Randomised Controlled Clinical Trials: An Example with an Anti-Depressant

INTRODUCTION

Any therapy or treatment needs to be assessed for its effectiveness or efficacy. The way to do this experimentally is to compare a group receiving the treatment or therapy with a group that does not. It would be expected that the former group shows a greater improvement over a set period of time.

Hill (1955) defined a clinical trial as "a carefully and ethically designed experiment with the aim of answering some precisely framed question".

However, there are a number of quasi-experimental variations of the clinical trial (1).

For a clinical trial to be carefully and ethical designed, there are a number of general problems to address. Particularly when aiming to design the "randomly controlled trial" (RCT), which is seen as the best type of clinical trial.

The general problems with clinical trials are:

i) The appropriate measurement of baseline and improvement.

It is necessary to use a measure that can be compared before and after the trial. In most cases today, self-reported questionnaires or psychometric tests are used.

ii) To control for equality in symptoms among the conditions.

Strict inclusion and exclusion criteria are used to try to equalise the level of the disorder among the different conditions.

iii) To overcome the knowledge of who is in the control or placebo group by the researchers or the participants.

This problem is addressed by the use of "blinding". In an "open label" trial, both researchers and participants know which group they belong to.

With "blind-at-randomisation", participants are divided into the conditions with no prior knowledge of

the condition, but they may soon learn as the trial develops. For example, the presence of side effects with the drug condition, and not with the placebo condition.

"Single-blind" design is where the participants cannot tell which condition, but the researchers know.

But, best of all, is "double-blind" design, where neither the researcher nor the participants know which condition is which (Cohen and Posner 1995).

iv) The ethics of denying treatment in the control or placebo group.

One traditional method used here is to make the control group those on a waiting list for treatment. Alternatively, gain informed consent for the participants: making them fully aware that they may be in the placebo or control group when randomised.

v) Participants dropping out during the clinical trial.

Johnson (1992) notes the reasons and points for drop-outs:

a) At baseline stage before randomisation;

b) Discovered later to have another disorder not being studied;

c) Randomised to one group but given wrong treatment;

d) Side effects of treatment leads to dose reduced or stopped;

e) Leaves during trial or defaults on treatment.

To some degree, the problem of drop-out is hard to stop. The simplest answer is to start with a large number of participants.

PERAHIA ET AL (2006) STUDY

Aims

Duloxetine (SNRI anti-depressant (2)) "was evaluated with regard to its efficacy, safety and tolerability in the prevention of relapse of MDD (major depressive disorder)" (p346).

Participants

All participants (patients) were at least eighteen years old, and met the criteria for "major depressive disorder without psychotic features" in DSM-IV (APA 1994). Exclusion included having a mental disorder other than major depressive disorder, having treatment-resistant depression, being a serious suicidal risk, and having a serious medical illness.

The severity of depression was rated by a score of eighteen or more on the Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960) [3], and a score of four or more on the Clinical Global IMpression - Severity (CGI-S) scale (Guy 1976).

The 681 participants initially screened were reduced to 533 who met the inclusion criteria. The study took place in France, Italy, Spain, and the USA, and all participants were outpatients.

Study Design

The study involved four phases, and was "a randomised active-treatment lead-in double-blind placebo-controlled multi-centre parallel-group study" [4].

1. Acute phase

All participants were given 60mg of duloxetine daily for twelve weeks, and both the patients and doctors knew what was being taken. This is an "open-label" study.

255 participants left the study by the end of this phase for reasons including patient's choice (n = 62), death (n = 1), or protocol violation (n = 27).

2. Continuation phase

Because the study was interested in prevention of relapse of major depressive disorder [5], only 278 participants (52% of the original sample), who were classed as no longer suffering from major depressive disorder, were included here. This was measured by a score of nine or less on the HRSD and two or less on the CGI-S scale.

The participants were randomised to continue duloxetine for twenty-six more weeks (n = 136) or a placebo (n = 142). The study was looking for the re-emergence of the symptoms of depression at any time over the twenty-six weeks (scored as twelve or more on the HRSD).

Forty-six participants completed the placebo group without a relapse and seventy-four in the duloxetine

group. Thirty-three participants in the duloxetine group discontinued and thirty-seven in the placebo group.

3. Rescue phase

Any participants who relapsed had the option of a double daily dose of duloxetine (twenty-nine from the duloxetine group, of which twenty-four completed the study; fifty-eight from the placebo group and forty-five completed).

4. Follow-up phase

No tablets were given to either group and data were collected after one more week. The study was completed by seventy-four participants in the duloxetine group and forty-seven in the placebo group (ie: none of them participated in the rescue phase.

A number of measures of efficacy were used including Quality of Life in Depression Scale (QLDS) (McKenna and Hunt 1992).

Main Findings

Those patients who received duloxetine had significantly longer time to relapse than the placebo group ($p = 0.004$), and significantly fewer relapsed ($p = 0.05$).

EVALUATION OF PERAHIA ET AL STUDY

A number of general problems with clinical trials were mentioned earlier. Here is how this study dealt with them.

i) Appropriate measures

Use of specific scores on HRSD and CGI-S scale to define major depressive disorder and recovery. These two psychometric measures are commonly used in psychiatry and clinical psychology. They are not perfect as psychiatrists or patients rate the answers to questions. There is always room for subjectivity.

ii) Inclusion and exclusion criteria

Strict criteria were used for the study (table 1).

INCLUSION CRITERIA	EXCLUSION CRITERIA
- At least 18 years old	- Having mental disorder other major depressive disorder
- DSM-IV diagnosis of "major depressive disorder without psychotic features"	- Primary diagnosis of anxiety disorders in previous one year
- moderate depression and improvement (based on eg: HRSD score)	- Treatment-resistant depression
	- Serious suicidal risk
- At least one previous episode of major depressive disorder before current one	- Serious medical illness

Table 1 - Inclusion and exclusion criteria for the study.

iii) Use of double-blinding

In other words, neither the participants nor the researchers knew who was in which group, and the researchers still did not know in the rescue phase. Though, then, the patients knew they were receiving duloxetine.

However, the presence of side effects would give the participants a clue to which group they were in. The authors claimed that there were "no statistically significant differences in the rate of adverse event reported" between the two groups. During the acute phase of the study, 36% of adverse events reported were nausea, and this was the most common.

iv) Ethics

The study was approved beforehand at each site by an ethics review board. The participants gave written informed consent before the study started, and were aware that they could be in the placebo group (which did seem to produce anxiety among a number of participants at the beginning of the continuation phase of the study).

The use of a rescue phase in the study was available to help participants who suffered badly with a relapse of depression. Participants were also seen on nine occasions during the twenty-six weeks of the continuation phase of the study.

v) Drop-outs

Table 2 gives the numbers of participants who dropped out and for what reasons. The total drop-out was 343 people (64.4% of those who began the acute phase of the study).

	ACUTE PHASE	CONTINUATION PHASE DULOX*	CONTINUATION PHASE PLACEBO	RESCUE PHASE DULOX*	RESCUE PHASE PLACEBO
Patient decision (eg: no longer willing to be part of study)	64	11	15	1	7
Adverse event (ie: unpleasant side effect or health risk)	60	5	5	-	-
Protocol randomisation criteria not met (patient not truly randomised to duloxetine or placebo group)	52	-	-	-	-
Lost to follow-up (eg: moved house and did not give new address)	43	6	7	1	2
Protocol violation (eg: changed diagnosis during study)	27	10	7	2	2
Lack of efficacy (eg: drug did not seem to be working)	10	1	3	1	2
Death (from reasons other than study)	1	-	-	-	-
TOTAL	255	33	37	5	13

(* = duloxetine)

(After Perahia et al 2006)

Table 2 - Reasons for and number of drop-outs from the study.

Overall, this study is seen as a good quality clinical trial with many strengths, and inevitably some weaknesses (table 3).

STRENGTHS

1. Larger sample size than many comparable studies (190 participants completed the study including those in the rescue phase) * (6)

2. Double-blinded * (7)

3. Similarity of groups - eg: all outpatients (8)

4. Clear inclusion and exclusion criteria (table 1)

5. Length of whole study reasonably long for clinical trials (39 weeks in total)

6. Multiple measure of symptoms and efficacy used *

7. All participants screened using Mini International Neuropsychiatric Interview (MINI) (Sheehan et al 1998) (9)

8. "(T)he similarity of the acute phase to clinical practice by virtue of the use of open-label treatment" (p352) *

9. Use of rescue phase in study (but entry was at doctor or

psychiatrist's discretion)

10. "(E)valuation of efficacy of double-dosing as a strategy for patients who experienced relapse" (p352) *

LIMITATIONS

1. Exclusion and inclusion criteria may mean that sample not representative of clinical population (*). The exclusion of treatment-resistant depression and high suicidal risk can be accused of "cherry-picking" the best participants

2. Problems of standardising procedures across many centres and countries, particularly where different languages used (10)

3. Frequency of visits and assessment by doctors or psychiatrists not typical of clinical practice *

4. Use of psychometric tests (11)

5. Participants could realise which group because of side effects or "discontinuation-linked adverse events"

6. Did not compare duloxetine to other anti-depressants *

7. Including those in rescue phase in the final data (as they received a double dose of duloxetine) is confounding variable to simply comparing treatment versus no treatment

8. All nine authors of the study are directly or indirectly employed by the manufacturers of duloxetine, Eli Lilly (12)

(* = proposed by Perahia et al themselves)

Table 3 - Strengths and limitations of the Perahia et al study.

FOOTNOTES

1. Quasi-experimental variations of clinical trials include post-test control group design which uses two groups (treatment/no treatment), but has no baseline measures before the treatment began.

2. SNRI = serotonin and noradrenaline uptake inhibitor. The upshot is that more of these two neurotransmitters are available in the brain.

3. HRSD measures the severity of depression in an unstructured interview with 21 items (or 17 as used in this version).

4. Multi-centre trials have several groups of treatment and no treatment/placebo at different centres (figure 1). For example, different hospitals or GPs caseloads and different countries. This is an experimental design, and can be classed as a randomised controlled trial (RCT).

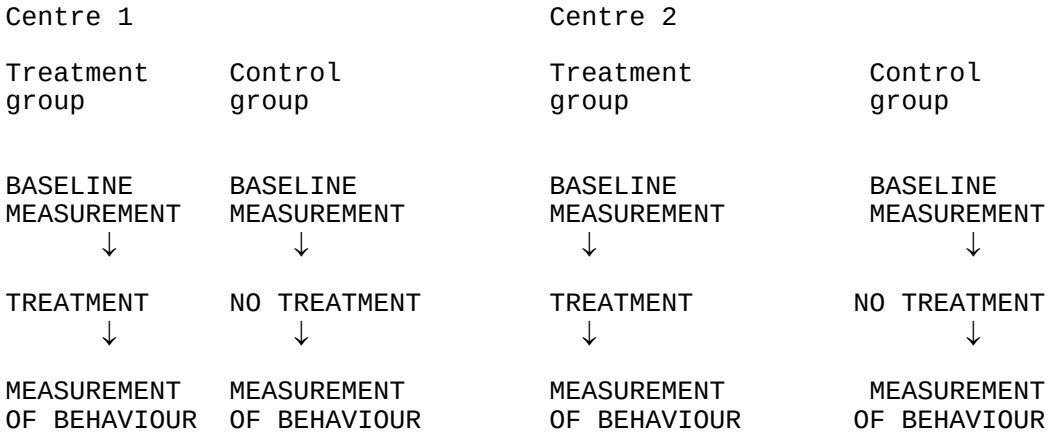

Figure 1 - Multicentre trial.

5. The World Health Organisation (1989) recommended continuation with anti-depressants for nine to twelve months even if the symptoms of depression appear to have gone, in order to avoid relapse.

6. Original screening of 681 participants - 72.1% drop-out/27.9% completed study; 533 participants began acute phase - 35.6% completed the study/64.4% drop-out.

7. The authors noted a general initial increase in symptoms for all participants at the beginning of the continuation phase. This was due possibly to anxiety about the 50% chance of being randomly allocated to the placebo group. However, the authors said, "investigator bias during the evaluation of patients might also be implicated in this observation, and it should be noted that the success of blinding for patients and assessors were not evaluated" (p351).

8. Table 4 lists the characteristics of the two groups in the continuation phase of the study.

	DULOXETINE	PLACEBO
Female (%)	67.6	77.5
Male (%)	32.4	22.5
Caucasian (%)	94.1	93.0
Mean age (years)	45.7	44.8
Mean HRSD score at baseline	4.9	4.6
Mean CGI-S scale score at baseline	1.4	1.4

(After Perahia et al 2006)

Table 4 - Similar characteristics of two groups of participants.

9. The bedrock of psychiatry is the clinical or diagnostic interview. Based on a combination of structured and unstructured questions, the psychiatrist builds up the information for diagnosis. Table 5 lists the advantage and disadvantages of this type of interview.

ADVANTAGE	DISADVANTAGES
- allows individual assessment of patient	- limited for unresponsive, overactive or confused patients
	- patients may present selves in better light ("prestige bias")
	- bias in diagnosis by psychiatrist; eg: influenced by first impressions
	- different responses given to different interviewers

Table 5 - Main advantage and disadvantages of clinical or diagnostic interviews.

10. Two authors based in Spain, two in England, and five in the USA. No details given of who carried out the study in France and Italy. It has to be assumed that local doctors or psychiatrists were used. There is also no detail of how many participants came from each country.

11. It is common practice now in psychiatry to use psychometric tests as a means of assessing the individual or as an outcome measure in studies of the efficacy of treatment. But the tests can have problems in terms of the question design and honesty of answers and scoring.

12. Moncrieff (2003) noted that "studies sponsored by drug companies are more likely to find evidence in favour of the sponsor's product than studies that do not have commercial sponsorship".

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