Schizophrenia is a serious brain disease affecting nearly 1% of the population and is recognised as being a leading cause of disability worldwide. Cognitive impairment in schizophrenia is a central problem. As a chronic disease, schizophrenia is associated with lifelong morbidity, increased mortality and a short lifespan. It is a costly mental illness to treat, with an estimated annual cost of $70 billion in the US. The chemical imbalance in schizophrenia is correctable by medications and choice of medication formulation is critical for a full long-term remission. Adherence is the single greatest reason for relapse and deterioration. Finally, a comprehensive biopsychosocial approach to treatment is vital and has proven very beneficial in schizophrenia.

Schizophrenia is characterised by several symptom clusters including psychotic (positive), deficit (negative) symptoms, mood symptoms, and cognitive deficits. Often, comorbid substance abuse is also present. Notably, all of these are features that contribute greatly to treatment nonadherence. Importantly, serious, progressive brain tissue loss is associated with every psychotic relapse. It is also widely acknowledged that patients with schizophrenia have a reduced capacity to experience themselves as separate and distinct entities from others; the weakened boundary between the self and the external world creates disturbances in perception and insight. This inevitably adds to the problem of nonadherence.

Pharmacological and psychosocial treatments may affect different outcome domains, with the former affecting symptoms and the latter affecting social outcomes, but each can enhance the effects of the other. Evidence suggests that the newer antipsychotics improve the participation of patients in psychosocial treatments, which in turn improve adherence to the medications.

Relapse fuels deterioration in schizophrenia

Nonadherence to the medication inevitably results in a relapse, which has huge implications for the illness. Each relapse fuels further deterioration in schizophrenia, with a progressive gray and white matter loss that results in a slower and less complete response to medication, more frequent admissions to hospital and development of treatment resistance. With every psychotic episode, the patient responds less to treatment than previously, which necessitates higher doses, perhaps a switch to another medication, the introduction of combination regimens, and, in some cases, the use of clozapine. There is an increased risk of self-harm and violence towards others, of homelessness, and it is harder for patients to regain their previous level of functioning. Patients lose self-esteem, experience social and vocational disruption and use more healthcare resources. The burden increases for families and caregivers.

As shown in Figure 1, following the initial prodrome, the patient becomes prepsychotic and then psychotic. The first schizophrenia episode is associated with a 50–60% loss of function, but also with subsequent recovery of function approaching baseline levels, with practically any antipsychotic; of all schizophrenia episodes, the first is the one that is most responsive to medication. This same degree of response is rarely repeated.

Unfortunately, patients and their families do not realise that this illness will return. Within weeks or only days, patients will stop their medication and instead of remaining close to their baseline level of functioning, they will experience another episode. The second is associated with further cortical atrophy, a longer time to recovery and a less gratifying level of treatment response. Subsequent nonadherence leads to another psychotic episode, with further loss of brain tissue and a much longer time to response. The patient then enters a period of chronic relapsing/residual symptoms and functioning at a level far below baseline capacity, accompanied by treatment resistance.

Professor Nasrallah stresses that this deterioration must be prevented by instituting a guaranteed adherence mechanism, a drug formulation that ensures continuous and uninterrupted drug delivery – the single most effective form of intervention for schizophrenia that goes beyond management renders this disease as less malignant if relapses are prevented early in illness. Further, recovery can eventually occur, after achieving and sustaining remission. It is time to change our focus.

Figure 1. The consequences of relapses in schizophrenia

In the traditional approach to the treatment of schizophrenia, the patient may experience as many as 10–15 psychotic episodes before being offered depot medication, as if it is a last resort. Instead, such medication should be viewed as a first resort, a compassionate treatment that prevents further relapse and restores function, advises Professor Nasrallah.

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Professor Henry Nasrallah is an internationally recognised psychiatrist, educator, and researcher. He received his BS and MD degrees at the American University of Beirut (AUB). Following his psychiatric residency at the University of Rochester and neuroscience fellowship at the NIH, he served as a faculty member at the University of California, San Diego and the University of Iowa before assuming the chair of the Ohio State University Department of Psychiatry for 12 years. In 2003, following a research sabbatical, he joined the University of Cincinnati College of Medicine as Associate Dean and Professor of Psychiatry and Neuroscience. Professor Nasrallah is the director of the Schizophrenia Program, and his research focuses on the neurobiology and psychopharmacology of schizophrenia and related disorders. He has published more than 360 scientific articles and 400 abstracts, as well as 11 books. He is Editor-in-Chief of two prominent journals (Current Psychiatry and Schizophrenia Research) and is the co-founder of the Schizophrenia International Research Society (SIRS). He has been board-certified in both adult and geriatric psychiatry. He is a Fellow of the American College of Neuropsychopharmacology (ACNP), fellow of the American College of Psychiatrists, distinguished life fellow of the American Psychiatric Association, and past President of the Cincinnati Psychiatric Society and the American Academy of Clinical Psychiatrists, and is currently the president of the Ohio Psychiatric Physicians Education and Research Foundation and President of the University of Cincinnati College of Medicine Faculty Forum (which represents 1500 faculty members). He has twice received the NAMI Exemplary Psychiatrist Award and was recognised as the U.S. Teacher of the Year by Psychiatric Times. He has received more than 80 federal, industry, and foundation research grants and is listed in several editions of Best Doctors in America.
Treatment discontinuation

It is vital to remember that early medication discontinuation in schizophrenia occurs in both the chronic and early phases of the illness, stressed Professor Nasrallah. In the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study, comprising chronic patients (mean age 39.6 years, mean years of illness 14.4 years), 74% of patients in the intention-to-treat analysis discontinued their assigned treatment before 18 months (mean 6.5). Another study, CAFÉ (Comparison of Atypicals in First Episode Psychosis), identical in design to CATIE, compared three atypicals in mostly treatment-naïve patients and found no difference in efficacy. However, within 3 months, regardless of treatment assignment, 68.4% of olanzapine-treated patients, 70.9% of quetiapine-treated patients and 71.4% of risperidone-treated patients discontinued the study. Thus, treatment discontinuation manifests early and involves both the patient and family. The families were resistant to maintaining their offspring on long-term medication, believing that the psychotic episode was only a minor and temporary setback and that continued medication was unnecessary. Professor Nasrallah noted that early in the course of schizophrenia, families often require a great deal of education about the illness. This teaching may be enhanced if they meet other families with a chronically ill son or daughter who has schizophrenia.

Nonadherence to medications is a common problem with many chronic illnesses and their successful treatment is compromised by the difficulty of taking medication continually over an extended period of time. This is especially challenging in the treatment of schizophrenia. Compared to other chronic conditions, schizophrenia is second only to staying on a strict diet in terms of the degree of difficulty, according to 20 surveyed psychiatrists, in maintaining adherence at a level sufficient to produce a therapeutic effect. Partial compliance is a major problem among patients with schizophrenia, beginning within days of discharge and increasing over time. Several studies have shown that many patients with schizophrenia are only partially compliant with the prescribed antipsychotic medication regimen. In any outpatient mental clinic, 40% of patients are 20% partially compliant with their medication. An investigation into the role of environmental support in medication adherence has found that, even under closely monitored conditions, outpatients have a nonadherence rate of almost 25% over a 7–10 day period following hospital discharge. Outpatient nonadherence rates have been reported to be as high as 50% within 1 year.

In a 52-week multicentre study that enrolled 400 first-episode patients with schizophrenia, randomly assigned to olanzapine, quetiapine, or risperidone, 115 discontinued treatment discontinuation against medical advice. Analyses found that treatment adherence and response appear to be mutually reinforcing; lower cognitive function, depressive symptoms, poor illness and treatment insight, ongoing substance abuse, and achieving remission, all predicted poor adherence, leading to poor treatment response and treatment discontinuation.

Poor adherence: a major problem in schizophrenia

While full adherence is difficult for anyone to maintain, e.g. exercise, dieting, adherence is extremely problematic in schizophrenia because of its many associated challenges, such as the disease-associated effects including lack of insight, severe memory deficits, treatment-related side effects, and psychological/social aspects including stigma (of disease and medication), environmental stressors, support from family/friends. Importantly, memory is severely impaired in schizophrenia (approximately 2 standard deviations below the community normal mean), which means that patients cannot be relied upon to remember their medication. Moreover, deficits in executive function undermine the patient’s ability to monitor their medication practice. The symptoms of schizophrenia undermine treatment adherence. For instance, as many as 70–80% of patients deny that they are ill (anosognosia); indeed, they are not aware that they are ill. A central feature of the negative symptoms is a lack of initiative and motivation. Patients are not motivated to take medication. Antipsychotic treatment-related side effects (e.g. extrapyramidal symptoms) may cause patients to discontinue medication. Finally, substance abuse (alcohol, drugs) contributes to a chaotic lifestyle, distracting patients from the need to take their medication.

In Professor Nasrallah’s experience, oral medication is only suitable for a small minority of patients with schizophrenia. Studies have shown that within 7–10 days of hospital discharge, up to 25% of patients have discontinued medication; 50% have done so within a year and 75% within 2 years. The risk for psychotic relapse is high; within a cohort of 104 patients with schizophrenia who had responded to treatment of their index episode, the cumulative first relapse rate was 81.9% within 5 years of recovery. That same study found that discontinuing antipsychotic medication increased the risk of relapse by almost 5 times (hazard ratio for an initial relapse, 4.89; hazard ratio for a second relapse, 4.57).

Professor Nasrallah describes partial adherence as a major treatment challenge, a critical impediment to successful treatment of schizophrenia. Numerous studies have shown that few people are fully compliant or fully noncompliant with medication. Most people with various disorders, including schizophrenia, fall somewhere in the middle, dipping doses at times. Conventional wisdom and clinical experience place satisfactory compliance at 70–80% of prescribed medication, but accumulating data suggest that even a few missed days may be of importance. Partial adherence dramatically increases rates of hospitalisation. Weiden and colleagues found that the presence of any gap in medication coverage increased the risk of hospitalisation, including gaps as small as 1–10 days (odds ratio (OR)=1.98). A gap of 11–30 days was associated with an OR of 2.81, and a gap of >30 days was associated with an OR of 3.96.

Suicidal behaviour also soars when patients stop medication, compared to when they are on medication. A study from the Netherlands that analysed dispensing and hospital discharge databases (n=865,000) identified 603 patients with schizophrenia, 204 (33%) of whom interrupted treatment for >30 days (i.e. drug holidays). After adjusting for age and gender, the relative risk for suicide attempts increased 4.2 times among these patients, compared with patients without drug holidays. Importantly, schizophrenia has the highest suicide rate of any mental disorder (mood disorders has the highest); approximately 15–17% of depressed individuals kill themselves if left untreated versus about 10% of those with schizophrenia. This underscores the need to ensure uninterrupted medication in schizophrenia.

How best to measure adherence?

A recent review of the adherence literature explored definitions and assessment of adherence to oral antipsychotics in patients with schizophrenia. None of the methods work very well, noted Professor Nasrallah. The most common method used to assess adherence was the report by the patient; a notoriously unreliable means of measuring adherence, as patients tend to unwittingly exaggerate their capacity for adherence. Subjective and indirect methods including self-report, provider report, significant other report, and chart review were the only methods used to assess adherence in over 77% (124/161) of studies reviewed. Direct or objective measures including pill count, blood or urine analyses, electronic monitoring, and electronic refill records were used in less than 23% (37/161) of studies. Even these methods are not infallible; for instance, patients can tamper with pill counts and electronic monitoring. Accurate assessment of adherence is difficult for both patients and clinicians. In a survey of medication compliance, although nearly 70% of patients claimed that they were taking all their medications, pill counts revealed they were compliant only 10% of the time. Similarly, in another survey, up to 95% of clinicians predicted that their patients were taking over 70% of their medications as prescribed, but electronic monitoring of medication doses showed that only 38% of those patients were compliant.

The evidence has been available for as many as 30 years, as to the greater ability of depot over oral formulations to forestall relapse among newly discharged schizophrenic patients. In a cohort of 105 such patients who were randomised to either long-acting fluphenazine decanoate or the oral formulation of fluphenazine and maintained under controlled conditions for 2 years or until relapse, the depot formulation was associated with a much lower risk of relapse over time. Such evidence unequivocally demonstrates that an effective mode of drug delivery exists for patients who are unable to adhere to oral medications, noted Professor Nasrallah. Withholding this effective means of treatment from patients, in the belief that they should be allowed to make fully autonomous decisions for themselves, is not only misguided but also unfair; the cognitively disabling brain disease of schizophrenia prevents patients from thinking logically and realising that they must self-medicate to stay well. Professor Nasrallah believes it is the psychiatrist’s responsibility to deliver what is best for the patient in the early phase of the illness by initiating long-acting antipsychotic preparations, until they have recovered sufficient brain function to allow restoration of insight and sound judgement and self-care decision-making processes are regained.

Historically, reluctance to use the older injectable antipsychotics continuously was due to the legitimate concern that such treatment would cause frequent EPS and tardive dyskinesia (TD). A review of the clinical evidence on the association between TD and use of the conventional antipsychotics demonstrates an annual incidence of 5% in younger patients (mean age 29 years), starting in the first year of therapy, levelling off at around 60% after 10–12 years. Even on small doses of haloperidol, the incidence of TD is very high among older patients (aged 50–85 years; mean 65), averaging at 26% in the first year and increases to 52% in the second year, then to 60% in the third year.

Atypical antipsychotics are associated with a much lower incidence of TD at 1 year; rates of 0.8% with atypical antipsychotics versus 3.5% with conventional antipsychotics have been reported in adult schizophrenia patients, versus 2.5% and 25%, respectively, in elderly patients.

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Neurobiology of schizophrenia

High resolution magnetic resonance imaging (MRI) reveals ventricular enlargement and anterior hippocampal volume reductions in first-episode schizophrenia patients, as well as evidence of progressive ventricular enlargement in patients with poor outcome schizophrenia. In addition, MRI has confirmed that a longer duration of treatment is associated with less ventricular enlargement over time.

A 1-year follow-up MRI study has documented brain volume changes in first-episode schizophrenia patients. The study involved 34 such patients who had taken antipsychotic medication for 0–16 weeks, and 36 matched healthy controls. MRI scans of the whole brain were obtained for all subjects at inclusion and after 1 year. Outcome was measured 2 years after inclusion. Compared with controls, patients experienced significant decreases in total brain volume (~1.2%) and gray matter volume of the cerebrum (~2.9%) and significant increases in lateral ventricle volume (7.7%). Outcomes measured at 2 years demonstrated that the decrease in global gray matter volume significantly correlated with outcome and, independently of that, with higher cumulative dosage of antipsychotic medication.

In childhood-onset schizophrenia, the cortical volume loss is estimated at 1–3% per year during the first 5 years. Periodic MRI scanning of adolescents with schizophrenia and age-matched healthy adolescents over 5 years, beginning at age 14, documented a loss of gray matter in the prefrontal cortex of the adolescents with schizophrenia at 4 times the rate of normal health adolescents (see Figure 2). This accelerated loss correlated with worsening psychotic symptoms and mirrored the progression of neurological and cognitive deficits associated with the disorder.

**Figure 2. Rate of gray matter loss in schizophrenia and control subjects**

Explorations into the pathophysiological aspects of schizophrenia and what function is lost during psychotic relapses have demonstrated shrinkage of the brain with reduced neurep. Postmortem tissue analyses have revealed reductions in dendrite length by a half, as well as decreases in the number and size of dendritic spines, the size (contraction) of neuron extension, and in the number of glial cells.

In addition, schizophrenia is associated with a decline in vital neurotropic factors; specifically, a loss of neurtin 3 (NT-3), nerve growth factor (NGF) and also brain-derived growth factor (BDNF). Neurotrophins have established roles in neuronal development, synaptogenesis, potentiation, neurite extension, synaptogenesis, neurogenesis and gliogenesis.

**Brain repair**

The brain atrophy relating to the psychotic relapses of schizophrenia can be avoided and even reversed. Further, evidence indicates that neuroregeneration can take place in the schizophrenia brain, with the right medication. Brain repair is about inducing neuroplasticity across a variety of steps, including dendritic spines and synaptic remodelling, axonal sprouting and long-term potentiation, neurotroph extension, synaptogenesis, neurogenesis and gliogenesis.

The discovery of adult neurogenesis was a breakthrough in neuroscience research. Scandinavian researchers demonstrated that functional neurons can, in fact, be generated in the adult human brain in several distinct regions including the dentate gyrus of the hippocampus and the subventricular zone. This process of adult neurogenesis occurs throughout the lifespan and involves proliferation of stem cells into neural progenitor cells, of which about 10% or more survive, joining the ranks of the existing healthy neuronal network in structure and function. In contrast to the first-generation antipsychotic haloperidol, antipsychotics have been shown in preclinical and clinical studies to be neuroprotective. Specifically, published studies show that atypical antipsychotics can prevent progressive brain tissue loss associated with psychosis and stimulate neurotrophic factor release, neurogenesis and cell survival. In animal studies of neurogenesis with first-generation antipsychotics, several rat studies found no effect of haloperidol on neurogenesis; in fact, haloperidol was found to be neurotoxic, inducing apoptosis and neuronal cell death.

Scientists have reported that acute administration of a large dose of haloperidol resulted in a microglial response indicative of neuronal damage in rats, accompanied by an increase in the number of apoptotic cells in the striatum (especially in the dorsomedial caudate putamen) and in the substantia nigra pars reticulata. These investigators discovered that haloperidol converts to a pyridine-based metabolite and increases glutamate excitotoxic neurotransmission. They surmised that the haloperidol-induced apoptosis of striatopallidal neurons resulted from the receptor blockade of the D2 receptor.

Another possibility is that HPT, the tetrahydropyridine analog of haloperidol, resembles the pro-neurotoxin MPTP, which is known to result in irreversible Parkinsonism through striatal damage.

In contrast to haloperidol, several atypical antipsychotics have been reported to stimulate neurogenesis in rat brains, after only 4 weeks’ administration: olanzapine, risperidone, paliperidone, quetiapine, and clozapine. It is thought that this difference in mode of action between drug classes is due to the blocking of dopamine alone by conventional antipsychotics, as seen with haloperidol, which predominantly blocks D2 receptor blockade and decreases BDNF. This is in contrast to the atypical antipsychotics, which all strongly block serotonergic receptors and increase BDNF.

Stress and depression result in neuronal atrophy and cell death. This is thought to occur as a result of hyperactivity of the stress-response system in depressed patients, which increases adrenal glucocorticoid release and decreases BDNF levels. The damaging effects of prolonged stress/depressive symptoms could contribute to the selective loss of volume of the hippocampus (a structure essential to learning and memory, contextual fear conditioning, and neuroendocrine regulation) observed in patients with depression. These morphological changes have been shown to persist long after resolution of the depressive symptoms.

In theory, antidepressants that affect serotonin and/or norepinephrine activity may affect neuronal survival and growth by decreasing glucocorticoid levels and increasing BDNF levels. It is hypothesised that similar morphological changes are induced by atypical antipsychotics (causing increases in BDNF, 5-HT and norepinephrine levels, and decreases in glucocorticoid levels), thereby resulting in neuroplasticity and neuroprotection.

Researchers have reported evidence of neurogenesis following atypical antipsychotic treatment in adult rat brain. Both risperidone and olanzapine stimulated a 2- to 3-fold increase in newly divided bromodeoxyuridine (BrDU)-positive cells in the subventricular zone when compared to control- or haloperidol-treated rats. No differences were seen between rats treated with haloperidol or with vehicle alone. A partial thickening in the subventricular zone (2 to 3 cell layers), suggesting hyperplasia, was seen in rats treated with atypical neuroleptics compared to either controls or haloperidol-treated animals. More BrDU-positive cells were also seen in areas outside the subventricular zone, such as the septum, corpus callosum, and cortical areas, in rats treated with atypical neuroleptics compared with controls. These results were confirmed by another study, which reported significant increases in olfactory epithelial BrDU-positive cell counts in both paliperidone- and risperidone-treated rats compared with controls. Other researchers explored the differential effects of typical and atypical antipsychotics on nerve growth factor (NGF) expression. In clinical studies, normal healthy controls have been shown to have plasma NGF levels of approximately 50 pg/mL. Plasma NGF levels were significantly lower in both never-medicated first-episode psychotic (FEP) and chronic medicated schizophrenia patients treated with typical antipsychotics (~17% in each group) compared to controls; the FEP group had lost about 65% of their NGF. In contrast, NGF levels were significantly higher in chronic schizophrenia patients who were receiving atypical antipsychotic treatment (~35%), as compared to the FEP group.

Differential effects of long-term treatment with typical and atypical antipsychotics have been examined in NGF and BDNF levels in rat striatum and hippocampus. The data indicate that atypical antipsychotics, compared to typical antipsychotics, induce less deleterious effects on neurotrophic factor levels in the brain and induce neurogenesis.

**Several inter-related causes have been implicated in the pathogenesis of brain tissue loss in schizophrenia:**

- Dopamine over-stimulation, which can lead to cell death
- Glutamate excitotoxicity
- GABA dysfunction
- Impaired anti-apoptotic signalling
- Mitochondrial dysfunction
- Decreased nitric oxide biosynthesis
- Hypertension/avasoregulation and Oxidative stress/free radicals.

Psychosis is clearly a very noxious state for the brain to experience and clinicians are duty bound to prevent future episodes of psychosis in their patients, Professor Nasrallah emphasised. Moreover, accumulating case study evidence indicates that the longer the duration of untreated psychosis (DUP), the worse the clinical and functional outcomes.
Neuroprotection with atypicals in humans

A 104-week-long study involving 263 FE patients and healthy volunteers found that olanzapine-treated patients have significantly less reduction over time in whole brain gray matter volumes and lateral ventricle volumes than haloperidol-treated patients and that gray matter and lateral ventricle volume changes are associated with changes in psychopathology and neurocognition.32

In other human MRI studies, cerebral gray matter volumes have been seen to increase with 1 month of atypical antipsychotic treatment in patients hospitalised for acute exacerbation of chronic schizophrenia (no medication for >2 months).33 During 28 days of treatment with risperidone and ziprasidone, cerebral cortical gray of 13 patients with schizophrenia expanded by 20.6 cc (p<0.0005). In contrast, cortical gray volumes were unchanged in the 6 patients treated with haloperidol or controls. Our goal is not simply symptom control – recovery is ultimately sought, noted Professor Nasrallah. Remission means minimal residual symptoms, at a level enabling the patient to then eventually recover. How can remission be measured by clinicians?

References