The "NICE Guideline" on the treatment of depression

SIR DAVID GOLDBERG

Abstract. The National Institute of Clinical Excellence (NICE) in the UK is responsible for producing evidence based guidelines for the treatment of most common illnesses, both physical and psychological. NICE uses a hierarchy of evidence, ranging from data from meta-analyses of randomised controlled trials (RCT's) at the apex, to the opinions of acknowledged experts at the bottom. The task of preparing guideline for depression involved us in performing clean meta-analyses of around 8,000 published RCTs of the treatment of this disorder. Where drug treatments were concerned we used three indicators of efficacy, as well as considering toxicity, tolerability and cost. We also distinguished between studies carried out in primary care, and studies in patients treated by the mental health services. We found it helpful to arrange our report in terms of a "stepped care" model, addressing the indications for patients being referred on for more specialised, and expensive, treatments. In the full guideline we included our doubts that depression was a homogenous clinical entity, and our awareness of the limitations of relying on randomised controlled trials (RCT's) as the only source of evidence. This Editorial summarises the content of the guideline on the treatment of depression and discusses how it was received and also what it did not say.

The *National Institute of Clinical Excellence* (NICE) in the UK is responsible for producing evidence based guidelines for the treatment of most common illnesses, both physical and psychological. The latter are produced on behalf of NICE by a joint collaboration between the Research Units of the College of Psychiatrists and the British Psychological Society who co-opt representatives of other professions relevant to the particular disorder: in the case of depression, we had representatives from general practice, from pharmacy and from nursing, in addition to three "Users". The Users were representatives of User's Groups – that is to say, people who had suffered from depression, and had experience both of its symptoms and the effects of various treatments. NICE uses a hierarchy of evidence, ranging from data from meta-analyses of randomised controlled trials (RCT's) at the apex, to the opinions of acknowledged experts at the bottom.

HOW THE GUIDELINE WAS PRODUCED

The task involved us in performing clean meta-analyses of around 8,000 published RCTs of the treatment of depression. To be accepted as "clean" we applied a number of criteria about the way the trial had been carried out, and then further eliminated individual trials that produced highly deviant findings, in order to eliminate heterogeneity. The fairly large committee contained systematic reviewers and experts from both psychopharmacology and clinical psychology, and in order to work more efficiently we divided ourselves into three subgroups dealing with the organisation of treatment services, with drug treatments and with psychological interventions. Each of these sub-groups contained a User, and the three groups came together to report their findings to the parent group at the end of each day's work.

Where drug treatments were concerned we used three indicators of efficacy, as well as considering toxicity, tolerability and cost. Many studies claiming to show that one drug is superior another base their conclusions on small differences which are statistically significant because of the large numbers in the study. Here the Users came to our assistance, as they told us how much better in terms of scores on the *Hamilton Depression Scale* a new drug would have to be before they wanted to change their medication: as a result, we declared differences of less than three points to be "statistically but not clinically significant".

We also distinguished between studies carried out in primary care, and studies in patients treated by the mental health services. We found it helpful to arrange our report in terms of a "stepped care" model, addressing the indications for patients being referred on for more specialised, and expensive, treatments. Stepped care asks three ques-

Address for correspondence: Sir D. Goldberg, Health Services Research Department, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF (United Kingdom).
Fax: +44-020-7848.0515
E-mail: spjudpb@hotmail.com
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tions: Who needs treatment? Who should give it? and when should patients be referred?

WHAT WE SHOWED

Step 1 – Detection

At the bottom of the stepped care model we considered studies on the detection of depression, and made recommendations about screening questions to be routinely used with various high-risk groups of patients – for example, those known to have had a previous episode of illness, or those disabled by physical illness.

Step 2 – Recognised Depression (mild, 4 symptoms)

We then considered studies of treatments that are effective for those depressions detected in primary care settings which are at, or just above, the diagnostic threshold for "depressive episode" (4 symptoms). We found good evidence for guided self-help, for physical exercise, for computerised cognitive behaviour therapy (CBT), and for problem solving. There was also evidence for the efficacy of St John's Wort, but we did not recommend it for routine prescription, since different preparations have different alkaloids, and there are interactions with other medications. However, we found that conventional antidepressants were no more effective than placebo tablets, and therefore did not recommend them, as the risk-benefit ratio is unfavourable. It should be noted, however, that placebo tablets, administered in RCTs, did very well in the treatment of mild depression!

Step 3 – Moderate and severe depression in primary care

When depression in primary care is of moderate (5-6 symptoms) or severe (7 or more symptoms) intensity we recommend *active drug treatment in all cases*, as this is easily the cheapest treatment, and is equally effective as psychological treatments. We found no evidence that any antidepressant was more effective than any other in primary care – but there are real differences in toxicity, in tolerability and in cost. We mentioned citalopram and fluoxetin as examples of suitable drugs, as they are well tolerated, or relatively low toxicity and low cost.

All patients prescribed antidepressants should be warned of the risk of discontinuation symptoms – paroxetin is particularly likely to cause them, as it has a short half-life. All those thought to present a suicide risk, and all those below the age of 30, should be warned of the increased risk of suicidal thoughts in the early stage of treatment, and should be seen again within one week, and then from time to time until the risk has receded.

Although tricylics are effective drugs, females do not tolerate them well, and they are relatively cardiotoxic. We made detailed recommendations about fears of addiction, and the need to continue antidepressants for six months after recovery. If a psychological treatment is preferred, we recommend problem-solving as a relatively inexpensive treatment, of equal efficacy as antidepressants in both mild and moderate depression. CBT is a more expensive treatment, but if patients do not respond to problem solving it is the treatment of choice, given for 16-20 sessions over about 9 months. We gave detailed advice on the management of depressions which do not respond to the first treatment offered.

If the patient fails to respond, first check that the drug is being taken regularly and in the prescribed dose. If so, increase dose within permitted range, with modest, incremental increases. If the first drug is poorly tolerated, or if there has been no response after one month, switch to another drug, we recommend another SSRI, but other drugs are also acceptable. Mirtazepine – if sedation and weight gain can be tolerated, or moclobemide if the previous antidepressant can be washed out first. If there is thought to be a risk of overdose, then lofepramine, mirtazepine & reboxetine are better than others. In the presence of ischaemic heart disease, sertraline is the best antidepressant, and dothiepin should be avoided.

Venlafaxine should be avoided as a first line treatment in primary care, but may be continued in primary care if it has been initiated by a psychiatrist. In our view, combined treatments, lithium augmentation and MAO-inhibitors should not be initiated in primary care.

Step 4 – Mental Health Services

When patients have either failed to respond, or responded incompletely to two different treatments, or when they have had frequent episodes, we recommend that they are referred to the mental health services. Here we divided patients into four groups: "acute phase non-responders", treatment resistant cases, relapse prevention and atypical cases.

Acute phase non-responders should be treated in the first instance by augmentation by another antidepressant – but not carbamazepine, lamotrigine or buspirone. If this is ineffective one should move to an effective psychotherapy – either cognitive or interpersonal. If the depression is severe, this can accompany continued drug therapy. There is no good evidence that lithium augmentation will help – but of course, it might.

Treatment resistance is defined as failure to respond to two different treatments given in proper dosage for an adequate time. Those who are moderately depressed

should be offered CBT, and if there has been a partial response to antidepressants this should accompany continued drug therapy. Once more, an augmentation strategy should be tried. If this fails, go on to venlafaxine. Adding lithium should help.

Antidepressants may help to prevent relapses, and to deal with frequent recurrences. If there has been a good response to antidepressants they should be continued for two years, and if lithium can be tolerated there is now evidence that it will often help. Those unable or unwilling to continue an effective drug should be offered either IPT or CBT.

Atypical depressions (mainly in females) usually respond to SSRIs, but may be offered MAOI's if they fail to respond. In psychotic depression there is some evidence that augmenting the antidepressant with an antipsychotic is helpful.

Step 5 – In-patient care

Treatment as an in-patient is recommended where there is a risk to life or a serious risk of self-harm. Here the recommendations are predictable, but with the exception of ECT are not evidence based.

In the full guideline we included our doubts that depression was a homogenous clinical entity, and our awareness of the limitations of relying on randomised controlled trials (RCT's) as the only source of evidence. We were aware that there are many exclusions in RCTs, that negative studies may not be published at all, and that positive studies may be multiply published. In particular, few severely depressed patients are randomised to a placebo condition, and many patients deemed "suitable" for inclusion may have mild illnesses about to remit spontaneously (Figure 1).

What the guideline did not say

Patients do not go to doctors for evidence based medicine (EBM), they go for patient-based evidence. Rather than be told what the best treatment is for the average member of the population (EBM), they want to know what is the best treatment for them, with their particular problems, and their own idiosyncrasies. We did not give advice about this problem, as to do so would have been outside our terms of reference. But why not do so now?

The health professional needs to know five things in order to make this decision: how long symptoms have lasted, whether there is a family or a past history of depression, whether there is social support available, and whether the severity is increasing or tending to remit. A person with no previous or family history, who is well socially supported and whose symptoms are either remit-

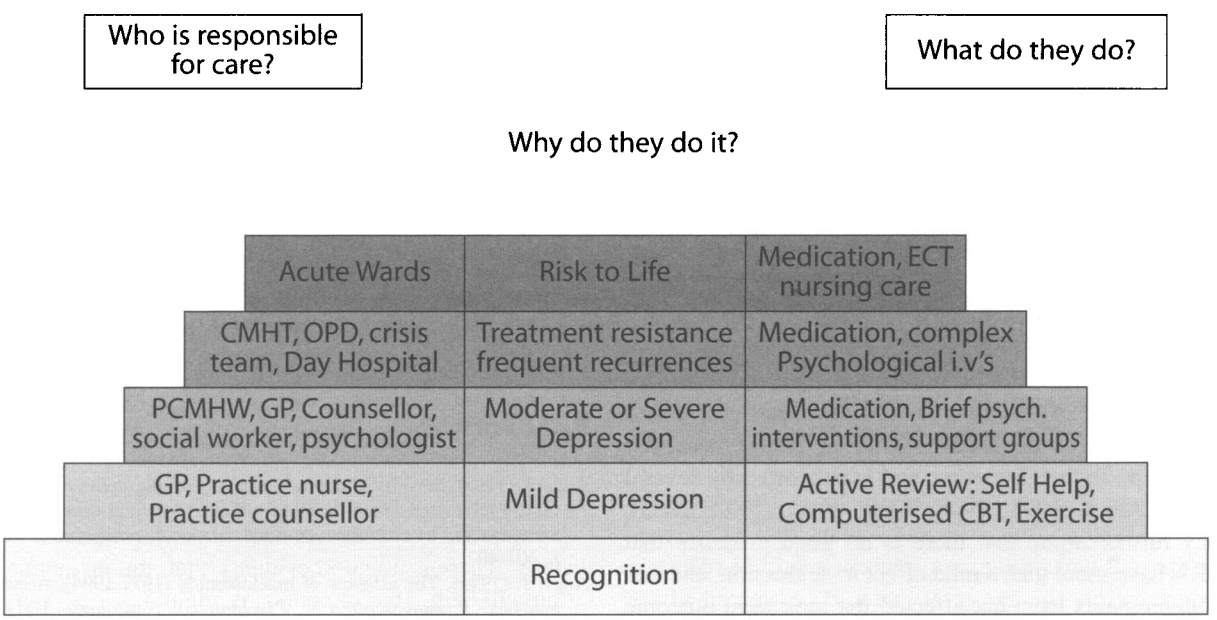

Figure 1. – *The steps of the primary care in the treatment of the depression.*

ting or are only just at threshold for "diagnosis" should have their problems discussed, be given helpful advice, and followed up. We called this "watchful waiting". But if any of these conditions are not satisfied, active treatment is a better option.

At present, general practitioners miss many cases of depression, but on the whole the depressions missed are not as severe as those detected, and have a somewhat better prognosis than the treated cases (Goldberg *et al.*, 1998). However, GPs also often prescribe antidepressants to those who are not clinically depressed (Berardi *et al.*, 2005), and may not recommend non-drug interventions, such as exercise, self-help, problem solving, watchful waiting or sleep hygiene. Since our guideline appeared, a Cochrane systematic review on the treatment of psychotic depression has appeared (Wijkstra *et al.*, 2004), but it agrees with our provisional advice in the guideline – the evidence appears to favour combinations of a neuroleptic and an antidepressant in the treatment of these cases.

How the guideline was received

The British Journal of Psychiatry (Whitty & Gilbody, 2005) welcomed the Guideline, but complained that it would not do any good because there were insufficient numbers of people trained in CBT. This appears to ignore the many other non-drug interventions for mild depression that we recommended that fall well short of CBT, and fails to understand that our task was to give the evidence on efficacy, not to give advice on manpower shortages. An editorial in the BMJ (Middleton *et al.*, 2005) gave the guideline a guarded welcome, but was happier with the advice on moderate to severe depression, than our advice on mild depression. Problems are connected with the diagnosis of "mild depression", and "until research has established who is likely to benefit from active treatment, practitioners will continue to be tempted to respond to requests for help by allowing such negotiations to result in a medical diagnosis".

More powerful criticism came from Moncrieff & Kirsch (2005) following this editorial. They doubted that the magnitude of the drug/placebo difference correlated with severity of depression. This of course is a key assumption in the Guideline, and is supported by several papers (Angst, 1993; 1995; Kahn *et al.*, 2002; 2005). They further argue that there is no good evidence that SSRIs have more than a mild effect in depression, and that antidepressants have not affected the long term outcome of depression. We were aware of Kirsch's views when the Guideline was written, and indeed reference five of his papers on the topic. In our reply (Pilling *et al.*, 2005) we argued that the long term response to antidepressants was documented by Geddes *et al.* (2003). Hatcher (2005) commented that if antidepressants are ineffective we must next consider psychological therapies – which are no more effective than antidepressants. Ankarberg (2005) makes the important point that the good results in the placebo arm of RCTs is associated with carefully given supportive therapy given on a regular basis, without such support, results might be far less impressive.

Harrison-Read (2005) argues that responses to antidepressants may be curvilinear, with a poorer treatment effect at both the mild and the severe ends of the severity continuum. Pandarakalam (2005) suggested that the term "antidepressant" might be a misnomer, while Taylor (2005) goes further, suggesting that they might be mere anxiolytics. Finally, Wohlfarth *et al.* (2005) object that responses to antidepressants are not necessarily normally distributed, and argue for a bimodal distribution, corresponding to those who do, and do not, respond to treatment. If this is so, it is misleading to analyse results as "mean reductions in symptoms", and they should be analysed in terms of responders/remitters. "Results of clinical trials that examine the effect of antidepressants in terms of responders/remitters indicate that the effect is moderate (15-20%) but not negligible, neither from a clinical nor from a public health perspective".

The Guideline has stimulated an active response, and the finding that the risk benefit ratio does not support prescription of antidepressants in mild depression is likely to have wide repercussions. Our detailed recommendations can be downloaded from the internet, at www.nice.org.uk/pdf/word/CG023NICEguideline.doc. The Guideline is available in many forms, all of them on the NICE website (www.nice.org.uk/page.aspx?o=235213): these include a pdf (Acrobat) format, a Quick Reference Guide, a form suitable for the lay public, an analysis of cost impact, and the full guideline with all appendices. The latter include details of all the meta-analyses. Hard copy can also be ordered from the NICE website.

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