

Antidepressant Treatments



With thanks to Dr Richard Lakeman

Yet another meta-analysis on antidepressant treatments: They don't work for most youth either

Recently a meta-analysis of the comparative efficacy and tolerability of antidepressants for major depressive disorder in young people (6-18 years) was published by Cipriani and colleagues (2016) in the *Lancet* (more on this later). The meta-analysis is at the pinnacle of the evidence based hierarchy for drug trials. However, meta-analyses on anti-depressants have generated controversy like few other classes of drugs. There are decades of experience using drugs and thousands of randomised controlled trials which have been published in order to have drugs approved for use. The meta-analysis, or aggregation of published and unpublished trial data calls the conventional wisdom that "anti-depressants" are really anti-depression into question.

It is now widely recognised that published randomised controlled trials are biased towards significant findings in favour of experimental treatments. Kirsch et al (2008) obtained data on all the clinical trials submitted to the FDA for the licensing of fluoxetine, venlafaxine, nefazodone, and paroxetine including data not published in journals. They then used meta-analytic techniques to investigate whether the initial severity of depression affected the improvement scores (measured on the Hamilton Depression Rating Scale - HDRS) for the drug and placebo groups in these trials. They found that there was only a significant clinical difference in response between drug and placebo in the most severe cases of depression (only those above 28 on the HDRS scored more than the mean 3 point improvement considered clinically significant). They concluded that this difference came about because profoundly depressed people do not respond to placebos. A later meta-analysis (Fournier et al, 2010) confirmed that antidepressants are no better than placebo in mild to moderate depression but concluded that they tend to be effective at the severe end of the spectrum. These studies have essentially added credibility to extant guidelines (e.g. NICE) that psychotherapy / counselling and lifestyle recommendations ought to be the only interventions for mild to moderate depression and pharmacological interventions reserved for the most severe cases. They also have brought attention to not only publication bias in studies, but also to selection bias of various sorts bringing doubt to the idea that depression simply differs in severity.

We should have as many words for types of depression as Eskimo's have for snow given that this "soup of emotions" (so eloquently described by Dr George Burkitt at this year's un-conference), cognitions and behaviours can be caused or triggered by all manner of problems such as pain, shame, loss, trauma, disrupted attachment, physical illness, disability or medical treatments. The publication of the Diagnostic and Statistical Manual III (APA, 1987) greatly improved reliability of the diagnosis of depression but it also removed the distinction between reactive and endogenous types (and many potential shades of grey). Organisations like the Black Dog Institute (see: <http://www.blackdoginstitute.org.au>) have resurrected a distinction between the ancient idea of melancholic and non-melancholic depression (more valid but as subtle as the difference between yellow snow and white snow). Depression has by and large simply become depression – a homogenous set of symptoms ripe for targeting with expensive drugs marketed as "anti-depressants". Australian prescribers have been quick to respond with rates of prescriptions for antidepressants now being second only to Iceland in the OECD and equivalent to some 10% of the adult population being prescribed antidepressant's continuously (See: <http://dx.doi.org/10.1787/888933281342>). At a population level it is not apparent that this has made any difference to people's well-being. The last survey of national well-being (Jorm & Reavley, 2010) noted that there was no improvement in adult mental health at all over a 16 year period when the availability and uptake of pharmacological, psychological and population interventions increased.

It is clear that the so called antidepressants do not represent a silver bullet for adults who present with depression. In children and younger people in which depression often manifests differently this is even more the case, with concerns about safety and exacerbation of suicidality. Whilst the newer drugs are rarely lethal in overdose, there are concerns that selective serotonin reuptake inhibitors exacerbate suicidality and in my experience prescribed medications are increasingly the overdose drug of choice in emergency departments in Australia. The present meta-analysis is therefore important to explore the tolerability, safety and efficacy of antidepressants in young people. This study is a 'network meta-analysis' which encompasses a range

of complex statistical analyses to compare a range of trials where drugs go head to head with placebo or other drugs, and one can extrapolate how drugs compare with one another even if they are not directly compared in any given trial (Mills et al, 2013). This study gathered data from 34 trials with 5260 participant exploring the safety and efficacy of 14 anti-depressants prescribed in clinical trials for depressed young people (various measures), aged 9-18 years (Cipriani et al, 2016). An interesting form of graphical representation and analysis in this emerging method is to represent what has actually been compared by connecting lines, the number of trials of paired treatments by width, and sample sizes by the size of circles (as below).

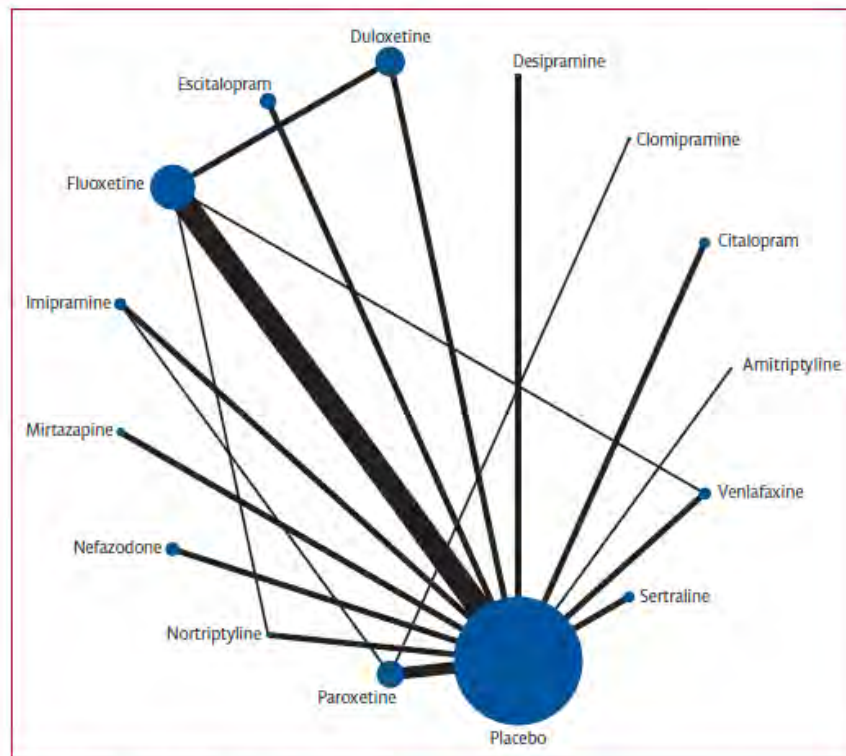


Figure 2: Network of eligible comparisons for efficacy

The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size).

It is fairly clear that fluoxetine has been compared the most with placebo and directly with three other drugs. The authors rated the quality of the studies as mostly poor and noted the potential for publication bias. The outcome of the review included a hierarchy of drugs in order of effectiveness and tolerability. They found that only fluoxetine was statistically superior to placebo and even then it was questionable whether the difference was clinically significant. Fluoxetine was also more tolerable than comparison drugs. Several drugs (e.g. imipramine, venlafaxine, and duloxetine) had more discontinuations due to adverse effects than placebo. The authors were somewhat tentative in their conclusion that fluoxetine should probably be the drug of choice in young people when a pharmacological treatment was indicated (i.e. when the depression is most severe and an 'evidence based' psychotherapy is not available).

Another reading of this meta-analysis is that the drugs simply don't work and the potential risks of adverse events out-weigh any benefits in young people. There of course shouldn't be any great difference between young people and adults in efficacy if the drugs simply correct a chemical imbalance underlying low mood or work like paracetamol in fever and improve mood regardless of cause. What these and other meta-analyses tend to prove is that depression does not reflect a simplistic chemical imbalance models and that antidepressants don't lift mood like an 'anti-depressant' (not withstanding they have effects which may be positive or negative). However, the controversy won't end there. People tend to believe the hype that anything marketed as an antidepressant is one, and every health professional has encountered someone who credits their improvement to finding the right drug. A meta-analysis can only be as good as the quality of the data from the randomised controlled trials which they sample and these are often of dubious quality. Arguably those that are most severely affected, or are 'treatment resistant' or chronically depressed are excluded, or those that might most benefit are not carefully targeted (will the real melancholic please stand up?). A further concern is that those enrolled in drug trials receive vastly more intensive follow-up than in the real world clinic (Sugarman, 2016) quite unreasonably amplifying the efficacy of the placebo effect for antidepressants beyond that experienced in routine care.

The first published response to this article was by Australian psychiatrist Jon Jureidini (2016) who observed that the case for using fluoxetine is even weaker than the meta-analysis suggests and pointed out further weaknesses and biases with trial design as well as the lack of access by the researchers to individual patient-level data. Jureidini suggested that a benign, supportive relationship with a clinician (outside of a formal psychotherapy relationship) had not been proven to be inferior to fluoxetine and had fewer risks. Therefore, a prescription for Prozac is not the last resort of a beleaguered clinician. There are of course a range of lifestyle prescriptions such as exercise (Blumenthal, 2007) which are as effective as antidepressants and with more certain positive health outcomes and fewer risks.

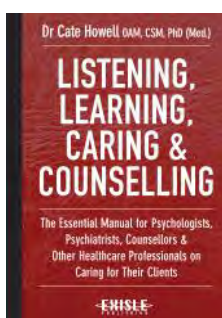
Jureidini (2016) suggested that some clinicians might perceive that their expertise and experience of prescribing antidepressants to adolescents was such that it might override any scepticism generated by this meta-analysis. They should therefore be honest to both themselves and their patients that such prescribing goes against the latest evidence as well as recommended guidelines for practice. If they do choose to prescribe antidepressants for anyone who is not the most severely depressed and in combination with psychotherapy then they probably shouldn't be critical of aromatherapists, crystal healers and colour therapists who just know that their stuff works. The difference is antidepressants have been demonstrated not to work and actually cause harm.

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Listening, Learning, Caring & Counselling

By ASPM Member Dr Cate Howell OAM, CSM, PhD (Med.)



This easily accessible guide demonstrates that the key to breaking down unspoken barriers, and unlocking real understanding, is not just technical knowledge, but learning to really listen. As any good health care professional knows, great outcomes rely on addressing more than just the physical challenges of their clients. At the centre of any caring role is listening attentively to the concerns, narratives and needs of others. True healing requires carers to develop the skills of listening, learning, caring and counselling (LLCC), and to do that requires support and training.

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