

mindovermatter

written by Professor Gordon Parker

Trials may not reflect real life

Are antidepressant drugs really any better than placebo?

A RECENT study claims antidepressants are only slightly more effective than placebo. In contrast, clinicians see the drugs as effective and, often, life saving. So why does this conflict occur?

While the recent Kirsch study¹ is not the first to challenge the efficacy of antidepressants, it has had the greatest media impact. A recent *BMJ* article concluded that “new-generation antidepressants aren’t all they’re cracked up to be”, with findings reinforcing “previous criticisms that regulators in the United Kingdom and the United States are not doing their duty to protect the public from useless or dangerous drugs”.²

RCT enrolment procedures require urgent review

The meta-analysis examined published and unpublished data from 35 randomised controlled trials (RCTs) involving fluoxetine, venlafaxine, nefazodone and paroxetine, with 5133 subjects receiving medication and 1841 receiving placebo having improvement scores of 9.6 and 7.8 respectively on the Hamilton Depression Scale.

Finding that this difference was not statistically significant, the authors stated that “the overall effect of new-generation antidepressant medications is below recommended criteria for clinical significance”.

Baseline depression severity was not associated with drug efficacy, but placebo efficacy increased when depression was less severe, allowing the authors to conclude that there was “little evidence to support the prescription of antidepressant medication to any but the most severely depressed patients”.

There have now been six meta-analyses in the last dec-

ade showing little difference between antidepressants and placebos, yet this is not commonly recognised in clinical practice.

WHAT IS GOING ON?

Several factors contribute to the disparity between efficacy-weighted RCTs and ‘real world’ clinical effectiveness:

Non-specific diagnosis

Most trials use the DSM criteria diagnosis of ‘major depres-

sion’ – DSM criteria are set at the “lowest order of inference”, risking inclusion of those with only mildly altered mood states.

Imagine if individuals were given a diagnosis of respiratory infection and tested in an RCT involving an antibiotic and a placebo. If only a small percentage had a bacterial infection and the remainder a “cold”, then a truly effective antibiotic might fail to differentiate from placebo due to the

high natural remission rate.

Overgeneralisation

A second RCT procedural problem comes from testing any antidepressant treatment (drug or other) as if it has ‘universal’ application.

If our group of individuals with respiratory infection all received a specific treatment (e.g. antibiotic, bronchodilator) in such an RCT, the specific drug’s capacity to outperform placebo would

be highly dependent on the number of individuals with the specific target condition.

Overselection

RCT selection effectively excludes those with the classically biological disorders (bipolar disorder, psychotic depression and melancholic depression).

Subjects cannot be suicidal (though clinicians rarely see depressed patients who lack some degree of suicidal ideation). Add to this that subjects must not have personality problems, anxiety disorders or any drug or alcohol problem, and that, often, they are paid.

CONCLUSIONS

RCTs recruit pristine subjects who do not reflect those seen in clinical practice, with many having less severe and transient conditions, and who are highly likely to spontaneously remit and/or show a placebo response. Selection ensures ‘depression’ closer to normal mood states, well away from the ‘real world’ clinical practice. At this point, the efficacy of treatments such as antidepressant drugs is challenged.

Every practitioner who prescribes antidepressants needs to consider the conflict between RCTs and real clinical situations. It is unwise to dismiss the meta-analyses with negative findings too simplistically. Meta-analyses with positive outcomes are generally not criticised and have led to antidepressant drugs being regarded as ‘evidence-based therapies’ (though problems arise here, too).

However, if the arguments just advanced have merit, then psychiatry has to abandon its current emphasis on severity-based models of depression, and RCT enrolment procedures require urgent review. Only then can we make more commonsense conclusions. ☺

References

1. *PLoS Med* 2008;5:260-68.
2. *BMJ* 2008;336:532-34