The dilemma of practicing evidence based medicine when it keeps changing

Suicide and antidepressants

It's 2002; An 18-year old male patient, suffering from depression and anxiety is seeking treatment. You prescribe him what evidence shows to be a safe and effective antidepressant—paroxetine.

Fast forward to 2008; does evidence suggest you prescribe this drug now? SSRIs have gone from being widely popular to being associated with suicide risk, and then used again as the level of risk was outweighed by untreated depression. Now a recent study claims that they do not work at all. The story is sure to continue.

The rate of antidepressant prescriptions in children and adolescents was steadily rising until 2003 when worldwide regulatory agencies issued public health advice ("black box warnings") in response to reports that young people starting antidepressants, especially SSRIs, were experiencing sudden onset of agitation and suicidal thoughts.[1] After the warnings were issued, antidepressant prescribing reduced considerably and some mental health professionals expressed concern that this may result in increased levels of untreated depression and subsequent suicide.

Conflicting evidence of an increase in youth suicides

Since the black box warnings, there have been two major observational studies published which investigated the possible association between antidepressant prescriptions and completed suicide or suicidal behaviour. These studies reached conflicting conclusions.

Researchers from the USA and Netherlands studied national health records to identify suicide rates, before and after the public health warnings were issued. In the Netherlands, the youth suicide rate increased by 49% between 2003 and 2005 and was significantly associated with the decline in SSRI prescriptions. The most significant association was for boys under 15 years. In the USA, the youth suicide rate increased by 14% between 2003 and 2004, which was the largest yearly change recorded since 1979. Prior to the warnings, SSRI prescription rates were increasing and suicide rates were decreasing in both countries.[2]

Data from a recently released ecological time series study from the UK, using national prescribing, mortality

and hospitalisation data, contradicts these results. Researchers found no evidence of an association between trends in antidepressant prescribing and suicide or hospital admissions for self harm, despite a large reduction in antidepressant prescribing since the warnings in 2003. There were no obvious differences between the populations in either study that would explain this discrepancy.[3]

While causal associations drawn from ecological studies are often difficult to prove, the results of these studies raise some important questions about the validity of the original black box warnings for SSRIs and perhaps more importantly, whether antidepressants actually work for young people with depression.

Was the black box warning valid?

It appears now that the black box warning was a reaction to weak evidence, which had serious consequences if true. There have been no observations of completed suicides in any of the SSRI trials to date.

There is a higher risk of suicide in real populations compared to study populations. In the trials, the rate of suicide related behaviours was 5% for people using SSRIs and 3% for people using placebo.[4] Community studies show that over a fifth of young people report serious suicidal ideation and around 7% report suicide attempts.[5] In most trials of medication, those at risk of suicide are typically screened out. So the population on which the trials have been done are at particularly low risk of suicide related behaviours and so are not those typically seen in clinical practice.

In addition, the studies were not set up to assess suicide risk and were not powered to do this. The ways in which suicide related behaviours were assessed varied from study to study. In the Treatment of Adolescents with Depression (TADS) study, a self-report measure of suicidal ideation was used and this showed a steady drop in suicide risk while on antidepressant medication.[6]

Are antidepressants effective treatments for depressive disorder in children and adolescents?

The evidence is inconclusive at this stage. Tricyclic antidepressants are not effective for children and adolescents with depression[7] and there is limited evidence that SSRIs other than fluoxetine have anything more than a placebo response.[8, 9] Even for fluoxetine the overall response rate is low.[10]

It is unclear whether long-term use of antidepressants in children results in adverse effects. Some studies suggest that children taking long-term antidepressants are at increased risk of developing bipolar disorder and other neurological effects.[1] Psychological therapies are recommended as first-line treatment for this age group.[11]

Changing evidence

The example of the antidepressants "story" demonstrates the complexity of trying to practice evidence based medicine when it keeps changing. In this case, the implicit consequence of the evidence, if proven true, has been the main influence on the cycle of treatment.

What we know now is that antidepressants are unlikely to increase suicidal behaviour in young people, but there is doubt over whether they work at all.

A 2005 study found that 16% of top-cited clinical research articles on medical interventions published in the last fifteen years have been contradicted by subsequent clinical studies. In addition, a further 16% of research was found to have initially stronger effects than later research found.[12] This is a worrying statistic for those who strive to practice evidence based medicine.

There is a huge volume of research published in medical journals each year but only a small minority of papers receive attention and dominate scientific thought and practice. Original highly cited articles are published almost

exclusively in three general medical journals – the New England Journal of Medicine, the Journal of the American Medical Association (JAMA) and Lancet.[12]

High impact research may be further influenced by several biases. "Publication bias" and "time lag bias" favour rapid and prominent publication of positive findings.[12] "Wish bias" is when researchers are selective in the results they choose to publish or the research they choose to refute due to their desire for their own beliefs to be true.[13]

The strength of a study's findings should be measured by the amount of supporting research. Observational studies are often contradicted by randomised controlled trials and small studies are contradicted by studies with much larger sample sizes.[12]

There are several reasons why researchers may get it wrong.

- Statistical significance is not always equal to clinical significance. Level of significance is arbitrary; traditionally a P value of <0.05 is considered significant, however significance should be interpreted in the context of the study.
- Initially stronger effects may be due to chance variability.
- Evidence from a unique trial may be refuted with subsequent study in the area.
- Studies may not be able to be replicated and therefore results cannot be confirmed.

There is no proof that subsequent contradictory studies are themselves true. However the overall effect is that it generates uncertainty for clinical practice.[12] In the course of developing both the HRT and antidepressant articles for this edition of best practice, evidence changed and advice had to be updated.

Trying to make sense of research evidence can be complex and time consuming and as seen here, even the experts get it wrong. It is often unavoidable to follow latest evidence, especially when it receives much media attention. However wherever possible, an informed but pragmatic approach is "best practice".

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