

Issues in treating depression in primary care

The last decade has provided a better evidence base for treating depression.

N R Horn, MB ChB, MRCPsych (Lond), PGDipCT (Man)

Senior Specialist Psychiatrist, Valkenberg Hospital Outpatients and Therapeutic Unit, and Senior Lecturer, University of Cape Town

After training for general/rural practice in the Eastern Cape, Neil Horn worked as a GP, then trained in psychiatry and cognitive therapy in the UK. His clinical and research interests include neuroimaging, genetics and psychotherapy of depression and bipolar disorder.

Correspondence to: N R Horn (doctor.neil.horn@gmail.com)

Overview

The last 10 years have seen exciting developments in the availability of new evidence-based treatments for depression. This includes the registration of new antidepressants (ADs) as well as new information about the effectiveness of ADs and psychological therapies. Many 'alternative' therapies, including exercise, herbal remedies, green tea and massage therapies, are promoted for depression, but discussion of these is beyond the scope of this article. Most new literature and conference proceedings focus on new drugs and treatment-resistant depression, leaving little room for questioning some of the basic assumptions. Evidence-based methods of review and the global access to information through the internet have led to new questions and information about the treatment of depression.

The treatment effect of ADs is small and it often takes a long time before they are effective.

Some of our patients' assumptions range from: 'If I feel a bit depressed. I should take an antidepressant for a while and when I feel better I can stop taking the antidepressant' to 'I'll never take antidepressant medication because I read on Google that it is a drug and will harm my body or my brain'. In turn, clinicians have to deal with the ever-expanding body of medical literature, the influence of the pharmaceutical industry and consumerism, and sometimes hold beliefs such as: 'Treating depression early with an antidepressant will prevent a more severe episode', and 'If one drug doesn't seem to work, adding another probably will'. 'Psychotherapy is really for people who want to understand more about, or analyse themselves.' 'If I'm not

sure how to treat someone I'll find the answer in *MIMS*, *SAMF*, a treatment guideline or, of course, I could Google it.' This article summarises some of the new information about these assumptions.

Assessing who should take antidepressants

Over the past decade, depression has been estimated to be the second leading cause of disability in the USA. However, despite much research, our understanding of the biology of depression remains limited. The treatment effect of antidepressants is small and it often takes a long time before they are effective. This is in contrast to the often oversimplified clinical diagnosis process, which usually consists of a tick-list of 5 out of 9 symptoms that should have been present for 2 weeks. In clinical practice the reporting of these symptoms often varies widely and is influenced by age, gender, personality and relationship with the clinician. Some of the more 'real world' symptoms that depressed patients present with are not readily identifiable on diagnostic checklists, and include relationship problems (often as a result of anhedonia and consequent social withdrawal from partners), demands for sleeping tablets (underlying sleep disturbance), vague or unexplained physical problems (fatigue, loss of energy), excessive worrying (thoughts of worthlessness) and inability to make decisions, which might prolong consultations (poor concentration). The high level of alcohol and stimulant use in many South African communities makes it difficult to understand whether substance abuse is a result of, or is caused by, an underlying depression. Patients who present with these symptoms are often resented by medical and other health professionals, because the symptoms are poorly defined or the patient is thought to be partly to blame. The clinician may experience a negative countertransference and act on negative feelings by discounting or not listening to

the patient, hastily drawing the consultation to a close.

The results of clinical drug trials can inform clinicians in the decision-making process around how to treat depression, but the translation of clinical trial results to clinical practice is complicated by several factors: recruitment by advertising, selecting out severely depressed or suicidal patients, and the natural suspicion of good results when these are drug-industry sponsored. Trials report on 'remission', 'response' and 'symptom reduction', and without familiarity with the detail of these definitions readers can potentially misinterpret the real meaning of trial outcome findings. Negative drug trials are under-reported,^[1] and 31% of FDA-registered phase 2 and 3 AD drug trials are not published, almost all have negative findings, and the majority of trials with positive results are published.

Should mild depression be treated with medication or psychotherapy?

A recent meta-analysis^[2] found no benefit over placebo of the ADs paroxetine, fluoxetine, amitriptyline and isocarboxazid – studied specifically in patients with 'minor' depression. More controversially, Andrews *et al.*^[3] in a meta-analysis of placebo-controlled AD trials for patients with major depression found that the risk of relapse after AD discontinuation was higher than the risk of relapse after remission on placebo. This finding, although unreplicated, lends some support to the homeostatic hypothesis^[3] and the clinical implication is that medication for depression may be harmful in some patients. AD advertisements now regularly carry information such as 'Antidepressants increase the risk, compared to placebo, of suicidal thinking and behaviour (suicidality) in children, teens, and young adults. Depression and certain other psychiatric disorders are themselves associated with

increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in *behaviour*. This may be confusing for a patient or relative who is considering AD treatment. Suicidal thoughts are common and do require monitoring, but a decrease in suicidal behaviour has been associated with AD use and this advice simply recommends caution and good clinical practice.

The high level of alcohol and stimulant use in many South African communities makes it difficult to understand whether substance abuse is a result of, or caused by, an underlying depression.

More rigorous evidence from meta-analyses for brief structured psychotherapies for depression is promising, but the findings are

not conclusive. Cognitive therapy appears to be only 'probably' effective,^[4] while the psychodynamic/interpersonal therapies show less evidence of efficacy.^[5] More exciting – group cognitive-behavioural therapy has been shown to be rapidly effective and to slightly lower the relapse rate of depression.^[6] It therefore seems reasonable to postpone the use of ADs in persons with mild depression, and to offer psychological therapies.

What about treatment after a poor response to antidepressants?

This is a frequent question from primary care practitioners. Most prescribe a selected serotonin re-uptake inhibitor (SSRI) as first-line treatment. Is a second SSRI, a tricyclic, a newer AD, or augmentation with nutritional supplements, thyroxine, a mood stabiliser, an antipsychotic, or psychotherapy advisable? Treatment guidelines such as the American Psychiatric Association guidelines^[7] and the UK National Institute for Clinical Evidence (NICE) Guidelines^[8] give helpful, but sometimes conflicting, recommendations for the treatment of mild, moderate and treatment-resistant depression.

Although important new information from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial^[9] has answered some questions on treatment choices, this study has raised many more questions. STAR*D is the largest independent study of the effectiveness of a variety of treatments for depression. The strengths of this study, increasing its generalisability to real-world clinical practice, were several-fold: participants could opt for certain treatments, were recruited by referral rather than advertisement, had moderate to severe depression, many co-morbid conditions were included and the sample size was large (3 000 people). As in clinical practice, subjects had high rates of chronic depression and other psychiatric or medical problems. The goal of treatment was remission – complete recovery from a depressive episode, rather than response – reduction in symptoms, because remission is associated with a better prognosis and should be the preferred goal of treatment.

In level 1 of STAR*D, the SSRI citalopram was prescribed to all subjects for up to 14

weeks. One-third became symptom free (remission), continued the medication and were monitored for a further 12 months, while those who did not remit or suffered intolerable side-effects moved to the next level. Participants who entered level 2 had the option of switching to another AD or the addition of a second treatment. Switching options were either cognitive therapy, sertraline (another SSRI) or an AD from a different class – either bupropion or venlafaxine. Augmentation options were either bupropion, buspirone, or cognitive therapy added to citalopram. After level 2, 25% of subjects who switched treatments remitted, irrespective of whether the switch was to any of the three different medications or cognitive therapy. Around 30% of subjects in the add-on group remitted, irrespective of treatment, although bupropion was slightly better tolerated. By the end of level 2 the overall remission rate was 57%. Subjects who reached levels 3 and 4 were considered 'treatment resistant', including some treatments usually initiated after psychiatric consultation, and the overall remission rate at level 4 was 67%.

More rigorous evidence from meta-analyses for brief structured psychotherapies for depression is promising, but the findings are not conclusive.

Several findings from STAR*D are of direct relevance for primary and secondary care. Firstly, different ADs did not produce substantial clinical differences. Predicting which medication will be efficacious was not possible using clinical profiles. Secondly, in most patients, remission of depressive episodes will usually occur after 6 months and up to two trials of AD medication. Gaynes *et al.*^[9] recommend that from treatment initiation physicians should ensure 'maximal but tolerable doses for at least 8 weeks before deciding that an intervention has failed'. Thirdly, if a first treatment doesn't work, both switching or augmenting and using medication or

cognitive therapy are reasonable choices. Augmentation may be preferred if the patient tolerates and receives partial benefit from the initial medication choice. Perhaps surprisingly, the study showed that either a within-class switch or an out-of-class switch is effective. Fourthly, the likelihood of improvement after two aggressive medication trials lasting 6 months is around 57%. Patients with poor response at this stage have suffered significant time off work or strain in relationships and require more complicated medication or psychotherapy treatment. They should be referred to psychiatrists for more aggressive and intensive treatment because with persistence and aggressive care there is hope for remission. Lastly, clinicians need to consider bipolar disorder in patients presenting with a depressive episode and in those who fail an adequate trial of treatment, although the relatively low rate of response to lithium suggests relatively few patients in the trial had undiagnosed bipolar depression.

New, and revisited, horizons

In the last few years, new ADs have become available, including duloxetine, another serotonin and noradrenaline re-uptake inhibitor (SNRI), and agomelatine, a novel agent with melatonergic agonist and 5HT_{2c} antagonist actions. Initial reports suggest a favourable side-effect profile for agomelatine,^[10] especially in relation to sexual dysfunction and sleep disturbance. It should be considered a possible first-line treatment, especially where these symptoms or side-effects in previous episodes have been problematic, although liver functions should be monitored. Escitalopram and desvenlafaxine are newer refinements of similar drugs which may be beneficial when there has been a good response, but poor tolerability of related agents (citalopram and venlafaxine).

Evidence for the use of antipsychotics as augmentation for treatment-resistant depression is accumulating.^[11] These include the atypical antipsychotics and sulpiride,^[12] which has curiously been registered as an AD along with flupenthixol in South Africa. Recently quetiapine has been licensed in South Africa as an augmentation therapy in major depression. Care with prescribing

these drugs is advised with regard to the risk of side-effects, including metabolic syndrome.

... different ADs did not produce substantial clinical differences. Predicting which medication will be efficacious was not possible using clinical profiles.

Relapse prevention

An ongoing challenge in primary care is for clinician and patient to recognise depression as a recurrent illness and to prevent recurrences. Adherence rates to medication in recurrent depression are below 50% and relapse is predicted by non-adherence.^[13] Non-adherence may be due to ignorance about the risk of relapse, adverse drug effects, costs of health care, or an inappropriate fear of dependence. Relapse of depression increases the risk of subsequent poor treatment response. Primary care clinicians may be able to mediate this risk by providing regular appropriate education. After initiation, early and regular follow-up, specifically asking about common side-effects and their tolerability, including dry mouth, gastrointestinal disturbances, weight gain, headache, and possibly the least comfortable to discuss – treatment-emergent sexual dysfunction (decrease in desire, arousal and orgasm). This affects 22 - 43% of people taking ADs, depending on the class of AD.^[14] Referral for psychotherapy should be considered to prevent relapse in both the acute and remission phases. Preliminary studies show that cognitive therapy reduced relapse rates over 5 years^[15] and mindfulness-based cognitive therapy^[16] reduced relapse rates after 2 years and has been recommended as part of relapse prevention in the latest NICE guidelines.

References available at www.cmej.org.za

IN A NUTSHELL

- Mild depression should be managed with non-drug interventions such as psychological therapy. Antidepressants (ADs) should not normally be prescribed as first-line treatment.
- Most patients with moderate to severe depression take 6 - 12 months to remit.
- AD response is not predictable, and the choice of first-line AD is usually an SSRI and should be guided by availability of medication, cost, history of side-effects from previous trials, and family history, rather than notions that a particular AD is more effective.
- If a patient suffers side-effects from an AD, cognitive therapy or an AD from a different class should be offered.
- Patients with treatment-resistant depression are likely to benefit from specialist assessment, particularly if symptoms are severe.
- Relapse prevention after several episodes can be improved with good adherence to medication, individual or cognitive therapy or mindfulness-based cognitive therapy.

References

1. Turner EH, Matthews AM, Linardatos E, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008;358(3):252-260.
2. Barbui C, Cipriani A, Patel V, et al. Efficacy of antidepressants and benzodiazepines in minor depression: systematic review and meta-analysis. *Br J Psychiatry* 2011;198:11-16.
3. Andrews PW, Kornstein SG, Halberstadt LJ, et al. *Front Psychol* 2011;2:159.
4. Jakobsen JC, Hansen JL, Storebø OJ, Simonsen E, Gluud C. The effects of cognitive therapy versus 'no intervention' for major depressive disorder. *PLoS One* 2011;6(12):e28299. Epub 2011, 9 Dec.
5. Jakobsen JC, Hansen JL, Simonsen E, et al. The effect of interpersonal psychotherapy and other psychodynamic therapies versus 'treatment as usual' in patients with major depressive disorder. *PLoS One* 2011;6(4):e19044.
6. Feng CY, Chu H, Chen CH, et al. The effect of cognitive behavioral group therapy for depression: A Meta-Analysis 2000-2010. *Worldviews Evid Based Nurs* 2011, 16 Dec 16 [Epub ahead of print].
7. <http://psychiatryonline.org/guidelines.aspx> (accessed 21 January 2012).
8. <http://guidance.nice.org.uk/CG90/QuickRefGuide/pdf/English> (accessed 21 January 2012).
9. Gaynes BN, Rush AJ, Trivedi MH, et al. The STAR*D study: Treating depression in the real world. *Cleveland Clinic J Med* 2008;75:157-166.
10. Kennedy SH, Rizvi S, Fulton K, et al. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. *J Clin Psychopharmacol* 2008;28(3):329-333.
11. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry* 2009;166:980-991.
12. Uchida H, Takeuchi H, Suzuki T, et al. Combined treatment with sulpiride and paroxetine for accelerated response in patients with major depressive disorder. *J Clin Psychopharmacol* 2005;25:545-551.
13. ten Doesschate MC, Bockting CL, Schene AH. Adherence to continuation and maintenance antidepressant use in recurrent depression. *J Affect Disord* 2009;115 (1-2):167-170.
14. Clayton AH, Pradko JE, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* 2002;63(4):357-366.
15. Bockting CL, Spinhoven P, Wouters LE, et al. Long-term effects of preventive cognitive therapy in recurrent depression: a 5.5-year follow-up study. *J Clin Psychiatry* 2009;70(12):1621-1628.
16. Kuyken W, Byford S, Taylor RS, et al. Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. *J Consult Clin Psychol* 2008;76(6):966-978.