During the past fifteen years, several new atypical antipsychotic medications suitable for the treatment of symptoms in schizophrenia entered the marketplace. In the process of drug development, the sponsoring pharmaceutical manufacturers designed and implemented multiple major clinical studies demonstrating efficacy for each of the new agents. The design and implementation of these sponsored preapproval clinical studies were intimately linked with the prerequsite to comply with regulatory requirements for approval of a new atypical agent. The conditions for approval motivate the pharmaceutical industry to perform efficacy studies using the same trial design elements, and uniform data analytic approaches for the evaluations. This presentation, using the FDA's Summary Basis of Approval database, will overview established practice of providing evidence to regulatory authorities about the claimed properties of new pharmaceutical products with regard to antipsychotic efficacy. The overall designs including the timing of evaluations, psychometric rating scales used for evaluations, and the use of both measured and derived outcome variables as well as other principal characteristics of the trials, such as the choice of population for efficacy analyses, and methods of handling missing data will be reviewed. The established conventions and procedures will be contrasted with scientific concepts and principles and practical utility.

Symposium: Pharmacological prevention of suicide

S34.01

Lowering suicide rates: Realistic or Quixotic

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Background and Aims: There have been concerns about the risk benefit ratio of treatment with antidepressants and antipsychotics in the light of recent evidence pointing to a risk of suicide induction during the course of treatment with antidepressants. These concerns have led to a series of recent studies exploring national rates of suicide and correlating these with data on antidepressant consumption, which apparently showed reductions in suicides since the advent of the SSRIs.

The data from controlled trials on antidepressants and antipsychotics however point to increased suicide and suicide attempt rates. Against this background we have looked at suicide rates in schizophrenia in North Wales from the pre- and post-antipsychotic eras and have compared suicide rates in the Nordic countries with autopsy and ill-defined death rates, and antidepressant sales, during the period 1961 through to 2003.

Results: There has been a 10-fold rise in suicide rates in schizophrenia since the introduction of the antipsychotics. In the Nordic countries, there is no relationship between antidepressant consumption and suicide rates but a close correlation between suicide rates and both autopsy and ill-defined death rates, which appear to need further clarification.

Conclusions: Combined these datasets suggest efforts to reduce suicide rates, in particular efforts that rely on psychotropic drug use may be quixotic.

S34.02

Prediction and prevention of suicide in mood disorders

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Background and Aims: Major mood disorders are quite prevalent, but frequently underreferred, underdiagnosed and undertreated illnesses. The early recognition and appropriate treatment of unipolar and bipolar mood disorders is particularly important, since untreated mood disorders carry extremely high risk of both attempted and committed suicide. Recent studies clearly show that suicidal behaviour in patients with major mood disorders is state and severity dependent and this means that suicidality markedly decreases or vanishes after clinical recovery from major depressive episode or from dysphoric mania. However, since the majority of mood disorder patients never committ and more than half of them never attempt suicide, special clinical characteristics of the illness as well as some familial and psycho-social factors should also play a contributory role in this self-destructive behavuour.

Results: Considering the clinically explorable suicide risk factors in patients with mood disorders (family and/or personal history of suicidal behaviour, early onset of the disorder, severe depressive episode/hopelessness, agitated/mixed depression, bipolar II diagnosis, comorbid Axis I and Axis II disorders, adverse life situations, lack of social and medical support), in the majority of the cases, suicidal behaviour is predictable with a good chance. There are also several evidences that (succesfull) long-term treatment of unipolar depressives (with antidepressants and/or lithium) and bipolar patients (with mood stabilizers and with antidepressants/antipsychotics) substantially reduces the risk of attempted and completed suicide, even in this high-risk population. Most recent studies also show that supplementary psycho-social interventions (psychoeducation, and targeted psychotherapies) further improve the results.

S34.03

Suicide prevention: Updated findings

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Background and Aims: International suicide rate in developed countries averages 13.3 x 100.000 population, a rate increased from 1955 to 2001 by 3.3% which has decreased from 1990 to 2001 by 11.7%. This decline may be associated with an improved health care, including medical interventions, with the most relevant role is attributed to treatments with antidepressants. Most of the studies showing an inverse correlation between increased usage of antidepressants and decreased suicide rates are based on ecological designs which do not provide information on the individual level.

Results: In order to prevent suicidal behavior it is fundamental to know that: [a] 90% of all suicides are associated with a psychiatric disorder, especially mood disorders that account for more than a half of all completed suicides; [b] the ratio of attempts to suicide in the general population is about 20:1, whereas the same ratio is about 5:1 in Bipolar Disorder (BPD) patients, showing higher lethality of suicide attempts. Indeed, the Standardized Mortality Ratio reaches the highest value (20; normal value = 1) in mood disorder patients among all psychiatric disorders, with little differences between BPD I and II, and Major Depressive Disorder.

Conclusions: Early interventions are important since suicide occurs in patients with BPD in the first years after illness onset. From

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a medical point of view, the use of antidepressants has not been associated with reduction of suicidal behavior. In BPD, the only treatment showing a consistent reduction of suicidal behavior is the maintenance therapy with lithium salts.

S34.04

Suicidal behaviour in the forthcoming classifications of mental disorders

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While suicidal behavior is not necessarily always related to the presence of a mental illness, most psychiatric conditions carry a higher suicide risk over the general population, and the lethality of suicidal behavior is clearly correlated with the presence of mental disorder. Hence, it is quite striking that suicide and related behaviour are barely addressed in the currently official classifications of mental disorders. The forecoming classifications DSM-V and ICD-11, to be due around 2012, should address the mentioned shortcomings of their predecessors. The best way to emphasize the importance of suicidal behavior is to facilitate its assessment across all mental conditions, and this should likely be done by means of dimensional assessment. Hence, both DSM-V and ICD-11 should include a dimensional module which would be complementary to the categorical module, and which would include, among other features, the assessment of suicide risk. As suicide is a behaviour linked to other relevant features also poorly covered in current nosology, such as impulsivity, guilt, and sometimes violence and psychosis, the dimensional assessment should also address all those psychopatological items. The categorical module should be refined and more data-driven. Other modules should include all the relevant information coming from biomarkers, physical health, psychological traits, social environment, treatment response, and family history, including family history of suicide. A major change in the classificatory systems should hopefully lead to better assessment of suicide risk and increased awareness on this issue by mental health care providers, resulting in more effective prevention of suicide.

8 April 2008 Core Symposium: Phenotype genotype endophenotype and the development in eating disorders

CS08.01

Gene-environment interaction in anorexia nervosa

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Purpose: To analyse GxE interactions assess non-shared environmental (E) risk factors for the development of AN specific for sisters discordant for an ED, polymorphisms in the serotonin transporter (G),.

Methods: We interviewed 128 sister pairs discordant for an eating disorder using the Oxford-RFI as part of the European "Healthy Eating" multicenter study at 3 university centres (Vienna, London, Barcelona) (AN-R: 58; AN-BP: 70; 128 sisters without ED). To examine association between AN, G and E, and G x E-interaction, conditional logistic regression was used with a Cox proportional hazards regression model using the exact method.

Results: Genotype (GT) distributions did not differ between the sister groups. Significant main effects were found for disruptive events, interpersonal problems and family dieting behaviour. The risk for AN increased with higher levels in these variables independently of the genotype. Significant interactions were found for G x parental problems and G x burden by parental psychiatric disorder. The increase of risk for AN with increasing number of problems with parents is larger for the S/S genotype than for L/L. However, a higher burden by parental psychiatric illness (subjective E according to Turkheimer 2000) increased the risk for AN-this was larger for the L/L than for the S/S GT.

Conclusions: This study suggests that there is an interaction between stress (problems with parents) and the ss GT which increases the risk of developing AN.

CS08.02

Developmental continuities in eating and nutrition

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Background and Aims: The research on the aetiology of eating disorders (EDs) has implicated many apparently disparate risk factors, which include: biochemical, genetic, familial and psychological factors. In the environmental domain, the presence of particular traits such as perfectionism, comorbidity in the family, eating patterns during childhood and exposures to adverse events have been revealed to be implicated in the aetiology of EDs. Whereas, from a biological point of view some recent new findings have suggested the important role of genetic factors, in combination with share and non-share environmental factors, developmental factors seems to have also a crucial role in the development of EDs later in life.

Method: In order to replicate these findings in a larger sample, we performed several combined population (case-control) and family-based studies of eight independently recruited samples from several European countries participating in the European Community Framework V "Factors in Healthy Eating" project. We analyzed as well genetic as environmental factors, but also developmental factors that might be implicated.

Results and Conclusions: The findings of our studies agree with the growing body of research indicating that a variety of environmental and social factors are associated with unhealthy individual and family eating patterns during childhood and early adolescence, and which if not detected early could result in the development of a subsequent eating disorder.

CS08.03

Cognitive inflexibility in anorexia nervosa - An FMRI perspective

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