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DOTTORATO INTERNAZIONALE
IN NEUROFARMACOLOGIA

IL PROMETEO

Bollettino di Dottorato

Direttore: Prof. Filippo Drago

L'OTTAVA EDIZIONE DELLA *SUMMER SCHOOL OF NEUROSCIENCE*: UN AGGIORNAMENTO SULLA SCHIZOFRENIA ED ALTRI PSICOSI (DALLA NEUROBIOLOGIA ALLA CLINICA)

Filippo Drago (Catania) e Stuart Montgomery (Londra) all'inaugurazione della Summer School.

I dati epidemiologici mostrano che i disturbi psicotici, e in particolare la schizofrenia, sono fra le patologie più frequenti e devastanti. Gli attuali farmaci antipsicotici hanno profondamente mutato il trattamento dei disturbi psicotici negli ultimi 50 anni. Tuttavia, questi farmaci ed in particolare la seconda generazione di antipsicotici, hanno soddisfatto solo in parte le aspettative iniziali lasciando ancora parecchi interrogativi circa la gestione dei disturbi psicotici a lungo termine, come ad esempio il trattamento dei sintomi negativi e dei deficit cognitivi. Si rendono quindi necessari nuovi antipsicotici, con una maggiore efficacia e sicurezza, come alternativa ai farmaci antipsicotici in uso oggi. Focalizzando l'attenzione sui trattamenti della fisiopatologia di queste malattie, si miglioreranno le possibilità di sviluppare cure in grado di superare le attuali terapie sintomatiche. Infatti, l'identificazione di nuove molecole coinvolte sia nella patogenesi della schizofrenia, che in altri disturbi psicotici, rappresenta il primo passo per la progettazione di nuovi e più efficaci farmaci in grado di modificare il percorso clinico di queste patologie. Lo sviluppo di modelli animali più vicini alla patologia è un altro punto chiave per la selezione di potenziali farmaci. Lavorare su target neurobiologici multipli può aiutare a bilanciare i rischi legati alla pipeline, e ad aumentare le speranze di offrire nuovi farmaci alla clinica. L'ottava edizione della Summer School of Neuroscience, organizzata nell'ambito del Dottorato di Ricerca in Neurofarmacologia ha avuto l'obiettivo di divulgare alla comunità scientifica locale le più importanti scoperte nel campo della neurobiologia della schizofrenia e di altri disturbi psicotici, e i nuovi approcci nella gestione clinica di queste patologie. Per il beneficio di tutti gli interessati a questi temi, ho il piacere di presentare questa edizione de Il Prometeo che contiene una selezione degli abstracts delle principali lezioni dei docenti che hanno partecipato alla Scuola.

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Selection of Abstract

Subjective well-being and quality of life under antipsychotic treatment

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Only recently success criteria became more ambitious and include a more thorough consideration of negative symptoms and cognitive dysfunction. The most important change within the last two decades, associated with the development of atypical antipsychotics subsequent to the development of clozapine, is the long overdue consideration of the patient's perspective. His/her quality of life or subjective well-being was neglected for a long time. One reason was the prejudice that schizophrenic patients are not able to self-rate well-being or quality of life. Another reason was the belief that such data are not necessary because the psychiatrists' perspective, "objective" psychopathology, includes these domains. However, recent data indicate that in addition to the positive influence of a good relationship between doctor and patient, the subjective experience of antipsychotic treatment is a major predictor of compliance. In addition to the distressing motor symptoms that often accompany treatment with typical or first-generation antipsychotics, marked adverse effects on drive and emotion may also be experienced. Patients report a reduced quality of life with restricted emotionality, straight thinking and spontaneity, a syndrome very similar to negative symptoms of schizophrenia.

Among other scales, a self-report instrument has been constructed to evaluate "subjective well-being under neuroleptics" (SWN). This scale was used in numerous open and controlled trials, indicating: a) schizophrenic patients, if no longer acutely psychotic or suffering from severe cognitive deficits, are able to reliably assess their subjective well-being, b) high SWN is correlated with high compliance, c) atypical antipsychotics increase SWN, d) individual improvements of SWN and of PANSS are not strongly related (r=-.30 - -.40), and e) dopamine D2 receptor blockade is highly correlated to reduced SWN (r = .66 - .76).

Recent trials reveal the relevance of early improvement of subjective well-being: In a 12-week trial 95% of those with early subjective response (within 4 weeks) showed later subjective and/or psychopathological improvement, but only 9% without early subjective response showed later improvement. In another 3-year trial again psychopathological response as well as symptomatic and functional remission were not only related to young age and treatment with atypical antipsychotics, but mostly to early (within the first 3 months) subjective improvement. Moreover in a five year trial of first episode patients, marked improvement of SWN within the first 6 weeks of antipsychotic treatment was found to be related to enduring remission, while early improvement of PANSS did not predict outcome.

Depression in schizophrenia – new perspectives in treatment

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Schizophrenia is a serious chronic relapsing disorder which is associated with a different response depending on the presence of different symptoms clusters. The positive symptoms appear to respond to a range of treatments with best response associated with typical antipsychotics and the same atypicals such as olanzapine. The presence of negative symptoms are associated with a poorer response to typicals and a better response to atypicals the best data seen with amisulpiride, which is licensed for the treatment of negative symptoms in schizophrenia.

Bipolar disorder is sometimes associated with frankly psychotic symptoms during both mania and depression which may be confused with schizophrenia. It is therefore important to review the diagnosis and separate bipolar disorder from schizophrenia since the treatment and outcomes are different. The presence of psychotic symptoms reduces the response rate in bipolar disorder compared with those without psychotic symptoms.

Depressive and anxiety symptoms in schizophrenia respond poorly or even worsen with typical antipsychotics such as haloperidol but appear to have a better response with some atypicals such as amisulpiride and olanzapine. The superior efficacy of olanzapine compared to haloperidol in schizo-affective disorder is reflected on the MADRS in those with moderate depressive symptoms. Add-on treatment with some newer generation antidepressants has been shown in placebo-controlled studies to provide significant extra benefit in treating the depressive symptoms of schizophrenia. The separation of depressive from negative symptoms is therefore important.

Suicide is an unfortunately common outcome in schizophrenia. The use of antipsychotics in other therapeutic areas, for example flupenthixol in personality disorders, has led to studies which have demonstrated that clozapine is effective in reducing the risk of suicide related events in schizophrenia.

Treatment of behavioural and psychological symptoms of dementia: which strategies?

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The behavioural and psychological symptoms of dementia (BPSD), such as agitation, aggression and psychosis cause distress for both the affected person and their caregivers, and often underlie the decision to institutionalise the affected individual.

Treatment may consist of a combined pharmacological and non-pharmacological approach although this should be individualised to the individual patient. The selection of a drug for pharmacological treatment should focus on avoiding polypharmacy and reducing side-effects. In general, this means that atypical antipsychotic drugs are preferred over conventional antipsychotics, such as haloperidol, as they have an improved tolerability profile with respect to extrapyramidal symptoms, tardive dyskinesia and anticholinergic effects.

In this presentation, the author will summarize the available data with regard to atypical antipsychotic agents such as risperidone, olanzapine, aripiprazole and quetiapine. Studies will be identified as focusing on BPSD, BPSD with aggression, psychosis/agitation. aggression in AD and psychoses of Alzheimer's Disease.

Nursing home and outpatient studies will be presented. An attempt will be made to identify the BPSD which are most responsive to treatment with atypical antipsychotics.

Side effect profiles, particularly with regard to extrapyramidal symptomatology, tardive dyskinesia, sedation and cognitive impairment, will be discussed. In addition, an anlysis of the increased incidence of cerbrovascular adverse events observed in this class of pharmacological agents will be presented.

Where available, differences between classical atypical antipsychotics will be dealt with.

Treating the acute phase and managing the long-term treatment of bipolar disorder

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Bipolar disorder is a severe long-term illness with a lifetime prevalence of approximately 2% that is characterised by cyclical episodes of mania and depression. The impact of bipolar disorder on the patient is highly significant, such that the illness leads to 2% of all disability-adjusted-life years associated with non-communicable diseases worldwide. The considerable impact and frequency of episodes of bipolar disorder emphasize the importance of managing effectively symptoms to achieve the ultimate goal of mood stabilization. Treating acute mania effectively, together with the comorbidities, is the goal for long-term treatment. Importantly, the side-effect burden has to be considered already in the acute phase in order to secure adherance for the necessary long-term treatment. Whereas in the past there were only typical antipsychotics and lithium available, we now have the possibility to initiate the treatment with atypical antipsychotics as well as valproic acid, lithium and lamotrigine. The different treatment guidelines that are available help to aid the clinician's choice when treating patients with acute mania or depression and thereafter for long-term treatment. The scientific evidence for established agents has significantly increased over the last 5 years and new medications have become available. The recommendations should be based, whenever possible, on randomized controlled double-blind trials. However, such studies do not always reflect clinical reality and have their shortcomings, e.g. exclusion of comorbid, suicidal or medically ill patients, which may in turn lead to disappointment with some medication in clinical practice. Accordingly, adherence to these guidelines can be far ensuring a successful outcome in every case. However, it may be a helpful framework for the educated psychiatrist, planning the individual treatment of a patient taking all sources of information and all available treatment options into account.

Knockout Mice in the Understanding of the Mechanism of Action of Lithium

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Objective: Lithium inhibits inositol monophosphatase activity as well as inositol transporter function. To determine if one or more of these mechanisms might underly lithium's behavioral effects, we studied inositol monophosphatase-1 gene knockout and inositol transporter (SMIT) knockout mice.

Methods: PCR for confirmation of genotypes, behavioral phenotyping, gas chromatography for brain inositol, enzyme activity measurement for inositol monophosphatase.

Results: In brains of adult IMPA1-/- mice, IMPase activity levels were found to be reduced; however, inositol levels were not found to be altered. Behavioral analysis indicated an increased motor activity in both the open-field test and the forced-swim test as well as a strongly increased sensitivity to pilocarpine-induced seizures, the latter supporting the idea that IMPA1 represents a physiologically relevant target for lithium. In SMIT-/- knockout mice, free inositol levels were reduced in the frontal cortex and hippocampus. They behave like lithium treated animals in the model of pilocarpine seizures and in the Porsolt forced swimming test model of depression. In contrast to O'Brien et al (2004), we couldn't confirm that GSK-3beta-/+ knockout mice exhibit reduced immobility in the Porsolt forced swim or reduced amphetamine-induced hyperactivity in a manner mimicking lithium's behavioral effects.

Conclusions: These data support the role of inositol related processes rather than GSK-3β in the mechanism of therapeutic action of lithium.

Cognition effects of antipsychotic drugs

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Because of its impact on the general social and vocational functioning, cognitive impairment has been at the forefront of schizophrenia research for the last 2 decades.
The prevailing clinical impression is that individuals who meet criteria for schizophrenia suffer from easy observable and at times severe cognitive impairment. However, when large populations of schizophrenics undergo classic psychological testing, the normal distribution of their composite scores is "shifted to the left" only moderately indicating that a large proportions of the general population perform similar to the schizophrenic patients.

Different from the classic brain degenerative disorders (dementias) the onset and progression of the cognitive impairment in schizophrenia is less predicable.
In many patients the cognitive impairment precedes the onset of psychosis, persists after psychosis remits and is occasionally detected in non-psychotic first degree relatives of patients. Most probably there is a stabilization of the cognitive performance 3-5 years after the onset of psychotics. Some elderly schizophrenia patients show very poor cognitive performance but it is not clear how much of it the the direct result of the illness and how much it is the result of factors associated with the illness (medication, poor education, institutionalization, apathy).

Before the emergence on the markets of SGA there was no consensus whether antipsychotic drugs improve or impair cognitive performance with mostly inconsistent and contradictory studies. The first wave of trials comparing SGA to FGA gave the former some small advantages in terms of cognitive performance. However this initial impression was not supported by a second wave of trials and by several large and independently funded trials.

The most recent trials indicate that all antipsychotics, first and second generation ones, are associated with small cognitive improvements but that there is no difference between FGA and SGA. A large number of factors might explain these results among which "practice effect" should not be overlooked. Most important it should be considered that antipsychotics have not been screened or developed as pro-cognitive drugs, hence, the lack of pro-cognitive effect should not be surprising.
Up to 3% of the general populations have psychotic experiences. Since there exists no putative biological substrate for psychosis or for the cognitive impairment it could be hypothesized that the presence of both in the same individual constitutes independent co-morbidities and not a common biological substrate. If this hypothesis is correct than the same pharmacological intervention should be effective in cognitively impaired psychotic and non-psychotic (normal) individuals.

Because any trial in schizophrenia patients is burdened by a large number of confounders, a rational approach would suggest that POC trials of compounds hypothesized to enhance cognitive performance in schizophrenia should first be tested in non-psychotic individuals. Only these compounds in whom a signal can be detected should be tried in schizophrenia patients in whom much progress has be achieved in the methodology of measuring cognitive impartment in schizophrenia (MATICS, BACS).

Neurodegeneration in Schizophrenia: implications for the treatment

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Imaging studies have revealed structurally affected brain areas in schizophrenia. Overall, brain volume is decreased by 3 percent in patients as compared to controls. Particularly the frontal and temporal cortices and hippocampus complex are shrunken in patients. By following patients longitudinally using magnetic resonance imaging we and others have found that with longer illness duration, brain abnormalities become more severe. The progressive brain tissue loss is most pronounced in the early phases of the disease but not restricted to recent onset patients. Indeed, progressive brain tissue loss also occurs in chronically ill patients who have been ill up to 20 years. What do we know about possible causes of these progressive brain changes in schizophrenia? The progressive brain tissue loss is at least partly attributable to genetic factors related to the disease. Since we find that the adult human brain continues to have plastic properties, including cortical thickness growth, normal brain plasticity may be arrested in schizophrenia. Finding causes for progression and continued brain growth could provide a portal to new treatments.

Cardiovascular risks of antipsychotic treatment

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Atypical antipsychotics are the treatment of choice for patients with schizophrenia. They are generally better tolerated than conventional antipsychotics since most do not cause debilitating extrapyramidal symptoms. They are associated though with an array of cardiovascular adverse events that may affect morbid-mortality of schizophrenic patients. Orthostatic hypotension, electrocardiographic changes and metabolic syndrome (MS) are the main cardiovascular effects of atypical antipsychotics. Some antipsychotic drugs have been found to prolong the QT interval on electrocardiographic (ECG) recordings, a phenomenon which, when severe, may facilitate the occurrence of complex ventricular arrhythmias such as torsade de pointes. However, the effects of these drugs on the cardiac repolarization process have not been evaluated extensively. They contribute to the overall disease burden associated with schizophrenia even though the benefit risk of such treatments still is highly favourable. In this lecture we will review the main cardiovascular side effects of antipsychotics, the pharmacological mechanisms involved, and to which drugs they are particularly attributed.

The genetics of bipolar spectrum disorders

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Bipolar disorder (BP) is a complex disorder caused by a number of liability genes interacting with the environment. In recent years, a huge number of linkage and association studies have been conducted producing an extremely large number of findings often not replicated or partially replicated. Further, linkage and associations studies results are not always easily comparable. Unfortunately at present a comprehensive coverage of available evidence is still lacking. The presentation will summarize results obtained from both linkage and association studies in BP.
A number of genes seem to be definitively involved in BP, such as SLC6A4, TPH2, DRD4, SLC6A3, DAOA, DTNBP1, NRG1, DISC1 and BDNF. A number of other promising genes, which have received independent confirmations, and genes that have to be further investigated in BP, will be discussed.
In conclusion, the combination of linkage and association approaches provided a number of liability genes. Nevertheless, other approaches are required to disentangle conflicting findings, such as gene interaction analyses, interaction with psychosocial and environmental factors and, finally, endophenotypes investigations.

Antipsychotic drugs and the risk of cerebrovascular events: which evidence ?

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After 2002, an association between stroke and antipsychotic use was reported in clinical trials and large database studies. A search of MEDLINE covering the period from 1966 to June 2009 was carried out using selected keywords. Inclusion criteria were (i) quantitative reviews on stroke and antipsychotics; (ii) double-blind, placebo-controlled clinical trials involving patients with dementia treated with antipsychotics; and (iii) observational database cohort studies and observational case-control studies investigating the association between stroke and antipsychotics. Clinical trials were excluded if they were single-blind or if patients were affected by dementia and/or other neurological illnesses. Four reviews with aggregate data, 2 meta-analyses, 13 randomized, double-blind, controlled trials, 7 observational cohort studies and 4 observational case-control studies were selected and analysed. The incidence of cerebrovascular accidents (CVAs) was found to be very low in aggregate reviews and meta-analyses (2-4%). When the number collected was sufficiently high, or different drug treatments were grouped together, the higher rate in subjects exposed to antipsychotics was statistically significant. Inspection of other randomized controlled clinical trials, not included in aggregate reviews and meta-analyses, reported similar rates of CVAs. The majority of observational cohort studies compared typical and atypical antipsychotics and no significant class differences were found. A comparison with non-users was carried out in some cohort studies. In case-control studies, the probability of CVAs in users compared with non-users was in the range of 1.3- to 2-fold greater. Preliminary data also indicate that the highest risk of stroke is related to the first weeks of treatment, and a risk profile for stroke is emerging, such as older age, cognitive impairment and vascular illness. Different pathophysiological pathways may be involved, ranging from the facilitation of thrombosis, pre-existing cardiovascular factors, sedation and a common diathesis for stroke of dementia, schizophrenia and affective illness. Before prescribing an antipsychotic, clinicians should weigh all the risk factors for a given patient and consider not only the indications as provided by the regulatory agencies, but also the overall effectiveness of typical and atypical antipsychotics.

Cognitive dysfunctions as endophenotypes of schizophrenia: neurobiological correlates

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Cognitive impairment in schizophrenia is considered a core feature of the syndrome since Kraepelin's definition of Dementia Praecox. It is present in the majority of subjects with schizophrenia, is not an epiphenomenon of the symptoms, is a risk factor for psychotic disorders and contributes to poor functional outcome. More recently, it ranks as a prime candidate for the endophenotype domain, as it shows moderate to large effect sizes in comparisons between schizophrenia patients and community controls, is state independent, is not due to medications and is observed in non affected relatives of patients. Impairments in Attention, Verbal Declarative Memory, Working Memory and Face Processing are regarded as the most reliable candidates. Electrophysiological indices of cognitive functions, such as P50 and P300, are also being studied as schizophrenia endophenotypes. The advantage of using cognitive endophenotypes in schizophrenia research is represented by the possibility to establish their neurobiological substrates and underlying genetic architecture, supposedly simpler than the one underlying the complex syndrome of schizophrenia. The utility of these measures for genetic studies depends on their heritability, and for most of them significant heritability has been demonstrated. Animal models for studying genetic and molecular alterations underlying cognitive dysfunctions in schizophrenia are also being developed and promise new insight in pathogenetic mechanisms of the syndrome. However, so far, it is premature to conclude that schizophrenia cognitive endophenotypes are going to represent a breakthrough in schizophrenia research.