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Main Points Supporting a Ban on the Forced Swim Test in Aotearoa, New Zealand

Introduction

Our petition asking for the New Zealand Government to pass legislation to ban the Forced Swim Test and to conduct a formal review and evaluation of the validity of *all* animal-based psychological tests used in New Zealand received 25,012 signatures. This petition was given to the Economic Development, Science and Innovation Select Committee on October 4, 2019.

The New Zealand Anti-Vivisection Society (NZAVS) is New Zealand's primary non-profit organisation defending animals used in science. We work to end animal experimentation and the harmful use of animals for research, testing and teaching in Aotearoa.

The arguments for this ban are:

1. The invalidity of the Forced Swim Test
2. The unethical treatment of animals
3. The negative impact on humans
4. The wastage of time, money and other resources
5. The global shift away from the use of this test
6. Public support for the ban

Executive summary

1. The Forced Swim Test does not reliably predict the human response — nullifying any scientific justification for carrying out the test.
2. Stress, anxiety and fear are inflicted upon animals in Forced Swim Test experiments, making the use of this test highly unethical.
3. There are many Kiwis suffering from depression who need effective treatments. It is essential for them that the research methods being used are reliable and relevant.
4. Due to its lack of translational value to humans, the Forced Swim Test is a waste of money, time and other resources.
5. Even the pharmaceutical industry itself is recognising this test as outdated and irrelevant, with global pharmaceutical giants such as Johnson & Johnson publicly announcing a ban of the Forced Swim Test. Four of the top five pharmaceutical companies worldwide (in terms of revenue) have committed to no longer use the Forced Swim Test.
6. Public opinion on the issue strongly supports a ban: a poll by Horizon Poll Ltd. showed that only 14% of New Zealanders supported the continued use of the Forced Swim Test; and over 25,000 people signed our petition asking for a ban.

Background description

What is the Forced Swim Test?

The Forced Swim Test, also known as the Porsolt Swim Test or the behavioural despair test, was created in 1977 by Roger D. Porsolt as a method for screening antidepressant drugs.¹

The Forced Swim Test is an animal test that involves forcing small animals such as rats or mice to swim in an inescapable beaker of water until they 'give up' and float (see Figure 1). Some researchers use the test as a misguided attempt to mimic multiple human conditions including depression or hopelessness in humans. The basic Forced Swim Test protocol, which may vary among different studies, involves forcing the animals to swim for anywhere from six to 15 minutes, once or multiple times. Video footage from each trial is analysed, and active (swimming and climbing) and passive (immobility) behaviour are examined.²

"The forced swim test is a rodent behavioural test used for evaluation of antidepressant drugs, antidepressant efficacy of new compounds, and experimental manipulations that are aimed at rendering or preventing depressive-like states. Mice are placed in an inescapable transparent tank that is filled with water, and their escape related mobility behaviour is measured."³

A video of the Forced Swim Test to accompany the above quote can be found [here](#).



Figure 1: A rat being subjected to the Forced Swim Test in a laboratory (Photo credit: The Irish Anti-Vivisection Society)

Where is this test being used in New Zealand, and what is it used for?

It is difficult for us to know the full extent to which this test is currently used in New Zealand because private companies are not subject to the Official Information Act. However, we submitted an Official Information Act request to all the main tertiary institutes in New Zealand asking if they have approved and conducted this test in the past five years. The results (see Figure 2 below) showed that two universities had: The University of Otago and Victoria University of Wellington. Their full responses can be supplied upon request.

¹ Porsolt, R. D., Le Pichon, M., & Jalfre, M. L. (1977). Depression: a new animal model sensitive to antidepressant treatments. *Nature*, 266(5604), 730.

² Slattery, D. A., & Cryan, J. F. (2012). Using the rat forced swim test to assess antidepressant-like activity in rodents. *Nature protocols*, 7(6), 1009.

³ Can, A., Dao, D. T., Arad, M., Terrillion, C. E., Piantadosi, S. C., & Gould, T. D. (2012). The mouse forced swim test. *JoVE (Journal of Visualized Experiments)*, (59), e3638.



Figure 2: Use of the Forced Swim Test in New Zealand tertiary institutes

We have found multiple publications that further prove that the Forced Swim Test has been approved by the Victoria University of Wellington Animal Ethics Committee and the University of Otago Animal Ethics Committee and used by researchers at these institutions.

In these publications, Victoria University-affiliated authors have described the Forced Swim Test as a way to assess for 'pro-depressive effects',^{4,5,6} and 'depressive behaviours',⁷ and as a way to evaluate 'depressive-like effects',^{8,9} despite the lack of a strong scientific basis to support its use.

These claims are also at odds with the Victoria University Animal Ethics Committee (AEC), the committee that approved the use of animals in the publications cited above. The Victoria University [AEC agree](#) with the research that the Forced Swim Test is not a valid measure of depression-like behaviour.

The Forced Swim Test has also been used in New Zealand for research into drug addiction, anxiety, infertility, stress, and stroke experiments on animals. While experimenters, including those at the University of Otago and Victoria University, conduct these tests in the hope of learning more about how these different conditions affect humans, their efforts are sadly misplaced. This is

⁴ Kivell, B., Paton, K., Kumar, N., Morani, A., Culverhouse, A., Shepherd, A., ... & Prisinzano, T. (2018). Kappa opioid receptor agonist mesyl Sal B attenuates behavioral sensitization to cocaine with fewer aversive side-effects than salvinorin A in Rodents. *Molecules*, 23(10), 2602.

⁵ Morani, A. S., Schenk, S., Prisinzano, T. E., & Kivell, B. (2012). Single injection of novel kappa opioid receptor agonist salvinorin A attenuates expression of cocaine induced behavioral sensitization in rats. *Behavioural pharmacology*, 23(2), 162.

⁶ Young, D. (2015). Pre-clinical anti-addictive and side-effect profiles of novel kappa-opioid agonists.

⁷ Morani, A. S. (2011). Behavioural pharmacology of novel kappa opioid compounds.

⁸ Mathew, S. et al. (2016). *Breaking the Cycle of Addiction; Investigating the side-effects of 16-Ethynyl Sal A (a potential anti-addiction drug)*. Retrieved from <https://www.victoria.ac.nz/news/2016/04/summer-gold-competition-2016-winners/MEDoR-SBS-109-Mathew,-Stephen.pdf>

⁹ Ewald, A. W., Bosch, P. J., Culverhouse, A., Crowley, R. S., Neuenswander, B., Prisinzano, T. E., & Kivell, B. M. (2017). The C-2 derivatives of salvinorin A, ethoxymethyl ether Sal B and β -tetrahydropyran Sal B, have anti-cocaine properties with minimal side effects. *Psychopharmacology*, 234(16), 2499-2514.

evidenced by the large amount of animal research that has already been conducted in these areas and the paucity of improvements that have resulted for humans who are suffering.

1. The invalidity of the Forced Swim Test

Any correlation between an animal's behaviour during the Forced Swim Test and their mood, or its relevance to human depression, or to the utility of a compound for treating human depression has been scientifically refuted, as thoroughly discussed in [this article](#) by Dr Trunnell titled, "*The Invalidity of the Forced Swim Test.*"

Scientific evidence suggests that floating is a learned and adaptive behaviour, one that saves energy and is beneficial for survival.¹⁰ Individual animals who are quicker to float also save energy and are less likely to sink, meaning that animals who more rapidly pick up on this and spend less time struggling, are simply learning this adaptive behaviour more readily.

Some researchers claim that the Forced Swim Test is a screening tool for antidepressant activity, since sometimes mice who are given human antidepressant drugs will swim more and float less. The immobility response however also occurs after treatment with drugs that do not have antidepressant effects, such as antihistamines, caffeine and other miscellaneous drugs.¹¹ Time spent swimming versus floating is also influenced by the genetic strain of an animal and experimental variables such as water depth or temperature.¹²

A problem with misinterpretation of the forced swim test is the assumption that it can serve as a measure, and sometimes the sole measure, to describe an animals' mood. In a [commentary](#) published in the peer-reviewed journal *Psychoneuroendocrinology*, Dutch scientists estimated that in the 4,300 papers reporting use of the forced swim test at the time of publication, at least 2,020 labeled an animal floating as depression, "sometimes with a remark that the validity of the test is debated but often without discussion."

Scientists from People for the Ethical Treatment of Animals (PETA) in the United States [have found](#) that, in the 30 years between 1989 to 2018, experimenters at four major pharmaceutical companies gave animals 47 different test drug compounds before subjecting them to the Forced Swim Test. 36 of the compounds "showed promise" based on the invalid interpretation of the test. But none of those are now on the market to treat human depression. PETA's analysis found that **the Forced Swim Test was less predictive than chance (50%) at determining if a compound would have antidepressant efficacy in humans.**

Noteworthy articles recently published that highlight problems with the Forced Swim Test:

- [Depression researchers rethink popular mouse swim tests](#) in [Nature](#)
- [Letter to the editor: Use of the forced swim test to assess "despair"](#) in [Brain Stimulation](#)
- [Forced-Swim Test Criticized as Uninformative, Cruel](#) in [The Scientist](#)

¹⁰ Molendijk, M. L., & de Kloet, E. R. (2015). Immobility in the forced swim test is adaptive and does not reflect depression. *Psychoneuroendocrinology*, 62, 389-391.

¹¹ Arai, I., Tsuyuki, Y., Shiimoto, H., Satoh, M., & Otomo, S. (2000). Decreased body temperature dependent appearance of behavioral despair in the forced swimming test in mice. *Pharmacological research*, 42(2), 171-176.

¹² De Pablo, J. M., Parra, A., Segovia, S., & Guillaón, A. (1989). Learned immobility explains the behavior of rats in the forced swimming test. *Physiology & behavior*, 46(2), 229-237; Jefferys, D., & Funder, J. (1994). The effect of water temperature on immobility in the forced swimming test in rats. *European journal of pharmacology*, 253(1-2), 91-94; Lucki, I., Dalvi, A., & Mayorga, A. J. (2001). Sensitivity to the effects of pharmacologically selective antidepressants in different strains of mice. *Psychopharmacology*, 155(3), 315-322.

If the Forced Swim Test is so flawed, why is it still being used?

The claim is often made that the Forced Swim Test is **commonly used** to model human depression.^{13,14,15,16} This claim appears to be the strongest justification that researchers have for why they still use the test today. As a result, the Forced Swim Test is used “widely” without sufficient evidence validating its translational value to humans.

2. The unethical treatment of animals

The Forced Swim Test is so traumatic to animals that the test is often used as a stressor in itself,¹⁷ in an effort to create a sense of helplessness. This test has also been conducted by affiliates of Victoria University for this reason.¹⁸

We’ve heard the claim that rodents enjoy swimming, but this is a redundant statement. The Forced Swim Test creates a situation where the animals are not swimming by choice, they are forced to swim against their will, and they have no way of escaping.

New Zealand law now recognises animals as sentient¹⁹ and this is not how sentient beings should be treated. Rats and mice are smart, social and curious animals who deserve to be treated with respect. The Forced Swim Test inflicts stress, anxiety and fear upon animals and this needs to be stopped.

3. The negative impact on humans

More than 95% of drugs that appear to work in animal experiments fail to lead to drugs or therapies for humans.²⁰ This means that there is a high probability that antidepressants thought to be of potential use for humans will subsequently be abandoned based on the misleading results of the Forced Swim Test.

Depression is a serious condition that affects many Kiwis. Between 50-80% of New Zealanders will experience mental ill health including depression or addiction challenges at some point in their lives.²¹ Therefore finding effective treatments is paramount. Our best chance at finding these treatments is by using human-relevant research methods that produce valid results. The Government could do more to promote such research methods, including increasing funding for this type of research.

Superior methods for antidepressant development include computational and mathematical modelling, human neuroimaging, and the use of patient-specific stem cells for personalized research,

¹³ Slattery, D. A., & Cryan, J. F. (2012). Using the rat forced swim test to assess antidepressant-like activity in rodents. *Nature protocols*, 7(6), 1009.

¹⁴ Yankelevitch-Yahav, R., Franko, M., Huly, A., & Doron, R. (2015). The forced swim test as a model of depressive-like behavior. *JoVE (Journal of Visualized Experiments)*, (97), e52587.

¹⁵ Bogdanova, O. V., Kanekar, S., D’Anci, K. E., & Renshaw, P. F. (2013). Factors influencing behavior in the forced swim test. *Physiology & behavior*, 118, 227-239.

¹⁶ Can, A., Dao, D. T., Arad, M., Terrillion, C. E., Piantadosi, S. C., & Gould, T. D. (2012). The mouse forced swim test. *JoVE (Journal of Visualized Experiments)*, (59), e3638.

¹⁷ De Kloet, E. R., & Molendijk, M. L. (2016). Coping with the forced swim stressor: towards understanding an adaptive mechanism. *Neural plasticity*, 2016.

¹⁸ Welsh, S. A. (2017). The effect of novel kappa opioid peptide receptor agonists on learning and memory in rats.

¹⁹ Animal Welfare Act 1999, title paragraph (a)(i).

²⁰ National Center for Advancing Translational Sciences. (2019). About New Therapeutic Uses. Retrieved from <https://ncats.nih.gov/ntu/about>

²¹ Paterson, R., Durie, M., Disley, B., Rangihuna, D., Tiatia-Seath, J., & Tualamali’i, J. He Ara Oranga: Report of the Government Inquiry into Mental Health and Addiction, 2018. The Government Inquiry into Mental Health and Addiction. Wellington, New Zealand, 219.

medicine, and drug discovery. These methods are based in human neuroscience and physiology and consequently do not need to overcome the fundamental and insurmountable species-specific differences inherent in animal tests.

Valid, ethical research methods for identifying potential human antidepressants include:

- The use of mathematical or computer modelling of human systems. [IBM Watson for Drug Discovery](#) in the United States, for example, analyses millions of documents and synthesises multiple sources of information to show connections and relationships among genes, drugs and diseases.
- Drug-repurposing programmes, such as Vanderbilt University's [Accelerating Drug Discovery & Repurposing Incubator](#), which is based on human genetics.
- The use of epidemiology, the study of naturally occurring disease and health in human populations.
- *In vitro* research which involves procedures in a controlled laboratory environment outside of a living organism. For example, using human cell-based tests and tissue models to assess the safety of drugs and chemicals.
- The use of functional magnetic resonance imaging (fMRI) which can be used to predict which patients will respond best to antidepressant treatments.
- Examining brain tissue from deceased human donors to identify genes involved in depression and other psychiatric illnesses.
- [Just last week](#), researchers at Alto Neuroscience in California announced they had used neuroimaging to develop a machine learning algorithm that could correctly predict the responses of individual humans to certain antidepressant medications and provide critical information about meaningful clinical outcomes for these patients—without the use of animals.

The Forced Swim Test doesn't predict if new treatments will be effective in humans and, as outlined above, there are multiple viable methods that could be used instead, making the use of the Forced Swim Test outdated, unjust and unethical for both humans and animals.

It is important to note that the forced swim test does not need a one-to-one replacement because it is simply a bad test which doesn't produce useful data. You might as well just be flipping a coin. No one needs to waste a single second more conducting the forced swim test.

4. The wastage of time, money and other resources

The annual cost of serious mental illness, in New Zealand, is an estimated \$12 billion,²² which highlights the need for human-relevant research to be prioritised.

Research funding is finite. Due to its lack of translational value to humans, each instance in which time or money is spent on research involving the Forced Swim Test is a waste of these valuable resources that could be better allocated elsewhere: towards human-relevant research methods and improving mental health care programmes already in place.

²² Paterson, R., Durie, M., Disley, B., Rangihuna, D., Tiatia-Seath, J., & Tualamali'i, J. He Ara Oranga: Report of the Government Inquiry into Mental Health and Addiction, 2018. The Government Inquiry into Mental Health and Addiction. Wellington, New Zealand, 219.

Animal experiments, such as forced swim test, have been cited as the primary source of failure in human clinical trials of neurobehavioral drugs. Significant differences in physiology between humans and other animals likely accounts for a large percentage of failed translation. Human-relevant research methods must be prioritized, and money and time must no longer be wasted watching mice and rats splash around in terror.

5. The global shift away from the use of this test

In December 2018, after talks with PETA, pharmaceutical giant [AbbVie](#) committed to not funding or conducting Forced Swim Tests. Pharmaceutical companies [Johnson & Johnson](#) (March 2019), [DSM Nutritional Products](#) (April 2019), [NutriFusion LLC](#) (May 2019), [Astraea Therapeutics](#) and [Roche Pharma](#) (June 2019) [Boehringer Ingelheim](#) (July 2019), [AstraZeneca and Novo Nordisk A/S](#) (August 2019) [Sage Therapeutics](#) (October 2019), [Pfizer](#) (November 2019), [Bayer](#) (December 2019) and [Bristol-Myers Squibb](#) (January 2020) have also committed to not use or fund this test in the future.

Johnson & Johnson is the world's largest pharmaceutical company, Roche is the second-largest, Pfizer is the third largest and Bayer is the fifth largest pharmaceutical company in the world. This means that four of the top five pharmaceutical companies worldwide (in terms of revenue), and also ten of the top 20, have committed to no longer use the Forced Swim Test.

This shows that even the pharmaceutical industry is recognising this test as outdated and irrelevant. Now let's make sure NZ keep up with this global shift!

Recently, major research university Kings College London became [the first known institution](#) to put an end to the forced swim test in an academic setting

There are many active campaigns against the use of the Forced Swim Test around the world. PETA US, Australia, UK, Germany and India have been campaigning against the use of this test since 2018. The Citizens for Alternatives to Animal Research and Experimentation (CAARE) launched a campaign against the use of the Forced Swim Test in August 2019. CAARE is a national group in the United States.

6. Public support for the ban

Students from over a dozen clubs (representing over 1500 students) at Victoria University, including the Psychology Club, have signed a letter to the Vice-Chancellor and members of the University's Animal Ethics Committee urging the institute to end use of the Forced Swim Test.

In addition, nearly 16,000 people have sent an email to the Vice-Chancellor of Victoria University and members of the Victoria University Animal Ethics Committee asking that they end the use of the Forced Swim Test.

Over 25,000 people signed the NZAVS and SAFE petition asking the New Zealand government to not only ban the Forced Swim Test in New Zealand but to also conduct a full review and evaluation of the validity of animal-based psychological tests in New Zealand.

Hundreds of people (including psychologists, researchers, mental health workers, counsellors, doctors, nurses, veterinarians and vet nurses) have provided a personal statement to support our call for a ban on the Forced Swim Test. Read these [here](#).

A public poll conducted by Horizon in October 2019 indicated that this call for a ban on the Forced Swim Test in New Zealand is supported by a majority of Kiwis, with only 14% of New Zealanders supporting the continued use of the test. More than half (54%) of the respondents supported a ban on the Forced Swim Test in New Zealand, and the remaining respondents (32%) were not sure.

Conclusion and recommendation

The evidence in this document clearly shows that:

1. The Forced Swim Test does not reliably predict the human response.
2. The use of the Forced Swim Test is highly unethical for animals.
3. It is essential for suffering humans that the research methods being used are reliable and relevant.
4. The Forced Swim Test is a waste of money, time and other resources.
5. Pharmaceutical giants have publicly banned the use of the Forced Swim Test, proving that this issue is relevant on an international scale.
6. The New Zealand public supports the ban:
 - A [Horizon Research poll](#) showed that just 14% of Kiwis supported the continued use of the Forced Swim Test in New Zealand.
 - Over 25,000 people signed NZAVS and SAFE's petition asking for a ban.

Given the evidence presented in this document, NZAVS and SAFE are asking the NZ Government to take immediate action to pass legislation to immediately ban the Forced Swim Test and to conduct a formal review and evaluation of the validity of *all* animal-based psychological tests used in New Zealand.