In this section...

Highlights from the latest news and research in obesity

- Obesity news
- Trial watch
- Drug watch
- Research highlights
  SJ MacFarlane
- Interview
  Dr Haslam speaks to Laura Dormer

Obesity surgery could save lives, in the right patients

An extensive study carried out by researchers in Sweden has found that surgery can reduce premature death in those suffering from severe obesity.

Researchers from the Sahlgrenska Academy (Gothenburg, Sweden), looked at the 4047 obese subjects who were part of the prospective, controlled Swedish Obese Subjects study. Of these, 2010 received bariatric surgery (surgery group) and 2037 received conventional treatment (matched control group). Conventional treatment included advice about lifestyle changes that would lead to weight loss. Some also received drug therapy to help weight loss. In their study, published in the *New England Journal of Medicine*, the researchers report the overall mortality during an average of 10.9 years of follow-up. They found that in the control group, average weight change was less than ±2%. By comparison, the weight loss results in the surgery group after 10 years were 25, 16 and 14% for gastric bypass, vertical-banded gastroplasty and banding, respectively. A total of 129 deaths occurred in the control group, compared with 101 in the surgery group, therefore it was concluded that mortality was significantly lower in those patients who had received surgery.

"We show for the first time that surgery against obesity not only leads to long-term loss of weight, it also significantly reduces mortality", says Lars Sjöström, Professor Emeritus at the Sahlgrenska Academy. He continued: "The mechanisms behind the lower mortality are not clear. It seems that the reduction in risk depends less upon the actual loss of weight itself than on the fact that the patients have undergone surgery against obesity. This observation opens new possibilities for discovering previously unknown mechanisms behind the increase in risk associated with obesity, and thus opens the possibility of developing new treatments".

Further research published in the same issue of the *New England Journal of Medicine* found that obese patients who undergo gastric bypass surgery are at a reduced risk of death from coronary heart disease, diabetes and cancer.

This second, 14-year study was carried out by researchers from the University of Utah School of Medicine (UT, USA), and looked at 15,850 severely obese patients. They found that mortality from coronary heart disease, cancer and diabetes was 56, 60 and 92% lower, respectively, in the surgery group compared with the control group.

Lead author Ted D Adams commented: "This study helps to further define the effects of gastric bypass surgery on long-term mortality. Reduction in death by any cause, and disease-specific deaths such as coronary heart disease, diabetes and cancer were significantly reduced in surgery patients compared to the nonsurgical control group. However, rates of death not caused by disease were shown to be greater in those who underwent the weight-loss surgery when compared to controls".

> *"We show for the first time that surgery against obesity not only leads to long-term loss of weight, it also significantly reduces mortality"*

These other deaths were due to reasons such as accidents and suicides, which the authors suggest may in part be due to unrecognized presurgical mood disorders or post-traumatic stress. The authors state that these results emphasize the need to carefully evaluation patients before recommending surgery.

Source: Sjöström L, Narbro K, Sjöström CD *et al.*: Effects of bariatric surgery on mortality in Swedish obese subjects. *N. Engl. J. Med.* 357(8), 741–752 (2007); Adams TD, Gress RE, Smith SC *et al.*: Long-term mortality after gastric bypass surgery. *N. Engl. J. Med.* 357(8), 753–761 (2007).

Upper trunk fat may lead to insulin resistance

A study conducted by researchers from the San Francisco VA Medical Center (CA, USA), has found that deposits of fat on the chest and back (known as upper trunk fat) may be associated with an increased risk of insulin resistance, a known precursor of Type 2 diabetes. They also found that visceral fat (between and around internal organs) was independently linked to an increased risk of insulin resistance.

The study is part of the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). However, the association was found to be equally strong in the HIV-infected subjects and the negative controls that were included in the study. The study consisted of 926 HIV-infected subjects and 258 negative controls. They looked at visceral and subcutaneous fat in the legs, arms, upper trunk and lower trunk; each population was then divided into thirds depending on the amount of fat that was found in each location. In the groups that were in the highest tertile for upper trunk fat, 57% of the HIV-infected patients and 61% of the controls were found to be insulin resistant. However, of those, half of the HIV-infected patients lacked high visceral fat, along with a third of the control patients.

"We knew about the insulin resistance risk associated with visceral fat, which has been shown in previous studies, but no one had ever looked at the contribution of upper trunk fat", says lead author and FRAM principal investigator Carl Grunfeld. "Strikingly, there was very little difference between HIV-infected people and controls. If you have fat up top, it's bad for you".

Grunfeld went on to explain why there was no difference in risk between the HIV patients and the controls: "With the new, highly effective antiretroviral medications, Americans with HIV now have the same weight problems as everybody else", he said. "No matter who you are, if you eat too much and you don't exercise, you're going to be at risk for insulin resistance, cardiovascular disease, and every other problem associated with being overweight".

> *"...If you have fat up top, it's bad for you"*

This research was funded by grants from the National Institutes of Health, which were administered in part by the Northern California Institute for Research and Education.

Source: Grunfeld C, Rimland D, Gibert CL *et al.*: Association of upper trunk and visceral adipose tissue. *J. Acquir. Immune Defic. Syndr.* DOI: 10.1097/QAI.0b013e31814b94e2 (2007) (Epub ahead of print).

Obesity vaccine a real possibility?

New research, conducted by scientists at the Pennington Biomedical Research Centre (PA, USA) has suggested that in some cases, obesity may be caused by a common virus. As such, a vaccine to cut the risk of obesity could be a possibility for the future. Although obesity is mainly caused by an imbalance between calorie intake and expenditure, it is possible that other factors may also have a role to play.

In research presented at the National Meeting of the American Chemical Society, it has been shown that infection with human adenovirus-36 (Ad-36) transformed stem cells, obtained from fatty tissue from liposuction patients, into fat cells. By contrast, cells that were not exposed to the virus remained unchanged. A viral gene was found that appeared to be involved in this effect, although the exact mechanism remains unknown.

The research was led by Magdalena Pasarica and was carried out in the lab of Nikhil Dhurandhar, who said: "Not all infected people will develop obesity. We're not saying that a virus is the only cause of obesity, but this study provides stronger evidence that some obesity cases may involve viral infections". However, he emphasized that before any work is carried out to develop a vaccine, it first needs to be proven that Ad-36 is indeed involved in human obesity.

> *"...this study provides stronger evidence that some obesity cases may involve viral infections"*

Dhurandhar said: "We would ultimately like to identify the underlying factors that predispose some obese people to develop obesity after infection with this virus and eventually find a way to treat it".

Previous research had also found a link to Ad-36, finding that 30% of obese people were infected, compared with just 11% of non-obese individuals.

Source: American Chemical Society www.acspresscenter.org/

A recent study has indicated that increased maternal obesity is associated with a higher risk for chronic disease, complications of pregnancy and adverse outcomes of pregnancy, including birth defects.

Children of obese mothers may have an increased risk for certain birth defects

"The dramatic increase in the prevalence of overweight and obese women of childbearing age is of great public health concern because they are at increased risk for chronic disease, infertility, menstrual irregularities, pregnancy complications, and adverse pregnancy outcomes, including birth defects," explains Kim Waller from the University of Texas (TX, USA).

The ongoing study from the National Birth Defects Prevention Study (NBDPS) looked at the index of pregnancies in eight US states, between October 1997 and December 2002. The body mass index (BMI) of each mother was calculated from height and weight and recorded, and then compared with the birth outcomes of mothers with normal BMIs. The study revealed that there is a strong relationship between the BMI of an expectant mother and the likelihood of a birth defect occurring; particularly spina bifida and anencephaly.

Waller explained the importance of the study: "To our knowledge, this is the first population-based study of its scale to examine pre-pregnancy obesity and a range of structural birth defects. These results suggest a weak-to-moderate positive association of maternal obesity with seven of 16 categories of birth defects and a strong inverse association with gastroschisis. The mechanisms underlying these associations are not yet understood but may be related to undiagnosed diabetes".

In a further study, published in the *British Journal of Nutrition*, scientists warn against the danger of pregnant and breastfeeding women increasing their fat and sugar intake; so-called 'eating for two'. In a study conducted in rats it was found that offspring born to mothers fed on a junk food diet developed an exacerbated preference for fatty, sugary and salty foods at the expense of protein-rich foods compared with offspring fed a balanced diet.

Stephanie Bayol, from the Royal Veterinary College in London, said: "Our study has shown that eating large quantities of junk food when pregnant and breastfeeding could impair the normal control of appetite and promote an exacerbated taste for junk food in offspring. This could send offspring on the road to obesity and make the task of teaching healthy eating habits in children even more challenging".

Source: Waller K, Shaw GM, Sonja A: Prepregnancy obesity as a risk factor for structural birth defects. *Arch. Pediatr. Adolesc. Med.* 161, 745–750 (2007); Bayol SA, Farrington SJ, Stickland NC: A maternal 'junk food' diet in pregnancy and lactation promotes an exacerbated taste for 'junk food' and a greater propensity for obesity in rat offspring. *Br. J. Nutr.* 1–9 (2007).

UK scheme to help overweight children

A scheme based in Guilford (Surrey, UK) has been established to help overweight children and their parents establish a healthier lifestyle.

Obesity in young people is a growing problem in the UK; it is estimated that by 2020, 20% of all boys and 33% of all girls will be obese.

The program, run by MEND (Mind, Exercise, Nutrition and Diet) consists of 9 weeks of training related to a healthy lifestyle in general. Paul Sacher, research director of the program and an honorary specialist dietician at Great Ormond Street Hospital (London, UK), said the focus of the program was not weight loss; "Weight is just one of the things we measure. It's more about living healthily," he said.

The program is a National Lottery-funded initiative, and will target children aged between 7 and 13 years.

Source: MEND Programme www.mendprogramme.org

Food adverts reaching fewer children in the USA

An assessment commissioned by the Association of National Advertisers and the Grocery Manufacturers Association/Food Products Association in the USA has found that there has been an 8.5% reduction in the number of food-related adverts being viewed by children aged between 2 and 11 years (between 2004 and 2006). Prior to this, research had shown a 13.5% reduction between 1993 and 2004.

"The steady decline in food advertising to children on broadcast and cable, coupled with the enormous changes in food advertising, signal a remarkable transformation in the marketplace," said Robert Liodice, ANA President and CEO. "Everyone – government, educators and parents – must do their part to combat childhood obesity in America. In that regard, the marketing industry has shown exceptional leadership by taking extremely strong, voluntary steps".

Source: Association of National Advertisers http://www.ana.net/news/content/754

TRIAL WATCH

Good results for zonisamide SR/bupropion SR combination

Company: Orexigen™ Therapeutics
Drug: Fixed-dose combination zonisamide sustained release and bupropion sustained release (Empatic™)
Indication: Obesity
Trial: Phase IIb

Orexigen™ Therapeutics has announced positive top-line results at the 24-week primary end point of the Phase IIb trial of its anti-obesity drug Empatic™. Empatic (formerly known as Excalia™), is a fixed-dose combination of zonisamide sustained release (SR) and bupropion SR, a combination that was originally discovered by Kishore Gadde from Duke University (NC, USA). From initial studies in a screening model it was found that Empatic may act to enhance satiety and energy expenditure. Zonisamide alone has been shown to cause weight loss in previous clinical trials.

The trial consists of six treatment arms, looking at different ratios of the two drugs in a total of 620 patients. Across all six arms of the study treatment was found to result in statistically significant weight loss ($p < 0.001$). It was also found that the drug was safe and generally well-tolerated.

It was found that at the highest dose tested a weight loss of 8.6% from baseline was achieved, compared with 1.1% weight loss for placebo in the intent-to-treat group; in the completer group 10.3% weight loss from baseline was achieved compared to 1.2% for placebo. It was also found that the trajectory of weight loss for all treatment arms appeared to continue downward through 24 weeks.

"These trial results illustrate that we can delay the early weight loss plateau often seen with dieting and many existing pharmaceutical approaches and also improve tolerability with a sustained release formulation of zonisamide," said Orexigen President and Chief Executive Officer, Gary Tollefson. "If the magnitude of weight loss evident in this trial continues to be seen, we believe that Empatic may be particularly useful in severely obese individuals".

Based on these results, development of the drug will continue, with further safety and efficacy data due to be reported following completion of an ongoing 24-week trial extension. The primary trial results are scheduled to be presented at the *2007 Meeting of the North American Association for the Study of Obesity* (October 20–24, New Orleans, LA, USA).

"Despite epidemic rates of obesity, few people seek drug therapy. This may be because, as published reports indicate, currently approved regimens typically achieve only modest weight loss that stalls at an early plateau", said Orexigen Chief Scientific Officer Michael Cowley, also from Oregon Health & Science University (OR, USA). "By contrast, our approach is designed to achieve and sustain weight loss by enhancing satiety, diminishing appetite, improving energy expenditure and counteracting the body's efforts to compensate for weight loss".

Orexigen also has another anti-obesity drug currently under trial; Contrave™. This drug is a fixed dose combination of naltrexone SR and bupropion SR, and a Phase III trial has recently been initiated.

Source: Orexigen Therapeutics, Inc. www.orexigen.com

Interim Phase I data for trodusquemine announced

Company: Genera Corporation
Drug: Trodusquemine (Empatic™)
Indication: Obesity and Type II diabetes
Trial: Ascending dose Phase I

Genaera Corporation announced their interim Phase I data for their obesity drug trodusquemine (MSI-1436) at the *IBC 12th Annual World Congress on Drug Discovery & Development of Innovative Therapeutics* (August 6–8, Boston, MA, USA).

Trodusquemine acts by selectively inhibiting protein tyrosine phosphatase 1B (PTP-1B); the drug acts both centrally and peripherally, and is a candidate for the treatment of both obesity and Type 2 diabetes. PTB-1B is involved in both the insulin and leptin pathways, and is therefore expected to decrease appetite and normalize blood sugar levels.

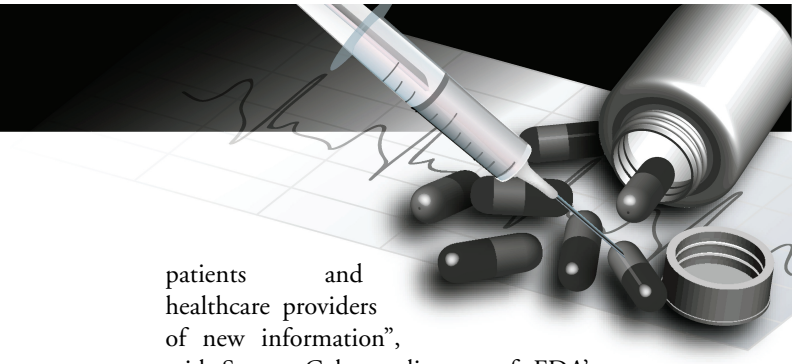
The trial is a single ascending dose Phase 1 study, and Anthony DelConte reported the trial design being used (to evaluate drug safety and pharmacokinetics [PK]). Interim data was also provided from the initial cohorts in the double-blind, randomized, placebo-controlled

trial which included safety and PK data from 20 treated subjects and eight vehicle controls in four sequential dose groups. It was reported that the PK profiles have a predictable pattern with minimal variability between subjects, and that no serious adverse events have been reported thus far.

"These initial findings validate the preclinical safety and PK work done by Genaera scientists. We are encouraged by these findings and will continue to further characterize the safety profile and provide proof of concept for trodusquemine in obesity and Type 2 diabetes management", commented Jack Armstrong, President and CEO of Genaera. "We anticipate a steady flow of clinical information in the second half of 2007 as our clinical studies progress to broader populations".

Source: Genaera Corporation www.genaera.com

Drug Watch



Heart failure warning strengthened for some diabetes drugs

Based on an FDA recommendation, some manufacturers have been asked to strengthen their warning related to heart failure risk for some drugs approved for the treatment of Type 2 (non-insulin-dependent) diabetes. The warning will come in the form of a boxed warning, which is the FDA's strongest form of a warning.

Having reviewed postmarketing adverse event reports, the FDA recommended the changes to the labeling of all of the thiazolidinedione class of antidiabetic drugs. The adverse event reports included incidences of weight gain and edema, which are warning signs for heart failure. In some cases, continuing therapy has been associated with poor outcomes, including death. Drugs include: Avandia® (rosiglitazone), Actos® (pioglitazone) Avandaryl™ (rosiglitazone and glimepiride), Avandamet® (rosiglitazone and metformin), and Duetact™ (pioglitazone and glimepride). These drugs are used in conjunction with diet and exercise to improve blood sugar control in adults with Type 2 diabetes.

"Under FDA's postmarketing surveillance program, we carefully monitor new safety information for marketed drugs and take appropriate action when necessary to inform patients and healthcare providers of new information", said Steven Galson, director of FDA's Center for Drug Evaluation and Research. "This new boxed warning addresses FDA's concerns that despite the warnings and information already listed in the drug labels, these drugs are still being prescribed to patients without careful monitoring for signs of heart failure".

> *"...despite the warnings and information already listed in the drug labels, these drugs are still being prescribed to patients without careful monitoring for signs of heart failure"*

There is an ongoing FDA review related to Avandia and the risk of heart attack; however, at the end of July the FDA's Endocrine and Metabolic Advisory Committee and the Drug Safety and Risk Management Advisory Committee recommended that Avandia continue to be marketed.

Source: FDA News
www.fda.gov/bbs/topics/NEWS/2007/NEW01683.html

Regulatory update for rimonabant

Sanofi Aventis have withdrawn their New Drug Application (NDA) for the drug rimonabant in the USA. However, they will work with the FDA to make their application at a later date, and state that they remain committed to making the drug available in the USA. Ongoing clinical trials involving the drug will continue.

Rimonabant is a member of a new class of drugs that block the CB1 receptors of the endocannabinoid system. The drug is currently approved in 42 countries, and is used for the treatment of overweight and obesity in patients with associated cardiovascular risk factors.

Source: Sanofi Aventis Press Release
www.sanofi-aventis.us/live/us/medias/07B70509-ED2F-4FCE-9533-EDB7187D57AB.pdf