

# Treatment Models and Designs for Intervention Research During the Psychotic Prodrome

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## Abstract

Recently, interventions for the psychotic prodrome have gained considerable interest. The goal of early interventions for prepsychotic, but symptomatic, individuals is to reduce disability and impairment by ameliorating subpsychotic symptoms and, potentially, preventing the progression into a full-blown psychotic disorder. However, several central questions regarding early interventions for the psychotic prodrome require clarification: Is it possible to prevent or to delay the onset of a psychotic disorder by intervening in the prodromal state? Is it possible to alter the natural course of the illness; i.e., to reduce subsequent symptom severity, relapse rates, treatment refractoriness, and/or functional disability, by treating subsyndromal symptoms? What is the relationship between treatment response of prodromal symptoms or specific symptom clusters and the prevention of disease progression or improvement of functional outcome? In the context of these questions, different treatment models and trial designs are presented, focusing on patient selection, target symptoms, interventions, control conditions, outcome measures, trial duration, and exit strategies, as well as statistical and ethical considerations. Finally, the methodology of completed and ongoing intervention trials in putative prodromal populations is discussed.

**Keywords:** Schizophrenia, psychosis, prodrome, prevention, trial design, methodology.

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In cutting edge treatment research there is often a dynamic tension inherent in the desire to intervene (prevent or treat) a “condition” before diagnostic criteria have been adequately validated, before assessment instruments have been proven valid and reliable, and even before the natural course of the untreated condition has been well established. There is no better example of this situation than prevention and intervention research for the psychotic prodrome. At the same time, prodromal psychosis

research is essential to provide a database for the risk-benefit evaluation of early interventions. (Although a true schizophrenic or psychotic “prodrome” can only be verified retrospectively after the disorder has become manifest, this term has frequently been used in the literature to characterize subjects with nonspecific symptoms and signs that are considered to be at risk for the development of a psychotic disorder, as well as for individuals with subsyndromal psychopathology. In this paper, the term “prodrome” is used in that same sense to characterize a clinical state that confers a high risk for the future development of a psychotic disorder.)

Other chapters in this issue discuss the current knowledge and research approaches to defining and delineating populations at risk as well as understanding the genetic, development, and environmental factors contributing to vulnerability and/or illness manifestation. In this chapter, we will attempt to describe potential methods for the clinical evaluation of pharmacologic and nonpharmacologic interventions, including issues in design and methodology as well as statistical and ethical concerns.

## What’s the Question?

It may be apocryphal, but supposedly Gertrude Stein on her deathbed lapsing in and out of lucid consciousness repeatedly asked “What’s the answer?” and in a moment of greater lucidity said “What’s the question?”

As basic as this issue is in clinical research, it is still remarkable how often investigators either lose sight of this fundamental issue in designing a trial or attempt to include a series of other questions, which cannot be adequately addressed in the same design, but rather end up creating potential confounds or adding unnecessary “noise” to the literature. As psychotic prodrome research develops, it

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will be necessary to carefully delineate the specific goal(s) that can be achieved with the chosen specific goal(s) that can be achieved with the chosen research design.

There are a series of questions (not necessarily mutually exclusive) that ultimately should be addressed in prodromal research (see table 1). First, can a treatment intervention reduce the risk of the disease manifesting itself? Second, can it reduce its "severity" in the most general sense (e.g., domains affected and to what degree, functional consequences, etc.) when and if it does become manifest? Third, can it delay the manifestation of the disease to a meaningful degree without influencing the ultimate nature of the illness? Fourth, can it alter the treatment responsiveness or course of the disease once it does develop?

Each one of these questions is important in and of itself and each one would deserve specific consideration in the design of a trial or trials. In this context, related questions are to what extent can the early, potentially nonspecific signs and symptoms associated with the prodrome (or high risk status) be ameliorated and to what extent will success in this effort relate to efficacy in any of the prevention questions posed previously.

The second set of questions also serves to introduce the very important issue that, up until the present, any pharmacologic treatment studied in the prodromal context has been a treatment associated with the amelioration of the subthreshold primary, positive signs and symptoms of schizophrenia itself, acknowledging the existing data that antipsychotics, particularly second generation medications, can have some, but far less consistent and dramatic, effects on negative symptoms, mood, and cognitive dysfunction (Keefe et al. 1999; Leucht et al. 1999; Levinson et al. 1999). Nevertheless, there is still considerable debate as to whether second generation antipsychotics have a relevant effect on cognitive and primary negative symptoms, or whether the existing data are, at least in part, an artifact of the novel agents' reduced liability to cause extrapyramidal side effects, coupled with the use of high doses of first generation antipsychotics in head-to-head comparisons (Carpenter and Gold 2002).

Given the well-established ability of antipsychotic drugs (and, to date, no other class of medication) to reduce the risk of psychotic "exacerbation" or "relapse" in individuals who have already manifested psychotic signs and symptoms justifying a diagnosis of schizophrenia (Davis 1985; Gilbert et al. 1995; Leucht et al. 2003), it is not unreasonable to think of these agents first in early intervention. At the same time, however, it should be emphasized that we have little established knowledge as to the cascade of biological and environmental factors that actually produce or precipitate the onset of prodromal symptoms or the first episode of frank psychosis. Clearly, there are a number of neurochemical and neuroendocrine systems that one could hypothesize as potential targets for early intervention, but, as we will discuss, the testing of specific hypotheses could at first seem daunting.

Although antipsychotic medications clearly can help to ameliorate florid signs and symptoms and to reduce the risk of subsequent relapse or worsening, it remains far from clear what effect these drugs have in altering the long-term progression of the underlying disease process in terms of ultimate psychosocial and vocational disability. If there were clear evidence of the latter, this would help to support the potential value of antipsychotics earlier in the disease process. In contrast to this line of thinking, there is some evidence suggesting that negative and cognitive symptom severity is a better predictor of functional outcome in psychotic disorders than positive symptoms (Green and Braff 2001) and that the considerable progress in the development of new antipsychotic compounds in the 20th century has not resulted in clearly improved overall outcomes in patients with schizophrenia (Hegarty et al., 1994). The lack of clarity about most adequate target symptoms and response criteria indicates that, ultimately, research in this context needs to be significantly broadened while, at the same time, recognizing the limitations of existing models of disease evolution.

Given this framework, we will discuss important issues in the design and conduct of clinical trials.

**Table 1. Relevant Questions for Prodromal Psychosis Research**

1. Can the risk of psychotic disease manifestation be reduced?
2. Is it possible to improve the severity of different symptom domains and functional outcome if a psychotic disorder emerges?
3. To what extent can the psychotic disease manifestation be delayed?
4. Can early interventions alter the course of the illness and/or treatment responsiveness once psychosis develops?
5. What is the relationship between the treatment response of prodromal symptoms and efficacy for preventing or delaying the onset of psychosis?
6. What is the relationship between the treatment response of prodromal symptoms and efficacy for improving the course, treatment responsiveness, and/or level of functioning once psychosis has developed?

## General Design Issues

Since in current prodromal research patients are identified through the presence of certain symptoms and symptom clusters, primary prevention, as in an asymptomatic genetic high-risk sample, is not yet the goal of early interventions. Rather, in the context we are discussing, a clinical trial could be secondary or tertiary prevention, aiming either at reducing the risk for progression into full-blown psychosis, or at decreasing disability and impairment through the treatment of identified prodromal clusters of signs and/or symptoms (e.g., cognitive, affective, psychosocial, sensory gating abnormalities, etc.). However, as prodromal symptom response and prevention of psychosis may very well be interconnected, this distinction is somewhat arbitrary and will also depend on whether or not the at-risk subject is truly prodromal for psychosis.

If subjects are selected based on high-risk characteristics and are not overtly psychotic, the outcome measures will include clinical symptomatology (given the current absence of established biological markers), although certain putative biological markers, like sensory gating abnormalities or cognitive abnormalities, might also be conceptualized as prepsychotic symptomatology and, thus, be used as secondary outcome measures.

The level and type of symptomatology required to define a case needs to be established. Appropriate assessment instruments need to be employed. The development of the two most widely used screening and rating instruments by the groups at Yale in the United States (McGlashan et al. 2001; Miller et al. 2002) and in Melbourne, Australia (Yung et al. 1996, 2003) has been an important step toward valid and reliable measures that are sufficiently comparable. In addition, it is important to consider that there may be a phase-of-illness-related selection bias in some prodrome studies in that patients are more likely to seek and/or accept help during a time of crisis. The crisis itself may be time limited and could arise from effects of stress or everyday problems as well as a psychotic illness diathesis. There might be a bias toward improvement in such patients regardless of the treatment, at least over the short term. Conversely, the possibility exists that patients with incipient psychosis appear phenotypically to be prodromal, even though the underlying disease process has already surpassed the threshold for psychosis. This could be one reason for the converging finding in the prospective studies by McGorry et al. (2002) and McGlashan et al. (2003b) that a substantial number of the conversions occurred early on in the trials. In addition, the integrity of the trial and generalizability of the results will also depend on minimizing a referral bias, the exclusion of certain patient groups (e.g., with long duration of prodromal symptoms, significant drop in psychosocial

functioning but without genetic risk, comorbid substance abuse, insurance problems, etc.), and of high refusal and drop out rates. In addition, there is the potential for patients to “drop in” to the active treatment group. This should also be considered in study design and analysis.

The sample size and duration of the trial should be informed by estimates of what rate of illness manifestation is expected in an untreated sample and what effect size would justify early intervention in a symptomatic, but sub-syndromal population. This information can be gleaned from naturalistic observations and followup studies or placebo-controlled trials. The nature of the potential adverse effects of the proposed treatment, as well as the potential for the social and psychological sequelae of identifying an individual as “at risk,” also need to be considered in establishing the benefit-to-risk ratio and the desired effect size. Clearly, the sensitivity and specificity of the risk indicator(s) will be critical in evaluating these issues.

Ideally, such a trial should be double-blind and involve random assignment. The appropriate control intervention should be determined based on equipoise regarding the effectiveness and safety of both conditions and/or the lack of established treatments for a given condition. An endpoint should be defined and provisions should be made to provide an appropriate treatment intervention for those who meet endpoint criteria (in both groups).

Response to intervention after endpoint, as well as subsequent course, are potentially important outcome measures in addition to time to endpoint. The longer patients can be followed, the more potentially critical information can be gleaned. Even when patients discontinue active treatment, they should be followed for as long as possible to determine their outcome. Whenever possible, intent-to-treat analysis should be carried out. The possibility that treatments can alter the course of illness even after they are discontinued is an important consideration.

It might be reasonable to assume that the emergence of positive signs and symptoms would be the primary endpoint leading to an additional or new treatment intervention. However, other outcome measures involving domains such as mood, affect, anxiety, psychosocial functioning, sensory gating, and cognitive measures should also be obtained during the trial, as it is unclear what domain of potential schizophrenia and other psychotic disorder psychopathology is most likely to benefit from prevention treatment. (And, needless to say, different treatments may have different roles in this context.)

The maximum average benefit for the largest number of at-risk subjects could have the broadest public health implications. If, rather than preventing psychosis in a small number of individuals, a putative treatment produces modest reductions in severity, reduced hospitalization, or better functioning in a larger number of patients, this has

major, though perhaps less “dramatic,” implications. Moreover, the relevance of targeting selected psychopathology and functional outcome is enhanced by the fact that the crossing of an arbitrary symptom threshold for psychosis can be a gradual process involving merely a modest worsening of symptoms.

The choice and dose of medication are difficult decisions to make given current knowledge. How does the dose necessary to treat an acute illness, or the presumably lower dose needed to prevent subsequent relapse, relate to the medication dosage necessary to prevent or delay the initial emergence of psychosis? Could too high a dose in this context have an effect that is ultimately counterproductive? The availability of second generation antipsychotics with an overall better benefit-to-risk ratio, with the exception of weight gain and metabolic abnormalities with some drugs (Allison et al. 1999; McIntyre et al. 2001), makes these decisions less difficult than they would have been a decade ago. However, the effectiveness of non-antipsychotic medications and nonpharmacologic interventions that have a reduced side effect liability should also be explored as potential treatment candidates.

Another critical dilemma in the design of a prevention trial is if and when to discontinue treatment in those individuals who have not developed psychotic signs and symptoms. Data from the trial itself might not inform this decision, but an “exit strategy” should be considered as early as possible in the process. Ultimately, a controlled discontinuation design in those individuals with no symptoms would be necessary, emphasizing that the medication discontinuation process should probably be a very slow one. Decisions about the rate of medication taper could possibly be informed by studies about the time course of receptor binding and the timing of relapse in psychotic patients after abrupt antipsychotic withdrawal. During the taper and discontinuation phase, the reemergence of prodromal symptoms and signs of deterioration should be closely monitored, and targeted intervention strategies should be offered.

## Treatment and Prevention Trials

The possibility exists that those treatments, which are effective in reducing and/or preventing prodromal symptoms, might not be equally effective in preventing further progression of the illness (and vice versa). Therefore, if subjects are entered into a treatment trial focusing on symptomatic relief for presenting psychopathology, careful thought has to go into the design of long-term treatment and the evaluation of the potential to prevent further progression of the disease process. Conceivably, two different treatments with different potential actions could be combined in this context (assuming that their effects would not be diminished in combination). Appropriate

controls for each intervention would still be necessary.

Design decisions have to focus on the following points: (1) patient population; (2) target symptoms; (3) intervention(s); (4) control conditions; (5) outcome measures; (6) trial duration/exit strategies; (7) statistical power, clinically meaningful effect size, and sample size; and (8) ethical considerations.

**Patient Population.** It has been repeatedly argued that one way of minimizing the risk of exposing subjects who are false positive for the endpoint condition is to “enrich” samples. Some groups, like The Zucker Hillside Hospital Recognition and Prevention (RAP) Program (Cornblatt et al. 2001; Lencz et al., this issue), have focused on the clinical categorization of risk within a sample of adolescents who are symptomatic and treatment-seeking. The clinical subdivision of prodromal “phases,” like predominant attenuated negative, attenuated positive, or subsyndromal psychotic symptoms, can lead to different intervention strategies and trials to investigate their effectiveness. Others, like the PACE clinic in Melbourne (Yung et al. 1996) or the PRIME Clinic in New Haven (McGlashan et al. 2003), have allowed for a combination, or, at least, an overlap with the genetic high-risk perspective in order to achieve an “ultra high-risk” sample that justifies early interventions and provides more power for clinical trials. Other potential ways of enriching samples include examples such as presence of putative biological “markers.” (Examples might include history of obstetric complications, sensory gating or eye tracking abnormalities, presence of neurological soft signs or minor physical anomalies, abnormalities in olfaction or cognition, presence of extrapyramidal signs, high cortisol levels, abnormal niacin flush test reaction, neuroimaging abnormalities, etc.) Although many of these signs and symptoms are rather nonspecific and not uncommon in the general population, the combination of one or several of these markers with subpsychotic symptoms could conceivably contribute to the identification of an enriched, high-risk sample.

**Target Symptoms.** Given the array of potential symptoms present during the prodrome ranging from poor school performance or social adjustment to diminished motivation or other negative symptoms, information-processing deficits, depression, and/or attenuated positive symptoms, there are a number of potential treatments that could have an ameliorative effect on some symptoms but not on others (effects that may even be phase-specific) (see below). In addition, specific components of the subsyndromal state could be targeted in order to examine the impact of treating these particular symptom clusters on the risk and time point of transition to psychosis, the course of illness, and/or level of functional disability.

**Intervention(s).** To date, the only published data available from prospective controlled trials (McGorry et al. 2002) support the value of antipsychotic drugs in preventing the development of psychotic signs and symptoms sufficient to warrant a diagnosis of schizophrenia or other major psychotic disorders. However, in many disorders, interventions during earlier phases of the illness differ from treatments for later stages. Moreover, treatments effective at preventing an illness may not reduce symptoms that are part of the full disease manifestation, and vice versa. The same possibility has to be considered for treatment/preventive interventions during the psychotic prodrome. The choice of treatments will depend on the targets chosen and whether the goal is prevention or symptom reduction. It will also depend on the discovery of pathological processes related to the progression from prodromal to psychotic symptoms. Results from a recent MRI study by Pantelis et al. (2003), for example, suggest that neuroprotective agents may have a role for prevention trials. In this study, the authors were able to show an attenuation of gray matter in subjects who had developed a first episode of psychosis compared to subjects with prodromal symptoms. More importantly for the potential role of early interventions, in the 21 patients available for a longitudinal comparison after at least 12 months of followup, cortical gray matter was further attenuated in the 10 patients with prodromal symptoms who had converted to psychosis compared to 11 patients who did not manifest a psychotic disorder. Although brain morphometric measures may not be the best tools to track processes underlying psychotic disease manifestation, these results support the possibility that agents that enhance or protect neuronal integrity might be useful for preventing or delaying the onset of psychosis.

Possible interventions besides low-dose antipsychotics include nonpharmacologic therapies (e.g., psychoeducation, supportive therapy, cognitive behavioral or interpersonal therapy, family and group therapy, social skills and stress management groups) and pharmacologic agents that are either effective for some prodromal symptom clusters or that have some evidence for being "neuroprotective" or both. While the evidence, so far, is mainly derived from preclinical and animal studies, several medications have potential neuroprotective properties. These include antidepressants (Salzman et al. 1994; Li et al. 2000; Michael-Titus et al. 2000; Thome et al. 2000; Sanchez et al. 2001), mood stabilizers (Nonaka et al. 1998; Manji et al. 1999; Hashimoto et al. 2002), essential fatty acids (Lauritzen et al. 2000; Seung et al. 2001), and magnesium (Bareyre et al. 2000; Yang et al. 2000; Saatman et al. 2001; Sameshima and Ikenoue 2001). Moreover, strategies combining pharmacological and nonpharmacological interventions or combining a higher with a lower risk pharmacological agent should be explored, given adequate

sample sizes. It might also be appropriate to consider sequential treatment interventions with different targets. For example, as acute subsyndromal symptomatology improves, patients could be randomized to one set of alternatives, whereas those with persistent symptomatology after a relatively brief trial would be eligible for different interventions. Although these designs become complex and statistical power diminishes, such cohorts are difficult to recruit and should be followed as long as possible under controlled conditions.

**Control Conditions.** Given the subsyndromal disease manifestation and lack of established treatments, placebo-controlled trials for medication effects seem reasonable and desirable, but control conditions can also include low-intensity case management, supportive therapy, a targeted psychosocial or psychotherapeutic intervention, non-antipsychotic pharmacological agents, or a combination strategy.

**Outcome Measures.** Although the concept of a prodrome to schizophrenia or any other psychotic illness already implies its central outcome, trials should not be limited in their assessment measures to psychopathology ratings alone. Psychosocial, educational, and vocational outcome and quality of life are as important as is the careful and multifaceted assessment of safety and adherence. Moreover, biological response parameters might also be considered. Potential candidates could include cortisol, bcl-2, phosphokinase C, tumor necrosis factor, interleukines, sensory gating abnormalities, functional magnetic resonance imaging, 31-phosphorus magnetic resonance spectroscopy of membrane lipid integrity, or positron emission tomography studies. However, much more validation research needs to be done before definitive conclusions can be drawn differentiating primary effects from epiphenomena.

**Trial Duration/Exit Strategies.** Despite some findings of conversion rates of about 40 percent in enriched and ultra high-risk samples over 1 year (Cornblatt et al. 2003; McGlashan et al. 2003b; Yung et al. 2003), the time to progression into frank psychosis in the entire at-risk group is unpredictable. Therefore, regular followup assessments should be provided to patients, even after completion of a prevention or intervention trial, ideally in the context of a controlled discontinuation trial. The rate of discontinuation of active treatment should most likely be very gradual to prevent potentially destabilizing rebound or withdrawal phenomena. Should patients desire either to not take any medications, or even not to receive any treatment, prospectively collected information on their symptomatic recovery or progression will be highly informative regarding base-rates or delayed treatment effects.

**Statistical Issues.** Statistical issues are critical in establishing an appropriate design and sample size. Judgment has to be made as to what would represent a clinically meaningful treatment effect, in both absolute and relative terms. In the case of delaying illness onset, for example, how many months' delay would warrant a treatment intervention and what other consequences would accrue from a potential delay. Risks of the treatment intervention itself need to be considered as well. Potential confounds should be considered and controlled for when possible, such as compliance status, duration of prodromal symptoms, comedications, and side effects. (In addition, in multisite studies analysis of the consistency of results across sites should be conducted.) Clearly, adequate sample sizes are necessary to have sufficient power for such analyses. As conversion to psychosis could occur after variable periods of time in prodromal subjects, long-term trials are essential. However, the high dropout rates, which are common in long-term studies, might require different analytic techniques than traditional ones, like the last observation carried forward. An example of this is a mixed effects, likelihood-based, repeated measures model (Mallinckrodt et al. 2003) that extrapolates future data for dropouts from subjects who continued in the trial, as used in the analysis of the placebo-controlled trial with olanzapine by the Yale group (McGlashan et al. 2003b). (However, none of these methods is ideal and every effort should be made to keep dropouts to a minimum.) Finally, translating the treatment effect into a clinically meaningful measure, like number needed to treat (Cook et al. 1995), should also be considered.

**Ethical Concerns.** In evaluating the ethical issues in prodromal and prevention research, clearly the sensitivity and specificity of risk predictors becomes a critical concern. The risks of the potential intervention should be considered as well as the psychological factors and the potential stigma associated with being considered to be a "high-risk" subject (Cornblatt et al. 2001; Heinssen et al. 2001; McGlashan 2001; McGorry et al. 2001). An adequate discussion of the risks of intervention as well as nonintervention must take place, and the potential exit strategy, with its associated risks and benefits, should also be presented. This is particularly important, as the true positive conversion rate in any given population that is judged to be prodromal for psychosis is unknown. The potential of exposing false positives to treatment has implications for the choice of both the active and the control conditions. The selection of an adequate control is traditionally based on equipoise. Equipoise is an assumption inherent in ethical experimentation. It indicates that based on current knowledge a set of treatment options are approximately equal in terms of likelihood of success, or that there is a reason-

able disagreement over which treatment has the superior risk-benefit ratio. As for interventions during the psychotic prodrome, the lack of certainty about the outcome of untreated at-risk individuals and about the most effective and safe treatment for prepsychotic symptom clusters makes a placebo control a scientifically important and ethical alternative (Carpenter et al. 2003). Moreover, consideration should be given to patient choice; i.e., a randomized schedule, in which the patient is offered alternative randomization strategies. Lavori et al. (2001) has suggested "equipoise stratified randomization." In this model, the clinician and patients would define or select specific study treatments that are acceptable and that also satisfy the equipoise criteria. Patients could then be randomized to a specific option within that array of possibilities. As Lavori et al. (2001, p. 795) suggest, this "design converts the clinician's judgment from an unspecified post randomization confound in a 'clinician's choice' design to a fully observed free randomization factor that can be balanced explicitly, and, therefore, statistically controlled." A thorough review of the potential application to prodromal studies and statistical techniques of this randomization paradigm is beyond the scope of this paper, but it is cited as an example of the type of consideration that affects patients' autonomy and physicians' and patients' willingness to participate, as well as the potential generalizability of the results.

All of these considerations represent particular challenges in the context of prevention and prodromal research. However, only by facing and addressing these issues can data accrue that is necessary to enhance the sensitivity and specificity of patient selection and establish the effectiveness of intervention strategies, with the ultimate goal to reduce and, hopefully, prevent morbidity and mortality in subjects at risk for schizophrenia and other major psychotic disorders.

## Discussion of Current Prodromal Treatment Trials

Following, we will give a brief overview of the designs of ten ongoing or completed intervention trials for subjects considered prodromal for psychosis. Four of the ten studies investigate the efficacy of low-dose novel antipsychotic medications, one trial follows patients naturalistically who are treated with various psychotropic drugs, three projects focus on non-antipsychotic agents, and two assess the effectiveness of a psychotherapeutic intervention for putatively prodromal populations.

McGorry et al. (2002) compared low-dose risperidone plus cognitive behavioral therapy (CBT) as a specific preventive intervention in a single blind design to needs-

based intervention (i.e., counseling and case management) for 6 months, followed by a 6-month observation period of all patients on needs-based therapy only. Although the combined intervention design of risperidone plus CBT of this landmark study was able to show a significant preventive treatment effect in a modest-sized population of 60 subjects, this methodology made it impossible to determine the relative contribution of the pharmacological and nonpharmacological interventions for the prevention of progression into frank psychosis. To assess the differential effect of risperidone and CBT for psychosis prevention, the Melbourne group is currently conducting a controlled three-cell trial comparing risperidone versus CBT versus needs-based treatment, and has already enrolled 60 subjects.

In a small, exploratory study, low-dose risperidone was also used open-label for 3 months in four prodromal patients, combined with six first episode schizophrenia subjects, measuring the response of prodromal psychotic and cognitive symptoms (Cannon et al. 2002). In a double-blind, multisite trial (McGlashan et al. 2003a; Woods et al. 2003), the efficacy of olanzapine plus supportive and family therapy is compared with supportive and family therapy alone, measuring prodromal and other psychopathology response and prevention of conversion to psychosis. One year of active treatment, which has recently been completed and presented (McGlashan et al. 2003b), is followed by another 12 months of observation. The same 24-month design with a 12-month active treatment and 12-month observation phase was chosen by the German Schizophrenia Network (Morrison et al. 2002; Ruhrman et al. 2002). However, this group is conducting two trials in a phase specific design. In one randomized, open-label study, amisulpride is compared to psychologically advanced clinical management for "late" prodromal symptoms, which consist of brief, limited, intermittent, subthreshold psychotic symptoms or attenuated subpsychotic symptoms (Ruhrmann et al. 2002). In a companion trial with different entry criteria, a multimodal psychotherapeutic intervention is tested against clinical management for symptoms that are consistent with the concept of an "early" prodrome (i.e., presence of genetic/obstetric risk in combination with a deterioration in functioning equivalent to a GAF drop of > 30 points, or "basic symptoms," consisting of prepsychotic disturbances of speech, thought process, and content that are below the level of attenuated positive symptomatology) (Bechdolf and Wagner 2003). One other 12-month trial focuses on a nonpharmacologic intervention for the psychotic prodrome, investigating the efficacy of a maximum of 26 CBT sessions over 6 months plus monitoring versus monitoring alone (Morrison et al. 2002).

In the study by Cornblatt et al. (2002), antipsychotics were used alone or in conjunction with other psychotropic medications and compared naturalistically with non-

antipsychotic medications, mainly antidepressants. Although the naturalistic design of this longitudinal study introduces many confounds, the results of such observations have the potential to inform more rigorous controlled studies. Finally, the three remaining projects investigate the usefulness of non-antipsychotic medications with potential neuroprotective activity and/or efficacy for negative symptoms as open-label treatment of prodromal psychopathology and prevention of psychosis. These include a 1-year trial with low-dose lithium (Berger and McGorry 2002), as well as a 2-month trial of glycine and a 3-month study with ethyl-eicosapentaenoic acid, an omega-3 fatty acid (Woods et al. 2002). These trials include outcome measures that range from psychopathology ratings and rates of progression into psychosis, to cognitive assessments and measures of structural cortical and cell membrane integrity to measures of apoptosis.

Each of these approaches has strengths and weaknesses and, clearly, much remains to be done in this developing field.

## Future Directions

Future directions will be influenced by developments in a number of areas. For example, once specific prodromal interventions have been shown effective in reducing subpsychotic psychopathology and/or delaying or preventing conversion to psychosis, the long-term course of patients who did not progress to a psychotic disorder (as well as of those who did) should be carefully studied. The investigation of treatments other than antipsychotic agents for the psychotic prodrome and for specific prepsychotic symptom domains should be explored further, paying attention to the possibility of phase-specific efficacy. Pending the elucidation of valid biological response parameters, these could become meaningful outcome measures in addition to psychopathology ratings. As risk factors or predictors for the conversion to psychosis are detected, treatments aimed at these disease elements or physiological processes should be investigated. Furthermore, as genes of interest are identified, investigators could conceivably examine illness- or treatment-related effects on gene "expression" arrays in a number of different brain tissues.

It is also likely that there are gene environment interactions that may contribute to the progression of schizophrenia. There might be problems in connectivity that interfere with the ability of the brain to "remodel" itself in the context of environmental demands. By the same token, the reduced ability to respond to environmental stimuli or demands might influence the motivation to, or anxiety associated with, experiencing such stimuli. The results would be further failures in remodeling and establishing the development of optimum connectivity.

Given the enormous importance of these efforts and the inherent difficulty in designing and conducting such trials, it is especially incumbent on investigators and sponsors to design trials that are most informative, while maintaining feasibility and ethical standards. This special issue of the *Schizophrenia Bulletin* should help to further that goal.

## References

- Allison, D.B.; Mentore, J.L.; Heo, M.; Chandler, L.P.; Cappelleri, J.C.; Infante, M.C.; and Weiden, P.J. Antipsychotic-induced weight gain: A comprehensive research synthesis. *American Journal of Psychiatry*, 156(11):1686–1696, 1999.
- American Psychiatric Association. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: APA, 1994.
- Bareyre, F.M.; Saatman, K.E.; Raghupathi, R.; and McIntosh, T.K. Postinjury treatment with magnesium chloride attenuates cortical damage after traumatic brain injury in rats. *Journal of Neurotrauma*, 17(11):1029–1039, 2000.
- Bechdolf, A., and Wagner, M. Cognitive behavioral therapy in the prepsychotic phase: An exploratory study. *Schizophrenia Research*, 60(Suppl.):319, 2003.
- Berger, G.E., and McGorry, P.D. "Neuroprotection in Early Psychosis—A New Avenue to Explore?" Paper presented at the XII World Congress of Psychiatry, Yokohama, Japan, August 2002.
- Cannon, T.D.; Huttunen, M.O.; Dahlstrom, M.; Larmo, I.; Rasanen, P.; and Juriloo, A. Antipsychotic drug treatment in the prodromal phase of schizophrenia. *American Journal of Psychiatry*, 159(7):1230–1232, 2002.
- Cook, R.J., and Sackett, D.L. The number needed to treat: A clinically useful measure of treatment effect. *British Medical Journal*, 310(6977):452–454, 1995.
- Carpenter, W.T., Jr.; Appelbaum, P.S.; and Levine, R.J. The Declaration of Helsinki and clinical trials: A focus on placebo-controlled trials in schizophrenia. *American Journal of Psychiatry*, 160(2):356–362, 2003.
- Carpenter, W.T., and Gold, J.M. Another view of therapy for cognition in schizophrenia. *Biological Psychiatry*, 51(12):969–971, 2002.
- Cornblatt, B.; Lencz, T.; Correll, C.; Smith, C.W.; Author, A.; and Nakamura, E. The schizophrenia prodrome revisited: A neurodevelopmental perspective. *Schizophrenia Bulletin*, 29(4):633–651, 2003.
- Cornblatt, B.A.; Lencz, T.; and Kane, J.M. Treatment of the schizophrenia prodrome: Is it presently ethical? *Schizophrenia Research*, 51(1):31–38, 2001.
- Davis, J.M. Maintenance therapy and the natural course of schizophrenia. *Journal of Clinical Psychiatry*, 46:18–21, 1985.
- Gilbert, P.; Harris, M.J.; and McAdams, L.A. Neuroleptic withdrawal in schizophrenic patients. A review of the literature. *Archives of General Psychiatry*, 52:173–188, 1995.
- Green, M.F., and Braff, D.L. Translating the basic and clinical cognitive neuroscience of schizophrenia to drug development and clinical trials of antipsychotic medications. *Biological Psychiatry*, 15;49(4):374–384, 2001.
- Hashimoto, R.; Hough, C.; Nakazawa, T.; Yamamoto, T.; and Chuang, D.M. Lithium protection against glutamate excitotoxicity in rat cerebral cortical neurons: Involvement of NMDA receptor inhibition possibly by decreasing NR2B tyrosine phosphorylation. *Journal of Neurochemistry*, 80(4):589–597, 2002.
- Hegarty, J.D.; Baldessarini, R.J.; Tohen, M.; Waternaux, C.; and Oepen, G. One hundred years of schizophrenia: A meta-analysis of the outcome literature. *American Journal of Psychiatry*, 151(10):1409–1416, 1994.
- Heinssen, R.K.; Perkins, D.O.; Appelbaum, P.S.; and Fenton, W.S. Informed Consent in Early Psychosis Research: National Institute of Mental Health workshop, November 15, 2000. *Schizophrenia Bulletin*, 27(4):571–583, 2001.
- Keefe, R.S.; Silva, S.G.; Perkins, D.O.; and Lieberman, J.A. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: A review and meta-analysis. *Schizophrenia Bulletin*, 25(2):201–222, 1999.
- Lauritzen, I.; Blondeau, N.; Heurteaux, C.; Widmann, C.; Romey, G.; and Lazdunski, M. Polyunsaturated fatty acids are potent neuroprotectors. *The EMBO Journal*, 19(8):1784–1793, 2000.
- Lavori, P.W.; Rush, A.J.; Wisniewski, S.R.; Alpert, J.; Fava, M.; Kupfer, D.J.; Nierenberg, A.; Quitkin, F.M.; Sackeim, H.A.; Thase, M.E.; and Trivedi, M. Strengthening clinical effectiveness trials: Equipoise-stratified randomization. *Biological Psychiatry*, 50(10):792–801, 2001.
- Lencz, T.; Smith, C.W.; Auther, A.M.; Correll, C.U.; and Cornblatt, B.A. The assessment of "prodromal schizophrenia": Unresolved issues and future directions. *Schizophrenia Bulletin*, 29(4):717–728, 2003.
- Leucht, S.; Barnes, T.R.; Kissling, W.; Engel, R.R.; Correll, C.; and Kane, J.M. Relapse prevention in schizophrenia with new-generation antipsychotics: A systematic review and exploratory meta-analysis of randomized, controlled trials. *American Journal of Psychiatry*, 160(7):1209–1222, 2003.



- Leucht, S.; Pitschel-Walz, G.; Abraham, D.; and Kissling, W. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophrenia Research*, 35(1):51–68, 1999.
- Levinson, D.F.; Umapathy, C.; and Musthaq, M. Treatment of schizoaffective disorder and schizophrenia with mood symptoms. *American Journal of Psychiatry*, 156(8):1138–1148, 1999.
- Li, X.M.; Chlan-Fourney, J.; Juorio, A.V.; Bennett, V.L.; Shrikhande, S.; and Bowen, R.C. Antidepressants upregulate messenger RNA levels of the neuroprotective enzyme superoxide dismutase (SOD1). *Journal of Psychiatry and Neuroscience*, 25(1):43–47, 2000.
- Mallinckrodt, C.H.; Clark, S.W.; Carroll, R.J.; and Molenbergh, G. Assessing response profiles from incomplete longitudinal clinical trial data under regulatory considerations. *Journal of Biopharmaceutical Statistics*, 13(2):179–190, 2003.
- Manji, H.K.; Moore, G.J.; and Chen, G. Lithium at 50: Have the neuroprotective effects of this unique cation been overlooked? *Biological Psychiatry*, 46(7):929–940, 1999.
- McGlashan, T.H. Psychosis treatment prior to psychosis onset: ethical issues. *Schizophrenia Research*, 51(1):47–54, 2001.
- McGlashan, T.H.; Miller, T.J.; Woods, S.W.; Hoffman, R.E.; and Davidson, L. Instrument for the assessment of prodromal symptoms and states. In: Miller, T.; Mednick, S.A.; McGlashan, T.H.; Libiger, J.; and Johannessen, J.O., eds. *Early Intervention in Psychotic Disorders*. Dordrecht, Holland: Kluwer Academic Publishers, 2001. pp. 135–149.
- McGlashan, T.H.; Zipursky, R.B.; Perkins, D.; Addington, J.; Miller, T.J.; Woods, S.W.; Hawkins, K.A.; Hoffman, R.; Lindborg, S.; Tohen, M.; and Breier, A. The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. I. Study rationale and design. *Schizophrenia Research*, 61(1):7–18, 2003a.
- McGlashan, T.H.; Zipursky, R.B.; Perkins, D.O.; Addington, J.; Woods, S.W.; Miller, T.J.; Lindborg, S.; Marquez, E.; Hawkins, K.; Hoffman, R.E.; Tohen, M.; and Breier, A. Olanzapine versus placebo treatment of the schizophrenia prodrome: One year results. *Schizophrenia Research*, 60(Suppl.):295, 2003b.
- McGorry, P.D.; Yung, A.; and Phillips, L. Ethics and early intervention in psychosis: Keeping up the pace and staying in step. *Schizophrenia Research*, 51(1):17–29, 2001.
- McGorry, P.D.; Yung, A.R.; Phillips, L.J.; Yuen, H.P.; Francey, S.; Cosgrave, E.M.; Germano, D.; Bravin, J.; McDonald, T.; Blair, A.; Adlard, S.; and Jackson, H. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Archives of General Psychiatry*, 59(10):921–928, 2002.
- McIntyre, R.S.; McCann, S.M.; and Kennedy, S.H. Antipsychotic metabolic effects: Weight gain, diabetes mellitus, and lipid abnormalities. *Canadian Journal of Psychiatry*, 46(3):273–281, 2001.
- Michael-Titus, A.T.; Bains, S.; Jeetle, J.; and Whelpton, R. Imipramine and phenelzine decrease glutamate overflow in the prefrontal cortex—a possible mechanism of neuroprotection in major depression? *Neuroscience*, 100(4):681–684, 2000.
- Miller, T.J.; McGlashan, T.H.; Rosen, J.L.; Somjee, L.; Markovich, P.J.; Stein, K.; and Woods, S.W. Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: Preliminary evidence of interrater reliability and predictive validity. *American Journal of Psychiatry*, 159(5):863–865, 2002.
- Miller, T.J.; Zipursky, R.B.; Perkins, D.; Addington, J.; Woods, S.W.; Hawkins, K.A.; Hoffman, R.; Preda, A.; Epstein, I.; Addington, D.; Lindborg, S.; Marquez, E.; Tohen, M.; Breier, A.; and McGlashan, T.H. The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. II. Baseline characteristics of the “prodromal” sample. *Schizophrenia Research*, 61(1):19–30, 2003.
- Morrison, A.P.; Bentall, R.P.; French, P.; Walford, L.; Kilcommons, A.; Knight, A.; Kreutz, M.; and Lewis, S.W. Randomised controlled trial of early detection and cognitive therapy for preventing transition to psychosis in high-risk individuals. Study design and interim analysis of transition rate and psychological risk factors. *British Journal of Psychiatry Supplement*, 43:S78–S84, 2002.
- Nonaka, S.; Hough, C.J.; and Chuang, D.M. Chronic lithium treatment robustly protects neurons in the central nervous system against excitotoxicity by inhibiting N-methyl-D-aspartate receptor-mediated calcium influx. *Proceedings of the National Academy of Sciences of the United States of America*, 95(5):2642–2647, 1998.
- Pantelis, C.; Velakoulis, D.; McGorry, P.D.; Wood, S.J.; Suckling, J.; Phillips, L.J.; Yung, A.R.; Bullmore, E.T.; Brewer, W.; Soulsby, B.; Desmond, P.; and McGuire, P.K. Neuroanatomical abnormalities before and after onset of psychosis: A cross-sectional and longitudinal MRI comparison. *Lancet*, 361(9354):281–288, 2003.

- Ruhrman, S.; Wagner, M.; Wieneke, A.; Bechdorf, A.; Maier, W.; and Klosterkötter, J. Intervention in the initial phase of psychosis. *Acta Psychiatrica Scandinavica*, 106(S413):19, 2002.
- Saatman, K.E.; Bareyre, F.M.; Grady, M.S.; and McIntosh, T.K. Acute cytoskeletal alterations and cell death induced by experimental brain injury are attenuated by magnesium treatment and exacerbated by magnesium deficiency. *Journal of Neuropathology and Experimental Neurology*, 60(2):183–194, 2001.
- Salzman, S.K.; Kelly, G.; Chavin, J.; Wang, L.; Puniak, M.A.; Agresta, C.A.; and Azim, S. Characterization of mianserin neuroprotection in experimental spinal trauma: Dose/route response and late treatment. *The Journal of Pharmacology and Experimental Therapeutics*, 269(1):322–328, 1994.
- Sameshima, H., and Ikenoue, T. Long-term magnesium sulfate treatment as protection against hypoxic-ischemic brain injury in seven-day-old rats. *American Journal of Obstetrics and Gynecology*, 184(2):185–190, 2001.
- Sanchez, V.; Camarero, J.; Esteban, B.; Peter, M.J.; Green, A.R.; and Colado, M.I. The mechanisms involved in the long-lasting neuroprotective effect of fluoxetine against MDMA ('ecstasy')-induced degeneration of 5-HT nerve endings in rat brain. *British Journal of Pharmacology*, 134(1):46–57, 2001.
- Seung Kim, H.F.; Weeber, E.J.; Sweatt, J.D.; Stoll, A.L.; and Marangell, L.B. Inhibitory effects of omega-3 fatty acids on protein kinase C activity in vitro. *Molecular Psychiatry*, 6(2):246–248, 2001.
- Thome, J.; Sakai, N.; Shin, K.; Steffen, C.; Zhang, Y.J.; Impey, S.; Storm, D.; and Duman, R.S. cAMP response element-mediated gene transcription is upregulated by chronic antidepressant treatment. *Journal of Neuroscience*, 20(11):4030–4036, 2000.
- Woods, S.W.; Breier, A.; Zipursky, R.B.; Perkins, D.O.; Addington, J.; Miller, T.J.; Hawkins, K.A.; Marquez, E.; Lindborg, S.R.; Tohen, M.; and McGlashan, T.H. Randomized trial of olanzapine versus placebo in the symptomatic acute treatment of the schizophrenic prodrome. *Biological Psychiatry*, 54(4):453–465, 2003.
- Woods, S.W.; D'Souza, D.C.; Wexler, B.E.; Hoffman, R.E.; and McGlashan, T.H. Novel early interventions for prodromal states. *Acta Psychiatrica Scandinavica*, 106(S413):12, 2002.
- Yang, Y.; Li, Q.; Ahmad, F.; and Shuaib, A. Survival and histological evaluation of therapeutic window of post-ischemia treatment with magnesium sulfate in embolic stroke model of rat. *Neuroscience Letters*, 285(2):119–122, 2000.
- Yung, A.R.; McGorry, P.D.; McFarlane, C.A.; Jackson, H.J.; Patton, G.C.; and Rakkar, A. Monitoring and care of young people at incipient risk of psychosis. *Schizophrenia Bulletin*, 22(2):283–303, 1996.
- Yung, A.R.; Phillips, L.J.; Yuen, H.P.; Francey, S.M.; McFarlane, C.A.; Hallgren, M.; and McGorry, P.D. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophrenia Research*, 60(1):21–32, 2003.

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