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PSYCHOSIS RISK SYNDROME: IS IT WORTH THE RISK?

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SUMMARY

The American Psychiatric Association is considering listing the 'Psychosis Risk Syndrome' as a diagnosis in its own right in the DSM-5. This decision recognises the paradigm shift in clinical psychiatry to a model of early intervention. However, this decision has aroused much discussion. The controversy which has arisen around this proposal reflects the difficulties in implementing the early intervention paradigm. Here we review the different opinions which have been expressed regarding this issue and consider whether this is the appropriate time to include 'Psychosis Risk Syndrome' as an independently listed psychiatric diagnosis.

Key words: *'Psychosis Risk Syndrome' - ultra high risk mental state*

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INTRODUCTION

Major divergence of opinion has arisen as a result of the proposal that the American Psychiatric Association should include "Psychosis Risk Syndrome" as a separate diagnosis in DSM 5 (Woods 2009, Woods 2010, Carpenter 2009).

As proposed, the criteria for this "Psychosis Risk Syndrome" are:

- Symptoms: At least one of delusions, hallucinations or disorganised speech that is of sufficient severity and/or frequency, but attenuated enough so as to preserve intact reality testing.
- Frequency: At the very least, the symptoms above must have been experienced weekly during the month preceding psychiatric consultation.
- Progression: The symptoms above must have commenced, or have worsened, in the past year.
- Distress, disability and treatment-seeking: treatment is sought as the symptoms above are sufficiently distressing and/or disabling to the patient and/or others.
- There is no better DSM-V diagnosis for the clinical presentation, and psychosis must never have occurred.

Similar criteria have been employed in research for years; McGorry and Yung were the first to develop the concept of "Ultra-High Risk" in order to study the development of frank psychotic illness (McGorry 2002). This concept of 'ultra high risk', and prodromal psychosis has driven the development of the Psychosis Risk Syndrome (PRS).

It is argued that PRS is a 'simpler concept' than its predecessors. However, one major argument against its proposed inclusion in the DSM-V is that it does not render the process of diagnosis 'simpler', and that PRS could lead to diagnostic confusion in the hands of inexperienced clinicians.

It is perhaps best to discuss this issue from five inter-related yet quite distinct angles: semantics, early intervention, the availability of supporting evidence, medical ethics, and compliance.

SEMANTICS

Note the first of the criteria listed above: "delusions… so as to preserve intact reality testing." The latter half of this statement distinguishes schizophrenia from PRS, both of which share the same core symptoms. Thus PRS can be argued to represent a 'mild schizophrenia' in a flawed or attenuated manner unless it also is understood to represent a single stage in the ongoing process of the development of a psychotic illness (at present such a developmental element is not mentioned in the specification of PRS). A delusion implies an impairment of 'reality testing'. This inherent incongruity renders the diagnosis of PRS difficult to apply, given the categorical, as opposed to the developmental, nature of psychiatric diagnosis.

Both the DSM-IV and ICD-10 classifications of psychiatric diagnoses are categorical. This means that they give a list of symptoms which, if present, suggest a particular end-point diagnosis. There is no attempt in these classifications to relate this cross section of symptoms to aetiology. But the aetiology of psychotic illness is at least polygenetic. This polygenetic inheritance is modulated by psychological and social factors. Hence we here argue for a classification based on spectra (Craddock 2005), which reflect the polygenetic inheritance. Thus schizophrenia, schizoaffective disorder, and bipolar disorder can be described as emanations of the schizophrenia spectrum. (Fleischhacker 2012) Over time, the same illness may be considered to develop over stages; we argue that there are at least three stages in schizophrenia: the prodromal phase, the first episode, and the chronic illness (Agius 2010). Thus we would argue that new classifications should reflect these

genetic and spectral issues and, through staging, the way in which illness develops.

A delusion with intact reality-testing is in fact an 'over-valued idea'. Progression from this to a delusion may represent a significant milestone in the evolution of schizophrenia; hence PRS, if clearly specified and defined, should be a sign of the ongoing development of schizophrenia.

Kaymaz & van Os (2010) identified another semantic issue in the proposed PRS criteria: "…symptoms are sufficiently distressing and/or disabling… to lead to help-seeking." They argue that individuals who require psychiatric intervention are no longer "at risk" but rather "in need of care" (Kaymaz 2010). A crucial delineating question relates to when the symptomatic experience may be deemed to be an early first episode rather than mere indicators of 'high risk'.

Given fingertip accessibility to medical information, patients may ascertain that their diagnosis was dependent upon the presence of sufficiently "attenuated" symptoms; as the degree of attenuation is not coherently specified ("…so as to preserve intact reality testing"), some patients may feel that their doctors have belittled their problems. Consequently, the doctor-patient relationship may become compromised, and this may lead to a deleterious effect on therapeutic concordance.

Ross (2010) noted that very broad interpretation of the PRS criteria can lead to unacceptable variation in diagnosis among different clinicians.(Ross 2010) This may occur most amongst physicians with limited experience in identifying psychiatric prodromes.

EARLY INTERVENTION

PRS may be regarded as an important acknowledgement of the recent psychiatric paradigm shift towards early intervention, a movement that has been met with much optimism. Early intervention has to be commended, and it has good empirical evidence to support it: a study by Larsen et al. and two meta-analyses by Perkins et al. and Marshall et al. demonstrated the strong association between the duration of untreated psychosis (DUP) and outcome. (Larsen 2006, Perkins 2005, Marshall 2005) The results showed that the greater the DUP, the worse the overall score on the global assessment of functioning (GAF) scale. (Perkins 2005) Response to pharmacotherapy was significantly worse in long DUP groups (Perkins 2005). However, patients often require psychiatric management before such a definitive diagnostic category can be assigned, and it may be argued that the inclusion of PRS is useful, since it acknowledges the reality that physicians tend to treat symptoms, not the DSM's codified diagnoses.

Johannessen & McGorry (2010) assert that recognising early phases of mental illness is a step in the right direction towards a "clinical staging model" that enables the selection of treatment strategies that are most efficacious, and least harmful, for a particular stage of disease (Johannessen 2010). Instead of advocating PRS, they offer an alternative: a 'pluripotential risk syndrome' (Johannessen 2010, Docherty 1978). They argue that this less specific prodrome reflects the unpredictable nature of "Ultra-High Risk" states (Johannessen 2010) which have been shown to be more likely to develop into a non-psychotic mood disorder than schizophrenia (Johannessen 2010). If this 'pluripotential risk syndrome' were to be successfully treated, then an effective secondary prevention strategy will have been developed in psychiatry.

SUPPORTING EVIDENCE

Extensive research has been conducted using UHR criteria, and variants thereof. None, as yet, has been done with PRS. So is its proposed inclusion into the next DSM a premature one?

The documented conversion (transition to full psychosis) rates for UHR groups are remarkably variable. With similar follow-up times, Hanssen et al. (2005) reported an annual conversion rate to full psychosis of 3.8%, whilst the equivalent figure obtained by Cannon et al. (2008) was 11.3% (Hanssen 2005, Cannon 2008). Van Os (2010) states that this discrepancy is difficult to explain, due in part to the undisclosed sample enrichment strategies employed by the North American study (Kaymaz 2010). There is difficulty in accepting new diagnostic concepts when the evidence which supports them is called into question. Notably, UHR differs from PRS insofar as it lacks 'Criterion D / Criterion 4' (ref. above), namely the criterion pertaining to disability, distress and suffering on the patient's part.

Given the lack of clinical evidence, psychiatrists must be confident that their practice guidelines are not affected by ulterior motives or biases, with potential medico-ethical implications. There is presently insufficient data to establish the risk of conversion to full psychosis in patients who fulfil the criteria for PRS. Thus, by logical continuation, PRS has scarce evidence to support its inclusion in the DSM-V. Some have argued that the incorporation of PRS will stimulate a drive for more research in this field; however others see this as an ethically dubious justification for this proposal.

MEDICO-ETHICAL IMPLICATIONS

Morrison et al. (2010) assert that the introduction of PRS prior to exhaustive research would be irresponsible owing to the possibility of causing more harm than good to a vulnerable and young patient group (Morrison 2010).

There has been an increase of the prescription of antipsychotic agents to under 18-year-olds in recent years. Morrison et al. (2010) argue that the inclusion of PRS may exonerate and exacerbate the over-medicalisation and over-prescription of anti-psychotic drugs (Morrison 2010, Pathak 2010). Add to this the lower specificity of positive psychotic symptoms to schizophrenia in children and adolescents – it is very concei-

vable that this would further fuel the psychiatrisation of transient and innocuous psychosis-like experiences in this demographic, particularly in the hands of the uninitiated and inexperienced (Arango 2011). However, several leading experts in the field have repeatedly asserted that this is an impotent argument against the inclusion of PRS, especially given the inadequacy of the current DSM-IV in catering for the relevant patients (Woods 2010).

The quintessential psychiatrist attempts to balance the adverse side-effects of treatment with symptomatic control. The undesired collateral effects of anti-psychotics are well known; on the other hand, those specific to developing brains are not (Morrison 2010, Bentall 2002). Morrison et al. (2010) argues that, in the absence of such information, it is unethical to prescribe antipsychotics; also, it is younger patients who are most likely to be affected by the PRS diagnosis.

Conversely some have argued that, since the patients who present are 'help-seeking', it is reasonable to treat them with the therapies that are available; this argument should hold even if the presenting problems are transient (Agius 2008). A team from Cambridgeshire has conducted a meta-analysis of trials of different treatments in order to establish those that are most efficacious (Kelly 2010). Treatments based on CBT alone have yet to prove their efficacy (Kelly 2010) Certainly the use of anti-depressants can be useful (Cornblatt 2007, Drake 2010) if mood symptoms are an important feature while the search continues for more effective non-antipsychotic agents with fewer side effects (Berger2007). The recent study of the use of omega-3 poly-unsaturated fatty acids also appears promising (Amminger 2010). The possibility that benign treatments may be effective in the early phases of disease is both exciting and promising, and justifies the research drive to identify such a therapeutic window.

As the side-effects of anti-psychotics can be very severe, not only may their prescription be potentially devastating to adolescent patients but compliance may also become a serious issue.

Concerns have been expressed that, if at-risk states are included in the classification of mental disorders, this could lead to further stigmatisation of individuals (Kingdon 2010).

Concerns have also been raised that, since schizophrenia is more often diagnosed in Western Society than in Afro-Caribbean patients, the possibility of the diagnosis 'Psychosis Risk Syndrome' may be applied disproportionately to these groups, hence affecting the human rights of these ethnic minorities (Fernando 2010).

THERAPEUTIC CONCORDANCE

The dropout rates in a trial that involved anti-psychotic medications and those in one that employed just cognitive therapy were 55% and 8%, respectively (McGlashan 2006, Morrison 2004). This is hardly surprising given the affected age group and the commonly intolerable side-effects that antipsychotics can produce.

Moreover, if the patient feels that their symptoms have been trivialised by their doctor, therapeutic concordance will become even more difficult to establish. Stigma and discrimination, which plague psychiatry to this day, would further hinder this.

A PREMATURE PROPOSAL?

Whilst PRS may spur on the development and expansion of early intervention services, the risks of entering it into a manual utilised by both the experienced and the inexperienced alike appear serious. There is doubt as to whether such an inclusion is helpful from an ethical standpoint, particularly if it mistakenly vindicates unnecessary treatment (Fusar-Poli 2012).

Larkin & Marshall (2010) made an interesting comparison between PRS and diagnostic tests (Larkin 2010). Their conclusion is that PRS is not sensitive, specific or predictive enough for it to be included in the DSM-V as a 'diagnostic test'.

While it is important to develop further preventive models in psychiatry (in particular early intervention) it is equally important to adopt a model which reflects the reality of the development of psychotic illness.

In light of this, another consideration is worthy of note. How does the suggestion of PRS fit with the longitudinal development of psychotic illness as demonstrated by neuroscience and, in particular, neuroimaging techniques? It has been demonstrated that loss of grey matter occurs in the brain even during the prodromal phase of psychotic illness; (Pantelis 2003, Meisenzahl 2008, Koutsouleris 2009) and, indeed Meisenzahl has shown that patients in the late 'at-risk mental state' have more grey matter loss than those in the early prodrome. This, as well as other demonstrable changes (such as in the pituitary) (Garner 2005, Pariante 2004) have enabled both McGorry (Pariante 2004, McGorry 2007) and our own group (Agius 2010), amongst others (Fleischhacker 2012), to argue for a staging approach to schizophrenia in which different stages are seen to have different neuroimaging correlates and different clinical pictures, different appropriate treatments and expected outcomes. This model has been developed to argue for developing more complete psychosis services in which the various phases of the illness are treated individualistically (Singh 2010, Cornblatt 2007). Perhaps it is time that classifications of disease should begin to take these developments into account. It would therefore be reasonable to substitute the present idea of PRS with one incorporating a number of stages of psychotic illness.

Meanwhile, it is important to remember the possibility that patients with 'ultra high risk mental states' often do not develop into full-blown psychosis, but may revert to normality or develop an affective

illness (interestingly, this is yet another contentious issue) (Woods 2010). Certainly Johannessen and McGorry's 'pluripotential risk syndrome' would be more in keeping with the naturally multiphasic evolution of many psychiatric disorders. The nebulous, indeterminate nature of its title should not detract from its utility in 'flagging' problems that require specialist attention; after all, this is the foremost aim of the PRS proposal. This alternative 'risk syndrome' also exhibits a dearth of empirical data, but it is one that, at least conceptually, is more holistic and less constricted than its PRS counterpart; and, in practice, its authors suggest the exclusive use of benign treatments so as to assuage the fear of treating 'false positives'.

CONCLUDING REMARKS

The search for a diagnostic utility in early psychiatric intervention is laudable. However, a decision such as this, with its panoply of economic, biomedical, social, legal and ethical implications, seems to have surfaced prematurely.

Without good quantitative evidence, and conclusions derived therefrom, it is difficult to recommend any radical alterations; and what of qualitative data? Nelson and Yung (2011) raised a praiseworthy point: what do the affected patients think of this (Nelson 2011)? The antediluvian age of medical paternalism seemingly lives on, at least implicitly in modern 'evidence-based medicine', and must be addressed.

Whilst there is little evidence for all of the 'risk syndromes', it may be deemed prudent to channel research efforts into the one that most closely describes the evolution of the illness. Thus we tentatively recommend that the McGorry 'pluripotential risk syndrome' be adopted instead of the presently proposed PRS with a view to promoting further research in this direction.

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