Are we throwing good antidepressants out with the swim test water?

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ABSTRACT

Depression is the leading cause of disability worldwide. It is estimated that a third of patients suffer from treatment-resistant depression. Yet, pharmaceutical companies have abandoned psychiatric drug development in recent years, citing high drug failure rates and a lack of reliable testing methods. Using data from major pharmaceutical companies, we show that the most commonly used behavioral test for antidepressants is not effective in predicting the clinical success of tested compounds.

FORCED SWIM TEST

Since the late 1970s, the most common preclinical behavioral test for antidepressant efficacy has been the forced swim test (FST), in which a mouse, rat, gerbil, or guinea pig is placed in a container of water with no way to escape and no place to rest out of the water. The time the animal spends swimming/struggling is compared to the amount of time they spend floating. When certain animals are administered classical antidepressant drugs, they will swim for longer (a reduction in immobility), a result that gave some experimenters the impression that a longer swimming time signifies a less depressed animal and that floating is a sign of "despair." However, there is evidence that floating is actually an adaptive behavior that saves energy and benefits survival—not a sign of depression—and that compounds which are not administered clinically to treat depression (e.g. caffeine) also increase swimming. In a recent review, Kathryn G. Commons and colleagues at Harvard Medical School wrote, "the connection between swimming and the human condition begs an abstraction at best. Behavior in the FST is a reaction to the acute stressful stimulus of being placed in a container without an escape route, and human depression reflects a chronic subjective emotional state rather than a reaction to an individual stimulus."

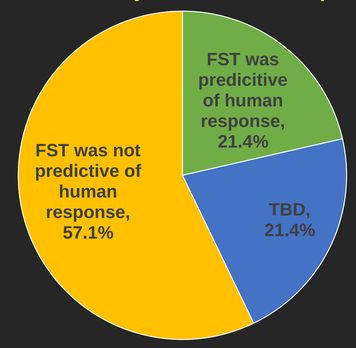
METHODS

Using PubMed database and Google Scholar, we identified published papers authored by individuals affiliated with and patents submitted by Abbott Laboratories, AbbVie, Bristol-Myers Squibb, Eli Lilly and Company, and Pfizer, Inc. We identified specific compounds administered to animals used in FSTs. We used PubMed, Google Scholar, and ClinicalTrials.gov to determine whether each compound had been used in human depression studies. A limitation of this analysis is that only publicly-available data were used.

RESULTS

We identified 47 compounds that were administered to over 4900 animals used in FSTs. Of these 47 compounds, 36 reduced immobility in the FST, thus indicating by the classical—and we believe incorrect—interpretation of the test, that they may have antidepressant qualities. Of the 36 positive results, 22 have not been further explored for human depression. Fourteen compounds with positive FST results have been investigated for their effect on this condition (See "Compounds that reduced FST immobility and were tested in human depression").

FST translatability for 14 tested compounds



Of the 3 compounds for which the FST did predict human antidepressant efficacy,

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are currently approved to treat human depression, due to adverse events.

COMPOUNDS THAT REDUCED FST IMMOBILITY AND WERE TESTED IN DEPRESSED HUMANS

Compound	Efficacy in humans	Was the FST predictive?	Currently approved to treat depression?
Captopril	Mixed results	No	No
Nomifensine (Merital, Alival)	Effective	Yes; but compound discontinued due to adverse events	No
R121919 (NBI-30775)	Effective	Yes; but compound discontinued due to adverse events	No
β-hydroxy-β-methylbutyrate (HMB)	Study Inconclusive	No	No
MK-869 (aprepitant)	Not effective	No	No
CP-122721	Not effective	No	No
Sibutramine	Effective	Yes; but compound discontinued due to adverse events	No
Moxonidine	Not effective	No	No; contraindicated
LY354740	Not effective	No	No
Biperiden (Akineton)	Not effective	No	No
Scopolamine	Some	To be determined	No; clinical trial recruiting
LY2940094 (BTRX-246040)	Some	To be determined	No; clinical trial ongoing
Pramipexole	Some	To be determined	No; clinical trial ongoing
Varenicline (Chantix)	Mixed results	No	No; implicated in suicidal and aggressive behavior

Compounds that reduced immobility but were not further explored for human depression:

Abbott/Abbvie
1. A-85380
2. Quinpirole
3. PD 12,9807
4. LY-341495
5. Compound 9c

Bristol-Myers Squibb
1. L-733060
2. BMS-795176
3. BMS-986169

Eli Lilly and Company
1. LY228729
2. LY41646
3. LY392098 + imipramine
4. MPEP
5. MTEP
6. LY2456302
7. GW803430
8. LY2607540
9. Pirenzepine
10. VU0255035
11. SCH226206
12. LY2940371-HCl
13. DETQ

Pfizer, Inc.
1. PF-04455242

Compounds that did not reduce immobility:

Abbott/Abbvie
1. ABT-200*
2. PD 168077
3. CP 226269
4. SNAP-7941
5. T-226296

Eli Lilly and Company
1. BU224
2. BU239
3. BDF 8082
4. Jiadifenolide

Pfizer, Inc.
1. CP-809101
2. Rimonabant*

*Only two of these compounds were tested for human depression. ABT-200 showed some efficacy in depressed humans, but was not pursued due to adverse effects. Rimonabant increased depression in humans.

CONCLUSION

In tests of compounds selected by four companies, the FST was less predictive than chance (50%) at determining whether a compound would have antidepressant efficacy in humans. Preclinical use of the FST did not predict whether a compound is currently approved to treat human depression. The FST has no utility in and is not advantageous for preclinical testing for antidepressant drugs. The U.S. Food and Drug Administration should not accept FST data in investigational new drug applications for potentially antidepressant compounds. The tail suspension test, which relies on a similar faulty interpretation of an animals' mood, should also not be used in drug development.

PROGRESS: Following our analysis, we filed shareholder resolutions with AbbVie, Bristol-Myers Squibb, Eli Lilly and Company, and Pfizer, Inc., requesting an end to their use of FSTs. Subsequently, AbbVie enacted a policy stating, "AbbVie does not currently use or intend to use or fund animal forced swim tests." This story has been covered by STAT News and Scientific American.

LINK TO REFERENCES