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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

Potential benefits of ketamine seen in antidepressent clinical trial

The largest clinical trial to date utilizing the anesthetic ketamine was led by researchers from the Icahn School of Medicine (Mount Sinai, NY, USA). The clinical trial enrolled patients diagnosed with treatment-resistant major depression who were treated with ketamine – and within 24 h the antidepressant benefits of the anesthetic were reported. Traditional antidepressants can normally take between several days to weeks to demonstrate an improvement in depression.

> "...within 24 h the antidepressant benefits of the anesthetic were reported."

The mechanism of action of traditional antidepressants such as selective serotonin reuptake inhibitors is to control the neurotransmitter activity of norepinephrine and serotonin to cause a reduction in depression. However, with these medications the response can be largely delayed, and according to statistics from the US Department of Health, up to 60% of patients do not respond to this type of treatment. Ketamine on the other hand controls the activity of the glutamine neurotransmitter, and appears to do so much quicker than the traditional antidepressants.

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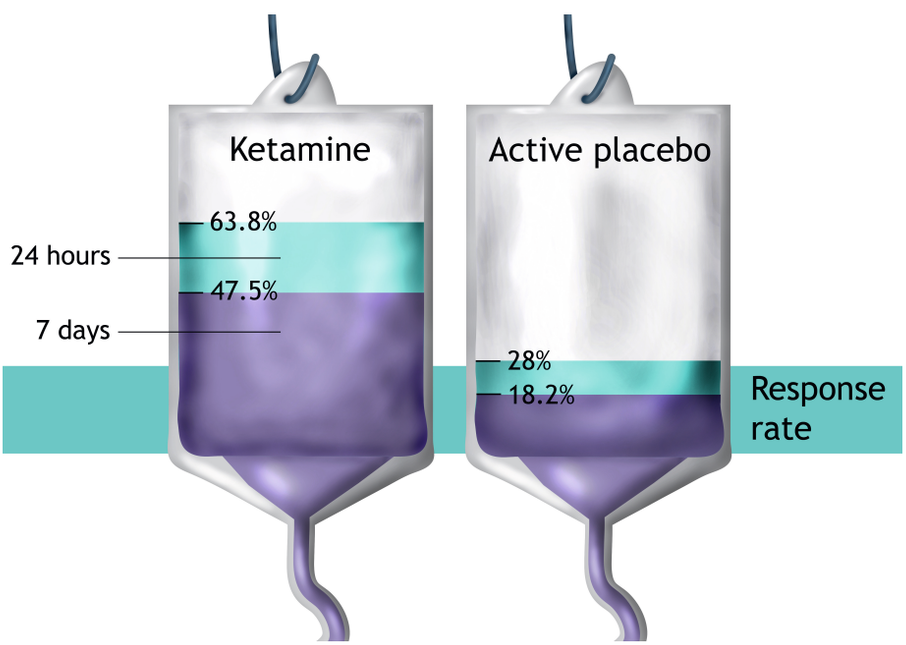
The study was led by Dan Iosifescu (Mount Sinai, NY, USA), Sanjay Mathew (Baylor College of Medicine, TX, USA) and James Murrough (Mount Sinai, NY, USA) along with their research team. Seventy two patients with treatment-resistant depression (classified as failure to respond to two or more medications) were evaluated and underwent either a single intravenous infusion of ketamine over the course of 40 minutes or were treated with the active placebo midazolam. Midazolam is also an anesthetic but does not possess antidepressant properties. Patients were interviewed after 24 h, and then again after 7 days had passed. The response rate was 63.8% after 24 h for patients in the ketamine-treated group in comparison with 28% in the active-placebo group. Seven days later the response to ketamine was lasting, with a 47.5% response for the ketamine-treated group in comparison with 18.2% for the placebo-administered group. For both groups the drugs were well tolerated.

Murrough summarized the study findings, "We found that ketamine was safe and well tolerated and that patients who demonstrated a rapid antidepressant effect after starting ketamine were able to maintain the response throughout the course of the study." He also added that for future studies, "Larger placebo-controlled studies will be required to more fully determine the safety and efficacy profile of ketamine in depression."

– Written by Priti Nagda

Sources: Mount Sinai Hospital, Newsroom, news releases: www.mountsinai.org/about-us/newsroom/press-releases/ketamine-shows-significant-benefit-in-people-with-treatment-resistant-depression



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Data reported for gefitinib use in Caucasian EGF receptor mutation-positive non-small-cell lung cancer patients

Novel data from the IFUM trial, presented at the European Multidisciplinary Conference in Thoracic Oncology (EMCTO; Lugano, Switzerland), have demonstrated that IRESSA™ (gefitinib; AstraZeneca, UK) is effective for Caucasian patients with EGF receptor (EGFR) mutation-positive advanced non-small-cell lung cancer (NSCLC) in the first-line setting, based on objective response rate and progression-free survival (PFS).

IFUM is a Phase IV open-label, multicenter, single-arm study aiming to characterize the efficacy, safety and tolerability of gefitinib in 106 EGFR mutation-positive Caucasian NSCLC patients. Jean-Yves Douillard, principal investigator of the study (University of Nantes Medical School, France), explained, "The primary end point of IFUM was to evaluate the objective response rate (confirmed complete response or partial response) based on investigators assessment in patients treated with gefitinib using Response Evaluation Criteria in Solid Tumours version 1.1. Overall response rate was 70% (95% CI: 61–78%)."

Data from the previous IPASS study demonstrated superior PFS for gefitinib compared with intravenous carboplatin/paclitaxel chemotherapy in a population of patients with advanced NSCLC in Asia. Explaining the significance of the novel IFUM results, Douillard noted, "The objective response rate seen in this EGFR mutation-positive Caucasian population is similar to that seen in the EGFR mutation-positive IPASS population. Therefore, gefitinib appears to be consistent in its efficacy in patients with this disease, irrespective of whether they are Asian or Caucasian."

The secondary efficacy end points of disease control rate, median PFS and overall survival were reported to be 91%, 9.7 months and 19 months, respectively. Douillard also explained, "The safety and tolerance profile in Caucasian patients did not show any new signal. Remarkably, the incidence of grade 3/4 adverse events was low with 0% grade 3 rash and 3.7% diarrhea." Overall survival data will require longer follow up.

As this evidence supports the use of gefitinib in Caucasian patients, Douillard hopes the results will increase physician confidence in prescribing gefitinib for such patients.

– Written by Francesca Lake

Source: Press release: New data presented at EMCTO showed that first-line therapy with gefitinib (IRESSATM) in Caucasian patients with EGFR mutation-positive advanced NSCLC resulted in an ORR of 70% (95% CI 61-78). Released 10th May 2013.

The potential of Kava to be used as an alternative therapy for anxiety sufferers

A world first study led by a research team from the University of Melbourne (Melbourne, Victoria, Australia) have found that Kava, a plant originating from the South Pacific, may cause a significant reduction in people who suffer from anxiety. Kava could become a potential alternative therapy for the many thousands of Australians suffering from generalized anxiety disorders (GADs). GAD is a complex condition that can drastically affect a sufferer's quality of life with existing therapeutics possessing only a modest clinical effect.

Jerome Sarris (University of Melbourne, Victoria, Australia) explained the need for newer and more effective medications for those suffering from anxiety, "Based on previous work we have recognized that plant based medicines may be a viable treatment for patients with chronic anxiety. In this study we've been able to show that Kava offers a potential natural alternative for the treatment of chronic clinical anxiety. Unlike some other options it has less risk of dependency and less potential for side effects."

The study revealed that polymorphisms in GABA transporters may modify a sufferer's response to Kava, with Sarris explaining that, "If this finding is replicated, it may pave the way for simple genetic tests to determine which people may be likely to have a beneficial anxiety-reducing effect from taking Kava."

The 8-week study consisted of 75 patients who were clinically diagnosed with GAD, being administered either Kava or placebo with their anxiety levels assessed regularly. Those in the Kava group were administered tablets containing a water-soluble extract of Kava; the peeled rootstock twice daily for a combined dose of 120 mg of kavalactones during the primary 3-week controlled phase. In the event of nonresponse, participants were increased to a double dose twice daily for the second 3-week phase. Patients in the placebo group were given dummy tablets in the same fashion. By the end of the study, results indicated that there had been a significant reduction in anxiety in the patients that had been taking Kava in comparison to those in the placebo group.

The effects of Kava were apparently greater in reducing anxiety in those enrollments whose GAD had been diagnosed as moderate-to-severe. After completion of the controlled phase, 6% of participants in the placebo group were shown to be in remission in comparison to the 26% of the patients in the Kava group.

Kava was seen to be well tolerated with no significant differences in patient liver-function tests across either group. In addition, no adverse effects were found that could be solely attributed to Kava and there were also no differences seen in the Kava and placebo groups regarding addiction and withdrawal.

Further studies will now concentrate on confirming the relationship between genetics and therapeutic response. The findings will be of potential benefit to both anxiety sufferers and the region of the South Pacific that relies on Kava as an export.

– Written by Priti Nagda

Sources: University of Melbourne, Melbourne Alumni eNews: http://alumni.news.unimelb.edu.au/clinical-trial-supports-use-kava-treat-anxiety; Sarris J, Stough C, Bousman CA *et al.* Kava in the treatment of generalized anxiety disorder: a double-blind, randomized, placebo-controlled study. *J. Clin. Psychopharmacol.* doi: 10.1097/JCP.0b013e318291be67 (2013) (Epub ahead of print).

Uncertainty over the benefits of diabetes drug in breast cancer patients

Metformin, a popular drug for diabetes treatment, might not affect survival in breast cancer patients, according to new results.

A new population-based study, published in *Diabetes Care* has not shown a difference in survival from metformin use as might have been expected, a result contrary to some evidence that suggests the drug improves survival in breast cancer patients.

Iliana Lega (Women's College Research Institute; Toronto, Canada), first author of the study, explains that, "Metformin is a drug commonly used by diabetic patients to control the amount of glucose in their blood." She goes on to explain the importance of these findings, "Although existing scientific literature suggests that drug may prevent new cancers and death from breast cancer, our study found the drug did not significantly impact survival rates in our patients."

Metformin, used to lower blood sugar levels in Type 2 diabetes patients, works by altering glucose production by the liver. According to other studies, metformin has previously been suggested to confer a reduction in cancer risk of up to 30%, as well as slowing tumor growth in breast cancer patients.

The study involved 2361 diabetic women over the age of 66, all diagnosed with breast cancer. The authors analyzed the associations between duration of metformin use and mortality in the population, broken down into all-cause mortality and breast cancer-specific mortality. Of the 1101 deaths during the study period, 16.3% were breast cancer specific but there was no statistically significant association between cumulative metformin use and either all-cause or breast cancer-specific mortality in the study population.

This population-based study differs from others in that it assessed the cumulative dose of metformin over time. Lega explained this further, stating, "What makes our study so unique is that while the effects of metformin have been well documented, previous research has not examined the cumulative effects of the drug on patients, particularly breast cancer patients with diabetes." Lega continued to say that, "This is important given that diabetic patients may switch drugs over the course of their treatment."

There are limitations to this study, as data on the stage of breast cancer and BMI were not included, and there were relatively short follow-up times (median follow-up time was 4.5 ± 3.0 years). However, in general these results suggest that more research is needed to clarify the role of metformin in cancer.

According to Lega, "Understanding the effects of metformin on breast cancer patients is critical in helping address the gap in cancer outcomes in patients with and without diabetes." Lega hopes that, "The findings will help physicians inform treatment plans for patients with diabetes."

– Written by Alisa Crisp

Sources: Lega IC, Austin PC, Gruneir A, Goodwin PJ, Rochon PA, Lipscombe LL. Association between metformin therapy and mortality after breast cancer: a population-based study. *Diabetes Care.* doi: 10.2337/dc12-2535 (2013) (Epub ahead of print); Women's College Hospital press release: www.womenscollegehospital.ca/assets/pdf/Lega_metformin_May%202013.pdf

CUSTOM demonstrates feasibility and challenges of genetics-guided clinical trials

Researchers from the USA have recently presented promising findings from their CUSTOM clinical trial, which, among other results, demonstrated that both patients and physicians are enthusiastic about genetics-guided cancer clinical trials; researchers reached their target number of participants 3 years earlier than anticipated. The findings were presented at the 2013 annual meeting of the American Society of Clinical Oncology, and the researchers propose that CUSTOM could be a model for more efficient clinical trials.

CUSTOM is the first completed prospective clinical trial that employed next-generation sequencing to assign cancer patients to the most appropriate treatment option. Patients with non-small-cell lung cancer, small-cell lung cancer or thymic cancer were recruited, and the trial's reception exceeded the researcher's expectations, "We expected it would take five years to enroll 600 patients into CUSTOM. But in less than two years, 668 patients were recruited," explained the study's lead investigator, Giuseppe Giaccone of the Georgetown Lombardi Comprehensive Cancer Center (DC, USA). Giaccone lead the CUSTOM trial while at the National Cancer Institute, which collaborated with Oregon Health & Science University (OR, USA) for the trial.

"This was a surprise to all of us, especially since patients with advanced cancer who already had biopsies needed to undergo an additional biopsy for the study. But we found patients and their doctors are quite interested in this type of personalized medicine. They know

that the molecular profile of the tumor is important," Giaccone added.

In the CUTSOM trial, tumor biopsies from eligible patients were screened for mutations in approximately 200 genes using next-generation sequencing. The turnaround time was 2 weeks and the trial also demonstrated that it is safe to obtain new biopsies for genetic analysis from patients with advanced cancer.

CUSTOM demonstrated that patients with KRAS mutations did not benefit from selumetinib; a single agent investigational drug being investigated in non -small-cell lung cancer, in addition to other cancers. However, despite this and the unanticipated popularity of CUSTOM which has reaffirmed patient and physician interest in such trials, one of the end points was not met; they were unable to produce an accurate statistical analysis of response to novel drugs.

Results for the small-cell lung cancer and thymic cancer groups were inconclusive owing to not enough patients having the specific mutations to assess therapy response, as Giaccone explained, "When we started the study, we didn't know how frequently the mutations occurred. Now we know that many mutations represent only 1 to 2 percent of patients and to do this right, you need to screen thousands of patients. That is only possible with a global study that involves, potentially, hundreds of institutions."

"The CUSTOM trial demonstrates both the feasibility of the approach for common mutations – that it is possible to have a real-time genetic analysis that guides treatment – as well as the difficulty of studying treatment for rare mutations," Giaccone concluded.

– Written by Sarah Miller

Sources: Georgetown Lombardi Comprehensive Cancer Center News Release: http://explore.georgetown.edu/documents/70469/?PageTemplateID=141

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