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The spurious advance of antipsychotic drug therapy

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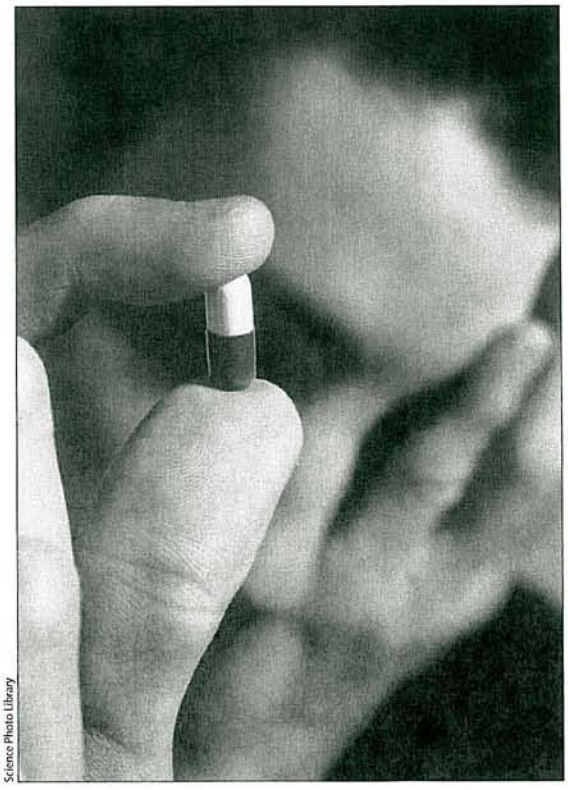
Clinicians are familiar with studies that claim to show major advances in therapy. They tend to greet early reports of such advances with a touch of scepticism and wait, usually for at least 10 years, for a raft of independent studies that show that the advance is genuine and not just another minor ripple in the treatment stream. In *The Lancet* today, Stefan Leucht and colleagues[1] deviate from this pattern by suggesting that what was seen as an advance 20 years ago—when a new generation of antipsychotic drugs with additional benefits and fewer adverse effects was introduced[2]—is now, and only now, seen as a chimera that has passed spectacularly before our eyes before disappearing and leaving puzzlement and many questions in its wake.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Leucht and colleagues' analysis of ten outcomes from 150 randomised trials, supported by some powerful studies,[3-5] shows that the name "second-generation antipsychotics" is inaccurate. This group of drugs is in fact a heterogeneous mix of compounds, with some superior to others. Antipsychotic drugs differ in their potencies and have a wide range of adverse-effect profiles, with nothing that clearly distinguishes the two major groups. Importantly, the second-generation drugs have no special atypical characteristics that separate them from the typical, or first-generation, antipsychotics. As a group they are no more efficacious, do not improve specific symptoms, have no clearly different side-effect profiles than the first-generation antipsychotics, and are less cost effective.[6-8] The spurious invention of the atypicals can now be regarded as invention only, cleverly manipulated by the drug industry for marketing purposes and only now being exposed. But how is it that for nearly two decades we have, as some have put it,[9] "been beguiled" into thinking they were superior?

Leucht and co-workers provide some clues. Of 150 trials in their meta-analysis, in 95 the second-generation antipsychotic was compared with the high-potency first-generation antipsychotic haloperidol. The use of haloperidol as the first-generation antipsychotic in these trials means that they were biased in favour of the second-generation drugs. This bias has been achieved through several routes—eg, by comparing the second-generation antipsychotic with a high-potency first-generation antipsychotic likely to be associated with a high rate of extrapyramidal side-effects. Another obvious way of favouring the second-generation drugs has been to avoid comparison with a medium-potency first-generation antipsychotic, because these drugs are

likely to be just as efficacious as the second-generation drug, but less likely than haloperidol to induce Parkinsonism. The picture can be complicated further with high doses of the first-generation drug. This approach favours the second-generation antipsychotic because side-effect rates are much lower than with the first-generation antipsychotic.[10] Moreover, there is often selective publication of trials[11-13] that can skew the evidence base in favour of a drug favoured by the investigators. On present evidence from all sources it is difficult not to conclude that the trials of the second-generation antipsychotics seem to be driven more by marketing strategy than to clarify their role for clinicians and patients.

This is not to say that all antipsychotic drugs are the same, they are not. Individual responses vary, and so a range of drugs is needed for good clinical practice. So where should we go now? First, the time has come to abandon the terms first-generation and second-generation antipsychotics, as they do not merit this distinction. The only second-generation antipsychotic that is obviously better than other drugs in resistant schizophrenia is clozapine,[14] and this is a very old drug indeed. Second, clinicians must remember to keep the benefit–risk ratio of each antipsychotic drug in constant perspective because all are associated in different ways with serious adverse effects, which should be important outcome measures.[13] Finally, it is prudent to remember that although science rules during a drug's development, the market usurps control once the drug is released for care of patients.

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PT declares that he has no conflict of interest. TK is involved in updating the schizophrenia guideline for the National Institute for Health and Clinical Excellence, including a review of antipsychotic drugs in the treatment of schizophrenia.

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Assessing bleeds clinically: what's the score?

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Acute upper-gastrointestinal haemorrhage is the most common life-threatening medical emergency faced by gastroenterologists, with an annual incidence of 50–150 per 100 000 people.[1] Mortality has been stubbornly high (14% in 1995), although a reaudit in 2007 by the British Society of Gastroenterology showed a UK mortality of 10%.[2] That reaudit identified several trends, including a doubling of cases due to variceal bleeding and a striking reduction in the use of surgery. Whether the falling mortality reflects improved management or an altered case-mix is not clear. Certainly, several mild cases do not undergo endoscopy or need blood transfusion.

Measures need to be developed to identify patients at low risk, who can be discharged early or for whom admission can be avoided, as well as to improve