CHAPTER 1

Introduction

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AT RISK MENTAL STATES IN PSYCHOSIS: AN INTRODUCTION

The idea that a set of subjective experiences exist which, in many cases, herald imminent psychosis has a long history in psychiatry. However, the operational delineation of these features, often coupled with alterations in functioning and a background of demographic risk factors, was only developed to the extent that it was reliably definable and therefore useable in research, by Alison Yung, Patrick McGorry and colleagues in the mid 1990s (Yung et al., 1998). These criteria, which comprise four sub-sets, have given rise to a paradigm of research which promises much in terms of early detection and secondary, or even primary, preventions. The closest previous attempt at a set of reliable criteria was made by the Bonn group in the 1970s (Huber & Gross, 1989).

Terminology in this area continues to be confusing. The term ‘prodrome’ to describe this collection of subjective features is widely used, although it is technically wrong and possibly misleading to the sufferer. Epidemiologists define a prodrome as a set of symptoms, which in all cases will lead on to the full syndrome. This is not the case with this set of features described by Yung and colleagues (1998). Only a proportion of such cases go on at follow-up to develop psychosis, which means that the epidemiologically correct term is that this set of features is a ‘precursor’. This term has not caught on, perhaps because it lacks clinical immediacy. Instead, the terms ‘at risk mental state’ (ARMS) or ‘ultra-high risk mental state’ (UHR mental state) have been applied in an attempt to convey the message that nothing is inevitable.

The descriptive epidemiology of ARMS, how common they are, who gets them, how long they last and so on, is still in its infancy. We have little reliable data about the incidence and prevalence of this constellation of symptoms in the general community. Part of the reason for this is that studies which have set out to identify such cases are often in the context of treatment studies or clinical trials where, for ethical reasons as well as reasons of convenient ascertainment, clients are seeking help for these symptoms. Factors which cause an individual to seek help on the basis of these symptoms are not well understood. Community surveys, especially in Europe, have shown that a surprisingly high proportion of apparently healthy individuals, perhaps 5–15%, will report isolated psychosis-like phenomena for which most will not seek help. Presumably, the decision to seek help is partly
driven by the subjective distress and this will vary from one individual to another. On top of that, individuals will vary in the extent to which they seek help for a given level of distress, which will depend on a range of internal and external trait and state factors, including health beliefs, perceptions that the abnormalities constitute a threat to health and might be amenable to intervention, availability of health care and so on.

These currently unmeasured factors will inevitably mean that sample structure will be very sensitive to social context and thus collected samples will differ from one another in ways which are likely to be important, and influence final transition rates to psychosis, but are essentially unknown. Nonetheless, follow-up studies are in general agreement that the risk of developing an operationally defined Axis 1 psychosis over the next 12 months is massively increased. Rates of transition to psychosis in follow-up studies published so far vary between 10% and 50%. While some commentators see this five-fold variation as a weakness in the field, it is small in comparison to the increased risk this represents over the base population. An age-matched community sample of young adults would show an incidence rate of new cases of no more than five per 10,000 per year. Even a 10% risk of psychosis in the year following detection of an ARMS will therefore represent a 200-fold increased risk. This huge increase in risk, particularly in a population of young people, immediately raises the prospect of intervention to head off the psychosis.

INTERVENTION STUDIES: GENERAL METHODOLOGICAL ISSUES

Two plausible treatment modalities present themselves straight away, by inference from the treatment of psychosis: antipsychotic drug treatment and specifiable psychological treatment, specifically cognitive behaviour therapy. The evidence base for the effectiveness of antipsychotic drug treatments in psychosis is incontrovertible. The evidence base supporting the effectiveness of cognitive behaviour therapy in psychosis is more recent and smaller. However, several systematic reviews and meta-analyses have supported its effectiveness (Cormac, Jones & Campbell, 2002; Pilling et al., 2002), although only as an adjunct to antipsychotic drug treatment: it has not formally been assessed in the absence of drug treatment.

Three randomised controlled trials of interventions have now published interim or final data. The first was the Personal Assessment and Crisis Evaluation (PACE) trial by McGorry and colleagues (2002) in Melbourne, which evaluated the effectiveness of a six-month combined intervention of low dose risperidone, a second generation antipsychotic drug, plus cognitive behaviour therapy in addition to case management, compared to case management alone. This was an open trial. The second trial by McGlashan and colleagues (2003) at Yale was a double-blind randomised placebo controlled trial of low dose olanzapine, another second generation antipsychotic drug, versus placebo, for 12 months. The third trial, the Early Detection and Intervention Evaluation (EDIE) trial by Morrison and colleagues (2004) in Manchester, compared the effectiveness of a six-month (26 sessions) package of cognitive behaviour therapy versus monthly monitoring. The trials had important similarities. Each used the Melbourne criteria for defining cases; had a 12-month follow-up after commencement of treatment; randomised about 60 subjects and had rates of transition to psychosis as the primary outcome. The trials had important differences too, particularly in case-finding strategies. Assessment measures at baseline differed too: the PACE trial
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used the Comprehensive Assessment of At Risk Mental States (CAARMS) structured assessment tool (see Chapter 2), the Prevention through Risk Identification Management and Education (PRIME) trial used the Structured Interview for Prodromal States (SIPS: Miller et al., 2003), and the EDIE trial used the Positive and Negative Syndrome Scale (PANSS).

Results showed that each of the interventions had some therapeutic effect in terms of reducing transition rate, although this tailed off after treatment was discontinued. Differences between the results of the trials appeared in other areas. One important finding to emerge was that consent rates from eligible subjects differed between these studies and were lowest for the double-blind drug study and highest for the psychological treatment study. This is in no way surprising given the way that subjects themselves tend to formulate their problems, often not in the framework of a medical model. It does have implications for the generalisability of any findings and for considerations about how useful any treatment might be. Even if a treatment is highly effective, if it is not acceptable to the target population it is of little use. This difference in ascertainment is the most likely reason that the three trials reported differences in final transition rates, regardless of randomised treatment group. Transition rates at one year were highest for the double-blind trial (27%) and lowest for the psychological treatment trial (15%). One explanation for this is that only those people who are most distressed and urgently seeking help will elect to go into a double-blind placebo controlled trial, whereas a higher proportion of the eligible population, including less distressed cases, will consent to an open psychological treatment trial. That this is the case appears to be supported by data from the PACE trial, which usefully followed up subjects who declined to go in to the trial (McGorry et al., 2002). Surprisingly, those subjects did better than the clients overall who consented to the treatment trial. In almost all other clinical trial contexts, refusers do worse than those consenting to go in to the trial: presumably the explanation here is that the non-consenters did not feel sufficiently distressed or in need of urgent treatment that they wished to go in to the trial.

One of the still unanswered issues which is important from the public health viewpoint when trying to judge the potential impact of an effective preventive intervention is not ‘How many help-seeking ARMS cases go on to develop psychosis?’ but ‘What proportion of new cases of psychosis came through the prior route of help-seeking ARMS?’ From this, the population attributable fraction can be estimated: what proportion of new cases of psychosis would be prevented by an effective intervention for people with ARMS? These are difficult data to collect accurately since they involve retrospective accounts by people with first episode psychosis.

ETHICAL ISSUES

There are particular ethical dilemmas thrown up by research and the possibility of treatment in this area. The first, and in some ways the most obvious, concerns the giving of treatment to a group of at risk individuals where most of whom (60% or more) will not, even without treatment, develop the disorder. To what extent is it justified to expose all the at risk group to treatment in that case? Not surprisingly, any answers in this area are not black and white but rather a matter of degree. What is the level of risk of transition at which it becomes acceptable to treat the whole group? To give a related real-life example, we know that about 20% of individuals following a first episode of psychosis will not have a subsequent episode, even without treatment. Yet we make the judgement clinically that treating all individuals with
maintenance drug treatment after the first episode is justified, since 80% will benefit. It is not possible currently to predict accurately who will be in the 20% who will not need ongoing treatment, in the same way that it is not currently possible to predict who are the 60% or more of ARMS who will not go on to develop psychosis. The assumption implicit with the relapse prevention example is that 80% is a sufficiently large number to justify intervention across the board. Clearly, a judgement is also being made about the undesirability of the outcome: one can argue that a first episode of psychosis (or a first relapse) is a sufficiently severe outcome to warrant intervention in all cases. Further dimensions are the effectiveness of the intervention (will it reduce transition rates from 30% to 0%, or merely to 20%) and the risk of adverse effects, which is clearly specific to the type of intervention used. For drug treatments the risk of adverse effects may be relatively high and the effects themselves serious. For psychological interventions it is assumed that risk is lower and this may indeed be the case, although there are plausible risks inherent in psychological treatments too, including stigmatisation.

The central ethical dilemma here can be circumvented if the main therapeutic target is defined differently. Currently, the debate circles on the issue of prophylaxis: how many cases of a psychotic disorder can be prevented is weighed against the cost of treating unnecessarily a majority who will not go on to get the disorder in any event. However, other outcomes may be at least as appropriate. Delaying the onset of psychosis or ameliorating its severity once it begins would also be important therapeutic gains from an intervention. The primary outcome of most immediate relevance to people seeking help for ARMS is reducing the severity and functional impact of the symptoms themselves. If the primary therapeutic target is to alleviate these current sub-threshold symptoms rather than explicitly to prevent future psychosis, then all those who receive an experimental treatment may expect benefits. Current models of how symptoms develop in early psychosis are still at an early stage, but it seems inherently likely that reducing current symptoms will lessen the risk of future transition, so as a therapeutic target it makes sense. Severity of baseline sub-clinical symptoms was one of two predictors of outcome, the other being treatment allocation in the EDIE trial. Furthermore, transition to psychosis sounds as if it is an all or nothing phenomenon. In fact, the operational definitions used are rating scales with continuously distributed properties and the definition of transition is based on passing an essentially arbitrary threshold of severity. Again, this makes it less clear that one is best off dealing with a binary or categorical outcome.

WHAT THE FUTURE HOLDS

Research in this emerging area of at risk mental states is only just beginning. On the epidemiological front, more clarity is needed about base rates and the natural history of ARMS. The role of external factors such as street drug use is still unclear. Biological issues have begun to be explored. Potentially important is the issue of progression with preliminary longitudinal evidence suggesting progressive regional structural abnormalities during this early phase can be replicated (Pantelis et al., 2003). The role of normal genetic variants in mediating risk, perhaps via particular cognitive traits and styles, is likely. Connected to this are two interfaces which require more exploration if models for psychological interventions are to be refined. One is the interface between ARMS and full psychosis. The other is the
presumed interface between isolated psychotic symptoms in the general community and the constellation of these symptoms, coupled with distress, which constitute ARMS.

The future role of psychological treatment seems certain to be important. There are good theoretical reasons why psychological interventions might be particularly appropriate at this early, transitional phase and they are certainly more acceptable for this help-seeking client group than drug treatments. However, the relative effectiveness of drug treatments and psychological treatments will at some stage need to be evaluated. It is entirely likely that clinical guidelines emerging from this area will see psychological treatments, particularly cognitive behaviour therapy, as first line treatments, with drug treatments indicated for clients whose symptoms do not respond to psychological intervention.

REFERENCES
