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Evaluation of Schizophrenic Activity in Experimental Animals

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Abstract: ***The use of current research into schizophrenia has remained highly fragmented, much like the clinical presentation of the disease itself. Differing theories as to the cause and progression of schizophrenia, as well as the heterogeneity of clinical symptoms, have made it difficult to develop a coherent framework suitable for animal modeling. However, a number of limited animal models have been developed to explore various causative theories and to test specific mechanistic hypotheses. Historically, these models have been based on the manipulation of neurotransmitter systems believed to be involved in schizophrenia. In recent years, the emphasis has shifted to targeting relevant brain regions in an attempt to explore potential etiologic hypotheses. The specific animal models developed within these frameworks are described in this review. Emphasis is placed on the critical evaluation of currently available models because these models help to shape the direction of future research.***

I. INTRODUCTION

Schizophrenia is a chronic debilitating neuropsychiatric disorder affecting approximately 1% of the population world-wide. Symptoms cluster into three categories: positive (including auditory and visual hallucinations, delusions, conceptual disorganization and thought disorder) negative (Emotional blunting social withdrawal an hedonic a volition, poverty of thought and content of speech) and cognitive dysfunction (including impaired executive function working memory and attention) (Andreasen1995).Patient present with extremely heterogeneous symptom combinations, making diagnosis and treatment problematic. Many patients undergo prolonged periods of remission interspersed with relapses of psychotic episodes. Disease onset is typically post adolescence (16–25 years with a higher incidence of psychotic symptoms in males and a bimodal later onset (40–60 years) in females. Although the etiologyof schizophrenia remains contentious, it is a multi factorial neuro developmentaldisorder influenced by both genetic and environmental factors (Lewis and Lieberman, 2000; Van O seta. (2010),such that monozygotic siblings of affectedindividuals show a 50–80% risk of developing the disorder.

The first drugs, found by serendipity rather than design in the 1950s, to treat the psychotic symptoms of schizophrenia (haloperidol and chlorpromazine,called classical neuroletics) are also known as the first-generation antipsychotics.

The second-generation or atypical antipsychotics, so called because of their different clinical profile (including clozapine, olanzepine, risperidone and aripiprazole) developed from the 1970s have less tendency to produce unwantedextra pyramidal side effects and hyper pro lactinaemia (Remington, 2003). While first-generation antipsychotics are classified according to chemical structure, the second-generation antipsychotics are characterized according to their pharmacology. These drugs were developed to treat the positive (psychotic) symptoms and not the negative or cognitive impairments. However, multisite, double-blind studies comparing several second- generation antipsychotics with a typical antipsychotic, perphenazine, failed to substantiate any major therapeutic advantage of the former (Lieberman et al., 2005). The cognitive symptoms of schizophrenia often precede the occurrenceof psychosis, and their treatment is considered a better predictor of therapeutic outcome (Mintz and Kopelowicz, 2007). However, while positive symptoms arecurrently treated to a varying degree by typical and atypical anti-psychotics, the negative, and in particular, the cognitive impairments, remain resistant to treatment with current antipsychotics even after remission of the psychosis (Nuechterleinetal2004; Keefeet al.2007; Mintz and Kopelowicz 2007). Consequently, there is an urgent need to develop novel compounds that demonstrate increased efficacy against cognitive dysfunction and negative symptoms most likely by the use of adjunct therapy in combination with existing antipsychotics. In recognition of this problem, the US National Instituteof Mental Health, in partnership with the US Food and Drug Administration andacademic partners developed the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) initiatives to attempt to establish a reliable, valid and consensus-derived method of assessing cognition, and improve the likelihood of successful development of new compounds that could be used alongside existing drugs to more effectively treat the cognitive and negative symptoms of schizophrenia.

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The MATRICS initiative identified seven core domains of cognition: working memory attention/vigilance, reasoning and problem solving, processing speed, visual learning and memory verbal learning and memory, and social cognition, that are deficient in schizophrenia which have to be treated to meet therapeutic needs and recommended a specific neuropsychological test battery to characterize these domains. A development of this initiative is the evaluation of the clinical relevance and predictive value of existing preclinical cognitive tasks and agreement for the need to develop a preclinical cognitive test battery to aid drug development (Hagan and Jones, 2005; Nuechterleinetal., 2005).

Flores co et al. (2005) suggested using two approaches in experimental animals: lesions or drugs to manipulate specific systems altered in schizophrenia and developing models with cognitive deficits that resemble those seen in the disorder, to improve translational reliability of data obtained. Young et al. (2009) extensively reviewed existing animal cognitive paradigms and critically appraised their translational relevance to the seven human cognitive domains identified as being affected in schizophrenia. However, such cognitive paradigms need to be examined, not just in normal healthy animals, but in credible validated models of the disorder which will be reviewed in this paper.

II. PHARMACOLOGIC MODELS

Pharmacologic animal models of schizophrenia are based on our current understanding of the alterations in various neurotransmitter systems. As such, these models generally have some degree of construct validity, although it is extremely limited given our poor understanding of the fundamental basis of thought and cognition. Also, as expected, these models suffer from limited face validity. In contrast, predictive validity, although somewhat variable, is often fairly good because most pharmacologic models involve the administration of drugs that induce or exacerbate schizophrenic symptoms in humans. Perhaps thebest known pharmacologic model, which is based on the dopamine hypothesis of schizophrenia, involves amphetamine administration

A. Dopamine

The dopamine (DA) hypothesis of schizophrenia proposes that dysfunction in DA neurotransmission is the underlying cause of the symptoms of the disorder. Specifically, hyperactivity of mesolimbic dopaminergic neurons is suggested to produce the positive symptoms of schizophrenia such as psychosis. A hypodopaminergic state in the frontal-cortical terminal fields of mesocortical DA neurons has also been pro-posed to be the basis of negative symptoms. Mesolimbic dopaminergic hyperactivity in schizophrenia may be maintained by pre- or post synaptic mechanisms. Evidence for pre synaptic hyper activity includes excess DA release in response to amphetamine and increased L-DOPA decarboxylase levels inschizophrenia. Further, amphetamine and related substances such as 3,4-methylenedioxymethampheta-mine (MDMA) have been shown to produce psychotic symptoms in healthy subjects. In addition, many patients with schizophrenia experience an exacerbation of psychotic symptoms in response to psycho stimulants such as amphetamine and methylphenidate at doses that are not psychotogenic to normal controls. Postsynaptic ally, an increased number of DA receptors or associated signal transduction elements could also result in heightened sensitivity to DA. Although initially classified into D1 and D2 receptors based on differing biochemical and pharmacological profiles these DA receptors are now recognized as 2 distinct receptor families. All typical antipsychotics are D2receptor antagonists, and there is a strong correlation between clinical efficacy (i.e., antipsychotic effect) and the degree of D2 receptor antagonism. Similarly, D2receptor density, as measured in post- mortem tissue and more recently in in-vivo brain imaging studies, has been reported to be increased in schizophrenia. However, the effects of long-term antipsychotic treatment on D2 receptors is a common confound in many of the earlier studies. Changes in other DA receptors have also been reported in schizophrenia, but many of these studies suffer from similar limitations. In animal studies, the administration of amphetamine and related psycho stimulants reliably stimulates behavioral alterations such as hyper locomotion and stereotypy. Although the relevance of these motor disturbances to those shown by patients with schizophrenia is debatable, their reliable expression allows for a comparison among animal models. Moreover, amphetamine- induced stereotypic behavior can be attenuated by treatment with antipsychotics, further supporting the validity of this model. The face validity of dopaminergic animal models is also supported by the disruptive effects of DA receptor agonists on PPI. PPI is a test of preattentional sensor motor gating, which is impaired in schizophrenia. Stimulus-evoked changes in PPI are similar in humans and rats, and the DA agonist apomorphine can disrupt PPI in both species, mimicking the PPI deficits observed in patients with schizophrenia. The administration of antipsychotic drugs can restore PPI function in rats treated with apomorphine, and this response has been correlated with both clinical antipsychotic potency and D2 receptor affinity. Interestingly, the atypical antipsychotic clozapine can also restore PPI in apomorphine treated rats. Although the mechanism of action of clozapine in this regards is unclear, it does not appear to support a direct D2-receptor-mediated effect as with apomorphine on PPI.

Finally, PPI can be disrupted in rats by the direct infusion of DA into the nucleus acumens (NAC), an effect which can be also blocked by antipsychotics,thus supporting some degree of both predictive and construct validity for this model.

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B. Glutamate

Non paranoid schizophrenia, especially when it includes negative symptoms, can perhaps be mimicked more faithfully by the administration of phencyclidine (PCP which appears to act predominantly on glutamatergic N- methyl-D-aspirate (NMDA) receptors.PCP and other NMDA receptor antagonists induce schizophrenic-like symptoms in healthy subjects and precipitate psychoses in patients with schizophrenia who have stabilized. This has led to the suggestion that schizophrenia may involve hypo function of NMDA receptors.

Long-term potentiating is disrupted by NMDA antagonists, and Kornhuber and colleagues report increased binding to NMDA receptors in post-mortem frontal cortex of patients with schizophrenia. Similarly, a decreased release of glutamate has been reported in the frontal and temporal cortices of patients with schizophrenia, as have higher blood concentrations of glycine, glutamate and serine. Reduced expression of non-NMDA glutamate receptor subtypes in the medial temporal lobe of patients has also been reported.

Glutamate may also be involved in schizophrenia through its interactions with DA subtle forms of excite toxicity or the developmental abnormality of cortical cortical connections. Repeated exposure to PCP has been reported to reduce both basal and evoked DA utilization in the monkey prefrontal cortex (PFC), an effect which persisted even after PCP treatment wasstopped.84 Taken together, these findings implicate altered glutamate neurotransmission and NMDA receptor function, in particular, in the negative and cognitive deficits observed in schizophrenia.

As in the case of DA receptor agonists, PCP administration can disrupt PPI and startle habituation in rats. Further, PCP and PCP-like drugs have also been shown to disrupt rat performance in the Morris water maze, 2-level alternation task and Y-maze brightness discrimination task. Altered social interactions have also been reported after treatments with PCP Moreover, PCP produces amphetamine-like effects in rodents, including increased loco motor activity, stereotyped movements, circling and ataxia, and these effects are attenuated by antipsychotics and 6-hydroxydopamine lesions of the meso limbic DA system. Repeated administration of PCP in monkeys also causes deficits in PFC-dependent tasks that can be ameliorated by the atypical antipsychotic clozapine. Taken together, these findings clearly support claims of face and predictive validity for this model, although construct validity remains difficult to ascertain, as with many current models of schizophrenia. Nevertheless, the glutamatergic basis of schizophrenia features prominently in many theories on the pathogenesis of this disorder, and the psychotropic effects of man neuro active agents are believed to involve direct effect on this system.

An important aspect of NMDA antagonist animal models is that many of the studies to date have involved single injections. The relevance of this mode of administration to the hypothesized persistent disruptions of glutamatergic systems in schizophrenia remains unclear.

C. Serotonin

The serotoninergic (5-HT) system has also been frequently implicated in schizophrenia. The 2 major classes of psychedelic hallucinogenic drugs, the indoleamines (e.g., lysergic acid diethylamide [LSD]) and phenethylamines (e.g., mescaline), are believed to mediate their effects through 5-HT2A receptors.

Polymorphisms of the 5-HT2A receptor gene are re-ported to be a minor risk factor for schizophrenia. A loss of PFC 5-HT2A receptors along with an accompanying increase in 5-HT1A receptors and a blunted neuroendocrineresponse to 5-HT2A agonists has been reported in schizophrenia. However, recent positron emission tomography studies have been somewhat equivocal in regard to 5-HT2A receptor changes in schizophrenia (for example, see Trichardtet al).Nevertheless, the relatively high affinity of atypical an-Tipsychotics such as clozapine for the 5-HT2A receptor supports a role of 5-HT systems in schizophrenia.

As in the case with dopaminergic and glutamatergic animal models, LSD has been shown to disrupt startle habituation and PPI in humans and rats. Further, this effect is believed to be mediated through direct stimulation of 5- HT2A receptors. Indeed, the disruptive effects of PCP on PPI have also been proposed to be mediated through indirect activation of 5-HT2A receptors. Interestingly, both LSD and mescaline have been shown to enhance glutamatergic transmission in rats. 5-HT3 receptor antagonists have also been shown to attenuate the behavioral hyperactivity caused by PCP as well as amphetamine administration but 5-HT3 receptor binding sites are not altered in schizophrenia and the efficacy of 5-HT3 antagonists in clinical trials of schizophrenia has been variable. Despite evidence for altered serotonergic markers in schizophrenia, there is comparatively little evidence of a primary dysfunction of serotonergic systems in this disorder. Moreover, the relevance of LSD administration in animal models is unclear; repeated administration of LSD in humans or animals leads to behavioral tolerance, unlike the situation in schizophrenia. Thus, despite some support for face and predictive validity in this model, construct validity remains as difficult to establish as in the DA and glutamate animal models.

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D. GABA

Alterations in γ-amino butyric acid (GABA) neurotransmission in the PFC of patients have also been pro-posed, on the basis of both theory and experimentalevidence. An interaction between dopaminergic and GABA ergic systems in schizophrenia is supported by the fact that GABA neurons in the middle layers of PFC receive direct synaptic input from DA terminals, exert inhibitory control over excitatory output of layer III pyramidal neurons and undergo substantial developmental changes in late adolescence, the typical age of onset for schizophrenia. Evidence for reduced GABA uptake sites in the temporal lobe, increased GABAA receptor binding in superficial layers of cingulated cortex and reduced gene expression for glutamic acid decarboxylase in the prefrontal cortex pro-vides direct support for GABA agric involvement in this disorder.

In animal studies, the GABAA receptor antagonist picrotoxin has been shown to reduce PPI in rats when injected into the medial PFC. Further, pre treatment with the DA antagonist haloperidol antagonized this effect, suggesting that blockade of GABA receptors in PFC impairs sensor motor gating in a DA- dependent manner. However, the lack of any other reported GABA-induced behavioral deficits related to schizophrenic symptoms makes the face and predictive validity of this model difficult to establish. Further studies are required to establish the relevance of GABA-based pharmacological models of schizophrenia.

III. LESION MODELS

There has been considerable debate over the years about whether schizophrenia could be considered a neurodegenerative or neuro developmental disorder. The clinical deterioration that occurs in some cases suggests that neurodegenerative processes maybe involved. Similarly, enlarged ventricles and decreased cortical volume may reflect an ongoing neurodegenerative process, but ventricular size does not seem to correlate with the duration of illness and appears to be present at the onset of symptoms, if not earlier. Moreover, this hypothesis suffers from both a lack of data supporting adult onset of pathologic cerebral changes and a lack of evidence of gliosis. Proliferation of glial cells is seen in most neurodegenerative conditions, and the absence of gliosis suggests that

Neuro pathologic events occurred before the responsively of glial cells to injury (i.e., before the third trimester of gestation). However, caution should be exercised in over interpreting the lack of data supporting gliosis because the linkbetween this injury marker and neuro degeneration remains unclear.

The neuro developmental theory of schizophrenia postulates that the pathogenic conditions leading to schizophrenia occur in the middle stage of intrauterine life, long before the formal onset of symptoms. Damage before this time would affect neurogenesis and thus lead to severe structural and cellular cortical abnormalities, which are not observed in schizophrenia. Further support for the theory is provided by reports of minor physical anomalies, based on the assumption that pre- or prenatal pathologic events may also lead to more visible physical abnormalities.

Abnormal limb length and angle, fingerprint pattern sand ridge counts and webbed digits have been re-ported in schizophrenia. Some studies also suggest the existence of premorbid neurologic abnormalities such as motor function and attention.

Some animal models of schizophrenia, based on the concept of pre- or prenatal insults, suggest that various obstetric complications (e.g., genetic, ischemic, hemorrhagic, infectious agents) could result in abnormalities in pruning, cell death and developmental connectivity; However, such injuries are typically characterized by gliosis and are difficult to reconcile with the cytoarchitectural changes seen in schizophrenia.

The nature of delivery complications also varies considerably between studies, making comparisons difficult. Nevertheless, studies of cesarean delivery and prenatal hypoxia or anoxia in rats have shown in-creased dopaminergic hyper responsively to psycho stimulants and stress. Further, the effect has been shown to depend on the genetic background of the animal. Although these models provide some degree of validity, further research is required to determine the potential mechanism(s) of action of obstetric complications in schizophrenia. To address some of the issues surrounding progressive neuro developmental or neuro degenerative changes in schizophrenia, a number of targeted lesion animal models have been developed. Although these can take the form of electrolytic or aspiration lesions, they more typically involve excite toxic agents, which destroy neuronal tissue through stimulation of excitatory glutamate release or by acting as direct glutamate receptor agonists.

Given the evidence for the involvement of the PFC in schizophrenia, it is not surprising that this region has drawn a lot of interest in lesion studies. The PFC is involved in higher cognitive functions such as attention, working memory, emotional expression and social interaction. Hypo function of dopaminergic projections at the level of the dorsolateral PFC, in particular, has been implicated in the metabolic hypofrontality seen in patients with schizophrenia. Moreover, the role of this region in regulating sub cortical DA activity makes PFC lesions particularly amenable to study in the current behavioral testing paradigms validated in pharmacological models of schizophrenia.

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Lesions of the adult rat PFC result in an enduring hyper-responsiveness to stress, as well as transient increases in loco motor exploration and amphetamine-induced stereotypy. As well, adult rats with PFC lesions show reduced PPI after apomorphine injections and reduced cataleptic response to haloperidol, suggesting that postsynaptic striatal DA neurotransmission is increased.
The hippocampus formation has also received a great deal of experimental attention because this region modulates PFC activity, especially at the level of its projections to the NAC. Thus, it exerts direct control over the mesolimbic dopaminergic system, believed to be affected in schizophrenia. Aspiration lesions of the hippocampus in adult rats have been reported to selectively increase loco motor behavior after amphetamine or DA receptor agonist administration. Interestingly, excitotoxic lesions of the dorsal hippocampus (DH) and ventral hippocampus (VH) produce different behavioral profiles, with DH lesions having no effect on amphetamine-induced locomotion and VHlesions resulting in increased spontaneous and DA-agonist-induced loco motor activity. The behavioral changes induced by VH lesions have been detected approximately 2 weeks postoperatively. However, these rats do not show PPI deficits in the absence of apomorphine or exaggerated locomotion in responseto stress. As well, they exhibit a decrease in stereotypic behaviors.

IV. NEONATAL LESION MODELS

A number of neonatal lesion models have also been developed to testneuro developmental theories of schizophrenia. One of the principal advantages of these models is the ability to demonstrate a delayed onset of symptoms that corresponds to the clinical presentation of schizophrenia in humans. For example, Goldman first showed that prenatal ablations of the PFC did not impair performance on a delayed response task until after adolescence. One possible explanation for this post pubertal emergence is that other brain regions compensate for damage before puberty, but by adolescence the brain becomes developmentally committed to use the cortex for this activity. This interpretation is consistent with data suggesting that limb abnormalities evident in schizophrenia are associated with an early developmental injury that does not manifest until adulthood. Previously, in rats that received PFC lesions as neonates, we reported a post-pubertal increase in loco motor activity in response to amphetamine and stress, with concomitant changes in DA receptors and DA release in the NAC Although discrepant data have been reported, the behavioral and biochemical profile of these animals remains to be fully characterized. In contrast, most of the research on neonatal lesion models of schizophrenia has focused on the VH. This is not surprising given the major roleof this region in regulating sub cortical DA. Rats with neonatal excitotoxic lesions of the VH demonstrate delayed onset of hyperdopaminergic behaviors. Although these animals are behaviorally similar to controls at postnatal day (PD), post pubertally at PD they display increased locomotion in response to novelty, forced swim stress and after saline or amphetamine injection. Interestingly, these behavioral effects are not observed after neonatal DH lesions. The post pubertal changes induced by neonatal VH lesions are believed to be the result of increased mesolimbic DA function but reduced DA release. The PD rats also exhibit reduced haloperidol induced catalepsy and enhanced apomorphine-induced stereotypies. As in the case of dopaminergic pharmacological models, rats with VH neonatal lesions also show impaired PPI. Further, the behavioral deficits exhibited by these animals are ameliorated after antipsychotic administration. Neonatal VH lesions also cause disturbed latent inhibition comparable to that seen in patients with schizophrenia. In terms of negative symptoms of schizophrenia, alterations in social interaction and increased aggressive behavior have also been reported in rats' wit neonatal VH lesions. However, deficits in social interaction are present both pre- and postpubertally. Further, the atypical antipsychotic clozapine had no effect on social interaction deficits despite ameliorating Hyper locomotion in this model. The source of these social interaction deficits is unclear but does not appear to involve anxiety; there were no differences observed between rats with lesions and control rats in the elevated plus maze. Interestingly, lesions of the VH in adult rats have no effect on social behavior, suggesting that lesion-induced impairments are of a neuro developmental nature. These findings are not limitedto rodent studies; similar results have also been obtained in primates withprenatal lesions of the medial temporal lobe, where greater deficits in loco motor activity and social interaction were observed with prenatal than with adult lesions. Interestingly, ICV clinic acid administration in pre weanling rats has also been reported to produce predominantly delayed neuronal loss in the hippocampus, unlike the immediate effects observed with adult lesions. One possibility for the post pubertal emergence of symptoms in the VH model may be a delayed effect on the dopaminergic system that occurs later in life. Both hippocampus physiology and the dopaminergic system are influenced by sexual maturation and related hormonal changes. It is also possible that the VH lesion affects the development of other neural systems, such as the PFC, which regulates meso limbic DA activity during stress. Interestingly, PFC physiology is immature pre pubertal and continues to develop into adulthood. In support of the theory of hypoactive glutamatergic function in the PFC in schizophrenia, increased specific glutamate binding and decreased as partate release in the frontal cortex of adult rats after neonatal VH lesions has been reported. As well, Bernstein et al found reduced numbers of neuron sand increased immune staining for ornithine decarboxylase and nitric oxide synthesis in the PFC.

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V. DRUG TREATMENT

Effective pharmacologic treatment of schizophrenia has been available since the 1950s. In the early 1950s, the term “neuroleptic” was introduced to denote the effects of chlorpromazine (Thorazine; brand no longer available in the United States) and reserpine on laboratory animals. It was intended to distinguish their effects from those of sedatives and other central nervoussystem depressants. Although “neuroleptic” is still used syn Ominously with “antipsychotic,” the term now usually refers to first-generation antipsychotics that confer an increased risk of extra pyramidal side effects, such as dystonic reactions (e.g., fixed upper gaze, neck twisting, facial muscle spasms), parkinsonian symptoms (e.g., rigidity, bradykinesia, shuffling gait, tremor), and akathisia (e.g., inability to sit still, restlessness, tapping of feet). Tardive dyskinesia, which is a chronic disorder of the nervous system characterized by involuntary jerking movements (primarily of the face, tongue, and jaw), often is considered an extra pyramidal side effect. However, it is actually a separate and mechanistically different phenomenon.

VI. SIGN AND SYMPTOMS

Schizophrenia changes how you think, feel, and act. It might affect you differentlyfrom someone else. The symptoms can come and go, too. No one has all of them all of the time. They usually start between ages 16 and 30. Men often get them earlier than women. Oftentimes there is a gradual change in the person before obvious symptoms start. This is sometimes called the prodrome phase.

A. Positive Symptoms of Schizophrenia

Things That Might Start Happening Positive symptoms are highly exaggerated ideas, perceptions, or actions that showthe person can’t tell what’s real from what isn’t. Here the word "positive" meansthe presence (rather than absence) of symptoms. They can include:

1) *Hallucinations:* People with schizophrenia might hear, see, smell, or feel things no one else does. The types of hallucinations in schizophrenia include:
2) *Auditory:* The person most often hears voices in their head. They might be angry or urgent and demand that they do things. It can sound like one voiceor many. They might whisper, murmur, or be angry and demanding.
3) *Visual:* Someone might see lights, objects, people, or patterns. Often it’s loved ones or friends who are no longer alive. They may also have trouble with depth perception and distance.
4) *Olfactory and Gustatory:* This can include good and bad smells and tastes. Someone might believe they’re being poisoned and refuse to eat.
5) *Tactile:* This creates a feeling of things moving on your body, like hands or insects.
6) *Delusions:* These are beliefs that seem strange to most people and are easy to prove wrong. The person affected might think someone is trying to control their brain through TVs or that the FBI is out to get them. They might believe they're someone else, like a famous actor or the president, or that they have superpowers. Types of delusions include:
7) *Persecutory Delusions:* The feeling someone is after you or that you’re being stalked, hunted, framed, or tricked.
8) *Referential Delusions:* When a person believes that public forms of communication, like song lyrics or a gesture from a TV host, are a special message just for them.

B. Negative Symptoms of Schizophrenia

Things That Might Stop Happening Negative symptoms refer to an absence or lack of normal mental function involving thinking, behavior, and perception. You might notice:

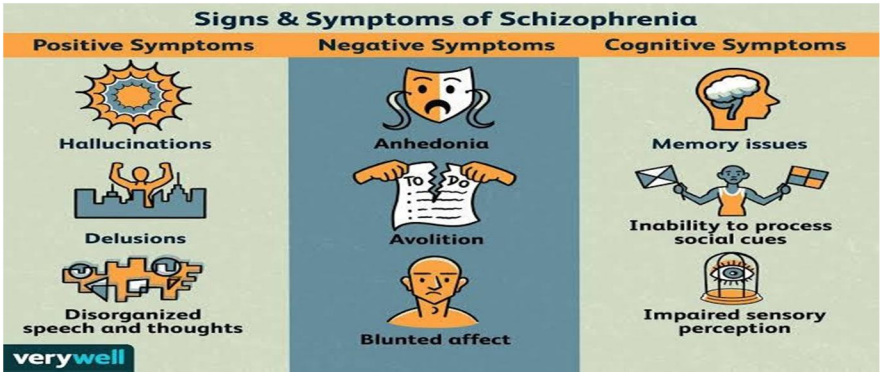


Fig-1-Sign And Symptom

1) *Lack of pleasure:* The person may not seem to enjoy anything anymore. A doctor will call this anhedonia.
2) *Trouble with Speech:* They might not talk much or show any feelings. Doctors call this alogia.
3) *Flattening:* The person with schizophrenia might seem like they have a terrible case of the blahs. When they talk, their voice can sound flat, like they have no emotions. They may not smile normally or show usual facial emotions in response to conversations or things happening around them. A doctor might call this affective flattening.
4) *Withdrawal:* This might include no longer making plans with friends or becoming a hermit. Talking to the person can feel like pulling teeth: If you want an answer, you have to really work to pry it out of them. Doctors call this apathy.

C. Cognitive Symptoms & Thinking Problems

These symptoms reflect how well the person's brain learns, stores, and uses information.

Someone with schizophrenia might have a hard time with their working memory. For example, they may not be able to keep track of different kinds of facts at the same time, like a phone number plus instructions.

Along with having trouble paying attention, it can be hard for them toorganize their thoughts and make decisions.

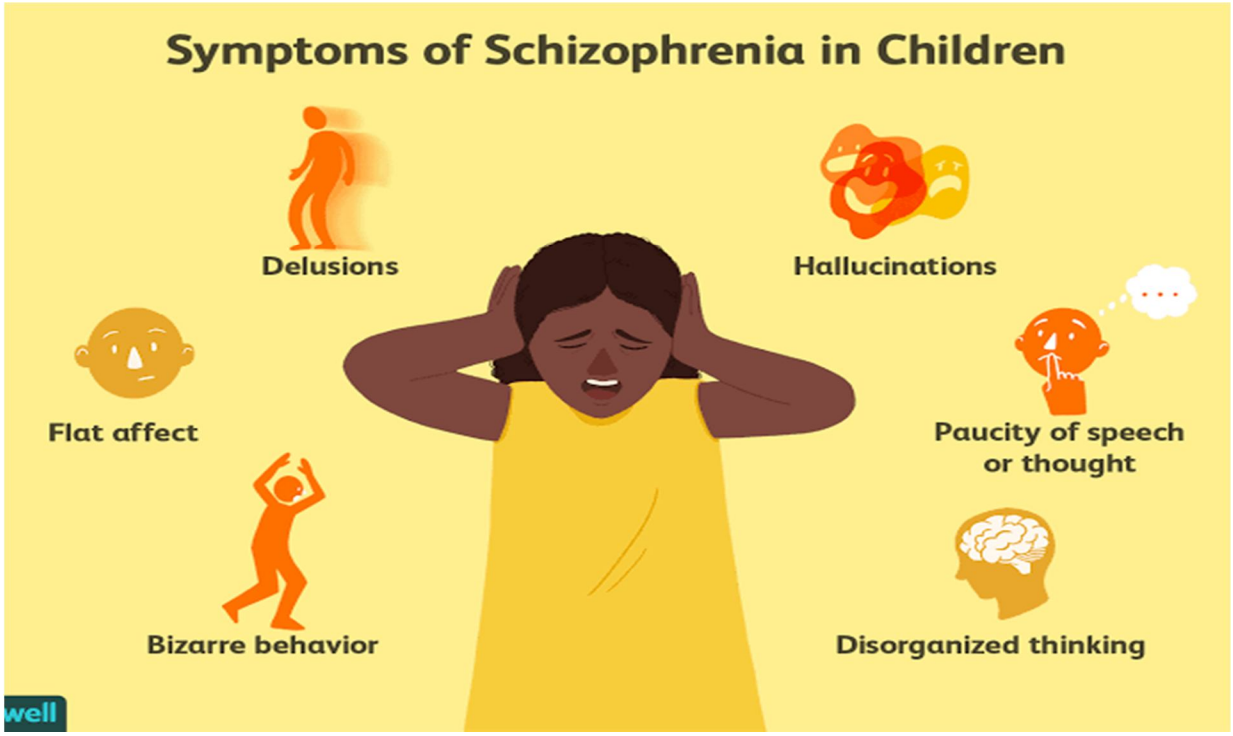


Fig-2-Sign And Symptoms in Children

VII. TYPES OF ANTIPSYCHOTIC MEDICATIONS

There are two groups of antipsychotics. Doctors call the older group ofmedications "first-generation," "typical," or "conventional" antipsychotics.

Some common ones are:

1) Chlorpromazine (Thorazine)
2) Fluphenazine (Prolixin)
3) Haloperidol (Haldol)
4) Perphenazine (Trilafon)
5) Thioridazine (Mellaril)
6) Thiothixene (Navane)
7) Trifluoperazine (Stelazine)

The newer ones are called "second-generation" or "atypical" antipsychotics.

Examples of these medicines include

a) Aripiprazole (Abilify)
b) Aripiprazole lauroxil (Aristada)
c) Asenapine (Saphris)
d) Brexpiprazole (Rexulti)
e) Cariprazine (Vraylar)
f) Clozapine (Clozaril)
g) Iloperidone (Fanapt)
h) Lumateperonee (Caplyta)
i) Lurasidone (Latuda)
j) Olanzapine (Zyprexa)
k) Olanzapine/samidorphan (Lybalvi)
l) Paliperidone (Invega Sustenna)
m) Paliperidone palmitate (Invega Trinza)
n) Quetiapine (Seroquel)
o) Risperidone (Risperdal)
p) Ziprasidone (Geodon)

VIII. SIDE EFFECTS

While the first-generation, older meds usually cost less, they can have different side effects than the newer antipsychotics. Some can cause higher levels of the hormone prolactin. This can affect sex drive, mood, menstrual cycles, and growth of breast tissue in both men and women. One of the common side effects of many of the newer antipsychotics is weight gain. You may also have trouble keeping your blood sugar and cholesterol levels under control.

One of the more serious side effects from long-term use of both the older and newer medications is a movement disorder called tardive dyskinesia. It makes your facial, tongue, and neck muscles move uncontrollably and can be permanent.

While both older and newer antipsychotics can cause tardive dyskinesia, researchers believe that the odds are higher with the older antipsychotics.

Antipsychotics come with other side effects as well. You could have any ofthe following:

1) Weight gain
2) Sexual problems
3) Drowsiness
4) Dizziness
5) Restlessness
6) Dry mouth
7) Constipation
8) Nausea
9) Blurred vision
10) Low blood pressure
11) Seizures

IX. PSYCHOSOCIAL TREATMENTS

Individual, group, and family treatments have been developed as therapies for persons with schizophrenia. Family interventions include therapy with individual families, psycho education with groups of families, and family group therapy. These interventions offer support, education about the illness, and options for reducing critical and emotionally over involved attitudes and behaviors toward the patients. Family treatments have the most empiric support for improving symptoms and reducing hospitalizations. These treatments are based on early findings that family environments that were high in “expressed emotion” (either critical and rejecting or emotionally over involved) were associated with relapse in patients with schizophrenia. Multiple studies have shown that family interventions reduce relapse rates and improve symptoms, adherence to medications, and functioning. However, a recent review suggested that there are weaknesses in many family intervention studies, and that there is a need for additional investigation.

There are several psychosocial rehabilitative interventions that have been shown to be effective in improving the quality of life in patients with schizophrenia. The

Intensive Psychiatric Rehabilitation Treatment, which is a program that teaches living, job, and social skills to patients, has resulted in improvements in functioning. Social skills training has improved independent living skills; supported employment programs have shown improvements in the number of hours worked and total wages earned; and in-home crisis intervention demonstrates promise by reducing treatment drop-out rates.

Studies have shown that individual cognitive behavior therapy for schizophrenia reduces positive and negative symptoms, but currently there is no evidence that it reduces relapse rates.

X. RESULTS

The two randomly selected groups did not differ from each other on any sociodemographic or clinical variables at baseline (Table I). Throughout the study, 80% of the OCM patients received a mean dose of 12.5 mg/day of olanzapine, 20% received the equivalent mean dose of 15 mg/day of haloperidol or another fi rst-generation anti-psychotic medication. In comparison, 75% of the RCM patients received a mean dose of 15 mg/day of olanzapine, and 25% received the equivalent mean dose of 15 mg/day of haloperidol or another fi rst-generation drug. Pharmacotherapy was therefore very similar for both groups and there was no signifi cant difference between two groups in terms of antipsychotic dosages.

	OCM $N = 50$	RCM $N = 50$	Statistical significance
Age: mean years (sd)	28.8 (7.4)	28.5 (7.7)	ns
Sex: male (%)	31 (62%)	35 (70%)	ns
Marital status: married (%)	20 (40%	20 (40%)	ns
Education: mean years (sd)	11.8 (2.6)	10.9 (3.2)	ns
Occupation:			
Student (%)	17(34%)	16 (32%)	
Housewife (%)	4 (8%)	4 (8%)	
Blue collar (%)	17 (34%)	14 (28%)	
Professional (%)	5 (10%)	6 (12%)	
Unemployed (%)	7 (14%)	10 (20%)	ns
Household			
Parental (%)	27 (54%)	28 (56%)	ns
Duration of disorder: mean years (SD)	5.2 (3.2)	5.5 (3.6)	ns
Age of onset: mean years (SD)	27.2 (16.3)	24.4 (6.7)	ns
Schizophrenia subtype			
Paranoid (%)	23 (46%)	21 (42%)	
Disorganized (%)	13 (26%)	18 (36%)	
Undifferentiated (%)	9 (18%)	5 (10%)	
Residual (%)	5 (10%)	6 (12%)	ns

Although the intention-to-treat policy included noncompliers in the data analysis, there were differences in the two groups regarding noncompliers and drop-outs. Those who did not attend two consecutive appointments after 3 months were reported as dropouts. Either partial or full noncompliance was identifi ed depending on whether patients refused any treatment or refused only some treatment. Three cases (6%) in the OCM cohort did not complete the 24-month evaluation. One of the three dropped out after moving to another part of the country, and the other two were partially noncompliant. These partial noncompliers expressed negative past experiences with medications and refused to take pills fromtime totime. Nine cases (18%) in the RCM group did not complete the 24-month evaluation. These schizophrenia patients were full non- compliers and did not attend two consecutive appointments.

XI. CONCLUSION

This review describes and quantifies the findings of 200 literature reviews assessing the humanistic burden of schizophrenia. This review focused specifically on schizophrenia, but it is likely that most of the dimensions of humanistic burden considered could also be discussed more generally in the context of psychiatric disorders. It has been shown that schizophrenia is associated with a broad humanistic burden, which needs to be considered appropriately; it is then of importance to consider the broader context in order to optimize clinical and social outcomes fromtreatment.

The humanistic burden in schizophrenia is considerable, and concernsnot only the patient but also his/her surrounding environment: caregiver burden remains considerable and treatment side effects have to be taken into consideration in the management of schizophrenia. Depression negatively affects the course of the disease, often with fatal consequences. Its management and the social reintegration of patients are a challenge for professionals.

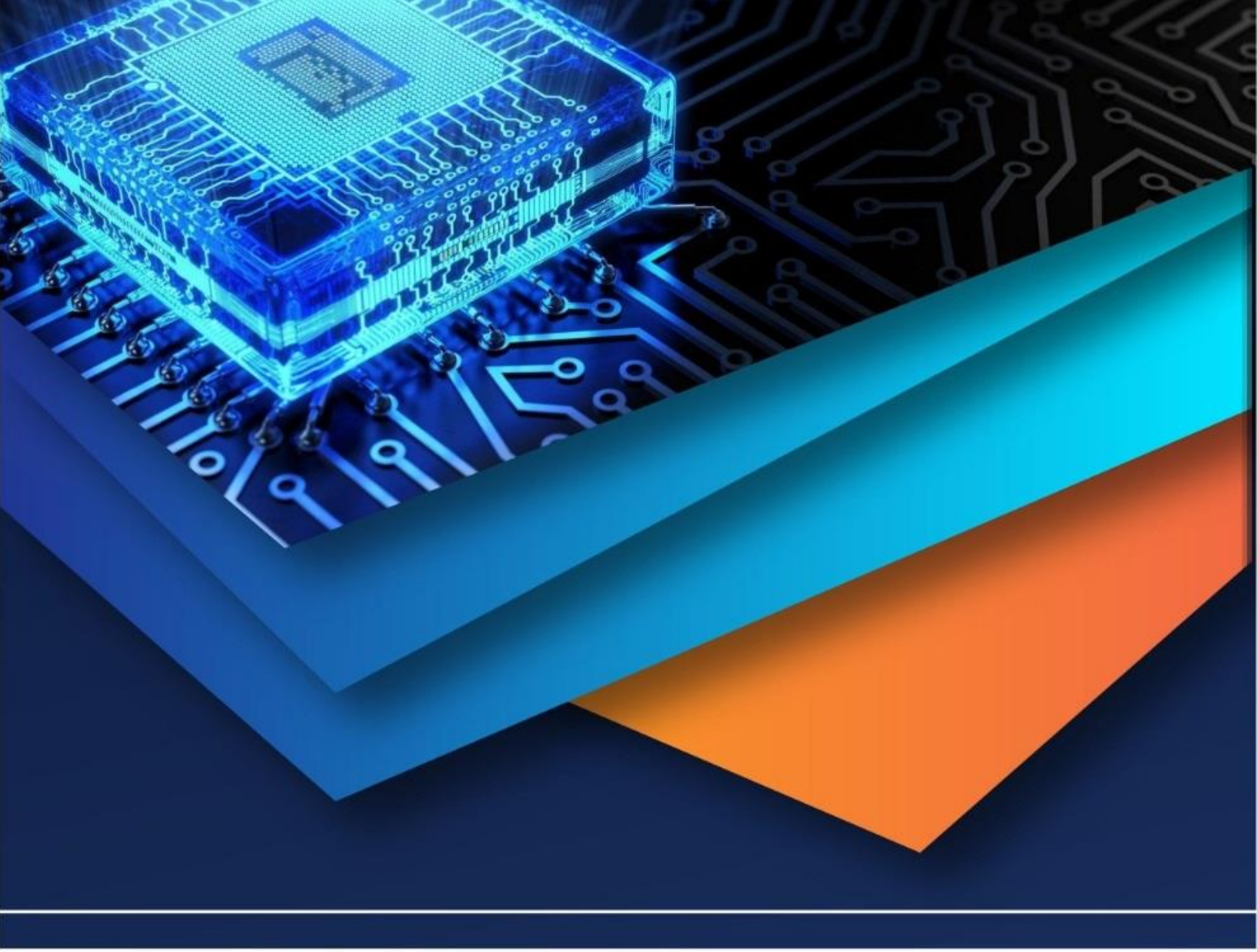
Cognitive impairment is known to add to the disease burden, and as a core symptom and specific disorder of schizophrenia, this neuropsychological dysfunction must be precisely defined and targeted for remediation if patients are to be treated effectively. The related social impairment is worsened by an underestimated stigmatization and lack of corresponding awareness within the professional and social bodies. Early intervention and action to reduce stigmatization helps to re-socialize patients and their families. Family education related to disease progression and the necessary interventions and treatments could be important family-related supports.

Lifestyle, morbidity and mortality in schizophrenia are also indicators of the overall burden of the disease; quality of life and other social aspects of a patient's life can be significantly degraded if they are not taken into account as part of antipsychotic treatment.

Mortality is mainly due to suicide, and although the main causes of suicide are known, the treatments are very complex and are not always successful. There is a need, especially in young patients, to implement prevention programs addressing social isolation, substance abuse, depression, hopelessness and disappointment about lowered expectations for the future.

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