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SCHIZOPHRENIA, A NEURODEGENERATIVE DISORDER WITH NEURODEVELOPMENTAL ANTECEDENTS

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Contents

Abstract

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1. Schizophrenia is a devastating disorder that has been referred to as youth's greatest disabler. Although a number of hypotheses have been proposed in an attempt to explain the pathophysiology of schizophrenia no single theory seems to account for all facets of the disease.
2. Each hypothesis explains some of the phenomena associated with schizophrenia and it is probable that many variables described in these hypotheses interact to produce a disorder characterized by heterogeneous symptomatology, progression and prognosis.
3. Compelling evidence suggests that the primary disturbance is a neurodevelopmental abnormality, possibly resulting from a genetic defect(s), resulting in a predisposition to schizophrenia.
4. Events later in life may then lead to the presentation of symptoms and a subsequent progression of the disease.
5. Recent evidence suggests that the progressive course of schizophrenia is associated with ongoing neurodegenerative processes.
6. Changes in brain derived neurotrophic factor (BDNF) may explain the various changes observed in schizophrenia.

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Keywords: brain-derived neurotrophic factor, neurodegeneration, neurodevelopment, schizophrenia, stress.

Abbreviations: artificial cerebrospinal fluid (ACSF), brain-derived neurotrophic factor (BDNF), neural cell adhesion molecule (NCAM), N-methyl-D-aspartic acid (NMDA), postnatal day (PND), polysialic acid (PSA), superoxide dismutase (SOD), tumor necrosis factor alpha (TNFa).

1. Introduction

Schizophrenia is a biological brain disease that affects approximately 1% of the world's population. Despite the prevalence and devastating effects of schizophrenia, very little is known about the underlying pathology. There has been shown to be a genetic component as evidenced by twin, family and adoption studies, but the results of these studies indicate that genetics is not the only factor involved in the expression of schizophrenia (Karayiorgou and Gogos, 1997; McGuffin *et al.*, 1995). Attempts have been made to explain the pathophysiology of schizophrenia by abnormalities in neurotransmitters such as dopamine (Carlsson, 1988) and glutamate (Coyle, 1996), however, these theories fail to account for pathological reports. In addition, the limitations in symptom treatment by neuroleptics suggest that neurotransmitters are not the primary disruption. The failure of neurotransmitter theories to adequately explain schizophrenia, in combination with the identification of morphological and cytoarchitectural abnormalities in schizophrenia (Arnold and Trojanowski, 1996) led to the hypothesis that schizophrenia is a neurodevelopmental disorder (Weinberger, 1987). This paper will briefly review the evidence for a neurodevelopmental component in schizophrenia and describe the mounting evidence for concommitant neurodegenerative processes.

2. The Neurodevelopmental Hypothesis

This hypothesis states that schizophrenia is a primary brain disease resulting from a fixed structural defect occurring early in life and interacting with maturational events. These maturation events include neuronal precursor and glial proliferation and migration, axonal and dendritic proliferation, myelination of axons, programmed cell death and synaptic pruning (Lieberman, 1999). A widely accepted model suggests that a neurodevelopmental insult results in altered morphology and cytoarchitecture and, therefore, a deficiency in the modulatory capacity of neurons (Duncan et al., 1999). During adolescence or early adulthood, this deficiency, in conjunction with environmental triggers, such as stress, lead to observable symptoms. This emergence is proposed to occur due to the elimination of synaptic connections that previously compensated for the deficiency. It has been demonstrated that obstetric complications, low birth weight (Cannon et al., 1989) and perinatal infections (Mednick et al., 1988) are positively correlated with the occurrence of schizophrenia. Minor physical abnormalities also lend support to a developmental correlate of schizophrenia (Waddington et al., 1990) as do the presence of childhood behavioral precursors (Baum and Walker, 1995, Done et al., 1994, Jones, P. et al., 1994, Walker and Lewine, 1990). Initial reports also suggested that structural defects are present at the onset of illness (DeLisi et al., 1991, Weinberger et al., 1982), are static (Illowsky et al., 1988,

Lieberman et al., 1992, Marsh et al., 1994) and are not associated with gliosis, a marker of necrotic cell death (Roberts et al., 1986, Stevens et al., 1988).

3. Neurodevelopment Versus Neurodegeneration

Despite the plethora of evidence supporting a role for aberrant neurodevelopment in schizophrenia, a number of researchers suggest that schizophrenia is an ongoing degenerative process, not the static disorder purported by the neurodevelopmental hypothesis. A role for neurodegeneration is evidenced by progression of symptoms (Fenton and McGlashan, 1994, Loebel *et al.*, 1992, Wyatt, 1991), especially negative symptoms which are more difficult to treat (Lieberman, 1999) and are directly correlated with ventricular enlargement (Flaum *et al.*, 1995) and frontal gray matter reductions (Zipursky *et al.*, 1992). Progression of structural defects such as ventricular enlargement and hippocampal volume reduction also lend support to a neurodegenerative component in schizophrenia (DeLisi *et al.*, 1997, DeLisi *et al.*, 1995, Jacobsen *et al.*, 1998, Nair *et al.*, 1997, Velakoulis *et al.*, 1999). These studies report that the length of time of symptom presentation prior to pharmacological treatment is a significant predictor of treatment response, relapse and long term outcome. Indications of disease progression led to the proposal that the biological defect in schizophrenia is a continual lifetime process of alterations in cell growth and repair, most likely resulting from a genetic defect(s) (DeLisi, 1997). A role for both neurodevelopment and neurodegeneration are proposed whereby aberrant neurodevelopment would lead to disorganization and dysconnectivity of neurons and subsequent susceptibility to neurodegenerative processes (Fig 1).

4. Indirect Evidence for Neurodegeneration

In addition to clinical evidence for neurodegeneration, dysfunctional glutamate neurotransmission in schizophrenia also supports a role for neurodegeneration. NMDA receptor antagonists, such as those used to model schizophrenia, have been shown to be neurotoxic (Olney *et al.*, 1989). The extent of cell death is dependent on age as neurotoxic effects are only evident at the onset of puberty and become maximal in early adulthood (Farber *et al.*, 1995), a time correlating with the peak age of onset of schizophrenia in males. Repeated NMDA receptor antagonist treatment has been demonstrated to result in subtle but permanent changes in neocortical and limbic structures that are reminiscent of those observed in schizophrenia (Olney & Farber, 1995). These authors further suggested that NMDA receptor hypofunction, as seen following NMDA receptor antagonist administration and as proposed in schizophrenia, exerts effects via the GABAergic system. NMDA receptor hypofunction is proposed to result in disinhibition of excitatory pathways normally tonically inhibited by GABAergic neurons under the control of NMDA receptors. This could result in increased excitatory neurotransmission and, therefore, excitotoxic damage to neurons.

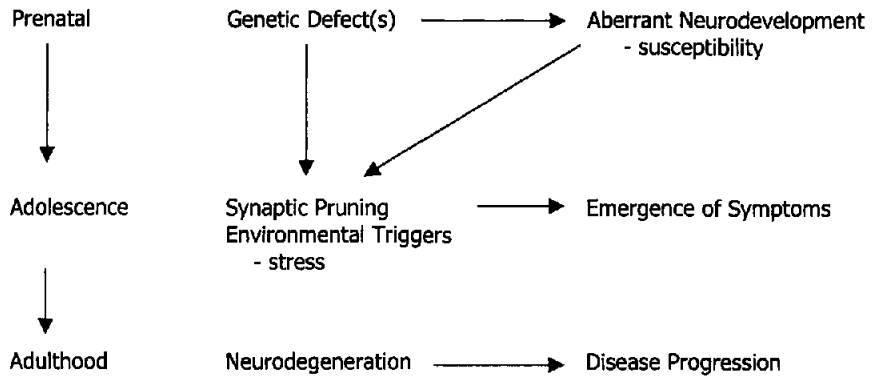

Fig 1. Hypothesized pathogenesis of schizophrenia. Schizophrenia is proposed to be a progressive lifetime disorder with neurodevelopmental and neurodegenerative components.

Neurodegeneration in schizophrenia can also be inferred from two major observations; the effect of stress and the effect of estrogen withdrawal (menopause). Stress has been shown to exacerbate the symptoms of schizophrenia, as well as precipitate the onset and relapse of schizophrenia (Brown and Birley, 1968, Dohrenwend and Egri, 1981, Mari and Steiner, 1994). Acute stress is generally a manageable phenomenon, but chronic stress can result in a disease process as the responses to stress become damaging over time. In particular, chronic or excessive exposure to glucocorticoids is especially damaging to hippocampal neurons (Sapolsky *et al.*, 1984, Watanabe *et al.*, 1992, Woolley *et al.*, 1990), an effect proposed to be mediated by glutamate via NMDA receptors (Armanini *et al.*, 1990). Chronic exposure to stress can result in dendritic atrophy as well as cell death. Liu *et al.* (1996) also demonstrated that stress results in lipid peroxidation, protein oxidation and nuclear DNA damage in the cerebral cortex as well as the hippocampus. This suggests oxidative stress and subsequent neurodegeneration can be induced by physiological stress, at least in extreme conditions. The hypersensitivity of schizophrenic patients to stress may also suggest an increased sensitivity to stress induced neuronal damage.

Estrogen withdrawal also indirectly supports a role for neurodegeneration in schizophrenia. Women demonstrate a later peak onset time of schizophrenia than men and in addition, show a second peak following the onset of menopause when estrogen levels are known to decrease (Häfner *et al.*, 1993; Hambrecht *et al.*, 1992). Symptom severity is also known to fluctuate with estrogen levels as evidenced by premenstrual exacerbation of symptoms, and symptom improvement during pregnancy (Chang and Renshaw, 1986, Gerada and Reveley, 1988, for a review see Seeman, 1996). The demonstration that estrogen is neuroprotective (Behl *et al.*, 1995, Singer *et al.*, 1996, Toung *et al.*, 1998) and that increased estrogen improves the symptoms of schizophrenia (Chang and Renshaw, 1986, Gerada and Reveley, 1988) implies that neurodegeneration may occur in schizophrenia.

5. Biochemical Evidence for Neurodegenerative Processes in Schizophrenia

A number of factors involved in neurodevelopment and/or neurodegeneration have been investigated in schizophrenia. For example, a 115 kDa isoform of neural cell adhesion molecule (NCAM) is increased in the CSF (Poltorak *et al.*, 1995), hippocampus and prefrontal cortex of schizophrenic patients (Vawter *et al.*, 1998). NCAMs are members of the immunoglobulin superfamily that are involved in axon guidance, cell migration and synapse stabilization, however, the 115 kDa isoform does not effectively mediate these actions. Rather, this isoform is a putative secreted protein that is potentially neurotoxic. Its increase in schizophrenia could be due to abnormal glial and/or neuronal processing or abnormal regulation (Vawter *et al.*, 1998). Increases in this soluble NCAM may have significant effects on synaptic plasticity and learning. Further evidence for alterations in NCAM was reported by Barbeau *et al.*, (1995) who demonstrated a reduction in polysialation of NCAM in the hilus region of the hippocampus. Polysialic acid (PSA) residues on NCAM increase interactions between multiple NCAMs, enhance the neurite growth promoting characteristics of NCAM and prevent aberrant neuronal connections during neurodevelopment. In adulthood, polysialated NCAM is present in areas that possess high degrees of plasticity such as the hippocampus (Miller *et al.*, 1993). Reductions in PSA-NCAM in schizophrenia may reflect abnormal neuronal connections between hippocampal neurons and may also have significant implications for hippocampal connectivity to cortical regions (Barbeau *et al.*, 1995). The question remains whether alterations in PSA-NCAM exist throughout neurodevelopment and are a primary cause of the disorder or whether these alterations result from other abnormalities in schizophrenia.

Neurodevelopmental abnormalities with neurodegenerative consequences are also seen by the reduction of reelin mRNA and protein in schizophrenic cortical regions (Impagnatiello *et al.*, 1998). Reelin is a protein involved in the regulation of cortical pyramidal cell, interneuron and Purkinje cell positioning and/or trophic support during neurodevelopment (Curran and D'Arcangelo, 1998). Heterozygote reelin knockout mice show a similar reduction in reelin expression to that seen in schizophrenia. These mice show a number of neuroanatomical abnormalities reminiscent of those seen in schizophrenia (Impagnatiello *et al.*, 1998). The abnormalities appear to be symptomatically silent with the exception of reduced prepulse inhibition of startle, a deficit also present in schizophrenia. A consequence of the neurodevelopmental abnormalities in the reelin deficient mouse appears to be an enhanced vulnerability to excitotoxicity. This is consistent with a neurodegenerative component in schizophrenia, especially with respect to the hypothesized excitotoxic effect of glutamate dysregulation.

Tumor necrosis factor alpha (TNF_a), a cytokine involved in neuron growth and differentiation, also appears to be affected in schizophrenia. Increased plasma levels of TNF_a were demonstrated in neuroleptic free schizophrenics as compared to controls (Monteleone *et al.*, 1997). This increase is specific to schizophrenia, as non-schizophrenic psychiatric patients showed no alterations in TNF_a. Also,

this increase was reduced by chronic clozapine treatment (Monteleone *et al.*, 1997). TNF_a has also been demonstrated to have neurotoxic properties (Grell *et al.*, 1994, Heller *et al.*, 1992, Zheng *et al.*, 1995) and, therefore, its increase in schizophrenia may also have neurodegenerative as well as neurodevelopmental consequences.

Neurodegenerative consequences in schizophrenia also result from the demonstration of altered RNA editing of the GluR-2 subunit of the AMPA-type glutamate receptor (Akbarian *et al.*, 1995). The GluR-2 subunit is a component of the AMPA receptor important for regulating calcium conduction. The edited form of the GluR-2 subunit originally contains a glutamine codon that is posttranscriptionally edited to an arginine codon (Sommer *et al.*, 1991). This edited form normally constitutes more than 99% of the total GluR-2 expressed and is responsible for restricting calcium permeability (Hollmann *et al.*, 1991, Verdoon *et al.*, 1991). In the prefrontal cortex of schizophrenics a significant increase in the ratio of unedited to edited GluR-2 molecules was found thus suggesting increases in calcium permeability (Akbarian *et al.*, 1995). Increased calcium conductance has significant implications for neurotoxicity and in support of this, known neurodegenerative diseases such as Alzheimer's and Huntington's also show altered editing (Akbarian *et al.*, 1995). The editing in Alzheimer's disease is decreased in the prefrontal cortex and in Huntington's disease, the effect is specific to the striatum. The effects in these diseases are also much greater than that seen in schizophrenia. It is not known if the alterations in editing are general or if they are specific to a subpopulation of neurons, thereby making a specific population more vulnerable to neurotoxicity.

Recently it was also demonstrated that schizophrenics have increased plasma levels of S-100b protein (Weismann *et al.*, 1999). The concentration of S-100b protein, a calcium-binding protein found in the CNS, has been shown to increase in CSF and blood in proportion to CNS damage and therefore, is considered a marker of damage in patients with neurological disorders. This finding indicates ongoing neural damage in schizophrenia. In accordance with this are findings of increased superoxide anion production (Melamed *et al.*, 1998) and reduced scavenging capabilities, thereby enhancing vulnerability to free radical damage. Reduced superoxide dismutase (SOD) activity has been demonstrated in neuroleptic naïve, first episode patients (Mukherjee *et al.*, 1994) and reduced SOD mRNA in postmortem tissue of schizophrenics has also been reported (Lau *et al.*, 1999). Glutathione is also reduced in schizophrenic patients (Do *et al.*, 1999) as is glutathione peroxidase (Reddy and Yao, 1996). A deficit in glutathione is proposed to result in free radical induced neurodegeneration. Glutathione also potentiates the effect of glutamate at the NMDA receptor, therefore, its reduction could also contribute to NMDA receptor hypofunction. Increased lipid peroxidation, indicating free radical damage, has also been demonstrated in the blood of schizophrenic patients (Murthy *et al.*, 1989). These findings, generally associated with poorer outcome, lead to the conclusion that oxidative stress leads to membrane abnormalities and neuronal dysfunction (Reddy and Yao, 1996). Further evidence for membrane abnormalities stems from the demonstration of decreased phosphomonoesterases,

precursors of membrane phospholipids, and increased phosphodiesterases, breakdown products of membrane phospholipids (Pettegrew *et al.*, 1990). This proposed decrease in synthesis and increase in breakdown of membranes in schizophrenia could be indicative of ongoing neurodegeneration.

In an attempt to further elucidate the potential role of neurodegeneration, mitochondrial function in schizophrenia was addressed. Mitochondria are responsible for energy production within cells and, therefore, play an important role in cell viability. Cavelier *et al.* (1995) reported a reduction in cytochrome c oxidase, a mitochondrial respiration enzyme and marker of mitochondrial function, activity in the frontal cortex and caudate nucleus of schizophrenics. It was proposed that this reduction reflected a general decrease in mitochondrial oxidative phosphorylation, and therefore, ATP production. Subsequently, another group investigated the number of mitochondria in the striatum from schizophrenic and control postmortem tissue. It was reported that the striatal neuropil of schizophrenic patients contained significantly fewer mitochondria than did controls (Kung and Roberts, 1999). This suggests either decreased energy demands or a reduced capacity to meet the energy requirements of structures with fewer mitochondria. The majority of striatal terminals arise from cortical neurons, therefore, the suggestion was made that a decrease in energy exists in the corticostriatal circuitry in schizophrenia. It remains to be determined if specific populations are affected and whether the mitochondrial reduction is present in other brain structures. Reduced energy supply, in combination with the above alterations, has significant implications for cell connectivity, neurotransmission and cell viability. Notably, specific mitochondrial abnormalities have been reported to occur in a number of neurodegenerative conditions (Beal, 1995, and references therein).

6. Alterations in Brain-derived Neurotrophic Factor in an Animal Model of Schizophrenia

The significant amount of research supporting a role for neurodevelopmental abnormalities resulting in a predisposition to schizophrenia and consequent neurodegenerative processes led to an investigation of alterations in brain-derived neurotrophic factor (BDNF) in an animal model of schizophrenia. In the hippocampus, cortex and *in vitro*, BDNF has been demonstrated to regulate the survival, differentiation, morphology and synaptic remodeling of neurons (Alderson *et al.*, 1990, Ghosh *et al.*, 1994, Jones, K.R. *et al.*, 1994, Korte *et al.*, 1995, McCallister *et al.*, 1995, Thoenen, 1995). It has also been demonstrated to modulate neurotransmitter synthesis, metabolism and release, postsynaptic ion channel fluxes, neuronal activity and long term potentiation (Altar *et al.*, 1997, Croll *et al.*, 1994, Kang and Schuman, 1995, Thoenen, 1995). Reports demonstrate a reduction in hippocampal BDNF mRNA (Brouha *et al.*, 1996) and serum BDNF in schizophrenic patients (Toyooka *et al.*, 1999). An allele variant of the BDNF gene has also been identified in a population of schizophrenic patients (Vicente *et al.*, 1996). In addition, support for a role for BDNF in schizophrenia also stems from the demonstration that it is decreased by factors correlated with first episode onset such as stress (Smith *et al.*, 1995a, 1995b) and estrogen withdrawal (Singh *et al.*, 1995). Interestingly, these stress induced

decreases in BDNF are blocked by 5-HT_2 receptor antagonists, a receptor binding property of many neuroleptics (Vaidya *et al.*, 1997). Electroconvulsive treatment (ECT), effective in treatment-resistant schizophrenia in combination with neuroleptics (Sajatovic and Meltzer, 1993), also upregulates the expression of BDNF (Lindefors *et al.*, 1995, Nibuya *et al.*, 1995). For these reasons, in addition to providing a link between neurodevelopmental and neurodegenerative phenomenon, BDNF is an attractive candidate molecule in schizophrenia. Changes in BDNF in a neurodevelopmental animal model based on that established by Lipska, *et al.*, (1993) have been studied (Ashe *et al.*, 1999, Ashe, 2000). Briefly, postnatal day (PND) seven Sprague-Dawley rat pups were lesioned bilaterally in the ventral hippocampus using ibotenic acid, sham lesioned animals were injected with artificial cerebrospinal fluid (ACSF). The animals were exposed to swim stress or a control environment at PND75 then killed 24 hrs later and assessed for alterations in BDNF mRNA by in situ hybridization. The results demonstrate that animals with hippocampal lesions express significantly lower basal levels of BDNF mRNA in the prefrontal cortex than sham animals (Fig 2). This suggests that animals with neurodevelopmental lesions may demonstrate increased susceptibility to neuronal damage. In addition, both lesioned and sham animals demonstrate a significant upregulation of BDNF mRNA following exposure to stress (Fig 2). This effect is contrary to previous reports of stress induced changes in BDNF expression (Smith *et al.*, 1995a, 1995b), however, it is in accordance with increased glutamate release during stress (Moghaddam, 1993) as glutamate can directly increase BDNF expression (Zafra *et al.*, 1990, 1991). Interestingly, the upregulation of BDNF mRNA following stress is significantly greater in lesioned animals than in sham treated animals (Ashe *et al.*, 1999). This suggests that lesioned animals are hypersensitive to stress and require greater resources to protect from the neuronal damaging effects of stress. Investigation of cell death demonstrates that even in the presence of increased BDNF there is an increase in cell death in lesioned animals exposed to stress as compared to sham lesioned animals exposed to stress (Ashe, 2000). While this increase was small, over extended periods of time, significant functional impairments could result.

7. Conclusions

In summary, evidence exists for both neurodevelopmental and neurodegenerative components in the pathophysiology of schizophrenia. These processes are not necessarily mutually exclusive but rather, it is possible that both components co-exist to produce the pathophysiology of schizophrenia. In addition, they are both attractive hypotheses in terms of their ability to accommodate neurotransmitter theories as alterations in neurodevelopment and/or neurodegeneration would not likely occur without consequent alterations in neurotransmission. The use of a neurodevelopmental animal model of schizophrenia to investigate BDNF expression suggests that a neurodevelopmental lesion can establish a system which may be more susceptible to neurodegeneration induced by subsequent stressors. While adequate treatment of at least the positive symptoms exists, there is no completely efficacious treatment of schizophrenia available. With increasing information regarding the genesis of the disease,

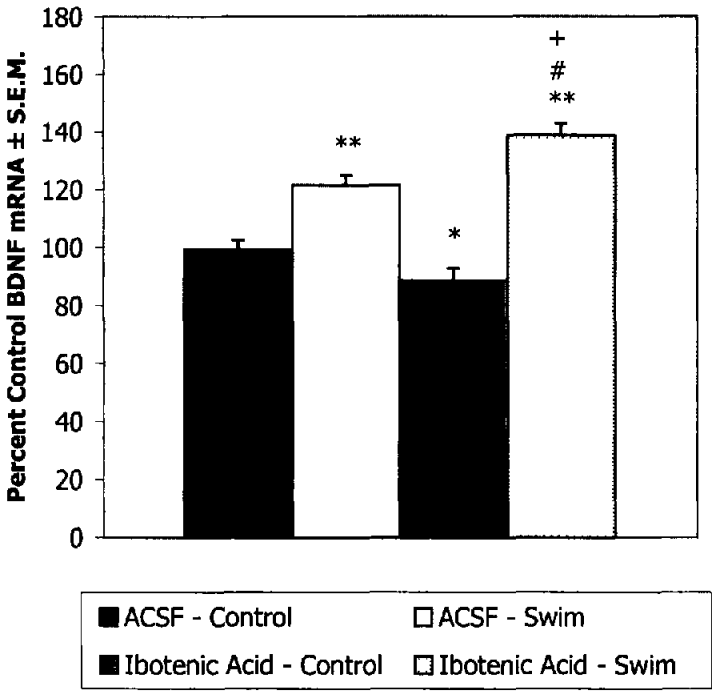

Fig 2. Hypothesized Pathogenesis of Schizophrenia. BDNF mRNA in the prefrontal cortex of lesioned and sham treated rats exposed to swim stress or a control environment. Values represent mean ± S.E.M., n=11-19. Two way ANOVA revealed a significant effect of treatment (control environment vs. forced swim) ($F_{(1,54)}$=88.43, p<.001) and a significant interaction between treatment and lesion status (ACSF vs. ibotenic acid) ($F_{(1,54)}$=13.03, p<.01). * significant with respect to ACSF-Control, p<.05; ** significant with respect to ACSF-Control, p<.01; # significant with respect to Ibotenic Acid-Control, p<.01; + significant with respect to ACSF-Swim, p<.05. (Ashe, 2000).

its emergence and its progression comes the knowledge of how to better treat this devastating disorder. Early intervention has been demonstrated to improve patient prognosis in a number of cases. Potentially, with increased understanding of the disorder, more effective pharmacological agents can be found to improve the quality of life of persons suffering with schizophrenia and to prevent its progression.

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