**TNF ANTIBODIES**

**AND RHEUMATOID ARTHRITIS**

A real difficulty with original treatments is that evidence emerges slowly. This is particularly the case for chronic diseases where treatments may have to be assessed over long periods. This slow emergence means that there can be some initial difficulty in assessing whether the treatment works, how well it works, in whom it works, and what the economics are if it does work.

There comes a point, though, when there is sufficient evidence on which to pass a judgement, which is one reason the UK government set up its National Institute for Clinical Excellence (NICE). As part of its work, NICE now publishes the evidence on which its judgements are based on its Internet site. The way in which it assessed the evidence on anti-TNF treatments for rheumatoid arthritis [1] demonstrates a growing quality and maturity in its processes.

**NICE evidence**

The 138-page report from Birmingham is a good background read on rheumatoid arthritis and its treatment. It examines the background, diagnosis, pathology, current service provision, the interventions, its search strategy, the results in the form of a meta-analysis of major outcomes, detailed summaries of the trials involved including adverse events, and the health economic arguments, as well as the implications for the NHS.

**Technology**

Infliximab and etanercept are partially humanised monoclonal antibodies aiming to reduce the actions of circulating tumour necrosis factor (TNF). Both exert their effects by removing TNF from the circulation, and consequently interrupt the inflammatory process.

**Old chestnuts**

Complementary therapy, placebo, and odd techniques make up most of Bandolier’s questions. So good information that doing nothing doesn’t make things happen, that acupuncture doesn’t work (this time with cocaine addiction), and a real puzzler over pulsed ultrasound and fracture healing. Statistical significance on tiny numbers is not always a good reason for doing something. The frustration is that no-one is helping us deal with the common situation of too little information.
**Efficacy**

With rheumatoid arthritis there are many possible outcomes, starting with the number of painful or swollen joints, through to health assessment questionnaires and quality of life. The most commonly used (though perhaps difficult to explain and use) measure is the American College of Rheumatology (ACR) response criteria, a composite measure of seven indices:

- Tender joint count
- Swollen joint count
- Global disease activity assessed by observer
- Global disease activity assessed by patient
- Patient assessment of pain
- Physical disability score (like health assessment questionnaire)
- Acute phase response (CRP measurement, or ESR)

The ACR 20 response is defined as a 20% improvement in the first two of these, plus a 20% improvement in any three of the remaining five items. This is not an easy outcome to reach, though also being used now are ACR 50 and ACR 70, which are similar to the ACR 20 but at 50% and 70% improvements. These are very high hurdles of treatment efficacy and represent very significant clinical improvement.

**Results**

To at least give a flavour of the results obtained with these two monoclonal antibodies, the results for ACR 20, 50 and 70 are looked at here. There are issues about dose, and about duration. The NICE evidence combines different doses and duration up to one year, but shows that, in the main, this is a reasonable thing to do, at least for now.

Results were consistent between trials comparing the new treatments with placebo. Those for the ACR 20 for infliximab are shown in Figure 1, and for etenercept in Figure 2. The results for ACR 20, 50 and 70 outcomes are in Table 1. NNTs were about 2-3 for ACR 20, about 4 for ACR 50, and about 8 for ACR 70.

**Figure 1: ACR 20 with infliximab and placebo**

![ACR 20 with infliximab and placebo](image1.png)

**Figure 2: ACR 20 with etenercept and placebo**

![ACR 20 with etenercept and placebo](image2.png)

The analysis also shows that what happens with placebo depends on the difficulty of the outcome. With placebo about 14% of rheumatoid arthritis patients achieved ACR 20. As the hurdle was raised to ACR 50 and 70, the percentage of patients achieving the outcome fell to about 6% and 1% respectively (Table 1).

Good information about adverse events is also given in the report, though not recounted here.

**Comment**

Given the evidence outlined in the report, it is clear why the British Society for Rheumatology recommended that infliximab and etenercept should be used if the following criteria were met:

- Patients satisfy ACR classification for RA
- Patients have highly active RA
- Patients should have failed treatment on methotrexate and at least one other disease modifying agent
- Treated patients should be entered on a central register, with drugs, dose, outcomes and toxicity reported on a quarterly basis.

**Early referral**

An essential accommodation to the NICE evidence is an evidence-based early referral recommendation for newly diagnosed rheumatoid arthritis [2]. Based on a wide literature search by an international group of influential rheumatologists, this review provides clear support for the observation that permanent structural damage occurs early in the course of active rheumatoid arthritis and that early disease modifying drug intervention slows the progression of structural joint damage and improves long term outcomes, as well as overall quality of life.

It provides an early referral algorithm for newly diagnosed rheumatoid arthritis. Early referral is advised in the event of clinical suspicion of RA, supported by the presence of any of the following:

**Figure 2: ACR 20 with etenercept and placebo**

![ACR 20 with etenercept and placebo](image2.png)
1 At least three swollen joints
2 A positive “squeeze” test (composite compression test) that clinically evaluates a group of small adjacent joints such as metacarpophalangeal and metatarsophalangeal
3 Morning stiffness of at least 30 minutes

Important points were:
♦ Patients with RA have been shown to have an improved long term outcome, when treated by a rheumatologist
♦ There is evidence that delay of more than 12 weeks in treatment results in a missed opportunity to improve long term outcome
♦ RF positivity, a raised acute phase response, and erosions on X-ray are associated with poor outcome, but absence at presentation should not preclude diagnosis or referral
♦ NSAIDs can mask signs and symptoms at presentation
♦ Corticosteroids should not be prescribed without an accurate diagnosis.

The algorithm combines all these points with a diagram of the squeeze test, and it would make a useful guide for teaching, or a surgery wall, or computer aide.

### Table 1: NNTs for infliximab and etenercept versus placebo at longest duration, and pooling all doses

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Outcome</th>
<th>Trials</th>
<th>Outcome [number/total (%)] with</th>
<th>Relative benefit (95%CI)</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>ACR 20</td>
<td>4</td>
<td>458/803 (57)</td>
<td>35/259 (14)</td>
<td>4.3 (3.1 to 5.9)</td>
</tr>
<tr>
<td></td>
<td>ACR 50</td>
<td>4</td>
<td>232/803 (29)</td>
<td>14/259 (5)</td>
<td>5.5 (3.3 to 9.2)</td>
</tr>
<tr>
<td></td>
<td>ACR 70</td>
<td>3</td>
<td>68/667 (10)</td>
<td>2/215 (1)</td>
<td>12 (3 to 47)</td>
</tr>
<tr>
<td>Etenercept</td>
<td>ACR 20</td>
<td>4</td>
<td>245/497 (49)</td>
<td>19/133 (14)</td>
<td>3.6 (2.3 to 5.4)</td>
</tr>
<tr>
<td></td>
<td>ACR 50</td>
<td>4</td>
<td>161/497 (32)</td>
<td>10/133 (8)</td>
<td>4.5 (2.4 to 8.3)</td>
</tr>
<tr>
<td></td>
<td>ACR 70</td>
<td>1</td>
<td>60/340 (18)</td>
<td>2/88 (2)</td>
<td>8 (2 to 31)</td>
</tr>
</tbody>
</table>

### Overall comment

There is much new in the field of rheumatoid arthritis, and probably much more to come, backed by good new evidence. Given that RA is the most common form of inflammatory arthritis affecting 0.5% to 1% of the population, and with a large economic impact because about 90% of patients have some form of disability with two decades, this is of increasing importance. Some or all of this could be incorporated into the delivery of a quality service.

A short review of new treatments can also be found in the STEER series from the Wessex Institute [3].

**References:**
3. C de Vries. Effects of TNF-alpha antagonists in people with rheumatoid arthritis. (http://www.signpoststeer.org)

**THAT OLD PLACEBO FEELING**

Bandolier continuously gets into trouble over placebo because people have their own very fixed views about what it is. The extremes of definition are shown in Figure 1.

One definition is that use of a placebo describes what happens when you do nothing, so that in the context of a clinical trial, for instance, a placebo group could describe the natural history of a disorder without the intervention under test. It is the effect we see when we do nothing.

This rather clumsy phrase is abbreviated to the placebo effect. The trouble is that placebo effect can be taken to mean that any effect seen is caused by placebo. The definition has now changed to mean that doing nothing causes things to happen. The idea that placebo does make things happen is reinforced by much interesting academic work, almost always in contrived situations and with small numbers of people. Extrapolating that to clinical practice is a big step, but one often assumed.

Is it possible to say that one definition is right and the other wrong? A systematic review and analysis comparing clinical trials in which patients were randomly assigned to placebo or no treatment suggests that the evidence for placebo having an effect is at best weak [1].
Placebo effect: doing nothing makes things happen

Review

The review sought studies comparing placebo with no treatment that were properly randomised and blinded. Exclusions were healthy volunteers, studies with high dropout rates, or if the alleged placebo had some clinical effect.

Results

The analysis included 114 trials in 40 clinical conditions.

For dichotomous outcomes in 32 trials with 3,800 patients (average 119 per comparison) there was no difference between placebo and no treatment overall, or with subjective or objective outcomes.

For continuous outcomes in 82 trials with 4,800 patients (average 59 patients per comparison) there was a small overall effect, all for subjective outcomes.

The only condition in which there was an effect was for pain for continuous outcomes in 27 trials with 1,600 patients (average 59 trials per comparison).

Comment

The interesting thing is that any possible effect of placebo was found with continuous outcomes for pain in small trials. This is likely to be an artefact. Firstly we know [2] that continuous pain outcomes are often reported as a mean of data with highly skewed distribution. Analysis of means is therefore meaningless [2]. Smaller trials in pain have also been shown to have more effect than larger ones, probably because they are of poorer quality [3].

Not much evidence there, then, that doing nothing makes things happen.

References:
2. HJ McQuay et al. Variation in the placebo effect in randomised controlled trials of analgesics: all is as blind as it seems. Pain 1996 64:331-335.

A big problem with complementary therapy is that so many of the trials are of such low quality that bias of some degree is likely. When a properly done trial of high quality comes along, it therefore deserves our attention. Such a study demonstrates that acupuncture is ineffective for cocaine addiction [1].

Trial

This trial compared acupuncture of the ear using criteria of the US National Acupuncture Detoxification Association with needles inserted into non-acupuncture points in the ear and a non-acupuncture relaxation regimen for eight weeks. Six hundred and twenty cocaine dependent adults were randomised. They had to have a recent cocaine-positive urine screen and self-reported cocaine use, but not be dependent on any other drug except nicotine or opiates, or currently receiving other treatment, be actively suicidal or psychotic, or received acupuncture in the previous 30 days.

Patients were told their treatment assignment, because blinding was not possible. Treatments were described in a standardised way, with all the treatment options described as ways to reduce stress and with potential benefits to reduce craving and cocaine use. Weekly (standardised) individual counselling sessions focusing on changing addictive behaviour were offered as adjunctive treatment.

Outcomes were positive urine screens, self-reported cocaine use, and a range of other outcomes.

Results

The three groups were identical in terms of age, sex and ethnic background. Over the eight weeks of the study retention was under 50% and equal in the three groups (Figure 1). The proportion of cocaine-positive urine tests (averaging about three a week) was the same in the three groups (Figure 1). While there was a reduction in cocaine use over the eight weeks, there was no difference between the three
treatment groups, either at the end of treatment or at three or six months of follow up (Figure 2).

**Comment**

This is a good study that looks at the result both by intention to treat and by completers. It failed to find any difference between acupuncture recommended by the key US association, sham acupuncture, and the non-acupuncture control of relaxation. It dealt with the fact that blinding was impossible, it was randomised, and it was large. The lack of blinding could cause bias, but should have been in the direction of acupuncture doing better if patients or therapists believed that it would. There was no difference.

Acupuncture doesn’t work on the basis of these results. What the paper does tell us is how to maximise methodological rigour in a difficult clinical situation, and helps set standards against which we can compare small, low quality studies that more often say that acupuncture does work. It helps explain why small, low quality studies in acupuncture, or anything else, should be ignored.

References:

**Figure 2: Percentage of patients completing the study who were abstinent at the end, and after three and six months**

[Graph showing percentage of patients completing the study who were abstinent at the end, and after three and six months]

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**PULSED ULTRASOUND FOR FRACTURE HEALING**

Some fractures have delayed healing or nonunion. Ultrasound has been suggested as a possible therapeutic agent to improve healing. Does it work? A new systematic review and meta-analysis shows how little evidence we have [1].

**Search**

This was impressive, using many databases and attempts to find unpublished material, plus hand searching key journals. Methods used were great, and clearly defined inclusion criteria were random allocation to pulsed ultrasound or control, skeletally mature patients, double blinding, with time to radiological healing as the main outcome.

**Results**

There were three trials involving 158 fractures (tibial shaft, distal radius and scaphoid, respectively). The mean times to healing are shown in Figure 1. Mean healing time was reduced by about 60, 40 and 20 days respectively.

**Comment**

The authors are justifiably cautious in their conclusions. They say that pulsed ultrasound may reduce time to fracture healing for fractures treated nonoperatively. They imply that we should beware because of the small amount of data. And the trials are good, with high quality scores, so this isn’t like some reviews with small amounts of poor information that ladle on heaps of weasel word sauce.

What we frequently lack in systematic reviews is some idea of how much information we need to be sure of the result. If there is little information, as here, then unpublished negative trials could be very important. Someone will be selling this to you soon on the basis that it is “evidence-based”!

Reference:

**Figure 1: Healing time with ultrasound and placebo**

[Graph showing mean time to healing (days) with ultrasound and control]
Depression is awfully common. In primary care, estimates of the prevalence of major depression range from 5% to 9%, and that’s just the patients. We all get fed up, we all get tired, we all get to feel a bit worthless from time to time. We may not be well, or be recovering from the last in a succession of viruses. Sometimes we pull ourselves together, and sometimes we can’t. The problem for primary care professionals is telling major depression from being fed up, and then whether that depression signifies some unrecognised problem.

A terrific new systematic review [1] pulls the subject together beautifully, and gives us a clear insight into the latest diagnostic criteria for depression plus good information on the performance of various simple screening and diagnostic systems for primary care.

**Diagnostic features**

Based on the criteria from Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), eight symptoms and criteria are defined, together with some suggested questions for patients (Table 1). Depending on the answers to the questions and the duration of the symptoms depression can be major or minor, or can just indicate dysthymia (melancholy, Table 2). Can diagnostic questionnaires be of any help?

### Table 1: DSM-IV diagnostic criteria and suggested questions

<table>
<thead>
<tr>
<th>Symptom</th>
<th>DSM-IV diagnostic criteria</th>
<th>Suggested questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood</td>
<td>Depressed mood most of the day, nearly every day</td>
<td>How has your mood been lately? How often does this happen? How long does it last?</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day</td>
<td>Have you lost interest in your usual activities? Do you get less pleasure in things you used to enjoy?</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Insomnia or hypersomnia nearly every day</td>
<td>How have you been sleeping? How does that compare with your normal sleep?</td>
</tr>
<tr>
<td>Appetite or weight change</td>
<td>Substantial change in appetite nearly every day or unintentional weight loss or gain (≥5% of body weight in a month)</td>
<td>Has there been any change in your appetite or weight?</td>
</tr>
<tr>
<td>Decreased energy</td>
<td>Fatigue or loss of energy nearly every day</td>
<td>Have you noticed a decrease in your energy level?</td>
</tr>
<tr>
<td>Increased or decreased psychomotor activity</td>
<td>Psychomotor agitation or retardation nearly every day</td>
<td>Have you been feeling fidgety or had problems sitting still? Have you slowed down, like you were moving in slow motion or stuck in mud?</td>
</tr>
<tr>
<td>Decreased concentration</td>
<td>Diminished ability to think or concentrate, or indecisiveness, nearly every day</td>
<td>Have you been having trouble concentrating? Is it harder to make decisions than before?</td>
</tr>
<tr>
<td>Guilt or feelings of worthlessness</td>
<td>Feelings of worthlessness or excessive guilt nearly every day</td>
<td>Are you feeling guilty or blaming yourself for things? How would you describe yourself to someone who had never met you before?</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Recurrent thoughts of death or suicide</td>
<td>Have you felt that life is not worth living or that you'd be better off dead? Sometimes when a person feels down or depressed they might think about dying. Have you been having any thoughts like that?</td>
</tr>
</tbody>
</table>

### Table 2: Diagnostic categories for depression and dysthymia (melancholy), and criteria for diagnosis

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>DSM-IV criteria</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depression</td>
<td>≥5 depressive symptoms, including depressed mood or anhedonia, causing significant impairment in social, occupational, or other important areas of functioning</td>
<td>≥2 weeks</td>
</tr>
<tr>
<td>Minor depression</td>
<td>2 to 4 depressive symptoms, including depressed mood or anhedonia, causing significant impairment in social, occupational, or other important areas of functioning</td>
<td>≥2 weeks</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>3 or 4 dysthymic symptoms, including depressed mood, causing significant impairment in social, occupational, or other important areas of functioning</td>
<td>≥2 years</td>
</tr>
</tbody>
</table>
MEDLINE and the Cochrane register of depression trials were searched for English-language studies evaluating the performance of case-finding instruments in primary care and the reliability of the clinical interview. Case-finding instruments had to have easy to average literacy requirements, be scored without a calculator, have a depression-specific component and be evaluated in at least one study with at least 100 subjects. Reliability studies had to have diagnoses made by two or more clinicians reviewing audio- or videotape interviews.

Results

Eleven questionnaires with between one and 30 items were found in 28 studies involving over 25,000 patients for case-finding. Major selection bias occurred in nine trials, which were then excluded. Three instruments, Beck depression inventory, Centre for Epidemiological Studies depressive screen and the Zung self-assessment depressive scale were developed specifically to identify depression. None of the instruments took more than five minutes to administer, and most could be done in two or three minutes.

The results for finding major depression in a primary care setting are shown in Table 3, with the mean likelihood ratios for a positive and a negative result. The likelihood ratio for a positive result was about 3 and for a negative result was about 0.2. In a clinic with an 8% prevalence of major depression of dysthymia, a clinician seeing 100 patients a week can expect that 30 will screen positive for depression, of whom seven would meet the criteria for major depression after a more careful interview. In the 70 patients who screen negative, one would actually be clinically depressed.

In seven studies using a semistructured interview, agreements between examiners was good, with kappa values generally above 0.7.

Comment

This is a splendid review, with much more useful information than can be conveyed by précis. For any primary care organisation or professions wanting to improve the determination of depression in a primary care setting reading this is an essential start. The Bandolier Internet version has a set of links to the various instruments used in the study. Not all of them have a website, but of those that do, the commonest are shown in the box below.

References:

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Number of Studies</th>
<th>Number of Patients</th>
<th>Likelihood ratio Positive</th>
<th>Likelihood ratio Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre for Epidemiological Studies depressive screen</td>
<td>10</td>
<td>3038</td>
<td>3.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Symptom driven diagnostic system</td>
<td>4</td>
<td>1682</td>
<td>3.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Beck depression inventory</td>
<td>4</td>
<td>952</td>
<td>4.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Zung self assessment depression scale</td>
<td>4</td>
<td>667</td>
<td>3.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Primary care evaluation of mental disorders</td>
<td>2</td>
<td>967</td>
<td>2.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Hopkins symptom check list</td>
<td>2</td>
<td>946</td>
<td>3.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Geriatric depression scale</td>
<td>2</td>
<td>165</td>
<td>3.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Patient health questionnaire</td>
<td>1</td>
<td>585</td>
<td>1.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Single question</td>
<td>1</td>
<td>291</td>
<td>2.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 3: Diagnostic utility of case-finding instruments for depression in primary care

Websites for common instruments

Centre for Epidemiological Studies at chipts.ucla.edu/Assessment_Instrument/asmt_dp2.html
Beck Depression Inventory at www.uea.ac.uk/~wp316/depression.pdf
Zung at: www.wellbutrin-sr.com/hcp/depression/zung.html
Primary care evaluation (PDF by email to Robert Spitzer on RLS8@colombia.edu)
Geriatric Depression Scale at www.stanford.edu/~yesavage/GDS.english.long.html
Patient Health Questionnaire at www.cmecenter.com/primeotoday/
Note that some deep links may not work, and you may have to use just the first part of the Internet address

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