The treatment of schizophrenia: from premorbid manifestations to the first episode of psychosis

Michael Davidson, MD; Asaf Caspi, MD; Shlomo Noy, MD, PhD

To achieve the best therapeutic results in schizophrenia—like most other disorders—primary prevention is preferable to early and prompt treatment, which, in turn, is preferable to treatment of chronically established illness. Unfortunately, there currently exist no accurate markers that can provide information regarding the future course of illness and guide treatment in asymptomatic or mildly symptomatic individuals. Therefore, most treatment efforts are currently focused on patients who have already experienced their first psychotic episode. This paper reviews the efforts to identify accurate markers heralding psychotic illness, as well as treatment considerations in the early phase of the disease.

 Dialogues Clin Neurosci. 2005;7:7-16.

Keywords: *schizophrenia; recent-onset psychosis; first episode; treatment; marker; risk factor*

Author affiliations: Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Address for correspondence: Michael Davidson, MD, Chaim Sheba Medical Center, Beitan 39A, Tel-Hashomer 52621, Israel
(e-mail: davidso@netvision.net.il)

Because schizophrenia is a progressively deteriorating disease that irreversibly affects quality of life, life expectancy itself, as well as cognitive, social, and vocational performance, attempts to detect it and treat it as early as possible are obvious goals of therapy. The importance of early detection and treatment is underscored by the fact that the onset and aggravation of psychosis occur in late adolescence and early adulthood, a time when many life-long vocational and social milestones are determined. Hence, it is reasonable to assume that any action that postpones the onset or aggravation of active psychosis will have long-term benefits.

The notion of early treatment of psychosis and schizophrenia was brought to the forefront of clinical research by an article by Wyatt,[1] who, after comparing the outcome of patients whose illness started before and after the availability of antipsychotic drugs, concluded that the latter had a better long-term outcome. Coupled with the observation that, in the years before psychosis and schizophrenia fully manifest, other less severe and less putative manifestations emerge, this raised the hope that these earlier manifestations could be used to diagnose impending illness and possibly prevent it or ameliorate its prognosis. Furthermore, as clues about the pathophysiology of schizophrenia are emerging, such as genes of predisposition, it becomes reasonable to hypothesize that, if these clues translate into reliable biological markers, they will assist early detection and, moreover, earlier treatment. Similarly, identification of environmental effects increasing (or decreasing) the risk for schizophrenia raised the hope that these risk factors could be manipulated toward primary or secondary prevention. Moreover, the observation that, even after the first psychotic episode has occurred, persistent pharmacological treatment can produce lengthy psychosis-free periods in most patients led investigators and clinicians to view the

early phase of the illness as a "window of therapeutic opportunity."[2] Supporting the view that early and persistent treatment has long-term benefits is a study demonstrating that the functional outcome after 15 years of follow-up is affected (negatively) by the cumulative time of active psychosis during the first 2 years of illness.[3]

For all these reasons, the last two decades have witnessed a proliferation of treatment structures focusing on the period surrounding the first episode of psychosis. Some of these structures are operating as clinics within the traditional medical/psychiatric establishment, some from youth centers and even malls, and others in the form of hotlines and Internet sites. All these efforts are aimed to detect future psychotic individuals as early as possible, bring them to treatment, and keep them in treatment.[4] Furthermore, a longstanding biannual international meeting (International Conference on Early Psychosis), hundreds of individual articles in peer-reviewed journals, special journal issues devoted entirely to the subject of premorbid and recent-onset psychosis, a plethora of books, as well as specific guidelines to treat early psychosis all serve as evidence of the importance clinicians and investigators assign to the very early phases of psychotic illness. Following the trend in academic psychiatry, in their quest to provide the most cost-effective care, governments and health care providers are investing in research and practice of early detection and persistent treatment of the early phases of psychosis. Government-funded research networks have proliferated in the USA, Germany, Norway, Australia, UK, and Canada, to name but a few.

An overview of the research and treatment activities associated with the premorbid and recent-onset psychosis reveals the acquisition of novel, valuable knowledge—and some disappointments. The valuable knowledge has been concentrated in identifying genes that may predispose an apparently healthy individual to discrete, putative manifestations related to schizophrenia (ie, endophenotypes). Putative manifestations, such as poor attention[5] and other cognitive deficits,[6] are present in patients and their non-ill first-degree relatives more often than in the general population. Investigating the endophenotypes related to schizophrenia is valuable in terms of both understanding the illness and developing markers that are likely to be present even in the absence of full-blown manifestation of illness. Furthermore, accumulating evidence indicates that environmental factors affect the likelihood of presenting schizophrenia[7] and that at least some of the risk factors can be modified and reduced.[8] Progress has also been made in understanding the characteristic response to treatment[9] of individuals recently affected by psychosis and improving their treatment.

The disappointments, on the other hand, consist mostly of the inability to utilize the early manifestations (behavioral, cognitive, and emotional deficits) as reliable, clinically useful markers predicting psychosis and schizophrenia and apply them toward secondary or primary prevention. This is because the subtle cognitive deviations from established norms and the occasional social withdrawal,[10] depressed mood, or apparently odd and even pathological behavior[11] that have been suggested as markers for future schizophrenic illness are all too common in the general population of adolescents and young adults. Also, schizophrenia as a fully manifested syndrome with the characteristic downhill course is a rare disease in the general population (<1%). Therefore, it is difficult to diagnose a rare disease based on behaviors, emotions, and performances (mostly cognitive) that are very common in the general population.[12] Consequently, effective treatment of individuals before they manifest psychosis, without unnecessarily treating those who will never manifest it, will remain an elusive goal until we can identify valid biological markers and environmental risks on the causative pathway to psychosis.

Finding reliable markers heralding schizophrenia and applying them toward prevention

Despite the undisputable evidence that the degree of relatedness of an individual to another individual already affected by schizophrenia increases the risk of manifesting the illness, most individuals diagnosed with the disease do not have an affected relative. Furthermore, the concordance among monozygotic twins is <50%. Taken together, these points indicate a genetic contribution to the illness, but rule out the possibility of simple mendelian inheritance and underscore the environmental contribution. To explain the mode of inheritance of this illness, as well as the delayed and very heterogeneous manifestation, it was hypothesized that multiple susceptibility genes interact with environmental influences. However, before such a hypothesis can be validated, major obstacles have to be overcome.

The first obstacle is in the realm of identifying *multiple susceptibility genes* acting additively or multiplicatively to affect brain function by modulating neural development and neurotransmitters and hence the corresponding brain microcircuits.[13] This task is particularly daunting since each gene probably confers a small risk or protective effect (no more than threefold) and, at the same time, could modulate the effects of other susceptibility genes. Hence, it is likely that more than one constellation of genes will act together to produce susceptibility to the same particular behavior, emotion, or pattern of thinking. Similarly, the same genetic constellation could have different behavioral manifestations depending on environmental interactions. Even after genes conferring susceptibility for psychosis have been identified, it is still essential to determine how the specific gene product (protein or enzyme) affects neural transmission and brain circuits, and translate these effects into well-defined emotions, behaviors, and cognitive functioning (or phenotype). Despite these obstacles, some biological markers associated with schizophrenia have been identified, such as met/val substitution on the catecholamine *O*-methyl transferase gene (*COMT*), which accounts for a small part of the cognitive impairment among some schizophrenia patients. More important, however, is the observation that the malfunction in COMT, an enzyme affecting dopamine metabolism, can be conceptually placed on the etiological pathway to the illness, which gives the finding a biological plausibility. Furthermore, despite the fact that markers like the *COMT* abnormality explain only a negligible fraction of the vulnerability for schizophrenia, such findings open the way to decompose the schizophrenic syndrome into biological subcategories with corresponding clinical manifestations. Thus, keeping the prevention paradigm in mind, it could be plausible to intervene pharmacologically in future patients and in their nonaffected first-degree relatives who carry the mutation. Unfortunately, at this stage, there exists no sufficient biological rationale or adequate and putative pharmacological tools to conduct large-scale definitive trials to test these hypotheses.

Second, constellations of genes might at best confer susceptibility for abnormal emotions, behaviors, and discrete intellectual deficits, which represent the illness intermediate endophenotypes for the illness, but not for *diagnostic classifications* agreed upon by expert committees. Yet, the designation of an individual as a sufferer of schizophrenia is still based on a cluster of abnormal behaviors, emotions, and perceptions, which together have an impact on social and vocational performances. Similar, but not identical constellations of susceptibility genes might determine the manifestation of any combination of anxiety, depression, and withdrawn behavior. All such manifestations are not only part and parcel of schizophrenia or comorbidities, but are also manifestations of other *Diagnostic and Statistical Manual of Mental Health* (*DSM*) disorders, such as anxiety disorder and dysthymia. This puts schizophrenia on a continuum with other mental disorders, and leaves the phenotype for which early predictive biological markers are investigated uncertain.

It is possible that our current knowledge of brain functioning and malfunctioning parallels the knowledge of the cardiovascular system functioning and malfunctioning several hundred years ago. At that time, it was far from obvious that a common atherosclerotic etiopathophysiology could underlie the occasional palpitations related to mild myocardial ischemia, the sudden chest pain related to acute myocardial infarction, the occurrence of night dyspnea, and the swollen legs related to congestive heart failure, all of which affect physical functioning on a continuum of severity. It was also not obvious how to distinguish between the transient elevation of glucose blood levels due to the stress of acute myocardial infarction, which is an epiphenomenal marker of active illness not etiologically related to the underlying atherosclerotic illness, and the persistently abnormal values of blood glucose level due to diabetes mellitus, which is a marker of risk etiologically related to the underlying illness. Moreover, it could not even be conceived that different constellations of genes, such as genes predisposing to abnormal lipid metabolism, abnormal glucose metabolism, and hypertension, could alone or in interaction increase the risk for the same lesion (the atherosclerotic lesion), which could be manifested as cognitive impairment (vascular dementia), chest pain, or the inability to walk or sleep flat. No wonder, therefore, that the classification and treatment of psychosis, anxiety, and depression might be revolutionized by a more profound biological understanding of brain functioning and malfunctioning. Perhaps then it will be possible to diagnose impending psychosis by observing aberrant behavior coupled with a biological marker in an adolescent and distinguish it from the eccentric behavior that is part of normative adolescent turmoil.

The third hurdle consists in linking between putative

environmental influences, genes, and the onset of schizophrenia symptoms. For example, famine during a specific period of pregnancy is a putative environmental effect that has an impact on the genetic vulnerability to schizophrenia[14] only during a limited time window (critical period) of development, but has no effect outside this period. However, periods as long as 10 to 15 years may elapse between exposure to the environmental influence and initiation of the disease process (induction period), or in the case of schizophrenia between initiation of disease process (ie, prodrome) and the diagnosis of the disease (latency period). Long periods of time between the critical, induction, and latency periods make it difficult to detect the real causal agents, and the strength of association between an exposure to the environmental influence and the disease. Furthermore, some of the risks for schizophrenia, such as intrauterine stress and birth complications, late age of father at conception, drug abuse, head trauma, urbanization, immigration, and poor social status, are common to other diagnostic categories and behavioral abnormalities than schizophrenia. The difficulties in defining the schizophrenic phenotype further increase the difficulties in associating between the risk and the illness. Again using the cardiovascular paradigm projected several hundred years ago, it would have been difficult to link smoking and plenty of food, both symbols or prosperity and happiness, to disease. It would have been even more difficult to take the next step and hypothesize that predisposition to smoke[15] or eat excessively[16] are affected by individual genetic makeup and that the end result (the metabolic syndrome, the atherosclerotic lesions, and the consequent cardiovascular malfunction) reflects the interactions between genes and environment.[17] Hopefully, in the foreseeable future, apparently puzzling findings, such as the synergism between family history and living in an urban area increasing the risk for schizophrenia,[18] will be unraveled.

Fourth, despite the broad agreement among schizophrenia researchers that premorbid and prodromal manifestations exist, the characteristics and prevalence of the manifestations are far from well elucidated. To fully elucidate the *premorbid and prodromal manifestations* and their respective prevalence, it is necessary to follow a randomly sampled birth cohort throughout the entire age of risk for schizophrenia. A related, but less informative, strategy is to follow apparently healthy individuals hypothesized to be at high risk for schizophrenia, such as first-degree relatives of affected individuals. Unfortunately, the birth cohort strategy is impractical because schizophrenia has a very low incidence and the age of risk spans more than four decades of life and appears to be different for males and females. Thus, following a birth cohort of 10 000 individuals for 40 years, starting at age 5 would detect approximately 90 cases of schizophrenia (not accounting for attrition), which is insufficient to make any statement regarding the premorbid and prodromal manifestations, considering the apparent low prevalence and heterogeneity. Also, the high-risk strategy is limited in scope since it excludes the overwhelming majority of future schizophrenics, who do not have affected first-degree relatives. Therefore, the most practical designs to learn about the premorbid and prodromal phenomena have been the taking of the personal and psychiatric history upon the diagnosis of psychosis or schizophrenia. However, this strategy is dependent on the availability of a good, objective informant and is vulnerable to recall biases. Occasionally, it has been possible to access detailed psychometric aptitude tests and scholastic records of schizophrenic patients collected many years before the illness was manifested and diagnosed or even suspected (the prospective historical design). However, since the information was not collected with the goal of elucidating the premorbid or prodromal characteristics of schizophrenia, it often lacks the putative details, which would be helpful to understand the path from premorbid manifestation to full-blown acute psychosis. Therefore, it is not very likely that in the foreseeable future it will be possible to map the trajectory leading from an apparently normal or only slightly deviant childhood to severe mental illness.

Fifth, the unavailability of reliable markers of impending illness vis-à-vis the stigma associated with the illness[19] and the impact that being "at risk" could have on the individual raise major *ethical dilemmas* for those who propose treatment of individuals who have not yet manifested psychotic symptoms.

Sixth, even if the ethical dilemmas could be resolved, there is still insufficient data proving that current *pharmacological and/or nonpharmacological interventions* are effective in preventing or delaying the transition from the prodromal stage to the active stage of the disease.[20]

In summary, until a better understanding of brain functioning and the biological pathway leading to severe mental illness and psychosis are achieved through a combination of basic research and translational research, it is reasonable to focus on improving the treatment of those who already manifest psychosis.

The characteristics and treatment of the first episode of psychosis

The notion that patients have different treatment needs and treatment responses during the first 1 to 3 years following the onset of psychosis and schizophrenia compared with the needs and response to treatment during the rest of the illness, has been raised and researched since the 1980s.[21] During the first few years of illness, patients have a more active illness with a course characterized by sharper distinctions between remissions and exacerbations. Many, but not all, patients have a downhill trend, which plateaus later on.[22] However, before embarking on comparisons between more and less recent-onset psychosis patients, and before hypothesizing what can account for these differences, two caveats should be considered: one related to the definition of the terms and the other to the patient population.

Recent-onset psychosis and first-episode psychosis are not *DSM* diagnostic terms, but terms of convenience often used as a criterion for intervention trials or to define patients enrolled in follow-up studies. Recent-onset psychosis often defines individuals who received a diagnosis of psychosis within the last year,[23] but other authors have used the term for individuals who have received the diagnosis within the last 3 years.[24] Regardless of the term used, or the definition of the term, it is difficult to determine the actual onset of psychosis.[25] Determining when the episode started, or even if this is the first episode, is based on memory of the patient or the individual providing collateral information. Unfortunately, the recall is often incomplete or biased.[26] The patient may not be aware that the perceptions and thoughts experienced before the diagnosis were manifestations of psychosis and/or might not have shared these experiences with the individual providing collateral information. Access to mental health services, the choice of the social environment to refer to treatment or to tolerate and contain the patient, and the severity of the illness,[27] all contribute to the gap between onset, diagnosis, and treatment of psychosis.

The *patient population* referred to with the terms recent-onset and first-episode psychosis is generally an adolescent population, since late adolescence is the time of peak incidence for psychosis and schizophrenia. Therefore, any conceptualization of recent-onset or first-episode psychosis must take into consideration the characteristics, needs, and often peculiarities of this age. For example, it is useless to focus on the lack of insight into the illness and the poor cooperation with treatment, without considering the rebelliousness, inexperience, and sensation-seeking behavior characteristic of this age.

With all these caveats in mind, a few characteristics of recent-onset psychosis patients and their response to treatment are apparent and distinguish them from more chronic patients:

- Significant improvement in psychotic symptoms occurs in the majority of patients.
- Inadequate improvement in negative symptoms and cognitive deficits.
- Enhanced sensitivity to extrapyramidal symptoms (EPSs).
- Doses of antipsychotics at the lower end of the therapeutic range are sufficient to achieve improvement in psychotic symptoms.
- Rapid, significant, and persistent weight gain occurs.
- Presence of comorbid symptoms, such as postpsychotic depression, suicide attempts, and violent outbursts.
- Frequent use of alcohol and cannabis.
- Lack of insight into the illness and, consequently, poor adherence to treatment.

Improvement in psychotic symptoms

Almost regardless of the antipsychotic drug employed, clinically significant improvement in psychotic symptoms occurs in about 80% of the recent-onset psychosis patients, which is a considerably higher proportion than the response reported for the most chronic patients. The worse response of the chronic patients may be due to an apparent desensitization of the biological mechanism mediating treatment response as the disease progresses, but it could also reflect the loss to follow-up of these few individuals who have a brief episode of psychosis and never relapse.[28]

The variance in response between trials ranges between 30% and almost 100%. This is probably due to the criteria used to define response and to the length of treatment, but not due to a preferential response to one antipsychotic versus another. The recommendation of two panels of experts[29,30] and a semi-regulatory body[31] to use second-generation antipsychotics (SGA) in this population is not based on the superior efficacy of these drugs, but on their better tolerability. Well-controlled trials comparing haloperidol with olanzapine[32] or risperidone[23] failed to show any clear advantage of the SGA to suppress or ameliorate acute psychosis.

There have been some suggestions that first-episode psychosis patients might need up to 3 months to show full response to treatment[33,34]; however, this notion was not supported by recent meta-analysis indicating that response to treatment is much more rapid.[35] It is conceivable that rather than a biologically driven delay in the antipsychotic effect, the apparent delay in response to treatment might reflect non–drug-related factors. The confusion and bewilderment associated with the first episode of psychosis and the first hospitalization, and the difficulties experienced by the patient and family to accept and adjust to the new circumstances of a chronic illness that affects most areas of life might delay recovery and hospital discharge.

There exist no firm guidelines on the treatment of the minority of patients who, despite treatment with antipsychotic drugs, do not experience remission of psychotic symptoms or at least significant amelioration. Raising the initial dose, switching between antipsychotics (typical and atypical), and combining two antipsychotics are among the pharmacological interventions frequently employed to treat refractory patients. However, this pervasive practice, which is anchored in clinical observations, is not supported by scientific evidence. Clozapine, the only antipsychotic shown to present some advantages over the rest of the antipsychotics in chronically ill, treatment-refractory patients, appears to be also effective and well tolerated in drug-naive recent-onset psychosis patients.[36] Whether this is sufficient evidence to infer that clozapine is more effective than the rest of the drugs in recent-onset patients who remain psychotic despite initial treatment remains an open question. Another question not yet addressed by controlled trials is how early should a recent-onset psychosis patient who does not respond to the antipsychotic drugs be switched to clozapine. On the one hand, if, as suggested, a longer duration of untreated psychosis has long-term detrimental effects[37] and if most other antipsychotics are not effective in treatment-refractory psychosis,[38] then the switch should occur as soon as it becomes apparent that the individual patient might not respond to the initial drug. Accumulating data indicate that lack of response during the first 1 to 3 weeks of treatment is predictive of lack of response during the subsequent weeks.[35,39,40] On the other hand, because of the rare and manageable, but potentially lethal, clozapine-induced agranulocytosis, most recent-onset psychosis patients in daily clinical practice are treated with several antipsychotic drugs before they are switched to clozapine. Whether this clinical practice is also the optimal one remains to be seen.

Negative symptoms and cognitive deficits

In contrast to the remission or at least marked amelioration of the psychotic symptoms, most patients show inadequate improvement in negative symptoms[23,24,32,33] and cognitive deficits.[41] Even when negative symptoms and cognitive deficits are improved by antipsychotic drugs, the benefit is limited to a 0.2 to 0.3 effect size. This is not surprising considering the process of drug development in schizophrenia and the nature of negative symptoms and cognitive deficits. In the absence of a good conceptual model for schizophrenia, since the serendipitous observation that chlorpromazine ameliorates psychosis, all subsequent drugs have been screened in vitro and in animal models on the basis of their similarities to chlorpromazine or to other drugs already proven to ameliorate psychosis. To reach the market, drugs had only to prove that they ameliorate psychotic symptoms in clinical trials, and not negative symptoms or cognitive deficits. Therefore, currently available agents have not been designed or selected to affect the two later manifestations of schizophrenia, negative symptoms and cognitive deficit. It also appears that the cognitive deficits and, possibly, negative symptoms are not of recent onset, but are long-standing, core features of the schizophrenic disease[6,10] and that cognitive impairment is inherited independently of psychosis.[42]

EPSs and therapeutic dose range

In addition to the fact that antipsychotic drugs benefit some but not other aspects of psychosis, many recent-onset psychosis patients show enhanced sensitivity to EPSs even at doses of antipsychotic that are within accepted therapeutic ranges.[43] The enhanced sensitivity to antipsychotic-induced EPSs appears to be true for both typical[44] and atypical drugs.[34]

Doses of antipsychotic at the lower end of the therapeutic range are sufficient to achieve improvement in psychotic symptoms in recent-onset psychosis and are as effective as doses in the middle and high therapeutic range. This finding holds for typical[45] as well as for atypical[23] drugs. In fact, in a posthoc analysis,[23] it was demonstrated that many recent-onset patients experience therapeutic benefits with 2 to 4 mg haloperidol or risperidone, after which the benefits plateau, but not the EPSs. Interestingly, even at low doses, haloperidol produces more EPSs than olanzapine[32] or risperidone.[23]

It is not clear at the present why patients who have been ill for several years or several decades need higher doses of antipsychotic drugs to reach therapeutic benefit and why they are less sensitive to EPSs. Biological and/or psychological tolerance to EPSs and to therapeutic benefit could be invoked to explain this phenomenon. For example, dopamine supersensitivity might have developed after many years of dopamine blockade[46] explaining why higher doses might be necessary. Alternatively, as the disease continues and remission and improvements become more elusive, patients, their families, and in particular the treating staff become increasingly frustrated and tend to raise the antipsychotic dose and discount the adverse effects. This is paradoxical considering the fact that most adverse effects are dose-dependent and that the only factor that predicts if a patient will remain in treatment at the end of the first year of illness is the dose of antipsychotic drug.[47]

Weight gain

Another adverse effect that affects young recent-onset psychosis patients is rapid, significant, and persistent weight gain.[24,32,48,49] Young patients treated with some but not all atypical drugs tend to gain approximately 5 kg over 2 to 3 months,[32,50] which is mostly abdominally deposited adipose tissue. Fasting insulin, C-peptide, and triglyceride levels significantly increase, suggesting the possible development of insulin resistance.[50] It is conceivable that the mechanism involved in weight gain is age-dependent, since elderly schizophrenic patients do not gain weight,[51] but it is also possible that elderly individuals have already suffered most of the antipsychotic-induced weight gain and/or that the weight gain is counterbalanced by an aging-dependent weight loss.

Comorbid psychiatric symptoms

Whether the presence of comorbid symptoms, such as depression, suicide attempts, and violent outbursts, are more frequent during the first few years following the first psychotic episode than during the later years is an unsettled area of research. Similarly, the treatment of comorbid symptoms and behaviors remains a challenge. Attempts to understand depression in recent-onset psychosis patients[52] and to treat it[53] have encountered conceptual and practical difficulties. It is not obvious whether the depressive symptoms are a core feature of the psychotic illness or a reactive response to a severe and debilitating illness. Also depressive symptoms tend to overlap with negative symptoms,[54] neither of which has a good response to treatment.[55,56]

The period around the onset of the first psychotic episode is also a period when patients are particularly vulnerable to self-injurious behavior and suicide.[44] As for depression, it is not clear whether such behavior is a direct result of active psychosis (eg, command hallucinations) that the patient has not yet learnt to ignore, or a result of demoralization due to a chronic debilitating illness.[57] While the ability to predict and prevent suicide is limited, treatment with clozapine[58] or risperidone[23] has been suggested to reduce suicide risk.

Similarly, outbursts of violence have been reported to occur in first-episode patients and are often treated with anticonvulsant medication. However, distinguishing between illness comorbidities and non–illness-related maladaptive behaviors in young adolescents is not always feasible. Exaggerated expression of normal frustration with hurdles of daily life is often viewed and treated as illness-related aggression. Most importantly, a recent analysis of the violent outburst in recent-onset psychosis patients reveals that the majority of the incidents are limited to verbal violence.[59] This, coupled with a recent review indicating that anticonvulsant drugs are not helpful in treating comorbid symptoms of schizophrenia,[60] should incite us to reconsider the clinical practice of medicating poor impulse control and violence in schizophrenic patients with antiepileptic drugs.

Alcohol and cannabis use

Poor impulse control, suicidal attempts, and violence in recent-onset psychotic patients have also been associated with frequent use of alcohol and cannabis.[61] The use of alcohol and mostly cannabis was found to be prevalent in recent-onset psychosis patients.[62] Data suggest that increased use of cannabis in this group of patients is not coincidental. One possible explanation is that patients use alcohol and cannabis as a method of self-medication and reduction of the social maladjustment associated with impending psychosis. However, many patients began to use cannabis many years before the symptoms of the illness manifest.[63-66] Furthermore, during the premorbid and prodromal phases, there is no relationship between the use of cannabis and premorbid social maladjustment.[67] An alternative explanation is that the premorbid

use of cannabis is on the etiological pathway to the illness, and that use of cannabis might interact with other risk factors contributing to the manifestations or aggravation of psychosis in vulnerable individuals. Support for this idea is drawn from a report that the density of cannabinoid receptors was increased in the dorsolateral prefrontal cortex in subjects with schizophrenia, compared with controls.[68] Regardless of the explanation, the increased use of illicit drugs in this population detrimentally affects the long-term outcome[69] and therefore constitutes an important target for treatment. Clozapine has been suggested to be effective in schizophrenia with comorbid drug abuse,[70] but this suggestion is based on a single small trial.

Poor adherence to treatment

Despite the obvious need for treatment of psychosis itself and the comorbid conditions, the treatment of recent-onset psychosis patients is a most challenging task. Substance abuse and lack of insight into the illness, and consequently poor adherence to treatment, are the most often quoted reasons for this difficulty.[71] Unfortunately, it appears that poor insight is more common and severe in recent-onset psychosis patients who have the most severe and pervasive form of illness in terms of general psychopathology, positive and negative symptoms, as well as cognitive domains.[72] This in turn underscores the challenge of treating the less insightful patients; they are the ones who need treatment most and are also the least likely to accept it.

While many of the first-episode patients with poor insight are admitted and occasionally treated involuntarily,[73] for the long-term maintenance treatment, the patient's active cooperation is essential. It is a particularly difficult challenge to convince patients who have remitted from their first episode of psychosis and who are not yet familiar with the cycling nature of the disease that, despite absence of active psychotic symptoms, they can benefit from maintenance treatment.[74] Long-term studies indicate that, if not maintained on antipsychotic medication, more than 50% of the patients who remitted from the first episode of psychosis will exacerbate during the first year following remission[75] and the percentage will rise during the subsequent years.

Although most practicing psychiatrists and guidelines will recommend that a remitted patient who had a single episode of psychosis should be treated for at least 1 year, there are a number of unanswered questions that reflect the limitations of the current clinical knowledge:

- Is there a preferred maintenance strategy or drug?
- Can we identify the 50% of the patients who despite lack of maintenance treatment, will not exacerbate during the first year?
- Can we identify the patients who will exacerbate despite maintenance treatment?
- Considering that there are no satisfactory answers for the last two questions and considering the drugs' adverse effects, how does pharmacological treatment impact on the quality of life?

Most guidelines recommend for maintenance atypical rather than typical[31] antipsychotics in this population. This recommendation is supported by a recent trial comparing low-dose haloperidol with low-dose risperidone in recent-onset psychosis patients, which demonstrated in a posthoc analysis that, once remitted, more patients randomized to risperidone maintained remission for longer periods of time than with haloperidol.[23] It is not clear at this time if this is a class effect or if it is limited to risperidone. A very large pan-European maintenance trail (European First Episode of Schizophrenia Treatment study [EUFEST]) comparing five of the most prescribed antipsychotics in first-episode psychosis is currently underway; hopefully, EUFEST will report definitive results in 2006 to answer this question. A related question is how early should depot injectable antipsychotics be considered. It is common practice that depot medications are reserved for the more chronic patient who after years of treatment have either failed on other drugs or showed persistent lack of adherence to treatment. However, in order to best take advantage of the "window of therapeutic opportunity"[2] presented by recent-onset patients, this practice should be reconsidered. Paradoxically, recent-onset patients appear to be the least adherent, but they are also the most responsive to treatment, and hence have the most to gain from treatment and probably most to lose from lack of treatment. Despite some attempts,[76,77] there are no accurate and clinically applicable markers to predict who will remain in remission despite lack of treatment and who will exacerbate despite treatment. Therefore, physicians, patients, and their families will have to make treatment decisions in an environment of uncertainty, well aware that some individuals will unnecessarily suffer drug-induced adverse effects. ❑

El tratamiento de la esquizofrenia: desde las manifestaciones premórbidas al primer episodio psicótico

Para conseguir los mejores resultados terapéuticos en la esquizofrenia –como en la mayor parte de los otros trastornos– la prevención primaria es preferible a un tratamiento precoz e inmediato, y éste a su vez es preferible a un tratamiento de la enfermedad que se ha establecido crónicamente. Desafortunadamente, en la actualidad no existen marcadores precisos que puedan aportar información en relación con el curso futuro de la enfermedad y orientar el tratamiento de sujetos asintomáticos o con síntomas leves. Por lo tanto, la mayoría de los esfuerzos terapéuticos actuales están enfocados hacia los pacientes que ya han experimentado su primer episodio psicótico. Este artículo revisa los esfuerzos para identificar marcadores precisos que sean precursores de una enfermedad psicótica, así como también las consideraciones terapéuticas en la fase precoz de la enfermedad.

Traitement de la schizophrénie : des manifestations prémorbides au premier épisode de psychose

Pour obtenir les meilleurs résultats thérapeutiques dans la schizophrénie – comme dans la plupart des autres pathologies – la prévention primaire est préférable à un traitement rapide et précoce, qui à son tour, est préférable au traitement d'une maladie chronique installée. Malheureusement, il n'existe actuellement aucun marqueur exact pouvant renseigner sur l'évolution future de la maladie et guider le traitement chez les sujets ayant peu de symptômes ou asymptomatiques. Par conséquent, la plupart des tentatives de traitement se focalisent actuellement sur des patients qui ont déjà vécu leur premier épisode psychotique. Cet article passe en revue les efforts d'identification de marqueurs précis annonciateurs d'une maladie psychotique, ainsi que les considérations thérapeutiques dans la phase précoce de la maladie.

REFERENCES

1. Wyatt RJ. Neuroleptics and the natural course of schizophrenia. *Schizophr Bull*. 1991;17:325-351.
2. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. *Br J Psychiatry Suppl*. 1998;172:53-59.
3. Harrison G, Hopper K, Craig T, et al. Recovery from psychotic illness: a 15- and 25-year international follow-up study. *Br J Psychiatry*. 2001;178:506-517.
4. Cornblatt BA, Auther AM. Treating early psychosis: who, what, and when. *Dialogues Clin Neurosci*. 2005;7:39-49.
5. Freedman R, Ross R, Leonard S, et al. Early biomarkers of psychosis. *Dialogues Clin Neurosci*. 2005;7:17-29.
6. Reichenberg A. Cognitive impairment as a risk factor for psychosis. *Dialogues Clin Neurosci*. 2005;7:31-38.
7. Dean K, Murray RM. Environmental risk factors for psychosis. *Dialogues Clin Neurosci*. 2005;7:69-80.
8. Weiser M, Noy S. Interpreting the association between cannabis use and increased risk for schizophrenia. *Dialogues Clin Neurosci*. 2005;7:81-85.
9. Gheorghe MD, Baloescu AV, Grigorescu G, Petrescu A. Functional neuroimaging in first-episode psychosis. *Dialogues Clin Neurosci*. 2005;7:50-51.
10. Davidson M, Reichenberg A, Rabinowitz J, Weiser M, Kaplan Z, Mark M. Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. *Am J Psychiatry*. 1999;156:1328-1335.
11. Weiser M, Reichenberg A, Rabinowitz J, et al. Association between nonpsychotic psychiatric diagnoses in adolescent males and subsequent onset of schizophrenia. *Arch Gen Psychiatry*. 2001;58:959-964.
12. Van Os J, Delespaul P. Toward a world consensus on prevention of schizophrenia. *Dialogues Clin Neurosci*. 2005;7:53-67.
13. Harrison PJ Weinberger DR. Schizophrenia genes within cortical neural circuits. *Mol Psychiatry*. 2005;10:5.
14. Susser ES, Schaefer CA, Brown AS, Begg MD, Wyatt RJ. The design of the prenatal determinants of schizophrenia study. *Schizophr Bull*. 2000;26:257-273.
15. Lessov CN, Martin NG, Statham DJ, et al. Defining nicotine dependence for genetic research: evidence from Australian twins. *Psychol Med*. 2004;34:865-879.
16. Marti A, Moreno-Aliaga MJ, Hebebrand J, Martinez JA. Genes, lifestyles and obesity. *Int J Obes Relat Metab Disord*. 2004;28(suppl 3):S29-S36.
17. Bays HE. Metabolic syndrome: what might be occurring? *Manag Care*. 2004;13(suppl):13-16.
18. van Os J, Pedersen CB, Mortensen PB. Confirmation of synergy between urbanicity and familial liability in the causation of psychosis. *Am J Psychiatry*. 2004;161:2312-2314.
19. Davidson M. What else can we do to combat stigma? *World Psychiatry*. 2002;1:22-23.
20. Marshall M, Lockwood A. Early intervention for psychosis. *Cochrane Database Systematic Rev*. 2003:CD004718.
21. Bradford DW, Perkins DO, Lieberman JA. Pharmacological management of first-episode schizophrenia and related nonaffective psychoses. *Drugs*. 2003;63:2265-2283.
22. Harvey P, Rabinowitz J, Eerdekens M, Davidson M. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. *Am J Psychiatry*. 2005. In press.
23. Schooler, N, Rabinowitz J, Davidson M, et al. Risperidone and haloperidol in first episode psychosis: a long-term randomized trial. *Am J Psychiatry*. 2005. In press.
24. Sanger TM, Lieberman JA, Tohen M, et al. Olanzapine versus haloperidol treatment in first-episode psychosis. *Am J Psychiatry*. 1999;156:79-87.
25. Friis S, Melle I, Larsen TK, et al. Does duration of untreated psychosis bias study samples of first-episode psychosis? *Acta Psychiatr Scand*. 2004;110:286-291.
26. Hambrecht M, Hafner H. Sensitivity and specificity of relatives' reports on the early course of schizophrenia. *Psychopathology*. 1997;30:12-19.
27. Cougnard A, Kalmi E, Desage A, et al. Pathways to care of first-admitted subjects with psychosis in South-Western France. *Psychol Med*. 2004;34:267-276.
28. Rabinowitz J, Bromet EJ, Davidson M. Are patients enrolled in first episode psychosis drug trials representative of patients treated in routine clinical practice? *Schizophr Res*. 2003;61:149-155.
29. Addington J. Draft consensus statement-principles and practice in early psychosis. In: Edwards J, McGorry P, eds. *Implementing Early Intervention in Psychosis: A Guide to Establishing Early Psychosis Services*. 1st ed. London, UK: Martin Dunitz; 2002:145-155.

30. Sartorius N, Fleischhacker WW, Gjerris A, et al. The usefulness and use of second-generation antipsychotic medications. *Curr Opin Psychiatry*. 2002;15:S1-S51.
31. National Institute for Clinical Excellence. Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care. Available at: http://www.nice.org.uk/pdf/CG1NICEguideline.pdf. Accessed January 27, 2005.
32. Lieberman JA, Tollefson G, Tohen M, et al. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. *Am J Psychiatry*. 2003;160:1396-1404.
33. Kopala LC, Fredrikson D, Good KP, et al. Symptoms in neuroleptic-naive, first-episode schizophrenia: response to risperidone. *Biol Psychiatry*. 1996;39:296-298.
34. Emsley RA. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. Risperidone Working Group. *Schizophr Bull*. 1999;25:721-729.
35. Agid O, Kapur S, Arenovich T, Zipursky RB. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. *Arch Gen Psychiatry*. 2003;60:1228-12235.
36. Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology*. 2003;28:995-1003.
37. Lieberman JA, Perkins D, Belger A, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. *Biol Psychiatry*. 2001;50:884-897.
38. Kinon BJ, Kane JM, Johns C, et al. Treatment of neuroleptic-resistant schizophrenic relapse. *Psychopharmacol Bull*. 1993;29:309-314.
39. Harvey PD, Davidson M, Powchik P, et al. Time course and clinical predictors of treatment response in schizophrenia. *Schizophr Res*. 1991;5:161-166.
40. Stern RG, Kahn RS, Davidson M, Nora RM, Davis KL. Early response to clozapine in schizophrenia. *Am J Psychiatry*. 1994;151:1817-1818.
41. Keefe RS, Seidman LJ, Christensen BK, et al. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. *Am J Psychiatry*. 2004;161:985-995.
42. Reichenberg A, Rabinowitz J, Weiser W, Mark M, Kaplan Z, Davidson M. Premorbid functioning in a national population of male twins discordant for psychoses. *Am J Psychiatry*. 2000;157:1514-1516.
43. Chakos MH, Mayerhoff DI, Loebel AD, Alvir JM, Lieberman JA. Incidence and correlates of acute extrapyramidal symptoms in first episode of schizophrenia. *Psychopharmacol Bull*. 1992;28:81-86.
44. Zhang-Wong J, Zipursky RB, Beiser M, et al. Optimal haloperidol dosage in first-episode psychosis. *Can J Psychiatry*. 1999;44:164-167.
45. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia. A controlled study of the neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry*. 1991;48:739-745.
46. Silvestri, S, Seeman MV, Negrete JC, et al. Increased dopamine D_2 receptor binding after long-term treatment with antipsychotics in humans: a clinical PET study. *Psychopharmacology (Berl)*. 2000;152:174-180.
47. Jackson H, McGorry P, Henry L, et al. Cognitively oriented psychotherapy for early psychosis (COPE): a 1-year follow-up. *Br J Clin Psychol*. 2001;40 (Pt 1):57-70.
48. Gutierrez FM, Segarra ER, Gonzalez-Pinto AA, Martinez JG. [Risperidone in the early treatment of first-episode psychosis: a 2-year follow-up study.] *Actas Esp Psiquiatr*. 2002;30:142-152.
49. Montes JM, Ciudad A, Gomez JC, on behalf of the EFESO Study Group. Safety, effectiveness, and quality of life of olanzapine in first-episode schizophrenia: a naturalistic study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27:667-674.
50. Graham KA, Perkins DO, Edwards LJ, et al. Effect of olanzapine on body composition and energy expenditure in adults with first-episode psychosis. *Am J Psychiatry*. 2005;162:118-123.
51. Barak Y. No weight gain among elderly schizophrenia patients after 1 year of risperidone treatment. *J Clin Psychiatry*. 2002;63:117-119.
52. Iqbal Z, Birchwood M, Hemsley D, Jackson C, Morris E. Autobiographical memory and post-psychotic depression in first episode psychosis. *Br J Clin Psychol*. 2004;43(pt 1):97-104.
53. Koreen AR, Siris SG, Chakos M, et al. Depression in first-episode schizophrenia. *Am J Psychiatry*. 1993;150:1643-1648.
54. Siris SG, Mason SE, Bermanzohn P, et al. Adjunctive imipramine maintenance in post-psychotic depression/negative symptoms. *Psychopharmacol Bull*. 1990;26:91-94.
55. Siris S, Pollack S, Bermanzohn P, Stronger R. Adjunctive imipramine for a broader group of post-psychotic depressions in schizophrenia. *Schizophr Res*. 2000;44:187-192.
56. Addington DD, Azorin JM, Falloon IR, et al. Clinical issues related to depression in schizophrenia: an international survey of psychiatrists. *Acta Psychiatr Scand*. 2002;105:189-195.
57. Hafner H, Loffler W, Maurer K, et al. Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. *Acta Psychiatr Scand*. 1999;100:105-118.
58. Meltzer HY, Alphs L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry*. 2003;60:82-91.
59. Foley SR, Kelly BD, Clarke M, et al. Incidence and clinical correlates of aggression and violence at presentation in patients with first episode psychosis. *Schizophr Res*. 2005;72:161-168.
60. Basan A. Kissling W, Leucht S. Valproate as an adjunct to antipsychotics for schizophrenia: a systematic review of randomized trials. *Schizophr Res*. 2004;70:33-37.
61. Gut-Fayand A, Dervaux A, Olié JP, et al. Substance abuse and suicidality in schizophrenia: a common risk factor linked to impulsivity. *Psychiatry Res*. 2001;102:65-72.
62. Green AI, Tohen MF, Brenner MJ, et al. First episode schizophrenia–related psychosis and substance use disorders: acute response to olanzapine and haloperidol. *Schizophr Res*. 2004;66:125-135.
63. Murray RM, Van Os J. Predictors of outcome in schizophrenia. *J Clin Psychopharmacol*. 1998;18(2 suppl 1):2S-4S.
64. Rabinowitz J, Bromet EJ, Lavelle J, Carlson G, Kovasznay B, Schwartz JE. Prevalence and severity of substance use disorders and onset of psychosis in first-admission psychotic patients. *Psychol Med*. 1998;28:1411-1419.
65. Hambrecht M, Hafner H. Substance abuse and the onset of schizophrenia. *Biol Psychiatry.* 1996;40:1155-1163.
66. Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self-reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ*. 2002;325:1199.
67. Weiser M, Reichenberg A, Rabinowitz J, et al. Self-reported drug abuse in male adolescents with behavioural disturbances, and follow-up for future schizophrenia. *Biol Psychiatry*. 2003;54:655-660.
68. Dean B, Sundram S, Bradbury R, Scarr E, Copolov D. Studies on [^{3}H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. *Neuroscience*. 2001;103:9-15.
69. Drake KTM. Substance abuse comorbidity. In: Lieberman JA, Murray RM, ed. *Comprehensive Care of Schizophrenia*. London, UK: Taylor and Francis; 2001:243-254.
70. Green AI, Salomon MS, Brenner MJ, Rawlins K. Treatment of schizophrenia and comorbid substance use disorder. *Curr Drug Targets CNS Neurol Disord*. 2002;1:129-139.
71. Keshavan MS, Rabinowitz J, DeSmedt G, Harvey PD, Schooler N. Correlates of insight in first-episode psychosis. *Schizophr Res*. 2004;70:187-194.
72. Coldham EL, Addington J, Addington D. Medication adherence of individuals with a first episode of psychosis. *Acta Psychiatr Scand*. 2002;106:286-290.
73. Kelly BD, Clarke M, Browne S, et al. Clinical predictors of admission status in first episode schizophrenia. *Eur Psychiatry*. 2004;19:67-71.
74. Thompson KN, McGorry PD, Harrigan SM. Reduced awareness of illness in first-episode psychosis. *Compr Psychiatry*. 2001;42:498-503.
75. Gilbert PL, Harris MJ, McAdams LA, et al. Neuroleptic withdrawal in schizophrenic patients. A review of the literature. *Arch Gen Psychiatry*. 1995;52:173-188.
76. Davidson M, Keefe RSE, Moh RC, et al. L-dopa challenge and relapse in schizophrenia. *Am J Psychiatry*. 1987;144:934-938.
77. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*. 1999;56:241-247.