SCIMAT/SPL

BY ALISON ABBOTT

The shock wave hit when they broke the code. It was January 2005, nearly four years since the start of a clinical trial to definitively compare schizophrenia therapies. The US$43-million trial, involving nearly 1,500 patients at 57 clinical sites in the United States, was testing whether a raft of anti-psychotic drugs introduced in the 1990s — and hailed as transformational — was any better than a 50-year-old pill called perphenazine, one of a generation of drugs that left patients with horrible side effects. Until investigators unblinded the trial, codes concealed who was receiving which drug.

As it turned out, it didn't matter. The Clinical Anti-psychotic Trials of Intervention Effectiveness (CATIE) made it clear that the new therapies were barely different from the old[1]. They were just as good as perphenazine at controlling psychosis — hallucinations and delusions. But patients taking the new drugs remained confused, socially withdrawn and bereft of drive, just as they did on perphenazine. And the new antipsychotics were not even convincingly freer of side effects — overall, three-quarters of patients abandoned their drug during the 18-month treatment regime, regardless of which drug they took.

"That was frustrating and humbling for the research community," says Jeffrey Lieberman, a psychiatrist at Columbia University, New York, and the trial's principal investigator. "And it had a chilling effect on the pharmaceutical industry." Within a few years, under intensifying pressure to rein in costs, several large companies, including London-headquartered AstraZeneca and GlaxoSmithKline, chose to pull out of psychiatric pharmacology altogether.

Chastened researchers also had to regroup. "It became a case of back to the drawing board," says Shitij Kapur, head of King's College London's section on schizophrenia, imaging and therapeutics. Scientists needed to learn much more about the disease's biology. They had to ensure that whatever they learned would be 'translated' more smoothly to the clinic, by way of better animal models, biomarkers and clinical trials. And they wanted to develop drugs to target not just psychosis, but also the 'negative symptoms' such as impaired cognition, blunted emotions and lack of initiative — the types of trait that render most people with schizophrenia incapable of holding down a job.

The scale of the work to be done was too daunting for individual labs. So in recent years, researchers working in the public and private sectors have decided to share more ideas and resources. Few expect a single molecule to do the entire job. "Fifteen years ago, we were naively optimistic," says Kapur. Now, there is still optimism — but with a hefty dose of pragmatism thrown in.

SCHIZOPHRENIA
Search for origins and treatments
nature.com/schizophrenia

No one questions the transformational impact of the first antipsychotic drugs when they were introduced in the 1950s. Psychiatric hospitals could, for the first time, release large numbers of patients with schizophrenia who would otherwise have spent their lives incarcerated. The prototype, chlorpromazine, spawned a whole class of drug known as 'typical' anti-psychotics, including perphenazine.

MOVING TARGET

But the price of that freedom was high. Typical antipsychotics exert their effect by blocking the dopamine type 2 (D2) receptor, modifying dopamine neurotransmission. But these silenced receptors also provoked distressing side effects such as twitching and jerking, leading to the misconception that movement disorders and antipsychotic efficacy were inextricably linked.

So entrenched was this idea that when, in the 1960s, industrial pharmacologists discovered a promising antipsychotic drug candidate that did not disrupt movement in animal tests, they had difficulty persuading their sceptical managers to develop it. Sandoz, a company based in Basel, Switzerland, that is now part of Novartis, eventually introduced clozapine to the market in 1971. As well as acting on D2 receptors, it blocked the 5-HT_{2A} receptor of the mood-modulating neurotransmitter serotonin, which seems to temper the movement side effects. The drug proved so much better that desperate

psychiatrists lobbied for its reinstatement after Sandoz withdrew it from the market in 1975 when its own rare side effect became apparent: a susceptibility to life-threatening infections.

The US Food and Drug Administration (FDA) relicensed clozapine in 1989 for treatment-resistant cases, in conjunction with regular blood tests. Within years, other drug companies had launched their own 'atypicals' (see 'Schizophrenia drug sales'), all with a clozapine-like pharmacology but intended to be safer. Yet some serious side effects, such as metabolic problems, emerged. By this point, clinicians were starting to question whether these new, and more expensive, drugs were any improvement on their predecessors. CATIE confirmed their worst fears.

A SELF-FULFILLING PROPHECY

A re-examination of the pharmacological profiles after the trial showed that although the atypical antipsychotics hit both D2 and 5-HT_{2A} receptors, the D2 blockade seemed to be responsible for their clinical effects. That is not surprising in retrospect, given that the animal models used to test the drugs were all designed to pick up D2-receptor blockade, says Mark Tricklebank, a behavioural pharmacologist and director of the Lilly Centre for Cognitive Neuroscience in Windlesham, UK. "It was all very circular, a self-fulfilling prophecy," he says. "We'd been tuning the engine, when what we really needed was a new engine."

To break out of this vicious circle, scientists realized that they needed some fresh thinking in basic and translational science. Clinical trials had been mostly focused on treating psychosis, but there was increasing recognition that cognitive deficits — poor memory, inability to maintain attention and poor problem solving — were a fundamental aspect of the disease. In 2005, Steve Hyman, then director of the US National Institute of Mental Health in Bethesda, Maryland, launched Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). The forum aimed to bring together academics, industry and the FDA to generate consensus about how best to design clinical trials to test drugs targeted at these cognitive deficits — and later extended to negative symptoms — through a battery of specially designed tests[2,3].

Guided by the MATRICS recommendations, several cognitive enhancers are already in early-phase clinical trial as potential add-ons to standard antipsychotic therapies. Also in clinical trial are several candidate drugs acting on receptors of the neurotransmitter glutamate — the only approach to have shifted focus away from dopamine. But the glutamate circuitry in the brain may prove hard to manipulate safely. And for the scientific community, the real challenge lies in understanding the system they are tinkering with. "We don't even understand schizophrenia at the biological level," says Thomas Laughren, the FDA's director of psychiatric drugs, voicing a frustration felt by many.

A European collaboration of researchers known as Novel Methods Leading to New Medications in Depression and Schizophrenia (NEWMEDS) is throwing every cutting-edge technology available at the problem in a very unusual public–private collaboration. Launched last year, the five-year, €20-million (US$28-million) effort funded by the European Commission includes seven academic partners, nine pharmaceutical companies (including AstraZeneca) and a few biotech companies. One of these is Icelandic genomics company deCODE genetics, which in 2008 identified in a large population study three variable genetic regions called copy number variations (CNVs), which, although very rare, confer a high risk of schizophrenia[4].

Scientists from industry say that it was initially hard to convince their companies of the value of sharing information in NEWMEDS. But they did — and to their evident glee, industrial pharmacologists can for the first time discuss openly, at least within the consortium, their individual approaches in psychiatric disease. Academic members, in turn, are gleeful about access to some of the industrial resources now on the table. They have pooled extensive information and material including data from many clinical trials in schizophrenia, sometimes with associated blood samples. "We now have the biggest database ever on this disease — more than 10,000 patients," says Tine Bryan Stensbøl, a pharmacologist at the Danish pharmaceutical company H. Lundbeck and the coordinator of NEWMEDS.

In a joint project led by geneticist Hreinn Stefansson of deCODE genetics, psychiatrist Andreas Meyer-Lindenberg from the Central Institute of Mental Health in Mannheim, Germany, and neuroscientist Michael Brammer from London's Institute of Psychiatry analysed magnetic resonance imaging data from 500 people identified by deCODE genetics as having the high-risk CNVs, as well as 500 control subjects. They hope that the study will identify brain structures that are disrupted by abnormal genetic signatures and might eventually point to new therapeutic targets. "We wouldn't be doing this without the NEWMEDS initiative," says Meyer-Lindenberg.

An essential but admittedly less glamorous task for NEWMEDS is to determine the robustness of methods used to test drug candidates, particularly the animal and human tests of memory, attention and other aspects of cognition that are notorious for their sensitivity to tiny differences in environment. Unreliable tests may explain why drug candidates that look hopeful in animals fail in the clinic. Industrial and academic scientists are now using standardized protocols in their own labs, then comparing results and trying to understand why some may vary.

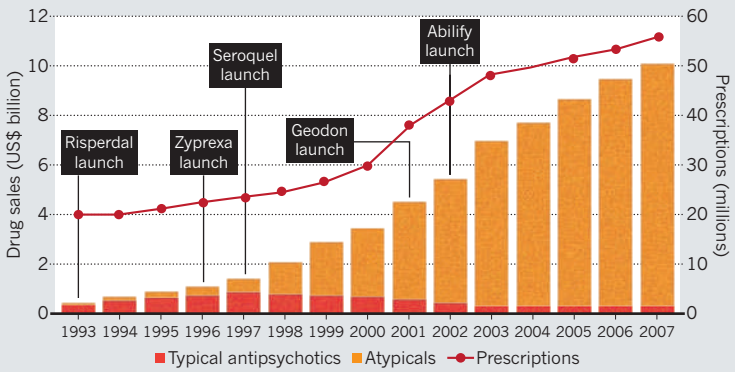
The consortium is also adopting rodent touch-screen technology, in which animals in behavioural tests tap a screen with their nose to get a reward for performing the experimental tasks, rather than press a lever or poke their noses into a hole. Being automated, it does not need constant observation. And crucially, results from such tests are potentially easier to translate into human psychology testing, which is increasingly based on touching screens.

The new concerted strategies could renew industry's optimism, even if there are few concrete signs of it just yet. With up to 1% of the world's population estimated to be affected by the disease, schizophrenia represents a huge potential market for any company that can find a new drug that genuinely improves any symptoms — particularly given that most patients develop the disease in their early twenties, and could be on daily therapy for the rest of their lives.

Maybe, after all, a shock wave was just what the field needed. ■

SCHIZOPHRENIA DRUG SALES

The worldwide market for schizophrenia drugs has grown tenfold since the introduction of atypical antipsychotics such as Risperdal. Annual prescriptions have also risen dramatically.



SOURCE: IMS

Alison Abbott *is* Nature*'s senior European correspondent.*

1. Lieberman, J. A. *et al. N. Engl. J. Med.* **353,** 1209–1223 (2005).
2. Buchanan, R. W. *et al. Schizophr. Bull.* **31,** 5–19 (2005).
3. Kirkpatrick, B., Fenton, W. S., Carpenter, W. T. Jr & Marder, S. R. *Schizophr. Bull.* **32,** 214–219 (2006).
4. Steffanson, H. *et al. Nature* **455,** 232–236 (2008).