Psychiatria Danubina, 2010; Vol. 22, No. 2, pp 211–220 *Conference paper*

THE STAGING MODEL IN SCHIZOPHRENIA, AND ITS CLINICAL IMPLICATIONS

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SUMMARY

Introduction: *Illnesses which develop in a complex way are best described in stages, and those stages will describe not only a particular point in the course of the disease but also the appropriate treatment for that stage. This approach has, over the years, proved to be very appropriate for planning the treatment of various cancers. It is suggested that in the same way, it can be very important in planning the treatment of a complex illness such as schizophrenia. We aim to describe the staging model of schizophrenia, show the neuroimaging and clinical evidence for it, and discuss its implications for treatment.*

Method: *We propose that the development of schizophrenia can be described in at least three stages; the prodrome, the firstepisode, and the chronic phase. In order to describe these stages, we will use data derived wherever possible from literature published in Europe, and we will compare this with data produced from other continents of the world, notably Australia. This is done by reference to and examination of the original published literature, in order that this evidence may be tested against criteria for evidence of a staging model which we propose.*

Results: *There is much data, from clinical studies which show that schizophrenia develops over time and that its presentation can be described in at least three stages in the development of a schizophrenic illness; the prodrome, the first episode, and the long term chronic phase. It is also true that there is a pre-morbid phase before the prodrome, where it is possible to identify delays in such signs of early neurodevelopment as early paediatric milestones which may suggest an increased risk of schizophrenia in the future. This is mirrored in descriptions of the MRI findings, with loss of gray matter beginning in the prodrome, as well as in changes in cognition which develop as the illness develops over time.*

Discussion: *It follows from this model that treatment is different in all these three stages, and that the expected outcome of treatment will be different in each of the various stages of the illness. In all the phases of the illness, evidence based psychological interventions, including psycho-education, cognitive therapy, family interventions, and other interventions to prevent relapse work together with medication in order to optimise treatment.*

Conclusion: *Consequently, any attempt to optimise treatment in schizophrenia must take into account the different stages of the illness, and target outcomes must be appropriate for these stages. The treatments, both pharmacological and psychological must be appropriate to the stage of the disease. The application of treatment protocols which are inappropriate to the stage of the disease may lead to sub-optimal outcomes, and even to iatrogenic harm.*

Key words: *staging – psychiatry – schizophrenia – neuroimaging - early intervention in psychosis*

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INTRODUCTION

Illnesses which develop in a complex way are best described in stages, and those stages will describe not only a particular point in the course of the disease but also the appropriate treatment for that stage. This approach has, over the years, proved to be very appropriate for planning the treatment of various cancers . It is suggested that in the same way, it can be very important in planning the treatment of a complex illness such as schizophrenia. We will first illustrate the above statement by reference to the use of a staging process with regards to cancers, the conventional way in which such a process is used.

The extent or age of cancer at the time of diagnosis is a key factor that defines prognosis. It is the most powerful predictor of survival, hence treatments are often planned accordingly, based on the experience and outcomes of groups of prior patients with similar stage. In addition, accurate staging is necessary to evaluate the results of treatments and clinical trials, to facilitate the exchange and comparison of information among treatment centres, and to serve as a basis for clinical and translational cancer research. Staging systems exist for most cancer types, and whilst there are competing staging systems, the most universally-accepted and clinically useful staging system is the tumour node metastasis (TNM) system, which classifies cancers by the size and extent of the primary tumour (T), involvement of regional lymph node (N), and the presence or absence of distant metastases (M), supplemented in recent years by carefully selected non-anatomic prognostic factors. This system is maintained collaboratively by the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC), and is periodically modified in response to newly acquired clinical data and improved understanding of cancer biology and factors affecting

prognosis. The agreement of classification of cancer cases at national and international levels provides a method of clearly conveying clinical experience without ambiguity (AJCC).

Hence, in order to develop an analogous model in a mental illness such as schizophrenia, it is necessary to demonstrate that there are well defined clinical presentations associated with each individual stage, and that these stages are mirrored by anatomical or pathological changes which can be observed in the brain which can be related to the changes in the clinical picture. The development of MRI techniques has enabled us to observe such anatomical, pathological changes in the brain, which also reflect changes in brain plasticity and are mirrored by changes in brain functioning, reflected by changes in cognition which can be observed and tested.

METHOD

We therefore propose the following tests in order to assess whether the idea of a clinical staging model of schizophrenia is appropriate;

1. Can we demonstrate that there are well defined clinical presentations associated with each individual stage?
2. Are these stages are mirrored by anatomical or pathological changes which can be observed in the brain which can be related to the changes in the clinical picture?
3. Does the application of a staging system actually help in assessing the patient and deciding appropriate treatment, as well as planning research into the treatment of the illness?

The concept of staging in schizophrenia developed as a result of Professor Patrick McGorry's work in Melbourne, Australia, and is supported by the work of Professor Christos Pantelis, also from Melbourne. While McGorry described clinical stages in the illness (McGorry et al. 2006), Pantelis demonstrated analogous stages in neuro-anatomy in the brain by MRI studies, and in these same studies demonstrated changes in gray matter which mirror changes in the plasticity of the brain (Pantelis et al. 2003). It is the concordance between these clinical and neuroimaging findings which make a staging model of schizophrenia so appropriate.

We propose that the development of schizophrenia can be described in at least three stages; the prodrome, the first episode, and the chronic phase. In order to describe these stages, rather than the Anglo-Australian data, we will use data derived wherever possible from literature published in Europe, and we will compare this with data produced from other continents of the world, notably Australia . Thus we can argue that a staging model for schizophrenia is appropriate for use in European Psychiatry.

As part of our method in this presentation we choose to use original quotes from other authors. We mark these by using italics and inverted comas, as well as fully referencing the quotes. These words, carefully weighed and chosen by the original authors, constitute the evidence itself, which provides the arguments for considering a staging model of schizophrenia, and they may or may not have been used by the authors for this purpose, indeed ,often they are used in order to describe precisely what the authors have observed, and in such a case we need to evaluate whether this evidence points to the appropriateness of a staging system. Therefore we feel it is not appropriate to change the words of those whom we quote, when carrying out a review such as this, because it is not really possible to express in better words what has been said by others ,who we gratefully acknowledge, our task being to bring these concepts together in one place and to assess whether the data presented and the arguments made actually fit together in order to support and demonstrate the concept of staging in schizophrenia.

RESULTS

There is much data, from clinical studies which show that schizophrenia develops over time and that its presentation can be described in at least three stages in the development of a schizophrenic illness; the prodrome, the first episode, and the long term chronic phase (Singh et al. 2005). It is also true that there is a pre-morbid phase before the prodrome, where it is possible to identify delays in such signs of early neurodevelopment as early paediatric milestones which may suggest an increased risk of schizophrenia in the future (Jones et al. 1994, Cannon et al. 2003). Hence it appears that there may be a neurodevelopmental process, already raising the risk for psychosis in the premorbid phase, which then develops, in the late teen/early twenties years ,into the prodromal phase.

This development into the prodromal phase of the illness is mirrored in descriptions of the MRI findings, with loss of gray matter beginning in the prodrome, as well as in changes in cognition which develop as the illness develops over time (Pantelis et al. 2003) (Meisenzahl et al. 2008). This loss of gray matter in the Prodrome was described for the first time in 2003 by Pantelis et al. (Pantelis et al. 2003), who showed for the first time that such loss of gray matter began in the prodromal period. He reported *'In the cross-sectional comparison, compared with people who did not develop psychosis, those who did develop the disorder had less grey matter in the right medial temporal, lateral temporal, and inferior frontal cortex, and in the cingulate cortex bilaterally (Pantelis et al. 2003). In the longitudinal comparison, when re-scanned, individuals who had developed psychosis showed a reduction in grey matter in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyri (Pantelis et al. 2003). In those who had not become psychotic, longitudinal changes were restricted to the cerebellum (Pantelis et al. 2003). Some of the grey-*

matter abnormalities associated with psychotic disorders predate the onset of frank symptoms, whereas others appear in association with their first expression' (Pantelis et al. 2003). It is worth commenting that as well as Australian colleagues, some of the authors of this study were British, including Philip McGuire and Ed Bullmore.

This finding was commented on by others, in particular, by Singh in his clinical study of the development of prodromal psychosis (Singh et al. 2005). Singh commented 'It appears that in a proportion of cases, particularly with schizophrenia, anti-psychotics are initiated during the prodromal stage, prior to the emergence of frank psychotic symptoms. A recent report that specific brain changes accompany prodromal decline and predate the emergence of frank psychosis, *if replicated*, will provide compelling justification for intervening in the prodromal phase' (Singh et al. 2005).

Of relevance to this discussion is also the comment by Marshall (Marshall et al. 2005) in his discussion of the evidence that a long duration of untreated psychosis led to poorer outcomes in schizophrenia. "In long vs. short DUP group comparisons, there was no obvious relationship between the effect size and the cut off point chosen to define the long and short DUP groups. These observations are compatible with a recently advanced hypothesis that the long – term harm caused by psychosis occurs principally in the first few months or even weeks after onset"… (Marshall et al. 2005).

When Pantelis continued to investigate the changes which occur in the prodromal phase of psychosis, he described the following process, which were the conclusions he reached by correlating neurocognitive tests with fMRI of patients with different phases of psychotic illness from the earliest prodromal , through first episode psychosis, to chronic schizophrenia. Based on these findings, he reported,

'Evidence is emerging to suggest that dynamic brain changes occur during the earliest stages of a psychotic illness , including around the time of transition to illness…' (Pantelis et al. 2003).

'Our initial longitudinal MRI findings in a group of individuals at ultra-high risk for developing a psychotic illness identified progressive neuroanatomical changes in those who went on to develop an illness, compared to the group who did not. (Pantelis et al. 2003)'…

'In the context of a staging model of psychosis (McGorry et al. 2006) we have undertaken a further series of longitudinal studies from ultra-high risk for psychosis and first-episode psychosis [FEP] through to chronic illness.' (Pantelis et al. 2006)...

'Using novel automated methods of analysis, ...we have identified progressive regionally and temporarily specific changes over the course of the illness.' (Pantelis et al. 2006)…

'Concurrently, neuropsychological evidence from our 10-year follow up study of FEP has identified progressive cognitive decline, specifically in attentional set-shifting ability and paired associate learning. Together, these changes are consistent with the neuroanatomical changes observed on the MRI scans of these patients.'…(Pantelis et al. 2006)

'…The subtle but complex nature of these neuroanatomical and neuropsychological changes throughout the course of schizophrenia can be placed in the context of what we know about normal and abnormal brain maturation. (Pantelis et al. 2006)'

…'The available evidence suggests that there are subtle regionally and temporarily specific neuro-biological changes through the course of psychosis (Pantelis et al. 2005), including:

(i) evidence for early (pre-and peri-natal) neuro-developmental anomalies

(ii) evidence of late (post-pubertal) neurodevelop-mental changes during the early stages of psychosis, involving an acceleration of normal brain maturational processes, associated with significant loss of grey matter in prefrontal regions, and

(iii) evidence for progressive grey-matter loss involving medial temporal and prefrontal regions around the time of transition to illness (Pantelis et al. 2006),

While the pathological processes underlying such progressive changes during 'late neurodevelopment' remain unclear they may reflect anomalies of synaptic plasticity, abnormal brain maturation, the adverse effects of stress, or other environmental factors'… (Pantelis et al. 2006), …'the features of schizophrenia (eg neuropsychological deficits(can be understood as a consequence of these multiple pathological processes at various neurodevelopmental stages, including genetic and nongenetic etiological factors' (Pantelis et al. 2006). Pantelis and his team has continued to carry out further studies which continue to validate these essential findings. These further studies include those on hippocampal and amygdale volumes, of the superior temporal gyrus, and of the anterior cingulate cortex by measurement of Brain surface contraction using Surface-based morphometry (Velakoulis et al. 2006, Pantelis et al. 2007, Fornito et al. 2008, Wood et al. 2008, Sun et al. 2009a, Sun et al. 2009b, Fornito et al. 2008, Takahashi et al. 2009, Takahashi et al. 2010). These studies are interesting and revealing, but we will not discuss them further, since, while they confirm and extend by adding detail to the earlier findings, they only further confirm that a staging model fits the development of schizophrenia.

The challenge to replicate these findings has been taken up by many groups, including Moller and Meisenzahl (Meisenzahl et al. 2008) in Munich.

Moller (Moller 2006) has, in a conference abstract, commented on the new developments in neurodeve-lopmental theory of schizophrenia.

'The neurodevelopmental hypothesis of schizo-phrenia is of greatest importance in the neurobiological

understanding of the aethopathogenesis of schizophrenia. This hypothesis focuses on insults to prenatal brain development, which lead to brain alterations (Moller 2006). Premorbid cognitive disturbances as well as behavioural abnormalities are interpreted as vulnerability markers in the context of this neurodevelopmental theory and are seen as a consequence of the premorbid brain alterations (Moller 2006). Given the fact that heritability alone cannot explain schizophrenia, nongenetic factors impairing development must also be part of a multifactorial aetiopathogenesis of schizophrenia (Moller 2006). The neurodevelopmental models have varied considerably with respect to specificity and timing of hypothesized genetic and environmental 'hits'.' (Moller 2006)

In recent years longitudinal brain imaging studies of both early and adult onset populations indicate that progressive brain changes are more dynamic than previously thought, with gray matter volume loss particularly striking in adolescence and appearing to be an exaggeration of the normal developmental pattern (Moller 2006). This supports an extended time period of abnormal neurodevelopment in schizophrenia in addition to earlier 'lesions' (Moller 2006).

In past years in addition to the neurodevelopmental disorder a neuroprogressive brain disorder is under discussion to explain the decline especially in the poor outcome subgroup of schizophrenic patients' (Moller 2006). The idea that there is a neurodevelopmental process starting in the pre-morbid phase, after a 'first hit'-genetic or otherwise-, and followed by an intensified neurodevelopmental process starting in the late teens and early twenties after a 'second hit' linked with apoptosis and the remodelling into the adult brain, and accentuating into the first psychotic episode, while later perhaps being replaced by a neuroprogressive disorder in the the poor outcome subgroup of schizophrenic patients argues very well for a staging model for schizophrenia.

Thus, the Europeans, while accepting the gray matter changes in the prodrome , have gone further and described the changes which occur in the following stages of the illness, both elegantly confirming the changes in the prodrome and the first episode, as described by Meisenzahl (Meisenzahl et al. 2008) – and thus answering Singh's challenge-, and then describing further in her work (Meisenzahl et al. 2006) the continuing changes in brain plasticity later in the disease which thus describe the more chronic stage of the schizophrenic illness, including subgroups with severe illness.

Meisenzahl describes the prodromal changes as follows (Meisenzahl et al. 2008);

'Forty Untreated high-risk (HR) individuals for psychosis and 75 healthy control subjects (HC) matched for age, gender, handedness and educational level were investigated by structural MRI. 'High Risk subjects were recruited at the Early Detection and Intervention Centre for Mental Crises (FETZ) of the Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Germany (Meisenzahl et al. 2008).

Measurements of gray matter volumes were performed by voxel-based morphometry using SPM5. The sample of High Risk subjects showed Gray Matter volume reductions in frontal, lateral temporal and medial temporal regions compared to the healthy control group (Meisenzahl et al. 2008). These regions are compatible with structural findings in the clinically apparent disease of schizophrenia.' (Meisenzahl et al. 2008).

Spencer from Edinburgh has also described, in his work on the Edinburgh high risk study, has also described changes in the prodrome of a psychotic illness. His findings also validate the changes in the prodrome of psychosis (Spencer et al. 2007).

Meisenzahl compares the findings in first episode psychosis to those in patients with recurrent schizophrenia as follows (Meisenzahl et al. 2008): 'Structural alterations in schizophrenia have mainly been regarded as the result of neurodevelopmental processes. However, it remains unresolved whether the pattern of morphological brain changes differs between different stages of disease (Meisenzahl et al. 2008). We examined structural brain changes in 93 first-episode (FES) and 72 recurrently ill (REZ) patients with schizophrenia (SZ) and 175 matched healthy control subjects (HC) using cross-sectional and conjunctional voxel-based morphometry (VBM) of whole-brain MRI data in a three-step approach (Meisenzahl et al. 2008). We found significant grey matter density (GMD) reductions in first episode patients compared to healthy controls bilaterally in the temporal and prefrontal areas, including the anterior cingulate gyrus, as well as in both thalami (Meisenzahl et al. 2008). Hippocampus and amygdala were affected on the left side ($P<0.05$, corrected)' (Meisenzahl et al. 2008).

'In recurrently ill patients this pattern was spatially extended. The basal ganglia were exclusively reduced in the recurrently ill group compared to controls'. (Meisenzahl et al. 2008) 'Common to both disease groups were reductions in the bilateral perisylvian regions, the opercular region, the insula, prefrontal cortex, left inferior temporal gyrus, limbic system including hippocampus and amygdala, and the thalami'(Meisenzahl et al. 2008).

'In first episode patients there were no regions affected that were not also affected in recurrently ill patients'(Meisenzahl et al. 2008).

'In contrast, recurrently ill patients showed extended alterations within the frontal and temporal regions, the hippocampus, amygdala and exclusively in the basal ganglia relative to the FES patients. (Meisenzahl et al. 2008). Our findings suggest a system-specific involvement of neuronal networks in schizophrenia. (Meisenzahl et al. 2008). Furthermore, our data suggest that in the advanced stages of schizophrenia additional cortical and subcortical brain areas become involved in the disease process.' (Meisenzahl et al. 2008)

A further quote from Meisenzahl, from a conference abstract, (Meisenzahl et al. 2006) describes changes observed in patients who were seen first in the first episode, and then six years later;

'At baseline, patients compared to controls showed a reduced hippocampal volume bihemispherically, a reduced ACC volume, enlarged CSF spaces in the temporal horns and an enlarged third ventricle (Meisenzahl et al. 2006). Preliminary analysis of the 6 year FU data show accelerated enlargement in cortical sulcal cerebrospinal fluid spaces bitemporally and the temporal horns in the 6 year course of schizophrenia.' (Meisenzahl et al. 2006), and she concludes 'There are ongoing changes in the brains of schizophrenic patients during the initial years after diagnosis. (Meisenzahl et al. 2006) Disruptions in neurodevelopment or neural plasticity may act alone or in combination to bring about these progressive brain deficits in schizophrenia' (Meisenzahl et al. 2006), thus giving credence to the suggestion by Moller of 'a neuroprogressive brain disorder is under discussion to explain the decline especially in the poor outcome subgroup of schizophrenic patients' mentioned above (Moller 2006).

What then of clinical studies of the development of schizophrenia? A number of studies stand out, one is the ABC study of Hafner (Hafner et al. 1992) (Hafner et al. 2003), which describes a prodromal phase of schizophrenia lasting up to five years, followed by a first psychotic episode, and then the chronic phase. Another study is the study by Singh mentioned above, which also describes a prodromal, followed by a first episode stage. The British 'Northwick Park Study' (Johnstone et al. 1992) did not emphasize the prodromal phase, since patients were identified from the first episode, but was key to the identification of the 'critical period' (Birchwood 1998), which is the first three years after the first episode, in which the general mental state of patients continued to decline over the first three years after the first episode, particularly after each relapse, after which the state of the patient tended to plateau out. Therefore ,these first three years were seen as critical (i.e. a critical period) to the prognosis of the patient. These clinical findings relate to the concept of duration of untreated psychosis , finally demonstrated to be of importance in prognosis by Marshall, as quoted above (Marshall et al. 2005), and relate well to the neuroimaging findings of continuing changes in plasticity of the brain for several years after the first episode, described by Meisenzahl above (Meisenzahl et al. 2006). Hence, clinical studies in England and Germany , as well as another clinical longitudinal study reported in poster form from Slovenia (Blinc-Pesek et al. 2006, Blinc-Pesek et al. 2007), all correlate well with Neuroimaging studies from Germany and from Scotland, in order to show that there are at least three distinct stages in the development of schizophrenia; the prodromal phase, the first episode phase, followed by the 'critical period', and then the chronic phase. Thankfully Shepherd has shown a long time ago that only about 43% of patients reach the final chronic phase (Shepherd et al. 1989). Under these circumstances, it seems clear that the model of the development of schizophrenia in a series of stages has been shown to be appropriate for describing the development of the illness 'schizophrenia'.

DISCUSSION

It follows from this model that treatment is different in all these three stages, and that the expected outcome of treatment will be different in each of the various stages of the illness.

In all the phases of the illness, evidence based psychological interventions, including psycho-education, cognitive therapy, family interventions, and other interventions to prevent relapse work together with medication in order to optimise treatment.

Consequently, any attempt to optimise treatment in schizophrenia must take into account the different stages of the illness, and target outcomes must be appropriate for these stages. The treatments, both pharmacological and psychological must be appropriate to the stage of the disease. The application of treatment protocols which are inappropriate to the stage of the disease may lead to sub-optimal outcomes, and even to iatrogenic harm.

The staging model of schizophrenia has indeed been most widely used in order to encourage earlier intervention, with more appropriate methods to the early course of the disease . Thus, McGorry defined early intervention in psychosis as follows; Early Intervention in Psychosis 'amounts to deciding if a psychotic disorder has commenced and then offering effective treatment at the earliest possible point and secondly ensuring that intervention constitutes best practice for this phase of the illness, and *is not just the translation of standard treatments developed for later stages and more persistently ill subgroups of the disorder'* (Prof. Patrick McGorry, quoted in IRIS Guidelines 1999). However, given that in Europe there are many patients who suffer from chronic schizophrenia and are still treated in large asylum style institutions, it is worth considering that many interventions, such as cognitive therapy for hallucinations and delusions (Freeman et al. 1998, Kuipers et al. 1997, Garety et al. 1997, Kuipers et al. 1998), and family interventions in psychotic illness (Falloon et al. 1985,Leff et al. 1982) were first developed for patients with chronic schizophrenia, before they were applied to working with patients in the first episode or the prodrome of the illness. Hence, it is important to decide the expected outcomes in each stage of the psychotic illness, and to adapt interventions accordingly.

We now summarise the types of intervention which could be adapted to each stage of the illness and how interventions have been developed across Europe in order to treat patients at each stage.

1st Stage; The prodrome of psychotic illness.

- The key biological interventions in this period must be aimed at modulating plasticity and controlling apoptosis, so as to prevent or reduce the risk of transition to full illness.
- A number of studies in prodromal psychosis have been described, using Anti-psychotic medication and or cognitive therapy to attempt to prevent psychotic illness. (McGorry et al. 2002, Morrison et al. 2004, McGlashan et al. 2006, Nordentoft et al. 2006). The results are encouraging, with further large trials ongoing prior to review and potential meta-analysis of results to allow definitive conclusions regarding further research and policy implications.
- Some evidence is emerging from work in Slovenia that treatment of patients in the prodrome with low dose anti-psychotic medication and antidepressants or anxiolytics when necessary may lead to better psychosocial outcomes, lower hospital admission rates, and lower medication doses for maintenance after the patients do develop full psychosis. (Novak et al. 2008a, Novak et al. 2008b). This evidence needs to be studied and replicated, however it is consonant with belief that biological change may start during the prodrome of the illness (Marshall et al. 2005, Singh et al. 2005), and not simply at the beginning of the first episode. This evidence suggests that treatment in the prodromal phase may improve outcomes.
- While present studies argue for the need of treatment in the prodrome in order to control the process of apoptosis and damage from oxidative stress, the fact that there are many side effects linked with present antipsychotic therapy argue for an optimisation of treatment approaches to the prodrome of psychotic illness by the search for new agents to control apoptosis (Berger et al. 2007).
- Early Detection, with reducing Duration of Untreated Psychosis, is believed to improve outcome.

Therefore, in the prodrome of the psychotic illness, the aim of treatment is the prevention of the illness to the fully psychotic, first episode stage, and this is the outcome which is desired. Working with these patients is still in the experimental stage, although there are now a number of clinics working with patients in this stage, such as PACE in Melbourne, OASIS in London, and the FETZ network in Germany. Recently, a European study has reported on transition rates to psychosis (Ruhrmann et al. 2010), and, while there have been several trials reported of treatments including antipsychotic medication (McGlashan et al. 2006, Ruhrmann et al. 2007), cognitive therapy (Bechdolf et al. 2007, Morrison et al. 2004) or both, (McGorry et al. 2002), as well as assertive working (Nordentoft et al. 2006) recently an Austrian study has reported on the use of omega fatty acids for preventing transition to psychosis (Amminger et al. 2010).

The aim in these studies is to achieve neuroprotection in emerging psychosis, in effect by finding compounds which will modulate apoptosis without too many side effects, since anti-psychotics do have important side effects, including metabolic syndrome (Berger et al. 2007).

In both prodromal and first episode projects, outreach work to identify and treat cases early is key to success in preventing symptom development and the TIPS project in Norway (Joa et al. 2008) is a classical example of what can be done in this regard. (Larsen et al. 2007, Larsen et al. 2008).

Stage 2; The first psychotic episode, and the three year critical period subsequent to this.

- In order to optimise outcomes in first episodes of psychosis, all the psychosocial interventions listed above will need to be provided; these include Family Interventions, CBT, Compliance therapy, Relapse Prevention, and Psychoeducation (Agius et al. 2007). The aim is to enable patients to control their own illness.
- The maintenance of Cognition is a key measure of outcome. Repeated measures of Cognition, perhaps using computer based neurocognitive tests, will be needed to monitor treatment.
- Medication needs to be optimised in order to treat acute symptoms, improve cognition, and avoid side effects where possible.
- Post-psychotic depression needs to be dealt with.
- Psycho-education must include advice to refrain from use of illicit drugs.
- All the psychosocial interventions listed above ,as well as all the social interventions to enable the patient to return to work and education, and to offer support with finance and housing will require an effective assertive form of care-coordination.

Therefore, in the first episode of psychosis , the aim of treatment is the full remission of symptoms ,and then the prevention of relapse during the critical period. The desired practical outcome is return to full functioning, including return to work and education, and this is achieved by a combination of atypical antipsychotics, psychoeducation, prevention of relapse by the identification and treatment of early warning signs, social interventions, cognitive therapy, and working with families. Our own work (Agius et al. 2007) and that of others in Denmark (Petersen et al. 2005, Rosenbaum et al. 2005), Sweden (Cullberg et al. 2002), England (Craig et al. 2004,Garety et al. 2006), and Russia (Zaytseva et al. 2008) shows that this can be achieved. All these studies taken together show that application of all these methods together by appropriately organised teams give better results than treatment as usual to patients recovering from a first psychotic episode.

Stage 3. Patients who suffer chronic schizophrenic Illness.

- Optimisation of Medication, including the appropriate use of clozapine is extremely important at this phase. There is a need to optimise medication approaches by the development of new medications and combinations of medications which will enhance cognition, and will have effective anti-psychotic and relapse prevention properties..
- Prevention of relapse is essential to optimisation of outcomes. This could be done by the large scale use of card-sort techniques to help patients (Agius et al. 2006) and families identify early warning signs of relapse, but then telemedicine techniques (Spaniel et al. 2008) using a mobile phone system could be considered in order to rapidly intervene with medication and advice to prevent relapse.
- All the psychosocial interventions listed above, including CBT, Family Interventions, and psychoeducation as well as all the social interventions to enable the patient to return to work and education, and to offer support with finance and housing will require an effective assertive form of care-coordination.

Some patients do follow a chronic course, and here, in the final stage of the illness, the expected outcomes must be more modest, but they should include symptom control, inclusion in society to the degree which is most possible, appropriate accommodation and general functioning to the patient's full potential, as well as ensuring patient safety and the safety of others. This too is achievable, by the use of such medications as clozapine, depot medication to improve compliance, proper accommodation, cognitive therapy, to the extent that this is possible (Drury et al. 1996a, Drury et al. 1996b), psycho-education, prevention of relapse by the identification and treatment of early warning signs, risk assessment, working assertively with patients (Burns et al. 1999, UK 700 group 1999) and behavioural family therapy (Falloon et al. 1985,Leff et al. 1982). A Czech project, ITAREPS, has provided a telemedicine method for identifying early relapse (Spaniel et al. 2008, Spaniel et al. 2008). A Croatian project has also made a study of early warning sign identification (Agius et al. 2006), adapting Birchwood's British work to a Croatian setting. The same team has recently published a study on risk assessment, again adapting British work for local use (Presečki et al. 2010). Slovene and Croatian teams have begun to develop assertive outreach projects (Agius et al. 2009, Gruber et al. 2008, Ivezić et al. 2010). It should be mentioned that cognitive deficits can be identified even during the first episode of the illness, but are prominent in patients with chronic schizophrenia, and this should encourage the development of a new generation of drugs, working perhaps on the glutamate pathway, which could improve cognition in chronic schizophrenia.

Thus, treatment in the three stages of schizophrenia is different, with different aims and different outcomes, and hence, it is clear that any attempt to optimise the outcome of treatment in schizophrenia must include at least three different treatment programs, which will optimise treatment in each of the stages of the disease.

CONCLUSION

We can cogently claim that the three tests which we proposed in the beginning of this article have been met by the staging model of schizophrenia.

1. We can demonstrate that there are well defined clinical presentations associated with each individual stage.
2. These stages are mirrored by anatomical or pathological changes which can be observed in the brain which can be related to the changes in the clinical picture.
3. he application of a staging system actually help in assessing the patient and deciding appropriate treatment, as well as planning research into the treatment of the illness.

The concept of a staging approach to the treatment of schizophrenia is gaining prominence. McGorry has argued cogently for such a model (McGorry et al. 2006, McGorry et al. 2007, McGorry et al. 2007, McGorry et al. 2010); He has written;*' A clinical staging model, widely used in clinical medicine, could improve the utility of diagnosis in psychiatry, especially in young people with emerging disorders (McGorry et.al. 2007). Clinical staging has immediate potential to improve the logic and timing of interventions in psychiatry, as it does in many complex and potentially serious medical disorders (McGorry et.al. 2007). Interventions could be evaluated in terms of their ability to prevent or delay progression from earlier to later stages of a disorder, and selected by consumers and clinicians on the basis of clear-cut risk-benefit criteria (McGorry et al. 2007). This would ensure that, as treatments are offered earlier, they remain safe, acceptable and affordable, and potentially more effective. (McGorry et al. 2007) Biological variables and a range of candidate risk and protective factors could be studied within and across stages, and their role, specificity and centrality in risk, onset and progression of disorders clarified. (McGorry et al. 2007) In this way, a clinicopathological framework could be progressively constructed (McGorry et al. 2007). Clinical staging, with restructuring across and within diagnostic boundaries and explicit operational criteria for extent and progression of disorder, should be actively explored in psychiatry as a heuristic strategy for developing and evaluating earlier, safer, and more effective clinical interventions, and for clarifying the biological basis of psychiatric disorders (McGorry et al. 2007).'*

However, the Europeans have, as we have demonstrated, also contributed, and calls for the

possibility of using such a staging system have recently been made from Italy (Fava et al. 1993) and Sweden (Archer et al. 2010), where the implications of epigenetics for staging have also been discussed (Archer et al. 2010).

However, the Europeans have , as we have demonstrated, also contributed, and calls for the possibility of using such a staging system have recently been made from Italy (Fava et al. 1993) and Sweden (Archer et al. 2010), where the implications of epigenetics for staging have also been discussed (Archer et al. 2010).

Hence, it is reasonable to assert that evidence from European, including central European, sources does support the concept of a staging model to describe the development of schizophrenia. Indeed, it appears reasonable to assert, on the basis of the discussion above, that it is the staging model of schizophrenia which underpins and makes systematic all the new developments in care for patients with schizophrenia in Europe which we have mentioned above and which improve care for patients in every stage of the illness.

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