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THE CONVERSATION

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There's more to Pradaxa's problems than meets the eye

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Pharmaceutical companies don't have a particularly good reputation, for some very good reasons. But we can't let suspicions about the motives of such companies cloud our assessments of drug safety because patients may also suffer.

People with abnormal heart rhythms and other diseases that cause blood clots (thromboses) often require blood-thinning (anticoagulation) medications. For many decades, warfarin has been the most widely used such drug but it's associated with a risk of bleeding (including fatal haemorrhage) and requires regular blood tests to monitor safety and efficacy.

So the advent of new oral anticoagulant drugs was [heralded as a major advance](#) by both patients and clinicians – principally on the grounds that they appeared as effective as warfarin, may be associated with a lower risk of serious bleeding, and are cost-effective because patients don't need ongoing blood monitoring.

For these reasons, a number of these new drugs, including dabigatran (Pradaxa) and rivaroxaban (Xarelto) were fast-tracked through the regulatory approval processes in the United States and in New Zealand.

Emerging problems

But reports now suggest Pradaxa might be less safe than it appeared to be in clinical trials. Specifically, it's claimed the drug may be responsible for [higher-than-expected levels](#) of abnormal bleeding, including hemorrhagic strokes, and that it may, in fact, be less safe than warfarin.

Just as significantly, a [recent investigation](#) by the British Medical Journal claimed that the manufacturer of Pradaxa, Boehringer Ingelheim [failed to disclose information](#) about the bleeding risks of Pradaxa, and the need for patient monitoring to reduce these risks.

The drug company has [forcefully denied the allegations](#). But it recently [settled several thousand lawsuits](#) in the United States for US\$650 million on the grounds that it failed to warn patients about the risk of irreversible bleeding.

While these accusations and legal settlements might suggest the company has been remiss in its research, reporting or marketing (or all three), it's important to note that they don't provide conclusive evidence of wrongdoing.

We also need to bear in mind that there are at least two other possible explanations for Pradaxa's fall from grace. One related to the way clinical trials are designed, and the other to how we monitor new medicines for adverse drug reactions.

Clinical trials

Even the best-designed clinical trials provide only preliminary information about adverse drug effects.

This is not ideal but it can't be helped because clinical trials are, by necessity, artificial set-ups, tightly controlled in terms of patient selection, drug dosages, length of treatment, monitoring, and so on. They don't, and can't, reflect the vagaries and complexities of real-world prescribing practice and patient behaviour.

So it's almost inevitable that at least some new adverse effects will emerge after a drug has been approved for marketing.

In the case of Pradaxa trials, we know elderly people and people with renal disease were relatively under represented when compared with those who were prescribed Pradaxa when it was released onto the market. This is important because those excluded are the very people who are most likely to develop bleeding complications.

We also know that the prescribing of Pradaxa following its release was often inconsistent with product information and clinical practice guidelines. So it's not unreasonable to expect bleeding rates might be higher in the real world than they were in clinical trials.

But the only way to determine whether Pradaxa is less safe than it appeared to be in clinical trials is to monitor adverse effects over time through systems of post-marketing pharmacovigilance. This is done in a number of ways, including adverse event reporting and formal monitoring of the medicine's effects in the real world.

The problem with pharmacovigilance

Still, even pharmacovigilance is not an exact science, and observed rates of adverse events in the real world can sometimes be just as misleading as rates observed in clinical trials.

While pharmacovigilance systems are gradually improving, most current pharmacovigilance systems rely on doctors, and occasionally patients, reporting adverse events as they arise.

A well-known artefact of such systems is adverse effects of new medicines, such as Pradaxa, are reported more frequently than those of older medicines, such as warfarin. This makes it difficult to assess the comparative risks, and benefits, of new drugs.

Significantly, [more robust comparisons](#) of Pradaxa and warfarin, based on systematically collected data (including registry analyses and Medicare reviews) rather than spontaneous reports, haven't revealed a significant difference in safety of the two therapies.

So whether Pradaxa is, in fact, less safe than it appeared to be in clinical trials, and whether the new anticoagulant drugs need to be monitored in certain situations and in certain patients is still open to question. As is whether Boehringer Ingelheim deliberately concealed relevant information about Pradaxa's safety or the need for regular blood tests to monitor treatment.

If the company did hide information, or if subsequent post-marketing research shows regular monitoring is required, then this will undoubtedly affect the drug's cost effectiveness. And it may well mandate changes in clinical practice guidelines and justify changes to regulatory approval and the funding of the drug by the Pharmaceutical Benefits Scheme. Only time will tell.

The lesson from this case is while all reports of adverse events detected through post-marketing surveillance need to be investigated, those doing the investigating should be mindful of the limitations of both clinical trials and post-marketing surveillance systems.

Unless we start from first principles each time this kind of information emerges, we run the risk of either exposing patients to dangerous treatments or forfeiting therapeutic advances.