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Review

Who needs antipsychotic medication in the earliest stages of psychosis? A reconsideration of benefits, risks, neurobiology and ethics in the era of early intervention

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ABSTRACT

In recent years, early intervention services have attempted to identify people with a first episode of psychosis as early as possible, reducing the duration of untreated psychosis and changing the timing of delivery of interventions. The logic of early intervention is based partly on accessing people in a more treatment responsive stage of illness in which psychosocial damage is less extensive, and partly on remediating a putatively active process of neuroprogression that leads to pathophysiological, symptomatic and structural changes, hence improving symptomatic and functional outcomes. However, as in other areas of health care, earlier identification of new patients may mean that different treatment approaches are indicated. The corollary of early detection is that the sequence and complexion of treatment strategies for first episode psychosis has been revaluated. Examples include the minimal effective dosage of antipsychotic medication and the content of psychosocial interventions. With the substantial reductions of DUP now seen in many early psychosis services, based on clinical staging and stepped care principles, it is even possible that the immediate introduction of antipsychotic medication may not be necessary for all first episode psychosis cases, but that potentially safer interventions, which may be more acceptable to many patients, such as comprehensive psychosocial intervention, may constitute effective treatment at least for a subgroup of patients. In this paper, we review this theoretical background and describe a randomised controlled trial currently underway at the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne designed to test outcomes for first episode psychosis patients in response to two different treatments: intensive psychosocial intervention plus antipsychotic medication versus intensive psychosocial intervention plus placebo. This is a theoretically and pragmatically novel study in that it will provide evidence as to whether intensive psychosocial intervention alone is sufficient for a subgroup of first episode psychosis patients in a specialised early intervention service, and provide a test of the heuristic clinical staging model. By experimentally manipulating duration of untreated psychosis, the study will also provide a methodologically strong test of the effect of delaying the introduction of antipsychotic medication, as well as helping to disentangle the effects of antipsychotic medications and the putative neurobiological processes associated with brain changes and symptom profiles in the early phase of psychotic disorders. The study has been carefully crafted to satisfy critical ethical demands in this challenging research domain.

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1. Background

During the past 15 years, there has been a growing worldwide focus on early identification, diagnosis, and staged treatment for psychotic disorders (Edwards and McGorry, 2002; McGlashan, 1998; McGorry et al., 1996; McGorry and Yung, 2003). The early intervention paradigm is based on the view that the earliest possible detection and effective intervention for psychosis will deliver the best outcome for patients and result in the least burden and cost over time for the health care system (Edwards and McGorry, 2002; McGorry et al., 1996). A key rationale has been the relationship between prolonged illness duration and poor outcome in psychotic disorders (Harrigan et al., 2003; Marshall et al., 2005). In a recent meta-analysis (Perkins et al., 2005) and systematic review (Marshall et al., 2005), longer duration of untreated psychosis (DUP) was associated with poorer response to antipsychotic treatment as measured by severity of global psychopathology, positive and negative symptoms, demoralization, depression, and functional outcomes. In most of the literature "untreated" refers to treatment with neuroleptic medication, in contrast to other forms of intervention, such as psychosocial treatment. Neuroimaging studies have also indicated that prolonged untreated illness is associated with more pronounced structural brain abnormalities, while this is less prominent earlier in the course of the disorder (Keshavan and Amirsadri, 2007).

Service reform and restructuring to adopt an early intervention approach has been effective in reducing the DUP of patients with first episode psychosis (FEP). This is shown by the significantly lower median DUP reported by specialist early psychosis services (e.g., Carbone et al., 1999; Linszen et al., 1998) compared to the DUP reported for first episode cases in non-specialised services (e.g., Melle et al., 2004) and in standard psychiatric services in the early 1990s (e.g., Loebel et al., 1992; Szymanski et al., 1996). Recent data indicates that the median DUP in our own early intervention service, the Early Psychosis Prevention and Intervention Centre (EPPIC), Orygen Youth Health is as low as 8.7 weeks (Schimmelmann et al., 2008), while the Norwegian TIPS study reported a median DUP of 5 weeks in a geographical region with a specialised early psychosis service compared to 16 weeks in a region without such a service (Melle et al., 2004). There is accumulating evidence for improved short-term [e.g., earlier remission (Loebel et al., 1992), fewer hospital admissions and improved functional outcome (Bertelsen et al., 2008)] and longer-term outcome [e.g., fewer relapses (Crow et al., 1986; Marshall et al., 2005)] as well as economic benefit for the health care system from the early intervention model (Killackey and Yung, 2007). Randomised controlled trials (RCTs) have also suggested that initiation of atypical antipsychotic medication at the first episode of psychosis can prevent progression of the structural brain changes associated with psychotic disorders (Lieberman et al., 2005b; Nakamura et al., 2007). Widespread antipsychotic use has also led to the most severe manifestations of schizophrenia such as catatonia and the severely disorganised phenotypes becoming rare in modern clinical settings, again suggesting an impact of treatment on limiting the expression of the most deteriorated forms of the disorder (van der Heijden et al., 2005). Similarly, in the TIPS study earlier detection was associated with a reduction in the degree of bizarreness of psychotic features (Larsen et al., 2006).

2. Revisiting optimal treatment for first episode psychosis

The earlier detection of FEP cases has resulted in young people receiving treatment for psychotic disorders earlier in the course of their illness than was previously the case (Johannessen et al., 2001; Larsen et al., 2006). Based on the clinical staging model, when patients are treated earlier, the risk/benefit dynamics change and it is important to consider whether more benign and less extensive treatment may be sufficient to achieve the same or ideally superior levels of remission and recovery. In addition to considering timing issues, the *composition* of FEP cohorts may be changing as a result of early detection programs associated with specialist early psychosis services. It is well established that psychotic symptoms occur on a continuum throughout the general population (Johns and van Os, 2001; van Os et al., 2000), that there are high rates of psychotic-like experiences in community studies (Laurens et al., 2007; Poulton et al., 2000; Yung et al., 2009) and that many people experience such symptoms without distress, lowered functioning or any discernable "need for care" (Yung et al., 2006). It is possible that early intervention efforts have resulted in some of these individuals being referred for treatment. It is also possible that more patients enter early psychosis programs without psychotic symptoms being their main source of clinical distress or reason for referral. That is, they are suffering from some form of psychiatric morbidity, such as depression or personality disorder, and FEP threshold-level psychotic symptoms are only detected upon referral to the service. This trend has been seen in recent years in the prodromal or "ultra high risk" (UHR) domain of clinical research where samples entering care may have become more inclusive and contain a lower level of risk for transition and potential chronicity (Yung et al., 2007). Positive symptoms may often be regarded as "incidental" psychotic-like experiences and not have the same diagnostic or therapeutic significance as earlier, more enriched and incipient cohorts (Yung et al., 2007). A greater number of these types of patients may be referred due to the "broadening" of early psychosis services to encompass the pre-psychotic period (the putatively prodromal or UHR population) and the restructuring of some services in accordance with the youth mental health model to encompass non-psychotic disorders (McGorry, 2007b). This trend may have spilled over to affect the composition of first episode cohorts.

In summary, with earlier detection and shorter DUP, the possible inclusion of a broader composition of patients, and the considerable diagnostic heterogeneity that occurs in first episode samples (Rosen et al., 2006; Subramaniam et al., 2007; Whitty et al., 2005), it is timely to reevaluate the mix and sequence of drug and psychosocial treatments in first episode psychosis.

3. The clinical staging model in psychiatry

We have previously argued that simpler and more benign treatments (i.e., treatments with fewer risks or side effects)

may be the most appropriate first line intervention for the earliest stages of the onset of psychiatric symptoms (McGorry, 2007a; McGorry et al., 2006; McGorry et al., 2007b), provided they can be shown to be efficacious. This concept is central to the clinical staging model of psychiatric disorders. The clinical staging model is a heuristic framework for developing more refined forms of diagnosis, developing and evaluating intervention strategies, and for studying the variables and processes underlying the evolution of psychiatric disorder (McGorry, 2007a; McGorry et al., 2006; McGorry et al., 2008). The concept of clinical staging is widely used in mainstream medicine, particularly in the treatment of malignancies, where the earliest possible delivery of effective interventions is vital to increase the chances of remission and survival. The potential cost of this approach as with all early diagnosis is unnecessary risks and anxieties resulting from the "overtreatment" of phenotypically similar benign conditions. The staging concept actually applies to a diverse range of diseases, including potentially many psychiatric disorders. Clinical staging differs from conventional diagnostic practice in that it defines the extent of progression of disease at a particular point in time, and where a person currently lies along the continuum of the course of illness (McGorry et al., 2008). The differentiation of early and milder clinical phenomena from phenomena that accompany illness extension, progression and chronicity lies at the heart of the concept. It enables the clinician to select treatments relevant to earlier stages, and assumes that such interventions will be both more effective and less harmful than treatments delivered later in the course (McGorry, 2007a; McGorry et al., 2006; McGorry et al., 2007b; Singh et al., 2004). While staging links treatment selection and prediction, its role in the former is more crucial than in the latter, particularly since early successful treatment may change the prognosis and thus prevent progression to subsequent stages. Staged treatment models for psychotic disorders (McGorry et al., 2007a), depressive disorders (Fava and Kellner, 1993; Hetrick et al., 2008), eating disorders (Le Grange and Loeb, 2007), and bipolar disorders (Berk et al., 2007) have recently been described.

4. Clinical staging for psychotic disorders

4.1. Drawing the boundaries in the right place; stepped care as a strategy

We have assumed that the timing of introduction of antipsychotic medication should be closely linked to the onset of threshold and sustained positive symptoms of a certain level of severity and persistence. However, this may be an inexact guide. Some patients with subthreshold positive symptoms but other clinical features may need antipsychotic medications to get better, while some who cross the positive symptom threshold for psychosis and attract a DSM diagnosis within the schizophrenia spectrum may respond to simpler non-biological interventions. Defining the boundary is complex, and probably depends on both symptomatic, functional and cognitive measures. For example, one feature of the research literature in UHR individuals is that cognitive impairment is fairly minimal prior to transition to psychosis (Brewer et al., 2006), with poorer performance being limited to tasks involving rapid processing and organization of information, such as recall of prose passages (Brewer et al., 2005) or Go/NoGo false alarms (Riecher-Rossler et al., 2009). The implication of these findings is that cognitive function should decline with the onset of full-threshold psychotic disorder, and while there is some evidence for this (Wood et al., 2007) it is not consistently identified (Becker et al.,). Clearly, the utility of such measures for defining stages remains dubious.

A staged approach to treatment choice for the earliest stages of psychotic symptoms could consist of psychosocial treatments with demonstrated efficacy and no significant side effects and would avoid the early introduction of antipsychotic medication, assuming the efficacy of psychosocial treatments at this stage of illness is proven (we note, however, that psychosocial interventions are not without side effects, e.g. increasing emotional arousal, and that further research into the possible negative impact of psychosocial interventions is required (see Berk and Parker, 2009)). Antipsychotic medications would then only be introduced as a second line treatment when more benign treatments have failed, or when a more aggressive course of disorder is evident, within a stepped care algorithm. Similar stepped treatment approaches have been trialed in the treatment of depression (e.g., the Sequenced Treatment Alternatives to Relieve Depression [STAR*D] study (Warden et al., 2007)) and bipolar disorder (e.g., the Systematic Treatment Enhancement Program for Bipolar Disorder [STEP-BD] (Sachs et al., 2003)). It should be noted that the standard stepped care logic does not incorporate the possibility of preventive interventions where therapies are prescribed to preempt what might be rather than resolve what is already apparent.

4.2. Risks and benefits of antipsychotic medications

The evidence to date with regards to pharmacological and psychological intervention for psychosis suggests that the staging model proposed above may be viable treatment approach. While antipsychotic medications have been shown to be effective for the treatment of acute psychosis, especially in first episode cases (Kahn et al., 2008), there are well-documented and sometimes serious side effects associated with these medications (Allison and Casey, 2001; Muench and Carey, 2001; Stahl et al., 2009; Tschoner et al., 2007). This is underscored by evidence of the iatrogenic risks of atypical antipsychotic medications in the short-term (Allison and Casey, 2001; Muench and Carey, 2001), possible morphological changes in the brain over the intermediate term (Corson et al., 1999; DeLisi, 2008; Konopaske et al., 2007), and the poorly understood longer-term effects that may include weight gain (Alvarez-Jimenez et al., 2008), altered glucose metabolism (Tschoner et al., 2007) and tardive dyskinesia (Llorca et al., 2002). Agents that increase the risk of developing the metabolic syndrome also contribute to a marked increase in long-term cardiovascular risk, and contribute to the increased mortality that is documented in the disorder (Lambert and Chapman, 2004). These risks indicate the necessity for a cautious and individualised risk–benefit analysis when prescribing antipsychotics. Conversely, research studies have also indicated that antipsychotics and other medications, notably lithium, valproate and SSRIs, and

some experimental options such as N-acetyl cysteine and omega 3 fatty acids may have neuroprotective properties (Amminger et al., 2010; Berger et al., 2008; Berk et al., 2008a; Lieberman et al., 2005b) and therefore may be important in protecting against putative "neurotoxic" effects of underlying illness or psychosis itself. These superficially diverse agents share common effects on a number of the biochemical pathways which may underpin neurovulnerability and neuroprogresssion, such as the L-HPA system (Takahashi et al., 2009), oxidative stress mechanisms (Berk et al., 2008b), inflammatory cytokines (Miller et al., 2009) and lipid metabolism (Berger et al., 2002, 2003) that seem to be shared across major psychiatric disorders. Depression, bipolar disorder and schizophrenia share alterations in inflammatory cytokines, oxidative stress and neurotrophins such as BDNF (Berk, 2009). Furthermore, lithium, antidepressants, atypical antipsychotics and anticonvulsants all share effects on oxidative stress defences (Berk et al., 2008b).

4.3. Antipsychotic medications may not be immediately popular with the treatment-naive

There is also substantial evidence that adherence with antipsychotic medications (as with most medications) is problematic. Many patients who will engage and accept supportive care are reluctant initially at least to accept particularly antipsychotic drug therapy. Coldham et al. (2002) found that approximately 60% of FEP patients at a specialised treatment service were not compliant or inadequately compliant with antipsychotic medication, consistent with other reports in the field (Oehl et al., 2000; Perkins, 1999). Moreover, the introduction of second-generation antipsychotics does not appear to have improved adherence to medication (Kane and Malhotra, 2003; Berk et al., 2008a). Critical issues in long-term adherence are engagement with the treating clinician or team, the therapeutic alliance and illness acceptance (Macneil et al., 2009). As schizophrenia and bipolar disorder are typically lifelong disorders needing long-term management, adherence has the capacity to powerfully shape the long-term prognosis. The person's initial clinical experience often shapes their view of the disorder, its treatment and issues such as self-stigma, and consequently, adherence. A psychotherapeutic treatment model that emphasises psychoeducation, support, engagement and alliance at the beginning of treatment may have core benefits in the long-term pharmacotherapy of these disorders. A stepwise approach which may well lead to most patients accepting antipsychotic medications on an experiential and more sustainable basis may produce more dividends for the patient.

4.4. Effectiveness of new psychosocial interventions in early psychosis

Recently, there has been increased interest in psychological interventions, particularly cognitive-behaviour therapy (CBT) and family interventions, for schizophrenia and other psychotic disorders. CBT for psychosis derives from strategies for treating mood and anxiety problems. It largely involves utilising strategies for managing positive psychotic symptoms, such as identifying and changing cognitive styles and behavioural patterns that may contribute to these symptoms, and promoting insight into illness (Garety et al., 2000; Garety and Freeman, 1999; Morrison, 2001, 2002). In a recent review, consistent evidence was found that CBT reduces persistent positive symptoms in patients with chronic schizophrenia, and has modest effects in hastening recovery from acute episodes (Tarrier, 2005). There is evidence in both schizophrenia and bipolar disorder that the impact of CBT is greatest in the early stages of the illness (Scott et al., 2006; Tarrier, 2005). In trials of CBT used specifically in FEP, CBT and supportive counseling were found to have significant advantages over routine care [the SoCRATES trial (Lewis et al., 2002)], CBT was superior to befriending in symptom and functioning outcome [the ACE project (Jackson et al., 2008)], and Cognitively Oriented Psychotherapy for Early Psychosis (COPE) led to an improved adaptation to illness (Jackson et al., 2001, 2005). In a review of psychosocial interventions for FEP, Penn et al. (2005) found that CBT was effective in the treatment of auditory hallucinations (Lewis et al., 2002; Tarrier et al., 2004), decreased hopelessness (Power et al., 2003), increased adaptation to illness (Jackson et al., 2001), contributed to better treatment adherence (Haddock and Lewis, 2005), and that CBT and supportive counseling were both effective in reducing comorbid substance abuse (Edwards et al., 2006).

Other, non-CBT psychosocial interventions have also been found to deliver positive outcomes. Family interventions have been shown to lead to shorter periods of hospitalisations in FEP patients, assisting parents in supporting their children within the community (Lenior et al., 2001). A family psychosocial module was also an essential component in a relapse prevention intervention, which was more effective than standard care at preventing the occurrence of a second episode of psychosis (Gleeson et al., 2009). In patients with schizophrenia, the evidence indicates that the relapse rate can be reduced by 20% if relatives are included in treatment (Addington and Addington, 2008). Furthermore, it appears that individual CBT and family interventions are highly acceptable to FEP patients (Haddock and Lewis, 2005). The Danish OPUS study found that integrated care, consisting of assertive community treatment, psychoeducational multi-family groups and social skills training, led to better course and outcome in young patients with schizophrenia-spectrum disorders compared to patients treated with standard care. At the 1-year follow-up the integrated care group demonstrated significantly less hopelessness, reduction in psychotic symptoms was greater, and clients and families were more satisfied with treatment (Nordentoft et al., 2002). Vocational recovery has also been a recent focus of psychosocial interventions for FEP (Killackey et al., 2008).

In addition to stage of illness, however defined, other factors such as symptom type and other clinical phenomena, degree of cognitive impairment, patient treatment preference, comorbid substance use, triggers and stressors, and side effect tolerance, may influence optimal treatment for a given patient. As already highlighted, the boundary or threshold for "caseness" for first onset of psychosis, or at least use of antipsychotic medications, may not be best set by symptom severity or profile alone. Some UHR cases, symptomatically subthreshold for "psychosis," may in fact benefit from treatment with antipsychotics, while some FEP patients, technically above threshold, may not, or at least may not derive extra benefit from antipsychotic treatment in addition to that provided by psychosocial interventions. It is not

yet known which patients will benefit most from which treatments. Further intervention research is required in order to shed light on these issues.

5. Can the introduction of antipsychotic medication be delayed and what are the consequences of this?

As described above, one of the most prominent reforms in international mental health care over the last decade has been the focus on early psychosis and the associated imperative to provide rapid optimal treatment. The aim of this approach is to prevent biological and psychosocial deterioration during the so-called "critical phase" or early years after psychosis onset (Birchwood, 2000). Within this paradigm, it has been accepted that optimal treatment includes the early introduction of novel atypical antipsychotics at low doses in order to minimise DUP (Group, 2005). However, it has not yet been established that antipsychotic medication is an essential component of effective treatment for all FEP cases, particularly in the context of comprehensive psychosocial care which is a common feature of many, even most, early psychosis programs.

Even prior to the era of early detection and shorter DUP, some have claimed a benefit for psychosocial interventions with minimal or no use of antipsychotic medications. In a recent meta-analysis, Bola (2006a) found a small, non-significant advantage for initially non-medicated groups with established schizophrenia over medicated groups in terms of improved outcomes (see also Bola et al., 2009). While this finding was based on a small number of studies, it suggests that an initial period without medication, but with other active non-pharmacological interventions, may in fact produce superior outcomes than immediate introduction of medication. At the very least, the results of Bola and Mosher (2003) indicate that long-term *harm* is not caused to psychotic patients by short-term medication-free periods, at least under certain conditions, i.e., that other forms of treatment are available, such as in the Soteria study. In this quasi-experimental study, patients with early episode schizophrenia-spectrum psychosis were treated either with antipsychotic medications in a hospital environment ("usual" intervention) or in an intensive psychosocial milieu that minimised use of antipsychotics for an initial 6-week period (the Soteria intervention; Bola and Mosher, 2003). Two-year outcome data favoured the Soteria intervention, in terms of psychopathology, vocational rehabilitation, and social functioning. Further evidence is provided by the RCT of three antipsychotic medications of Johnstone et al. (1999), plus a fourth placebo arm, with the aim of examining the potential effects of delaying antipsychotic medication for a 4-week period. At the 2.5-year follow-up, the occupational functioning, psychopathology, treatment needs and cognitive functioning of those who experienced the 4-week non-medication period was no different from those who were initially medicated. The authors concluded that a 4-week delay in the introduction of antipsychotic medication does not produce long-term deleterious effects, compared to those who receive medication. Consistent with this, Carpenter (1997) reviewed the evidence on medication-free intervals in schizophrenia and concluded that there was no evidence of later harm from such intervals. Together, these findings have led some researchers to advocate the provision of psychosocial interventions with short-term withholding of medication (Bola, 2006b; Bola et al., 2006; Carpenter et al., 2003; Lehtinen et al., 2000).

However, there is a paucity of quality research addressing the effects of delaying medication in schizophrenia, in situations where active non-pharmacological treatment is provided, mainly due to the ethical concerns about conducting such research (Bola, 2006a; Bola et al., 2009). However, the ethical perspectives of this issue may be changing. In a series of commentaries on the Bola (2006a) paper, a number of eminent schizophrenia researchers endorsed the notion that medication-free trials are ethical, even in patients with established illness, given the capacity of patients to provide informed consent and the lack of evidence of harm demonstrated from medication-free intervals (see below) (McGlashan, 2006; McNulty, 2006; Schooler, 2006). Some authors (e.g., Schooler, 2006) have emphasised that medication-free research, at least for short periods, may be especially illuminating in medication-naïve patients or those who have experienced relatively brief exposure to medication because this allows study of the processes of early psychosis without the potentially confounding effects of medication. It also has the potential to shed light on the efficacy of non-pharmacological treatment at the earliest stages of illness without the confounding effects of medication.

6. Current medication-free RCT for first episode psychosis

This background has led us to examine the issue of medication-free intervention for FEP in an experimental setting. The TIPS study took a traditional line that withholding of antipsychotics for FEP was unethical (McGlashan and Johannessen, 1996) and hence studying the effect of changing DUP experimentally through an RCT design was not appropriate, prompting them to adopt a quasi-experimental design. However, with falling DUP levels and in the context of our staging model, we disagreed with this position, believing that there could be circumstances under which an RCT could be ethically conducted to not only test the "DUP hypothesis" but to explore other key issues, and have consequently spent some years crafting such a design.

We recently started recruiting to an RCT at EPPIC with FEP patients randomised to one of two groups: antipsychotic medication plus intensive psychosocial intervention or placebo plus intensive psychosocial intervention. The FEP participants recruited to this study are assessed as being at low risk (in terms of operationally defined levels of suicidality and aggression) and assured of receiving adequate support outside the mental health service (family or other social support). All patients and families must give fully informed consent to be randomised. The intervention period is for up to 6 months. The primary outcome of interest is social functioning (as assessed by the SOFAS) at the end of the six-month treatment period, with the hypothesis being that placebo plus intensive psychosocial treatment will be no less effective than conventional treatment with antipsychotic medication plus intensive psychosocial intervention (i.e., a non-inferiority design). This primary outcome is in line with the recent trend of focusing on functional outcomes, rather than focusing solely on reduction in clinical symptoms (Killackey and Yung, 2007; Malla et al., 2005). Clinical symptoms, remission

and recovery are being assessed as secondary outcomes. Outcomes up to 2 years post study entry will be assessed. Strict withdrawal criteria are in place. These include worsening of symptoms, persistent symptoms (continuing for 3 months), increase in suicidality or hostility, or breakdown of community support.

The intensive psychosocial intervention consists of four components:

1. Case management. A case manager is assigned to each study participant. Case management includes patient engagement, problem solving, and advocacy and support, as described in (EPPIC, 2001).
2. Close monitoring and crisis response. Participants are seen up to twice per week by their case manager and weekly by their psychiatrist during the first 2 months of the study, and continue to be seen frequently throughout the study. In addition, all study participants are "on alert" with a crisis response team and an individually tailored crisis plan is in place so that rapid assessment and intervention can be provided should this be required.
3. Cognitive-Behaviour Therapy (CBT). The CBT provided in the trial is a specific therapy developed for the first episode psychosis population (EPPIC, 2001). It focuses on symptom and stress reduction, facilitating adaptation to illness, and treatment of secondary morbidity such as anxiety, depression, and substance abuse. The case manager provides this formulation-driven psychological therapy within the case management setting. Therapists receive regular individual and group supervision and draw on appropriate therapy resource materials, in addition to completing a checklist of interventions to ensure adherence with the protocol.
4. Family support and education. Families of participants are seen by the case manager who provides information and education about psychosis and recovery in young people. In addition, a specialist family worker is available for further input and can provide regular supportive counseling sessions when required as determined by the needs of each participating family.

The study will allow us to experimentally investigate whether a subgroup of FEP patients can achieve improved functioning, symptom reduction and remission with intensive psychosocial treatment in the absence of antipsychotic medication (i.e., a long drug naive time period but with intensive psychosocial treatment). It will also allow us to identify clinical predictors of recovery from FEP with intensive psychosocial treatment in the absence of antipsychotic medication. A wide range of factors, including DUP, diagnosis, demographic variables, substance use and social support, will be assessed with respect to their importance in determining response to type of treatment (psychosocial, medication or a combination of the two) in FEP.

Aside from investigating whether intensive psychosocial treatment in a specialised early intervention service constitutes an effective treatment for a subgroup of FEP patients, the study is also a direct experimental test of whether prolonging DUP (in terms of antipsychotic medication) leads to worse symptomatic and functional outcome. To date, reduction in DUP has been a cornerstone of the rationale for the early intervention movement, but has not been directly experimentally tested. The TIPS study (Johannessen et al., 2005) has been the closest test of this premise to date, finding differences in favour of an early detection program at baseline on a number of symptomatic variables (Melle et al., 2004), as well as reduced suicidality (Melle et al., 2006).

The final important aspect of this trial is an experimental investigation of the extent to which the neurobiological changes seen in the early phase of psychotic disorders, such as grey matter loss and reduced hippocampal volume (Dorph-Petersen et al., 2005; Konopaske et al., 2007; Lieberman et al., 2005b; Pantelis et al., 2003; Velakoulis et al., 2006), are due to neurobiological processes associated with psychosis and to what extent these changes are due to medication effects (i.e., the possible toxic effect of early introduction of antipsychotic medication). There is some evidence that these changes can occur in the absence of medication (Job et al., 2005), and that medication does not necessarily induce brain changes (Thompson et al., 2001), but long-term antipsychotic treatment of primates has been shown to have a widespread effect on brain volume (Dorph-Petersen et al., 2005; Konopaske et al., 2007). In our study, we will investigate the extent of these changes over the intervention period (6 months). If both intervention groups display similar structural brain changes over the course of intervention then we can infer that these changes are more likely to be associated with the progression of psychosis rather than due to antipsychotic medication, especially if the experimental groups are similar in other respects. However, if certain structural brain changes only occur in the group treated with medication then these changes are more likely to be related to medication. Of course it is entirely possible that antipsychotic medications could be neuroprotective and retard or prevent brain changes which derive from underlying neuroprogressive changes (DeLisi, 2008; Lieberman et al., 2005a).

7. Ethical issues

Clearly, this study is not without ethical issues. The basis for this being a study that is ethically acceptable derives from the belief that the question we are examining has come into clinical equipoise by virtue of the earlier diagnosis of patients with psychotic syndromes, the lack of harm that appears to be derived from conducting medication-free research in established illness, and the increasingly appreciated risks identified with antipsychotic medications. In addition, by focusing on a clinically low risk sample who can give informed consent to participation and using multiple strategies to maximise the safety of participants the risks associated with the study can be minimised to acceptable levels. Although this strict patient selection procedure may limit generalisability of the results, it is necessary for ethical and safety reasons. In a discussion of ethical approaches to clinical trials in schizophrenia in the light of the 2002 Clarification of the 2000 Declaration of Helsinki, Carpenter et al. (2003) list five criteria that research studies must satisfy in order to meet the ethical standards set by the Clarification. These criteria are listed below along with reasons why the current study meets all of these specifications.

1) *The likelihood that the intervention being tested has a clinical advantage over existing treatments.* The risk–benefit ratio has changed as a result of earlier diagnosis in the context of the staging model principles, more serious adverse effects of

existing treatments, and patient preference within a stepped care model. It is possible that utilising the described intensive psychosocial treatment without medication could have clinically significant advantages over existing treatments for at least a subset of patients, as the psychosocial intervention is a more benign treatment option which may be suitable for patients in an earlier stage of illness (McGorry et al., 2006) and avoid the long-term adverse effects of antipsychotic medication, including neurologic, endocrine and metabolic effects (see Gardner et al., 2005 for a review). The non-trivial side effects of and adherence problems with antipsychotic medication provide a compelling reason to seek new treatments that are effective and have fewer adverse effects than those that are currently available (Carpenter et al., 2003). Finally, the evidence base for antipsychotics in FEP does not necessarily extend to the "new FEP" cohorts described above, some of whom at least may, in line with the clinical staging model, have different treatment needs.

2) *The application of careful informed consent procedures*. Entry to the study is contingent upon informed consent provided by the participant and a family member.
3) *The presence of compelling reasons for placebo use*. Participants in the non-medication arm are issued a placebo in order to maintain the blind with those receiving medication. This provides a proper, rigorous control for taking active medication. These participants are not denied *all* forms of treatment, only antipsychotic medication.
4) *The selection of participants that minimises potential serious adverse consequences*. All patients referred to our first episode service are screened in order to assess their eligibility for the study and only those with low risks to themselves and others and adequate community support are recruited into the trial. The enhanced care at EPPIC, including close monitoring and 24 hour crisis response, minimises potential serious adverse consequences. We note that the study may not be considered safe in other early psychosis or standard settings that do not have these additional supports in place.
5) *A risk-versus-benefit analysis that favours the advantages from placebo use over the risk to participants*. With predetermined strict withdrawal criteria, any participant whose symptoms worsen or become unacceptable to the participant or who experiences a further decline in functioning, is withdrawn from the trial and then offered antipsychotic medication. This should become apparent within a matter of weeks. Furthermore, if a more benign treatment option such as the intensive psychosocial treatment is found to be effective, the benefits for those with FEP will outweigh the risks of being assigned to the non-medication group.

8. Conclusions

Service reform focused on early intervention for psychotic disorders has been effective in reducing the DUP of patients with FEP. Consequently, FEP patients are now being identified and treated very early in the course of their symptoms. The early phase of psychotic disorders is also characterised by considerable diagnostic heterogeneity. These factors point to a need to rethink the essential components of efficacious treatment for early psychosis. In line with the clinical staging model (McGorry, 2007a; McGorry et al., 2007b), it is possible that more benign forms of treatment, such as psychosocial intervention and close monitoring, may be sufficient to enable satisfactory recovery for a subset of FEP patients without the risks and side effects caused by even the most modern antipsychotic medications. Additionally, a short delay in commencement of antipsychotic medication may not be harmful for other FEP patients if they are well supported with psychosocial interventions. The evidence that psychosocial intervention can be effective in reducing symptom severity, improving functioning and in reducing the number of psychotic episodes supports this treatment model, at least for a subgroup of FEP patients. The moderate transition rates in prodromal studies and the epidemiological data revealing that there are surprisingly high rates of psychotic-like experiences in community samples that are not associated with significant distress or impairment also supports the systematic staged use of interventions in accordance with clinical evolution and need (i.e., the clinical staging model of intervention). Conversely, with the potential neuroprotective components of pharmacological treatments and the potential harm of longer DUP, withholding antipsychotic medication may further negatively affect the early course of psychosis in FEP patients. There is also the possibility that such medications can cause structural changes which have been previously interpreted as deriving from the pathology of the underlying illness.

These issues are best addressed in the context of well-designed clinical trials with strict inclusion and exclusion criteria and low thresholds for withdrawal. We have recently commenced such a trial. While not without ethical and practical implementation issues, the trial represents a unique attempt to investigate whether intensive psychosocial treatment alone in a specialised early intervention service constitutes effective treatment of FEP in a selected subgroup of FEP patients. It will also help to clarify the twin issues of whether a longer duration of psychotic symptoms before treatment with antipsychotic medication results in a worse outcome than a shorter duration of symptoms and the extent to which neurobiological changes associated with early psychosis are attributable to medication effects or to progression of illness. The findings should provide a basis for future larger scale studies and will ultimately have important clinical implications for early intervention treatment strategies for psychotic disorders.

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NA.

Contributors

All authors contributed to and have approved the final manuscript.

Conflict of interest

Michael Berk receives research support from Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma, Servier and acts as a consultant for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen-Cilag, Lundbeck, and Servier. No other declarations of interest.

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