Introduction

It is a privilege to be speaking at this congress and I would like to thank Professor Kaiya and the Program Committee for their generous invitation. It is also a great pleasure for me to return to Japan after I first visited on the occasion of the 3rd Congress of the International Neuropsychiatric Association in Kyoto in 2000. My task is to summarize recent developments in panic research from an American perspective. Some cautionary remarks are in order. First, either by choice or by lack of understanding, any such review is by nature idiosyncratic and selective. My choices and idiosyncrasies are based on my medical education and specialty training in the United States, but also in Germany and France, and on the fact that I practice neurology as well as psychiatry and psychotherapy. I will limit the material to the last 3-4 years and allude to some non-US material where indicated. For instance, some of the most exciting new basic neuroscience research on panic comes from Brazil.

Some trends have continued: Panic disorder has not been at the forefront of funded research in North American psychiatry for some time. New pharmacological treatment studies of panic disorder are sparse. In most of the psychiatric and psychological research literature on anxiety, the confusion of anticipatory fear and panic has continued despite phenomenological and neurochemical evidence to the contrary.

On the other hand, more attention has been paid to the varied phenomenology of human anxiety, and progress has been made in cross-disciplinary approaches and cross-cultural understanding.

Unsurprisingly, the phenomenology of human anxiety depends in part on the cultural context. Some patients will primarily complain of insomnia or cognitive difficulties, others of chest
pain or headaches, yet others of having ataques de nervios or the fear that their neck will explode from too much pressure—the sore-neck syndrome described in the Khmer—that is an apparent close relative of the globus hystericus known to Western medicine.

Moreover, with DSM-V on our doorstep, it has become incontrovertible that while DSM style schematic categorization has facilitated our understanding of mental disorders in some ways, its erroneous to the letter implementation has often been unhelpful to scientific progress in its simplification of complex psychobiological phenomena.

From the perspective of the psychiatrist and neurologist with an interest in medically unexplained physical symptoms, it is important that there has been more awareness of the physical nature of panic disorder. Panic disorder is central to psychiatry, but it is perhaps even more relevant to general medicine. Today, individuals suffering with anxiety may seek relief from psychopharmacology and psychotherapy, but more often they will present to a general medical practitioner with a relatively limited number of physical symptoms.

The patients with the most disabling physical anxiety symptoms—phenomenologically most intriguing—are almost never seen by psychiatrists, but, just like during Freud’s and Breuer’s Fin de Siècle, present to neurologists and other specialists who may find themselves ill-equipped to diagnose and treat the underlying anxiety disorder.

The unifying, universal aspect of panic lies in its underlying psychobiology. Cultural and multiorgan expressions of panic are symptom variants that should eventually be explainable by a unified, testable and falsifiable psychobiological hypothesis.

I will briefly return to these considerations at the end of my presentation.

1. Recent treatment studies

One important global development in the biological psychiatry literature on panic has been the first revision of the guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) Task Force for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-traumatic Stress Disorders, a consensus panel of international experts for anxiety disorders, OCD and PTSD (Bandelow et al. 2002), several of whom are present at this congress. The guidelines, nothing short of a massive effort to streamline treatment recommendations, were published in the World Journal of Biological Psychiatry in the fall of 2008 (Bandelow et al. 2008). Their full text is available online at:


The following stresses some relevant points from the Guidelines that while well known, bear repetition:

Anxiety disorders are among the most frequent psychiatric disorders. (Kessler et al.
While the prevalence of anxiety disorders did not change during the decade, the rate of treatment increased (Kessler et al. 2005c). Median age of onset is 24 years for panic disorder, very similar to 23 for PTSD (Kessler et al. 2005a). While anxiety disorders may indeed diminish in the fifth decade (Bandelow 2003; Kessler et al. 2005a; Rubio and Lopez-Ibor 2007a, b), I suspect they are in many cases simply overshadowed by somatic expressions of anxiety, and the physical toll of long-term anxiety. Because patients with anxiety disorders are frequent users of emergency medical services (Klerman et al. 1991; Wang et al. 2005), costs associated with the anxiety disorders represent approximately one third of the total expenditures for mental illness (DuPont et al. 1996; Rice and Miller 1998; Wittchen 2002). Keeping in mind that much anxiety is expressed and categorized as physical and never comes to the attention of the mental health field, the economic and human cost is in reality probably much higher.

The Guidelines provide a good historical overview of drug treatment studies in Panic Disorder and Agoraphobia. As already mentioned, there has been little new development in that area in the past few years, and much less so from North America. One U. S. paroxetine study showed again efficacy in a double-blind placebo-controlled (DBPC) (Sheehan et al. 2005) and a comparator-controlled study (Pollack et al. 2007b). In the US, sertraline has not been studied recently. The efficacy of the antidepressant venlafaxine was demonstrated in DBPC studies (Bradwejn et al. 2005) and in two studies, venlafaxine was more effective than placebo and was as effective as the comparator drug paroxetine (Pollack et al. 2007a; Pollack et al. 2007b). They have been no recent studies for either Tricyclic Antidepressants (TCAs), fluoxetine, or Monoamine Oxidase Inhibitors (MAOIs), all of which had been previously shown to improve panic disorder.

Other components not available in the US were studied in Europe, such as reboxetine and moclobemide, with mixed results.

Unsurprisingly, for treatment-resistant panic disorder, atypical antipsychotics were suggested. Olanzapine was studied in an open trial (Hollifield et al. 2005), followed by risperidone (Simon et al. 2006). Papp (2006) found the anticonvulsant levetiracetam, to be useful in an open-label, fixed-flexible dose study.

In 2003, the United States Food and Drug Administration (FDA) issued a what many believed premature and ill-conceived public health warning on the basis of preliminary evidence that SSRIs and related antidepressants might be associated with excess suicidality in children and adolescents. Since, the drug treatment of children and adolescents has become more complicated, and there has been little recent pharmaceutical research activity in the US.

In clinical practice, the standardized, mono-morbid, physically healthy anxiety study patient...
is more fiction than reality. This becomes even more clear in the treatment of anxiety in the elderly, in the debilitated, the neurologically and physically impaired individuals that require even more cross-disciplinary considerations. Paying attention to medical comorbidities will be increasingly relevant in developed societies with ever larger numbers of elderly citizens. Further, a process of informed consent of patients and if indicated, their families, is key to successful treatment and risk management.

2. Non-Pharmacological Treatment—Comparisons of Psychological and Pharmacological Interventions and Their Combination

Numerous meta-analyses have led to contradictory results regarding the efficacy of the psychological and pharmacological treatment of panic disorder (e.g., Clum et al. 1993; Cox et al. 1992; van Balkom et al. 1997; Mitte 2005; Furukawa et al. 2006). The inclusion of heterogeneous studies and influences of selection biases have been severely criticized (Klein 2000). In addition, using the wait-list control condition in comparative panic disorder research may make little sense in a condition that tends to fluctuate. Relaxation, the control condition used in Milrod et al. (2007) may make panic worse etc.

Although not from the US, we note that there has been one meta-analysis that only included studies using a direct comparison of pharmacological, psychological, or combined treatments (Bandelow et al. 2007a). According to this meta-analysis, drug treatment and cognitive behavioral therapy were equally effective, but combined pharmacological and psychological treatment was substantially superior to the monotherapies in panic disorder patients. All in all, there is enough evidence for Cochrane to recommend the combination (Furukawa et al. 2007).

Manualized psychodynamic psychotherapy was superior to ‘applied relaxation’ (Milrod et al. 2007). Some patients received additional SSRI treatment in this trial. As pointed out in the Guidelines, applied relaxation is a therapist-aided relaxation technique that does not involve systematic therapeutic interventions. In future studies, psychodynamic therapy should also be compared with a psychological placebo.

All research on the effect of physical exercise on panic symptomatology has been done in Europe. One study from Germany had found that aerobic exercise (jogging) was more effective than a pill placebo, but less effective than clomipramine (Brooks et al. 1998). While there has been no treatment study of exercise in panic disorder in the US, there is one study where exercise was shown to reduce reactivity to the 35% CO2 challenge in normals (Smits et al. 2008).

In this study, 92 young female and male healthy nonpsychiatric volunteers were exposed to the anxiogenic 35% CO2 single breath challenge. Participants were randomized to moderate
treadmill exercise or rest prior to the challenge. Compared to resting participant, those who exercised prior to 35% CO2 inhalation showed significantly reduced reactivity.

The reverse seems to be true, in that physical inactivity might worsen panic (Smits and Zvolensky 2006).

3. Panic and comorbid conditions

While papers on panic disorder proper have ebbed off, there is more awareness of the relevance of panic states in other clinical contexts, both predominantly emotional and physical.

As a reminder, in the USA, nearly half of panic patients are nowadays initially seen in the medical emergency room of a hospital. Economic decline and lack of proper health insurance may further increase that number. Panic patients may undergo extensive diagnostic medical procedures, such as MRI scans of the brain for headaches, or coronary angiograms for chest pain. Cardiovascular symptoms, particularly pseudo-anginal chest pain resembling a heart attack are the most common symptoms in these PD patients’ experience. Accordingly, 25% or more of outpatients seen by a cardiologist have a current diagnosis of PD (Ballenger 1998).

Panic worsens the outlook for other, related disease states. Panic symptomatology during the asthmatic attack predicted longer hospitalizations in asthmatic patients (Baron et al. 1986; Brooks et al. 1989; Jurenec 1988). Panic comorbidity was associated with increased medication use and worse quality of life asthmatics (Lavoie et al. 2005).

In a cohort of elderly patients with major depression, comorbid panic disorder accelerated memory decline (DeLuca et al. 2005).

Interestingly, an increased comorbidity between sleep paralysis and panic disorder has been reported in both East Asian and African-American patients (Yeung et al., 2005; Hinton et al. 2005; Paradis and Friedman 2005).

PTSD was highly comorbid with both in these studies.

As previously noted (Breslau et al. 2001), migraine and other headaches are highly comorbid with panic disorder (Hamelsky and Lipton 2006).

Having PD increases the risk of migraine four-fold, and vice versa. This bidirectionality suggests that the migraine-panic association is unlikely to be merely coincidental and that shared environmental and familial factors are involved (Breslau et al. 2001).

But panic disorder is also comorbid with other somatic pain (Johnson et al. 2006). In a cross-sectional survey of 1,219 female veterans studying the prevalence and frequency of mastalgia, women reporting frequent mastalgia were much more likely to have comorbid panic disorder (OR 7.1), but also PTSD, mood disorders, and other somatic pain syndromes, such as fibromyalgia, chronic pelvic pain or irritable bowel syndrome.
While panic disorder in its most typical form may be characterized by prominent air hunger, a number of patients present with other subtypes, including vestibular symptoms. It has long been suggested that unspecific dizziness/lightheadedness, but also true vertigo may be a common presentation of panic disorder (Benedikt 1870 ; Fromberger et al. 1994). This questions yet again the current rigid distinction between psychiatry and neurology (Staab 2006).

In Mandarin Chinese, tou 1’un refers to the disabling sensation of a constant state of movement of oneself or one’s surroundings. This dizziness (note that tou yun also describes vertigo), is probably the most common expression of panic disorder in Chinese patients (Park and Hinton 2002), so by sheer numbers, this may well be the most prevalent panic subtype worldwide.

Another interesting neurological comorbidity is restless legs syndrome (Winkelmann et al. 2005). In this study, patients with restless legs syndrome were almost five times more likely to suffer from panic disorder than normal controls.

Taken together, the various comorbidities of panic anxiety and the sequelae of untreated anxiety have a massive impact on people’s quality of life (Sareen et al. 2006).

It seems self-evident that developing stable funding mechanisms to support complex, longitudinal, person-oriented and physiologically sophisticated studies of all aspects of human anxiety ought to be a priority worldwide.

4. Basic Science

It has long been known that stimulation of the dorsal periaqueductal gray matter (DPAG) produces aversive emotions and visceral responses in humans (Nashold et al. 1969; Young 1989) and unconditioned defensive behaviors in rats (Bittencourt et al. 2004; 2005) that have been proposed as a model of panic attacks (Jenck et al. 1995; Schenberg et al. 2001). Low intensity stimulation of the DPAG produces a freezing response likened to agoraphobia. High intensity stimuli give rise to a vigorous galloping accompanied by cardiovascular and respiratory responses and, less often, micturition and defecation (Schenberg et al. 1983, 1993, 2005; Bittencourt et al. 2004). Schenberg et al. (2008) recently published a study showing that stimulation of the DPAG with 1-min electrical pulses failed to produce significant increases of ACTH. This parallels the counter-intuitive lack of hypothalamic-pituitary-adrenal (HPA) activation in panic thereby supporting the splitting approach of anxiety disorders (Klein 1993; Preter and Klein 2008).

Further, another phenomenological feature distinguishing panic from fear is the prominence of air hunger in panic. Chronic sighing and CO2 hypersensitivity exist outside of the acute attack (Wilhelm et al. 2001). Smoking is an independent, multiplicative risk factors for PD,
but not for other anxiety disorders (Pohl et al. 1992; Amering et al. 1999). Panic is more prevalent in torture victims who specifically suffered suffocation torture rather than other assaults (Bouwer and Stein 1999).

Seemingly unrelated, there frequently is excessive separation anxiety in the childhood of panic patients as well as sudden loss or bereavement prior to an illness episode (Faravelli and Pallanti 1989; Kaunonen et al. 2000; Klein 1993; Milrod et al. 2004).

Pine et al. (2000; 2005) documented a relationship between respiratory dysregulation and specific childhood anxiety disorders. Respiratory hypersensitivity to 5% CO2 was significantly present in children with separation anxiety disorder, to a lesser degree in generalized anxiety disorder, but not in social phobia.

In an attempt to integrate these observations that cross multiple domains and are apparently unrelated, an amplification of the suffocation false alarm theory (SFA) of spontaneous panic (Klein 1993) was offered (Preter and Klein 2008). Original SFA postulates the existence of an evolved physiologic suffocation alarm system that monitors information about potential suffocation. Panic attacks maladaptively occur when the alarm is erroneously triggered.

The recent amplification of SFA centers on the observation that separation anxiety and CO2 sensitivity are both under endogenous opioidergic control. We hypothesized that PD may be due to an episodic functional endogenous opioid deficit (amplified SFA theory). The following is a necessarily brief explanation.

The endogenous opioid system was discovered in the early 1970's. Electrical stimulation of the periaqueductal gray (Mayer et al. 1971) produced naloxone-reversible analgesia, strongly suggesting the existence of an endogenous opioid system. Opioid molecules are among the oldest evolved signaling substances. Remarkably conserved structurally, they are involved in diverse functions, e.g., pain perception, respiration (Stefano et al. 1996). Dyspnea is modulated by central and peripheral opioid levels in both rodents and humans (Santiago and Edelman 1985). Mice exposed to severe, intermittent hypoxia prolonged their survival during subsequent lethal suffocation (Mayfield and D'Alecy 1992). Naloxone blocked this effect, suggesting that endogenous opioids increase adaptability to low-oxygen environments. Opioid receptors, including 'non-conventional' ones, are located throughout the respiratory tract. Nebulized morphine is being investigated as a chronic dyspnea treatment (Baydur 2004; Bruera et al. 2005; Zebraski et al. 2000).

Numerous experimental data link opioids and separation. Following birth, mammalian infants cannot survive independently. Survival requires reliable distress signaling mechanisms to elicit parental care and retrieval. Distress vocalizations (DVs) are a primitive form of audio-vocal communication (Panksepp 1998). Using electrical brain stimulation (ESB), DVs have
been elicited in many species from homologous areas, including the midbrain and dorsomedial thalamus. In monkeys, stimulation of the rostral cingulate gyrus in monkeys consistently elicits distress calls (Jürgens and Ploog 1970; Ploog 1981). The cingulate cortex, found exclusively in mammals, is particularly well developed in humans and contains high densities of opioid receptors (Wise and Herkenham 1982). Naloxone-blockable opioid agonists specifically reduce isolation-induced distress vocalizations (DV) across mammalian species (Hofer and Shair 1978; Kalin et al. 1988; Kehoe and Blass 1986; Panksepp et al. 1978). Based on these observations, the brain opioid theory of social attachment was posited. Originally formulated by Panksepp, it drew upon phenomenological similarities between social and narcotic dependence, including the stages of euphoria, tolerance and withdrawal. It predicted that opioid release would result in feelings of comfort and alleviation of emotional distress arising from loss and social isolation (Panksepp 2003, 2005, Panksepp et al. 1978, 1980). Opiates, mimicking endogenous opioids, artificially create feelings of social comfort but decrease motivation to seek out social contact. Opiate antagonists increase social motivation, but reduce the reward afforded by endogenous opioid release. This evolutionary, neurobiologic attachment theory has received much empirical support (Nelson and Panksepp 1998). It is now appears that: (1) the endogenous opioid system is activated by several positive social interactions, ranging from mutual grooming in young animals (Keverne et al. 1989; Knowles et al. 1989) to sexual gratification; (2) opioids attenuate the reaction to social separation; (3) a low (but not a high) basal level of opioids increases motivation to seek social contact.

5. Testing the panic-suffocation-false alarm-endogenous opioid connection

As is well known, sodium lactate infusions and CO2 inhalation regularly produce panic attacks in patients with panic disorder (Liebowitz et al. 1984; Gorman et al. 1984; Papp et al. 1993). However, normal control subjects or patients with other anxiety disorders almost never show such reactivity (Klein 1993; Preter and Klein 1998). Both spontaneous and lactate induced panic attacks in panic patients produce air hunger and marked, objective increases in tidal volume (VT) (Goetz et al. 1993; Martinez et al. 1996). Since sodium lactate infusion causes a metabolic alkalosis, a compensatory decrease in ventilation would be expected. This would homeostatically buffer blood pH, by increasing CO2 retention. However, the converse actually occurs indicating a specific lactate stimulating effect on respiration.

The usual response of healthy control subjects to a sodium lactate infusion is a minor, but definite increase in VT (Liebowitz et al. 1985), replicated translationally in a rat model (Huesgen et al. 2004). The lesser tidal volume response in lactate challenged normal subjects may be due to buffering by their intact endogenous opioid system.
An open pilot study (Sinha et al. 2007) showed that naloxone infusion (ranging from an initial 0.5mg/kg to a maximum of 2mg/kg) followed by lactate, caused significant tidal volume increments similar to those observed during clinical and lactate induced panic attacks in 8 of 12 normal subjects. The four subjects who received the maximum dose all manifested clear tidal volume increments. Four of the eight subjects then received placebo followed by lactate. The tidal volume increment did not recur, supporting the hypothesis that naloxone pretreatment was necessary for lactate to produce marked increase in tidal volume in normal subjects.

Therefore we decided to conduct a properly controlled, randomized experimental study to investigate whether naloxone, an opioid receptor antagonist, could change the regularly resistant normal controls to become more sensitive to intravenous lactate as a respiratory stimulus to tidal volume increment. We used double-blind, controlled, pair wise comparisons. A design modification was incurred by interim data analyses that showed no measurable effect from naloxone (2mg/kg) followed by saline. Our final definitive study was of 26 healthy male and female volunteers who underwent cross-over intravenous challenges naloxone (2mg/kg) followed by lactate (NL), or saline followed by lactate (SL).

Respiratory physiology was objectively recorded with the LifeShirt apparatus, (Vivometrics, Inc., Ventura, CA, U. S. A.) “a multi-function ambulatory device capable of simultaneously monitoring several physiological signals and patient reports of symptoms and well being. The LifeShirt system is an extensible data acquisition and processing platform consisting of a garment, a data recorder, and PC–based analysis software.” (Grossman 2004).

The complex processing of massive amounts of respiratory data (50/second) is detailed elsewhere (Lee et al. 2008). The study showed that the increases in respiratory tidal volume seen in panic patients who panic on lactate could be paralleled in normals by opioid antagonist pretreatment of lactate infusion. These results are consonant with the hypothesis that a functioning endogenous opioid system may serve to buffer normal subjects from the behavioral and physiological effects of lactate. The naloxone-lactate (NL) interaction may provide an experimental model of the clinical panic attack in normal subjects, keeping in mind our goals for controlled replication of respiratory findings while behavioral response was exploratory. However, the NL model of clinical panic requires testing by double-blind experiments that block the NL effect by specific anti-panic drugs, but not by panic irrelevant drugs. If specific blockade by anti-panic agents were found, this confirmation affords several useful advances.

First, there is currently no specific, ecologically valid screening method for testing putative anti-panic drugs except by the experimental treatment of panic disorder patients in phase 2 and 3 clinical trials. This would be provided by the NL model.

Second, support for the theory that an opioidergic dysfunction is the pathophysiological
mechanism underlying Panic Disorder allows new approaches to related illnesses, such as migraine (Breslau et al. 2001; Jette et al. 2008) or cyclic vomiting syndrome (Fleisher et al. 2005; Tarbell and Li 2008).

If opioidergic dysfunction underlies panic pathophysiology (particularly when associated with air hunger), the appropriateness of opioidergic therapeutic agents comes into question. The use of morphine or other simple agonists would probably be rejected for fear of inducing addiction although the evidence for addiction during indicated treatment is slim. However, recent work with opioidergic mixed agonist-antagonists (Gerra et al. 2006; Wallen et al. 2006), e.g. buprenorphine, may be relevant since the concern about addiction would be mitigated by the fact that higher doses become receptor blockers rather than agonists.

Positive results would foster investigations into basic molecular mechanisms. For instance, we note that the dose of naloxone used in our study (2 mg/kg) exceeds that needed for \( \mu \) opioid receptor (MOR) blockade (Sluka et al. 1999), suggesting a role for the \( \delta \) opioid receptor (DOR).

Investigations of \( \mu \) knockout mice and \( \delta \) knockout mice (Gaveriaux-Ruff and Kieffer 2002; Nadal et al. 2006) also indicate that the DOR is distinctively related to emotionality. A possible approach is to study lactate and CO2 sensitivity in DOR knockout mice as compared to other mouse strains and preparations. Based on our result, the expectation would be that lactate and CO2 would distinctively elicit emotional/respiratory responses in DOR knockout as compared to other mice strains or knockout preparations. This could spark interest in the development of specific DOR agonists suitable for use in humans. Currently, such agents have not been developed.

**Conclusion**

By way of conclusion, let me for a moment return to my initial considerations. At today's congress in Tokyo, one cannot help but be reminded of a landmark conference on Anxiety and Anxiety Disorders, organized by the Anxiety Section of the Clinical Division of the NIMH with the aim of reviewing the state of knowledge about these disorders and outlining directions for research. Just like an NIH conference on depression, held ten years earlier, which had provided the framework for studies of depression in the 1970s, there was much excitement, except that this time panic disorder was the central exhibit. Robert Spitzer is reported as stating at the end of the event, "I would predict that the major growth industry in this field in the next decade will be panic." (quoted in Good 2002).

Today, East Asian psychiatry seems to be at a similar crossroads. Ideally, mistakes made by others should be avoided. Some of these mistakes are: adherence to overly schematic psychi-
atric classification, training of psychiatrists without much interest in or knowledge of medical and neurological comorbidities, the use of pharmacology without much regard for developmental, psychodynamic and cultural themes. Neuropsychiatric thinking has a long and lively tradition in Japan, so there is much reason to be optimistic.

Writing about the culture-specific aspects of anxiety research and treatment, Good and Kleinman (Good 2002) cautioned against the assumption that “diagnostic criteria and categories relevant to North America could simply be translated or that they would prove universal”. Modern psychiatry worldwide would benefit from paying close attention to certain simple underlying questions to avoid committing the “category fallacy”. Some useful questions one might ask are (Good 2002):

” Are the specific subtypes of anxiety disorders described in DSM-III—including panic disorder—found across cultures? Are the symptom criteria derived from American research appropriate in specific cultural settings in Japan or China or other parts of Asia or Latin America or Africa? What is the relation between North American diagnostic categories and theories of anxiety disorders, and specific non-Western categories of illness (including so-called ‘culture-bound disorders’) or theories about anxiety-like conditions in other literate or non-literate medical traditions? Are treatments for anxiety which are effective here effective in other cultural settings?”

I look forward to a spirited and productive discussion of these themes with you in the next few days. Thank you for your attention.

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Notes: CORPORATE NAME: Paxil CR Panic Disorder Study Group.


