Intervention Research in Psychosis: Prevention Trials

by Barry D. Lebowitz and Jane L. Pearson

Abstract

Prevention trials have not been a central focus in mental health research in general and in the psychoses in particular. In this article we provide the basis for development of a model for prevention trials, define the parameters of the model, and provide some illustrative examples. The article expands upon traditional approaches to prevention by incorporating perspectives from the fields of treatment and services research. Approaches to prevention are based upon models of etiology, pathophysiology, and risk. A number of barriers to the development of a major emphasis on prevention are identified, and those that are embedded in the infrastructure of the field are highlighted.

Keywords: Mental disorders, prevention, treatment, rehabilitation, geriatrics.


Three types of studies fall under the general rubric of intervention research. Treatment studies are geared toward the management of symptoms and the improvement of function in both the short and long term. Rehabilitative interventions are directed toward the reduction or elimination of residual symptomatology remaining after treatment in order to optimize long-term functioning. In the context of treatment, preventive interventions are directed toward reducing the risk of relapse or recurrence and toward minimizing excessive or inappropriate levels of disability. Preventive studies are also directed toward eliminating or reducing the development of illness in those at risk.

In this article we discuss an approach to prevention research and prevention trials that is used to inform program development efforts at the National Institute of Mental Health (NIMH). Our thinking has been guided by two important reports prepared by the National Advisory Mental Health Council (1998, 1999), one on prevention research and one on the linkages between treatment and services research.

Prevention in the mental health field has been seen, traditionally, as relevant only to issues in childhood and adolescence. If anything, trying to prevent chronic diseases such as the psychoses or diseases in geriatric populations was considered oxymoronic. Very simply, prevention meant youth, and it meant avoidance of the onset of illness.

Why be concerned with prevention in late life or in chronic disease? First, there is a demographic imperative—the aging of the population. By 2050, the U.S. population over age 65 will double, and the population over age 85 will be five times as great as it is now. As pointed out in the classic papers by Gruenberg (1977) and Kramer (1980), the same factors—public health measures, technological development, and lifestyle changes—that contributed to this growth in the overall population would also result in growth of the numbers of people with chronic illnesses and disabilities. The conclusion of their analyses was that in the absence of cures or effective preventive strategies there would be an explosion in the number of older persons with serious and persistent disabling illnesses, particularly mental disorders. The availability of more efficacious treatments and the accessibility of a wide range of appropriate services in the community combined to produce huge gains in the life expectancy of those with mental disorders who in earlier times would have died long before reaching old age. This demographic imperative leads to the conclusion that prevention must be an important part of the research agenda in the coming years.

Prevention trials represent a new opportunity for research in this field. Models for this type of research are still in development. This paper contains the elements for the construction of such a model. This is only a first step, and it is largely inductive. That is, it proceeds not from a single overall theory but from the empirically validated...
knowledge that has come from research in the field. The approach is developmental and sequential: to identify those lines of research that could contribute to a new conceptualization of prevention in the field.

At the same time, there is considerable rethinking of some of the basic ideas about prevention in the mental health field in general. There is a growing consensus that the traditional public health view of primary, secondary, and tertiary prevention is not optimal. The 1994 Institute of Medicine (IoM) report (Mrazek and Haggerty 1994), for example, takes a different tack and adapts a scheme developed by Gordon (1983) to characterize preventive interventions as universal (targeted to a general population), selective (targeted to individuals at increased risk), or indicated (targeted to individuals with minimal levels of signs or symptoms).

The IoM approach is clearly based on the position that prevention refers to the reduction of the likelihood of emergent disease. In our view, significant advantage is gained when prevention is extended to questions of functioning and disability in those who have an illness as well as to posttreatment relapse or recurrence.

It is our conviction that an appropriate model of prevention must (1) be tied closely to treatment research; (2) have strong connections to service systems and services research; and (3) be based upon models of etiology, pathophysiology, and risk. Following the recommendations of Kraemer and colleagues (1997), we use the terms "risk" and "risk factor" very narrowly to indicate an empirically demonstrated agent or exposure that influences the likelihood of a particular event in a defined population. It should be clear, then, that when we speak of prevention we mean intervention directed at reducing risk of the development, exacerbation, or adverse consequences of mental disorders.

In particular, this definition does not include interventions directed toward reducing the risk of development of risk factors. We propose this distinction for several reasons, but primarily because prevention of risk factors is a strategy without definable boundaries, one for which there are neither adequate resources nor appropriate expertise in the mental health field alone. For example, given that stroke appears to constitute a major risk factor for depression, should the mental health field launch a program of stroke prevention? Or if viral infection during pregnancy increases the risk for schizophrenia, should the mental health field launch a major initiative of influenza vaccination? In our view these are responsibilities more properly given to other fields of health care. On the other hand, an intervention to prevent development of depression in those with stroke is appropriate for mental health researchers to consider and is consistent with the assumptions of these researchers' overall approach.

Targets for Prevention Trials

Within this expanded view of prevention trials there needs to be a clear understanding of the objectives of or targets for intervention research. In particular, intervention trials can be considered preventive if they are seeking to optimize functioning, to enhance compliance with long-term treatment and disease management strategies, to reduce hospitalization, to reduce excess disability, or to control symptoms or side effects of treatment for these symptoms.

Within this comprehensive view of preventive intervention research, it needs to be underscored that no field owns this perspective. A preventive intervention could be based on clinical, biological, behavioral, psychosocial, or services research, and it could adopt the tools and methods of any of these perspectives.

Prevention Trials in the Context of Treatment Research

Prevention of Relapse and Recurrence. The good news about the mental disorders of late life is that they are treatable. Many reviews, consensus statements, and practice guidelines have demonstrated that older patients respond robustly to treatments that are appropriately applied with adequate intensities. These data are largely based on relatively brief, randomized controlled trials addressing the short-term efficacy of treatments to manage the symptoms of serious illnesses like schizophrenia (Lehman et al. 1998), depression (Nathan and Gorman 1998), and Alzheimer's disease (Small et al. 1997). More recently, the prevention of relapse and recurrence has emerged as a major orientation in treatment. As recognition has grown that serious mental disorders are likely to be chronic, recurring illnesses with substantial residual disability, so, too, has the acknowledgment that treatment must be approached with a much longer-term perspective. In this light, a trial could be considered preventive if the acute treatment response is considered the starting point of the study and if the major purpose of the ongoing intervention is to prevent relapse or recurrence and not to manage active symptoms.

Prevention of Side Effects and Adverse Reactions. Patients require antipsychotic treatment for management of behavioral disturbance in schizophrenia, depression, and Alzheimer's disease. Movement disorders are common side effects of the older types of these medications, the conventional neuroleptics. Although doses given to older patients tend to be quite low compared to doses given to young or middle-aged adults, older age and longer duration of treatment are major risk factors for the development of these
The clinical research tradition has contributed useful intervention in those at highest risk that could delay the time of disease onset (i.e., developing an approach by developing the notion of prevention for those at risk. Though the models have been interesting and thoughtfully articulated, the outcomes would alter selection of treatment agents based on this side effects (Paulsen et al. 1996). Recent data suggest the possibility that the newer antipsychotics present a much lower risk for movement disorder, even in older patients, and that the development of tardive dyskinesia may be preventable through use of different medication (Katz et al. 1999). Similarly, trials of agents (antioxidants, for example) hypothesized to treat these side effects have been proposed, though the data from some of the early studies have been inconsistent (Adler et al. 1998; Lohr and Lavori 1998). It is at least possible, however, to consider that these studies should have been designed as prevention trials rather than treatment trials, with the subjects being those with a first exposure to neuroleptics who would then be randomized to receive vitamin E in addition.

Comorbidity and the associated polypharmacy that come from treatment of multiple conditions are characteristic of patients with psychotic disorders. New information on the genetic basis of drug metabolism and on the action of drug-metabolizing enzymes provides us with important perspectives on clinically significant alterations in drug concentration levels or on complex drug interactions (Nemeroff et al. 1996). For example, many of the newer antidepressant agents, the selective serotonin reuptake inhibitors, compete for the same metabolic pathway used by beta-blockers, type 1C antiarrhythmics, and benzodiazepines. Using this knowledge, the clinician can select therapeutic agents that will minimize such metabolic problems and thereby prevent side effects.

Body sway and postural stability are affected by many drugs, though there is substantial variability within classes of drugs (Laghrissi-Thode 1995). In those patients, particularly the elderly, where the prevention of falling is a major concern, a useful preventive strategy would alter selection of treatment agents based on this side effect profile.

### Clinical Models for Prevention Trials

The traditional clinical models for prevention trials (the "prodromal" studies in schizophrenia, the early bereavement interventions in depression, and the early interventions in Alzheimer's disease) focused on early intervention for those at risk. Though the models have been interesting and thoughtfully articulated, the outcomes have been only suggestive and have contained no clear guidelines for prevention (Mrazek and Haggerty 1994; McGlashan 1996). Trials in Alzheimer's disease have also modified this approach by developing the notion of prolonging the time of disease onset (i.e., developing an intervention in those at highest risk that could delay the development of the disease by several years).

This traditional view of prevention can be expanded. The clinical research tradition has contributed useful conceptual models that can be applied in prevention trials. Treatment research has come to focus on a set of common dimensions of psychopathology: positive symptoms, negative symptoms, mood, and cognition. These dimensions can be observed within diagnostic categories such as schizophrenia, depression, and the dementing disorders and have been the targets of considerable research attention. Using this dimensional approach, there could be prevention trials that could delay the emergence of particular symptoms if they are the ones that are particularly problematic from a service need or family burden perspective.

A final clinical perspective on prevention trials acknowledges the widespread comorbidity of mental disorders with a broad range of other common conditions. Comorbidity is one of the hallmarks of mental disorders throughout the life course. The nature of the comorbidity changes with age. In childhood and adolescence, the most common sources of comorbidity are developmental disorders and learning disabilities. In young adulthood and middle age, the typical sources of comorbidity are other mental disorders (including the Axis II disorders) and substance abuse. In late life, the most frequently observed comorbidities are physical illness and brain disease. A clear priority for prevention trials should be interventions in people with mental disorders to reduce the likelihood of comorbid conditions. Similarly, there should be interventions with people with conditions known to be associated with certain mental disorders so as to reduce the likelihood of the development of those disorders.

### Biological Models for Prevention Trials

Improved understanding of the etiology and pathophysiology of mental disorders can potentially lead to interventions that will prevent the onset or progression of disease. A useful model here is the large simple trial in a broad population; incident cases represent the primary outcome. The state of researchers' knowledge is not sufficient to support this type of research as of yet. Nonetheless, there are some interesting possibilities developing as people learn more about oxidative and inflammatory processes, apoptotic mechanisms, hormonal correlates, and genetic factors in disease. These studies may lead to large simple prevention trials with antioxidants, anti-inflammatories, hormone replacement, or similar agents for those at identifiable risk.

The genetics of mental disorders is an area of expanded activity (Risch and Merikangas 1996). Notably, several genes are now implicated in different forms of Alzheimer's disease, and there is active research in the genetics of bipolar illness and schizophrenia. At present, the genetic correlates of mental disorders are not sufficiently specific to be used for population screening. It is
entirely conceivable, however, that trials directed at delaying onset of disease or minimizing excess disability could be launched using some of this genetic information as a basis for subject selection.

Services Research Models for Prevention Trials

There is a substantial body of knowledge demonstrating the effects of family-based or systems-oriented interventions on services-related issues such as prevention of premature or inappropriate hospitalization, rehospitalization, and nursing home placement (Falloon et al. 1996; Mittelman et al. 1996; Hogarty et al. 1997; Lehman et al. 1998). This vital body of research has informed program and policy development in a range of areas.

Infrastructure Considerations

In this article we have identified directions for the development of a model of prevention research for the mental disorders of late life. We would now like to suggest that the research infrastructure of the mental health field is not yet configured in such a way as to support large-scale prevention trials.

In our view, which we exaggerate for purposes of illustration only, prevention trials should be longitudinal, large-scale, community based, and outcomes oriented. Yet most research is cross-sectional or short term, small-scale, academically based, and symptoms oriented. In treatment studies this translates to the difference between a narrowly defined regulatory model of research and a more broadly defined public health model (Lebowitz and Rudorfer 1998); other people use the terms “efficacy” and “effectiveness” in somewhat the same ways.

For studies done in accordance with what we call a regulatory model, the inclusions and exclusions are so limiting, the conditions of treatment delivery so optimized, and the outcomes so narrowly defined that generalization is virtually impossible. Research following the regulatory model is specifically geared to the legal requirements of drug approval and registration. In that situation, it is essential that pure disease entities are isolated and that dimensions of outcome are limited to the direct symptomatic measures of that disease. To prevent administrative or delivery problems from masking the effect of the treatment, clinicians are typically specially selected and trained. Intrusions such as the administrative requirements of a health care plan or third-party payer are minimized, and the treatment is provided in optimal form, often in an academic health center. Specific measures are taken to ensure compliance of the clinician with the protocol and adherence of the patient with the procedures and treatments. The conclusion of such a study becomes the gold standard of what is possible under closely controlled or ideal situations.

In a public health model, on the other hand, exclusion criteria are minimal (and based only on concerns for safety). Age, gender, and comorbidity are not the basis for exclusion, but rather present important dimensions to ensure sample representativeness and clinical generalizability. Outcomes are broadly construed, to include performance, personal and family relationships, daily functioning, disability, quality of life, morbidity, mortality, institutionalization, and health care resource use. Settings are widely selected from a full range of academic and nonacademic institutions, specialty and primary care settings, and public and private facilities. Sample sizes are large enough to ensure adequate power.

To carry out such studies, whether they are treatment studies, preventive interventions, or rehabilitative interventions, researchers need to identify the structural barriers in the ways in which research is organized and to innovate approaches to overcome these barriers.

Researchers and their laboratories are largely based in academic health centers. The role of the academic health center is being redefined in the context of health care system reorganization, and access to patients for research has become problematic. Many academic health centers are part of clinical systems that include community hospitals, primary care and specialty care office practices, and capitated contracts. The nonacademic settings of these large networks involve the majority of patients. The challenge is to turn these clinical and administrative networks into research networks for the development and management of trials.

Advancement for academic investigators is based on research productivity, usually measured by significant publications and success in developing extramural funding. In large-scale longitudinal studies, there are typically a large number of investigators and a very long period of time before important publications are developed. Individual intellectual contributions can be difficult to assess in such projects. If there is a commitment to developing this type of research, promotion and tenure policies will need to be adapted to properly recognize individual contributions in this type of research.

Similarly, much of the training of new investigators is based upon a model of individual scientific activity: the independent investigator directing a small group of junior colleagues, fellows, students, and technicians. Training typically does not prepare investigators for participation in large-scale endeavors. Nor are there established training pathways into some of the newer roles in large-scale studies (e.g., database management, clinical coordination, site management).
Methodological Considerations

The National Advisory Mental Health Council workgroup on clinical treatment and services research (1998) has argued that the commonly used methodologies of the mental health field are not ideally suited for the emerging public health orientation of intervention research. Instead, the workgroup has called for “hybrid” designs and innovative approaches to improve individual and public mental health. These designs might incorporate both experimental and observational aspects and might include innovative methods for evaluating trade-offs between internal and external validity.

Recommendations

Throughout this article we have identified specific examples of research that could contribute to the development of a model of prevention in the psychoses. In this section, we make a set of strategic recommendations that could significantly enhance the mental health field.

It is easy to say that the biggest need in the field is for the development of new prevention trials. That is too obvious and too easy, though. Some may disagree, but we believe that we are not ready to launch or carry out successfully such an initiative. Instead, we propose a series of smaller, more discrete activities to be carried out within an overall agenda of preventive intervention research. The development of this overall agenda and a strategic plan is the responsibility of all of us in the mental health field. This is something too important to leave to any single agency, particularly a public agency subject to ebbs and flows in annual appropriations. In the meantime, we propose the following recommendations.

Enrichment and Collaboration. The research agencies of the Federal Government, particularly the National Institutes of Health and the Department of Veterans Affairs (VA), should aggressively identify targets of opportunity by encouraging and underwriting the expansion of planned and ongoing clinical trials. Funds can be used to extend the followup time in ongoing trials, to add assessment or outcome instruments, and conceivably to add conditions or treatment arms. Incentives must be provided that foster collaboration rather than competition among agencies or that encourage the development of certain programs.

Partnerships. Managed care organizations and the pharmaceutical industry should enter into partnerships with Federal research agencies to underwrite the costs of usual treatment for patients in trials and to accelerate the adoption of clinically appropriate interventions in prevention and treatment.

Capacity. Managed care organizations and agencies (e.g., the VA) that administer large health care systems need to take advantage of the opportunity to transform their clinical service networks into research networks that encourage controlled experimentation and innovation in actual practice settings. Major investments in infrastructure development should be made in such areas as information technology, instrument development, and training.

Training. Academic institutions and professional associations must collaborate on the development of appropriate training models so that a new generation of investigators is prepared to pursue research careers in preventive intervention research. Specialized institutes, training seminars, and sessions at association meetings should be established with support from the Federal research agencies, industry, and foundations.

Career Development. Professional associations and academic institutions must collaborate on the development of new standards for promotion and tenure that take into account the new scientific infrastructure necessary for carrying out the large collaborative studies that will move the field forward.

Methods and Models. Federal research agencies and foundations need to launch a major initiative to encourage investment in the development and standardization of new methods and models for preventive intervention research.

Conclusion

In this article we sketch some broad parameters of programmatic development in the prevention of psychotic disorders. In our view there is no established approach to prevention research that could be easily adapted to meet the needs of the mental health field. Instead we have suggested that a change in culture is needed and that we need to look at preventive interventions in a new way.

The view of prevention being developed at NIMH and in the field is tied closely to experience in treatment research, has strong connections to services research, and is based upon models of etiology, pathophysiology, and risk. We use examples from research in the field to demonstrate that although this view of prevention may be new, it is entirely consistent with the empirical tradition and scientific and clinical knowledge base of the field.

At the same time, all of us at NIMH and in the field recognize that a commitment to prevention research will require some significant changes in the academic and governmental organization of science and in the training of the next generation of investigators in the field.
The challenge is enormous, and we do not believe that we have all the answers. We do not even believe that we have identified all the important questions. We anticipate that there will be active dialogue about the directions in which our work should go. A new approach to prevention can be a significant development for the field, and we are certain that success is achievable. The journey will be exciting and intellectually risky. If researchers are successful, the rewards for patients, their families, and clinicians will be substantial.

References
The Authors

Barry D. Lebowitz, Ph.D., is Chief, Adult and Geriatric Treatment and Preventive Interventions, Research Branch, and Jane L. Pearson, Ph.D., is Associate Director for Preventive Interventions, Division of Services and Interventions Research, National Institute of Mental Health, Bethesda, MD.