CFS PHOENIX

PHOENIX RISING: A CFS/FMS NEWSLETTER by Cort Johnson	SPECIAL EDITION:LAYMEN'S GUIDE TO THE 8th IACFS CONFERENCE
Subscribe to PHOENIX RISING!	PART III: The IMMUNE SYSTEM, the GUT, PAIN and SLEEP

These overviews do not follow the conference's agenda (fatigue, pain, gender, sleep, etc.). Several of those sessions were undersubscribed and had papers on different subjects shoehorned in to fill them out. In order to obtain a more orderly presentation some new sections (cardiovascular/vascular, Exercise and CFS) are added in this overview while others are retained (Brain, Immune, etc.). Papers that I found most interesting are highlighted. Some overviews are found under more than one category.

THE IMMUNE SYSTEM

Natural Killer Cell Subsection

The Unnatural Natural Killer Cells in CFS (and elsewhere) - Mary Fletcher, Xiao Zeng, Martin Rosenthal and Nancy Klimas. Immunological comparison of GWI and CFS.

Here they are again – the irrepressible Miami group. If there's an NK cell in the vicinity you can bet they'll be all over it. These studies from the Miami group are part of a major effort to examine the clinical, immune, autonomic and neuroimmune status of both Gulf War Illness (GWI) and CFS patients relative to that of controls.

We're just getting an early look at the results. Thus far they're indicating that not only do many Gulf War Vets act like CFS patients (see Epidemiology section) they also test like them. Here they show that the NK cells of both CFS and GWI patients had about half the normal levels of their main cytotoxic factor, perforin. The killing capability of the NK cells in the GWI patients, however, was worse, in fact substantially worse, than that of the CFS patients – which was already pretty bad. They also found that the level of activated NK cells is lower than normal in both CFS and GWI**.**

Klimas, N., Rosenthal, M and M. Fletcher. Immune effects of an acute exercise challenge in Gulf War Illness (poster).

This is another preliminary report from a large study focusing on immune markers and gene expression before and after exercise in GWI, CFS patients and healthy controls. It found that NK cell counts went way up following the exercise period but that T-cell counts remained the same. Unfortunately they don't tell us if this pattern was different in the controls vs. the CFS or GWI illness subjects but this study does show that NK cells are sent into a tizzy after exercise and given the NK cell abnormalities found in CFS this is an interesting finding.

NK Cell Summary – A positive result for NKC dysfunction in GWI is good news - it means we have another potential revenue source for study into what's causing this problem. These studies are another win for the CFIDS Association of America's research program; they, along with the VA, co-funded this study.

This research team is continuing their work on this topic - they were awarded one of the grants in the recent NIH Neuroimmune RFA for CFS. It looks like they were on the right track in that study as well, as Dr. Fletcher indicated that levels of the subject of interest, neuropeptide Y, were decreased in both CFS and GWI patients. This study is really intriguing as it examines a potential link between nervous system dysfunction (sympathetic nervous system) and immune dysfunction (NK cells). The RFA studies will be covered in an upcoming paper.

CONFERENCE HIGHLIGHT

Tracking Down the Genesis of Post-Infectious Fatigue

Toni Whistler, Wiliam Lonergan and Suzanne Vernon. Alterations in apoptosis play a role in Post-Infection Fatigue.

This represents the next step of the Dubbo project, an important CDC and Australian government-sponsored series of studies examining what happens to people as they come down with post-infectious fatigue syndrome (PIFS) or CFS. The ability to identify and study these people in detail suggests the post-infectious subset will be the first in CFS to be deciphered.

This group has been looking a gene expression changes in the entire genome during the course of a year. It has found that people who develop PIFS are hit harder symptomatically by the initial infection and now it is uncovering a possible reason why. It appears their genes involved in apoptosis or cell suicide and mitochondrial functioning are behaving abnormally. Since many viruses replicate inside of cells it is important that infected cells kill themselves before they become a safe haven for virus replication. One of the most important cell suicide triggers is initiated in the mitochondria.

This study found that genes associated with the mitochondrial apoptotic pathway were not turned on in those people who developed CFS. Instead of using the mitochondrial apoptotic pathway to kill the cells infected with the pathogen the PIFS patients used an unusual one involving ceramide signaling. This suggests that the cells in this subset of people with CFS are unable to kill themselves before viruses replicate in them.

This study also indicated there was no activity in the toll-like receptors that are supposed to alert the cells that pathogens are present. Intriguingly the study also found evidence of a boosted anti-inflammatory (IL-10) response. The immune system uses anti-inflammatory cytokines in its efforts to kill extracellular pathogens and pro-inflammatory cytokines in its efforts to kill intracellular pathogens. Since the anti-inflammatory response inhibits the pro-inflammatory response an upregulated IL-10 response could have prevented these patients from mounting as effective an intracellular pathogen search and destroy program. This finding confirms the speculation prompted by an earlier study.

Dr. Whistler also talked of how quickly this technology is changing. She stated the methodology she used in this study had changed in just six to eight months. This study has just been published and will be covered in the next regular issue of Phoenix Rising.

Dr. De Meirleir's theories are looking better and better. He indicated that low mitochondrial apoptotic activity was present in CFS in his 2002 book; CFS A Biological Approach (see Chapter Five – click here), and here we again see mitochondrial issues illuminated.

Dr. De Meirleir's theories also suggest problems with ion channel functioning are present in CFS – another process that the CDC's gene expression studies seem to be confirming. There was a recent report on the internet that Dr. De Meirleir had successfully identified the CFS patients in a blinded set of blood samples sent to him by the CDC. I asked him if this was true. He laughed and said the CDC wasn't interested in his work.

RNASE-L Subsection

I mentioned the big Japanese contingent at the conference but besides the U.K. representatives, who are always present, there was another big foreign presence – the Spanish contingent. Two groups from Spain presented multiple papers and posters on the brain, genes and immune system. We turn next to two of their studies.

J. Alegre-Martin,T. Soriano Sanchez, C. Javierre, J. Quintana, E. Ruiz, T. de Sevilla, K. De Meirleir, and A. Quintana. Associations between biological markers, ergonometric parameters and cognitive function in a cohort of patients.

Study of biological markers, ergonometric parameters and cognitive function in a cohort of patients with Chronic Fatigue Syndrome.

There are two gratifyingly large studies (150 CFS/FM patients) that unfortunately had no control group but were very interesting given what we've seen thus far. The first study found that the majority of the CFS patients had increased rates of RNase L activity (83%), RNase L fragmentation (88%) and a whopping 95% had increased elastase levels. A second study that employed an exercise period found that RNase L activity in CFS was correlated with lactate concentrations, an intriguing finding given the increased lactate levels in the brain found earlier.

Herpesvirus Subsection

DIAGNOSING AND TREATING HHV-6A - Dharam *Ablashi. Overview of HHV-6 in CFS and diagnostic assays for Detecting chronic active HHV-6 and EBV.*

Dr. Ablashi, now 'retired', is the Scientific Director of the HHV-6 Foundation. Much of what he said focused on the activities of that organization.

HHV-6 is not an easy virus to study. Primarily found in the central nervous system (CNS) it is not present in large amounts in the cerebrospinal fluid or the blood even when it is active. This means that even very sensitive PCR tests have difficulty differentiating between active and latent infections.

Physicians, therefore, usually rely on tests that indicate that a strong immune response to HHV-6 is present. These tests measure levels of antibodies that have been produced in response to proteins produced by HHV-6. Even here there is room for error; antibody tests are somewhat subjective and results can differ between laboratories. Setting the threshold at which antibody levels denote active vs latent infections is inherently somewhat arbitrary as well.

Dr. Ablashi stated that a threshold of >1:320 (IgG) at Specialty laboratories suggested an active HHV-6 infection may be present. This degree of antibody activity correlates well with other measures of immune activation including antibody levels to early HHV-6 antigens (EA), antigenemia (persistence of antigen in the blood), avidity analysis (strength of antibody binding), upregulated antiviral pathways, etc. *IgM antibody tests are only accurate early in an infection.* Studies indicate that a very high percentage of CFS patients (@80%) have IgG antibody levels >1:320; i.e. appear to test positive for an active HHV-6 infection.

The HHV-6 Foundation is not, however, satisfied with these tests. Their highest priority is a test that definitively differentiates between active and latent HHV-6 infection. If my notes are correct the Foundation is currently examining two assays (early antigen and PCR test) that appear promising.

The HHV-6 Foundation is also engaged in finding and/or developing effective antiviral agents. Progress in this area has been slow; they have checked out over 60 compounds, only two of which (red marine algae, amantadine) have worked in more advanced testing. Dr. Ablashi noted, however, a variety of antivirals (ampligen, Isoprinosine, alpha 2a interferon (?), acyclovir, valcyclovir, valganclyclovir) that have been successful in small trials. *Three of these will be covered in the Clinical trials session of the conference.*

Susan Levine. Incidence of HHV-6 and EBV infection in Chronic Fatigue Syndrome patients.

The herpesviruses have long been of interest in CFS. Several researchers believe that EBV and HHV-6 reactivation plays an important role in a subset of CFS patients. Questions regarding proper diagnostic procedures have, however, muddied this issue considerably. Dr. Levine's study was designed to bring some clarity to this issue.

Dr. Levine employed a variety of different tests (EBV, HHV-6 – IgG, IgM, PCR; EBV – viral capsid antigen (VCA), early antigen (EA), EBV nuclear antigen (EBNA); HHV-6 – antigenemia), to determine if HHV-6 and EBV reactivation was present in CFS patients, and if it was, to determine the best means of testing for it.

She found that CFS patients tested normally to two common antibody tests (VCA, EBNA) but that about a third of CFS patients - compared to zero controls – tested positive for high levels of antibodies to EBV's early antigen (AG). About a third of the CFS patients also exhibited elevated levels of antibodies to HHV-6 and about 20% were positive in the HHV-6 antigenemia tests vs. zero controls.

PCR tests of the blood lymphocytes indicated that the CFS patients all harbored the HHV-6A virus while the controls harbored the HHV-6B virus. *Several researchers believe that not only are these different viral types but they are completely different viruses and should be denoted as such. (See HHV-6 and CFS).*

Dr. Levine's study, then, presented evidence that a substantial subset of CFS patients have an active chronic low level herpesvirus infection. Antibody tests suggest that HHV-6A is active and replicating in about 30% of CFS compared to zero controls. EBV replication, on the other hand, does not appear to be occurring. Instead this study appears to back up Dr. Glaser's theory that EBV is active enough in CFS to produce immune system altering proteins but is shut down before it can replicate.

Summary - Once again we see that if researchers look closely enough they will see that a significant subset of CFS patients test positive for herpesvirus activation. Just as Dr. Gurbaxani did in his cytokine study Dr. Levine noted that standard means tests would not have picked up the subset of CFS patients with high antibodies to EBV and HHV-6.

A NEW VIRAL DISEASE MODEL? - *Ronald Glaser, Monica Litsky, Marshall Williams, Stress, Chronic Fatigue Syndrome and viral latency.*

There is a great deal of evidence that both the immune and the stress response are involved in CFS. Dr. Glaser's theory regarding EBV and HHV-6 activation ties these two subjects closer than any I am aware of.

We will see evidence that antiviral treatment in CFS can be effective in those patients with high antibody titers to EBV and HHV-6. But what about CFS patients who don't display evidence of viral reactivation but still appear to have immune problems? Are pathogens still involved? Dr. Glaser's theory suggests that they may be. He believes that the immune system in many CFS patients works well enough for them to prevent these pathogens from replicating but not well enough to stop them from pumping out injurious proteins, and that it is these proteins that are causing CFS.

What is the weak link in the CFS immune system? A predominant Th2 cytokine response may leave some CFS patients particularly susceptible to EBV reactivation. EBV hides out in the very cells that dominate the Th2 cytokine response – the B cells – and it uses these cells to replicate. Some CFS patients experience another condition that may make them particularly susceptible to EBV reactivation – high rates of stress. Several studies suggest that CFS patients encountered unusually stressful conditions just prior to their becoming ill. Many studies have shown high rates of EBV reactivation occur even in healthy people when they are unusually stressed. Dr. Glaser believes these factors make CFS patients ripe for a type of EBV reactivation that has been difficult to spot.

The key player, Dr. Glaser believes, is a protein called EBV dUTPase that EBV produces early in its life cycle. This protein provokes monocytes/macrophages to pump out pro-inflammatory cytokines (TNF-a, IL-1. IL-8, IL-6 as well as IL-10) that are able to produce many of the symptoms found in CFS. He has found increased dUTPase levels in a significant subset of CFS patients. He has also just identified an HHV-6 protein that may perform a similar function.

Low antibody levels to EBV do not, therefore, necessarily indicate that an EBV associated disease process is not occurring in a CFS patient.

LYME INFECTION RATES IN CFS PART I: *Garth Nicolson – Chronic bacterial co-infections in Chronic Fatigue Syndrome and Chronic Fatigue Syndrome patients subsequently diagnosed with Lyme disease.*

Dr. Nicolson was another impressive speaker. He has been involved in elucidating pathogen prevalence in CFS for many years now. *Some researchers lost interest in pathogens when they failed to find the pathogen that caused CFS. It's clear now that no one pathogen causes CFS.* We know that CFS patients are more susceptible to viral reactivation and bacterial and viral infection than are healthy people but we didn't really know how much more susceptible until now. Dr. Nicolson apparently added up all the numbers and found that CFS **18x's** more likely to harbor a pathogen than expected!

Dr. Nicolson also presented the first data on Lyme prevalence in CFS. Dr. Nicolson noted that ticks carry a number of different diseases, then indicated that he found that that 9% of Western U.S and a higher percentage of Eastern U.S. CFS patients tested positive on a Western Blot test for *Borrelia burgdorfii* antigens. These patients appeared susceptible to multiple infections as about 2/3rds of them also tested positive for a mycoplasma infection.

LYME INFECTION RATES IN CFS PART II: *Aristo Vojdani, Bernard Raxlen. In vivo induced antigen technology for detection of antibodies against Borrelia burgdorferi and its cross-reactive antigens in patients with Chronic Fatigue and Fibromyalgia (poster)*

As with some other pathogens associated with CFS the diagnostic capability of the different Lyme tests has been in question. Here Dr. Vodjani introduces a new test for Lyme disease called *In Vivo*-Induced Antigen Technology (IVAT) that identifies antigens or immune reactive proteins produced by *Borrelia* infections. *An antigen is something that provokes the immune system. Many pathogenic tests look not for the pathogen itself but for indications that the immune system has been activated by an infection. The test Dr. Vodjani is describing appears to be looking for specific proteins that Borrelia produces.*

Dr. Vodjani subjected 206 samples from CFS and Fibromyalgia patients to two Lyme tests; the ELISA and Western Blot (WB) tests and the new IVIAT multiple peptide-based ELISA (IVIAT-MPE) test. He found a much higher rate of positivity – about 45% (92/206 samples) using WB than Dr. Nicolson did. *Hence the questions regarding the efficacy of these tests! Were Dr. Vodjani's patients from a Lyme hotspot? Or are the tests just unreliable?* The IVIAT-MPE was positive in almost all of these as well (88/92).

The IVIAT-MPE test was also positive in a high percentage (32/42) of the WB tests with equivocal results AND it was positive in a good number of the samples the WB test found were negative (26/44). All told the IVIAT-MPE test was positive in almost 60% (146/206) of the CFS/FM samples.

Does this mean that 60% of CFS patients have Lyme disease? Not necessarily so. Dr. Vodjani indicates that the IVIAT-MPE test "*detects antibodies against unrelated peptides and proteins of different infectious agents*". He further notes that because of this physicians must make sure that other spirochetes such as *Yersinia entercolitica, Brucella, Chlamydiae pneumoninae, Ricketssia ricketsii* and even the glutathione-S-transferase protein need to be excluded before a physician begins on a protocol of long term antibiotic treatment to attack the Lyme pathogen. He suggests that this test should be used in combination with the Western blot test.

THE GUT STUDIES

CONFERENCE HIGHLIGHT

An Old Pathogen in a New Place

John Chia, Andrew Chia. Chronic Fatigue Syndrome is associated with persistent enteroviral infection of the stomach.

One of the more impressive speakers at the conference, Dr. Chia gave a direct and articulate presentation on enteroviruses and CFS. Researchers have looked for enteroviruses in the muscles and blood of CFS patients before but this is the first time I am aware of that anyone has looked in the guts of CFS patients.

In this study Dr. Chia took biopsies from 108 CFS patients with abdominal complaints, stained them with a monoclonal antibody for an enteroviral protein, noted the degree of inflammation present, and then classified them according to how much staining they displayed (rare or zero staining, 1-50%, >50% stained).

Dr. Chia found almost all the CFS biopsies (92%) showed evidence of mild chronic inflammation, and enteroviral presence (80%) compared to 10% of healthy controls. About half the CFS biopsies exhibited high antibody levels with 30% exhibiting intermediate ones.

This presentation was quite impressive visually with the deeply stained CFS slides alternating with the lightly stained healthy controls. Dr. Chia noted that antiviral drug administration (interferon-a, ribivarin, interferon-a/y) was able to resolve many of the patients complaints and eliminate enteroviral RNA from their leukocytes but that they

relapsed when the drug was discontinued. He believes that controlled trials with newer antiviral drugs will prove that enteroviruses are a significant pathogenic agent in CFS.

Kenny De Meirleir. P. De Becker, L. De Leerssnijder, L. De Meirleir. Lactose Intolerance and/or fructose malabsorption: a predisposing factor for the development of CFS? (poster)

We saw Dr. De Meileir highlight gastrointestinal issues in the patient conference. Here he presents the results of a large study (200 CFS patients) that examined how well CFS patients were able to break down two common sugars; lactose (milk sugar) and fructose (fruit sugar).

Dr. De Meirleir believes many of the problems in CFS originate in the gut (click here for patient conference).

CFS patients were given a hydrogen breath test every 30 minutes for 3 ½ hours after ingesting either a lactose or fructrose solution. High amounts of hydrogen in the breath indicate incomplete breakdown of these products. They suggest the patient is suffering from malabsorption syndrome. Twenty percent of the patients tested positive for lactose deficiency and 45% tested positive for fructose malabsorption. About 10% of these patients tested positive for bacterial overgrowth.

Brigitta Evengard. Comparison of the composition of the intestinal microflora of CFS patients when in the acute phase of illness (poster).

Dr. Evengard compared the overall levels of anaerobic/aerobic bacteria and staphyloccal, *Clostridum* and *E. Coli* bacteria and *Candida albicans* yeast in fecal samples of 20 CFS patients either in the acute phase (really sick) or in remission. CFS patients not in remission had higher levels of *Candida albican* than those in remission.

A. Sullivan, C Nord, B. Evengard. Effect of supplement with lactic-acid producing bacteria on fatigue and physical activity in patients with Chronic Fatigue Syndrome (poster).

In a recent edition of Phoenix Rising we saw *Lactobaccillus acidophillus (LA)* bacteria improve immune functioning in people with overtraining syndrome (**click here**). Here Dr. Sullivan states that LA can 'normalize the cytokine profile' and has anti-oxidative effects. In this conference we have seen increasing evidence that if CFS is not an inflammatory disease, that it at least has a strong inflammatory component. These researchers gave a probiotic product (Cultura Dofilus Natural Yoghurt, Arla Foods) to 15 CFS patients for 30 days and found that 40% of them reported improvement. *If this is simply a yogurt product its interesting that such a weak formulation would be helpful; lactobaccillus capsules, which are readily available in health food stores, contain far more probiotics than does yogurt.*

Gut Summary: Dr. Chia's finding that gut tissues of CFS patients commonly exhibit mild inflammation and enterovirus infection suggests that this hitherto understudied aspect of CFS should be better studied. We heard Dr. De Meirleir state in the Patient Conference that he believes gastrointestinal problems play a role in initiating CFS. Dr. Cheney has in the past called the gut the most toxin area of the body. The above studies suggest that the gastrointestinal environment in CFS is not healthy and that measures such as avoiding sweets and enhancing the natural gut flora can be helpful. Given that a substantial subset of CFS patients have problems absorbing fructose, it was perhaps not surprising that ill CFS patients have higher levels of a carbohydrate loving yeast, Candida albicans, than CFS patients who are in remission. This jibes with self reports from CDC Wichita studies indicating a very high incidence of yeast infection (50%) in women with CFS.

THE PAIN SESSION

The Pain Session was undersubscribed as it featured only one paper that was actually on pain. It did, however, contain both an excellent introduction by Karen Berkeley and overview by Dr. Clauw.

Daniel Clauw, Pain Session Summary: *State of the Art With a CFS Perspective (from the abstract).*

Dr. Clauw won the award for articulately covering the most information in the shortest amount of time. Most of his presentation concerned fibromyalgia (FM) but Dr. Clauw clearly believes that CFS is akin to FM in some ways and shares some of the same pathophysiology.

Dr. Clauw believes that sensory amplification plays at least something of a role in the so-called 'somataform disorders' (CFS, FM, TMJ and others). These disorders whose symptoms, at least at this point, are largely unexplained are not uncommon, effecting about 4% of the population. He noted that many symptoms and syndromes are associated with FM including migraine, tension headache, TMJ, CFS, sleep disorder, IBS, idiopathic low back pain, MCS, mitral valve prolapse, non-cardiac chest pain, shortness of breath due to respiratory muscle movement dysfunction, vulvodynia, etc. Of these FM exemplifies the prototypical chronic central (central nervous system) pain state.

He believes FM is caused by a dysfunctional sensory process apparatus in the brain and spinal cord characterized by both reduced pain inhibition and increased pain amplification processes. The sensory problems in FMS are not limited simply to pain but extend to other stimuli such as heat/cold and noise. Several areas of the brain are affected *almost all of which have been mentioned in association with CFS* including the somatosensory cortices, anterior cingulate, thalamus, prefrontal cortex, amygdala, and anterior insula. Besides problems with sensory processes, again - similar to CFS - the autonomic nervous system and neurendocrine system are affected in FM.

There is strong evidence that genetics plays a role in FMS. Interestingly several of the genes Dr. Clauw highlighted (serotonin transporters, dopamine receptors, COMT) are have been highlighted by CFS researchers as well. *But see the Fructuoso paper in the Gene Section of the Conference Overview for evidence of genetic differences in these diseases (click here).*

Several stressors, some also found in CFS, are known to trigger FM, including infection, physical injury, hormonal problems (hypothyroidism, *hypocortisolism?),* psychological stress, drugs, peripheral pain syndrome, vaccines and war.

Both physiological and psychological factors play a role in at least a subset of FM patients.

Dr. Clauw believes that the emphasis on tender points as a diagnostic criteria for FM has highlighted both an aspect of FM and a subset of FM patients that are not representative of the disease. The emphasis on tender points suggests a muscle disorder is present – which is not true – and spotlights one segment of the FM population, largely unfit females with high rates of distress and 'catastrophizing'. *Castrophizing involves a process in which dwelling on ones symptoms results in their amplification.*

He identified three psychologically based subsets of FM patients;

- Psychological makeup does not effect symptoms – this group has low rates of depression and anxiety, not very tender tender points, low catastrophizing and moderate control over their pain.
- Psychological makeup exacerbates symptoms – this group has high rates of depression and anxiety, high catastrophizing, very tender tender points and no control over pain.
- Psychological makeup improves symptoms – extremely tender tender points but low rates of depression, anxiety, very low catastrophizing, high control over pain.

Treatment – Dr. Clauw uses both pharmacological and non-pharmacologica treatments in his practice. Pharmacological treatments are used to improve the symptoms caused by the altered sensory processing and/or inflamed tissues found in FM. Non-pharmacological

therapies address the by-products of these symptoms, i.e. the distress, reduced activity, isolation, poor sleep and maladaptive illness behaviors that often found in conjunction with a chronic pain state.

Pharmacological Treatment – Dr. Clauw has found strong evidence for the efficacy of tricyclic compounds such as amitryptyline, cyclobenzaprine), SNRI's and SSRI's (gabapentin, pregabalin); modest evidence for tramadol and SSRI's; weak evidence for growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe), and no evidence for opiods, corticosteroids, nonsteroidal anti-iflammatory drugs, benzodiazepine and nonbenzodiazepine hypnotics and *the popular remedy* guanifenesin. He noted that nearly any class of drug that raises both serotonin and norepinephrine has demonstrated efficacy in FM.

Non-pharmacological Treatment – There is strong evidence that education, aerobic exercise and cognitive behavior therapy are helpful; modest evidence for strength training, hypnotherapy, biofeedback; weak evidence for acupuncture, chiropractic, manual and massage therapy, electrotherapy and ultrasound and no evidence for tender point injections and flexibility exercise. *No evidence for stretching? Dr. Klimas that stretching was important for her CFS/FM patients.*

Exercise – he stated that exercise is nearly universally beneficial. *Its too bad he didn't get into this further. Exercise studies have had positive results in F but they are not talking about running marathons; these are low impact exercises that start out in small and slowly build over time.* Dr. Clauw said the biggest problems with exercise were tolerance and compliance.

Cognitive behavior therapy – Dr. Clauw observed that CBT has been shown to be effective for nearly any chronic illness and that not all CBT regimes are the same and that their success is practitioner and approach dependent. He showed a chart showing that CBT regimes can be very effective in increasing activity levels, moderately effective in reducing sensory pain and not very effective in reducing 'affective pain'.

Overall Treatment Approach – His overall treatment approach is to identify and treat problems in the periphery (body) that may be causing pain. For patients who need or want pharmaceuticals he starts with low doses of mixed tricyclic antidepressants (TCA's) (amitriptyline, cyclobezaprine). His motto is to start low and go slow.

If the patient tolerates the TCA's but still needs more help he adds mixed reuptake inhibitors (e.g. venlafaxie, duloxetine) or SSRI's perhaps in higher doses. If more pain inhibition is needed he adds pegabalin, gabapentin, tramadol, tizanidine.

If patients do not tolerate TCA's he uses zolpidem, zaleplon, trazodone.

In all patients he aggressively introduces non-pharmacological therapies.