Randomised controlled trials

PEBM
2013

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Warm up quiz.....
1985-90 International collaboration to prepare systematic reviews of controlled trials in pregnancy and childbirth and the neonatal period
Effectiveness and efficiency

A. L. Cochrane
Sickness in Salonica: my first, worst, and most successful clinical trial-1941.

“. . . I recruited 20 young prisoners . . . I gave them a short talk about my medical hero James Lind and they agreed to co-operate in an experiment. I cleared two wards. I numbered the 20 prisoners off: odd numbers to one ward and evens to the other.

Each man in one ward received two spoonfuls of yeast daily. The others got one tablet of vitamin C from my "iron" reserve. The orderlies co-operated magnificently . . . They controlled fluid intake and measured frequency of urination.

. . . There was no difference between the wards for the first two days, but the third day was hopeful, and on the fourth the difference was conclusive . . . there was less oedema in the "yeast" ward. I made careful notes of the trial and immediately asked to see the Germans.”
“It could be argued that the trial was randomised and controlled, although this last was somewhat inadequate. In those early days, when the randomised controlled trial was little known in medicine, this was something of an achievement.”

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS
A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Colindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reeve; Pathologist: Professor J. W. McLeod.

Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

The clinicians of the centres met periodically as a working subcommittee under the chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank. Dr. Marc Daniels, of the Council’s scientific staff, was responsible for the clinical co-ordination of the trials, and he also prepared the report for the Committee, with assistance from Dr. D. A. Mitchison on the analysis of laboratory results. For the purpose of final analysis the radiological findings were assessed by a panel composed of Dr. L. G. Blair, Dr. Peter Kerley, and Dr. Geoffrey S. Todd.

Introduction

When a special committee of the Medical Research Council undertook in September, 1946, to plan clinical trials of streptomycin in tuberculosis the main problem faced was that of investigating the effect of the drug in pulmonary tuberculosis. This antibiotic had been discovered two years previously by Waksman (Schatz, Bugie, and Waksman, 1944); in the intervening period its power of inhibiting tubercle bacilli had been demonstrated. If based on adequately controlled clinical trials (Hinshaw and Feldman, 1944). The one controlled trial of gold treatment (and the only report of an adequately controlled trial in tuberculosis we have been able to find in the literature) reported negative therapeutic results (Amberson, McMahon, and Pinner, 1931). In 1946 no controlled trial of streptomycin in pulmonary tuberculosis had been undertaken in the U.S.A. The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin
Evidence Based Medicine

Patient concern

Improved patient outcomes

Best research evidence

Clinical expertise
Practicing EBM – the 5 A’s

Step 1: Ask a clinical question
Step 2: Acquire the best evidence
Step 3: Appraise the evidence
Step 4: Apply the evidence
Step 5: Assess your performance
Practicing EBM – the 5 A’s

- Ask a clinical question
- Acquire the best evidence
- Appraise the evidence
- Apply the evidence
- Assess your performance
Levels of evidence
Levels of evidence tables

<table>
<thead>
<tr>
<th>Question</th>
<th>Step 1 (Level 1*)</th>
<th>Step 2 (Level 2*)</th>
<th>Step 3 (Level 3*)</th>
<th>Step 4 (Level 4*)</th>
<th>Step 5 (Level 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How common is the problem?</td>
<td>Local and current random sample surveys (or censuses)</td>
<td>Systematic review of surveys that allow matching to local circumstances**</td>
<td>Local non-random sample**</td>
<td>Case-series**</td>
<td>n/a</td>
</tr>
<tr>
<td>Is this diagnostic or monitoring test accurate? (Diagnosis)</td>
<td>Systematic review of cross sectional studies with consistently applied reference standard and blinding</td>
<td>Individual cross sectional studies with consistently applied reference standard and blinding</td>
<td>Non-consecutive studies, or studies without consistently applied reference standards**</td>
<td>Case-control studies, or &quot;poor and non-independent reference standard&quot;**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What will happen if we do not add a therapy? (Prognosis)</td>
<td>Systematic review of inception cohort studies</td>
<td>Inception cohort studies</td>
<td>Cohort study or control arm of randomized trial*</td>
<td>Case-series or case-control studies, or poor quality prognostic cohort study**</td>
<td>n/a</td>
</tr>
<tr>
<td>Does this intervention help? (Treatment Benefits)</td>
<td>Systematic review of randomized trials or n-of-1 trials</td>
<td>Randomized trial or observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the COMMON harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect</td>
<td>Individual randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**</td>
<td>Case-series, case-control, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the RARE harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials or n-of-1 trial</td>
<td>Randomized trial or (exceptionally) observational study with dramatic effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this (early detection) test worthwhile? (Screening)</td>
<td>Systematic review of randomized trials</td>
<td>Randomized trial</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
</tbody>
</table>
Types of evidence

Critical appraisal
Risk of Bias

• The degree to which the result is skewed away from the truth
• Causal inferences from randomised trials can, however, be undermined by flaws in design, conduct, analyses, and reporting
• leading to underestimation or overestimation of the true intervention effect
Confounding factors

• Other patient features/causal factors, apart from the one being measured, that can affect the outcome of the study e.g..
Assessing risk of bias for an RCT

- Recruitment
- Allocation
- Maintenance
- Measurement
  - Unbiased
  - Objective

RAMMbo
Depression Management

Risk and f/u

Pharmacological
- TCA
- SSRI
- SNRI

Non-pharmacological
- Psychological therapies
- Self help and lifestyle modification
- Structured exercise

Psychological therapies
- Mindfulness group
- Behavioural activation
- Individual CBT

Self help and lifestyle modification
- Alcohol, diet, social networks, sleep

Structured exercise
- Individual CBT
taking regular physical exercise

RECOGNISED DEPRESSION – PERSISTENT SUBTHRESHOLD DEPRESSIVE SYMPTOMS OR MILD TO MODERATE DEPRESSION
Exercise does little to help the symptoms of depression, new study finds

By SUZANNAH HILLS

PUBLISHED: 08:23, 6 June 2012 | UPDATED: 11:31, 6 June 2012

Exercise does little to help alleviate the symptoms of depression, a new study has found.

The findings contrast with current clinical guidance which recommends exercise to help those suffering from the mental illness that affects one in six adults in Britain at any one time.

But research published in the British Medical Journal suggests that doing a physical activity combined with usual treatment did not reduce symptoms of depression more than the treatment alone.

Affecting millions: One in six adults in Britain suffer from depression at any one time.
Facilitated physical activity as a treatment for depressed adults: randomised controlled trial

Melanie Chalder research fellow, Nicola J Wiles senior lecturer, John Campbell professor, Sandra P Hollinghurst senior lecturer, Anne M Haase senior lecturer, Adrian H Taylor professor, Kenneth R Fox professor, Ceire Costelloe research associate, Aidan Searle research associate, Helen Baxter research associate, Rachel Winder associate research fellow, Christine Wright associate research fellow, Katrina M Turner lecturer, Michael Calnan professor, Deborah A Lawlor professor, Tim J Peters professor, Deborah J Sharp professor, Alan A Montgomery reader, Glyn Lewis professor

School of Social and Community Medicine, University of Bristol, Bristol BS8 2BN, UK; Primary Care Research Group, Peninsula Medical School, Exeter, UK; School of Policy Studies, University of Bristol; Sport and Health Sciences, University of Exeter, Exeter; School of Social Policy, University of Kent, Canterbury, UK; School of Clinical Sciences, University of Bristol

Abstract

Objective To investigate the effectiveness of facilitated physical activity as an adjunctive treatment for adults with depression presenting in primary care.

Design Pragmatic, multicentre, two arm parallel randomised controlled trial.

Setting General practices in Bristol and Exeter.

Participants 361 adults aged 18-69 who had recently consulted their general practitioner with symptoms of depression. All those randomised had a diagnosis of an episode of depression as assessed by the clinical interview schedule-revised and a Beck depression inventory score of 14 or more.

Interventions In addition to usual care, intervention participants were offered up to three face to face sessions and 10 telephone calls with a trained physical activity facilitator over eight months. The intervention was based on theory and aimed to provide individually tailored support and encouragement to engage in physical activity.

Main outcome measures The primary outcome was self reported symptoms of depression, assessed with the Beck depression inventory at four months post-randomisation. Secondary outcomes included use of antidepressants and physical activity at the four, eight and 12 month.

-0.54 (95% confidence interval -3.06 to 1.98; P=0.68). Similarity, there was no evidence that the intervention group reported a change in mood by the eight and 12 month follow-up points. Nor was there evidence that the intervention reduced antidepressant use compared with usual care (adjusted odds ratio 0.93, 95% confidence interval 0.19 to 2.06; P=0.84) over the duration of the trial. However, participants allocated to the intervention group reported more physical activity during the follow-up period than those allocated to the usual care group (adjusted odds ratio 2.27, 95% confidence interval 1.32 to 3.89; P=0.003).

Conclusions The addition of a facilitated physical activity intervention to usual care did not improve depression outcome or reduce use of antidepressants compared with usual care alone.

Trial registration Current Controlled Trials ISRCTN16900744.

Introduction

Depression is one of the most common reasons for consulting a general practitioner within the United Kingdom, and its associated economic burden is considerable. Although antidepressants are effective, many patients and healthcare professionals would like other options to be available as an alternative or adjunct to drug therapy. Some evidence shows
Risk of Bias

The degree to which the result is skewed away from the truth
Recruitment

• Were the subjects representative of the target population?
  – What were the inclusion & exclusion criteria?
  – Were they appropriate?
  – How/where were they recruited from?

• Methods Recruitment of participants and baseline assessment & Results 1st para
Allocation

• Same sorts of participants receive the intervention and comparison

• Based on 2 processes:
  1. Allocation process through randomisation
  2. Concealment of the allocation

• Adequate use of both prevents selection bias
Randomisation and Allocation concealment

New drug makes you “stronger”
Types of randomisation

- Quasi-random allocation e.g. date of birth, alternating
- Simple randomisation e.g. repeated coin tossing, random sequence
- Stratified/blocked randomisation
- Minimised randomisation
  - Good for small trials
  - Calculates imbalance between groups
  - Dynamic
  - Allocation of the next patient into the trial depends on the characteristics and allocation of patients already randomized
- Cluster randomisation
Ensuring Allocation Concealment

BEST – most valid technique
- Central computer randomization

DOUBTFUL
- Envelopes, etc
Allocation

• Were the groups comparable at the start?
  – “Table 1”
• Randomised appropriately?
• Allocation to group concealed beforehand?

• Methods: Randomisation, concealment, and blinding and “Table 1”
Maintenance

• Were both groups comparable throughout the study?
  – Managed equally bar the intervention?
    • What was the intervention?
    • What was the comparator?

• Methods: Follow up and Intervention and comparator (usual care)
Adequate follow up?

• How many people were lost to f/u?
• Why were they lost to f/u?
• Did the researchers use an intention to treat (ITT) principle?
  – Once a participant is randomised, they should be analysed to the group they were assigned to
• Figure 1 and Statistical analysis
Measurement - blinding

• Were the outcomes measured blindly by researchers and participants?
  – Double blinding (low risk of bias)
    • Subjects and investigators (outcome assessors) both unaware of allocation
  – Single blinded (moderate risk of bias)
    • Either subjects OR investigators (outcome assessors) unaware of allocation
  – No blinding (high risk of bias)
    • Subjects and investigators aware of allocation

• Methods: Randomisation, concealment, and blinding
Statistics


**P - values and CI**

- **P values**
  - Measure of probability that a result is due to chance
  - The smaller the value (usually $P<0.05$) less likely due to chance

- **Confidence intervals**
  - Estimate of the range of values that are likely to include the real value
  - 95% chance of including the real value
  - Narrower the range $>$ more reliable
  - If value does not cross 0 for a difference, or 1 for a ratio then pretty sure result is real ($P<0.05$)
Measurement - outcomes

• What were the outcomes?
  – Primary
  – Secondary
  – Were they appropriate?

• How were the results reported?

• Were they significant?

• Methods: Outcomes and Results
1. Sadness
0  I do not feel sad.
1  I feel sad much of the time.
2  I am sad all the time.
3  I am so sad or unhappy that I can't stand it.

2. Pessimism
0  I am not discouraged about my future.
1  I feel more discouraged about my future than I used to be.
2  I do not expect things to work out for me.
3  I feel my future is hopeless and will only get worse.

3. Past Failure
0  I do not feel like a failure.
1  I have failed more than I should have.
2  As I look back, I see a lot of failures.
3  I feel I am a total failure as a person.

4. Loss of Pleasure
0  I get as much pleasure as I ever did from the things I enjoy.
1  I don't enjoy things as much as I used to.
2  I get very little pleasure from the things I used to enjoy.
3  I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
0  I don't feel particularly guilty.
1  I feel guilty over many things I have done or should have done.
2  I feel quite guilty most of the time.
3  I feel guilty all of the time.

6. Punishment Feelings
0  I don't feel I am being punished.
1  I feel I may be punished.
2  I expect to be punished.
3  I feel I am being punished.

7. Self-Dislike
0  I feel the same about myself as ever.
1  I have lost confidence in myself.
2  I am disappointed in myself.
3  I dislike myself.

8. Self-Criticalness
0  I don't criticize or blame myself more than usual.
1  I am more critical of myself than I used to be.
2  I criticize myself for all of my faults.
3  I blame myself for everything that happens.

9. Suicidal Thoughts or Wishes
0  I don't have any thoughts of killing myself.
1  I have thoughts of killing myself, but I would not carry them out.
2  I would like to kill myself.
3  I would kill myself if I had the chance.

10. Crying
0  I don't cry anymore than I used to.
1  I cry more than I used to.
2  I cry over every little thing.
3  I feel like crying, but I can't.

11. Agitation
0  I am no more restless or wound up than usual.
1  I feel more restless or wound up than usual.
2  I am so restless or agitated that it's hard to stay still.
3  I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest
0  I have not lost interest in anything.
1  I have lost interest in things that I used to enjoy.
2  I have lost most of my interest in other people or things.
3  It's hard to get interested in anything.

13. Indecisiveness
0  I make decisions about as well as ever.
1  I find it more difficult to make decisions than usual.
2  I have much greater difficulty in making decisions than I used to.
3  I have trouble making any decisions.

14. Worthlessness
0  I do not feel I am worthless.
1  I don't consider myself as worthwhile and useful as I used to.
2  I feel more worthless as compared to other people.
3  I feel utterly worthless.

15. Loss of Energy
0  I have as much energy as ever.
1  I have less energy than I used to have.
2  I don't have enough energy to do very much.
3  I don't have enough energy to do anything.

16. Changes in Sleeping Pattern
0  I have not experienced any change in my sleeping pattern.
1a  I sleep somewhat more than usual.
1b  I sleep somewhat less than usual.
2a  I sleep a lot more than usual.
2b  I sleep a lot less than usual.
3a  I sleep most of the day.

17. Irritability
0  I am no more irritable than usual.
1  I am more irritable than usual.
2  I am much more irritable than usual.
3  I am irritable all the time.

18. Changes in Appetite
0  I have not experienced any change in my appetite.
1a  My appetite is somewhat less than usual.
1b  My appetite is somewhat greater than usual.
2a  My appetite is much less than before.
2b  My appetite is much greater than usual.
3a  I have no appetite at all.
3b  I crave food all the time.

19. Concentration Difficulty
0  I can concentrate as well as ever.
1  I can't concentrate as well as usual.
2  It's hard to keep my mind on anything for very long.
3  I find I can't concentrate on anything.

20. Tiredness or Fatigue
0  I am no more tired or fatigued than usual.
1  I get more tired or fatigued more easily than usual.
2  I am too tired or fatigued to do a lot of the things I used to do.
3  I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex
0  I have not noticed any recent change in my interest in sex.
1  I am less interested in sex than I used to be.
2  I am much less interested in sex now.
3  I have lost interest in sex completely.
### Outcomes

<table>
<thead>
<tr>
<th>Measure</th>
<th>Narrative</th>
<th>Numerical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome:</strong> short term symptoms of depression</td>
<td>Beck depression inventory score</td>
<td>no evidence that participants in the intervention group had a better outcome at four months than those in the usual care group</td>
</tr>
</tbody>
</table>
| **Secondary outcomes**  
Longer term symptoms of depression | Beck depression inventory score | no evidence of a difference between the treatment groups over the duration of the study | difference in mean Beck depression inventory score −1.20, 95% confidence interval −3.42 to 1.02; P=0.29 |
| Anti-depressant use | participants reporting use of antidepressants | no evidence to suggest any difference between the groups at either the four month follow-up point or duration of trial | adjusted odds ratio 1.20, 95% confidence interval 0.69 to 2.08; P=0.52 |
| Physical activity | self completion seven day recall diary | there was some evidence for a difference in reported physical activity between the groups at four months post-randomisation | adjusted odds ratio 1.58, 0.94 to 2.66; P=0.08) |
Conclusions of the study

What is already known on this topic

Depression is a leading contributor to disability in the United Kingdom and is associated with a decrement of health greater than many other chronic diseases

Many patients and healthcare professionals would like an effective and accessible non-drug treatment for depression

Numerous studies have reported the positive effects of physical activity but most of the current evidence originates from small non-clinical samples using interventions that are not practicable in healthcare settings

What this study adds

A physical activity intervention in addition to usual care did not improve symptoms of depression or reduce the use of antidepressants compared with usual care alone

The intervention increased self-reported physical activity and this effect was sustained for 12 months

Clinicians and policy makers should alert people with depression that advice to increase physical activity will not increase their chances of recovery from depression

Cite this as: BMJ 2012;344:e2758
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Exercise ‘of no benefit’ in The Telegraph

Exercise 'fails to lift clinical depression'
Exercise should not be “prescribed” to people with clinical depression, according to a study which found it did nothing to improve their moods.

Exercise ‘no help for depression’ research suggests
Exercise ‘no help for depression’ research suggests

By Branwen Jeffrey
Health correspondent, BBC News

Combining exercise with conventional treatments for depression does not improve recovery, research suggests.

In the NHS-funded study – published in the British Medical Journal – some patients were given help to boost their activity levels in addition to receiving therapy or antidepressants.

After a year at 361 patients had fewer signs of depression, but there was no difference between the two groups.

Current guidelines suggest sufferers do up to three exercise sessions a week.

The National Institute for Health and Clinical Excellence (Nice) drew up that advice in 2004.

At the time it said that on the basis of the research available, it could not.

Press Release: the BMJ, suggests to usual care did than usual care a

Press Release - designed research appear to be effe
External validity/applicability

Would you advocate exercise for depression based on this study?
Summary

- Lots of “evidence” in healthcare
- RCTs provide an opportunity to deliver answers to the effects if interventions
- But dependent upon minimising risk of bias
- Critical appraisal assess this
- Lots of tools (PICO-T, GATE, RAMMbo) to assess risk of bias
- Application (external validity) based on your interpretation of results
Thank you for listening

kamal.mahtani@phc.ox.ac.uk  j Jeremy.howick@phc.ox.ac.uk
In hypertensive patients, dark chocolate reduces blood pressure when compared to normal milk chocolate.
Task

• Design the outline of a protocol for a pilot RCT with a sample size of 40 patients to test this theory

• 2 groups
  – 1h group work
  – 30 mins discussion