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Treatment Implications of the Schizophrenia Prodrome

Tejal Kaur and Kristin S. Cadenhead

San Diego, USA

Kristin S. Cadenhead: kcadenhe@ucsd.edu

Abstract

Schizophrenia is a debilitating neurodevelopmental disorder that strikes at a critical period of a young person's life. Early identification of individuals in the prodromal phase of a psychotic illness can lead to earlier treatment and perhaps prevention of many of the devastating effects of a first psychotic episode. International research efforts have demonstrated the success of community outreach and education regarding the schizophrenia prodrome and it is now possible to use empirically defined clinical and demographic criteria to identify individuals at a substantially increased risk for a psychotic illness. The development of clinical staging criteria for psychosis that incorporates type and severity of clinical symptoms, level of global and social functioning, family history, substance use, neurocognitive functioning, and perhaps neurobiological information, could help to specify appropriate treatment for vulnerable individuals at different phases of the prodrome. Preliminary psychosocial and pharmacologic treatment studies report initial success in reducing severity of prodromal symptoms in "at-risk" samples, but further work is needed to refine the prodromal criteria and perform well controlled treatment studies in adequately powered samples. Treatment algorithms can then be tailored to presenting symptoms, number of risk factors present, and evidence of progression of the illness, to assure appropriate, safe and effective interventions in the early stages of psychosis.

1 Introduction

Schizophrenia has been conceptualized as a chronic and debilitating disease with ongoing cognitive, social, and functional losses since dementia praecox was first described at the turn of the twentieth century. Up until the 1950s, those with psychotic illnesses were locked away, imprisoned by the notion that life could not exist beyond the desolate spaces of state hospitals. Then with deinstitutionalization, while many patients with psychotic illness relished new found freedoms, others were relegated to lives of poverty and homelessness. In the past two decades, schizophrenia researchers and clinicians have challenged this notion of inevitable decline, demonstrating that early intervention and treatment of psychotic illness can mitigate losses in psychotic illness, improve functional outcomes, and provide hope to patients and families (Addington et al. 2004; Hafner and an der Heiden 1999; Hegarty et al. 1994; McGlashan et al. 2005).

Despite the more favorable prognosis for individuals with psychotic illness compared to those of Kraepelin's time, up to two-thirds of patients with schizophrenia never return to their previous level of functioning (Addington et al. 2003). College students may never again return to school after a first psychotic episode, young adults early in their careers may find themselves unable to maintain the cognitive demands required in their jobs, and most young people encounter persistent difficulties in interpersonal relationships (Ballon et al. 2007;

Grant et al. 2001). Current research supports these clinical observations as studies show significant cognitive (Bilder et al. 2006; Eastvold and Cadenhead 2003) and social functioning (Ballon et al. 2007) deficits in the first episode of psychosis that may have been present before the illness began (Caspi et al. 2003).

Clearly, schizophrenia cannot be best characterized as beginning with the onset of frank psychosis, as biological changes occur long before this period (Niendam et al. 2006). Rather, it is better conceptualized as an illness characterized by premorbid, prodromal, acute, and chronic phases that correspond to neurodevelopmental changes (Lieberman 1999). The premorbid phase is characterized by a period of stable social and cognitive deficits, alongside frequent subtle neurological abnormalities which long precede the first episode of psychosis (Davidson et al. 1999). In contrast, the “prodromal” period is defined by its lack of stability, worsening positive and negative symptoms, and a deteriorating course of psychosocial impairment culminating in the onset of frank psychosis (Keith and Matthews 1991; Yung and McGorry 1996). With the onset of frank psychosis comes a period of recurrent exacerbations and remissions from psychotic symptoms as well as ongoing functional decline until an individual settles into the chronic phase of illness where deficits and symptoms reach a level of symptomatic stability.

While in the latter two phases (acute and chronic), symptoms are more externally identifiable, the subtle, nonspecific symptoms that first emerge during the prodrome are often overlooked. The failure to recognize these early changes is particularly concerning as the duration of untreated psychosis (DUP) corresponds to further functional decline (Melle et al. 2005). Yet, the idea of early identification itself challenges the notion that downward decline is inevitable. Although researchers have studied changes in the first episode of psychosis in the hopes that intervention at the onset of psychosis may prevent further decline and morbidity, recent research has delved further back to the prodrome. However, as the prodrome can only be accurately defined retrospectively, research efforts strive to develop measures which may predict risk of future psychosis with increasing sensitivity and specificity (Cannon et al. 2008; Ruhrmann et al. 2003).

In 1996, Yung and her colleagues heralded the field of early identification by establishing “prodromal” criteria which appeared to predict conversion to psychosis in 40% of individuals at 1 year follow-up. Individuals between the ages of 16–30 were recruited if they had developed subsyndromal psychotic symptoms within the last year or had a familial risk for schizophrenia plus a recent functional decline (Yung et al. 2003). As many of these individuals may not convert to psychosis, and to avoid early stigmatization, the prodromal literature uses terms such as “at-risk,” “ultra high risk,” or “clinically high risk” to better describe a population who meets such “at-risk” criteria, but whose individual prognosis is yet unknown.

In order to measure dimensions of psychopathology as well as to operationally define at-risk criteria, the Melbourne Australia group developed the Comprehensive Assessment of At-Risk Mental State (CAARMS; Yung et al. 2002). The CAARMS operationally defined the at-risk state by creating three distinct at-risk criteria. The vulnerability group, defined by genetic risk and recent functional deterioration, includes those who experienced a significant functional loss in the past year and who either meet DSM-IV criteria for schizotypal personality disorder and/or have a first-degree relative with a diagnosed psychotic disorder. The attenuated positive symptom group includes individuals with recent onset (<1 year) subsyndromal psychotic symptoms which do not reach psychotic intensity. The third group includes those with brief limited intermittent psychotic symptoms (BLIPS), which do not meet full criteria for psychotic disorder due to limited frequency or duration. Subsequently, McGlashan developed the Scale of Prodromal Symptoms (SOPS) which also utilizes a

structured assessment, the Structured Interview of Prodromal Symptoms (SIPS) to elicit whether individuals meet criteria for three distinct at-risk criteria, similar to those created by Yung's group (Miller et al. 2004). In original reports, both the CAARMS and the SOPS predicted conversion to psychosis at rates as high as 40–54% over the course of 6 months to 1 year, implying these instruments have increased sensitivity in late phases of the psychosis prodrome.

However, as numerous “basic symptoms,” such as subtle disturbances of thought, speech, and perception, may be altered years prior to onset of frank psychosis, the Bonn Scale for the Assessment of Basic Symptoms (BSABS; Huber and Gross 1989) has shown that the presence of such basic symptoms predicted schizophrenia with a probability of 70% over 10 years, while the absence of such symptoms excluded schizophrenia with a probability of 96% (Klosterkotter et al. 2001). Particular disturbances, such as thought interference, disturbances of receptive language, or visual distortions, predicted schizophrenia with a probability up to 91% (Klosterkotter et al. 2001). In the current literature, the BSABS is thought to define individuals in an “early” prodromal phase that is characterized by the more negative or deficit-like symptoms as well as neurocognitive deficits.

In the last decade, early identification centers worldwide have adapted similar prodromal criteria and instruments, establishing themselves both as resources for help-seeking youth as well as critical centers of academic research (Cornblatt et al. 2002; Haroun et al. 2006; Klosterkotter et al. 2001; Larsen et al. 2000; Miller et al. 2002). The centers can be classified generally as either descriptive, treatment, or neurobiological translational studies, with many centers employing a combination of strategies. Descriptive studies monitor at-risk youth for conversion to psychosis in order to validate and further identify risk. In addition to monitoring at-risk youth, treatment studies apply either pharmacologic or nonpharmacologic treatment strategies during the putative prodrome in the hopes of delaying or preventing psychosis. Lastly, neurobiological translational studies follow neurobiological markers in order to better understand the biological processes contributing to the development of psychosis, as well as to validate biological measures that may indicate vulnerability towards psychosis (McGlashan et al. 2007).

1.1 Early Identification of Psychotic Illness

As international research efforts have demonstrated the success of community outreach and education regarding the schizophrenia prodrome, it is now possible to use empirically defined criteria to identify individuals at a substantially increased risk for a psychotic illness (Addington et al. 2007). Yet, combining “at-risk” criteria with objective biological markers, may further improve predictive potential, and thereby open up a window of opportunity for primary prevention (Cannon et al. 2008; Haroun et al. 2006; McGorry et al. 2006).

1.2 Duration of Untreated Psychosis: Individual and Public Health Concern

Imagine the patient who comes into the hospital, handsome, conversant, and even charming at times, but starkly psychotic. Clinical experience paints a portrait of steady decline with each subsequent hospitalization for psychotic decompensation. It is possible that untreated psychosis is “toxic,” with longer durations of untreated illness corresponding to depression, anxiety, negative symptoms, positive symptoms, and overall poor functioning (Marshall et al. 2005; Perkins et al. 2005). Preliminary studies suggest that early intervention can decrease DUP and improve short-term clinical outcomes (Marshall et al. 2005; Melle et al. 2004).

In the real world, however, most individuals do not receive early intervention, and the onset of positive symptoms often occurs 2 years prior to initial treatment, while negative

symptoms date back about 5 years prior (Häfner et al. 1992; Salokangas and McGlashan 2008). Furthermore, biological correlates of illness appear to coincide with this period of untreated symptoms. Studies show a greater temporal and frontal gray matter reduction in patients with a long duration of illness suggesting either a progressive pathological process prior to treatment or a more insidious onset of illness and a later presentation to services (Lappin et al. 2006; Takahashi et al. 2007).

As schizophrenia occurs during late adolescence and early adulthood, the illness sets in during a period of critical development, thwarting normal brain processes that sustain cognition, function, and independence. Even beyond an individual loss, functional loss occurs at a community level, impairing an individual's potential contribution to society, making schizophrenia among the leading causes of disability in the United States (Murray and Lopez 1996). An analysis in 2002 showed the overall cost of schizophrenia in the United States to be \$62.7 billion, with total indirect excess costs due to unemployment of \$32.4 billion (Wu et al. 2005). Although the cost of early identification may initially appear higher, it is suggested that even at 24-month follow-up, early identification may be cost-saving (Valmaggia et al. 2009). But now, beyond individual centers in particular communities, efforts at community education show potential in decreasing DUP, even to a matter of weeks. The Norwegian TIPS study examined whether specialized community education and a mobile detection program could affect DUP (Johannessen et al. 2005). When comparing two health service regions in which an early psychosis detection program was introduced with two areas without such a program, DUP was reduced to a matter of weeks, with a greater reduction in the experimental regions where community education and mobile detection teams were provided. Positive clinical differences were maintained at all 3-month, 1-year, and 2-year follow-ups (Larsen et al. 2006; McGorry et al. 2007).

1.3 Identifying and Predicting Risk for Psychotic Illnesses

As we stand now over a decade following the development of Yung's initial criteria, it appears that as the number of early identification centers has grown, the conversion rates at these centers has diminished (Haroun et al. 2006; Yung et al. 2007). From 1 to 2 years follow-up rates of 40–50% seen in earlier studies (Yung et al. 2006); subsequent studies have yielded rates closer to 25% per year using the same prodromal criteria (Cannon et al. 2008; Haroun et al. 2006; Yung et al. 2007). It is possible that variability in conversion rates may be attributable to the development of such centers, such that knowledge regarding at-risk states has actually increased the process of inherent treatment, subsequently delaying, or even preventing the onset of psychosis (Yung et al. 2007).

As current centers strive to intervene early, it is very possible that simple measures such as regular assessments, frequent clinical contact, and referrals addressing emerging affective and psychotic symptoms may be ameliorating current symptoms. It becomes clear in clinical practice that those who continue to present for such research studies are likely seeking more than financial compensation. Individuals followed in at-risk studies often present as a unique population characterized not only by being putatively prodromal, but by being distressed, help seeking, and open to clinical contact (Cornblatt et al. 2001; Haroun et al. 2006). As comorbid affective, anxiety and attentional symptoms are often prominent, these individuals come to expect a level of concern and advisement from early identification centers (Haroun et al. 2006). However, to identify each individual who meets at-risk criteria as "prodromal" would be misleading as simply meeting at-risk criteria does not indicate the certainty of future psychosis, especially considering the phenomenon of decreasing conversion rates in areas of early identification (Yung et al. 2007). To improve the predictive validity of the established criteria and better identify which individuals are at highest risk of conversion to psychosis, schizophrenia researchers strive to strengthen the sensitivity of current at-risk criteria to best predict imminent risk.

For instance, particular clinical symptoms have been identified across studies that show an increased association with later conversion to psychosis. Klosterkotter et al. (2001) reported that the basic symptoms of thought blocking, disturbances of receptive speech, and sensory perceptual disturbances were found more often in those who converted to psychosis. In the Cognitive Assessment and Risk Evaluation (CARE) sample in San Diego, individuals meeting at-risk criteria who converted to psychosis at 1 year follow-up were more likely to have a history of cannabis abuse or dependence than the nonconverted group and similarly to other samples, higher ratings on measures of delusional-like experiences, suspiciousness, and thought disorder (Haroun et al. 2006).

A number of prospective population studies have suggested that cannabis use, likely in those displaying vulnerability for psychosis, confers a clear increase in the relative risk of subsequently developing psychosis (Arseneault et al. 2004; Caspi et al. 2005). Furthermore, by identifying specific clinical factors as conferring particularly high risk, such studies allow research to inform clinical practice by encouraging psychoeducation regarding high risk behaviors.

In an attempt to increase the power of prodromal studies to predict psychotic conversion, the NAPLS (the North American Prodromal Longitudinal Studies) Consortium was created as a collaboration between seven early identification centers with NIMH funding (Addington et al. 2007). A recent analysis of the NAPLS dataset revealed that individuals who were most likely to convert to psychosis had a family history of psychosis, symptoms of suspiciousness or delusional-like experiences, a decline in social functioning, and/or a history of drug abuse. A combination of any three of these criteria increased the positive predictive power to 80% suggesting that it may be possible to develop an algorithm for treatment that will target those at highest risk (Cannon et al. 2008). Yung et al. (2003) also report that combining certain predictive variables, such as long duration of prodromal symptoms, poor functioning at intake, low-grade psychotic symptoms, depression, and disorganization, can yield a strategy for psychosis prediction with good sensitivity (86%), specificity (91%), positive predictive value (80%), and negative predictive value (94%) at 6-month follow-up. Other groups suggest that further specificity could be reached by applying the concept of basic symptoms to current at-risk criteria (Meng et al. 2009). Klosterkotter et al. (2001) found that basic symptoms, defined as subtle, subclinical self-experienced disturbances in thought, speech, and perception processes, were highly sensitive indicators of subsequent psychosis. While the study is limited by its retrospective design, it suggests that basic symptoms may be used as complementary approach to current at-risk criteria, perhaps even by aiding in timing the onset of a psychotic disorder by assessing onset of basic symptoms as well as attenuated psychotic symptoms (Schultze-Lutter et al. 2010).

While clinical criteria aid in identifying risk, subsequent gains in schizophrenia research will likely come from understanding the neurobiological mechanisms of psychotic processes and incorporating such biological markers into current at-risk criteria. Numerous deficits in information processing which serve as endophenotypes have been clearly defined in the schizophrenia spectrum including prepulse inhibition of the startle response (Cadenhead et al. 2000; Maier et al. 2008; Tenn et al. 2005), P50 event related potentials (Cadenhead 2005), and mismatch negativity (Umbricht and Krljes 2005). Longitudinal follow-up will determine whether these deficits are predictive of later psychosis in addition to providing insight into the mechanism of neuropathological change in the early stages of the illness.

Neurocognitive deficits, appear to be quite predictive of later conversion to psychosis in the at-risk sample, especially measures of verbal learning and general intelligence (Brewer et al. 2005; Cosway et al. 2000; Eastvold et al. 2007; Jahshan et al. 2010). In addition, one early study (Brewer et al. 2003) demonstrated that at-risk subjects with olfactory identification

deficits prior to the onset of illness were more likely to later convert to psychosis. It is conceivable that measures of neurocognition or olfactory identification performed during initial assessment could add to the clinical assessment in determining which individuals are at greatest risk and might benefit from early cognitive remediation or pharmacologic intervention that enhances cognitive functioning.

A number of small scale neuroimaging studies have suggested that those at-risk individuals who progress to psychosis appear to display both structural and functional deficits prior to the onset of illness (Cannon et al. 2007, 2008; Pantelis et al. 2003; Wood et al. 2003). Specifically, progressive cortical volume loss may be associated with the onset of psychosis, indicating ongoing pathological processes during the progression to illness (Sun et al. 2009). Moreover, white matter development may be altered in individuals at-risk for psychosis, possibly due to disrupted developmental mechanisms (Karlsborg et al. 2009).

With the advent of the Human Genome Project and subsequent advances in the field of genetics, it is foreseeable that the addition of genetic markers could further increase the positive predictive power of current at-risk criteria (Cannon et al. 2003). Ultimately, by understanding the neuropathological processes in the early phase of psychosis, treatment may be targeted earlier based on identified neurobiological deficits, ideally preventing some of the devastating aspects of a first psychotic episode.

1.4 Review of Treatment Studies in the Psychotic Prodrome

Early identification and treatment in the early phase of psychosis has been an area of increased interest and ethical debate over the last decade. Various studies have been conducted worldwide that highlight the potential of intervening in the early phase of illness with both pharmacologic and psychosocial treatment (see Table 1). According to a recent Cochrane review, while at this time there are likely still insufficient trials to draw definitive conclusions (Marshall and Rathbone 2006), recent and ongoing studies continue to build a foundation of evidence based medicine to guide preliminary treatment guidelines in at-risk youth.

1.5 Nonpharmacologic Interventions

The validation of nonpharmacologic interventions in the treatment of chronic schizophrenia has lead to similar studies in earlier stages of illness. As rigorous trials conducted in at-risk youth are limited, psychosocial, randomized controlled trials conducted in first episode patients will also be briefly discussed because of their applicability in this population. Future studies are necessary to validate whether such interventions can be effective in individuals meeting at-risk criteria.

A UK-based study (EDIE) randomized 58 people with prodromal symptoms to 6 months of cognitive behavioral therapy (CBT) or a monitoring group. Morrison et al. (2004) report that the CBT group had a lower risk for conversion to psychosis with 1-year longitudinal follow-up (Morrison et al. 2004). The CBT group displayed fewer indicators towards conversion on all measures. However, an analysis of the EDIE data in the Cochrane report stated that of the two outcomes reported, neither the rate of psychotic conversion nor the rate of subjects leaving the study was significantly different between groups (Marshall and Rathbone 2006).

Other trials focused on first episode psychosis have shown promise, but are also similarly limited in applicability. LifeSPAN-Australia, a randomized controlled trial of a phase-specific brief individual cognitively orientated therapy for people in the first episode of psychosis with suicidal ideation (Power et al. 2003), noted benefits in the treatment group on indirect measures of suicidality such as hopelessness; however, these findings did not reach statistical significance. A Chinese trial by Zhang et al. (1994) also utilized a phase-specific

intervention (family therapy) by randomizing 78 males diagnosed with schizophrenia to either family therapy or treatment as usual upon discharge from their first psychiatric hospitalization. Over the 18-month follow-up, there was a significantly lower rate of hospital readmission in the family intervention group than in the control group, and the mean hospital-free period for those who were readmitted was significantly longer in the experimental group than in the control (Marshall and Rathbone 2006). A Dutch randomized controlled trial ($N = 76$; Linszen et al. 2001) comparing phase-specific intervention including family therapy plus a specialized team for individuals in their first episode of schizophrenia found no difference between intervention and control groups at 12 months for the outcome of relapse (Marshall and Rathbone 2006). Finally, the OPUS-Scandinavia study included 547 people with a diagnosis of first episode schizophrenia in which 275 were randomly assigned to integrated treatment (consisting of an assertive community treatment, family therapy, social skills training, and modifications of medication regime) and 272 to standard treatment (Petersen et al. 2005). At 1 year follow-up, global GAF significantly favored integrated treatment by 1 year, but neither group differed significantly at 2 year follow-up (Marshall and Rathbone 2006).

While psychosocial interventions often complement treatment in chronic schizophrenia, further studies are necessary to validate such strategies in both the prodrome and first episode of psychosis.

1.6 Psychopharmacologic Interventions

Relatively few psychopharmacologic studies have been performed in individuals meeting prodromal criteria (see Table 1). The absence of information is in part related to the short history of prodromal research but also the difficulty in recruiting sufficient numbers of subjects who are willing to enter into a clinical trial for nonspecific symptoms and diagnosis. It is also difficult to obtain approval for large scale studies when the prodromal phase of a psychotic illness is not a defined diagnostic entity, the majority of at-risk youth are adolescents and there are many ethical concerns on the part of the pharmaceutical industry and federal granting agencies in performing such studies.

The PRIME (Prevention through Risk Identification, Management and Education) study is the only placebo-controlled double blind study of an antipsychotic in the prodromal phase of illness. In the PRIME study, olanzapine vs. placebo was compared in 60 at-risk individuals over the course of 1 year with subsequent 1-year follow-up (McGlashan et al. 2006). No significant differences were found between olanzapine and placebo in preventing conversion to psychosis by 12 months or improving symptoms. In the placebo group, 11 out of 29 converted to psychosis compared to 5 out of 31 in the olanzapine group, yielding a nonsignificant difference. It is interesting, however, that all of the psychoses in the olanzapine group occurred in the first 4 weeks of the clinic trial when doses of olanzapine were relatively low, implying that perhaps those who converted in this group may not have had sufficient time on olanzapine for it to affect the active processes leading to psychosis in these particular youth. Furthermore, by week 8, it appeared that prodromal symptoms had significantly decreased further in the group treated with olanzapine compared to that given placebo. It is noteworthy to mention that the weight gain in the olanzapine group as 8.79 kg compared to the 0.30 kg weight gain in the placebo group.

The PACE (Personal Assessment and Crisis Evaluation) study ($N = 59$) randomized individuals meeting at-risk criteria with low dose risperidone and CBT vs. “needs-based intervention” and found that individuals who received the treatment were significantly less likely to develop psychosis at a 6-month follow-up than people who only received need-based treatment (McGorry et al. 2002). After the 6-month treatment period, 10 of 28 people who received needs-based intervention converted to psychosis in comparison to 3 of 31 from

the specific preventive intervention group. However, using intention-to-treat analysis, the difference was no longer significant at 12-month follow-up ($N = 59$, 1 RCT, RR 0.54 CI 0.2–1.3; Marshall and Rathbone 2006). It is interesting to note, however, that in the subsequent 6-month follow-up period, it appeared that those who were not adherent to the risperidone were those who were most likely to convert to psychosis.

A report from the PRIME clinic (Woods et al. 2007) included 15 participants in an open-label, single site trial with fixed-flexible dosing of aripiprazole (5–30 mg/day) for 8 weeks. There was improvement from baseline in the total number of prodromal symptoms and none of the participants converted to psychosis. Neuropsychological measures showed no consistent improvement. There was a mean weight gain of 1.2 kg and akathisia emerged in over half of the participants. While results are promising, the significance of these findings are complicated by small sample size as well as lack of control group and blinding.

A study by the German Research Network compared treatment with amisulpride in combination with needs-focused intervention to needs-focused intervention alone in a sample of 124 people in an open-label 3-month design (Ruhmann et al. 2007). Individuals in the antipsychotic group showed reductions in attenuated psychotic symptoms, negative symptoms and basic symptoms as well as a greater improvement in GAF scores. Amisulpride did not cause weight gain or extrapyramidal symptoms but it did increase prolactin levels. Again, applicability is limited due to open-label design, but can inform further rigorous studies.

One study conducted by RAPP (Recognition and Prevention of Psychological Problems) examined the effects of antidepressants using a prospective naturalistic treatment study of clinical high risk adolescents comparing individuals who received antidepressants ($N = 20$) vs. second-generation antipsychotics ($N = 28$; Cornblatt et al. 2007a, b). The group who received antipsychotics showed evidence of more disorganized thinking at entry, was less compliant with medication, and more likely to become psychotic at follow-up. Interestingly, there were no conversions among antidepressant-treated adolescents. It is possible that the adolescents treated with antidepressants were less ill at entry and the authors acknowledge that a substantial number of false positives may have been present among the antidepressant-treated subgroup. However, as animal models have demonstrated increased neurogenesis, dendritic arborization, and synaptogenesis with SSRI treatment (Richtand and McNamara 2008), it is plausible that treating these young people with psychotropic agents may provide an element of neuroprotection even during the initial stages of a psychotic illness. While the naturalistic nature of this study prevented generalization of these results, such studies invite subsequent randomized controlled trials to further evaluate treatment efficacy. Future studies ideally would also integrate larger sample sizes such that more definitive conclusions may be reached regarding the efficacy of pharmacologic intervention in early identification.

1.7 Pharmacologic Potential for Neuroprotection

Ideally, understanding brain changes that accompany early psychosis can help to inform not only treatment strategies but ultimately neuroprotection. In a comprehensive review, Berger et al. (2003) outline what is known about the early and late neurodevelopmental abnormalities in early psychosis and how altered regulatory mechanisms of progenitor cell generation and death in some brain areas could explain these changes.

Although researchers previously believed that stem and progenitor cell generation in mammals was only possible in early life, recent research suggests that the hippocampi (Kornack and Rakic 1999), periventricular zone (Steindler and Pincus 2002), and olfactory bulbs (Byrd and Brunjes 2001) retain the capacity to generate progenitor cells which differentiate into neurons. Therefore, disequilibrium of pruning or trophic processes during

the prodrome may account for manifestation of psychosis above and beyond pre-existing neurodevelopment injury (Feinberg 1982). The dysregulation of mechanisms for apoptosis in individuals with schizophrenia likely further contributes to the longitudinal biological changes seen in early psychosis on magnetic resonance imaging (Catts and Catts 2000; Jarskog et al. 2000; Pantelis et al. 2003).

A number of compounds that are under consideration for their neuroprotective qualities include agents that modulate apoptosis pathways (lithium, sodium valproate, BDNF, clozapine, quetiapine, lamotrigine, omega-3 fatty acid), block necrosis pathways (vitamin E), increase synaptogenesis (selective serotonin reuptake inhibitors), or block the inflammatory response (Cox-2 inhibitors; Jacobs et al. 2000; Malberg et al. 2000; Vaidya et al. 1997).

Atypical antipsychotics appear to display neuroprotective effects by inducing BDNF mRNA expression which serves to increase the threshold for apoptosis (Bai et al. 2003). Patients treated with antipsychotics near the time of death display increased levels of bcl-2 compared to those not exposed to antipsychotics (Angelucci et al. 2000), while postmortem analysis of patients with schizophrenia shows a 25% reduction in bcl-2 transcription factor in the temporal cortex (Jarskog et al. 2000). Furthermore, inducers of apoptosis, such as TNF- α , also correlate with illness and appear elevated in the serum of antipsychotic-naïve patients (Erbagci et al. 2001). Interestingly, clozaril appears to normalize TNF- α levels (Monteleone et al. 1997).

Other novel therapies such as eicosapentaenoic acid, an omega-3 fatty acid, or estrogen are also suggested as adjunctive agents due to neuroprotective properties. One randomized, double-blinded, placebo-controlled trial by Berger et al. (2007) suggests that augmenting antipsychotic medication with omega-3 fatty acids may improve tolerability of, and accelerate response to, antipsychotic medications. Protective effects of omega-3 fatty acids may be modulated by phosphoinositide-protein kinase C (PI-PKC) signal transduction as omega-3 fatty acids antagonize PI-PKC and are found to be deficient in the peripheral tissue of individuals with schizophrenia (McNamara et al. 2006). Estrogen is postulated to indirectly interfere with mitochondrial properties, and therefore protect against apoptosis (Arnold and Beyer 2009). Applying such treatments at early stages of illness when neuronal pathways may not be irrevocably damaged may maximize the neuroprotective potential of such agents.

Neuroprotective strategies should thus be instituted at early stages of illness when such biological developmental abnormalities could be averted. Further research will elucidate the mechanisms by which particular pharmacologic treatments induce neuroprotection. Understanding the pathophysiology of such changes will inform the literature as to when and what to implement during specific stages of early intervention.

1.8 Preliminary Treatment Recommendations

Although the literature is mixed, the majority of studies support the notion that shortening the DUP improves outcome and course of illness (Addington et al. 2004; Harrigan et al. 2003; Larsen et al. 2000; Malla et al. 2002; Melle et al. 2005). This can lead to the assumption that starting treatment even before the onset of psychosis may further improve outcomes. However, current research does not adequately inform us *which* treatment modalities are most indicated in the prodromal period. Although clinicians and researchers differ on thoughts regarding treatment protocols, it is universally agreed upon that the prodromal population is ill and necessitates some type of treatment. Ballon et al. (2007) revealed that quality of life and everyday functioning in at-risk youth are nearly as low as patients who have already developed psychosis, with numerous other studies confirming the

presence of significant social deficits (Cornblatt et al. 2007a, b; Niendam et al. 2007). Even in those who fit at-risk criteria, but may never develop psychosis, research is needed to determine whether the initiation of proposed treatments can ameliorate the course of other psychiatric disorders which may arise in this high risk population. Yet, even when such treatments are proposed, there are no guidelines that can inform us *when* in the course of illness to initiate particular interventions.

1.9 Ethical Implications

Although understanding risk and protective factors can help to inform potential preventative and treatment strategies, the ethical implications of such treatments also remain complex. Considering the large number of at-risk youth who may never convert to psychosis, the ethical considerations including potential stigmatization, loss of confidentiality, and insurability become particularly significant. Furthermore, as Corcoran (2005) eloquently points out, it is not safe to assume that individuals or institutions will appreciate the difference between a risk assessment and a diagnosis. Subsequently, even the act of providing medical information in the form of risk assessments can affect wellbeing in unintended and potentially unexpected ways (Corcoran et al. 2005). When keeping in mind this potential group of false positives, the need for an exit strategy is critically important (Cornblatt et al. 2001). If prophylactic treatments are begun, how long does one continue to administer them and what factors do we consider in deciding to stop? How do we weigh risks and benefits of providing unnecessary treatment, and yet, how to do we weigh the risk that stopping may elicit psychosis in true positives (Cornblatt et al. 2001; Haroun et al. 2006)?

Specifically, if clinicians begin to treat at-risk youth with atypical antipsychotic medications, they run not only the risk of potentially treating false positives with unnecessary medication (McGlashan 2001; Schaffner and McGorry 2001), but they will also unnecessarily expose individuals to the known metabolic risks of such medications. Atypical antipsychotics are known to cause weight gain of more than 10 pounds in 3 months in young people, a risk significant not only for long-term medical health but also for psychosocial development (Correll and Malhotra 2004). Furthermore, as the long-term effects of these medications on the adolescent brain is yet speculative, implications of dopamine blockade on psychosexual development are also unknown. Risks and benefits will need to be weighed if incorporating into clinical practices.

And yet, we cannot assume that treating false positives is unwarranted. It is possible that “false positives,” are individuals who may yet convert to psychosis but had not converted during the study design. Conversely, it may be that indirect treatment administered as a result of early identification may have delayed or prevented the onset of psychosis. As the putatively prodrome group is well documented to display significant clinical symptoms and functional decline (Haroun et al. 2006), it is possible that individuals could have been offered a variety of psychosocial intervention or even treatment indicated psychotropic medications which may have had neuroprotective effects. Or this “false positive” group could truly be comprised of individuals whose clinical symptomatology only masqueraded as subsyndromal symptoms of psychosis and they would never have developed psychosis (Haroun et al. 2006).

As the prodrome can only truly be identified retrospectively, those considered *putatively* prodromal are a heterogeneous group, most of whom present with elevations on a variety of psychiatric symptom scales. Even those who do not convert to psychosis within the window of such research studies appear to remain quite ill, such that by follow-up, many meet the criteria for a number of affective Axis I conditions (Haroun et al. 2006).

When we advise at-risk patients of their risks, however, certain individuals who display multiple risk factors may be at particularly high risk for psychosis (Cannon et al. 2008). Given that degree of risk likely varies even within a high risk cohort, clinicians must also consider the ethical consideration of *not* informing of risk. McGlashan discusses that although the risks of stigma and treating false positives are widely discussed, we often fail to discuss the greater stigma involving the social consequences of psychotic behavior which leads to social losses, hospitalizations, and even incarceration (McGlashan et al. 2007).

At-risk subjects are symptomatic and present with a range of symptoms and comorbid anxiety, mood, attentional, and substance abuse diagnoses that do not necessarily require a “one size fits all” treatment approach but are better suited to needs-based treatment that includes a comprehensive multidimensional approach (Haroun et al. 2006).

1.10 Development of Clinical Staging Criteria

While the concept of clinical staging is not new in the field of medicine, its application to psychiatric illness remains largely untouched. Clinical staging is a more refined form of diagnosis in that it attempts to define where an individual may lie in the course of an illness. It can be a useful algorithm in disorders which either tend to *or* may progress.

In the field of psychiatry, naturalistic studies inform us of the course of psychiatric illness, but the next step would be for research to then translate this into clinical stages, thereby facilitating early recognition and therefore early intervention. Ideally, staging would be defined by a system of clinicopathological indicators in which endophenotypic markers can be integrated into clinical profiles, lending to the further refinement of the validity of clinical staging.

McGorry et al. (2006) have promoted the concept of clinical staging for psychotic disorders much like what is done in the treatment of illnesses such as cancer or diabetes. The fundamental assumptions to clinical staging are two-fold. First, patients in earlier stages of an illness are more likely to respond to treatment than those in the later stages of illness. Second, treatments offered in the earlier stages should be more benign as well as more effective in order to be in accordance with ethical risk-benefit considerations. These assumptions are based on lessons learned from other areas of medicine where aggressive treatment in early stages of illness carries significant complications which may negate the potential benefits of that particular early intervention (McGorry et al. 2006).

If we were to apply such an algorithm to at-risk individuals, those individuals with milder symptoms and/or fewer risk factors would be treated with psychosocial treatments such as CBT, crisis intervention, or supportive psychotherapy, while those who have more severe symptoms and risk factors would be treated with pharmacotherapy in addition to psychosocial treatment.

Clearly, biological research is needed to continue to elucidate appropriate treatment strategies. While critics of the clinical staging model for psychotic illness would argue that staging should begin with biological correlates, the complexity of psychotic disorders precludes a systematic approach as we do not yet know which biological changes are inherent to the disorder and which are merely epiphenomenon. Moreover, it is entirely unclear which endophenotypes are static and which reflect disease progression (Jahshan et al. 2010; McGorry et al. 2006). Yet, the syndromal and help-seeking nature of at-risk youth preclude the luxury of waiting until definite algorithms are created, especially as clinical practice currently already employs a variety of treatments, not limited to antipsychotic medication. As such, it is imperative that the guidelines we do develop as a community are conservative in nature to reflect the preliminary nature of the current evidence.

To date, a variety of treatment algorithms have been proposed based on our current knowledge of the psychotic prodrome. McGorry et al. have developed an algorithm that begins with individuals with increased risk (e.g., first-degree teenage relatives) who do not have symptoms currently (Stage 0), and progresses through the prodrome (Stage 1a and 1b) to the acute (Stage 2–3) and chronic stages of psychosis (Stage 4). Potential intervention at each stage would include family education, substance abuse reduction, and psychosocial treatments such as CBT. Neuroprotective strategies such as omega-3 fatty acids as well as atypical antipsychotics and/or antidepressants and mood stabilizers would be initiated at Stage 1b when the individual meets full prodromal criteria. The proposed algorithm also proposes that neurocognitive deficits be incorporated as part of the definition of the Ultra High Risk or prodromal state (McGorry et al. 2006).

One clear benefit of using clinical staging models is that it encourages clinicians to realize that functional disability and early symptoms occur long before the onset of frank psychosis. As such, by intervening early, patients and family can be offered consultation for symptoms comorbid with the prodromal state, such as affective symptoms or substance abuse. Furthermore, patients may begin to develop a therapeutic alliance with clinicians at a stage in illness where trust, cognition, and decisional capacity are not yet compromised by frank psychosis (McGlashan et al. 2007). In clinical practice, patients often enter care at the time of a first psychotic break, often coming to the attention of clinicians due to hospitalizations or incarceration, clearly situations less conducive to building rapport and establishing long-term treatment alliances. However, when conversion occurs in the context of early identification centers providing education, support, and treatment, clinical outcomes appear better. In one published report by McGlashan, among the New Haven clinical trial sample of prodromal patients who converted to schizophrenia, no patient required hospitalization. All but one continued their daily schedule at work or school, maintained social relationships, and were characterized by an average medical compliance pill count of 93% (McGlashan et al. 2007).

Beyond improving function and symptom severity if conversion occurs, it appears that such early intervention and effective treatment may also be contributing to a decline in psychotic conversion rates (Yung et al. 2007). Therefore, with even earlier identification of the prodrome, the treatment algorithm might involve a period free of specific psychotropic medication and instead a period of observation, monitoring, and treatment of psychiatric disorders, such as depression, anxiety disorders, and substance use problems. By identifying young people with mental health problems earlier, it is likely that a range of disorders would be identified close to their onset and early intervention could reduce the burden of these other illnesses as well.

1.11 Recommended Treatment Guidelines

Individuals who meet the prodromal syndrome criteria or individuals at clinical high risk group for psychosis are clinically heterogeneous but help-seeking. Less than 40% of those who meet the SIPS criteria are likely to become psychotic, but those with additional risk factors such as a family history of psychosis, more severe ratings on delusional-like symptoms, social functioning deficits, or substance abuse are even more likely to develop schizophrenia or an affective disorder (Cannon et al. 2008). Additional risk factors such as neurocognitive deficits will likely improve the positive predictive power of current prediction algorithms.

As delineated in Table 2, treatment needs to be tailored to the presenting symptoms and risk factors. An important step in determining the most appropriate treatment requires a full diagnostic assessment, including differential diagnosis by a well trained clinician. It is important to recognize that presenting symptoms could be emerging anxiety, affective,

substance use or the iatrogenic effects of medications. Pervasive developmental disorder, learning disabilities, and attention deficit disorders should also be carefully considered as comorbid conditions. A full medical work up should rule out metabolic, endocrine, or neurological etiologies.

Psychosocial treatment including crisis intervention, stress reduction, CBT, supportive therapy, social skills training, cognitive remediation, psychoeducation, dual diagnosis, multifamily groups, case management, school intervention, or vocational rehabilitation should be considered at all stages of illness but especially in the early stage of illness that are more mild or characterized by nonspecific symptoms.

Individuals who are considered “high risk” based on family history of a psychotic disorder would benefit not only from the above psychosocial treatments, but also from regular follow-up and assessment. In those individuals who are considered at clinical high risk, with or without family history of psychosis, our staging criteria recommends that SIPS rating scales, in conjunction with clinical risk factors, can be used to categorize risk severity and specific treatment interventions.

For instance, for those without a family history but who now present with functional decline and mild symptoms corresponding to a “3” on SIPS positive or disorganized items, specific symptom clusters may be targeted with nonpharmacologic treatment such as CBT while current pharmacology may be reassessed to ensure medications may not be exacerbating or causing symptoms. On the other hand, for those with functional decline and moderate symptoms corresponding to a “4–5” on SIPS, who may also have other risk factors, such as family history of psychosis, drug abuse, or neurocognitive and social deficits, more aggressive treatment plans are recommended, employing strategies such as neuroprotective and pharmacologic treatments as delineated in Table 2. Finally, when individuals reach the stage of severe symptoms, corresponding with a “6” on the SIPS, when they no longer have insight, intervention may entail crisis intervention, pharmacologic intervention as well as possible hospitalization.

When pharmacologic intervention is considered, it should be tailored to the differential diagnosis and target the presenting symptoms. Often, even on initial presentation to prodromal clinics, patients are more often than not already suffering from a variety of complaints for which pharmacotherapy may have already been initiated. In these cases, it is essential to recognize that medication could be exacerbating symptoms as antidepressants might induce a hypomanic/manic or mixed episode in a depressed individual prone to bipolar illness, just as high doses or abuse of stimulants might induce subsyndromal psychosis.

Usually, however, if the individual is already being treated with medication for mood, anxiety, or attentional problems, it is most prudent to continue such treatment as long as it is clinically indicated and risk–benefit ratios are thoroughly assessed. Although such treatment may be termed “symptomatic” in nature, it is far from clear that such treatment does not also contribute to declining conversion rates (McGlashan et al. 2007). Thus, the use of antidepressants and mood stabilizers should be considered early if indicated by presenting symptoms. Also, given the potential neuroprotective properties of the SSRIs and mood stabilizers as well as omega-3 fatty acids, they are good first line pharmacologic interventions. Brief trials of antipsychotics should be used to target worsening subsyndromal psychotic or disorganized symptoms if the above interventions are not effective. More severe symptoms such as suicidal or homicidal thoughts as well as agitation will likely require an inpatient stay along with intensive crisis and pharmacologic intervention.

The development of clinical staging criteria for psychosis that incorporates type and severity of clinical symptoms, level of global and social functioning, family history, substance abuse, neurocognitive functioning, and perhaps neurobiological information could help to specify appropriate treatment for vulnerable individuals at different phases of the prodrome and first episode of psychosis. If we could use knowledge gained from neurobiological markers in these populations to not only improve our ability to predict who will develop psychosis but also target specific deficits identified with these markers; it might be possible to better personalize treatment in the early stages of psychosis. Treatment algorithms can then be tailored to presenting symptoms, number of risk factors present, and evidence of progression of the illness to assure appropriate, safe, and effective interventions in the early stages of psychosis.

Yet, as we discuss such treatment strategies it is imperative to keep in mind that since the at-risk state is a new clinical syndrome; all treatments to date are still considered preliminary and “off-label.” Ideally, randomized controlled trials of large samples will be necessary before clear and convincing treatment guidelines may be codified. However, in the absence of the strictest evidence based medicine, clinicians faced with complexity of the prodrome must be armed with guidelines based on clinical practice across prodromal centers internationally.

1.12 General Summary

Given the range of possible presentations of the psychotic prodrome, ethical issues, and potential treatments, it is not surprising that clinicians do not know what to do with individuals who present in an at-risk state. Clearly, translational studies are needed to better inform treatment, but it is also apparent that more work is needed to characterize the psychotic prodrome and develop clinical, demographic, and vulnerability marker assessment tools to better identify those who are at greatest risk. The predictive data can then inform preventive treatment and the development of treatment algorithms based on clinical staging. Finally, treatment studies are needed that target specific stages of early psychosis and select individuals at greatest risk for pharmacologic trials and those with more mild symptoms or few risk factors for psychosocial interventions. For now the best recommendation is to treat at-risk youth using the best clinical wisdom recognizing that it may be transient or evolve into a more serious condition.

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Table 1

Treatment studies in the psychotic prodrome

Study	Study	Result
PRIME (USA)	Olanzapine vs. placebo ($N = 60$, double blind)	No difference in rate of psychotic conversion. Significant weight gain
PACE (Australia)	Risperidone + CBT vs. specialized care ($N = 59$)	Reduced psychotic conversion rate at 6 months but not at 12 months
EDIE (UK)	CBT vs. monitoring ($N = 58$)	Reduced rate of antipsychotic use in CBT group; no difference in psychotic conversion or symptoms
German Research Network	Amisulpride vs. needs-focused intervention ($N = 124$, open-label)	Reductions in attenuated psychotic, negative, and basic symptoms, but no reduction in conversion. Greater improvement in GAF scores. No weight gain or EPS but increased prolactin levels
RAPP (USA)	Naturalistic study of antidepressants vs. antipsychotics ($N = 48$)	No conversions among antidepressant-treated adolescents. The antipsychotic group was more disorganized at entry, was less compliant with medication, and more likely to become psychotic
Prime (USA)	Aripiprazole ($N = 15$, open-label)	Improvement in the total number of prodromal symptoms and none of the participants converted to psychosis. Neuropsychological measures showed no consistent improvement. There was a mean weight gain of 1.2 kg and akathisia emerged in over half of the participants

Table 2

Treatment guidelines for at-risk individuals

Stage	Treatment
<ul style="list-style-type: none"> • All stages • Mild symptoms (“3” on SIPS positive or disorganized items) • Recent functional decline • Moderate symptoms (“4–5” on SIPS positive or disorganized items) • Functional impairment • Significant risk factors for psychosis <ul style="list-style-type: none"> Family history Drug abuse Decline in social functioning Neurocognitive deficits • Axis I anxiety or mood disorder • Severe symptoms (“6” on SIPS positive or disorganized items) • Intermittent psychosis • Severe depression, mania, suicidality, homicidality • Poor functioning 	<ul style="list-style-type: none"> • Psychoeducation regarding the presenting symptoms and risk of ongoing substance abuse • Psychosocial treatment, including crisis intervention, reduction of stress, and ongoing support. CBT to target specific symptoms. Social skills training in a group setting • Stop or reduce agents that might worsen symptoms (e.g., stimulants or antidepressants causing hypomania) • Psychosocial treatment including multifamily groups • Case management • School support/vocational rehabilitation • Pharmacologic intervention to target specific symptoms <ul style="list-style-type: none"> Depression/anxiety – antidepressant, anxiolytic Hypomania – mood stabilizer Worsening auditory hallucinations, ideas of reference, paranoia – antipsychotic • Neuroprotection (e.g., omega-3 fatty acid) • Crisis intervention • Inpatient hospitalization • Pharmacologic intervention