The Therapeutic Relationship and the Ubiquitous Placebo: From New RCTs to Anecdotage

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Overview

- Anecdotage
- How appropriate are RCTs in evaluating interventions such as hypnotherapy?
- 4 illustrative trials
- What are the practical clinical implications?
- Conclusions

Anecdotage

1960s
The act of observing or studying something changes its behaviour. “Research effect.”
- Principle of uncertainty (Heisenberg)
- “Hawthorne effect” (Mayo)
- Demand characteristics (Orne)
- Expectancies and self-fulfilling prophecies: Pygmalion effect (Rosenthal)
Henry Ford (1863-1947)

Think you can, or think you can’t: either way you’ll be right.

Anecdotage

1971
PhD - Rehabilitation through work.
Performance improved before research commenced - ‘The Researcher Effect’

Relevant to interpretation of clinical trials:
“experimental group” versus “control group”.

Anecdotage

D A Alexander and L G Walker
19.1.1972

Placebo: L. placere - I shall please or placate.

A commonplace method or medicine (Motherby’s Medical Dictionary, 1785)

The effects of any medication or procedure given with therapeutic intent which are not related to the specific effects of the medication or procedure and operate through a psychological mechanism.

Until 125 years ago, the history of medicine was largely the history of the placebo effect.

The Ubiquitous Placebo

• Placebo: L. placere - I shall please or placate.
• A commonplace method or medicine (Motherby’s Medical Dictionary, 1785)
• The effects of any medication or procedure given with therapeutic intent which are not related to the specific effects of the medication or procedure and operate through a psychological mechanism.
• Until 125 years ago, the history of medicine was largely the history of the placebo effect.

The Ubiquitous Placebo

• Effects can be positive or negative.
• Related to the beliefs and expectancies of the patients and the “doctor”.

Armand Trousseau (1801-1867)

“Treat many patients with the new drugs while they still have the power to heal.”
The Ubiquitous Placebo

- Usnea
- Eunuch fat
- Crocodile dung
- Unicorn horn
- Lung of lark
- Inverted suspension by feet

The Ubiquitous Placebo

- Medication
- Surgery for angina pectoris:
  - Enthusiastic surgeons: up to 80% success
  - Sceptics up to 28% success
  - RCT no difference (Diamond, 1958)

Why RCTs?

- Controlled - to control for the ‘placebo’ or ‘non-specific’ effects (attention, expectancy, etc.)
- Randomised - to minimise systematic bias

Blinding

- “Double blind” – neither therapist nor patient knows whether placebo or active treatment given
- “Single blind” – therapist, but not patient, knows whether placebo or active treatment given

Placebos: Conclusions

- Because of the placebo effect, we have often been completely wrong regarding the specific effects of many compounds and procedures.
- Therefore, there is a need for ways of removing systematic bias; hence the RCT.
- However: this does not remove the Research and Researcher Effects.

Moreover....

- Single (patient) or double (patient and therapist) blinding may not be possible in some studies (e.g. psychotherapy)
  although usually the assessor can, and should be, blinded.
- Choice of ‘placebo’ or comparator intervention may make a crucial difference to interpretation of results.
1980s: Anecdotage

- Combat demoralisation - hope
- Healing setting
- Healing ritual
- Conceptual framework to give meaning
- Emotionally charged, confiding relationship

Common Factors

Control condition may include some of these “healing” factors.

1980s: Chemotherapy Side Effects

- Nausea
- Vomiting
- Treatment-related anxiety
- Miss B and a case series


RCT

To evaluate the effects of relaxation with, or without, hypnotherapy, on chemotherapy side effects.

Interventions

- Training in progressive muscular relaxation and cue controlled relaxation by means of audio-recordings.
- 1-6 sessions of hypnotherapy: direct suggestion, nausea management training, ‘ego strengthening’.

Design

Diagnosis and Randomisation

Standard antiemetic Medication (SM) for 3 cycles

SM, SM + RT, SM + RT + HT
Patients

- 69 patients with HD, NHL or Teratoma
- No contraindications to hypnotherapy
- Willing to attend at least twice

Results

- Hypnosis reduced anxiety
- Relaxation reduced nausea
- Very low incidence of side effects during first 3 cycles (early nausea <2% at cycle 3)
- Intervention prophylactic

Conclusions

- Hypnotherapy and relaxation are beneficial for patients receiving cytotoxic chemotherapy.
- There was a very low incidence of side effects in all three groups, including treatment as usual.
- Why?

1980s: Gynaecological Cancer

Follow-up study: 118 women with gynaecological cancer.
Clinically significant distress was related to dissatisfaction with relationships with the doctors and information following diagnosis.

Paraskakidis, Kitchener and Walker. Psycho-Oncology, 1993, 2, 195-200

Rudyard Kipling: 1865-1936

'Words are the most powerful drug known to mankind.'

Psychoneuroimmunological effects of relaxation therapy and guided imagery
39% of women had clinically significant anxiety, depression and/or sexual problems 3 months, and 12-18 months, following diagnosis of breast cancer (Maguire, 1988).

Of 269 women with early breast cancer, 49.6% were clinically anxious and 37.2% were clinically depressed in the first 3 months (PSE) (Hall et al., 1999).

Of 222 women with early breast cancer, 48% were clinically anxious and/or depressed in the first year (DSM III-R) (Burgess et al., 2005).

Need to help women cope with the diagnosis and treatment.

Stress can be immunosuppressive and immunosuppression may affect clinical outcome.

Psychosocial interventions can offset stress-induced immunosuppression.

To evaluate the effects of relaxation and guided imagery on:

- Quality of Life
- Mood
- Coping
- Host defences

CVAP chemotherapy
6 cycles every 3 weeks
Surgery  RT  FU
1 18 22 25 29 37

Professional but informal atmosphere.
Welcome to telephone or visit at any time.
Staff trained to elicit and respond quickly and appropriately to concerns.
Customized information.
Peer group and staff support.
Chemotherapy given in the Unit.
Co-ordination of investigations and treatments.
Summary: Psychological Effects

The Intervention:
- Improved mood and quality of life.
- Enhanced coping.


Summary: Immunological Effects

The Intervention:
- Enhanced LAK cell activity.
- Increased number of various T lymphocyte subsets (CD3+, CD25+ and CD56+).
- Reduced TNF-α.

Imagery vividness correlated with changes in LAK and NK cell activity, and IL1β.

Eremin et al, 2008

Virgil (70-19BC)

Hos successus alit: possunt, quia posse videntur.
To these success gives heart: they can because they think they can.

Publius Vergilius Maro

Conclusions - 1

- Relaxation and guided imagery improve key aspects of quality of life.
- The clinical significance of the biological effects needs further study.

Conclusions - 2

The incidence of clinically significant distress in both groups was only a fraction of the level expected.

HADS Anxiety

Significant

Pre chemotherapy 21%
**HADS Anxiety**

**Significant**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study One (n=96)</th>
<th>Study Two (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre chemotherapy</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>Pre surgery</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>12 weeks post DXT</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

- Female police officers: 24%
- Female psychiatric nurses: 16%
- Wives of police officers: 19%

**Other Assessments**

Other psychometric tests and Structured Clinical Interviews (DSM III R) confirmed the low rate of clinically significant distress.

**Anxiety (HADS): Study 2**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study One (n=96)</th>
<th>Study Two (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Chemotherapy</td>
<td>21%</td>
<td>24%</td>
</tr>
<tr>
<td>End Chemotherapy</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>12 Weeks post RT</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Conclusion**

With appropriate staff training and service integration, a drop in centre can prevent most psychological and psychiatric problems.

A randomised, controlled study of reflexology on quality of life, mood, coping and host defences in patients with early breast cancer.

**Aims**

To evaluate the acceptability and biopsychosocial effects of reflexology in women with newly diagnosed early breast cancer.

**Design**

Prospective, randomised, controlled trial:
- SIS: access to the Oncology Health Centres as determined by the patients (records kept). Includes access to information, support, and self-help techniques. If required, treatment for clinically significant distress (comparator intervention).
- SIS + Scalp Massage: weekly for 8 weeks, commencing 2 weeks post surgery (control for physical and social contact – no acupuncture points).
- SIS + Reflexology: weekly for 8 weeks, commencing 2 weeks post surgery.

All received BCN and other support according to current local practice.

**Interventions**

- **SIS**: Self-initiated support (SIS) in the OHCs.
- **SIS** plus 8 sessions of reflexology.
- **SIS** plus 8 sessions of scalp massage.

**Trial Design**

- Reflexology Advisor
- Design of reflexology and massage protocols
- Selection of therapists
- Regular monitoring of interventions
- Training sessions for nurses
- Ongoing recruitment and data monitoring
- Remote randomisation (Institute of Rehabilitation)

**Quality Assurance**

- Reflexology Advisor
- Design of reflexology and massage protocols
- Selection of therapists
- Regular monitoring of interventions
- Training sessions for nurses
- Ongoing recruitment and data monitoring
- Remote randomisation (Institute of Rehabilitation)
Compared with SIS alone, patients randomised to massage had:
- Increased percentage of CD25+ lymphocytes
- Increased percentage of CD25+ lymphocytes
- Increased percentage of Th1 type cells
- Decreased percentage of Th2 type cells

Conclusions
- R and M were highly acceptable within the setting of the OHCs.
- R and M have significant, but relatively small, benefits over SIS in terms of TOI.
- Effect of R and M may be due to relaxation resulting from increased physical and/or social contact.
- The incidence of clinically significant problems was very low in all three interventions at EP1 and 2 - stringent test of R and M.
A randomised, controlled study of the Psychoneuroimmunological Effects of Relaxation therapy and guided Imagery, alone and in combination, in patients with colorectal cancer.

Aims

To evaluate the psychoneuroimmunological effects and acceptability of relaxation and guided imagery, alone and in combination, in patients with newly diagnosed colorectal cancer.

Questions

- Should we combine RT and GI?
- How similar are the safety, acceptability and effects of RT plus GI in CRC compared to LABC?

Interventions

- SIS: access to the resources in the Oncology Health Centres as determined by the patients (record kept).
- Relaxation: daily practice with the audio recordings used in breast cancer study (record kept).
- Guided Imagery: daily practice with ad hoc audio recording (record kept).

Outcomes

Primary outcomes (week 36):
- FACT C
- Cortisol
- Th1/Th2 balance

Secondary outcomes (weeks 8, 16, 24 and 36)
- Quality of life
- Host defences
- Neuroendocrine activity
- BP/pulse
**Inclusion and Exclusion Criteria**

**Inclusion criteria:**
- operable Duke’s B (T4), C, or D colon or rectal cancer
- suitable for chemotherapy
- male or female

**Exclusion criteria:**
- previous history of cancer
- Karnofsky performance status less than 80%
- contraindications to relaxation therapy or guided imagery
- unwilling or unable to give informed consent
- unable to complete the study questionnaires
- unwilling to give blood or saliva samples

**Patients Recruited**

- Mean age 64 years (SD 9 years)
- 47% female
- 72% colon cancer
- Dukes B – 20%; Dukes C – 70%; Dukes D – 5%
- 84% 5FU +/- other agent
- Hull – 59%; Grimsby – 26%; Scarborough – 72%

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**Quality of Life (TOI)**

- Relaxation (MRS)

**Anxiety (HADS >10)**

<table>
<thead>
<tr>
<th></th>
<th>SIS</th>
<th>Other 3 groups</th>
<th>Fisher’s Exact</th>
<th>P value (4 groups)</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>5.4%</td>
<td>7.9%</td>
<td>6.9</td>
<td>0.32</td>
</tr>
<tr>
<td>Week 8</td>
<td>8.8%</td>
<td>5.6%</td>
<td>5.1</td>
<td>0.54</td>
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<tr>
<td>Week 16</td>
<td>8.9%</td>
<td>6.9%</td>
<td>9.9</td>
<td>0.09</td>
</tr>
<tr>
<td>Week 24</td>
<td>3.0%</td>
<td>3.2%</td>
<td>6.1</td>
<td>0.36</td>
</tr>
<tr>
<td>Week 36</td>
<td>2.9%</td>
<td>6.4%</td>
<td>7.5</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Point prevalence in a large non-clinical sample (N=1,792) is 12.6% (Crawford et al. 2001)

**Conclusions**

- In colorectal cancer, RT and GI taught using recordings do not have significant effects on mood, coping and quality of life. Why?
- Incidence of psychological morbidity low in all groups, including SIS alone.
- Compared to the study of RT plus GI in locally advanced breast cancer, no live training sessions (minimise placebo effect).
- Currently carrying out a study of training of audio-recorded training alone with audio recorded training plus live training (LIVEREL).
Specially trained nurses
Own recordings ("my voice will go with you")
Live sessions in our clinical research suite

The RCT is considered the gold standard method to evaluate new treatments (control for placebo effects).
However, enlisting patients to a trial, observing them and assessing them in itself may be a powerful intervention (research effect, researcher effect, demand characteristics, expectancies, common psychotherapeutic factors).
- A control intervention, therefore, may be a powerful intervention that does not mimic "treatment as usual" or no treatment.
- The magnitude of the effect depends on the control group.
- Therefore, consideration of the outcome of the control group is important in interpreting all RCTs, and particularly so in unblinded trials.

Conclusion

- Our RCTs have shown that a range of interventions (hypnotherapy, relaxation, imagery, reflexology, massage) are effective, but effectiveness is relative.
- In our own studies, the control groups have done uniformly well compared to national/local norms.
- By applying what we have learned from our RCTs, and those of others, we can prevent morbidity and improve the quality of life of our patients...NOW.

Acknowledgements

For further information
http://www.lgwalker.com