

Kaleidoscope

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Preventing recurrence after recovery from a major depressive episode is a key clinical goal: but what are the best strategies?

During an acute episode, antidepressants and cognitive-behavioural therapy (CBT) are equally efficacious and their combination is typically shown to be superior to either alone. However, there are surprisingly few randomised controlled trials (RCTs) on the longer-term impact of CBT on major depressive episode recurrence, particularly when combined with medication. DeRubeis *et al* report on 292 individuals who had recovered from a chronic or recurrent major depressive episode through the use of antidepressant medication either with or without CBT.¹ The participants in remission were randomised to either stay on their medication or have it gradually withdrawn, and followed up over 3 years. Those kept on antidepressants did substantially better than those taken off them, regardless of how they had initially attained remission. Interestingly, previous treatment with CBT did not have an impact on the likelihood of recurrence; this is all the more surprising given that those who received both interventions showed superior outcomes in the acute recovery phase. The authors raise an intriguing possibility that medication might interfere with the impact of CBT in the acute phase, and note that a CBT-only arm is needed in future studies.

Antidepressant harms are almost as frequently debated as data on their effectiveness. Studies have been somewhat inconsistent, so Dragioti *et al* report on what they label a ‘systematic umbrella review’ of 45 meta-analyses of observational studies on the topic.² Crucially this graded the available evidence – rather than ‘just’ report it as often occurs in meta-analyses – to better understand any drug harms. Observational studies are usually considered better than RCTs when it comes to monitoring harms, as they have more ‘real-world’ representation and longer follow-up. Overall, the data were mixed: of the 120 affirmative correlations, 74 were nominally statistically significant, 52 had large heterogeneity, small-study effects were found in 17 and an excess significant bias was found for 9. Convincing data were found for an association with suicide attempts and completion in children and adolescents, and exposure in pregnancy and preterm births, low Apgar scores and subsequent autism spectrum disorders. However, critically, these did not reflect causality, and none of these associations remained supported after sensitivity analysis adjusted for confounding by indication. The take-home message is that these medications have no absolute contraindications and the data on harms are actually not that well supported.

In both papers there are dangers of misinterpretation of the data: the first study does not downplay the utility of CBT in acute treatment of a major depressive episode, but shows limitations at preventing future recurrence, possibly because of medication interference;¹ in the second, it is critical to note confounding by indication when considering the associations with suicidality, autism spectrum disorders and so forth.² In both, no doubt, more prospective work is needed.

The previous two studies highlighted some of the limitations of our ‘gold-standard’ RCTs. Davis *et al* give an overview of where observational pharmacoepidemiology might lead us.³ Such work taps into large publicly available data-sets that, allied to the use of specialist statistical analysis, can serve to enhance result validity. These can include traditionally under-researched yet valuable ‘real-world’ samples. The authors note the tricky issue of consent:

although, of course, essential to an RCT, this loses many vulnerable individuals – for example those with severe psychosis or intellectual disability – about whom important anonymised clinical data are held, and for whom better treatments are urgently needed. Pharmacoepidemiological studies are also cheaper and quicker than RCTs, and can address complex issues – including co-prescribing and side-effects (‘pharmacovigilance’) both common and rare – over far longer periods of time than a RCT. Such large data-sets also hold out promise for personalised medicine, and which drug might work in whom, albeit pay-off has been scarce so far. So, what’s not to like? Of course, most notably, observational data cannot directly address the issue of causality. Further challenges include the erstwhile mentioned confounding by indication, but the authors argue this can be managed via active comparison groups and within-individual designs.

Kennis *et al* meta-analysed the best available prospectively analysed data ($n = 75$ studies) to evaluate the current utility of proposed biomarkers for major depressive disorders.⁴ This took in a full raft of neuroimaging ($n = 24$), gastrointestinal ($n = 1$), immunological ($n = 8$), neurotrophic ($n = 2$), neurotransmitter ($n = 1$), hormonal ($n = 39$) and oxidative stress putative factors ($n = 1$). The study only showed a predictive effect for cortisol on the onset/relapse/recurrence of major depressive disorder (although not the time until this occurred). Notably 17 studies addressed cortisol, and it is clear that there are far fewer data on the other factors studied, most of which were studied for quite short follow-up durations. Further, the neuroimaging literature is very heterogeneous in brain regions focused upon, and, in this study, this precluded calculating an overall effect. The authors note that their work does not indicate that causal biomarkers do not exist; but, at this time the data, by and large, do not support biomarkers of this illness and delineating depressions remains elusive.

Maladaptive reward memories are learned pairings between an environmental cue – like the smell of whiskey or the sound of the cork popping in a wine bottle – and drug reward that when triggered, make people vulnerable to relapse. Current treatments such as CBT and cue exposure take a top-down approach, suppressing these memories through alternative learning, leaving the original maladaptive reward memory intact. All memories destabilise to be able to incorporate new information, making them vulnerable to interference before rewriting and storage, a process dependent on *N*-methyl-D-aspartate (NMDA)-receptor mediation. Das and colleagues tested the impact of targeted-alcohol maladaptive reward memory interference via ketamine, a high-affinity non-competitive NMDA antagonist.⁵ A total of 90 beer-preferring participants with hazardous or harmful drinking patterns were recruited and split into three groups: retrieval of alcohol memories followed by ketamine or placebo (RET + KET and RET + PBO, respectively), and no retrieval followed by ketamine (NoRET + KET). Baseline measures were taken using a cue reactivity task and self-report scales on the hedonic and motivational aspects of alcohol. Then the task was recreated, memories were destabilised (or not) and intravenous ketamine or saline was administered. Plasma ketamine and metabolite levels were measured pre- and post-infusion. A week later, participants reported perceived changes in their volume, enjoyment and craving of drinking with additional follow-up assessments of drinking behaviour measured remotely at 2 weeks, 3, 6 and 9 months.

Balancing against the issues with self-report and the attrition levels across the study duration, the RET + KET condition had a unique impact on alcohol reward. There were decreases seen in the urge to drink, as well as the anticipated and actual enjoyment of drinking. Long term, this group halved their weekly consumption from roughly 84 alcohol units to 41 by the study’s end, although

there were reductions across all groups. Interestingly, plasma ketamine and metabolite levels during the memory reconsolidation window predicted subsequent drinking in the RET + KET group, but not the NoRET + KET group, in a dose-dependent manner, showing promise as a potential biomarker for treatment response in this paradigm. Reconsolidation interference by ketamine appears to weaken the maladaptive memories and rewrite the reward contingencies around alcohol with lasting effect after just one administration. This more direct, bottom-up approach to a basal drive and core mechanism in substance use disorders is an exciting new area of investigation for single session or adjunctive therapy.

Finally, reviewer two, reviewer two: what did we ever do to upset you? Although essential for protecting the integrity of research, we're all familiar with the vagaries and, at times, sense of unfairness of the review process. A recent paper in the *BMJ* that analysed over six million journal articles showed that men generally used more superlatives in the abstracts of their work – such as 'unique', 'first', 'excellent' and 'remarkable' – which was subsequently more cited.⁶ Women authors appeared far more modest (or perhaps honest), and also typically had their work spend 3–6 months more under review. There has been less focus on qualitative content of reviews, and how this might have an impact on researchers' sense of scientific worth. Silbiger & Stubler undertook an anonymous international survey of the experiences of researchers in science, technology, engineering and mathematics (STEM) subjects.⁷ Respondents across gender and ethnicity groups commonly reported having received unprofessional reviewer comments, something that had occurred to about half of those surveyed. However, underrepresented STEM groups were more likely to perceive a negative impact on their aptitude, productivity and career progression after such a review. White men were least likely to subsequently question their ability – perhaps they believe their own superlatives.

There is never any need for unprofessional reviewing, and this survey suggests such rudeness has the most impact on those who should be most supported to advance diversity in our field. Reviewers have traditionally been protected by anonymity, and there are cogent arguments supporting this, but there perhaps needs to be an allied focus on the tone and content of reviews, as well as prospective analysis and redressing of gender differences in review time and acceptance rates. There is a problem in self-promotion and reviewing of science: it appears to be pale, male and stale.

References

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