Institution: University of Oxford

Unit of Assessment: 4

Title of case study:

Rapid Prediction and Screening of Novel Antidepressant Drugs: The Emotional Test Battery

1. Summary of the impact

The Emotional Test Battery (ETB) was developed by Goodwin, Harmer and others in Oxford from 1998 onwards. Notably, a person's performance on the ETB is sensitive to single doses of antidepressant drugs, even in healthy subjects, and without any change in mood. The ETB has played a key role in the success of P1Vital, a Clinical Research Organisation for experimental medicine, set up in 2004. The ETB has been responsible for ~60% of its business since 2008, worth over £9.5M and with 10 jobs created. Through P1Vital, the ETB has become a key part of the testing process for new antidepressants for several pharmaceutical companies, allowing substantial cost and time savings. For one antidepressant, the ETB results changed understanding of how the drug worked, and shaped its marketing.

2. Underpinning research

Background and context

Conventionally, antidepressant drug action has been considered biochemically (e.g. 'they increase the level of serotonin in the synapse'). It has also generally been believed that the drugs have no therapeutic effects for 1-2 weeks. This perspective complicates evaluation of antidepressants, since brain biochemistry is difficult to study, and the delayed onset of effect implies that studies need to last several weeks. Research in Oxford since the late 1990s, led by Guy Goodwin and now Catherine Harmer, has fundamentally changed the state of affairs: it has shown that, in fact, antidepressants have rapid emotional effects, which precede their effect on mood, and which occur in healthy subjects. The work has had major impacts in terms of how new antidepressants are investigated, developed, and marketed, and in the conceptualisation of how they work.

Development of the Emotional Test Battery (ETB)

The rationale for looking at direct drug effects on emotional experience derived from the fact that antidepressants and cognitive behaviour therapy are comparably effective for treating depression. Harmer and Goodwin proposed that there might be a common mechanistic pathway underlying both effects, and that the most consistent features of depression – the negative perceptions, view of self and memory – were candidate domains for investigation. It turned out that, indeed, recognition of emotion in faces, speed to process negative self-descriptors, and emotional memory, were all changed by antidepressants in a direction that reversed the biases seen in depression (1, 2). Behavioural effects were paralleled by changes in brain activity (3). Changes in emotional bias produced by a *single dose* of antidepressant in depressed patients were the same as seen in healthy volunteers, and predicted treatment response over several weeks (4). The Emotional Test Battery (ETB) consists of the laboratory tests that Harmer and Goodwin showed to be sensitive to short term treatment with antidepressants. Many subsequent research studies, by this group and others, have utilised the ETB and confirmed its ability to detect subtle, but reliable, effects of antidepressant drugs on emotional processing.

The findings together led to the hypothesis that antidepressants work by an immediate effect on subconscious emotional bias, which only translates into improved mood via behavioural activation and re-learning (5). This sequence of events may explain the known delay in onset of mood improvement, hitherto attributed to complex secondary biochemical changes induced by the drugs.

Contextual Note: The methods for investigating face processing arose from an initial collaboration with Professor David Perrett, St Andrews University.

Results on the ETB can distinguish between antidepressants

Subsequent work showed that the ETB can help identify clinically meaningful differences between antidepressants. In 2006 the Head of Neuroscience Research and Development at Servier asked

Harmer and Goodwin to investigate their novel antidepressant, agomelatine (Valdoxan). He correctly predicted it would not show SSRI-like effects on emotional blunting. This was confirmed experimentally (6), a finding of academic interest as well as producing a direct impact (Section 4).

Summary implications of ETB research

The ETB research shows that antidepressants affect emotional processing, and that they do so very early in treatment, *before therapeutic effects on mood*, and are also seen in healthy volunteers. The work led to an influential theoretical model, which helps integrate pharmacological and psychological views of depression and its treatment (5). The more recent findings, such as with agomelatine (6), have highlighted that antidepressants may differ from each other in their emotional effects. Overall, the research has been influential and 'game-changing', in terms of the impacts described below, and more broadly by encouraging similar experimental medicine approaches elsewhere in psychiatry.

P1Vital and the role of the ETB

P1Vital Ltd is a contract research organisation (CRO) (www.p1vital.com), established in Oxford in 2004. Their ambition was to be the first early-phase CRO for psychiatry and neurology, using novel and pre-competitive experimental medicine models to make drug development more successful and more time- and cost-effective. The ETB was one of the several such models included in a £4M consortium programme in 2007, funded by 5 major pharmaceutical companies, and linking Oxford with several other UK universities. The ETB was the most successful and popular of the models tested, and since 2008 has formed the basis for the majority of P1Vital's business (see Section 4).

3. References to the research

1) Harmer CJ, Hill SA, Taylor MJ, Cowen PJ, Goodwin GM (2003) Towards a neuropsychological theory of antidepressant drug action: potentiation of noradrenaline activity increases positive emotional bias. *American Journal of Psychiatry* **160**, 990-992. DOI: 10.1176/appi.ajp.160.5.990**.**
The first paper to show that even a single dose of an antidepressant improves positive emotional processing, and in the absence of changes in mood. (126 citations).

2) Harmer CJ, Shelley N, Cowen PJ, Goodwin GM (2004) Increased positive vs. negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *American Journal of Psychiatry* **161**, 1256-1263. PMID: 15229059.
This paper reveals consistent early effects of two different classes of antidepressant on emotional processing in healthy volunteers. (221 citations).

3) Harmer CJ, Mackay CE, Reid C, Cowen PJ, Goodwin GM (2006) Antidepressant drug treatment modifies the neural processing of non-conscious threat cues. *Biological Psychiatry* **59**, 816-820. PMID: 16460693.
First paper to show that antidepressants have early effects on brain function (measured by functional MRI) in healthy people. Previously it had been assumed that such effects would only be evident after prolonged treatment, and when change in mood had already occurred. (195 citations).

4) Harmer CJ, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reinecke A, Goodwin GM, Cowen PJ (2009a) Effect of acute antidepressant treatment remediates negative affective bias in depressed patients. *American Journal of Psychiatry* **166**, 1178-1184. PMID: 19755572.
The first paper to show early effects of an antidepressant, compared to placebo, on emotional processing in depressed patients, and before any improvement in mood. (93 citations).

5) Harmer CJ, Goodwin GM, Cowen PJ (2009b) Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *British Journal of Psychiatry* **195**, 102-108. PMID: 19648538.
This hypothesis paper proposes the cognitive neuropsychological model of antidepressant drug action, based largely on the ETB findings. (89 citations).

6) Harmer CJ, de Bodinat C, Dawson GR, Dourish C, Waldenmaier L, Adams S, Cowen PJ, Goodwin GM (2011) Agomelatine facilitates positive versus negative affective processing in

healthy volunteer models. *Journal of Psychopharmacology* **25**, 1159-1167. (6 citations).
Shows that the ETB can reveal emotional effects distinguishing one antidepressant from another.

Major grants supporting the underpinning research

1999-2002: MRC Training Fellowship, Catherine Harmer.
2005-8: MRC Strategic grant (PI: Harmer), Psychological mechanisms of antidepressant drug action, £180K.
2009-12: MRC Strategic grant (PI: Harmer): Cognitive biomarkers of antidepressant action, £350K.

Guy Goodwin, then Head of the Oxford University Department of Psychiatry, initiated this work in 1997, joined by Catherine Harmer in 1998. Professor Philip Cowen, MRC Clinical Scientist, directed the laboratory in which the work was started and has contributed key expertise.

4. Details of the impact

The research summarised above has had several impacts:

Formation and success of P1Vital Ltd

As described in Section 2, the ETB was an integral part of the rationale for, and the initial success of, P1Vital, being the most popular of the various experimental models included in the company's portfolio (Section 5, Sources 1-3). Since 2008, P1Vital has grown, and the ETB has become the primary instrument used in 6 commercial studies to screen and characterise novel compounds in development for depression. The income from the various commercial grants between companies and P1Vital for work using the ETB since 2008 is over £9.5M, or about 60-70% of the company's total income. The work is carried out in Oxford and in other UK academic centres. Interest in the ETB continues to grow, and P1Vital income for these services in 2013 is likely to exceed £4.8M. P1Vital has created 15 jobs since 2004, with 10 people currently working on projects which largely or exclusively use the ETB.

Use of the ETB to drive more rapid and cost-effective development of new antidepressants

Together with this direct spend on experimental studies, there has been a direct impact on drug development decisions within the companies concerned (Section 5, Sources 4 and 5). Our positive study with an AstraZeneca drug, AZD6765, led the company to approve a development programme for the drug, with a budget of ~£10M. Conversely, another AstraZeneca drug had only weak ETB effects, leading to termination of its development programme, with resulting cost savings of a similar magnitude.

Revealing clinically and commercially meaningful differences between antidepressants

The finding (Section 2, ref. 6) that agomelatine, unlike existing antidepressants, did not produce emotional blunting - led directly to a major change in how Servier has marketed the drug since authorisation in 2009 (Section 5, Source 6). It will have had a direct effect on sales, and on patient benefit, by focussing prescribing on patients intolerant of emotional blunting. The ability of the ETB to differentiate between antidepressants has also contributed directly to Servier's development programme to seek a successor to agomelatine.

Broader impacts of the ETB and its applications

The ETB and P1Vital have been highlighted by the Medical Research Council (MRC) as an example of successful translational research in psychiatry, in a field with few such achievements (Section 5, Source 7). The ETB has also been reported on BBC News, and other media, helping explain the importance and nature of the research field, and linking pharmacological with psychological aspects of depression and its treatment (Section 5, Source 8).

5. Sources to corroborate the impact

ETB and the success of P1Vital

1. The table shows the commercial contracts obtained by P1Vital. All contracts listed since 2008 refer solely to the studies that have used the ETB. The sum of ETB-related post-2008 contracts is £9.6M, out of a total P1Vital income over that time of ~ £14M.

Type	Amount	Source
2005 Commercial contract	£157,150	Pharma company
2006 Commercial contract	£761,920	Pharma company
2007 Commercial contract	£4,000,000	Pharma Consortium
2007 Commercial contract	£369,709	Pharma company
2008 Commercial contract	£486,451	Pharma company
2009 Commercial contract	£1,065,000	Pharma company
2010 Commercial contract	£538,275	Pharma company
2011 Commercial contract	£2,218,776	Pharma company
2012 Grant	£220,000	MRC
2012 Commercial contract	£150,000	Technology Strategy Board
2012 Commercial contract	£2,698,303	Pharma company
2012 Commercial contract	£1,100,000	Pharma company
2012 Commercial contract	£1,200,000	Pharma company
	£14,965,584	

2. Press release, describing the 2007 consortium of pharmaceutical companies which funded £4M to P1Vital to test a range of their predictive tests, including the ETB: http://www.p1vital.com/public_documents/consortium_press.pdf.

3. Description of how the ETB is used within P1Vital: http://www.p1vital.com/Oxford%20Emotional%20Test%20Battery/index.html

Evidence of ETB value for pharmaceutical companies in antidepressant development

4. Letter on file from Senior Medical Advisor/Program Phase Neuroscience, Eli Lilly and Company: '*Lilly confirms that the Emotional Test Battery (ETB) was part of the clinical development pathway (Phase II) for a novel antidepressant. The expectation is that the results from the ETB will help to facilitate the development of the compound...'*

5. Letter on file from senior scientist at Astra Zeneca: *'I am happy to confirm that the Emotional Test Battery was part of the clinical development pathway (Phase II) for our novel antidepressant AZD6765. The work…helped facilitate the development of AZD6765 by helping us to understand its mechanism of action and by adding to the evidence that AZ6765 has a beneficial safety and tolerability profile. The compound is now progressing through Phase II/III clinical trials…'.*

6. Letter on file from Head of Research and Development, Servier. He confirms that the findings on agomelatine (section 3, ref. 6) *'will have had a direct effect on sales (currently 155 M euros in 57countries)'* and that the results contributed directly to a second development programme by Servier, which '*could translate in future commitment expenditure of around 1M euros.'*

Other impacts

7. The MRC has highlighted the impact of the ETB as an exemplar of translational medicine: *'Antidepressant medication increases positive emotional processing before having an effect on mood (Harmer et al, 2009). These insights…can lead to new science-driven pharmacological and psychological interventions as well as sensitive and efficient methods of early phase evaluation of new approaches to prevention, detection, screening and diagnosis, and development of personalised treatments.'* MRC Review of Mental Health Research 2010, p.35.

8. BBC News, 26 October 2009: *Antidepressants 'work instantly'*. Article describes the ETB findings. Includes a quote from Dr Michael Thase, University of Pennsylvania, that the findings were potentially '*paradigm-changing*'. http://news.bbc.co.uk/1/hi/health/8304782.stm