Antidepressants are not all created equal

Even psychiatrists can sing the blues. Not just because of the current economic depression, but because of recent research findings. A series of pivotal effectiveness studies in psychiatry—STAR*D, CATIE, and STEP.BD—have compared real-world performance of various treatments in depression, schizophrenia, and bipolar disorder. STAR*D showed that virtually all antidepressant strategies had low and similar efficacy in major depression. CATIE showed low effectiveness and similar comparability of antipsychotics. And STEP.BD showed that antidepressants are not effective for bipolar depression. At the same time, depression prevalence rates are rising and major depression is due to be the leading cause of disability worldwide.

The practitioner treating depression is faced with an additional hurdle: how to make an effective choice out of the many available antidepressants. Another decision is how to understand the relative merits of the various newer antidepressants, which often have a meta-analysis funded by the drug’s manufacturer that “shows” the superiority of that particular compound.

In The Lancet today, Andrea Cipriani and colleagues provide the field with a major answer. Free of any potential funding bias (and including an analysis of studies based on pharmaceutical-company sponsorship), these researchers used a newer methodology, multiple treatments meta-analysis, to examine 117 head-to-head randomised trials in almost 26,000 patients. They did two types of analysis: of efficacy (at least 50% symptom reduction at week 8) and acceptability (dropout rates for any reason during the first 8 weeks of treatment). As the researchers stress, these outcomes were chosen for clinical reasons, because evidence-based medicine calls for rigorous studies and statistics while providing treatment recommendations on the basis of comprehensibility and ease of implementation. Of 12 newer antidepressants, four emerged as superior in efficacy: escitalopram, mirtazapine, sertraline, and venlafaxine. One agent, reboxetine, was significantly less effective than the 11 other agents. In terms of acceptability, four agents were better tolerated: bupropion, citalopram, escitalopram, and sertraline. Balancing efficacy and acceptability and lower drug costs, the researchers concluded that sertraline might be particularly appropriate as a first-choice treatment.

Such findings have enormous implications. For the clinician, prudent engagement of the patient in treatment ideally involves giving the patient a choice. Now, the clinician can identify the four best treatments, 

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identify individual side-effect profiles, explore costs and patients’ preferences, and collaborate in identifying the best treatment for that patient. Furthermore, clinicians can honestly state that this selection of drug, and the reports of the side-effect profiles, are from the combined results of many clinical trials, and have been judged to be relatively clear of potential bias from the drug industry. The size of the patients’ sample used to derive these results is more convincing than referring to what every country’s regulator approves for publication in a national standard compendium of pharmaceutical agents. A new gold standard of reliable information has been compiled for patients to review, particularly because these researchers have also made their data and analyses available on a public website.

Such research invites a key clinical question: is superiority at 8 weeks meaningful and sustained over a treatment that minimally lasts 6 months? A similar meta-analysis could answer this vital question. Additional clinical questions include clarifying the effect of using the identified stronger agents, or the best tolerated agents, in combination studies with psychotherapy. Historically, combination strategies have not always been superior, but perhaps future ones will be by choosing a more appropriate antidepressant.7,8 A key challenge now involves the issue of costs and benefits; although the generic agents are cheaper to buy, proper studies are needed to aid societal choices among the four strongest antidepressants. As Patel and colleagues9 have emphasised, such cost concerns are particularly crucial from a global perspective, because most people live in low-income and middle-income countries.

Intriguingly, Cipriani and colleagues also challenge the field of clinical trials to use sertraline as a benchmark in the development of new compounds; by raising the efficacy bar beyond “beating placebo”, they hope to discourage the development of drugs of routine efficacy and also side-step the ethically challenging position of using placebos in an era of multiple proven treatments for depression. With such a host of clinical and research implications, this pivotal meta-analysis of antidepressant efficacy and acceptability will surely change the tune of psychiatrists.

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The inverse impact law of smoking cessation

In 1985 I argued for the abandonment of smoking cessation clinics,1 which make an inconsequential contribution to reducing smoking in whole populations2—3—the test of their public health significance. Their labour intensity devours resources which could be better used in mass campaigns4 to motivate cessation in far more smokers than the best evidence shows are interested in attending clinics, let alone benefiting from them.

But the most powerful argument against a frontline role for clinics is their reiterating message “you need help and are unlikely to succeed alone”. Over 25 years, with the advent of nicotine-replacement therapy (NRT), bupropion, and varenicline, this arguably misleading message has been turbocharged through heavy pharmaceutical advertising directed at both consumers and physicians. Whilst legions of clinical trials5 and more equivocal real-world evaluations6 show that assistance