Population Health

Sir Iain Chalmers
A selection of treatment evaluation landmarks in the James Lind Library

Iain Chalmers
(ichalmers@jameslind.net)

Edinburgh International Conference of Medicine
12 September 2016
Iain Milne, Sibbald Librarian, RCPE
Estela Dukan, Assistant Sibbald Librarian
RCPE Fellows who have written articles for the James Lind Library [subsequently republished in the JRSM]

Christopher Booth
Iain Chalmers
Alan Craft
John Crofton
Iain Donaldson
Derek Doyle
Chris Kelnar
Michael Lee
Alfredo Morabia
David Sackett
Leonard Sinclair
Stefan Slater
Jan Stjernsward
Ulrich Tröhler
Jan Vandenbroucke
Martin Vessey
Jimmy Volmink
Simon Wessely
On the rare occasions when effects of treatment are **dramatic**, carefully controlled evaluative research is unnecessary.
When are randomised trials unnecessary? Picking signal from noise

The relation between a treatment and its effect is sometimes so dramatic that bias can be ruled out as an explanation. Paul Glasziou and colleagues suggest how to determine when observations speak for themselves.

Some historical examples of treatments with dramatic effects:
- Insulin for diabetes\(^5\)
- Blood transfusion for severe haemorrhagic shock\(^4,2\)
- Sulphanilamide for puerperal sepsis\(^3\)
- Streptomycin for tuberculous meningitis\(^4,1\)
- Defibrillation for ventricular fibrillation\(^5\)
- Closed reduction and splinting for fracture of long bones with displacement\(^6\)
- Salicylates for acute rheumatism\(^7,6\)
- Neostigmine for myasthenia gravis\(^8\)
- Tracheostomy for tracheal obstruction\(^9,8\)
- Suturing for repairing large wounds
- Drainage for pain associated with abscesses
- Pressure or suturing for arresting haemorrhage
- Ether for anaesthesia
- One way valve or underwater seal drainage for pneumothorax and haemothorax\(^9,9\)
- Phototherapy for skin tuberculosis\(^10\)
- Combination chemotherapy with cisplatin, vinblastine, and bleomycin for disseminated testicular cancer

Different degrees of signal: noise in single patient

Stable and sudden change

Fluctuating and sudden change
- Natural course
- Course with treatment
- Start of treatment

Fluctuating and gradual change

Episodic and partial change
Derek Doyle. Thomas MacLagan’s 1876 demonstration of the dramatic effects of salicin in rheumatic fever.
NOTE ON THE TREATMENT OF MYXŒDEMA
BY HYPODERMIC INJECTIONS OF AN
EXTRACT OF THE THYROID GLAND
OF A SHEEP.

Read in the Section of Therapeutics at the Annual Meeting of the
British Medical Association held in Bournemouth, July,
1891.

By George R. Murray, B.A., M.B.Camb., M.R.C.P.Lond.,
Newcastle-on-Tyne.

Many cases of myxœdema doubtless do improve to a certain
extent when untreated, and it is not wise to draw many con-
cclusions from a single case; but the return of perspiration
and menstruation when they have not occurred for four years,
together with the many other signs of improvement which
have followed the treatment, are, I think, sufficient indica-
tion that this treatment really has a beneficial effect.

Stefan Slater. Assessing the effects of thyroid replacement therapy.
Charilaos Stylianou and Chris Kelnar.
Assessing the effects of insulin for diabetes.
2 December 1943

- German Junkers 88 bomber
- Location of Bari, Italy
- US Liberty ship *John W Brown*
- Mustard gas shells
In the common circumstances that any effects of treatment are likely to be moderate, carefully controlled evaluative research is needed to distinguish treatment effects from the effects of biases and the play of chance.
Conceptualising fair evaluation of treatments
“I once heard a Physician of great reputation speaking thus:... if one hundred or one thousand men, of the same age and character and [eating] the same diet, one and all affected by the same disease, one half shall turn to the advice of Doctors of the kind that there are in our time, and the other [half] without any Doctors shall follow natural instinct and their own discernment then I have no doubt that of the former [half] many shall die and of the latter [half] many shall escape”
Ex Libris Bibliothecae
ORTVS MEDICINÆ
Collegii ID EST, REGII
INITIA PHYSICÆ INAUDITA.
Progressus medicinæ novus,
Medicor in Edinburg,
MORBORUM ULTIMUM,
AD VITAM LONGAM.
AUTORE
IOANNE BAPTISTA VAN HELMONT,
Toparchi in Merode, Regensborch, Oorchoer, Poliana, &c.
Natus Antverpiae 1648.
FRANCISCO MERCATRO VAN HELMONT,
Consul Provansiae et Belgicae medicus.
AMSTRODAMI,
Apud Ludovicum Elzevirium,
1648.
“...Let us take from the itinerants’ hospitals, from the camps or from elsewhere 200 or 500 poor people with fevers, pleurisy etc. and divide them in two: let us cast lots so that one half of them fall to me and the other half to you. I shall cure them without blood-letting or perceptible purging, you will do so according to your knowledge ... and we shall see how many funerals each of us will have: the outcome of the contest shall be the reward of 300 florins deposited by each of us...”
Implementing fair evaluation of treatments

Comparing like with like

Controlling for placebo effects
Implementing fair evaluation of treatments: comparing like with like

James Lind

Lind 1753

Iain Milne. *Who was James Lind, and what exactly did he achieve?*
On 20\textsuperscript{th} May 1747, I took twelve patients in the scurvy, on board \textit{The Salisbury} at sea. Their cases were \textit{as similar as I could have them}. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They \textit{lay together in one place}, being a proper apartment for the sick in the fore-hold; and \textit{had one diet common to all}.

Two patients allocated to each of a quart of \textbf{cyder} a day, twenty-five gutts of \textbf{elixir vitriol} three times a-day, two spoonfuls of \textbf{vinegar} three times a-day, a course of \textbf{sea water}... half a pint every day, two \textbf{oranges and one lemon} every day the bigness of a \textbf{nutmeg} three times a day....The most sudden and visible good effects were perceived from the use of \textbf{oranges and lemons}.
Distinguishing moderate treatment effects from the effects of biases and the play of chance

Use of unbiased allocation to treatment comparison groups

Use of systematic reviews, meta-analyses, and large trials for:

- detecting treatment effects
- testing novel hypotheses
Alexander Lesassier Hamilton (1816). Use of unbiased allocation to treatment comparison groups
“It had been so arranged, that this number (366) was admitted alternately, in such a manner that each of us had one third of the whole. The sick were indiscriminately received, and were attended as nearly as possible with the same care and accommodated with the same comforts...
“Neither Mr. Anderson nor I ever once employed the lancet. He lost two, I four cases \textbf{[mortality 2.5\%]}; whilst out of the other third [treated with bloodletting by the third surgeon] thirty five patients died.” \textbf{[mortality 28.7\%]}

Iain Milne and Iain Chalmers. *Alexander Lesassier Hamilton’s 1816 report of a controlled trial of bloodletting.*
Irvine Loudon. *The use of historical controls and concurrent controls to assess the effects of sulphonamides, 1936-1945.*

**SULPHANILAMIDE IN THE TREATMENT OF MEASLES**

*BY*

**THOMAS ANDERSON, M.B., Ch.B., M.R.C.P.Ed.**

*Deputy Superintendent, Ruchill Hospital, Glasgow*

**Plan of Investigation**

The cases were allocated, in order of admission, alternately, to two groups. The first, or control group, received the usual nursing and expectant medical treatment; the second group received in addition sulphanilamide (para-aminobenzenesulphonamide).
Using systematic reviews, meta-analyses and large trials for detecting treatment effects


Secondary prevention of vascular disease by prolonged antiplatelet treatment

ANTIPLATELET TRIALISTS’ COLLABORATION

Abstract

Thirty one randomised trials of antiplatelet treatment for patients with a history of transient ischaemic attack, occlusive stroke, unstable angina, or myocardial infarction were identified. Six were still in progress, and the results of the remaining 25 were reviewed. They included a total of some 29 000 patients, 3000 of whom had died. Overall, allocation to antiplatelet treatment had no apparent effect on non-vascular mortality but reduced vascular mortality by 15% (SD 4%) and non-fatal vascular events (stroke or myocardial infarction) by 30% (4%). This suggested that with good compliance these treatments might reduce vascular mortality by about one sixth, other vascular events by about one third, and total vascular events by about a quarter. There was no significant difference between the effects of the different types of antiplatelet treatment tested (300-325 mg aspirin daily, higher aspirin doses, sulphinpyrazone, or high dose aspirin with dipyridamole), nor between the effects in patients with histories of cerebral or cardiac disease. Thus antiplatelet treatment can reduce the incidence of serious vascular events by about a quarter among a wide range of patients at particular risk of occlusive vascular disease. The balance of risk and benefit, however, might be different for “primary” prevention among people at low absolute risk of occlusive disease if antiplatelet treatment produced even a small increase in the incidence of cerebral haemorrhage.
Using systematic reviews, meta-analyses and large trials **for testing new hypotheses**

**Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials**

*Peter M Rothwell, F Gerald RFowkes, Jil FF Belch, Hisao Ogawa, Charles P Warlow, Tom W Meade*

**Interpretation** Daily aspirin reduced deaths due to several common cancers during and after the trials. Benefit increased with duration of treatment and was consistent across the different study populations. These findings have implications for guidelines on use of aspirin and for understanding of carcinogenesis and its susceptibility to drug intervention.

**Funding** None.

*Lancet; Published online 7 December 2010.*
In summary

On the rare occasions when effects of treatment are *dramatic*, carefully controlled evaluative research is unnecessary.

In the common circumstances that any effects of treatment are likely to be *moderate* or *non-existent*, carefully controlled evaluative research is needed to distinguish treatment effects from the effects of *biases* and *the play of chance*. 