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Schizophrenia: Its Complications and Treatments

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Abstract:- Schizophrenia affects a person ability to think, feel and behave clearly. Schizophrenia characterized by disorganize speech or behavior, decrease participation in daily activities, difficulties in concentration and memory. Causes of schizophrenia are still unknown so treatment focuses on eliminating the symptoms of the disease. This article summarizes the mechanisms of action of antipsychotics with respect to the treatment of schizophrenia. There are many different medications and types of therapy and support that can be used to eliminate different symptoms of schizophrenia. The most effective treatment for schizophrenia is a combination of using antipsychotic medications and therapeutic and social support. There is no one best treatment for this mental illness that causes hallucinations, delusions, disorganized thoughts, and other symptoms that make life challenging, but most patients respond well to this combination.

Keywords:- *Schizophrenia, Antipsychotics, Cognitive Deficit & Treatment, Dopamine.*

I. INTRODUCTION TO SEIZOPHRENIA

Schizophrenia is a serious mental disorder which affect a person's ability to perceive the world around them, Most people with untreated schizophrenia hear voices or see things that aren't there. They may also have false beliefs about the world that vary in content, but share the common characteristic of being untrue. Language, Perception, Thinking, Volition, Social activity are affected in schizophrenia. The etiology of schizophrenia is complex and it involves neurodevlopemental, environmental and psychological functions.

The symptoms of schizophrenia fall into three categories positive symptoms, negative symptoms and cognitive symptoms.

"Positive" symptoms of schizophrenia include psychotic behaviors which are not generally seen in healthy teenagers. Hallucinations (distortion of reality), Delusions (false beliefs, they are not based on reality), Thought disorders (unusual or dysfunctional ways of thinking),movement disorders (agitated body movements)

"Negative" symptoms are associated with disruptions to normal emotions and behaviors. This include reduce facial expression & voice tone, reduction of excitement in everyday life, difficulty in beginning and strengthen activities& reduce speaking are also the symptoms seen in schizophrenia.

Cognitive symptoms are difficult to analyze in few patient but in other severe symptoms are notice associated with schizophrenia, symptoms include time inability, inability to make decisions, problem in concentration, poor working of memory function.

Most people who have schizophrenia do not experience a total disappearance of symptoms. However, this disorder can be managed by a combination of different psychosocial therapies and medications.

II. ETIOLOGY OF SEIZOPHRENIA

The exact causes schizophrenia of still unknown, etiology of schizophrenia include combination of different physical factor, genetic factor, drug abuse, neurotransmitter, pregnancy and birth complications.

- **Genetic factor**: If both parents affect with, risk of schizophrenia is greater in offspring. Monozygotic twins are more susceptible than dizygotic tweens.
- **Physical factor**: physiological conditions not cause schizophrenia, they only trigger in its development. The main psychological trigger of schizophrenia are stressful life event such as divorce, physical, emotional & sexual abuse, loosing home and loosing family .
- **Drug Abuse:** Misuse of drugs increases the risk of developing schizophrenia or similar illness.
- **Neurotransmitter:** Dopamine and Serotonin are two neurotransmitter present in brain, change in level of this neurotransmitter causes schizophrenia.
- **Pregnancy and birth complications:** Low birth weights of child, premature labor, lack of oxygen during birth are also the causes of Schizophrenia. [1]

III. CLASSIFICATION OF SCHIZOPHRENIA

- **Paratinoid schizophrenia:** patient act on things may be extreme and behave oddly, have inappropriate emotional responses and show little pleasure in life
- **Cationic schizophrenia:** The person shuts down emotionally, mentally and physically. "People appear to be
- **Undiffentiated schizophrenia:** The patient shows various vague symptoms. "They might be talk or express themselves much. They can be confused and paranoid
- **Schizoaffective disorders:** The person suffering from mood disorders ,mania,depression.[2]

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IV. PATHOPHYSIOLOGY OF SEIZOPHRENIA

The individual having symptoms associated with schizophrenia are similar to "**Dementia Praecox"** disease which is discovered by dr. kraepelin**.** [3]. Various neuropathologists are fail to find causes of schizophrenia, so some famous neurologist's said that "Schizophrenia is the graveyard of neuropathologists" [4].

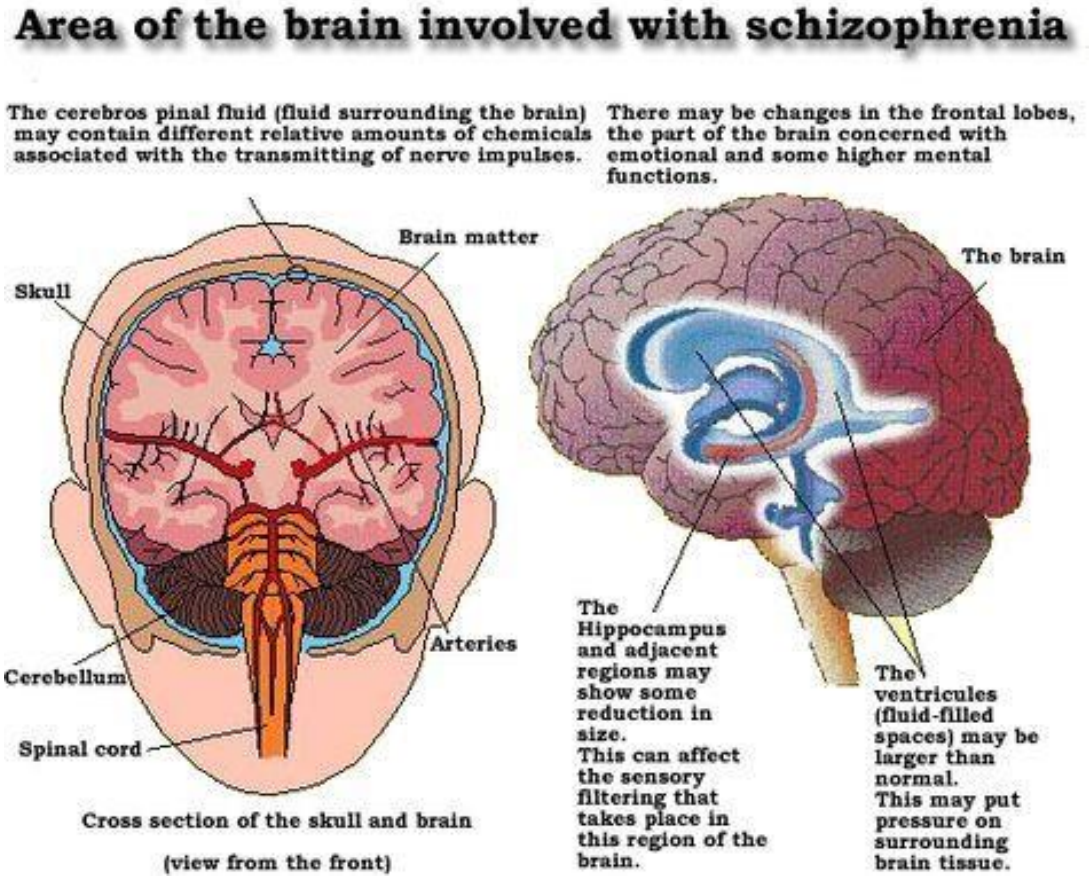

Fig 1:- Area of Brain Associated with Pathophysiology of Schizophrenia.[5]

There are several parts of brain that are affected in patients with schizophrenia such as prefrontal cortex, visual and auditory cortices. Basal ganglia, hippocampus, other medial Temporal and limbic regions [6]

- **Prefrontal cortex:** it involves in memory encoding
- **Hippocampus**: It is located in temporal region and responsible for memory functions.
- **Visual& Auditory Cortices**: responsible for facilitate language, also associated with memory & emotions.
- **Basal Ganglia:** Balance of muscle activation, voluntary motor functioning and rapid actions are associated with basal ganglia**.**

This disorder is more complex than originally suppose, it involves combination of genetic and abnormalities related to neurotransmitter such as Dopamine, Glutamate, and Serotonine. Most of theories of pathophysiology of schizophrenia based on excess or a deficiency of neurotransmitters, including dopamine, serotonin, and glutamate. Other theories based on aspartate, glycine, and gamma-amino butyric acid (GABA) as part of the neurochemical imbalance of schizophrenia.[**7]**

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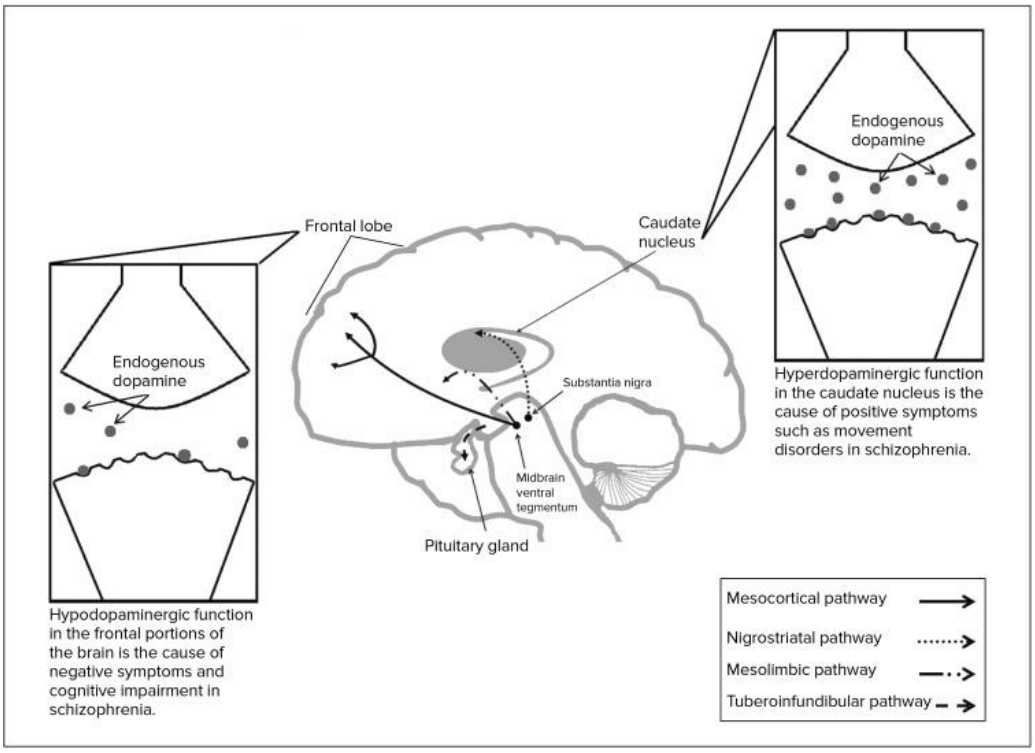

Fig 2:- Pathophysiology of schizophrenia [8]

There are 4 major dopamine pathways.

- **Mesocortical pathway** is dopaminergic pathway connects ventral tegmentum to prefrontal areas.
- **Nigrostriatal pathway** that connects substancia nigra with dorsal striatum.
- **Mesolimbic pathway** connects ventral areas of midbrain to ventral areas of forebrain.
- **Teberoin fundibular** pathway connects infundibular nucleus to hypothalamus.

V. KEY FACTS IN THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

A. Abnormalities in Brain Structure:

- Ventricular enlargement – excess fluid in the brain gradually enlarges the ventricle. [9]
- Subtle reductions in total gray matter volume-lack of grey matter, psychotics have lower grey matter than healthy people [10]
- Reductions in gray matter volume of the hippocampus and other medial

Temporal and limbic regions- hippocampus is a part of limbic system & plays an important role in consolidation from short term memory to long term memory. Grey mater reduction also takes place in hippocampus, medial temporal and limbic regions.[11]

B. Abnormalities in Brain Functions:

- Hypofrontality- It is a state of decrease cerebral blood flow in the prefrontal cortex it leads into decreased activation of prefrontal cortex- auditory with middle and superior temporal cortex. [12]
- Increased activation of temporal regions during hallucinations –auditory hallucinations associated with middle and superior cortex. [13]
- Electrophysiological abnormalities-abnormalities in electrophysiological activities were seen in Schizophrenia.
- Diminished prepulse inhibition of startle response – Prepulse inhibition of startle reflex response state the ability of weak Prestimulus to transiently inhibit the response to strong sensory stimulus. [14]
- Abnormalities in gamma oscillations-Brain Areas related to visual, motor and cognitive information processing are accompanied by gamma oscillations. [15]

C. Oxidative, Immunological Neuroendocrine Dysfunctions

- Clinical status of markers of oxidative stress is elevated [16]
- Abnormal dexamethasone suppression takes place and it is responsible for dysfunction of the hypothalamic–pituitary–adrenal axis [17, 18]
- Inflammatory response of cytokines increases abnormally [19]

D. Neuropathology

- Size of pyramidal neurons and dendritic spines Reduces. [20]
- Relative preservation of total number of neurons [21]
- The absence of gliosis and other neurodegenerative features [22 , 21]
- Reduced expression of GAD-67 in the dorsolateral prefrontal cortex [23]

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E. Neurochemical

- N –acetyl aspartate reduces in frontal and temporal regions of brain [24]
- PME (marker of membrane phospholipid synthesis) reduces in prefrontal Regions [25]
- Presynaptic dopamine function elevated [24]

VI. CLASSIFICATION OF ANTIPSYCHOTICS

Generation	First generation (Typical Antipsychotics)			Second generation (Atypical Antipsychotic)	Third generation (atypical Antipsychotics)
Drug	Butyrophenones	Phenothiazines	Thioxanthenes	Clozapine	
	Haloperidol	Chlorpromazine	Chlorprothixene	Olanzapine	Aripiprazole
	Droperidol	Fluphenazine	Clopenthixol	Risperidone	
		Perphenazine	Flupenthixol	Quetiapin	
		Prochlorperazine	Thiothixene	Ziprasidone	
		Thioridazine	Zuclopenthixol	Amisulpride	
		Trifluoperazine		Asenapine	
		Mesoridazine		Paliperidone	
		Periciazine		Iloperidone	
		Promazine		Zotepine	
		Triflupromazine		Sertindole	
		Levomepromazine		Lurasidone	
		Promethazine			
		Cyamemazine			
		Pimozide			

Table 1:- Classification of Antipsychotic Drugs with Reference to Schizophrenia [26]

VII. TREATMENT OF SCHIZOPHRENIA

Schizophrenia is usually treated with combination of therapy and medicine. Most people with schizophrenia are treated by community mental health teams .The goal of this team to provide day-to-day support and treatment while ensuring you have as much independence as possible. This team can be made up of community mental health nurses, pharmacists, ounselors and psychotherapists ,psychologists and psychiatrists.

Current Forms of Treatment: First-Generation Antipsychotics and Second-Generation Antipsychotics [27]

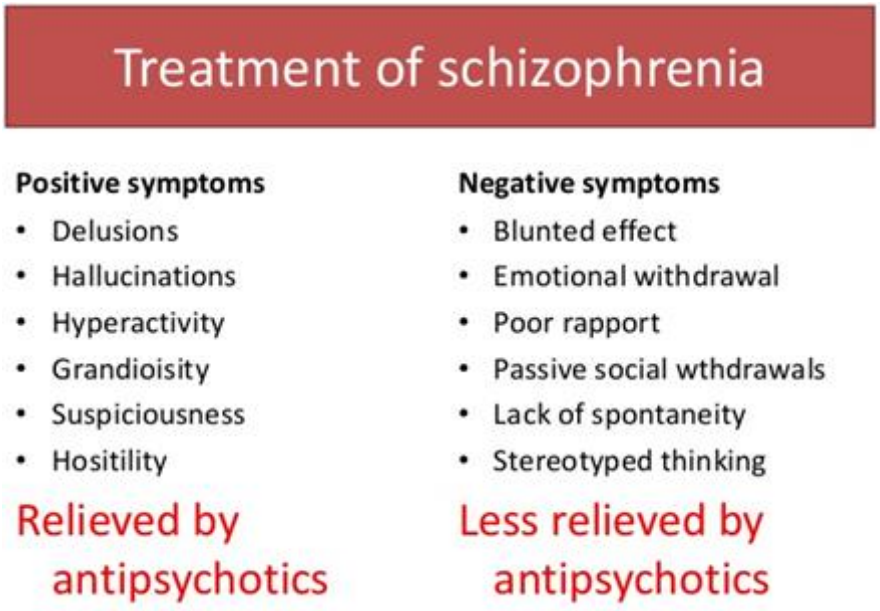

Fig 3

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VIII. CLINICAL PHARMACOLOGICAL PROFILES OF ANTIPSYCHOTIC DRUG

Antipsychotic Drug Classes: Potencies and Toxicities

Chemical Class	Drug	Potency	Extrapyramidal Effects	Sedation	Alpha blockade: hypotension
Phenothiazine: aliphatic	Chlorpromazine (Thorazine)	1	3	4	4
Phenothiazine: piperazine	Fluphenazine (Prolixin)	4	4	2	1
Thioxanthene	Thiothixene (Navane)	4	3	3	3
Butyrophenone	Haloperidol (Haldol)	4	5	2	1
Dibenzodiazepine	Clozapine (Clozaril)	3	1	2	3
Thienobenzodiazepine	Olanzapine (Zyprexa)	4	1	3	1

Table 2:- Antipsychotic Drugs with their Extra Pyramidal Effect, Potency, Sedation [28]

1-low, 5-very high

IX. FUTURE STRATEGIES FOR DRUG DEVELOPMENT IN SCHIZOPHRENIA

Dopamine plays a important role in psychiatric and movement disorder. In schizophrenia tied to hallucinations and delusions, that's why brain area become overactive. Antipsychotic drugs stop this over activity .Development of new generation antipsychotics start from clozapin. The D_2 receptor [Dopamine receptor] very important in development of antipsychotics drug and act as Holy Grail for the development of antipsychotics. therapeutic mechanism of psychosis is represent by D_2 receptor by reducing neurotransmission.[29,30,31,32,33,34] . By studding the complexity of schizophrenia and diversities in the symptoms, it seems logical to develop compound with at least a small moiety with affinity to D_2 receptor. Another strategy is to developed single-target-agent. This single-target-agent increases the activity of multitarget agent. Until the pathophysiology of schizophrenia fully explained the mystery of single-target-agent versus multitarget agent will remain in most important position in development of antipsychotics drug.

According to all above studies current and future drug development strategies described below:

- Remove unwanted moiety of previously develop antipsychotics to modify mechanisms of action to provide drugs with high efficacy.
- Development of antipsychotics drug with novel mechanism.
- Development of drug particularly associated with those symptoms of schizophrenia which are not eliminated by traditional antipsychotic drugs. antipsychotics drug
- There is need to focus on cognitive enhancing drugs.[35]

Hypothesis of impairment of an individual's mental processes in schizophrenia separately implicate dopaminergic, cholinergic, noradrenergic, serotonergic, glutamatergic deficits. This neurotransmitter actually involves in dysfunctoning. To overcome this dysfunctoning creative approaches are necessary. [32]

One more approach to the future strategy of treatment of schizophrenia is development of those drugs which are specifically target the prefrontal cortex, medial temporal region and limbic association area. Preclinical and clinical studies of drug action on specific brain regions is very important in developing such a drug.[36]. Some neuropathologist done important progress in identifying various susceptibility genes associated with schizophrenia. Susceptibility genes includes neureglin1 (NRG1), dysbindin (DTNBP1), regulator of g protein signaling 4(RGS4), catechol–o –methyl transferase (COMT).[37]

Identification of individual treatment plan is necessary to optimize development of novel method. Cytochrome P450 (CYP) is the enzymes which affect the metabolism of antipsychotics, due to this efficacy and tolerability of antipsychotics is directly affected, to improve this development of genetic test for prediction of drug response and side effect is more important in treatment of schizophrenia.[38]

Proper treatment of schizophrenia require focus on early detection and early intervention.[39] pathophysiological changes occur in cortical and subcortical brain regions in patients with schizophrenia associated with disease progression, clinical deterioration and functional decline.[40] In early intervention aimed at lack of confidence or reversing progressive pathophysiological processes in schizophrenia could yield

substantial improvements in outcomes in the future. Therefore, there is need of more sensitive and specific diagnostic tools as well as safe and effective interventions[41]

X. CONCLUSION

Schizophrenia is a serious mental disorder results in hallucinations, delusions, thought and movement disorder, time inability. Dopamine hyperactivity, a strong genetic link and utero disturbance in pregnancy are etiological factors associated with schizophrenia. Antipsychotics are generally used to minimize symptoms of schizophrenia. Psychotherapy and pharmacotherapy are the best treatment option for schizophrenia. Future strategy for treatment of schizophrenia is development of cognitive enhancing drugs and development of antipsychotics with novel mechanism of action.

REFERENCES

[1]. https://www.pharmacology2000.com/Central/psychotics/Antipsy_obj1.htm
[2]. https://www.medicalnewstoday.com/articles/192770.php#classification_and_diagnosis
[3]. Kraepelin E. Dementia Praecox and Paraphrenia, 1919. Robertson G, editor. New York: RE Krieger; 1971.
[4]. Plum F. Prospects for research on schizophrenia. 3. Neurophysiology. Neuropath logical findings. Neurosci Res Program Bull. 1972;10(4):384–8.
[5]. https://www.google.com/search?q=areas+of+brain+involved+in+schizophrenia&source=lnms&tbm=isch&sa=X&ved
[6]. Shepherd AM, Laurens KR, Matheson SL, Carr VJ, Gree MJ. Systematic meta-review and Quality assessment of the structural brain alterations in schizophrenia. Neurosci Biobehav Rev. 2012;36(4):1342–56
[7]. Lavretsky H. History of Schizophrenia as a Psychiatric Disorder. In: Mueser KT, Jeste DV, editors. Clinical Handbook of Schizophrenia. New York, New York: Guilford Press; 2008. pp. 3–12.
[8]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4159061
[9]. Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet. 1976;2(7992):924–6.
[10]. Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET. Meta- analysis of regional brain volumes in schizophrenia. Am J Psychiatry. 2000;157(1):16–25
[11]. Shepherd AM, Laurens KR, Matheson SL, Carr VJ, Green MJ. Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. Neurosci Biobehav Rev. 2012;36(4):1342–56.
[12]. Berman KF, Meyer-Lindenberg A. Functional brain imaging studies in schizophrenia. In: Charney D, Nestler E, editors. Neurobiology of mental illness. 2nd ed. Oxford, MA: Oxford University Press; 2004
[13]. Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. Am J Psychiatry. 2011;168(1): 73–81.
[14]. Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology (Berl). 2001;156(2–3):234–58.
[15]. Kwon JS, O'Donnell BF, Wallenstein GV, Greene RW, Hirayasu Y, Nestor PG, et al. Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. Arch Gen Psychiatry. 1999;56(11):1001–5
[16]. Flatow J, Buckley P, Miller BJ. Meta-analysis of oxidative stress in schizophrenia. Biol Psychiatry. 2013;74(6):400–9.
[17]. Yeragani VK. The incidence of abnormal dexamethasone suppression in schizophrenia: a review and a meta-analytic comparison with the incidence in normal controls. Can J Psychiatry. 1990;35(2):128–32.
[18]. Phillips LJ, McGorry PD, Garner B, Thompson KN, Pantelis C, Wood SJ, et al. Stress, the hippocampus and the hypothalamic-pituitary-adrenal axis: implications for the development of psychotic disorders. Aust N Z J Psychiatry. 2006;40(9):725–41.
[19]. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry. 2011;70(7): 663–71.
[20]. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch Gen Psychiatry. 2000;57(1):65–73
[21]. Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain. 1999;122(Pt 4):593–624
[22]. Piper M, Beneyto M, Burne TH, Eyles DW, Lewis DA, McGrath JJ. The neurodevelopmental hypothesis of schizophrenia: convergent clues from epidemiology and neuropathology. Psychiatr Clin North Am. 2012;35(3):571–84
[23]. Akbarian S, Kim JJ, Potkin SG, Hagman JO, Tafazzoli A, Bunney WE, et al. Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenics. Arch Gen Psychiatry. 1995;52(4):258–66.
[24]. Brugger S, Davis JM, Leucht S, Stone JM. Proton magnetic resonance spectroscopy and illness stage in schizophrenia—a systematic review and meta-analysis. Biol Psychiatry. 2011;69(5):495–503.
[25]. Smesny S, Rosburg T, Nenadic I, Fenk KP, Kunstmann S, Rzanny R, et al. Metabolic mapping using 2D 31P-MR spectroscopy reveals frontal and thalamic metabolic abnormalities in schizophrenia. Neuroimage. 2007;35(2):729–37.

[26]. https://www.google.com/search?q=classification+of+antipsychotic+drugs&source=lnms&tbm=isch&sa=X&ved=2ahUKEwi2j6OQpcHmAhXdwjgGHUVdDjQQ_AUoAXoECA4QAw&biw=1366&bi
[27]. https://image.slidesharecdn.com/antipsychotics-160502063014/95/antipsychotics-19-638.jpg?cb=1462170719
[28]. Antipsychotic Agents and Lithium, in Basic and Clinical Pharmacology, Appleton-Lange, 1998, p 468.
[29]. Kim DH, Maneen MJ, Stahl SM . Building a better antipsychotic: receptor targets for the treatment of multiple symptom dimensions of schizophrenia. *Neurotherapeutics* 2009; **6**: 78–85
[30]. Kim DH, Stahl SM . Antipsychotic drug development. *Curr Top Behav Neurosci* 2010; **4**: 123–139.
[31]. Emsley R . Drugs in development for the treatment of schizophrenia. *Expert Opin Investig Drugs* 2009; **18**: 1103–1118.
[32]. Agid O, Kapur S, Remington G . Emerging drugs for schizophrenia. *Expert Opin Emerg Drugs* 2008; **13**: 479–495.
[33]. Roth BL, Sheffler DJ, Kroeze WK . Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. *Nat Rev Drug Discov* 2004; **3**: 353–359.
[34]. Stahl SM . Multifunctional drugs: a novel concept for psychopharmacology. *CNS Spectr* 2009; **14**: 71–73.
[35]. Carter CS, Barch DM . Cognitive neuroscience-based approaches to measuring and improving treatment effects on cognition in schizophrenia: the CNTRICS initiative. *Schizophr Bull* 2007; **33**: 1131–1137.
[36]. Hill SK, Bishop JR, Palumbo D, Sweeney JA . Effect of second-generation antipsychotics on cognition: current issues and future challenges. *Expert Rev Neurother* 2010; **10**: 43–57.
[37]. Carpenter WT, Koenig JI . The evolution of drug development in schizophrenia: past issues and future opportunities. *Neuropsychopharmacology* 2008; **33**: 2061–2079.
[38]. Arranz MJ, de Leon J . Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. *Mol Psychiatry* 2007; **12**: 707–747.
[39]. Marrs W, Kuperman J, Avedian T, Roth RH, Jentsch JD . Alpha-2 adrenoceptor activation inhibits phencyclidine-induced deficits of spatial working memory in rats. *Neuropsychopharmacology* 2005; **30**: 1500–1510.
[40]. Lieberman JA, Bymaster FP, Meltzer HY, Deutch AY, Duncan GE, Marx CE *et al*. Antipsychotic drugs: comparison in animal models of efficacy, neurotransmitter regulation, and neuroprotection. *Pharmacol Rev* 2008; **60**: 358–403.
[41]. Insel TR . Rethinking schizophrenia. *Nature* 2010; **468**: 187–193.