Researchers find evidence of shelved negative results in preclinical studies of anxiety

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A systematic review of rodent studies of anxiety drug targets has found a possible reason for thwarted drug development in the field: researchers might not reveal all the data they collect.

"In a perfect world of open data, researchers would publish every single datum," says Adam Claridge-Chang, who led the investigation at the A*STAR Institute of Molecular and Cell Biology (IMCB). "But there is a stigma attached to negative results, so these data are often censored by the researchers themselves, even though they are useful."

Claridge-Chang's in-depth probe into preclinical data could lead to better treatments for the cluster of mental health disorders that affect more than 7 per cent of the global population.

Treatments for anxiety have been fraught with problems. In the early twentieth century, pharmaceutical companies began selling barbiturates, which put patients at risk of lethal overdose. These were followed by diazepam (first sold as Valium), which can be habit-forming and can cause severe withdrawals.

A new class of drugs was released in the 1990s called selective serotonin reuptake inhibitors (SSRIs). These drugs, including Prozac and Zoloft, increase serotonin levels in the brain by blocking the proteins that pump them into neurons. But scientists have grave doubts about their effectiveness.

Claridge-Chang's group at A*STAR studies anxiety in the vinegar fly, a powerful genetic model. When they turned to the mouse and rat literature for guidance, they found many contradictory results. This lack of consensus was especially striking, as preclinical studies of rodents typically form the basis for psychiatric drugs entering clinical trials.

To make sense of the background, team members Farhan Mohammad and Joses Ho analyzed more than 300 mouse and rat studies published between 1985 and 2015 for ten types of anxiety drug targets, including the targets of SSRIs. Eight of the interventions were found to have strong effects on anxiety in the animals.

However, when the researchers plotted the published data on a graph, they found an unexpectedly skewed pattern. "Where dots should have been, they weren't," explains Ho. Medical statisticians show that such skewed distributions usually indicate that researchers are shelving statistically insignificant results, a phenomenon called 'publication bias'.

This wasn't the only inconsistency: mutant mice lacking the SSRI target protein had higher anxiety levels, even though SSRIs are prescribed as anti-anxiety medications. Yet the literature didn't reflect this. "This is a direct contradiction, but about half of the authors didn't even mention it in their papers," says Claridge-Chang.

More information: Farhan Mohammad et al. Concordance and incongruence in preclinical anxiety models: Systematic review and meta-analyses, *Neuroscience & Biobehavioral Reviews* (2016). DOI: 10.1016/j.neubiorev.2016.04.011

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