

Now let's go to the evidence on efficacy and effectiveness. And now we really move to the absolutely highest level of evidence. That's the patient-level data meta-analysis. This project is led by Andrew Vickers, and this is really a joint collaboration where we have pulled data and it's funded by NCCAM.

What have we done? We have pulled data from several countries. And you can see here the majority of data is coming from Europe, and especially from Germany, that just due to the fact that we had this large acupuncture initiatives where the health insurance companies sponsor a lot of acupuncture research. But we have also two trials from the States included in this data set. That's a trial by Berman and a trial by Cherkin.

So 31 studies on chronic pain have been eligible to be included in the meta-analysis. All had good allocation concealment and randomization. We only took randomized trials, and we ended up with nearly 18,000 patients in the data set. Eighteen trials had a non-acupuncture control, a non-acupuncture control and an active control. This could be usual care, standard care or rescue medication. And 20 trials had a sham control. As you see from the numbers that some trials had both a sham control and an active control.

So let's have a look for the results, and we start first with the comparison acupuncture versus active controls. You see here, three meta-analyses—headache, musculoskeletal pain and osteoarthritis. And first you think, "Why is this so different from a typical meta-analysis, this first plot looks very similar." But each of the values which you see here is really derived from the original patient data, it's not taken out of the publication. So each value behind the study is calculated in a co-variant analysis, it's adjusted for baseline values and then the standard mean difference effect size is calculated out of the real data. In this case you can really do the calculation on the real primary end points of the studies.

And as you can see we have calculated two models here. And we have a fixed effect model and we have a random effect model. But you see for all three meta-analyses it's on the plus side for acupuncture which means we have here significant difference between acupuncture and active control which is in favor for the acupuncture treatment.

But now we come to the more exciting comparison—acupuncture versus sham acupuncture. So remember all these nice cartoons. And we have here four meta-analyses. And you get it very easily from these pictures—for all four disease groups, acupuncture is superior to sham acupuncture.

Now bringing us to one picture, to get an idea how it looks like. We have here acupuncture versus sham acupuncture, and here acupuncture versus active control. And you see the effect sizes here, from both statistical models and the primary model was fixed-effects model. So you can see the effect size for acupuncture versus sham is between 0.15 and 0.23 here. This is statistically significant but it's a small effect and it's usually not seen as clinically relevant.

When we compare acupuncture with active control, effect sizes get bigger and get clinically relevant. And in this analysis we have even deleted those data from those trials which have been very positive. Trials from Jorge Vas from Spain. In Spain we get huge effects between acupuncture and sham

acupuncture. That's an interesting observation. You see this in several trials, so we excluded them to be more conservative and still have these results. So we have been even more conservative in that we do sensitivity analysis and we model for publication bias.

So what we have done first we restricted analysis to only those sham trials which are low likelihood of unblinding. Then we did adjustment for missing data as you do usually in single trials and you only can do this when you have patient-level data. We included the summary data of the two missing trials. We included summary data of four trials which have been published afterwards. It did not change the results.

Then we assumed in the next step that other trials might have been not published and we don't know about them. So and they have an average size of 100. So how many trials would it need which show no significant difference between acupuncture and sham acupuncture to change our result. More than 100 trials. And if it would be a negative result which means that sham would be better than acupuncture you would still need 47 trials. Gives you a feeling this result is pretty stable.

So but we've also seen that non-specific effects play a role because we only have a moderate effect if we have an active control where we usually have much more non-specific effects in our data. So this is a meta-analysis done by Klaus Linde, and this meta-analysis compared sham acupuncture versus no acupuncture treatment, very often a waiting list control for example. And it has a subset of trials and on chronic pain and as you can see, the difference between sham acupuncture and no treatment is of moderate effect size. And what also is the case when we have trials with larger effects of sham acupuncture versus no treatment, then they have smaller effects between acupuncture over sham acupuncture. Which is very plausible.

Another study which helps us to understand the subject of outcomes could be a problem is a trial which has been done by Ted Kaptchuk and Irving Kirsch. This is on asthma patients. So they had asthma patients and randomized them into four groups. One group got the typical treatment, albuterol. We had two placebo groups, one was a placebo pills the other one was a sham acupuncture, non-penetrating sham. And then we had a no intervention control in this trial.

And on the left hand side here you have the objective outcome measure, on the right hand side you have the subjective outcome measure. And as you easily can see for the objective outcome measure there's not so much response in those placebo groups. Whereas on the subjective outcome measure this is the case. And in chronic pain, we always use subjective outcome measures, which might explain that we have a very high non-specific effect in our data.

So now I'd like to move to another disease. Because there are three trials now coming up on allergic rhinitis. One has been a cooperation between China and Korea, the other one between China and Australia. And the third one is from our group in Germany and all trials are not published yet but I can show you the results of the German trial.

We have randomized 400 patients into three groups. They were treated by 50 physicians and we concluded patients, the seasonal allergic rhinitis. We did the prick tests, they had to have a moderate

disease severity and then they got either acupuncture, which was semi-standardized; sham acupuncture, which was standardized; or standard rescue medication and dehistaminic.

So it's always difficult to define sham acupuncture. For instance with penetrating sham at non-acupuncture points it's usually a long discussion on an international level before you really come up with these defined points. It's often much easier to come up with acupuncture treatment protocol. But we got it done, we had the proper consensus procedure and this trial is mainly led by my colleague Benno Brinkhaus. And here is the result—we had two primary outcome measures, one was a rhinitis quality of life questionnaire—you see it here on the left hand side. And the other one was a rescue medication score. This was the medications the patients took and we got it from the diary which the patients completed.

And as you can see we have acupuncture here, the sham acupuncture group, and the rescue medication group, and higher values mean less good results. And we have significant differences for both primary outcomes and we adjusted our alpha for having two primary outcomes, but the differences are between acupuncture and rescue medication, and also acupuncture and sham acupuncture. And I'm really interested to see if both other studies which are not published yet come up with very similar results.

But allergic rhinitis is a totally different disease than chronic pain. So mechanisms might be totally different here.