Adoption of the double dummy trial design to reduce observer bias in testing treatments

Ana Marušić[1] • Stella Fatović Ferenčić[2]

[1]Department of Research in Biomedicine and Health, University of Split School of Medicine, Split, Croatia; [2]Department for History and Philosophy Sciences, Division for the History of Medicine, Croatian Academy of Sciences and Arts, Zagreb, Croatia

Correspondence to: Ana Marušić. Email: ana.marusic@mefst.hr

DECLARATIONS

Competing interests

None declared

Funding

None declared

Ethical approval

Not applicable

Contributorship

AM and SFF jointly performed the research and wrote the manuscript.

Acknowledgements

None

Although the use of placebo controls and blind assessment to decrease observer bias in clinical trials was introduced at the end of the 19th century, it was not until the second half of the 20th century, coincident with the rapid proliferation of pharmaceutical drug trials, that placebo controls became more widely used.[1] In comparisons of drugs that are administered by different routes, however, the preparation of the placebo interventions (dummy treatments) becomes more complicated: to control for both delivery methods, the trial needs to have adequate control groups for both treatments – an approach referred to as the 'double dummy' trial design.

Bibliographic recognition of the double dummy trial design in the 1970s

Our interest in the double dummy trial design was prompted by a report published in 1975 by a group of rheumatological researchers in Zagreb, Croatia, led by Theodor Dürrigl.[2] The report by Dürrigl *et al*. is the earliest yielded by a search of the PubMed database using the search strategy 'double dummy'[All Fields] AND ('1970/01/01'[PDAT]: '1979/12/31'[PDAT]. Up to that time, corticosteroids had been used in treating rheumatoid arthritis because of their anti-inflammatory and immunosuppressive effects.[3] As steroids had serious adverse effects, non-steroid anti-inflammatory drugs (NSAID) were introduced to treat chronic rheumatoid arthritis to reduce the need for corticosteroid therapy. In the 1970s, research focus was on the synthesis of NSAIDs with high activity and high tolerability.[4] Diclofenac sodium (*Voltaren*) was released by Ciba-Geigy in 1973 (Ciba-Geigy, http://www.novartis.com/about-novartis/company-history/index.shtml) as a non-steroid, non-pyrazole compound with few side-effects and significant anti-inflammatory and analgesic activities in animal models[5] and clinical studies.[6]

Professor Dürrigl and his team at the Institute for Rehabilitation of Rheumatic Patients of the School of Medicine in Zagreb, Croatia (then Yugoslavia), were among the first to test the efficacy and tolerability of diclofenac sodium against other NSAIDs (indomethacin in their study). The challenge presented for the design of this trial was that the two drugs looked different: diclofenac sodium was provided as enteric-coated tablets, whereas indomethacin was available as capsules. To address this problem, the researchers randomized the patients into three groups receiving either (i) diclofenac sodium and indomethacin placebo, or (ii) indomethacin and diclofenac sodium placebo, or (iii) both dummy preparations. They described the trial design as follows:

> *The trial design was a between-patient comparison of a 14-day treatment with either diclofenac sodium (25 mg t.i.d.), indomethacin (25 mg t.i.d.) or placebo. In order to preserve the double-blindness of the trial a double-dummy technique was used owing to the different appearance of the enteric-coated tablets of diclofenac sodium and indomethacin capsules. Each patient was allocated blindly to one of the three treatment groups. After each week of therapy the number of tablets and capsules of trial medication was recorded.*

Out of 50 patients included in the trial, 48 completed the treatment. After seven and 14 days of

treatment, diclofenac sodium was judged superior to both indomethacin and placebo in alleviating symptoms (duration of morning stiffness, joint tenderness and severity of rheumatoid condition assessed by patients or physicians). Both active treatments were well tolerated.[2]

It is interesting that the investigators planned for possible confounding from the effects of the 'rescue' medications that patients would take, as needed, if the relief provided by the trial preparations proved inadequate. To address this potential source of bias, they provided the patients with rescue analgesics and counted (at two time points) the number of tablets they had used. There was no statistically significant difference in the proportion of patients in the trial comparison groups who had used rescue medications, although, on average, patients on placebo took half a 'rescue' tablet more than the two treatment groups.

Later in the year that the study by Dürrigl *et al*.[2] was published, the use of the double dummy trial design was reported to reduce observer bias in a comparison of two routes of administering diazepam as a premedication prior to anaesthesia.[7] A further nine articles published in the 1970s reported use of the double dummy trial design.[8–16]

The introduction of the double dummy trial design in the 1960s

Careful reading of these 1970s studies, however, revealed that the Croatian study was not the earliest to report the use of the double dummy trial design. The earliest reports that we have identified so far were two published in 1964 and 1965. Percy *et al*.,[17] at the Royal Victoria Infirmary in Newcastle-upon-Tyne, UK, compared indomethacin and phenylbutazone in the treatment of a variety of rheumatic diseases. Their description of a double dummy design is clear:

> *As it was not possible to produce identical tablets of both drugs, an inert tablet corresponding to each active compound was made and the four resultant tablet types (active Indomethacin; dummy Indomethacin; active phenylbutazone; dummy phenylbutazone) were so dispensed that a week's supply of each drug was given together with dummy tablets identical with the other drug.*

The following year, Dudley Hart and Boardman,[18] at the Westminster Hospital in London, UK, compared indomethacin and phenylbutazone in the treatment of rheumatoid arthritis. Their article also clearly describes a double dummy design:

> *To provide double-blind conditions they received active indomethacin and dummy phenylbutazone in one month, and in the other active phenylbutazone and dummy indomethacin.*

In 1969, the report of a comparison of indomethacin and phenylbutazone by Wright *et al*.[19] also carries a clear explanation of a double dummy trial design:

> *The trial was conducted in three periods of 4 weeks, during each of which the patient received either red phenylbutazone tablets (100 mg. each) and yellow placebo capsules, or yellow indomethacin capsules (50 mg. each) and red placebo tablets, or yellow placebo capsules and red placebo tablets.*

Although they did not use the term 'double dummy', Figure 1 [not shown in this article] in a paper published by the same authors two years later[20] makes clear that the two preparations compared (indomethacin as a capsule and phenybutazone as a tablet) were given using the double dummy trial design.

The National Library of Medicine did not use the term 'double dummy' in indexing any of the articles published before the 1970s. Although some of them used the term 'dummy', search using 'dummy' as a keyword did not identify any of the trials that we found by following leads from reports published in the 1970s. It thus seems that double dummy method originated in rheumatological research in the 1960s, but its introduction may have been even earlier.

Some reflections by Theodor Dürrigl

We contacted Theodor Dürrigl to ask him how he came to use the double dummy trial design. He recalled that he had been frustrated by the fact that, although there were many preparations for use in rheumatic diseases, none was ideal and it was difficult to know how to chose among them. He remembered that it was help

from the pharmaceutical industry's statistics experts that led him and other clinicians to implement the double dummy trial design. Although the statisticians were confident that their company's products had advantages, they were eager to test them using rigorous study design. Dürrigl remembered the collaboration being successful and productive.

Theodor Dürrigl's research was driven by his wish to reduce the significant burden and poor quality of life of the large number of people with rheumatological disease. In his recently published memoirs he wrote:

> *I want and I hope that the terms 'rheuma' and 'rheumatism', and also 'rheumatology', will one day become obsolete because the cause (or causes) of all those diseases we have called 'rheumatic' for centuries will finally be discovered! Then the doctors who treat these diseases will give them proper names and, what is more important, find possibilities for their certain cure.*[20]

Our understanding of the aetiology of rheumatic diseases remains far from complete, despite the many biological drugs currently in use. However, the work of enthusiastic and conscientious rheumatological researchers in the 1960s and 1970s has left us with an important methodological legacy for tackling observer bias, which remains an important cause of biased estimates of treatment effects.[21]

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