoamine hypothesis. How does its blockade of glutamatergic NMDA receptors alleviate depressed mood? New data[1] suggest that a critical step is that this stabilises an adaptor protein, 14-3-3η, which decouples $GABA_B$ receptor signalling and influences the activity of the intracellular protein mTOR. The upshot is a change in synaptic structure that produces a therapeutic effect; the rather innocuously named 14-3-3η protein seems to be the essential link for fast-acting antidepressants. Formidable problems exist with using ketamine as a therapeutic option, including a very quick decay in effectiveness, as well as concerns about the intravenous administration of a compound that is an anaesthetic, a commonly misused recreational drug, and a pro-psychotic. However, an improved understanding of its mechanisms of action is essential in enhancing our knowledge of the neuropathology of depression, offering the potential for development of novel compounds circumventing some of these limiting factors.

Continuing with the theme of depressive disorders, it is clear that not all individuals with depression respond to treatment to the same extent. Etkin and colleagues[2] have evaluated the predictive role of neurocognitive performance in over 1000 medication-free individuals with a major depressive disorder. Participants were assessed on a battery of 13 cognitive tests before being randomised to receive treatment with sertraline, escitalopram or venlafaxine. Analysis using a pattern discrimination classifier determined that an 'impaired' subgroup of patients with poor cognitive performance (accounting for almost a quarter of the sample) could be identified with a high degree of accuracy, and that this cohort's *response* rate was inferior at 8 weeks to those in the average-range 'intact' group. Subanalyses showed that the degree of cognitive performance in the 'impaired' group also predicted the likelihood of *remission*, but only for escitalopram. The authors argue that what is exciting about this is that it can thus be used to guide individual drug prescribing: in 'impaired' testers whose scoring predicted remission there was a very clinically significant effect size to support escitalopram prescribing; in those predicted not to remit, another drug should be given. Pharmacologically it is interesting that venlafaxine, a serotonin–noradrenaline reuptake inhibitor touted to have pro-cognitive effects from its additional noradrenergic actions, did not demonstrate any such differential effect, although the authors acknowledge that prescription of this drug was typically at the lower end of its dose range. We know that only a third of our patients attain remission on a single antidepressant: in the future, depressive disorders may need a spectrum of assaying biomarkers, including cognitive measures, in addition to neuroimaging and genetics.[3]

Much is written about ultra-high-risk psychosis populations, following Kierkegaard's assertion that 'life can only be understood backwards; but it must be lived forwards', but what happens to the two-thirds of those in this group who never transition to a psychotic illness? Lin *et al*[4] assessed 226 such individuals who had been so-defined in the previous 2–14 years, and identified significant mental health problems in 68%, including mood disorders (49%), anxiety disorders (35%) and substance misuse (29%). The majority had such disorders at baseline, but there were high rates of their developing additional difficulties during the period of follow-up. We are reminded of the shared genetic and environmental factors that influence many mental illnesses, but also of the need for clinical services to be observant for a range of pathology, not just the emergence of psychosis.

Where people do go on to develop a psychotic illness, how closely does treatment map onto evidence-based guidelines? An examination[5] of prescription patterns in over 400 individuals from first-episode psychosis services – all treated with anti-psychotic medication for less than 6 months – identified that almost 40% might benefit from medication change. The reasons identified for change included above-maximum dose prescribing, polypharmacy, coprescribing of an antidepressant without clinical justification, failure to have an antipsychotic prescribed, and, in one-third, the use of olanzapine (PORT guidelines[6] advocate against the use of olanzapine in first-episode populations because of a greater propensity for adverse metabolic effects). Among other findings in this American study, those with private health insurance were less likely to receive polypharmacy; first-generation drugs were more commonly prescribed to uninsured and African–American patients; and women were more likely to be coprescribed antidepressants. As is ever the case, there is considerable freedom to prescribe outside of guidelines and licensing regulations, but informed consensual prescribing, with careful monitoring and documented clinical justification help fulfil the precept of *primum non nocere*.

In cognitive science, devising an algorithm that imitates human performance and demonstrating its implementation on a computer was thought to provide clues to how the same behaviour is exhibited by evolution's own 'wetware' computing device, the brain. In the 1950s John Nash and John von Neumann applied mathematical models to understand the theoretical end-points of interactions between people, modelled as games with simple rules. But there are important differences, notably, most 'killer apps' involved computer algorithms for playing chess, checkers or variants of games where the algorithm has complete information; thus, given unbounded space (i.e. memory) a computer can find an optimal solution within some prescribed time. For example, when trying to find the best counter-play to an opponent in chess, algorithms have access to every move played by the opponent in the current game, and a 'dictionary' of all possible counter-moves. The early problem was one of having sufficient computing resource to exhaustively search the dictionary and the sequence of plays that might consequently arise. Clearly, computing power has now developed to facilitate that process, but it is also evident that humans do not have the same capacity. It suggests that actually the exhaustive search strategy is not a good model for our behaviour, with the Nobel laureate Herbert Simon describing human decision-making as 'bounded rationality'. To make things worse, in most games (other than chess, checkers etc.) humans rarely have access to perfect information. In poker, for example, one does not have access to the complete state of the game; card hands are private, and opponents' betting behaviour gives inconsistent information as it does not necessarily map one-to-one onto the content of their hand (i.e. they can bluff).

Now in a paper in *Science*[7] Bowling *et al* have presented a solution for an imperfect information game – heads-up limit hold 'em poker (or HULHE for short). Using 200 computers – each

with 24 core CPUs, 23 GB of memory, 1 TB of hard-disk storage, and running continuously for 68.5 days – an exact solution to the game was derived. As well as now being statistically incapable of being beaten by an average human playing it for their entire lifetime, the algorithm confirmed the apparently widely held belief that the dealer has a substantial advantage in HULHE poker. It learned by using 'counterfactual regret minimization' – what we might call 'learning from our mistakes'. Interestingly, the practice of clinical medicine, perhaps no more so than in psychiatry, is similar to imperfect information gaming models as we make complex treatment decisions while faced with incomplete clinical information and sophisticated illnesses; the computer science team is now collaborating with diabetes researchers to test such medical paradigms. Will playing poker make us better doctors? Knowledge (they say) is knowing that a tomato is a fruit, but 'counterfactual regret minimization' is knowing not to put it in a fruit salad.

It is well-recognised that stress makes smokers light up, whether playing poker or not, and noradrenergic pathways have been implicated in both stress-induced reinstatement to nicotine and prefrontal cognitive control and adaptive behaviour. Guanfacine is a noradrenergic receptor agonist that preferentially binds at the α_{2A} receptor that is highly concentrated in the prefrontal cortex and locus ceruleus. In the central nervous system it acts to enhance executive functioning, while peripherally it reduces sympathetic tone, resulting in its use as an antihypertensive. Recent work[8] has demonstrated that a laboratory stress paradigm significantly increased systolic blood pressure and tobacco craving, and decreased the latency to *ad libitum* smoking in nicotine- deprived smokers; but these effects were significantly reduced or absent in those on guanfacine 3 mg/day, although complete abstinence rates were not increased during the 4-week trial. Concomitant neuroimaging showed that the drug increased prefrontal activation during a cognitive control task.

Guanfacine's pharmacodynamics mean that it may also have a use in cocaine dependency, where drug withdrawal is associated with tonic overactivation of the adrenergic system centrally and in the sympathetic nervous system, contributing to recognised symptoms of anxiety, agitation and emotional dysregulation. Early data[9] have shown that, compared with placebo, guanfacine attenuated anxiety and improved neurocognitive performance in early-abstinent cocaine-dependent individuals over a 3-week period. Tobacco use remains the leading global cause of preventable mortality, but existing nicotinic receptor agents often have limited effectiveness, and there is a far greater dearth of pharmacological options for cocaine dependency. Any novel agent that might support these certainly justifies further investigation.

Finally, what *causes* the placebo effect? We know it confounds research (at a growing rate), and we all casually accept that it gets people well, so how does this seemingly magical but profound phenomenon occur? Peciña & Zubieta[10] describe how positive expectations activate several neuronal networks comprising endogenous opioid and non-opioid systems (including dopamine and endocannabinoids) that are maintained by environmental conditioning and reward learning to produce positive physiological and psychological changes. Inter-individual biological differences in placebo-response mechanisms can now be measured, and the neurological underpinnings are linked to a resiliency mechanism construct. If we better understood this process, might we be able to utilise it therapeutically or would such research be further hampered by its own placebo effect in a vortex of paradoxical circularity? The authors propose we can make clinical use of this knowledge – potentially stratifying study participants by placebo-responsiveness biomarkers – and this ongoing work is also pointing to biological aspects not targeted by traditional treatments. Which musings on positive expectations and experiences made us reflect on the wisdom of the father of English medicine, Thomas Sydenham, who said 'The arrival of a good clown exercises a more beneficial influence upon the health of a town than of twenty asses laden with drugs'.

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