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A Review on Chronic Disorder - Schizophrenia

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Abstract

Schizophrenia also known as split-personality disorder, a chronic psychological disorder, characterized by perturbations in cognition, delusion, hallucinations, thought and behaviour disorder. The original name for Schizophrenia is dementia praecox.During the last three decades, understanding level of the etiology, psychopathology, pathophysiology and clinical manifestations has been increased. In addition to these advanced antipsychotics, has optimized the potential use for the recovery from illness. Allopathethic drugs in combinations of herbal drugs have been provided more effective results. This review shows overview and the researches done on schizophrenia to know the epidemiology and understand its etiology, pathophysiology so that it can be treated completely. Along with treatment of antipsychotic drugs many alternative treatment such as Cognitive Behavioural Treatment (CBT), music therapy, vitamin therapy has also shown significant results.

Key words: Schizophrenia, Chronic Disorder, Treatment

Introduction

Schizophrenia is a chronic, severe, and disabling brain disease. Approximately 1 percent of the population develops schizophrenia during their lifetime – more than 2 million Americans suffer from the illness in a given year. Although schizophrenia affects men and women with equal frequency, the disorder often appears earlier in men, usually in the late teens or early twenties, than in women, who are generally affected in the twenties to early thirties. People with schizophrenia often suffer terrifying symptoms such as hearing internal voices not heard by others, or believing that other people are reading their minds, controlling their thoughts, or plotting to harm them. These symptoms may leave them fearful and withdrawn. Their speech and behaviour can be so disorganized that they may be incomprehensible or frightening to others. Available treatments can relieve many symptoms, but most people with schizophrenia continue to suffer some symptoms throughout their lives; it has been estimated that no more than one in five individuals recovers completely.

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It is also suitable for local drug delivery to the stomach and proximal small intestines [3]. Several approaches have been studied to prolonging the residence time of the dosage at the absorption site and the development of oral controlled release bioadhesive system. Various gastro retentive dosage forms, such as microspheres, and bilayer tablets, have been thoroughly prepared and reported by several research groups [4].

Microspheres constitute an important part of these drug delivery systems by virtue of their small size and efficient carrier capacity. However, the success of these microspheres is limited due to their short residence time at site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres [5].

Atenolol is a β-selective adrenergic blocking agent which is prescribed widely in diverse cardiovascular diseases like hypertension, angina pectoris, arrhythmias and myocardial infractions, Atenolol shows maximum absorption in the upper GI regions, also shows bioavailability 40% orally, half life 4-5 hr[6]Administration of conventional dosage form of Atenolol has been reported to exhibit fluctuation in the plasma drug level resulting either in manifestation of side effect or reduction in the drug concentration at the receptor site. So, the development of oral controlled release dosage form would clearly be advantageous.

Moreover the site absorption of Atenolol is in the stomach and proximal portion of the small intestine, the dosage form that is retained in the stomach would increase the absorption, improve drug efficiency and decrease dose requirement[4].

Thus, Atenolol is a candidate for the development of a gastro retentive drug delivery system Atenolol is better absorbed from gastric region, hence it is need to develop gastro retentive drug delivery system i.e. mucoadhesive microspheres. This is a time of hope for people with schizophrenia and their families. Research is gradually leading to new and safer medications and unravelling the complex causes of the disease. Scientists are using many approaches from the study of molecular genetics to the study of populations to learn about schizophrenia. Methods of imaging the brain's structure and function hold the promise of new insights into the disorder.(NHMS).

Schizophrenia was initially thought to be hereditary based on studies of high incidence in certain families. Additionally, studies on specific genes suchas *ZDHHC8* and *DTNBP1* seem to suggest susceptibility to the onset of this disorder. In addition, current data suggests neurodevelopmental or environmental causes such as viral infections and prenatal/perinatal complications.

Here we can see that interest in schizophrenia only began about two hundred years ago and the proper study of it, probably, only about a hundred years ago. Perhaps in another few decades, researchers will be able to find out exactly what the cause of schizophrenia is.

HISTORY

The disorder, schizophrenia, was first recognized by an Englishman, John Haslam (1809) in his book, "Observations on Madness and Melancholy". He noticed a consistent pattern in the people with this disorder and called it "a form of insanity". A greater stride was made in 1898 when a German psychiatrist, Emil Kraepelin, described the illness more and had the symptoms grouped under the Latin term, "dementia praecox". It was EugenBlueler, a Swiss psychiatrist who first introduced the term "Schizophrenia" in 1908.

The word "Schizophrenia" comes from the combination of the Greek words for split (skhizein) and mind (phren). Blueler believed that underlying all the unusual behaviours shown by people with this disorder was an associative splitting of the basic functions of personality. This concept emphasizes the "breaking of associative threads" or the destruction of the forces that connect one function to the next. It is illustrated by a difficulty keeping a consistent train of thought.Unfortunately the concept of "split mind" inspired the common but incorrect use of the term schizophrenia to mean "split personality". (Barlow & Durand, 2002.)

EPIDEMIOLOGY

Incidence studies of relatively rare disorders, such as schizophrenia, are difficult to carry out. Surveys have been carried out in various countries, however, and almost all show incidence rates per year of schizophrenia in adults within a quite narrow range between 0.1 and 0.4 per 1000 population. This has been the main finding from the WHO 10-country study (Jablensky, 1992).

Taking into account differences in diagnostic assessment, case-finding methods,we can say that the incidence of schizophrenia is remarkably similar in different geographical areas (Warner and de Girolamo, 1995). Exceptionally high rates that emerged from the Epidemiologic Catchment Area Study in the United States (Tien and Eaton, 1992) may be due to biase assessment. Although few data are available on incidence in developingcountries, early assumptions on consistently lower rates outside the western industrialized countries have not been confirmed by recent thorough investigations in Asian countries (Lin et al., 1989; Jablensky et al., 1992; Rajkumar ,1991).

In the last 15 years a variety of reports from several countries have suggested a declining trend in the number of people presenting for treatment of schizophrenia (Der, 1990). However, changes in diagnostic practices and patterns of care or more rigorous definitions of new cases as a result of improved recording systems, have not been ruled out as an explanation. So far,the case for a true decrease in incidence is suggestive but not proven (Jablensky, 1995).

Much wider variation has been observed for prevalence, which has been moreextensively studied. Point prevalence on adults ranges between 1 and 17 per 1000 population, one-year prevalence between 1 and 7.5 per 1000, and lifetime prevalence between 1 and 18 per 1000 (Warner and de Girolamo, 1995). Variations in prevalence can be related to several factors, including differences in recovery, death and migration rates among the affected individuals.

ETIOLOGY

Over the past 100 years, many theories have been proposed by scientists to explain the cause of schizophrenia. The majority of them have believed that the illness is biological in nature and involves some type of disturbance in the brain.

However, advances in biological research have led this theory to be abandoned by most practitioners. The profound effects of antipsychotic medications on the

symptoms of schizophrenia suggest that the illness is related to disordered brain functioning and is not a psychological response to disturbed family or marital relationships.

To understand the onset, course, severity and relapse of schizophrenia; the Stress-Vulnerability Model provides a valuable framework in understanding (Mueser & Gingerich, 1994).

The Stress-Vulnerability Model

The Stress-Vulnerability Model explains that a person who has biological vulnerability to schizophrenia will have schizophrenia if he is exposed to excessive stress and, at the same time, lacks coping skills. (Mueser & Gingerich, 1994).

The development of schizophrenic symptoms is determined by three different factors: biological vulnerability, stress and the individual's coping skills.

1) Biological Vulnerability

Biological vulnerability refers to the biological predispositionto experience the symptoms of schizophrenia. Biological vulnerability can be due to any one of these two encompassing reasons: an inherited tendency due to genetic factor or exposure to early biological risks (Mueser & Gingerich, 1994).

2) Stress

If a person has a biological vulnerability/predisposition to schizophrenia, excessive stress can trigger the symptoms of schizophrenia according to the Stress-Vulnerability Model (Mueser & Gingerich, 1994).

3) Coping Skills

Coping skills refers to a patient's ability to handle stress effectively and thereby reduce the negative effects of stress. Some evidences of poor coping skills are a lack of social skills and the inability to relax. Having had a biological vulnerability to schizophrenia, the excessive stress a person experiences and is unable to cope with will trigger an onset of schizophrenia or a relapse. (Mueser & Gingerich, 1994.)

SYMPTOMS

Unlike some disorders which we can generally define with a particular symptom eg. Depression always includes feelings of sadness, panic disorder is always accompanied by intense feelings of anxiety .Its symptoms vary from person to person. Researchers have identified clusters of symptoms that make up the disorder. These clusters of symptoms are called "positive symptoms", "negative symptoms" and "disorganized symptoms". There is not yet a universal agreement about which symptoms should be included in these categories as well.

Positive symptoms generally include the more active manifestations of abnormal behaviour which are delusions and hallucinations. Negative symptoms involve deficits in normal behaviour in such areas as speech and motivation Disorganized symptoms include disorganized speech, erratic behaviour and inappropriate affect

(a) Delusions

Delusions are strong bizarre beliefs that would be seen by most members of a society as a misrepresentation of reality. Because of its importance in schizophrenia, delusion has been called "the basic characteristic of madness" (Jaspers, 1963) (cited in Barlow & Durand, 2002). There are two main types of delusions: delusion of grandeur and delusion of persecution.

A person with delusion(s) of grandeur would believe that he is famous and important (such as Mother Teresa or Jesus Christ) and he would be trying to "save the world.

(b) Hallucinations

Normal ordinary human beings sometimes get the sensation that someone called theirname (when no one was there) or something moved by them (when nothing did).There are fleeting moments like this but in the case of a schizophrenic, theseperceptions are very real and occur on a sufficiently regular basis. The experience ofsensory events without any input from the surrounding environment are called ahallucination.

An interesting research d in London (McGuire, Shah & Murray, 1993) discovered that the part of the brain most active during hallucinations was the Broca's area

Negative Symptoms

The negative symptoms usually indicate the absence or insufficiency of normal behaviour ("deficit"). They include emotional and social withdrawal, apathyand poverty of thought or speech.

(a) Avolition

Avolition comes from the words, "a" (which means "without") and "volition" (which means "an act of willing, choosing or deciding"). Avolition is the inability to initiateand persists in activities. People with this symptom (also called "apathy") show littleinterest and initiative in performing even the most basic day-to-day functions, including those associated with personal hygiene. (Barlow & Durand, 2002).

(b) Alogia

Derived from the combination of "a" (without) and "logos" (which means "words"),alogia refers to the relative absence of speech. A person with alogia may respond to questions with very brief replies that have little content, and may appear uninterestedin the conversation. His reply can also be delayed or slow. (Barlow & Durand, 2002).

(c) Anhedonia

Similarly, this word means without "hedonia" (hedonia pertains to pleasure). Aperson with anhedonia

experiences a lack of pleasure or indifference in activities thatwould typically be considered pleasurable, including eating, sex and socialinteractions. (Barlow & Durand, 2002).

(d) Flat Affect

Flat affect is characterized by a lack of emotion shown, particularly obvious with alack of facial expressions. The person may stare at you vacantly, speak in a flat and toneless manner and seem unaffected by things going on around them. Although they do not react openly to emotional situations, they may indeed be responding on theinside. According to World Health Organization (WHO, 1973), approximately two-thirds of the people with schizophrenia exhibit flat affect. (Cited in Barlow & Durand, 2002.)

Disorganized Symptoms

(a) Disorganized Speech

This is precisely what Blueler (1908) called "associative splitting". Paul Meehl (1962) calls it "cognitive slippage". People with schizophrenia, while talking, jump from topic to topic and at other times, they talk illogically. Signs of derailment or going off at a tangent are very obvious, too.

(b) Inappropriate Affect

Occasionally, people with schizophrenia display inappropriate affect; laughing or crying at improper times. They could be laughing during a funeral or crying when it is a happy moment.

(c) Disorganized Behaviour

Sometimes schizophrenics exhibit bizarre behaviours such as hoarding objects or acting in unusual ways in public. One unusual behaviour is catatonic immobility in which patient hold unusual posture, as if she was fearful of something terrible happening if she moved.

This, thus, leads us to differentiating people with schizophrenia into sub-types.

SUB-TYPES OF SCHIZOPHRENIA

People with schizophrenia are classified into 5 sub-types, namely "Paranoid Type","Disorganized Type", "Catatonic Type", "Undifferentiated Type" and "ResidualType".

Paranoid Type

They stand out because of their delusions or hallucinations. At the same time, their cognitive skills and affect arerelatively intact. They generally do not have disorganized speech or flat affect. Theytypically have a better prognosis than people of the other sub-types. Researchsuggests that the paranoid sub-type may function better before and after episodes ofschizophrenia than the other sub-types. (McGlashan & Fenton, 1991). (Cited inBarlow & Durand, 2002).

Disorganized Type

They show marked disruption in their speech and behaviour (eg. disorganized speech and behaviour); they also show flator inappropriate affect. (American Psychiatric Association, 2000a). They also seemusually self-absorbed, and may spend considerable amount of time looking atthemselves in the mirror (Black & Andreasen, 1999

Catatonic Type

This type shows a certain kind of disorganized behaviour, but in the form of catatonic immobility, waxy flexibility and wild agitation plus pacingexcitably

Undifferentiated Type

People with major schizophrenic symptoms but who do not fit neatly into anyof the sub-types mentioned above are classified as the "undifferentiated type".

Residual Type

People who have had at least one episode of schizophrenia but who no longer manifest major symptoms are diagnosed as having the residual type of schizophrenia.

CLINICAL ISSUES

Diagnosis

• Its diagnosis does not carry enough information for treatment planning. Symptoms suggestive can be found in a number of neurological and psychiatric disorders. Therefore, differential diagnosis should consider the following conditions:

• Epilepsy (particularly temporal lobe epilepsy);

• Central nervous system neoplasms (particularly frontal or limbic);

• Central nervous system traumas;

• Central nervous system infections (particularly malaria and other parasitic diseases, neurosyphilis, herpes encephalitis);

• Cerebrovascular accidents;

• drug-induced psychosis (especially related to use of amphetamines, LSD and phencyclidine);

Clinical Pictures

Although its clinical presentation varies widely among affected individuals and even within the same individual at different phases of the illness, some of the following symptoms can always be observed:

• Thought disorder

• Delusions:

• Hallucinations

• Abnormal affect

• Disturbances in motor behaviour

Furthermore, considerable empirical evidence points to a continuity between most psychotic symptoms and ordinary experience. The tendency to bizarre thinking and peculiar sensory experiences is spread across the

population more widely than is usually acknowledged by clinicians (Claridge, 1990). Therefore, symptom assessment may be a threshold issue and should always be seen within the context of the person's overall emotional state and social functioning.

PATHOPHYSIOLOGY

A number of models have been proposed to explain the mechanism for the development of schizophrenia in terms of the nature, timing and the course of brain changes; processes which are still not well understood. The major models for the cause of schizophrenia are summarized here. The potential links between brain structures and neuronal signalling and the development of schizophrenia. In order to improve treatment options and prognostic outcomes for schizophrenia it is necessary to understand the pathophysiology that contributes to this disease state.

Oligodendrocytic computation capacity theory

White matter abnormalities in the brain have also been correlated with schizophrenia. The net result of these abnormalities is specific defects in brain lateralization. Some investigators have suggested that damaged or immature Oligodendrocytic can prevent or hamper the properties of axonic formation. Based on this, Mitteraue postulated the Oligodendrocytic computation capacity theory, which ascertains that decomposition of the oligodendrocyte-axonic system may be responsible for symptoms leading to complete incoherence as seen in schizophrenia [Barch DM, Csernansky JG,2007]. This is also extended to astrocyte-neuronal interactions in tripartite synapses. In line with this argument, Mitterauer stated that all macroglial cells with their syncytia must be considered in their interactions with the neuronal system [Barch DM, Csernansky JG,2007].

Genetic inheritance in schizophrenia

Schizophrenia manifestations are more common in some families. Although not strictly due to heredity, newer models have been proposed that suggest that specific allelic inheritance may contribute to the development of schizophrenia.

Foley *et al*. suggested that the inheritance variation and selection of schizophrenia operates more through a Darwinian mechanism rather than a Mendelian mode of inheritance. It has also been hypothesized that schizophrenia has been the psychiatric result of a gene that confers disease risk in the current environment, but that it may have provided a survival and/or reproductive advantage in an evolutionarily ancestral environment [Mitterauer B,2007]. Supporting the theory of inheritance in gene susceptibility, Crow proposed that that the susceptibility genes for schizophrenia were inevitable 'trade-offs' for adaptations related to the development of language by humans [Pearlson GD, Folley BS,2008].

More recently, it was also shown that a deletion in the *ZDHHC8* gene affects the ratio of an intron-4-containing unspliced form, resulting in the encoding of a truncated inactive form of the transmembranepalmitoyltransferase that modifies postsynaptic density (PSD) proteins such as PSD-95. These enzymes have important roles in excitatory synaptic transmission of the human brain. Subtle change can cause a 1.5-fold increase in disease risk.

Disrupted in schizophrenia 1 (DISC1) is a protein with a wide array of functions suspected to be involved in the pathogenesis of schizophrenia. Decreased levels of the *DISC1* gene in the brain cause abnormal growth, disrupted migration, and accelerated integration of adult neurons. Abnormalities such as these can lead to seizures and may be involved in the development of schizophrenia [Liao SY, Lin SH, Liu CM, Hsieh MH, Hwang TJ, Liu SK, Guo SC, Hwu HG, Chen WJ 2009, .Fournier NM, Caruncho HJ, Kalynchuk LE 2009].

Alterations in neurotransmission

There has been extensive evidence that glutamatergic *N*-methyl-D-aspartate (NMDA) neurotransmission is also highly disrupted in schizophrenia. Spinophilin, a neuronal protein implicated in the regulation of NMDA signaling, was also reported to be downregulated in the striatum after repeated phencyclidine (PCP) treatment. These results demonstrated that repeated treatment PCP drugs, an NMDA receptor antagonist, could produce specific cognitive deficits that are associated with alterations in gene expression in brain regions that appear to play a significant role in the pathophysiology of schizophrenia [. Itokawa M, Arai M, Kato S, Ogata Y, Furukawa A, Haga S, Ujike H, Sora I, Ikeda K, Yoshikawa T,2003].

Other studies indicated that dopamine D2 receptor expression is also highly implicated in the disturbance associated with schizophrenia. In studies using transient overexpression of D2 receptors in the striatum of transgenic mice, abnormal prefrontal cortex function was observed. Supporting this finding, studies in primary neurons showed that the siRNA knock-down of dysbindin, a protein thought to modulate D2 but not D1 receptor internalization and signalling, resulted in reduced glutamate release. This suggests that decreased dysbindin may decrease exocytosis of glutamate-containing synaptic vesicles, which alter neuronal transmission and may be responsible for the disturbances associated with schizophrenia. *In vitro* studies using the rat pheochromocytoma P12 cell

line siRNA to dysbindin was also shown increase dopamine secretion. *In vivo*, dopaminergic transmission and turnover is increased in the cortex of the dysbindin mutant mice with decreased dopamine levels [Beraki S, Diaz-Heijtz R, Tai F, Ogren SO,2008].

Gamma-aminobutyric acid (GABA) has also been associated with the development of schizophrenia. Schizophrenia patients exhibit expression insufficiencies in GABA transcripts that encode GABA neurons, certain GABA(A) receptor subunits and regulators that are involved in GABA neurotransmission. Such abnormalities cause cognitive function impairments that typically affect working memory in schizophrenia patients. To date, several studies suggest that altered GABA neurotransmission, particularly in the dorsolateral prefrontal cortex, leads to impaired working memory in patients with schizophrenia [Iizuka Y, Sei Y, Weinberger DR, Straub RE,2007].

TREATMENT

The treatment of schizophrenia is guided by three general principles that follow directly from the stress-vulnerability model.

Reduce environmental stress

Together with drug therapy, individual psychotherapy is administered to helpthe patient manage the psychological factors that can also contribute to the illness.(Barlow & Durand, 2002).The most beneficial treatment is some combination of antipsychotic medication and therapy (Sue, Sue & Sue, 2003; Barlow & Durand, 2002).

It has been found that traditional institutional treatments providing custodial care have yielded poor results (Sue, Sue & Sue, 2003).

Improve coping skills

Research have shown that the addition of social skills training, familyintervention and vocational rehabilitation has been more effective in preventingrelapse than drug treatment alone (Falloon, Brooker& Graham-Hole, 1992 as cited inBarlow & Durand, 2002 and Hogarty et al., 1997 as cited in Nolen-Hoeksema, 2004).

Medication and Drugs

Antipsychotic medications have been available since the mid-1950s.These medications reduce the psychotic symptoms of schizophrenia and usually allow the patient to function more effectively and appropriately. Antipsychotic drugs are the best treatment now available, but they do not "cure" schizophrenia or ensure that there will be no further psychotic

A number of new antipsychotic drugs (the so-called "atypical antipsychotics") have been introduced since 1990. The first of these, clozapine (Clozaril®), has been found to be more effective than other antipsychotics, but has of severe side effects – in particular, a agranulocytosis (loss of the white blood cells that fight infection) – requires that patients be monitored with blood tests every one or two weeks.

Even newer antipsychotic drugs, such as risperidone (Risperdal®) and olanzapine (Zyprexa®), are safer than the older drugs or clozapine, and they also may be better tolerated. They may or may not treat the illness as well as clozapine, however. Several additional antipsychotics are currently under development.

Most conventional antipsychotic drugs in common use are listed in Table2.

Table : Conventional Antipsychotic Drugs

Class and generic name	Relative potency
Phenotiazines	
Chlorpromazine*	100
Thioridazine	100
Prochlorperazine	15
Perphenazine	10
Trifluoperazine	5
Triflupromazine	25
Fluphenazine	2
Fluphenazine decanoate[1]*	—
Thioxanthenes	
Thiothixene	5
Chlorprothixene	100
Flupentixol	2
Zuclopentixol	2
Butyrophenones	
Haloperidol*	2
Haloperidol decanoate[1]	-
Pimozide	2
Droperidol	4
Dibenzoxazepines	
Loxapine	10
Dihydroindolones	
Molindone	10

* Included in the World Health Organization's essential drugs list (WHO Expert Committee on the Use of Essential Drugs, 1995)

[1] Long-acting injectable preparations.

Alternative treatment

Treatment of schizophrenia usually includes antipsychotic medications. It may also include group or individual therapy, psychoeducation, and rehabilitation. Complementary and alternative medicine (CAM) treatments are another option. CAM includes

- Vitamin treatments: folic acid and B6, B9, and B12 containing supplements.
- Fish-oil supplements and protein such as glycine should be intaken.
- Diet management: ketogenic diet showed promising results.
- Chinese Herbal medicine: herbs such as *dang gui cheng qi tang*, *Ginkgo biloba* with combination of chlorpromazine group (NNT with chlorpromazine 4, 95% CI 2 to 14) is very effective. (trials John Rathbone, Lan Zhang,2007)

Preventive interventions

Following preventive measures should work against relapses.

(a) Healthy lifestyle

Healthy lifestyle from the physical, spiritual and mental aspect is most important. There should be a healthy exercising of the mind. Sleep must be sufficient.

(b) Avoid excessive stress / Stress management

Excessive stress is discouraged. Learn to relax. The many stress management seminars and talks of late should be given a consideration.

(c) Happy social relationship

Good social relationships with family and friends should be cultivated. Effective social skills can be learned.

(d) Improve prenatal care and nutrition

Taboos for pregnant women may actually be very sound after all! Vaccinations against viruses (eg. influenza) for women of childbearing age may be a valid preventive measure.

Conclusion

Schizophrenia is a disorder associated with high levels of social burden andcost, as well as an incalculable amount of individual pain and suffering. However, there is evidence that the outcome of care can be as successful as it is inmany other diseases treated by medical or surgical procedures. Although, the symptoms of schizophrenia are frightening to an on looker and although complete recovery is rare, about 55% of the people with schizophrenia can return to normal condition. Implementation of an effective care system for schizophrenia, however, is more than a technical endeavour. It has to be sustained by a vision and must be put with in a unifying overall frame of reference.

The vision can be that of a recovery-oriented mental health system, a service oriented to promote recovery from mental disorders. This is done by initiating self-motivation, attitude to disability, empowerment and self-determination. Psychosocial rehabilitationcan provide this vision with a frame of reference, linking mental healthservices to a complex and ambitious social perspective that encompasses different sectors and levels, from hospitals to homes and work settings, with acentral aim of ensuring full citizenship for people irrespective of their disabilities.

Atypical neuroleptics are found to be safer and effective for its treatment. With the help of preventive measures and advancement in the researches it will soon be completely treatable.

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