Editors’ Introduction: Intervention Research in Psychosis: Past, Present, and Future

by Dilip V. Jeste and Ira D. Glick

The ultimate purpose of most research is to improve the management of diseases and enhance the physical and mental health of at least some sections of the population. Intervention research targets these goals directly, whereas other non-intervention-related clinical and basic science research focuses on intermediate aims such as improving the understanding of the etiopathology of those disorders. “Intervention” is derived from the Latin root intervenire, meaning “to come between.” As defined by the American College Dictionary (Barnhart 1970), “intervention” may have a desirable connotation (“to come in by way of modification to settle a quarrel”), an undesirable one (“to interfere, usually by force or threat of force, in another nation’s internal affairs”), or a neutral one (“to enter as an irrelevant feature or circumstance”). It is indeed true that different interventions in medicine over the centuries have been either helpful, harmful, or irrelevant to a patient’s condition. Stedman’s Medical Dictionary (Stedman 1990) defines an intervention as “an action or ministration that produces an effect or that is intended to alter the course of a pathologic condition.” Whereas the Hippocratic oath emphasized the principle of primum non nocere (do no harm), the goal of intervention research should be more assertive than merely preventing additional harm; it should aim at cure or prevention or at least symptom relief. Over the past decade, the field has begun to broaden the objectives of treatment research, attempting to find ways to make patients (and their families) with severe and persistent mental illnesses more comfortable and functional—in other words, to improve the quality of life and reduce the family burden.

History of Biological Intervention Research in Psychosis

Intervention research in psychosis is hardly new. Rauwolfia alkaloid (the main ingredient in reserpine) was used in India for centuries to sedate patients suffering from mental illnesses. It was, however, not until the 1940s that Indian researchers produced the first well-documented clinical findings, and thereafter interest in this compound spread to scientific circles outside India (Bein 1984). Over the past 1,000 years, a number of treatments for schizophrenia and other psychotic disorders were tried. The first successful biological treatment of any major mental illness occurred when von Jauregg used malaria therapy to treat neurosyphilitic psychosis (Kalinowsky 1984). Notably, von Jauregg remains the only psychiatrist to date to win the Nobel prize. The second major biological treatment for psychosis was convulsive therapy—initially chemical and then electric convulsive therapy. The notion of such treatments grew from the observation that psychosis and epilepsy generally did not coexist. Next came frontal leukotomy, the first psychosurgical intervention for schizophrenia developed by Moniz, a neurosurgeon who went on to win a Nobel prize for his discovery. The most effective therapy for schizophrenia was, however, the introduction into psychiatry of chlorpromazine by Delay and Deniker in the early 1950s. It may appear that most of the discoveries of treatments for psychotic disorders, predominantly schizophrenia, have been serendipitous. Yet a careful look at the events preceding those discoveries shows that, while luck might have played a role, it was primarily the creativity and persistence of the scientists involved that led to these treatments being used for patients (Jeste et al. 1979).

Over the past four decades, a large number of double-blind placebo-controlled studies, including several randomized multisite clinical trials, have clearly demonstrated the efficacy of the “typical neuroleptics” over that of placebo both for symptom relief and for prevention of relapse. The newer atypical antipsychotics have begun a new era of safer and somewhat more effective drugs; however, they do have efficacy and safety limitations. A number of efficacy studies of these drugs published dur-
ing the past 10 years have yielded useful data, although
the conclusions are limited by the trials' focus on meeting
regulatory requirements of the Food and Drug
Administration as well as a paucity of non-industry-spon-
sored psychopharmacological efficacy research. Hence
there remain questions about how much more effective
the atypical antipsychotics are compared to the conven-
tional drugs for treating specific symptoms of schizophre-
nia at different stages of illness (e.g., first break, chronic,
residual). The new leadership of the National Institute of
Mental Health (NIMH) has emphasized the importance of
intervention research of effectiveness type that has rele-
vance to "real-world" patients. As a result, it is antici-
pated that there will be many well-designed multisite
intervention studies during the next decade that will com-
pare different treatments for psychotic disorders using
meaningful outcome measures in representative patient
populations. Furthermore, these investigations will
include not only medications but also nonpharmacologi-
cal treatments such as individual and family psychother-
apy, cognitive behavior therapy, psychoeducation, and
social skills training.

Special Section

This Special Section on Intervention Research in
Psychosis includes four articles written by some of the
best-known experts in their fields. Robinson and col-
leagues (this issue) discuss issues related to clinical
assessment. There has been a growing emphasis on broad-
based patient recruitment during recent years. Two impor-
tant challenges of broad-based patient recruitment are (1)
developing brief yet reliable and valid diagnostic proce-
dures as well as instruments for evaluating psychopath-
ologic symptoms and (2) bridging the gap between efficacy
and effectiveness studies by modifying recruitment and
assessment strategies. The authors give specific examples
of instruments and methodological suggestions to help
intervention researchers in psychosis. Awad and Voruganti
(this issue) present an overview of the literature on mea-
surements of quality of life. They point to the great oppor-
tunity that is now present for studying quality of life in
people with schizophrenia, given the recent heightened
interest in this area. Just as important, they offer sugges-
tions for choosing an appropriate scale for assessing qual-
ity of life in an individual study. Kraemer (this issue) dis-
cusses common pitfalls related to initiation, structure and
organization, performance, and closure of multisite ran-
domized clinical trials (RCTs). She reminds readers that
researchers must learn from others' mistakes in order not
to repeat them. She gives trial design pointers that would
combine the strengths of both efficacy and effectiveness
multisite RCTs while avoiding the shortcomings of each.

Finally, Lebowitz and Pearson (this issue) provide the
basics of developing new models of prevention trials.
Traditionally, prevention has been restricted to childhood
and adolescence and refers only to onset of illness. The
authors show how prevention can be relevant to older
adults and people with chronic illnesses too. They offer
suggestions regarding collaborations, partnerships, train-
ing, and development of methods and models of preven-
tion trials.

This short special section cannot cover all, or even
most, topics that are critical to intervention research in
psychosis. The following brieflly discusses bioethics and
nonpharmacological interventions, two topics not dis-
cussed in the other articles, and then considers how these
two issues may apply to elderly people with psychotic
disorders, a group that will grow significantly during the
next several decades.

Bioethics

In recent years, there has been increasing discussion about
the issues of decision-making capacity and validity of
informed consent in patients with schizophrenia (Grasso
and Appelbaum 1995; National Bioethics Advisory Com-
mission 1998, 1999; Chamey 1999; Oldham et al. 1999; Saks 1999)
as well as the ethics of neuroleptic withdrawal and challenge
studies in people with psychotic disorders (Jeste et al. 1999b;
Lieberman and Aghajanian 1999). These are critical con-
cerns in intervention research, and it is hoped that the ongo-
ing debate will lead to better protection of patients' rights
while not denying patients the benefits of research participa-
tion. Researchers should work closely with bioethicists in
defining guidelines for intervention research, especially in
higher risk protocols involving particularly vulnerable sub-
jects. It is important to view the relationship between scien-
tists and bioethicists as collegial, not adversarial. We believe
that people with expertise in bioethics and research, just like
biostatisticians/methodologists, need to be included at the
conceptual stage of and prior to the implementation of any
major study. Such a collaborative relationship would result in
a better understanding of both bioethicists' and researchers'
concerns and lead to intervention protocols that serve
patients' needs better. On the basis of the experience of the
Geriatric Psychiatry Intervention Research Center at the
University of California, San Diego, we also recommend the
use of community advisory boards that include some
research participants, some family members of patients, and
some outside consultants from the community. We have
found this board's input into study conduct invaluable.

There is also a vital need to carry out research into
determinants of decision-making capacity in patients with
psychotic disorders and ways of improving the "informed" nature of the informed consent (Christensen et
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Nonpharmacological Interventions

There have been far fewer systematic, well-controlled investigations of nonpharmacological interventions for schizophrenia or other psychotic disorders than investigations of pharmacological interventions. Since the antipsychotic drugs that are available now or will be available in the near future are not likely to be curative, it is critical to assess the usefulness of other treatment approaches in improving treatment adherence and complementing pharmacotherapy. Individual, family, or group therapy; cognitive behavioral therapy; social skills training; and cognitive rehabilitation are among the modalities of therapy that deserve further exploration, especially in patients who are now being treated with the newer atypical antipsychotics. Likewise, there is a desperate need for controlled research to determine the effectiveness of patient and family psychoeducation delivered by mental health professionals and other individuals in conjunction with advocacy groups such as the National Alliance for the Mentally Ill.

Elderly Patients With Psychotic Disorders

During the next 30 years, there is going to be an unprecedented increase in the number of people over age 65 with mental illnesses (Jeste et al. 1999a). The two prototypical psychotic disorders in the elderly population are schizophrenia and psychosis of dementia. The latter is much more common than schizophrenia in late life. Nonetheless, given the phenomenological and other differences between these two conditions (Jeste and Finkel 2000), we will discuss below some of the issues related only to schizophrenia in older age.

In the past, relatively little systematic research was done on treatment of psychotic disorders (including schizophrenia) in the elderly. Thus, in contrast to the large number of single-site and multisite double-blind placebo-controlled studies of the use of typical neuroleptics in younger adults, only a handful of such intervention trials have been conducted in older patients with schizophrenia (Jeste et al. 1993). To our knowledge, no such trials investigating use of the newer atypical antipsychotics among elderly subjects have so far been published. Yet the number of elderly people with schizophrenia is expected to increase substantially over the next several decades (Palmer et al. 1999). In part, this increase will result from the aging of the population at large, with a consequent rise in the number of older people with schizophrenia, including late-onset schizophrenia. But in addition, there will be disproportionate growth in the population of aging patients with schizophrenia. At present, the life span of those afflicted with schizophrenia is significantly shorter than that of nonschizophrenia individuals because of a higher incidence of suicide and other unnatural and natural causes of death. With improved treatments for schizophrenia, it is hoped that people with schizophrenia will be able to enjoy longevity similar to that of the rest of the population; this increased longevity will, in the absence of a cure for or means to prevent the illness, lead to a greater prevalence of the disorder among elderly persons. Hence, it is necessary to focus on issues of intervention strategies for older people with schizophrenia.

Recruitment Criteria. Physical illnesses, cognitive impairment, and polypharmacy are common in older people. Therefore, trials studying older adults need to have fewer exclusion criteria pertaining to physical illnesses, cognitive impairment, and polypharmacy than trials of younger adults to obtain a representative sample of elderly subjects.

Diagnosis. The DSM-IV (American Psychiatric Association 1994) and other criteria for schizophrenia have typically been based on studies of younger adults and primarily include positive symptoms. Elderly patients with schizophrenia have prominent negative rather than positive symptoms. As with most other psychiatric illnesses, there is a need to develop diagnostic criteria that are applicable to older individuals (Jeste et al. 1999a).

Assessment. The rating scales commonly used for assessing psychopathology in younger adults with schizophrenia are suboptimal for older patients, not only because of the prominence of negative symptoms but also because of the need to separate common age-related phenomena from psychopathologic symptoms. An example is the motor retardation item in the Brief Psychiatric Rating Scale (Overall and Gorham 1962). Motor retardation in an elderly person may not signify psychopathology but may result from a physical comorbidity such as arthritis. Similar considerations pertain to the evaluation of everyday functioning. Scales developed either for younger adults with schizophrenia or for elderly patients with dementia are usually not appropriate for older community-dwelling individuals with schizophrenia.

In studies of effectiveness, an evaluation of everyday functioning and quality of life is even more important.
than an evaluation of the severity of psychopathologic symptoms. Many elderly patients wonder whether their lives are worth living. The few available validated instruments for daily functioning and quality of life are not optimal for evaluating older individuals with schizophrenia who are living in the community. For example, the scales for activities of daily living and instrumental activities of daily living used in research on patients with dementia are typically too insensitive for community-dwelling persons with schizophrenia who have problems with using mass transportation but not with eating or grooming (Klapow et al. 1997). And many elderly patients with schizophrenia do not have caregivers, which hampers the use of instruments that rely on caregiver input (Patterson et al. 1996).

**Study Design Issues.** Older age is generally associated with a greater risk of many side effects, a need for lower dosages, a longer latency of response, and a different dose-response curve than what is observed at a younger age. These issues make dosage, duration, and study monitoring requirements different in older adults. The problem of treatment nonadherence also becomes more serious in older adults.

Thus, for all the reasons discussed above, it would be inappropriate to translate results of interventions based on investigations of younger adults to elderly patients. There is no substitute for conducting well-designed controlled studies of elderly individuals with schizophrenia in order to obtain data that are meaningful for this group.

**Conclusion**

The future of intervention research in psychosis is very bright, if only because of the need to improve the treatment of patients with schizophrenia, arguably the most expensive psychiatric disorder. From a public health perspective, the shift from the efficacy end to the effectiveness end of the spectrum of study design is welcome. A multipronged effort focusing on better pharmacological treatments along with more specific psychotherapeutic, cognitive, behavioral, psychosocial, and rehabilitative interventions is warranted. Such work must be complemented by enhanced efforts in assessment, prevention, and bioethics.

It is worth noting that relatively little systematic clinical research on antipsychotics is being performed without pharmaceutical industry support (Davis and Glick 1999). There are several reasons for this state of affairs, ranging from the massive costs of adequately powered multisite trials to the ethical, political, and practical constraints on recruitment and other procedures (Michels 1999); a full discussion of these topics is beyond the scope of the present article. We believe that it is important for NIMH to support carefully planned and focused head-to-head, short-term and long-term trials of new medications in real-world settings that are capable of carrying out this type of intervention research. Such investigations should also include combining drugs with psychosocial therapies to improve not only adherence to treatment but also patients’ and caregivers’ quality of life. We agree with Klein (submitted) in advocating a partial return to the era several decades ago when NIMH, not the pharmaceutical industry, was the organizer, planner, and agent for controlled efficacy trials of new medications for new and old disorders. It is gratifying to note that NIMH has taken a number of steps in this direction during the past couple of years. A collaboration between NIMH and the pharmaceutical industry would be appropriate and even warranted in certain ways; however, it is also obvious that the two have different roles to play.

The importance of investing in well-designed intervention research is clear. Either we invest a little now, or we pay a lot for patient care later.

**References**


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