Can we individualize antidepressive treatment depending on clinical subtypes? Anxious vs. non-anxious depression in the German Algorithm Project (GAP)

M. Adli1, K. Wiethoff1, T.C. Baghai2, D. Hollinde1, T. Stamm1, H.J. Möller2, M. Bauer1

1Department of Psychiatry and Psychotherapy, Charité-Universitätsmedizin Berlin, Charité Campus Mitte
2Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-Universität Munich

Implementing treatment algorithms in the clinical care of patients suffering from major depressive disorder (MDD) is considered as an important instrument in increasing treatment efficacy, independent from the clinical subtype of depression. The German Algorithm Project GAP has evaluated algorithm-guided treatment of inpatients with MDD. Phases I (open observational trial) and II (randomized controlled trial) demonstrated the feasibility and efficacy of a standardized stepwise drug treatment regimen (SSTR) compared to treatment as usual (TAU). Anxious depression defined as MDD with a high level of anxiety symptoms is regarded as a common subtype of depression. We present the results of the recently finished third phase (GAP III) with regard to differential efficacy of algorithm-guided treatment in anxious vs. non-anxious depression.

GAP III compared an SSTR and a computerized documentation and expert system (CDES) with TAU in 429 inpatients treated for MDD in a five-arm multicenter randomized controlled trial. We performed multivariate cox regression analysis as well as an analysis of interaction to identify differential response patterns in clinical and sociodemographical subgroups of patients. In addition, we searched for an association of the 50-T/C SNP of the glycogen-synthase-kinase 3beta (GSK3B) gene with response to lithium augmentation in non-responders to an initial antidepressant monotherapy (n=81). A baseline Hamilton Rating Scale for Depression (HAMD-21) Anxiety/Somatization factor score of $\geq 7$ was considered indicative of anxious depression.

The prevalence of anxious depression in this study was 48.6%. Patients with anxious MDD were significantly more likely to be older and prematurely retired and to endorse higher subjective symptom severity. Anxious MDD was associated with longer duration of the current episode. Compared to TAU, SSTR treatment was associated with a significantly higher probability of achieving remission (HR: 1.5; p=.01) but not CDES (HR: 1.06; p=.81) in the total population. We did not identify any significant confounding factor or statistical interaction which would be suggestive of differences in response to algorithm-guided treatment for any clinical subgroup. We found a significant association of the response to lithium augmentation in treatment-resistant patients with the GSK3B 50T/C SNP (HR: 2.7; p=.007).

Algorithm-guided treatment of depression following an SSTR increases efficacy of antidepressive pharmacotherapy independent from the clinical subtype. A genotype-based
modulation of treatment pathways may represent an option to tailor algorithm-guided treatments to individual needs.

German J Psychiatry 2006; 9: S2

Anticipating emotional visual stimuli in social anxiety disorder – an fMRI study
A. Brüh1, M. Rufer2, A. Delsignore2, L. Jäncke3, U. Herwig1

1Division of Psychiatry Research and Psychogeriatric Medicine, Psychiatric University Hospital, Zürich, Switzerland, 2Department of Psychiatry, University Hospital, Zürich, Switzerland, 3Department of Neuropsychology, University of Zürich, Switzerland

Background: Fear in patients with phobic anxiety disorder can be interpreted as a negative bias towards upcoming events: Patients expect specific situations to be bad, threatening, and giving reason for fear. To identify functional neurobiological differences between patients with anxiety disorders, in particular in those with social anxiety disorder, and healthy subjects, we used a paradigm that specifically assessed the anticipation of emotional events: Emotional pictures taken from the IAPS were announced by simple visual cues (negative, positive, neutral, unknown) during functional magnetic resonance imaging. Our hypothesis was to observe an increased activity during the expectation of stimuli with negative and unknown emotional content compared to the neutral and the positive condition.

Method: Eight outpatients with social anxiety disorder and fourteen healthy control subjects underwent functional MRI viewing a task of 56 emotional pictures after an anticipation period.

Results: The patients with social anxiety disorder showed in comparison to healthy control subjects increased activity during anticipation of negative and unknown emotional pictures in bilateral anterior insula, left medial prefrontal cortex (MPFC), left bed nucleus stria terminalis (BNST) and right hippocampus.

Discussion: We revealed differences in brain activation between anxiety-patients and healthy controls implying a more ‘pessimistic’ or ‘fearful’ anticipation of events with unknown emotional valence.

Guidance of facilitating rTMS treatment with functional Near-Infrared Spectroscopy (fNIRS) in panic disorder
A. J. Fallgatter, M.M. Plichta, A-C. Ehlis, M. M. Richter, J. Deckert

Department of Psychiatry and Psychotherapy, University of Wuerzburg, Germany

Current research in patients with anxiety disorders suggests functional deficits within the prefrontal cortex, which result in reduced inhibition of the amygdalae, in turn accounting for increased fear perception in these clinical populations. Principally, such a pathophysiological model would allow to positively influence the supposed prefrontal hypofunction via repetitive transcranial magnetic stimulation (rTMS) in a facilitating mode (high-frequency stimulation). Such a facilitating treatment may strengthen the inhibitory activity of the prefrontal cortex, resulting in a better control of panic-associated amygdalae hyperactivity and, in turn, in a reduction of panic attacks.

Based on this theoretical framework, we propose the application of a non-invasive optical imaging technique (functional Near-Infrared Spectroscopy; fNIRS) for the measurement of anxiety-related hypoactivity of the prefrontal cortex, and for the control of a treatment success on the brain metabolic level. In a single patient with panic disorder we could detect a pattern of hypoactivity in the prefrontal cortex during an emotional Stroop task. Facilitating rTMS treatment (15 sessions within three weeks, add-on) was associated with (1) an improvement of prefrontal activity in the emotional Stroop task and (2) with the absence of further panic attacks. This is the first report of a NIRS-guided and –controlled facilitating rTMS treatment of a patient with a panic disorder. Given the excellent clinical applicability of the methods, the combination of fNIRS and rTMS might have the potential to establish new treatment options in psychiatry aiming on the modulation of pathological regional brain activity patterns.
In both humans and animals, anticipation of aversive stimuli (e.g., electric shocks) can lead to two types of aversive states: A phasic fear response if the aversive stimulus is signaled by a threat cue (explicit cued fear) or a more sustained anxiety state to the experimental context (contextual anxiety), especially when the aversive event is unpredictable. The understanding of the neurobiology of cued fear and contextual anxiety may help to elucidate the pathophysiology of anxiety disorders in humans. While specific phobia is an example of a cued fear disorder, general anxiety disorder is prototypal of contextual anxiety. There is now experimental evidence based on startle studies to suggest that sustained contextual anxiety may be also relevant to disorders such as posttraumatic stress disorder and panic disorder. The goal of this study was to compare cerebral blood flow (CBF) associated with cue and contextual anxiety. Unpleasant electric shocks were administered predictably (i.e., signaled by a cue) and unpredictably to 17 healthy volunteers. [O-15]H2O PET imaging was used to measure CBF. Presenting a cue in a threat condition was associated with increased CBF in the left amygdala. A cue predictive of a shock was specifically associated with CBF increases in the ventral PFC, the hypothalamus, ACC the left insula, and left and right putamen. The threat context increased CBF in the right hippocampus, the left and right striatum, the middle cingulate cortex, the PAG, the thalamus and the occipito-parietal cortex. The context of an unpredictable threat was specifically associated with CBF increases in the subgenual PFC. Brain regions associated with sustained anxiety showed important structural and functional abnormalities in prior studies on mood and anxiety disorders.

We do not know what future will provide. An essential strategy to cope with upcoming events of potentially or certainly unpleasant emotional impact is to perform a cognitive control of the situation. By using functional magnetic resonance imaging we examined the involved brain regions while performing a psychotherapeutic intervention for stopping negative expectations. Two groups of healthy subjects were biased to expect and then to perceive visual stimuli with known emotional valence (pleasant, unpleasant, neutral), and stimuli of unknown valence that were either pleasant or unpleasant. One group was instructed just to expect the stimuli and to be aware of concomitant emotions. The other group was instructed to exert a cognitive control strategy in the sense of a reality check during the unpleasant and unknown expectation conditions, not before pleasant and neutral. This strategy consisted in a trained standard intervention derived from cognitive behavioral therapy for anxiety disorders. In the analysis (each group n=14), we compared the control condition with the native condition during expectation of the unpleasant and the negative events. While expecting negative stimuli, the ‘cognitive control’ group showed compared to the native group higher activity particularly in medial frontal cortex areas and the left dorsolateral prefrontal cortex, but reduced activity in the left amygdala, left lateral geniculate gyrus (LGN) and left fusiforme cortex. While expecting the stimuli of unknown emotional valence, the ‘cognitive control’ group showed no higher activity but as well reduced activity in the amygdala. The results implicate that in particular while expecting certainly unpleasant events, cognitive control may be exerted by prefrontal cortical areas that inhibit emotion processing brain areas as the amygdala, and, notably in early perception processing areas as the LGN. Relatively reduced activity in amygdala and other brain areas associated with cognitive control was also found during expectation of events of unknown valence. Principally, we add evidence for the possibility to demonstrate neurobiological correlates of psychotherapeutic interventions. The applied cognitive control strategy was shown to be efficient in terms of attenuating brain activity found to correlate with the level of anxiety.
The therapeutic alliance and treatment outcome in cognitive behaviour therapy of generalized anxiety disorders: differences between therapist-patient-alliance, patient-therapist-alliance, mutual therapeutic alliance and therapist-patient-concordance

C. Müller, T. Bär, D. Zubrägel, M. Linden, B. Muschalla

Research Group Psychosomatic Rehabilitation of the Charité University Medicine Berlin and Rehabilitation Center Tel-tow/Seehof, Germany

Background: The therapeutic alliance is of great importance in psychotherapy. The question is whether there is a relation between alliance and outcome. Alliance is not a uniform concept but there are different views: the alliance of therapist to patient, the alliance of patient to therapist, the therapist-patient-concordance and the mutual therapeutic alliance as rated by an observer.

Method: In a study on the treatment of generalized anxiety disorders by cognitive behaviour therapy therapist-patient alliance (the view of the therapist), patient-therapist alliance (the view of the patient), and mutual therapeutic alliance (the view of an observer) have been measured. Additionally therapist-patient-concordance, the similarity between patient and therapist ratings on their mutual relationship has been calculated.

Results: Cognitive behaviour therapists reach high positive scores in all perspectives for all dimensions of therapeutic alliance, such as empathy, transparency, focusing and cooperation. Correlations are significantly higher for ratings between therapist and patient than between observer and patient. A relation with outcome (measured with the Hamilton Anxiety Scale) was only found for observer ratings.

Conclusion: Different perspectives should be considered and taken into account when discussing the therapeutic relationship. The different dimensions of therapeutic alliance are related, but not identical. Although cognitive behaviour therapists are often said to have a more technical orientation, they nevertheless do also have a good relation to their patients. The connection between therapeutic alliance and therapy outcome is not linear but rather complex in nature.

References:

Workplace-related anxieties and general anxiety disorders

B. Muschalla, M. Linden

Research Group Psychosomatic Rehabilitation of the Charité University Medicine Berlin and Rehabilitation Center Tel-tow/Seehof, Germany

Background: Workplaces are anxiety-provoking from their very nature: there are social hierarchies and concurrence, sanctions and demand for achievement. In this context workplace phobia can emerge and cause sick leave. The question is whether workplace-related anxieties occur independent from "general", i.e. workplace-unrelated anxiety disorders.

Method: In 132 inpatients of a psychosomatic rehabilitation centre workplace-related anxieties and mental disorders in general were examined by a standardized clinical interview.

Results: 54% of the patients reported about anxieties in general as well as in their special workplace-situation, 14% did only suffer from anxieties at their workplace. Different forms of workplace-related anxieties were observed: workplace phobia, workplace-related panic, workplace-related post-traumatic stress disorder, workplace-related specific social phobia, workplace-related unspecific social phobia, workplace-related anxieties of insufficiency and exploitation, workplace-related hypochondriac anxieties, workplace-related generalized anxiety and workplace-related specific worrying (fears of existence).

Conclusion: Workplace-related anxieties are disorders which can result in disability. To understand their development and symptomatology one has to take into account the workplace-situation. Workplace-related anxieties may occur independent from other anxiety disorders. However, workplace-unspecific anxiety disorders may also lead to workplace-related anxieties and therefore get a new quality.

References
Role of the mineralocorticoid receptor in anxiety, cognition, and HPA axis regulation: studies in healthy men and patients with PTSD

C Otte¹, C Muhtz¹, S Moritz¹, S Daneshkhah¹, M Koop¹, A Madrischewski¹, S Bettinger¹, A Yassouridis², K Wiedemann¹, M Kellner¹

¹Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf
²Max Planck Institute of Psychiatry, Munich

Alterations of the Hypothalamic-Pituitary-Adrenal (HPA) axis leading to cortisol dysregulation are involved in mood and anxiety disorders. Cortisol exerts its effects via two different receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). Animal studies have shown that blockade of MR has anxiolytic effects and impairs several aspects of cognitive function. Furthermore, an increase in hippocampal MR density after psychological stress has also been demonstrated in animals but no studies exist in humans. In a series of studies, we examined the role of MR in cognition, experimentally-induced panic, and HPA regulation in healthy men and in patients with posttraumatic stress disorder (PTSD). In healthy men, blockade of MR with spironolactone increases baseline cortisol secretion and impairs cognitive function but has no effect on experimentally induced panic symptoms. The domains of cognitive function that are impaired after blockade of MR in men, i.e. selective attention, visuospatial memory, and mental flexibility/set shifting appear to be remarkably similar to those described in animal studies. No alterations of MR function were found in two different studies with patients suffering from PTSD compared with healthy controls. Limitations and implications of our findings as well as future directions will be discussed.

References

Otte et al. (in press), Blockade of the mineralocorticoid receptor in healthy men: effects on experimentally induced panic symptoms, stress hormones, and cognition, Neuropsychopharmacology

Otte et al. (in press), Mineralocorticoid receptor function in posttraumatic stress disorder after pretreatment with metyrapone, Biological Psychiatry


Disgust sensitivity – central to a range of clinical disorders

S. Rohmann, S. and H. Hopp

Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany

There is a lack of experimental psychophysiological investigation in disgust sensitivity. The present study was concerned with the question if subjects high and low in a disgust sensitivity show different responses to a disgust inducing film.

160 students classified according to the Questionnaire of Disgust Sensitivity (FEE, Schienle al., 2004) into high and low disgust sensitive subjects (FEE+/ FEE-) were exposed to a disgust-inducing film. Their physiological, subjective, facial, and coping responses were assessed.

FEE+ showed more psychophysiological disgust responses than FEE-: They showed more pronounced increases in electrodermal activity and cortisol in saliva, reported more disgust and reduction of well-being, and showed more facial disgust expression. Furthermore, FEE+ used fewer defensive coping strategies than FEE-.

These results are of clinical relevance, since a disturbed perception and processing of disgust relevant cues plays a central role in some clinical disorders like specific phobia (e.g. spider phobia, blood phobia), compulsive disorders, and eating disorders.

Symptom dimensions in obsessive-compulsive disorder: temporal stability and predictive value for treatment outcome

M. Rufer, S. Fricke, S. Moritz, I. Hand

¹UniversitätsSpital, Department of Psychiatry, Zürich, Switzerland
²Universitätsklinikum Eppendorf, Klinik für Psychiatrie und Psychotherapie, Hamburg, Germany

Background: Considerable advances have been made in subtyping obsessive-compulsive disorder (OCD) based on factor-analysed symptom dimensions. In particular, if these symptom dimensions are temporarily stable, it would be valuable to evaluate their predictive value for treatment outcome. Therefore, we examined in two prospective studies (a) the temporal stability of OCD symptom dimensions over six years, and (b) whether these symptom dimensions were associated with the outcome of cognitive-behavioral therapy (CBT).

Methods: In the first study, 43 of 54 OCD patients (80%) were re-assessed with the clinician-rated Yale-Brown Obses-
sive–Compulsive Scale symptom checklist (Y-BOCS-SC) after 6 years on average. In the second study, symptoms of 104 inpatients with OCD were assessed with the Y-BOCS-SC before and after CBT (alone or plus a serotonin reuptake inhibitor).

Results: Over the 6-year follow-up period, significant changes occurred within the symptom dimensions aggressive/checking, symmetry/ordering, and contamination/cleaning, whereas the others (hoarding, sexual/religious) remained unchanged from baseline to follow-up. Shifts between different dimensions from baseline to follow-up were rare; the score of each dimension at follow-up was most strongly predicted from the score of the same dimension at baseline. Concerning the predictive value of symptom dimensions, regression analyses revealed that higher mean scores on the hoarding dimension predicted poorer CBT outcome, even after controlling for symptom severity, depression and concomitant medication.

Conclusions: Symptom dimensions seem to be remarkably stable over several years in adult OCD, despite a significant reduction in OCD severity. Furthermore, our results strongly indicate that inpatients with obsessive-compulsive hoarding respond poorly to CBT. Thus, modified or new treatments for this OCD patient group need to be developed to improve their outcome.

German J Psychiatry 2006; 9: S6

Proof of concept studies in anxiety: the academic perspective

R. Rupprecht, D. Eser, C. Schüle, T.C. Baghai

Department of Psychiatry, Ludwig-Maximilian University Munich

There is considerable need for novel anxiolytic compounds. Such compounds should be fast acting anxiolytic agents, which lack the side effects of benzodiazepines such as sedation, tolerance development and abuse liability. Proof of concept studies should be suitable to translate data gained from animal studies into the clinical situation. The induction of anxiety, e.g. by pharmacological means such as cholecystokinin tetrapeptide (CCK-4), offers the possibility to evaluate novel anxiolytic compounds already in phase I proof of concept studies. This would be a tremendous advantage concerning timelines until large scale clinical development and minimize the risk for a development failure. As such proof of concept studies have go/no go character for further development, such studies superimpose large scale responsibility to academic institutions. Institutions should be prepared to guarantee a sophisticated logistics and personnel for such studies. Usually, a close collaboration with a clinical research organisation is required. Responsibilities between the institution, the sponsor and the CRO should be settled in detail prior to the study. Such studies may constitute a valuable fund raising instrument for the institution and the CRO, provided the budget plan is carefully executed. Moreover, they offer the unique possibility to translate scientific results into clinical research at a very early stage. On the other hand, publication issues are usually handled according to the communication rules of the sponsor. Finally, an example of a proof of concept study for a novel anxiolytic compounds will be presented thereby illustrating the academic perspective of such a joint venture.
applied to be influenced more strongly by the degree of depression.

Conclusion: Strong focus should be placed on anxiety when considering the multidimensional treatment of depression, especially after recovery from depressive symptoms. Anxiety is correlated with neuropsychological impairment (visual working memory). Further studies are necessary to investigate the correlation between anxiety and cognitive symptoms in the long-term course of depression.

German J Psychiatry 2006; 9: S7

Effects of exogenous glucocorticoid treatment on heart rate reactivity in patients with social phobia during a psychosocial stress test

A. Steiner, A., L.M. Soravia1, U. Ehlert1, D. J.-F. de Quervain2, & M. Heinrichs1

Institute of Psychology, Department of Clinical Psychology and Psychotherapy, University of Zurich
Division of Psychiatry Research, University of Zurich

Social phobia is characterized by excessive fear and avoidance of exposure to social situations that involve potential scrutiny by others. When confronted with a fearful situation, negative self-evaluative thoughts are associated with memories of past social failures and negative beliefs of how they will perform. We could recently show that exogenously elevated glucocorticoid levels are able to reduce fearful memories in patients with social phobia. The main objective of this project was to identify the effects of a pharmacologically elevated cortisol level on heart rate reactivity in patients with social phobia. Twenty-one male patients who fulfilled DSM-IV criteria for a diagnosis of generalized social phobia were exposed to a standardized socio-evaluative stress test (Trier Social Stress Test). In a placebo-controlled double-blind design, all participants were randomly assigned to receive orally 25mg of cortisone or placebo one hour before stress exposure. In addition to repeatedly measured psychological parameters (anxiety, mood), endocrine parameters (salivary cortisol) and heart rate were assessed. The results showed that during the stress test heart rate significantly decreased in the cortisol group while no such effect occurred in the placebo group.

German J Psychiatry 2006; 9: S7

Physical activity and the prevalence and incidence of mental disorders in adolescents and young adults


Department of Psychiatry and Psychotherapy, Charité – University Medicine Berlin, Campus Charité Mitte, Berlin, Germany

Background: Regular physical activity can reduce the risk for some major medical disorders. Although positive effects of physical activity on mental health indicators have been reported as well the relationship of physical activity and the development of specific mental disorders is unclear.

Methods: Cross-sectional (12-month) and prospective-longitudinal epidemiological study over 5 years (3 waves) in a community cohort of N=2548 individuals, aged 14-24 years of age at outset of the study. Physical activity and mental disorders were assessed by interview using the DSM-IV-CIDI with an embedded physical activity module. Multiple logistic regression analyses controlling for age, gender and educational status were used to determine the cross-sectional and prospective associations of mental disorders and physical activity.

Results: (1) Cross-sectionally, regular physical activity was associated with a decreased prevalence of any and comorbid mental disorders, due to lower rates of substance use disorders, anxiety disorders and dysthymia. (2) Prospectively, subjects with regular physical activity had substantially lower overall incidence of any and comorbid mental disorders. Further, a lower incidence of anxiety, somatoform and dysthymic disorder, not however for substance use disorders was found. (3) In contrast, incidence of bipolar disorder was increased among those with regular physical activity at baseline. (4) In terms of the population attributable fraction the potential for preventive effects of physical activity appeared to be considerably higher for men as compared to females.

Conclusions: Regular physical activity is associated with a substantially reduced risk for some, but not all mental disorders and seems to also reduce the degree of comorbidity. Further examination of the evidently complex mechanisms and pathways underlying these associations might reveal promising new targets and procedures for targeted prevention.
Impact of multidrug-resistance gene 1-type p-glycoprotein (ABCB1-type P-gp) inhibition on neuroendocrine and behavioral responses to stress

C. K. Thoeringer1,2, T. Wultsch1, A. Shahbazian1, M. Mitrovic1, M. Edelsbrunner1, E. Painsipp1, and P. Holzer1

1Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Austria
2Max Planck Institute of Psychiatry, Munich, Germany

The multidrug-resistance gene 1-type p-glycoprotein (ABCB1-type P-gp) is considered to be a major gatekeeper at the blood-brain barrier protecting the central nervous system against the accumulation of toxic xenobiotics and various drugs. Additional evidence points to a role ABCB1-type P-gp as a modulator of intracerebral glucocorticoid hormone access. Based on the hypothesis that glucocorticoids strongly impact behavior, the present study investigated the effects of ABCB1-type P-gp inhibition on neuroendocrine and behavioral responses to stress in mice. C57BL/6J mice received an oral injection of tariquidar (12 mg/kg; Xenova), an ABCB1-type P-gp inhibitor, or its vehicle and were subsequently exposed to a mild water-avoidance (WA) stressor. Basal and stress-induced anxiety-related and stress-coping behavior was investigated in the elevated-plus maze (EPM) and the open field (OF) paradigms as well as in the forced swimming test (FST). In addition, stress hormone levels, i.e. plasma corticosterone concentrations, were determined after WA stress and behavioral testing.

As a major result, we found that mice injected with tariquidar did not show a stress-induced change in their anxiety-related phenotype, whereas vehicle-treated mice presented with increased anxiety levels in the EPM and the OF after WA stress. No treatment effects, however, were found for FST behavior. At the neuroendocrine level, ABCB1-type P-gp blockade caused a substantial attenuation of the stress-induced elevation in peripheral glucocorticoid concentrations.

In conclusion, these results strongly support the hypothesis that inhibition of ABCB1-type P-gp improves stress hormone feedback, which in turn prevents the induction of anxiety-related behavior towards a stress-associated stimulus. ABCB1-type P-gp thus appears to be a putative drug target in the treatment of affective disorders.

Polymorphisms in the serotonin receptor gene HTR2A are associated with disease related traits in panic disorder

P. G. Unschuld1, M. Ising1, A. Erhardt1, S. Lucae1, S. Kloiber1, M. Kohli1, D. Salyakina1, T. Welt1, N. Kern1, R. Lieb1, M. Uhr1, E. B. Binder1,2, B. Müller-Myhsok1, F. Holsboer1, M. E. Keck1,3

1Max Planck Institute of Psychiatry, München, Germany
2present address: Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, USA
3present address: Division of Psychiatry Research, Psychiatric University Hospital, CH-8032 Zürich, Switzerland

Anxiety disorders and specifically panic disorder (PD) are caused by complex interactions of environmental and genetic factors. The latter comprise many different genes, from which those involved in serotonergic neurotransmission have received particular attention. Here we report the results from an association candidate-gene approach, where we analyzed 15 single nucleotide polymorphisms (SNPs) within the gene coding for the serotonin-receptor 2A (HTR2A) in patients suffering from PD and a control sample. We found that the SNP rs2296972 shows an association between the number of T-alleles and severity of symptoms in PD. By performing tests according to the Fisher product method, an association between HTR2A and the personality trait reward dependence could be shown. Most pronounced effects were observable for the SNPs rs2770304, rs6313 and rs6311. Furthermore, the polymorphisms rs3742278, rs2296972 and rs2770292 form a haplotype, which may be associated with higher susceptibility for PD. These results further underline a possible important role of genetic variations within the system controlling serotonergic neurotransmission for the development and course of disease in PD.
Oxytocin and social support attenuate cardiovascualr stress response in social phobia

B. von Dawans1, 2, L. M. Soravia1, I. D. Neumann1, C. S. Carter4, D. de Quervain1, U. Ehlert1 and M. Heinrichs2, 3

1Department of Clinical Psychology and Psychotherapy, University of Zurich, Switzerland
2University Research Priority Program „Foundations of Human Social Behavior”, University of Zurich, Switzerland
3Department of Molecular and Behavioural Neuroendocrinology, University of Regensburg, Germany
4Department of Psychiatry & The Brain Body Center, University of Illinois at Chicago, USA
5Division of Psychiatry Research, University of Zurich, Switzerland

Background: Social Phobia ranks as the third most common mental health disorder after depression and alcoholism. Besides marked and persistent fear of social interactions, patients report various autonomously regulated physical symptoms including sweating or tachycardia, which in turn reinforce phobic fear. Both cognitive-behavioral and pharmacological therapy have been shown to be effective in less than two thirds of all patients. A new approach could be the nonapeptide oxytocin which is associated with positive social interaction and reduced stress reactivity in animals and humans. Moreover, the combination of oxytocin and social support was shown to suppress salivary free cortisol during psychosocial stress.

Methods: In a placebo-controlled, double-blind study, 44 men with social phobia were exposed to a socio-evaluative stressor (Trier Social Stress Test), consisting of 5 min of an unprepared speech followed by a 5 min mental arithmetic task in front of an audience. All participants where randomly assigned to receive intranasal oxytocin (24 I.U.) or placebo 50 minutes before stress, and either social support from their spouse during the preparation period or no support.

Results: Oxytocin significantly reduced heart rate responses to stress over the entire stress protocol. More importantly, the combination of oxytocin and social support exhibited the lowest heart rate reactivity during the unprepared speech.

Conclusions: Oxytocin reduces autonomic stress responses in patients with social phobia during psychosocial stress. In the socio-evaluative stress task (unprepared speech), the increased availability of central oxytocin improves the stress-protective effect of social support. These results concur with previous findings from animal and human research, thereby emphasizing possible therapeutic implications of oxytocin in social anxiety disorders.

Randomized, controlled trial on the effects of paroxetine versus placebo in combination with aerobic exercise or relaxation training in the treatment of panic disorder

D. Wedekind, A. Broocks, N. Weiss, P. Rotter-Glattkowski, K. Engel, and B. Bandelow

Department of Psychiatry and Psychotherapy, University of Göttingen

Objective: The purpose of this study was to compare the therapeutic effect of a drug treatment of proven efficacy (paroxetine) to placebo combined with either aerobic exercise or relaxation training for patients with panic disorder with or without agoraphobia.

Method: 75 outpatients suffering from moderate to severe panic disorder with or without agoraphobia (DSM-IV criteria) were randomly assigned to a 10-week treatment protocol of paroxetine 40 mg daily or placebo pills combined with either regular aerobic exercise (running) or regular relaxation training. Patients were aged between 19 and 51 years and 70% were female. Primary efficacy measures were the Panic and Agoraphobia scale (PAS) and Clinical Global impression (CGI). Secondary efficacy measures were the Hamilton Anxiety scale (HAMA) and the Montgomery-Asberg Depression Scale (MADRS).

Results: The dropout rate was 20% altogether and did not differ significantly between groups. Compliance was good for all groups. Patients of all four groups showed a significant improvement on the primary and secondary efficacy measures over time (p<.05). Patients treated with paroxetine reached significantly better improvement compared to placebo treated subjects (p<.05). On the CGI, patients treated with additional aerobic exercise showed a trend to better improvement compared to the relaxation group (p=.06), however, PAS-scores showed no significant differences. HAMA and MADRS showed significant improvement over the treatment period, endpoint values, however showed no significant group differences. Interestingly, patients randomized to the aerobic exercise group showed, in comparison to the relaxation group, significantly better improvement on the PAS (p<.05) and on the HAMA (p<.01) at week 4, however endpoint scores were not significantly different. Overall response and remission rates were significantly higher in the paroxetine compared to the placebo groups (p<.05), however no differences in this concern could be detected between exercise and relaxation. Adverse events occurred in 30% of the patients, however, no serious adverse events were recorded. Correlations between scales rated by the blinded and non-blinded rater were good.

Conclusions: These results suggest that any of the four treatments went in line with significant improvement of panic disorder. Patients receiving paroxetine had significantly better endpoint scores on PAS and CGI and better response- and remission rates. Subjects treated with additi-
onal aerobic exercise showed a trend to better improvement on the CGI compared to the relaxation group. Improvement as measured with the PAS and HAMA was significantly better in the exercise group compared to relaxation at week 4 but not at endpoint. The results demonstrate a beneficial effect of all treatments on panic disorder with paroxetine having the biggest impact. Aerobic exercise tends to be possibly superior to relaxation training, especially in the first 4 weeks of treatment. Therefore, relaxation training and especially aerobic exercise appear to be suitable additional treatment strategies in panic disorder.

German J Psychiatry 2006; 9: S10

Temazepam triggers the release of vasopressin into the rat hypothalamic paraventricular nucleus – Novel insight into benzodiazepine action on hypothalamic-pituitary-adrenocortical system activity during stress

T. Welt1,2, ; Engelmann4, U. Renner1, A. Erhardt1, M. B. Müller1, R. Landgraf1, F. Holsboer1, M. E. Keck1,3

1Max Planck Institute of Psychiatry, Munich
2Division of Psychiatry Research, Psychiatric University Hospital Zurich, Zurich
3Klinik Schlössli AG
4Otto-von-Guericke University Magdeburg

We investigated the influence of a representative classical benzodiazepine on the regulation of the hypothalamic-pituitary adrenal (HPA) axis activity both under basal conditions and stress. Adult male Wistar rats were i.v. administered with temazepam (0.5, 1, 3 mg/kg) and plasma concentrations of corticotropin (ACTH) and vasopressin (AVP) were measured via chronically implanted jugular venous catheters. Simultaneously, the release of AVP within the hypothalamic paraventricular nucleus (PVN) was monitored via microdialysis. Plasma AVP levels remained unaffected by the different treatment conditions. Temazepam blunted the stressor exposure-induced secretion of ACTH in a dose-dependent manner. Concurrently, and also in a dose-dependent manner temazepam enhanced the intra-PVN release of AVP, known to originate from magnocellular neurons of the hypothalamic neurohypophyseal system. Furthermore, temazepam did not affect the in vitro secretion of ACTH from the adenohypophysial cells. Taken together, the results of this study suggest that temazepam modulates the central nervous regulation of the HPA axis by altering intra-PVN AVP release. An increasingly released AVP of magnocellular origin seems to provide a negative tonus on ACTH secretion most probably via inhibiting the release of ACTH secretagogues from the median eminence into hypophysial portal blood.

German J Psychiatry 2006; 9: S10

Anticonvulsants in anxiety? No effects of the selective GABA-reuptake inhibitor tiagabine in panic disorder


Department of Psychiatry, Ludwig-Maximilian University Munich, Germany
*Department of Psychiatry, Westfälische-Wilhelms-University, Münster, Germany

Background: There is increasing evidence that a dysregulation of the gamma-amino-butyr ic-acid (GABA) system plays an important role in the pathophysiology of panic disorder (PD). Treatment with the selective GABA-reuptake inhibitor tiagabine has been shown to improve anxiety in experimental animals (Schmitt et al. 2002, Thoeringer et al. 2004). Moreover in humans, treatment with tiagabine showed reduction of experimental induced anxiety in healthy volunteers (Zwanzger et al. 2003). Therefore, the putative anxiolytic properties of the tiagabine were investigated in a placebo-controlled study in patients with panic disorder.

Methods: 23 patients with panic disorder received tiagabine in a flexible dose design up to a daily maximum of 30 mg. Panic symptoms were assessed using the Panic-Agoraphobia-Scale (PAS), the HAM-A and a panic diary.

Results: Preliminary analysis showed that there were no effects of tiagabine treatment compared to placebo with regard to the HAM-A, PAS or panic attack frequency. Moreover, tiagabine treatment was accompanied by dizziness and vertigo when dose was increased followed by study discontinuation in a number of subjects.

Conclusion: First results suggest that treatment with tiagabine shows no effect on panic symptoms in patients with PD. Although these results are in contrast to findings, which have suggested possible anxiolytic effects of tiagabine in experimental animals and healthy volunteers the findings are in line with reports of weak effects of tiagabine in generalized anxiety disorder in a placebo-controlled study.