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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

Physiological intervention studies often fail to adequately control for the placebo effect

Researchers from the University of Illinois (IL, USA) and Florida State University (FL, USA) claim the majority of physiological intervention studies have a critical design flaw, whereby they do not satisfactorily account for the placebo effect. In order to draw casual conclusions about the efficacy of a psychological intervention, the active control group must have the same expectation of improvement as the experimental group. In this recent study, the researchers illustrate how the use of an active control group does not eliminate differences in expectation of improvement on measures of perception and attention after video-game training.

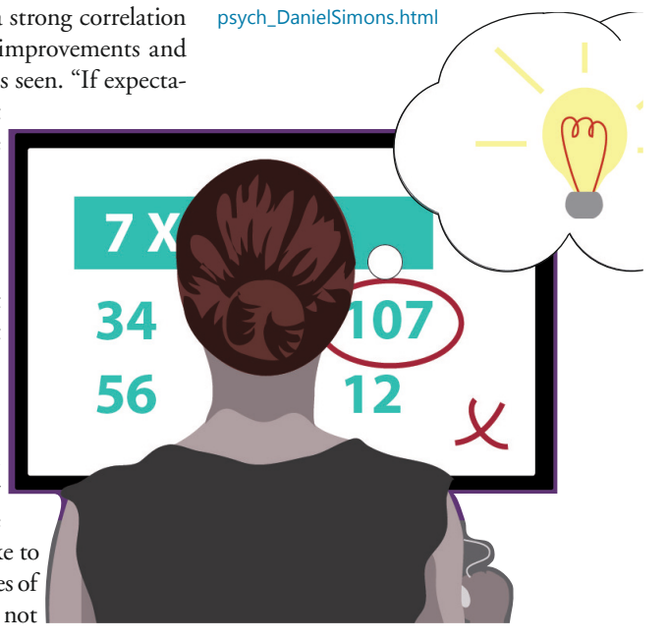
Many of the studies referred to by brain-training companies fail to look at the differing expectations between the treatment and control group. Although it is more difficult to account for the placebo effect in psychology interventions – as participants are aware of the nature of the intervention – without doing so can weaken any claimed benefits. Daniel Simons from the University of Illinois explained "It's not possible to use a brain-training program for 10 h without knowing the type of training you received … people can form expectations for what will improve based on their experiences with the training tasks, and the existence of differences in expectations between people in treatment and control groups potentially undermines any claim that improvements were due to the treatment itself." By simply having an active control group that does an activity for the same amount of time as the treatment group does not protect against the placebo effect, due to the differences in expectation of improvement.

The study carried out by the researchers involved comparing performance on attention and perception tasks and measured expectations between a treatment group and a control group, each consisting of 200 participants. The treatment group underwent training with the action video game 'Unreal Tournament' (GT Interactive Software, NY, USA) whereas the control group used the non-action video games 'Tetris' or 'The Sims' (Electronic Arts, CA, USA). After watching a short video on their respective games, the participants were then informed about the cognitive tests used in the study and asked to comment on whether they thought their performance in the tests would improve as a result of the training they had received. The results showed that there was a strong correlation between the predicted improvements and the actual improvements seen. "If expectations for improvement align perfectly with the actual improvements, then any claim that the treatment was effective is premature," Simons commented, adding that "Researchers must first eliminate differences in expectations across conditions."

Walter Boot from Florida State University explained "There are steps researchers can take to ensure that the advantages of the treatment group are not due to expectations." Such methods include misleading participants in the expected benefits of an intervention and recruiting a separate group of participants to assess their expectations for the intervention. "Only by using better active controls that equate for expectations can we draw definitive conclusions about the effectiveness of any intervention," Simons concluded.

– Written by Emma Elliston

Sources: Boot WR, Simons DJ, Stothart C *et al.* The pervasive problem with placebos in psychology: why active control groups are not sufficient to rule out placebo effects. *Perspect. Psychol. Sci.* 8(4), 445–454 (2013); News Bureau: University of Illinois news release: placebo effect largely ignored in psychological intervention studies: http://news.illinois.edu/news/13/0709placebo_psych_DanielSimons.html



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Study suggests that erlotinib may not be an effective treatment for the majority of advanced lung cancer patients

Erlotinib (Tarceva®; Genentech, CA, USA) is an anticancer drug licensed for use in advanced or chemotherapy-resistant non-small-cell lung cancer (NSCLC), which acts to inhibit the often mutated or overexpressed EGF-receptor to slow or reverse excessive cell proliferation. However, in patients who display wild-type *EGFR* tumors, the use of erlotinib is still debated. A recently published comparative effectiveness trial has reported that chemotherapy is more effective than erlotinib for second-line treatment of patients with NSCLC who have wild-type *EGFR* tumors.

"Docetaxel is not a magic bullet and targeting other genes such as *ALK*, *RO1* and *RET* is also important."

The study, funded in part by the Agenzia Italiana del Farmaco, enrolled 222 patients across 52 Italian hospitals and assigned half to receive 150 mg/day oral erlotonib and half to receive 75 mg/m^2 docetaxel intravenously every 21 days or 35 mg/m^2 on days 1, 8 and 15, every 28 days. Median overall survival in the docetaxel group was 8.2 months compared with 5.4 months in the erlotinib group. Although this difference was not significant ($p = 0.05$), progression-free survival was significantly increased in the docetaxel group compared with patient receiving erlotinib, with median progression-free survivals of 2.9 and 2.4 months, respectively ($p = 0.02$). Indeed, lead author Marina Garassino from Fatebenefratelli e Oftalmico Hospital in Milan, Italy, commented "Docetaxel is superior in all the end points, overall survival, progression-free survival and recurrence rate in wild-type *EGFR* patients."

The authors also states that wild-type *EGFR* cancers make up the majority of NSCLC cases and thus it is possible that this study may lead, if future studies concur with these results, to a radical change in NSCLC treatment policy – the discontinuation of erlotinib as the standard second-line treatment. Garassino comments: "This is an important goal for personalizing therapy in lung cancer and to save high useless costs for society," but warns: "Docetaxel is not a magic bullet and targeting other genes such as *ALK*, *RO1* and *RET* is also important."

– Written by Adam Born

Source: Garassino MC, Martelli IO, Broggini M *et al.* Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type *EGFR* tumours (TAILOR): a randomised controlled trial. *Lancet Onc.* doi:10.1016/S1470–2045(13)70310–3 (2013) (Epub ahead of print).

Potential of common pain reliever for the treatment of Type 2 diabetes

Study results released from the Joslin Diabetes Center (Boston, USA), have shown that salsalate lowers blood glucose levels and improves glycemic control in patients with Type 2 diabetes mellitus (T2DM). This anti-inflammatory drug sparked interest within the Joslin scientists once Steven Shoelson and colleagues from Harvard medical school (Boston, MA, USA) acknowledged inflammation as a key player in the development of T2DM. Salsalate, which is normally used to treat arthritis, may therefore be valuable in the treatment of T2DM.

"...salsalate lowers blood glucose levels and improves glycemic control in patients with Type 2 diabetes mellitus."

A series of short duration studies, sponsored by the National Institutes of Health (MD, USA), were used to assess 1-year efficacy and safety of salsalate in T2DM. Stage one of TINSAL-T2D evaluated varied doses of the anti-inflammatory drug in 108 patients for 14 weeks in 2010. The present findings, however, are based on the larger stage two trial that assessed 286 participants with T2DM for 48 weeks. These participants were randomly assigned to salsalate and placebo groups. Measurements of the mean hemoglobin A1c levels, which determines blood glucose control, revealed a reduction by 37% in the salsalate group after 48 weeks compared with the placebo group. The decline in fasting glucose concentration within the salsalate group was also 15 mg/dl greater than the placebo group. Furthermore, despite reductions of associated diabetes medications within the salsalate group, glycemia still improved in comparison with the placebo recipients.

"It's exciting that salsalate is effective in lowering blood sugar … salsalate may have an important role in diabetes treatment and may also help us learn more about how inflammation contributes to the development of T2DM" commented Allison Goldfine, lead author, head of the Section of Clinical, Behavioral and Outcomes Research, and an Associate Professor of Medicine at Harvard Medical School.

"Goldfine is currently conducting a study that assesses the effects of salsalate in coronary artery disease; the findings of this study are expected to be published in 2 years time."

Not only did the salsalate group show improvements in T2DM, they also demonstrated a 9% decline in triglycerides, an 18% decline in uric acid – which is associated with cardiometabolic conditions – and a 27% increase in adiponectin, which is thought to be a cardioprotective protein. Thus, the salsalate group showed improvements in markers related to coronary risk. "The reductions in these cardiovascular risk factors paralleled improved glycemia," summarizes Goldfine. Moreover, the anti-inflammatory effects of this drug were evident in the reduction of circulating leukocyte, neutrophil and lymphocyte counts. However, paradoxically

weight and LDL cholesterol levels did increase in the salsalate group.

To the authors' knowledge, this was the first study on the effects on salsalate using a randomized, double-blind, multicenter, placebo-controlled trial format with a duration that was longer than 3 months. Limitations of this stage two trial, however, include the small number of patients used and the length of the trial; therefore, in the future, these limitations should be accounted for to determine long-term effects of salsalate in T2DM. Such studies will provide an insight into the safety of using this drug as a diabetes medication and will assess the cardiovascular outcomes. Goldfine is currently conducting a study that assesses the effects of salsalate in coronary artery disease; the findings of this study are expected to be published in 2 years time.

– Written by Deepa Pindoria

Sources: Goldfine A, Fonseca V, Jablonski K *et al.* Salicylate (salsalate) in patients with Type 2 diabetes: a randomized trial. *Ann. Intern. Med.* 159(1), 1–12 (2013); Joslin Diabetes Center press release: common pain reliever may provide a new medication option to treat Type 2 diabetes: www.joslin.org/news/salsalate-lowers-blood-glucose-in-Type-2-diabetes.html

OncoGenex Pharmaceuticals announce completion of enrollment in trial

Enrollment has been completed in the company-sponsored trial Borealis-1™ and was announced by OncoGenex Pharmaceuticals (Bothell, WA, USA). Borealis-1 is a Phase II, placebo-controlled, randomized study of first-line gemcitabine and cisplatin in combination with OGX-427 for use in patients diagnosed with metastatic bladder cancer.

> "There are approximately 400,000 newly diagnosed global cases of bladder cancer annually. By the point of diagnosis, nearly 30% of patients have cancer at the locally invasive or metastatic stage..."

There are approximately 400,000 newly diagnosed global cases of bladder cancer annually. By the point of diagnosis, nearly 30% of patients have cancer at the locally invasive or metastatic stage; however at present there is a lack of options for both first- and second-line treatment for advanced forms of the illness. Therefore more therapeutic options are required in this patient group, especially given the short survival time and high frequency with which patients develop resistance to chemotherapies.

A total of 180 patients have been randomized into the trial from 55 clinical sites spanning Europe and Northern America. Patients entering the three-arm trial will receive either gematicine, cisplatin and placebo versus gematicine or cisplatin and OGX-427. Patients receiving OGX-427 will be receive the drug at two doses; 600 or 1000 mg. The primary end point of the trial is overall survival. In addition, analyses will be performed to evaluate the benefit–risk ratio of using the two different doses via clinical benefit, tolerability and safety outcomes for each dose.

> "We expect data results to be available in the second-half of 2014..."

Cindy Jacobs (OncoGenex, Pharmaceuticals, WA, USA) states that: "We expect data results to be available in the second-half of 2014, and if the trial is positive, we will initiate discussion with the Food and Drug Administration regarding the next steps."

The Borealis-1 trial is one of two ongoing studies utilizing OGX-427 as a potential treatment option for metastatic bladder cancer.

– Written by Priti Nagda

Source: OncoGenex™ News releases: http://ir.oncogenex.com/releasedetail.

Radium-223 injection yields encouraging results in Phase III prostate cancer trial

A recent Phase III trial assessing the efficacy and safety of radium-223 dichloride (radium-223) injections in the treatment of patients with metastatic prostate cancer has demonstrated significant benefits. The trial, led by researchers at The Royal Marsden NHS Foundation Trust (London, UK) and The Institute of Cancer Research (London, UK), showed such promise that it was stopped early, allowing patients previously taking the placebo injection to have the radiation treatment.

The study involved administrating six injections of radium-223, or matching placebo to 921 patients with advanced prostate cancer that had spread to the bone. Efficacy of the radiation injection was evaluated using the primary end point of survival. Results of the trial revealed that men treated with radium-223 lived for an average of 14.9 months compared with 11.3 months for those men given the placebo injection. Furthermore, the treatment with the radioactive injection also significantly improved patients' quality of life.

> "Not only did they live longer, these men had a much better quality of life."

"We were delighted to show that radium-223 allowed many men in our trial to live to see a few extra, precious months. Not only did they live longer, these men had a much better quality of life," commented study leader Chris Parker of The Royal Marsden NHS Foundation Trust. The study was terminated earlier than planned in order to start treating patients given the placebo injection with radium-223.

Radium-223 is an alpha emitter that is targeted to tumors in the bone owing to its similar chemical properties to calcium. The treatment delivers high-energy alpha particles of short range, which means that the radiation causes minimal damage to non-cancerous cells. "We're excited by the

prospects for this ingenious new treatment, which takes advantage of the properties of tumors growing within bone to home in and deliver a highly targeted dose of radiation," explained Parker.

According to the researchers, radium-223 has great potential in treatment for men with advanced prostate cancer, both in conjunction with other treatments and on its own for those patients who can't use other treatments. "The study paves the way for radium 223 to be used to extend the lives of more men with advanced prostate cancer," concluded Parker.

– Written by Emma Elliston

Sources: Parker C, Nilsson S, Heinrich D *et al.* Alpha emitter radium-223 and survival in metastatic prostate cancer. *N. Engl. J. Med.* 369(3), 213–223 (2013). The Institute of Cancer Research press release: www.icr.ac.uk/press/press_archive/press_releases_2013/23917.shtml

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