A Question of Faith: Mind-body medicine and placebo

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“The body is the shadow of the soul.” Marsilio Ficino (1433-99)
Stressful events and heart attacks

- Football – a major risk factor
- FIFA World Cup (Germany 2006)
- On days of matches involving the German team the incidence of cardiac emergencies was higher than usual
  - Men 3.26 times higher
  - Women 1.82 times
  - Incidence higher in those with pre-existing heart disease
Conditioning and the immune system

- “Paper rose” can induce allergic reaction in susceptible individuals
  - Mackenzie, Am J of Medical Science 1896;91:45-57.
- Exposure to “symbolic non-allergenic environment” can induce asthma
Conditioning and the immune system

- Mice exposed to saccharin water with a single dose of cyclophosphamide exhibited conditioned immunosuppression – premature death
  
Generic symptoms: benefits of diagnosis

- Patients given a diagnosis and told they would be better in a few days
- Patients told that the doctor “could not be sure what was wrong”

Percent of patients who improved
The placebo response

- The placebo response was one of the first fields of mind-body medicine to attract attention
- Refers to where a clinically significant effect is derived from the use of an inert substance or intervention
- It has long been the bane of the researcher’s life when researching the effects of drugs
- The placebo response can also produce unwanted ‘side effects’ sometimes called the ‘nocebo’ effect
The placebo effect

- [https://www.google.com.au/?gfe_rd=cr&ei=8WxLU66QPKeN8QejyYHwCw#q=youtube+the+strange+powers+of+the+placebo+effect](https://www.google.com.au/?gfe_rd=cr&ei=8WxLU66QPKeN8QejyYHwCw#q=youtube+the+strange+powers+of+the+placebo+effect)
Parkinson’s Disease and placebo

- In Parkinson's disease, a placebo treatment induces a release of dopamine in the brain regions controlling movement.

- Placebo administration for the first time induces neither clinical nor neuronal improvement in Parkinson patients who undergo the implantation of electrodes for deep brain stimulation.

Parkinson’s Disease and placebo

- However, this lack of placebo responsiveness can be turned into substantial placebo responses following previous exposure to repeated administrations of the anti-Parkinson agent apomorphine.

- As the number of apomorphine administrations increased from 1 through 4, both the clinical response and the neuronal activity in the thalamus increased.

- After 4 apomorphine exposures, placebo administration induced clinical responses that were as large as those to apomorphine, along with long-lasting neuronal changes.

- “Learning plays a crucial role in placebo responsiveness and suggest that placebo non-responders can be turned into responders, with important implications in the clinical setting.”

The placebo response

- Conditions with a high level of subjectivity are most responsive to the placebo effect, i.e. most susceptible to emotion, perception and interpretation
  - E.g. mood, sleep and pain perception
- Placebos are more effective in people with higher hopes of beneficial outcomes, have had positive experiences with therapies in the past, and have higher trust in the therapy and therapist giving them the treatment
Nausea and placebo

- Prospective, randomized, double-blind, placebo-controlled trial compared efficacy of ondansetron and metoclopramide with placebo for 270 adults with emergency department (ED) nausea and vomiting.

- Primary outcome was mean change in rating of nausea severity from enrollment to 30 minutes after drug administration.

- No significant decrease in nausea scores of drugs compared with placebo.

- Satisfaction with treatment was reported by 54.1%, 61.6%, and 59.5% for ondansetron, metoclopramide, and placebo, respectively.

  - Reductions in nausea severity similar for 4 mg IV ondansetron, 20 mg IV metoclopramide, and placebo.

The placebo response

“Some placebo responses, such as analgesia, are initiated and maintained by expectations of symptom change and changes in motivation/emotions. Placebo factors have neurobiological underpinnings and actual effects on the brain and body. They are not just response biases. Other placebo responses result from less conscious processes, such as classical conditioning in the case of immune, hormonal, and respiratory functions.”

Figure 1  Comparison of analgesic effects of opioid (morphine, tramadol, buprenorphine) and nonopioid (ketorolac, metamizol) medications across hidden versus open intravenous injections in patients with postoperative pain. (Data are from Amanzio et al. 2001.)

Price DD, et al. 2008
A Rn. Rev. Psychol. 59:565–90
Mindfulness and pain

- With mindfulness meditation group reported pain intensity reduced by 27% and by 44% for the emotional aspect of pain
- Placebo cream reduced the sensation of pain by 11% and emotional aspect of pain by 13%

Mindfulness and pain

- Mindfulness meditation produced patterns of brain activity that are different than those produced by the placebo cream.

- Mindfulness meditation reduced pain by activating brain regions (orbitofrontal and anterior cingulate cortex) associated with the self-control of pain.
  - Placebo cream lowered pain by reducing brain activity in pain-processing areas (secondary somatosensory cortex).

- Thalamus deactivated during mindfulness meditation, but was activated by placebo.
  - Thalamus is a gateway that determines if sensory information is allowed to reach higher brain centers.
  - By deactivating this area, mindfulness may have caused signals about pain to simply fade away.

The drug management of depression

- Though commonly used, evidence is questionable for the use of antidepressants in adult mild-moderate depression (strong publication bias) and for children and adolescents

- Placebo response significant – no clear therapeutic effect for mild-moderate depression attributable to the drug itself


Anti-depressants and the placebo response

- The level of placebo effect of anti-depressants varies between 60% to 80%

- fMRI brain scans show that the placebo response is biologically similar to that in people who receive the active anti-depressant

Antidepressants trials and placebo

“According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive. Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and was 32% overall.”

MBCT and depression

- RCT investigated the effects of Mindfulness-based cognitive therapy (MBCT) on the relapse in depression, time to first relapse and the quality of life
  - 106 recovered depressed patients with a history of at least 3 depressive episodes
  - Treatment as usual (TAU) vs MBCT plus TAU 1 year f/up
- Relapse/recurrence significantly reduced and the time until first relapse increased in the MBCT plus TAU c/w TAU
- MBCT plus TAU group also showed a significant reduction in both short and longer-term depressive mood, better mood states and quality of the life

Spirituality, coping and cancer

- Effect of religious (R) / spiritual (S) beliefs and coping style on mental health and adjustment
- 114 individuals (Median age = 65; 59% female) under care for non-terminal cancer
- High R/S (45%) associated with the lowest depression
- Low R / High S (25%) associated with good adjustment
- Negative Religious Copers (14%) (e.g. Being punished by God) associated with the highest depression
- Low R/S (16%) associated with the poorest adjustment to cancer

Religious commitment and health status

- “A large proportion of published empirical data suggests that religious commitment may play a beneficial role in preventing mental and physical illness, improving how people can cope with mental and physical illness, and facilitate recovery from illness.”

- Protective for:
  - Depression and suicide
  - Substance abuse
  - Physical illness
  - Longevity / mortality rates

- Links tend to hold even when controlled for other known risk factors
Spirituality, religion and health

- Levels of spirituality and religious beliefs and behaviour relatively high in Australia but lower than the USA
- Mounting scientific evidence of a positive association between religious involvement and indicators of health
- Strongest evidence exists for association between religious attendance and mortality – higher levels of attendance predictive of a strong, consistent and graded reduction in mortality risk
- Negative effects of religion on health also documented for some aspects of religious beliefs and behaviour
- Health practices and social ties are important pathways by which religion affects health. Other pathways include the provision of systems of meaning and feelings of strength to cope with stress and adversity

Religious commitment and longevity

- 22,000 people - 9 y f/up
- All-cause mortality reduced for those with active religious dimension to life
- Life expectancy
  - 75 y - non-attenders
  - 79 y - < once per week
  - 82 y - once per week
- Controlled for other variables
  - Demography 1999;36:273-85
  - Significantly protective against all-cause mortality
    - relative hazard 0.64 and when controlled for social and physical variables still 0.76
  - Am J Public Health 1998;88:1469-75
Spirituality and depression

- Meta-analysis on association between religiousness and depressive symptoms
  - 147 independent investigations (N=98,975)
- The correlation b/w religiousness and depressive symptoms was –.096, i.e. greater religiousness is mildly associated with fewer symptoms
- Religiousness–depression association stronger in studies involving people who were undergoing stress due to recent life events
Spirituality and depression

“Extrinsic religious orientation and negative religious coping (e.g., avoiding difficulties through religious activities, blaming God for difficulties) associated with higher levels of depressive symptoms, the opposite direction of the overall findings.”

- Religious orientation
  - Intrinsic  4,445  -.175
  - Extrinsic  6,361  +.155

- Religious coping
  - Positive  2,274  -.167
  - Negative  1,999  +.136

Spiritual experiences and brain activation

- During religious recitation religious subjects activate areas of the prefrontal and parietal cortex
- Activity in temporal lobes of the brain associated with religious and psychological phenomena including blurring of interpersonal or ego boundaries

Chemotherapy and 5-year survival

- “It is very clear that cytotoxic chemotherapy only makes a minor contribution (2%) to cancer survival. To justify the continued funding and availability of drugs used in cytotoxic chemotherapy, a rigorous evaluation of the cost-effectiveness and impact on quality of life is urgently required.”

- Exceptions e.g. childhood leukaemia, lymphoma, testicular cancer
Chemotherapy and publication bias

- Studies that reported pharmaceutical company involvement more likely to be positive (84% vs. 54%)
  - i.e. less likely to be negative (16% vs. 46%)
- “Pharmaceutical involvement in published clinical breast cancer research may affect study design, focus, and results.”
Surgery, The Ultimate Placebo: Ian Harris

Examples
Back Fusion Surgery
Hysterectomy
Caesarean Section
Knee Arthroscopy
Appendicitis
Coronary Stenting

Knee OA and surgical debridement

- Cochrane review of “randomised controlled trials (RCT) or controlled clinical trials (CCT) assessing effectiveness of Arthroscopic Debridement” for pain relief or improved function
  - AD compared to other surgical procedures, including sham or placebo surgery and other non-surgical interventions, in patients with a diagnosis of primary or secondary OA of the knees, who did not have other joint involvement or conditions requiring long term use of non-steroidal anti-inflammatory drugs (NSAIDs).
- Three RCTs with a total of 271 patients
- “There is 'gold' level evidence that AD has no benefit for undiscriminated OA (mechanical or inflammatory causes).”
Medical myths – oxygen after AMI

- Three trials (387 patients) included assessing oxygen use post AMI for effects on mortality and pain relief
- 14 deaths – RR death 3.03 (95% CI 0.93 to 9.83) in patients with confirmed AMI
  - Small numbers; could be a chance occurrence
- No impact upon pain as indicated by analgesic use
- “There is no conclusive evidence from randomised controlled trials to support the routine use of inhaled oxygen in patients with acute AMI.”

Mind-body medicine and fertility

- Study determined if women who were randomized to a mind/body program before starting their first IVF cycle would have higher pregnancy rates than control subjects
  - 143 women aged ≤40 years who were about to begin their first IVF cycle
- Subjects were randomized to a ten-session mind/body program (MB) or a control group and followed for two IVF cycles
- Pregnancy rates for cycle 1 were 43% for all subjects
- Pregnancy rates for cycle 2 were 52% for MB and 20% for control
- MB participation was associated with increased pregnancy rates for cycle 2, prior to which most subjects had attended at least half of their sessions.

Compassion, stress & inflammation

- Study of healthy adults randomized to 6 weeks of training in compassion meditation or participation in a health discussion control group
- Followed by exposure to a standardized laboratory stressor (TSST)
- Meditation practice correlated with decreased TSST-induced IL-6 and POMS distress scores
- Individuals with meditation practice times above the median exhibited lower TSST-induced IL-6 and POMS distress scores compared to individuals below the median, who did not differ from controls

Happiness, genetics and immunity

- Immunity in individuals with high levels of hedonic wellbeing (pleasure seeking / gratification) characterized by:
  - an increased expression of genes involved in inflammation (implicated in diseases such as arthritis and heart disease)
  - decreased expression of genes involved in antiviral responses
- This immune response (known as CTRA) is also associated with chronic stress and uncertainty
- The opposite effect was found for eudaimonic wellbeing (meaning / engagement)
- Both forms of wellbeing associated with similar self-reported affect

Yogic meditation, genes and immunity

- Study on effect of Yogic meditation on genetic expression
- 68 genes were found to be differentially expressed (19 up-regulated, 49 down-regulated) after adjusting for potentially confounded differences in sex, illness burden, and BMI
- Up-regulated genes included immunoglobulin-related genes
- Down-regulated genes included pro-inflammatory cytokines
Feeling old vs. being old

- Study on 6489 individuals 52 years and older
- Mean age was 65.8 and mean self-perceived age was 56.8 years
- 69.6% felt 3 or more years younger than their actual age
- 25.6% had a self-perceived age close to their chronologic age
- 4.8% felt more than 1 year older than their chronologic age
- The mortality rate during the mean follow-up period of 99 months was:
  - 14.3% in participants who felt younger
  - 18.5% in those who felt about their actual age
  - 24.6% in those who felt older
- After adjustment for covariates feeling older than actual age remained a significant independent predictor of mortality (hazard ratio, 1.41)

Genetic ageing & pessimism

- Combination of low optimism & high pessimism increases risk for disease and early mortality

- Study investigated whether tendency towards optimism or pessimism associated with Telomere Length and increased inflammation in healthy post-menopausal women

- Pessimism is independently associated with shorter Telomere length and higher inflammation (Interleukin-6 concentrations)
  - About 10 years of accelerated ageing
Work stress and aging

- Study on whether work-related exhaustion (prolonged work stress – Maslach’s Burnout Inventory) associated with accelerated biological aging (telomere length)

- Data from sample of 2911 of the Finnish working-age population aged 30-64

- Individuals with severe exhaustion had leukocyte telomeres on average 0.043 relative units shorter than those with no exhaustion
  - Association remained significant after adjustment for other factors

- “These data suggest that work-related exhaustion is related to the acceleration of the rate of biological aging.”

Hostility and telomere length

- High-hostile men had significantly shorter leukocyte TL than their low-hostile counterparts

- The relationship between hostility and disease is stronger in men than in women, and men generally have a shorter life expectancy than women
Racial discrimination and telomeres

- Racial discrimination has a strong influence on the mental and emotional health of racial minority groups in the community.

- A study in the US found that "interpersonal experiences of racial discrimination and the internalization of negative racial bias, operate jointly to accelerate biological aging" as measured by telomere length in African American men.

Mind wandering and ageing

- The greater the level of mind wandering, the greater the level of telomere shortening (a marker of biological age)
Mindfulness and cellular ageing

- Meditation may slow genetic ageing and enhance genetic repair
  - “...we propose that some forms of meditation may have salutary effects on telomere length by reducing cognitive stress and stress arousal and increasing positive states of mind and hormonal factors that may promote telomere maintenance.”
Is heart disease reversible?

- Heart disease is reversible given the right lifestyle
  - Significant improvement possible in both the disease progression and quality of life.
- People with already well established CVD given conventional medical management plus or minus an intervention (comprehensive lifestyle program)
The Ornish Program

- People followed angiographically and symptomatically
- The program (intervention) consisted of:
  - group support
  - stress management consisting of meditation and yoga
  - a low fat vegetarian diet
  - moderate exercise
  - stopping smoking
- Stress management was central to being able to improve other lifestyle risk factors
## Results

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<tr>
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<th>Intervention</th>
<th>Control</th>
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<tbody>
<tr>
<td>Progression</td>
<td>82% regressed</td>
<td>53% progressed</td>
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<tr>
<td>Symptom frequency</td>
<td>91↓</td>
<td>165↑</td>
</tr>
<tr>
<td>Duration</td>
<td>42↓</td>
<td>95↑</td>
</tr>
<tr>
<td>Severity</td>
<td>28↓</td>
<td>39↑</td>
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Reduction in healthcare costs

- $3,900 for the Ornish program
- C/w $40,000 for bypass surgery
- Average cost savings were $US58,000 per patient after 3 year follow-up
Lifestyle change and CHD

- 5 year follow-up of the Ornish program
- Most of the original intervention group maintained changes
- Outcome measures
  - angiographic changes
  - risk ratio for cardiac events
Five year follow-up of Ornish program

- Most of the original intervention group maintained changes.
- Outcome for Ornish group was even better blood flow through the coronary arteries.
- 2.5 times the risk for cardiac events in control group.
Ornish program for cancer

- Men with early prostate cancer (biopsy and raise PSA) who chose not to have treatment (watch and wait)
- 92 patients randomised to lifestyle (experimental) group vs. usual treatment (control) group

Ornish lifestyle intervention

- **Vegan diet**
  - Fruits, vegetables, whole grains, legumes and soy
  - 10% calories from fat
  - Supplemented by soy (tofu), fish oil (3gm daily), vitamin E (400IU daily), selenium (200mcg daily), vitamin C (2gm daily)

- **Exercise**
  - Walking 30min 6 times weekly

- **Stress management**
  - Gentle yoga, meditation, breathing and PMR

- **Support group** 1 hour weekly

PSA readings

- After 1 year PSA decreased by 4% in experimental group and increased by 6% in control group
- No patients in the lifestyle group had gone on to have aggressive prostate cancer vs. 6 in the control group
- The more people applied the program the better their outcome
Level of lifestyle change and PSA

Ornish program for cancer

- 2-year follow-up
  - 27% (13/49) patients in control group have gone on to require cancer treatment because of disease progression but only 5% (2/43) patients in lifestyle group
- Ornish program down-regulated prostate cancer gene expression
- Comprehensive lifestyle change increased genetic repair (telomerase activity)
Lifestyle change and telomeres

- At 5 years relative telomere length increased from baseline in the lifestyle intervention group, but decreased in the control group.

- Adherence to lifestyle change significantly associated with relative telomere length after adjustment for age and the length of follow-up.

- "Our comprehensive lifestyle intervention was associated with increases in relative telomere length after 5 years of follow-up, compared with controls, in this small pilot study. Larger randomised controlled trials are warranted to confirm this finding."

The Inner Life of a Cell

- An animation made for Harvard University Medical School
Free 6-week online mindfulness course

- https://www.futurelearn.com/courses/mindfulness-wellbeing-performance
- Collaboration between Monash University and FutureLearn (UK)