Our meta-analysis on the placebo effect has been published [1]

For quite some time now, I have been investigating a phenomenon that I find very curious: the improvement rates of patients in clinical trials who are in the treatment groups and those who are in the placebo groups are highly correlated, regardless of the disease and treatment. The correlation is somewhere between r =.70 and r =.78. A typical correlation plot, which we published years ago in an initial meta-analysis, looks like this:

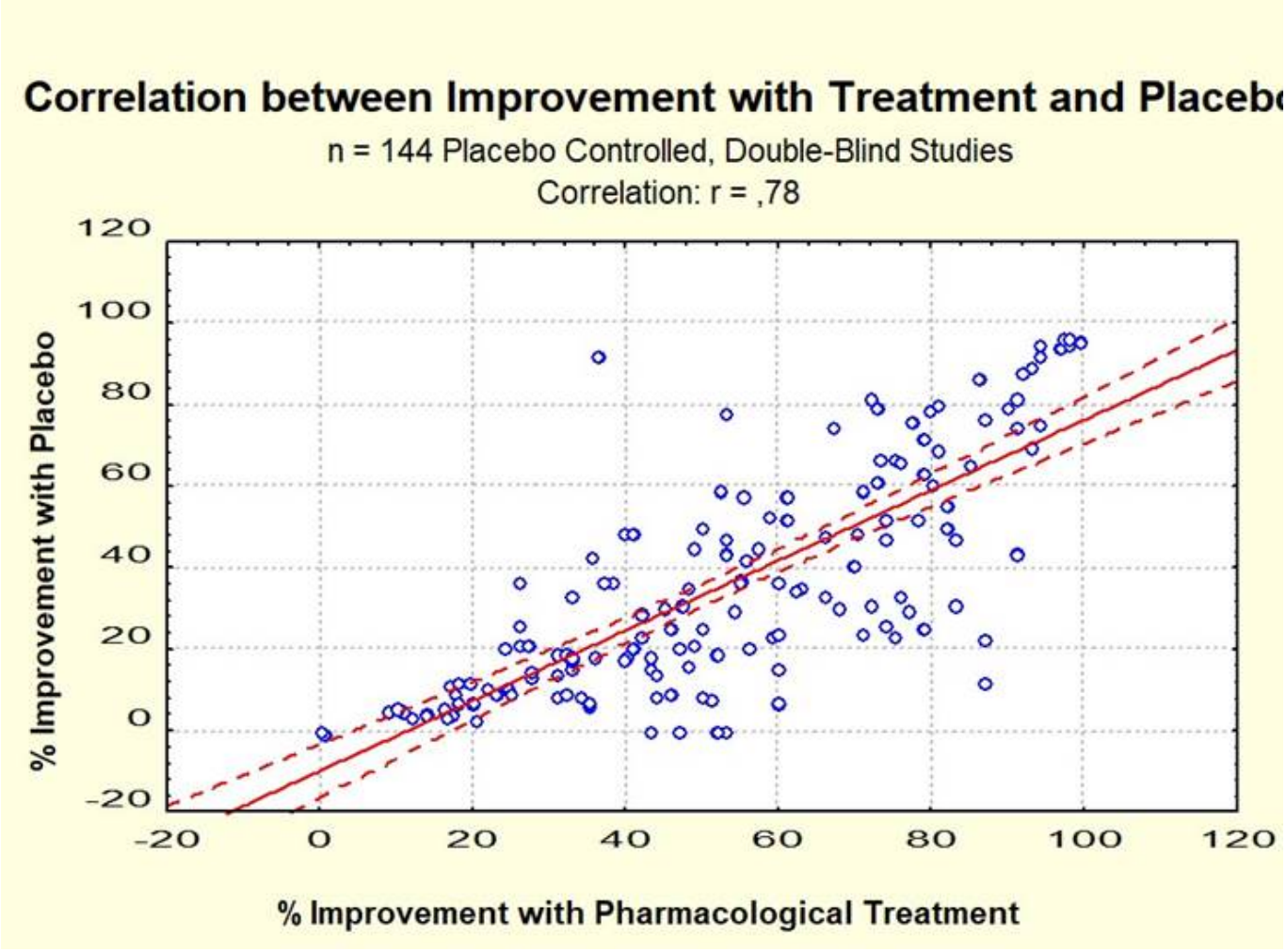

Figure 1 – Correlation of improvement in patients in treatment and placebo groups in 144 studies [2]

The predecessor study [2]

Each of these points represents a study. The x-axis shows the percentage improvement of the treatment group. The y-axis shows the percentage improvement in the placebo group of

the same study. The database is a collection of 144 double-blind, placebo-controlled studies of any pharmacological substance in any disease. This database was collected by Katharina Sadaghiani for her doctoral thesis, which I supervised, after she had already seen similar findings in her diploma thesis. What is important here is that the collection was systematic, in that it searched the four major medical journals backwards for studies that met our inclusion criteria. These were simple: long-term studies lasting more than 12 weeks, pharmacological intervention and placebo as a control.

You can see at a glance: The correlation is very high (r =.78). Whenever a study had a high treatment effect, the treatment effect in the placebo group was also high (or vice versa). Whenever a study had no high treatment effect, the effect in the placebo group was also low. The fact that the correlation was not perfect (r # 1.0) is another reassuring sign. If it were perfect, the medical intervention would not make any positive contribution at all. But the fact that the correlation is so high is actually very worrying for fans of pharmacological efficacy. This means that the contribution of the specific pharmacological effect is relatively small. Ideally, one would even expect a zero correlation, because confounding effects should average out across studies. But they don't. Interestingly, this high correlation cannot be explained by analysing different diseases. We concluded at the time that clinical studies seem to represent a strong therapeutic ritual. Or, in other words, there is an unexplained correlation between these groups that may have to be evaluated as an entanglement correlation.

Now, in a new study, we have tried to replicate this old finding and to explain it in even more detail.

The replication study [1]

In the new study [1], we therefore tried to replicate this old finding. However, we also wanted to analyse the components of the placebo effect in more detail. In the placebo groups of clinical studies, several effects are controlled at the same time; I analysed this in more detail at the time under the term 'efficacy paradox': [3-5].

Regression to the mean

There is the so-called 'regression to the mean': in every study in which measurements are taken twice, at the beginning and at the end, a tendency known as 'regression to the mean' occurs. People who have a very high value in the first measurement tend to have a lower value in the second measurement. This is because the measuring instruments – questionnaires, other types of measurement – are not perfect. Technically speaking, the reliability of the measurement is not 1, but lower. For questionnaires, it is usually around 0.7 to 0.8. This is a statistical artefact. It leads to the suggestion of an improvement where

there may not be one at all. This artefact can be compensated for mathematically, provided that you know the reliability. This is usually the case with standardised questionnaires. That is why we only used studies in this follow-up study in which the same instruments were always used.

Natural course of the disease

There are only a few diseases that would not change on their own if left untreated. Most of them improve at some point. Migraines, or depression, or sleep disorders would often improve on their own if observed long enough. Most patients go to the doctor or take part in studies when they are particularly bad. Therefore, there is a tendency for them to improve on their own to a certain extent. However, we often don't know this because it is rarely investigated. That's why we looked at illnesses in this study for which the natural course could be estimated from some studies.

Five disease diagnoses, each with 30 studies

For these reasons, we used five different disease diagnoses, all measured with the same methods, and for each diagnosis we searched for 30 similar studies, again systematically going backwards. For each diagnosis, we only used studies in which a pharmacological intervention was investigated, regardless of the intervention.

The diagnoses were:

- Osteoarthritis
- Migraine
- Sleep disorders
- Depression
- Irritable bowel syndrome (IBS)

For osteoarthritis, there is a widely used questionnaire instrument, the WOMAC (Western Ontario and McMasters University Osteoarthritis Index). Migraine is recorded in diaries. The Pittsburgh Sleep Inventory is often used for sleep disorders. Irritable bowel syndrome is recorded using the Irritable Bowel Syndrome Quality of Life Questionnaire, and depression using the Hamilton Depression Rating Scale. For our analysis, we only used studies that had used these instruments.

For this study group, too, we found a high correlation of r = .73 between improvement with pharmacological substances and improvement with placebo. The correlation plot looks very similar:

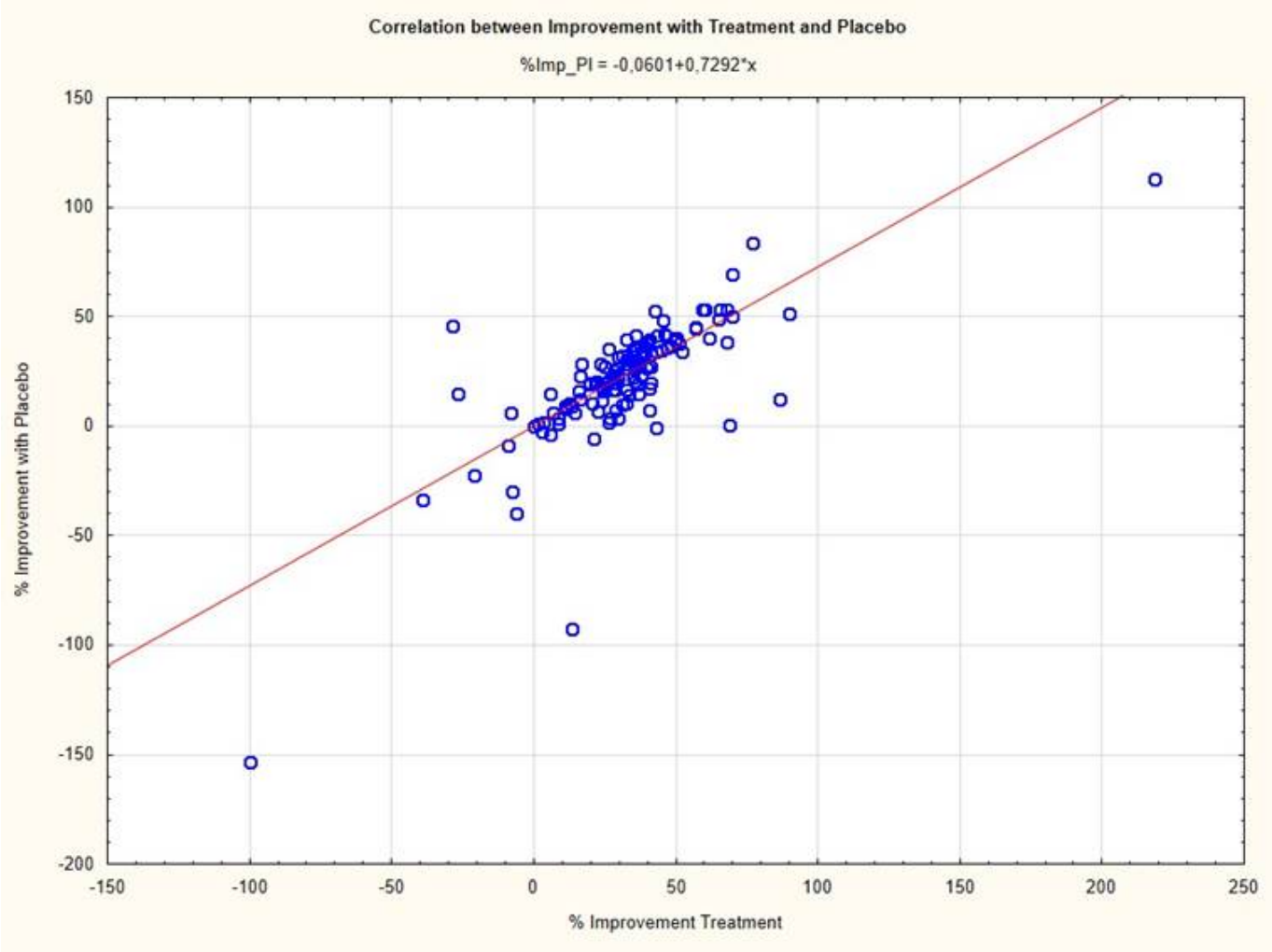

Figure 2 – Correlation between improvement under treatment and placebo in a total of 150 studies on the treatment of migraine, IBS, depression, osteoarthritis or sleep disorders from [1]; r =.73

So we see a similarly high correlation in this ensemble of 150 studies as well. Now we wanted to find out whether this high correlation can be explained and which elements contribute to it. If we analyse the diagnostic categories separately, we see that the correlation is higher for migraine studies and depression studies (r =.85) and even higher for IBS (r =.92) and lower for osteoarthritis (r =.43) and sleep disorders (r =.42).

We used regression models to try to explain treatment and placebo effects and their variance. This was relatively successful, and the models can explain 72% of the variance.

The treatment effect is lower in sleep studies and in multicentre studies; in addition, regression to the mean plays a role. But the placebo effect, adjusted for the natural tendency of the disease, is still correlated with the treatment effect at beta = .83. In other words, even when all the variables we have recorded are used for clarification, the placebo effect still remains the main component in explaining the treatment effect.

Conversely, one can also try to explain the placebo effect using such a regression. Here, too, 72% of the variance can be explained. The placebo effect is higher in multicentre studies and lower when a study is evaluated with 'intention to treat'. This is an evaluation method in which all patients who were once included are evaluated, even if they dropped out. But again, the effect of the treatment, adjusted for the effect of the natural tendency of the disease, with beta =.84, plays the most important role.

To put it another way: the correlation between verum and placebo remains, even when methodological artefacts, the natural tendency of the disease and study characteristics are taken into account.

We also assessed the study quality using an instrument known as the Detsky score. Compared to the widely used 'Risk of Bias' tool from the Cochrane Collaboration, this has the advantage of providing a numerical value that can be used in a regression analysis. And we see: the study quality has no influence on the size of the placebo effect (or the treatment effect) in this study sample.

We can therefore conclude that the correlation between the verum and placebo is not an artefact. Placebo effects in such studies are not simply a result of statistical regression to the mean, the natural tendency of the disease to change, or a consequence of poor study quality or different disease entities.

Rather, this correlation is robust and placebo and treatment successes in a study are very highly correlated with each other. Perhaps such studies are simply very potent healing rituals, just as all healing rituals have been potent since shamanic times, stimulating self-healing effects.

In any case, the commonly held belief that it is the specific effects of drugs that are the main source of therapeutic benefit is wrong. We can explain 72% of the variance with our regression equations. In other words, a maximum of 28% of the effect, probably less, can be attributed to the pharmaceutical substance. The rest is the result of a healing ritual.

Personally, I have another explanation for this effect, which I mentioned briefly in the earlier publication [2]: the design of a clinical study, with blinding and randomisation, fulfils the formal criteria necessary to establish a generalised entanglement correlation [6-8]. This would mean: part of the therapeutic effect of a pharmacological substance is also found in the control group; but only because an entanglement correlation was generated by the blinding and randomisation. To put it another way: it is not really possible to draw any conclusions about the true effects of verum interventions based on such studies. Rather, one would have to use very different study types and extract the effect by combining the different data, as we once proposed [9]. If one were to take these effects really seriously,

the methodological canon would crumble quite quickly. But they are also the reason why, in interventions where the specific effects may be very small, it is not possible to separate ‘real’ from ‘fake’ effects by means of blinded, placebo-controlled studies.

Sources and literature

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