Personalised Medicine for Psychiatry Requires Novel Trial Designs

Neuropsychiatric disorders are some of the most complex in healthcare, especially when it comes to depression. Designing a trial for these vulnerable patients involves careful and complex protocols

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For decades, cancer treatment was a one-size-fits-all process. Patients underwent surgery to remove a tumour, and then endured several rounds of chemotherapy or radiation to kill cancer cells. The words precision and personalisation rarely cropped up in oncological circles. Nowadays, it is almost unthinkable to treat cancer patients without accounting for their individual genes and specific disease. That is why nearly all cancer drugs that are currently in development have a companion diagnostic: an *in vitro* test that determines the applicability of the therapeutic drug to a specific person. These tests allow clinicians to quickly diagnose if a tumour has a specific gene change or biomarker that is targeted by the drug.

Unfortunately, psychiatry has lagged behind oncology when it comes to offering more precise and personalised

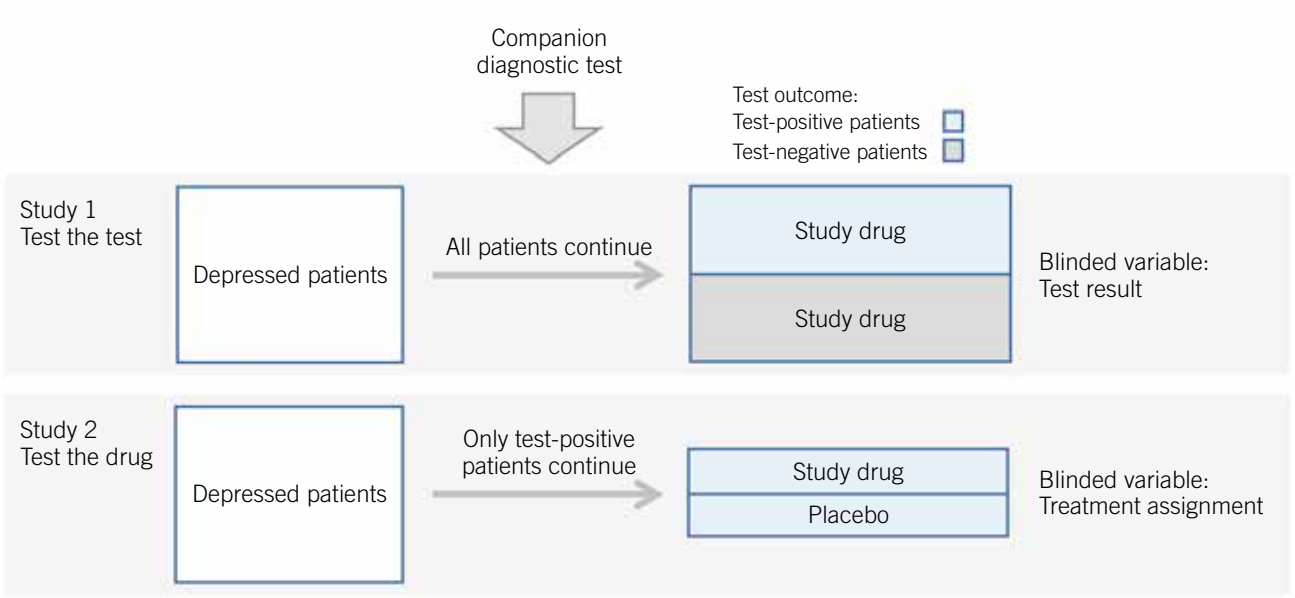

Figure 1: The above graphic demonstrates the process for a companion diagnostic test and how to achieve a result to determine treatment

Case Study

One study involving an antidepressant medication – a vasopressin V1b receptor antagonist with the internal compound code 'BH-200' – showed an efficacy that was not markedly superior to any standard, widely used, off-patent antidepressant on the market today. However, that efficacy may be driven by a subset of patients who are more responsive to the drug's mechanism of intervention.

This subset of patients appears to suffer from a disturbance in their body's stress hormone system. The body's adrenal glands, which are located close to the kidneys, are responsible for producing cortisol, the human stress hormone. The brain strictly controls this cortisol production, sending signals from the hypothalamus to the pituitary down to the adrenals via the so-called hypothalamus-pituitary-adrenals axis, or stress axis. For most people, that stress axis works smoothly. But that's not the case for some severely depressed individuals. In fact, the axis appears to be in a hyperactive mode and cannot be calmed.

A diagnostic test, which is carried out via a blood sample, can identify that subset of patients. It checks to see if the patient has the same genetic signature – or DNA variations – as individuals suffering from this abnormal regulation of their stress hormone axis. Carrying this genetic signature should be a strong predictor of responsiveness to the BH-200 antidepressant, which aims to calm the hyperactive stress axis. The companion diagnostic helps to develop medication that may benefit the subset of patients who test positive for the genetic signature, while freeing up those who don't want to pursue alternative treatments.

treatment. This is perhaps not surprising; every disease of the brain is as unique as the patient who suffers from it, whereas many forms of cancer are the consequence of a single mutation. However, that is starting to change, with the pharmaceutical industry now exploring why some patients see great benefit from their medications for severe depression, anxiety, and schizophrenia, while others don't. There is an emerging consensus that, while patients might share the same diagnosis, it doesn't always follow that they share the same disease-causing mechanism, and, therefore, require the same medication.

Many firms are harnessing sophisticated biomarker analysis to produce highly personalised therapies that break down the usual diagnostic boundaries to define patient groups that will respond particularly well, less well, or not at all to a recommended drug, despite having the same diagnosis. It is heartening to see novel approaches to diagnosing and treating neuropsychiatric disorders, but they require fresh thinking when it comes to the design, management, and delivery of clinical trials. That's principally because the trials often involve statistical hypothesis, or conjectures, about a statistical population.

Design of Clinical Trials

Traditionally, Phase II trials determine whether drugs have any efficacy, but in the case study above, the second phase trials actually have two objectives – to demonstrate that both the companion diagnostic test and the actual medication work, and that both are safe for patients. Running two studies in parallel can help achieve this: one tests the compound, while the other tests the test. The study to test the compound has a relatively standard design within an enriched population and the molecule exerting efficacy is the same as in other approaches. However, a pair of trials for the companion diagnostic require innovative design and management to maximise valuable scientific information.

Let's start with the randomised trial. Traditional Phase II studies of this nature require a certain number of

patients with a disease or disorder, who are arbitrarily split into two groups. One group receives the medication, while the other gets the control, which can be an active compound, but is usually placebo. Since this hypothesis is that drug efficacy is driven by a subset within a subset, this requires pre-selecting several hundred individuals suffering from treatment resistant depression, as opposed to any form of depression. It is expected that one third of patients in that large subset will test positive for the previously mentioned genetic signature. Only then are those patients put into separate groups that will receive the active compound or placebo.

Both of these groups then receive eight weeks of treatment, which is standard in psychiatry trials. Then it is gauged whether the improvement in the depression severity rating scale from baseline is better for the group who received the active compound vs those who were given a placebo. Provided the randomised trial is conducted properly, and enrols enough participants, it should provide statistical control over confounding factors to deliver a useful comparison of compound vs placebo.

The parallel trial for the companion diagnostic test is, despite its simple design, hugely scientifically informative. Approximately 150 individuals suffering from major depressive disorder are pre-selected and tested for the same genetic signature. The patients are expected to fall equally into three categories: positive, negative, and intermediate.

The test results are double-blinded: neither the investigators nor the patients know the outcomes of the companion diagnostic. All trial participants then receive the same active compound on an 'open label' basis, whereby both investigators and participants are fully aware of the treatment. Measurement takes place after eight weeks, comparing the change in the depression severity scores from baseline to endpoint for all three groups.

Superficially, the trial appears to be a classic open label study, but the interesting variable is the test outcome, which has been blinded to eliminate any experimental bias. There could be a more pronounced change from baseline, in terms of decreased severity of depression, for the patients who tested positive for the genetic signature, than in the other two categories. In addition, this trial can begin slightly earlier than the traditional placebo-controlled study, a design feature that offers the opportunity for interim analysis.

Challenges

The intricate design and management of these trials boosts their scientific credibility, but there will be some challenges related to their design, management, and delivery. For example, it won't be easy to pre-select a large cohort of individuals for the randomised component of the trial. We are prepared for a heavier compliance burden; the development of a novel medication in conjunction with a companion diagnostic test not only increases the study complexity, but also the regulatory requirements. It is, therefore, crucial that the development of the medication and the test go hand in hand.

In terms of the design of the trial, some may argue that the hundreds of individuals suffering from treatment-resistant depression should be treated with the same medication, on the grounds that the same information will be obtained as the combined studies. Here, the counter argument is simple: if we went down this route, we would be dealing with an even larger group of individuals who are likely to be unresponsive to treatment.

Conclusion

There is scope to reconsider the design, management, and delivery of trials elsewhere in neuropsychiatry. For example, some of the compounds currently in development exert profound psychological effects, which means there is a high risk of unblinding. It would be sensible for investigators to consider alternative approaches in such cases, for example by using a control condition that doesn't use the medication being studied, but a different compound. That compound might produce a psychological effect, but is not expected to have any efficacy. Investigators might also employ a wide dose range of the drug under study, allowing them to compare efficacy and safety for the higher doses against the lowest dose.

In the meantime, it is clear that new approaches to diagnosing and treating neuropsychiatric disorders that emphasise precision and personalisation have huge potential. However, the clinical trials need to be similarly innovative and creative to maximise statistical control and minimise experimental bias, thereby enhancing their scientific value.

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