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Kaleidoscope

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Antidepressants and electroconvulsive therapy (ECT) are two areas of mental health where there are strong polarised views on the available data. Writing in the *BMJ*, Stone et al[1] explored 232 placebo-controlled randomised controlled trials (RCTs) of antidepressant monotherapy for major depressive disorders submitted by a drug manufacturer to the Food and Drug Administration between 1979 and 2016. Individual participant level analysis was undertaken on the more than 73 000 subjects and showed positive drug efficacy, which was greater in more severe illness. After controlling for baseline severity, age and gender, effects were stable across the period in both placebo and active intervention groups, rebutting the common claim that placebo responses have been increasing with time. More interesting was the trimodal response distribution into large, non-specific and minimal responses. Those treated with active medication were more likely to show a large response and less likely to show a minimal response. The authors argue that delineating trials more simply into responders/non-responders misses this nuance, and that averaging out results hides subpopulations. This brings us back to an issue we have discussed in Kaleidoscope previously: the range of *depressions* and how we prospectively delineate the genetic, psychological and social factors that make individuals more or less likely to show an optimal response to an antidepressant.

On to ECT, where the challenge is typically about the lack of adequate placebo-controlled RCTs. This is not an unreasonable observation, though not unique to ECT. Emergency and urgent issues, such as rapid tranquilisation or managing a ruptured aorta, present particular ethical issues when considering randomisation to a placebo group. This has been clearly one of the key issues for ECT, which is most commonly given as an urgent intervention in very profoundly depressed and vulnerable individuals. There are sham-controlled trials, but they are pretty dated now and were often methodologically challenged. However, there are ways to work around the RCT problem, and recent work has compared ECT with medications and other forms of neuromodulation. Kaster et al[2] took a Canadian data-set to retrospectively explore the risk of death by suicide in the year following a psychiatric admission for depression, comparing those who had ECT (just under 5000) with those who had not (over 62 000). The study is notable for its attention to bias and confounders, with propensity score weighting used to account for over 100 covariates, including illness severity and social supports. ECT was associated with an approximately 50% reduced rate of death by suicide and a 25% reduction in all-cause mortality. Interestingly, no association was found between the number of ECT treatments and risk. It is worth considering that even a very well-designed RCT on ECT could not have found this: suicide is all too frequent, yet it is 'relatively rare' at a population level, and no RCT could ever be adequately powered to detect such change. Each trial method carries its own strengths and weaknesses. Will these new papers convince those seemingly philosophically opposed to either intervention? We shall have to see.

Continuing the discussion on science and beliefs, Philip K. Dick wrote that 'Reality is that which, when you stop believing in it, doesn't go away'. Some people display behaviour around their beliefs about a topic which seems disproportionate to their observable expertise: the Dunning–Kruger effect tells us that people with lower objective ability on a task nevertheless tend to have excessively positive self-assessments. In this post-truth social-media-fuelled age, this can manifest in the kinds of 'us versus them' conspiracy around topics such as climate change, that an election was rigged and that vaccines contain covert surveillance devices. In a new paper, Light et al[3] seek to examine whether overconfidence is more associated with anti-consensus views on 'hot' scientific topics: genetically modified foods, the validity of the big bang theory, the effectiveness of homeopathy, anthropogenic climate change and Covid mitigation/prevention policies. Nationally representative volunteers were first asked to express their 'opposition' to the dominant scientific consensus on one of seven topics, with those who expressed most opposition given further questionnaires. These measured their objective knowledge of the topic, their confidence in their answers, their own subjective evaluation of their knowledge of the topic, and their political alignment and religiosity.

The results were remarkably consistent: participants' estimates of their own (subjective) knowledge level increased as a function of higher levels of opposition, but their actual objective understanding was lower. The more an individual opposes a scientific consensus *a priori*, the more confident they are in their own knowledge of the topic, but the less they appear to actually know. There were exceptions – for example, level of opposition had no association with better/worse self-reported subjective knowledge for the big bang theory and evolution. This is perhaps as, for these topics, people often hold 'hard' beliefs: if one is opposed to evolution, there is no issue of 'knowing more or less about' the topic, it simply rests on a fixed belief. However, for both the big bang theory and evolution, lower objective knowledge was still associated with increasing opposition. When examining Covid-19 vaccines, one must consider that this experiment was performed in the summer of 2020 prior to the vaccine roll-out. Despite that caveat, higher opposition was again associated with lower levels of objective knowledge of the science – including how vaccines work and the science of virology and, predictably, higher subjective evaluation of one's own expertise on these topics. Plato and Galileo taught that conforming to consensus isn't always the right path, but these data caution that if the reasons for opposing consensus are driven by incorrectly high subjective belief in one's own expertise, then society has to do better at orienting people to the science.

Back to Covid, and, presuming you're on-board with vaccine effectiveness, have we adequately learned for another pandemic? An editorial in *Nature Medicine* says no and challenges us that we are sleepwalking into the next one.[4] The rapid scientific process of the past couple of years are applauded, but it's noted that we had a 15 year lull prior to that following the 2004 severe acute respiratory syndrome coronavirus, and monkeypox, an orthopoxvirus related to smallpox, is foreshadowing what lies ahead. Research into orthopox viruses plummeted after the eradication of smallpox, but an animal reservoir (primarily rodents, not monkeys) has always persisted, with occasional jumps to human populations, mainly in Africa. The editorial calls out how research efforts and funding typically only take off when high-income countries are affected, highlighting the millions of annual cases and thousands of deaths from dengue, with its scarcity of treatment options. The World Health Organization's research and development blueprint and hub for pandemic and epidemic intelligence are lauded, but much more is needed internationally. Infrastructure for better virus surveillance, genome sequencing, vaccines, antiviral agent developments, and broader research and development are needed now, especially for conditions emerging in low- and middle-income countries. Although this should not be the driver, it is rightly noted that investment in research and development gives a positive return of up to 20%, and the costs lost to Covid-19 are evident for all to see.

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'Adapt or die' call out Trisha Greenhalgh et al,[5] describing how the pandemic necessitated an urgent shift from evidence-based medicine (EBM) to 'EBM+'. The RCTs lauded at the start of this month's column had their limits tested by Covid-19, being often ill-suited to a rapidly changing and multifaceted environment. The use of face-masks and individual and collective responses to social restrictions are ready case examples. The authors introduce us to their construct of EBM+, which includes mechanistic research, complexity science, engineering and social science, providing a framework to develop and evaluate interdisciplinary evidence. Evidence of putative mechanisms is allied with that from clinical trials and other, non-randomised data such as the results of observational and comparative studies. Without assuming a primacy for any one, their expert dynamic summation is where the value lies; aligning with the prior piece on the 'next pandemic' the authors note that we need answers to many questions such as how to make education, employment and healthcare environments as safe as possible, how to protect as many people as possible without shutting down the economy, and how to minimise healthcare inequalities amplified by Covid-19.

The social aspects of vulnerability to psychiatric illness were examined in a recent model in *Lancet Psychiatry*.[6] Focusing on the known relationship between childhood maltreatment and mental health outcomes, McCrory and colleagues set about clarifying the dynamic interplay of factors in this space. The result is a transactional and bidirectional model that centres on the construction of our social world. Defined broadly by repeated exposure to neglect, abuse of any kind or both, maltreatment generates neurocognitive adaptations that help an individual to function in the adverse environment. The authors hone in on three alterations that they posit affect psychiatric vulnerability via indirect effects on social functioning: threat, reward and autobiographical memory processing. Alterations in each of these can leave a person poorly equipped to negotiate social interactions or learn from them, creating negative feedback that, without protective influences, can lead to further exacerbation of these brain-based changes and social problems over time.

The difficulties seen with social relationships in instances of maltreatment are well explored and manifest specifically in smaller social networks and fraught relationships that are themselves stress generating. Each iteration of this social transaction cycle focuses the trajectory towards, or away, from mental health. As such, the proposed model offers us a potential and much needed preventive intervention point in the escalation of maltreatment to psychiatric disorders. The proposed implications highlight the need for a purposeful shift in educational and social care systems to prioritise a child's social experience and relational needs, recognising them as an external vulnerability point, rather than focussing on the individual or their symptoms. Of course, there is much refining to be done, and neuroscience will be a huge factor in optimising intervention points and targets, but the recommendations as they stand are practical and potentially very achievable.

Finally, have you ever kept a secret from your partner? We know you have, we all do; but does it 'matter'? Brick et al report on so called 'secret consumer behaviours' in close relationships[7]. They start off with examples of secretly eating a chocolate bar on the way home for work or hiding a delivered package of rather expensive online impulse purchases. We're quite sure you can think of others, though like us you might have erstwhile been unfamiliar with one name of this sin – 'financial infidelity'. Reviewing the literature on the topic, they concur with the Kaleidoscope team that it's very common, and further, typically very mundane (unless your example of what you keep hidden from your partner was more exotic). More important was the downstream work as to whether such intentional deception adversely affected relationships, with an exploration of emotional, behavioural and relational aspects. The most common outcome was a sense of guilt in the (let us call them) secret-chocolate-scoffers. However, this led to greater investment into the relationship as a compensatory mechanism. It highlights that there has been less work on *motives* behind non-disclosure, which can be benevolent in intent, such as not wanting to eat junk food in front of a partner trying to lose weight. The authors emphasise that openness and mutual disclosure are hallmarks of close relationships, so you don't have *carte blanche* here. But a modest excuse when a used Snickers wrapper (or equivalent) is found in your pocket: it's only because you care that you didn't say anything.

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