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RESEARCH ARTICLE

SCHIZOPHRENIA: CAUSES, TREATMENTS AND NEGATIVE SYMPTOMS

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Abstract

Schizophrenia, although it is a disorder that is widely known to the general public, is a condition that is generally misunderstood by the population at large as it is extensively more complicated than just hallucinations; less extravagant symptoms such as negative symptoms, for example, are lesser known. Furthermore, the causes, factors and their interactions which lead to the development of the disorder is not totally clear and is still being researched to this day. However, theories and models such as the dopamine and glutamate hypothesis have developed as more studies have been conducted. Although a general guideline for treatment methods exist in terms of pharmacology and psychology, they are not equally effective to all patients and are not available to many; full recoveries are rare. Following this, this article seeks to summarize and clarify the facets of schizophrenia, especially that of the negative symptoms domain, along with possible causes, the known factors which affect the development of schizophrenia and the current treatment methods available.

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Introduction:-

Schizophrenia, a psychotic disorder which affects roughly 1% of the population (Cardno and Gottesman, 2000; Sullivan et al., 2003), is characterized by three main symptom domains: positive, negative and cognitive. The widely known symptoms of schizophrenia such as hallucinations (visual, auditory, etc.), delusions (grandeur, paranoia, etc.) and agitation are categorized as positive symptoms (Javitt and Coyle, 2004). However, negative symptoms, consisting of alogia, amotivation, blunted affect, anhedonia and a sociality (Kirkpatrick and Fenton, Carpenter Jr. and Marder 2006), are lesser known. Symptoms such as having difficulties in abstract thinking, deficits in memory and problem solving skills are also considered cognitive symptoms.

The conceptualization of schizophrenia has varied over the time period after the recognition of the disorder. Initial ideas of schizophrenia were proposed by Emil Krapelin, terming the disease dementia praecox as he viewed the course of the disorder as one which worsens over time, similar to the course of dementia; the disorder was then later renamed to schizophrenia by Eugen Bleuler (Jobe and Harrow, 2010). In the beginning, there were two main approaches to the disorder: disjointed mental functions caused by negative psychosocial factors and diminished brain functions (Walker and Tessner, 2008). The modern perception of schizophrenia, the diathesis-stress model, developed after the inclusion of the genetic approach to the disorder along with the combining of bioenvironmental and psychosocial factors as environmental factors (Walker and Tessner, 2008).

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Focusing on negative symptoms, the five main symptoms can be grouped to form two symptom factors of diminished expression and avolition/apathy (Galderisi, Mucci, Buchanan, Arango, 2018; Kirkpatrick and Fischer, 2006; Messenger, Tremeau and Antonius, 2011); diminished expression includes blunted affect and alogia while avolition/apathy consists of asociality avolition and anhedonia. Symptoms in the diminished expression factor are identified with an overall reduction in the expression of emotions (facial expressions, hand gestures during conversations, emphasizing specific words when speaking, etc.) Avolition on the other hand indicates a general diminution of motivation and goal-directed behavior.

Furthermore, negative symptoms can be classified into primary and secondary negative symptoms. Negative symptoms which are intrinsic, chronic and persistent are deemed primary symptoms while secondary symptoms are caused by other factors such as side-effects of medication or social isolation caused by positive symptoms (Barnes and Paton, 2011). Treatment methods in general usually have low effectiveness in improving primary symptoms, be it with antipsychotics (Chan, Chang, Chiang, Chen, Chen and Sun, 2010), other forms of medication such as antidepressants (Cerveri, Gesi and Mencacci, 2019) or with non pharmacological methods (Bitter, 2021).

Body

History of conceptualization

Ever since the initial recognition of schizophrenia as a mental disorder in the late 1800s and early 1900s, the conceptualization and understanding of it in domains such as its origins, what characteristics should be included and treatment methods have changed greatly. This change can be mostly attributed to research on the illness which has not only increased in quantity but also in quality. Initially, schizophrenia, or dementia praecox as it was known at the time, was understood in two different ways: as a problem of mental processes resulting from psychosocial dysfunction or as a problem of the brain’s functioning (Walker and Tessner, 2008). Focusing on the psychosocial hypothesis, it theorizes that psychotic symptoms rose from mental strifes which an individual has repressed and the symptoms are symbolic of these conflicts. However, this was not supported by research results.

Following this, characterisation of schizophrenia turned to the neuropsychological approach where researchers connected regions of the brain with symptoms of the disorder. For example, Heaton, Baade, & Johnson, 1978 found that damage to the frontal or temporal lobes in non-schizophrenic patients led them to show similarities to those with schizophrenia such as psychosis.

As more research progress was made, the idea of genetics was introduced to schizophrenia. Large contributors to this were twin studies and adoption studies. In twin studies, the concordance rates of monozygotic and dizygotic twins which have schizophrenia are compared; the results typically show higher rates in monozygotic twins than in dizygotic twins (Walker and Tessner, 2008). In adoption studies, children who have parent(s) with schizophrenia are raised in an adoptive family and their rate of schizophrenia is compared with adopted children without schizophrenic biological parent(s). In these studies, those with schizophrenic biological parent(s) are more likely to develop schizophrenia themselves. What these studies show is that schizophrenia has a genetic aspect to its cause. Although there is a genetic component, it is almost certain that multiple genes all contribute to the development of a heightened risk for schizophrenia (Gottesman, 1991).

Following this, the diathesis-stress model developed. In this model, it is theorized that genetic factors increase the predisposition to the illness. The chances of those with a predisposition to then develop schizophrenia are increased by negative life events. An example of research supporting the model is Tienari et al. (1987) which found that adopted children with schizophrenic biological parents are more likely to develop schizophrenia when their adopted family has considerable problems.

More factors such as bioenvironmental and neurodevelopmental factors are then incorporated into a model based on the diathesis-stress model. An important bioenvironmental factor are the prenatal elements. Kunugi, Nanko, and Murray, 2001 posit that prenatal problems and issues during delivery are linked with schizophrenia while Huttunen and Niskanen, 1978 also show that children of mothers that had psychological and social stresses during pregnancy had an increased risk of developing schizophrenia. Other factors such as older parent age at conception (Wohl & Gorwood, 2007), low birth weight (Cannon et al., 2002), the mother having an infection when pregnant (Brown and Derkits, 2010), the mother being malnourished during pregnancy (Brown and Susser, 2008) and the mother being stressed (going through significant life events) during pregnancy (Khashan et al. 2008) are also linked to schizophrenia.

All of these developments lead to the current concept of schizophrenia. Pre and postnatal events together form the acquired inherent components, genetics form the inherited inherent components which together form the predisposition. Environmental stresses and neurological development then act upon the predisposition to increase the likelihood of the outcome of the disorder's development; genetics set the stage while environmental stresses catalyze.

Symptom Domains

In the symptomatology of schizophrenia, there are three distinct domains: positive, negative and cognitive symptoms. Within each domain, there are further categorizations of specific symptoms, each with differing levels of prevalence. Positive symptoms are characterized by the perception of experiences without actual stimuli. These include hallucinations (auditory, visual, etc), delusions and paranoia, for example. Within positive symptoms, not all symptoms are equally common. For example, Rahim and Kareem, 2017 found that within their cohort, delusions were the most common while hostility was the least. Cognitive symptoms on the other hand are characterized by symptoms such as disorganized thought patterns, cognitive deficits within domains such as memory and problem solving and difficulties with learning. Lastly, negative symptoms are classified as diminished expression and apathy. Within these two categories are specific symptoms: diminished expression contains blunted affect and alogia while apathy contains avolition, asociality and anhedonia.

Course and Outcomes

The overall course of schizophrenia and improvements in symptoms is debatable as some sources, such as Lilienfeld and Arkowitz, 2010, suggests that when treatment is received there are considerable improvements while others such as Harrow, Sands, Silverstein, and Goldberg, 1997, Harrow, Jobe, and Astrachan-Fletcher, 2008 propose that there is a "poor long-term course." Furthermore, there are factors that predict a worse outcome: worse cognitive skills, drug abuse, long periods of time where the illness is not treated (Harrow, Jobe, and Astrachan-Fletcher, 2008), developmental issues before schizophrenia onset (Zigler and Glick, 2001) and an insidious onset instead of an acute one (Vaillant, 1978). However, since schizophrenia is a heterogeneous disorder with most aspects such as severity of symptoms and functional outcome and being distributed in a range, the overall course is difficult to pin down.

Some evidence suggests that there are subtypes of schizophrenia. One such subtype is deficit schizophrenia, proposed by Kirkpatrick, 2001. Within deficit schizophrenia, patients have more enduring symptoms, opposed to episodes of symptoms with higher intensity which is more common (Harrow and Jobe, 2010). Those with deficit schizophrenia tend to have a more insidious onset (Fenton and McGlashan, 1992), worse functioning both before the onset of the first psychotic episode (Fenton and McGlashan, 1994; Kirkpatrick, Ram and Bromet, 1996) and after a lengthy period of time in follow-ups (Fenton and McGlashan, 1991, Fenton and McGlashan, 1994). There is also evidence to suggest that childhood-onset of schizophrenia typically results in a worse outcome in the long run. However, schizophrenia in children is rare, affecting roughly 0.025% of the population, and difficult to diagnose (Collins and Fay, 2016). The overlap in the appearance of positive symptoms and children's imaginative play and psychotic symptoms being possible in other mental disorders in children makes the diagnosis process very challenging. Furthermore, Collins and Fay, 2016 illustrates that a multitude of predictive signs of childhood-onset schizophrenia overlaps with a variety of other disorders including bipolar disorder, major depression and ADHD as well; withdrawal from social interactions can also be seen as symptoms of major depression or autism spectrum disorder while issues with cognitive abilities may also be attributed to intellectual disability. Lastly, due to the children being in the process of development, changes to their personality can be misinterpreted as being due to the volatile nature of children. These factors then make diagnosis of childhood-onset of schizophrenia especially challenging and the associated worse outcome makes it very demanding to deal with.

Negative symptoms

Specificity of symptoms

From the previously mentioned negative symptoms, each symptom has further details that are quite specific. One of the symptoms, blunted affect, characterizes an overall diminished amount of emotional expression. Evidence for the symptom comes from studies which have looked at how patients act and interact with their doctors (Brune, Sonntag, Abdel-Hamid et al., 2008; Kupper, Ramseyer, Hoffmann et al., 2010; Lavelle, Healey, McCabe, 2013). Furthermore, blunted affect is not a side effect of medication as it is seen in patients that are being treated with antipsychotics and those that are not (Aghevli, Blanchard and Horan, 2003). Another symptom, alogia, is a decrease in the amount of speech. Alogia is associated with pauses between speaking rather than a decrease in the amount of

words said although it also is diminished (Cohen et al, 2014). Moreover, there is also a relationship between alogia and a worse outcome on tests of verbal fluency (Bowie, Harvey, Moriarty et al., 2004) which may be explained by a lessened ability of those with schizophrenia to recall information (Docherty, Berenbaum and Kerns, 2011). Therefore, it takes longer to produce speech hence the pauses. However, an alternative explanation to this proposed by Cohen et al, 2014 is that a large amount of cognitive resources is needed for speech which schizophrenic patients may not have, resulting in less speech. Asociality is another key negative symptom which is described as a decrease in social interactions, relationships and motivation to have social interactions. Although outwardly it can be a secondary negative symptom due to medication side effects or due to worsening positive symptoms resulting in social withdrawal, it is still regarded as a symptom on its own. This is likely due to asociality many times being present before the onset of the psychotic episode and the subsequent drug treatment (Cannon, Jones, Gilvarry et al. 1997). Therefore, the possibility that it is always caused by side effects as a consequence of positive symptoms is eliminated. A possible pathway to asociality is that the individual with schizophrenia believes that attempts toward social interactions would either not be successful or are not rewarding, leading to a decrease in motivation to form social connections (Beck, Grant, Huh et al., 2013). Anhedonia, another crucial aspect of negative symptoms, is identified with a decrease in the ability to feel positive emotions. However, there is more nuance to this symptom than what meets the eye. Anhedonia is not associated with the inability to feel positive emotions in the moment of engaging in pleasant activities but is instead associated with a decrease in the ability to anticipate that they will experience these feelings in the future (Gard, Kring and Gard et al., 2007). Lastly, there is avolition which is identified with a decrease in motivation and goal-directed behaviors. Avolition is linked to the worsened ability of the patient to function in real life (Harvey, Koren and Reichenberg et al., 2006). This possibly is due to avolition leading to diminished participation in activities which would lead to a positive outcome such as finding and improving at an occupation. A model for avolition is that it is caused by impairments in the individual's ability to anticipate future rewards (Juckel, Schlagenhauf and Koslowski et al., 2006); a model where schizophrenia patients are less willing to work towards receiving a reward is also of interest (Barch, Treadway and Schoen, 2014).

Significance in Course and Functional Outcome

Negative symptoms can be observed before the onset of the first psychotic episode in the period called the prodromal phase (an der Hieder and Hafner, 2000). As time passes, negative symptoms tend to increase, level off and linger. Following from this, more severe negative symptoms are associated with worse social functional outcomes as those with schizophrenia are impaired in a variety of social skills (Mueser, Bellack, Douglas and Morrison, 1991) and functional outcomes in general (Fervaha, Foussias, Agid and Remington, 2014). However, it is not exactly clear as sources differ in their conclusion of whether the course of negative symptoms vary much over time or not (Austin, Mors, Budtz-Jorgensen et al., 2015).

Social Cognition

Social cognition and negative symptoms such as avolition are linked (Marder and Galderisi, 2017) as that they are both linked to functional outcomes (Foussias, Agid, Fervaha and Remington, 2014 (2)); lack of motivation to engage socially is part of avolition. In schizophrenia, social cognition is typically impaired. Emotional processing is one of the areas of social cognition. It is the ability to perceive, manage and classify emotions; affect perception is often assessed in studies of schizophrenia. Another area is social perception which is identified with the ability to perceive social rules, social cues, roles and relationships. Additionally, typically measured by questionnaires, attribution bias is a domain which is characterized by the ability to connect events to their causes (caused by the situation, other people, oneself, etc). Lastly, there is the theory of mind which is the ability to recognize others' intentions. Measures of theory of mind can include testing the understanding of things such as sarcasm by organizing pictures into a comprehensible order. Deficits in the theory of mind have also been shown by Bora et al., 2007 to be linked to the patients' lack of understanding of their own illness. The explanation proposed was that insight into one's own illness comes from being able to observe oneself from the perspective of others, an ability that is impaired in schizophrenia.

Causes

Although schizophrenia is an illness where multiple factors contribute to the etiology, models have been developed as possible pathways to the onset of schizophrenia such as the dopamine hypothesis. Moreover, there has been research into factors that are associated with an increased risk for schizophrenia. For example, prenatal factors and genetics.

Dopamine hypothesis

The dopamine hypothesis is one of the most popular and long-lasting models of the cause of schizophrenia. Essentially, it posits that schizophrenia is caused by an abnormally high level of dopamine. However, as further research into schizophrenia has been conducted, this hypothesis' accuracy is also called into question.

One of the pieces of evidence for the dopamine hypothesis is that antipsychotic medications act upon the D_2 receptor, a receptor for dopamine (Seeman, Chau-Wong, Tedesco and Wong, 1975). According to Seeman and Kapur, 2000, there is a strong link between the ability of a drug to inhibit the D_2 receptor and its effectiveness in reducing symptoms; therefore, it can be theorized that the D_2 receptor is a factor which underlies schizophrenia as a whole. Additional support for this model is also provided by studies such as Abi-Dargham, et al., 2000 illustrating that schizophrenia patients have an increased number of D_2 receptors compared to the control group; this is observable once the level of endogenous dopamine has been decreased and observable ligands given to patients were able to bind to more D_2 receptors which were previously occupied by dopamine. Abi-Dargham goes on to further elaborate dopamine's link to schizophrenia in her 2004 article. In the article, she concludes that there is an "excess of dopamine subcortically and presumably a deficit of dopamine cortically." Another connection between schizophrenia and dopamine is made through the observation that taking amphetamines which in large quantities produces positive symptoms that are identical to those of schizophrenia (Coyle, 2012). Overall, there can be seen that there is an undeniable link between schizophrenia and dopamine, although the specificities of dopamine's role is still being investigated

However, as previously mentioned, the dopamine hypothesis is not without criticism. A major criticism of the model is that it accounts for mostly positive symptoms and does not explain the negative symptoms and cognitive deficits facets of schizophrenia. Since the psychosis in schizophrenia appears in episodes while negative and cognitive symptoms are more persistent, the dopamine hypothesis is missing significant pieces.

Genetics factors

In addition to the above criticisms, genetic research into schizophrenia has also called into question the validity of the dopamine hypothesis. As Cardno and Gottesman, 2000 pointed out, there is a clear genetic component to schizophrenia: first degree relatives of a schizophrenia patient have up to a 10 times increase in the probability that they will develop the illness. Though previously mentioned twin and adoption studies provide solid evidence, further research has been conducted to attempt to identify the specific genes responsible for schizophrenia. Due to multiple genes contributing to the etiology, further research is done with the use of association studies which better identify alleles with smaller effects (Risch and Merikangas, 1996). Association studies use the complete genome to identify genes that are associated with a particular condition and according to Nieratschker, Northern and Rietzschel, 2010, 24 variations of 16 genes have been demonstrated to be noteworthy by 118 meta-analyses. Nieratschker, Northern and Rietzschel, 2010 then go on to further theorize that dopamine dysfunction is a consequence of the genetic factors. Overall, genetic studies are able to provide further insight into the complicated etiology of schizophrenia even though the specific ways which different genes lead to the illness' development are still being investigated.

Developmental factors

As previously discussed in the History of conceptualization section, there are occurrences during a person's development, pre and postnatal, which affects the development of schizophrenia.

Focusing on endogenous facets, King, St-Hilaire and Heidkamp, 2010 summarise that the two factors are problems during birth and pregnancy and the age of parents. In terms of issues during birth and pregnancy, those that encountered them have roughly twice the probability to have schizophrenia (Cannon, Hones and Murray, 2002). The reason for this may be due to these issues causing a lowered amount of oxygen received by a child, which would adversely affect their neurological development; support of this hypothesis is also found in Cannon, Hones and Murray, 2002's finding that asphyxia is one of the complications associated with schizophrenia. Turning to the age of the parents, Wohl and Gorwood, 2007 illustrated that the chance of a child having schizophrenia increased 25 times as the father's age increased, from 35 to 55 years old. A possible explanation is that as more time passes, more mutations accumulate in the sperm cells.

With exogenous facets, there are a larger variety of factors compared to the endogenous ones, many of which are without as clear of an explanation. A factor is the birth season: Torrey, Miller, Rawlings and Yolken, 1997 found that those who have schizophrenia, compared to the general population, are 5 to 8% more likely to have been born in

winter and early spring. Additionally, being born in a metropolitan and busy area is demonstrated by Tandon, Keshavan and Nasrallah, 2008 to increase the probability of developing schizophrenia by 2.4 times. Other factors are concerned with the mother's health at the time of pregnancy such as the mother and fetus' nutrition, the experiencing of stressful life events and having an infection such as influenza. Nutrition's link to schizophrenia is suggested to be due to the lack of certain nutrients increasing the number of mutations or hindering the development of the fetus' nervous system in the case of malnutrition. With overeating, it may be explained by the potential experiencing of issues with metabolism (King, St-Hilaire and Heidkamp, 2010). In terms of stressful life events, support has been shown by both human studies and animal studies: the death of a relative during pregnancy has been shown by Hutten and Niskanen, 1978 to increase the risk for schizophrenia by 67%. In animal studies, the experience of stressful events increases the concentration of stress hormones in the mother's blood which passes into the fetus through the placenta. Consequently, there are enduring changes to the fetus' brain. The encompassing theme with exogenous factors seems to be that they alter the development of the nervous system in some way. However, these factors are not linked to only schizophrenia but also a variety of other mental disorders , such as bipolar, cerebral palsy and lowered IQ (Kunugi, Nanko and Murray, 2001) as well and so they individually are not outright causes.

NMDA receptors and glutamate

Recently, an interest in glutamate and its receptor, the NMDA receptor, in the pathway and treatment of schizophrenia has developed. A main contributor to this is the ability of NMDA receptor antagonists, such as PCP and ketamine, to induce psychosis and hallucinations (Allen and Young, 1978). Further evidence provided by postmortem studies such as Schwarcz et al. 2001 and Tsai et al. 1995 showed that a possible explanation of the role of NMDA receptors is that there is a higher level of antagonists of NMDA receptors in those with schizophrenia.

The actual way in which glutamate and the NMDA receptor lead to schizophrenia is complicated though a summary is provided by Abi-Dargham, 2004. Overall, in the brain, the glutamatergic neurons in the ventral tegmental area (VTA) are able to excite dopamine neurons while the GABAergic neurons act to decrease their activity; in the healthy population these two systems are roughly equal in activity and there is little change in dopamine levels. When the inhibitory system is inadequate, there are effects on the subcortical transmission of dopamine. In schizophrenia where there is an increase in the dopamine level there is not sufficient inhibition to bring the dopamine level back down to normal. However, there may, at the same time, be not enough activity of mesocortical dopamine, meaning that the D_1 receptor found in the cortex does not receive enough stimulation. Since the D_1 receptor is involved in memory, insufficient stimulation leads to deficits in memory which are observed in schizophrenia. Furthermore, cortical dopamine activity has been demonstrated by Pycock, Kerwin and Carter, 1980 to inhibit subcortical dopamine activity. Therefore, a decrease in cortical dopamine activity may lead to an increase in subcortical dopamine activity. One such as in the nigrostriatal pathway where the many D_2 receptors are found. This would then have an overall result of an increase in the subcortical dopamine and a decrease in the cortical dopamine levels. In terms of treatments, clinical trials showed that when NMDA receptors' functioning is improved, there is a decrease in schizophrenia's symptoms (Tsai and Lin, 2010). Evidence also shows that certain genes, such as the one that codes for the mGluR3 receptor, that are involved in NMDA and glutamate functioning and pathways are linked to schizophrenia (Coyle, 2006)

Treatments

Pharmacological Treatment

Since psychosis is a major symptom in schizophrenia, antipsychotics are the main medical treatment. Antipsychotics, as previously mentioned, typically work by inhibiting dopamine receptors. In general, atypical antipsychotics are able to treat positive symptoms well (Breier et al., 1994). However, treatments with other medications such as antidepressants also have been investigated. In terms of antipsychotics, clozapine is one of the most popular. Clozapine along with other atypical antipsychotics such as olanzapine and risperidone are effective in reducing positive symptoms and negative symptoms to some degree. Although there is a reduction in negative symptoms, this may have been caused by a reduction in positive symptoms and clozapine's low extrapyramidal effects (Carbon and Correll, 2014) and in general, antipsychotics are restricted in their ability to treat negative and cognitive symptoms (Leucht, Komossa and Rummel-Kluge, et al. 2009).

In terms of the treatment of those with more severe negative symptoms, a meta-analysis of 21 randomized-controlled trials was conducted by Krause and colleagues in 2017. The study found amisulpride to be more effective than placebo, cariprazine to be more effective than risperidone and olanzapine being more effective than

haloperidol. Though amisulpride was the only antipsychotic to show improvements more than the placebo. This further reinforces the notion that antipsychotics have limited abilities to treat negative symptoms.

Due to individual responses to antipsychotics varying, a combination of multiple medications is often used. There has been interest in the use of antidepressants alongside antipsychotics to treat negative symptoms. Regardless, evidence for antidepressants' effectiveness remains tentative and inconclusive: Rummel-Kluge, Kissling and Leucht, 2006 suggests that the positive effects they found was enough to proceed with a larger trial and Galling et al., 2018 found that augmentation of antidepressants and antipsychotics showed better results than placebos while Sepehry, Potvin, Elie and Stip, 2007 did not recommend the use of selective serotonin reuptake inhibitors (SSRIs) to alleviate negative symptoms. The use of antidepressants in schizophrenia treatment may still be a possible way to improve symptoms but much further research is required for any conclusive judgment to be made.

Zandifar et al., 2021 has also looked into the use of spironolactone along risperidone to treat negative symptoms, finding promising results. In the study, the positive and negative syndrome scale (PANSS) was used to evaluate the symptoms while clinicians and family members check for side effects of the medication; the extrapyramidal symptom rating scale (ESRS) was used to evaluate extrapyramidal symptoms. Improvements in both negative and positive symptoms were found and no significant difference in side effects were observed between the placebo group (only risperidone) and the treatment group (risperidone and spironolactone). Furthermore, risperidone's effectiveness in overall treatment of schizophrenia was also demonstrated since both groups showed improvements in PANSS measures.

Additionally, due to the recent developments in the glutamate hypothesis of schizophrenia, treatments focusing on the glutamate pathway have also been investigated. Results of treatments targeting the NMDA receptor have, similarly to antidepressants, been mixed. For example, Tuominen, Tiihonen and Wahlbeck, 2005's meta-analysis found some studies showing treatment with glycine or D-serine to lead to reduction of negative symptoms; a bigger study in the meta-analysis later on showed that the effects of glycine on negative symptoms was not significant. Other studies such as Kelly et al., 2011 suggests that the concurrent use of minocycline alongside second generation antipsychotics might lead to improvements in positive and negative symptoms.

Although the specific effectiveness of the various treatments is not totally clear, there appears to be at least an overall indication that these treatments have some positive results on negative symptoms. A meta-analysis of 168 randomized placebo-controlled trials, Fusar-Poli et al., 2015 found treatments with second-generation antipsychotics, antidepressants, glutamatergic drugs and psychological therapy to result in decreases in negative symptoms.

Psychological Treatment

Although positive symptoms often respond well to antipsychotics, it is not always the case with negative symptoms and overall functional outcome. Psychological treatments are typically used alongside medication to provide a more holistic treatment. One of the main treatments is cognitive behavioral therapy (CBT) which is used in the treatment of depression and has been modified for schizophrenia. According to Addintgon, Piskulic and Marshall, 2010, CBT has been shown by over 30 meta-analyses to be decent at reducing positive symptoms such as delusions. Furthermore, Gumley et al., 2003 illustrated CBT's ability to prevent relapse while Trower et al., 2004 showed a decrease in command hallucinations. Another form of psychosocial treatment is social skills training (STT). In this method, the abilities of social perception, cognition and expression are trained; Addintgon, Piskulic and Marshall, 2010 state that "goal setting, modeling, role playing, positive reinforcement, corrective feedback, and community-based homework assignments" are areas which STT focuses on. STT also incorporates practicing communication both verbally and nonverbally. Research such as Elis, Caponigro and Kring, 2013 showed improvements in negative symptoms using social skills support groups while Kurtz and Mueser, 2008 found improvements in social skills such as assertiveness and social interactions. STT in general allows patients to better cope with stressors and improve their ability to function. Family intervention is another important psychosocial treatment. It gives support to the family members of the patient by providing psycho-education, helpinging with managing crises and communication and emotional support. Support for family members is especially important for outpatient care where these members are involved in providing the demanding care. Furthermore, it has been encouraged to start working with the patient's family early on. This allows the family to better adapt to the new situation, reduces disturbances to the family members' lives and decreases the emotional detriments. Family intervention is beneficial when applied on a long-term basis; it does not need to be often but needs to be consistent over time (Addintong, McCleery and

Addingtong, 2005). Additionally, cognitive remediation (CRT) is also a psychosocial treatment that is often used. In cognitive remediation therapy, focus is on restoring patients' cognitive abilities and social cognition (Medalia and Saperstein, 2013). Puig, Penades and Baeza et al., 2014 shows that CRT have some improvements on the avolition aspects of negative symptoms although other studies such as Elis, Caponigro and Kring, 2013 showed that CRT does not result in significant improvements of negative symptoms on its own; a combination of CRT and SST is more effective. Following this, Carbon and Christoph, 2014's suggestion that CBT, CRT and STT ought to be used in conjunction with pharmacological treatment appears reasonable.

Conclusion:-

Schizophrenia is a psychological disorder that was conceptualized over 100 years ago. Over the last century models of the illness have developed substantially: from as an issue of mental processes, psychological and brain dysfunction to the current diathesis-stress model. The diathesis-stress model is significantly more sophisticated, including aspects such as genetics, bioenvironmental, neurodevelopmental and stressful life events.

At present, schizophrenic symptoms are classified into t specific categories of positive, negative and cognitive symptoms. Positive symptoms are identified with perception without stimuli and include symptoms such as hallucinations and delusions. Negative symptoms on the other hand are deficits in expression (blunted affect and alogia) and motivation (avolition, asociality and anhedonia). Negative symptoms can also be grouped as primary or secondary negative symptoms. Primary negative symptoms are those that are inherent to the illness and do not respond as well to treatment. Secondary symptoms on the other hand result as byproducts of factors such as side effects of medicine or due to positive symptoms. Secondary symptoms often respond well to treatment such as changes in medication or reductions in psychotic symptoms. Lastly, cognitive symptoms are characterized by difficulties intellectually such as with memory and problem solving skills.

It is difficult to be precise with predictions of schizophrenia's course and outcome for the patient as many factors contribute to the final result. Factors such as poor cognitive abilities, extended periods of untreated psychosis and an insidious onset tend to result in a worse outcome. Additionally, there has been a proposal of a subtype of schizophrenia: deficit schizophrenia. Within this category, patients have persistent symptoms that are resistant to treatment and typically have worse functional outcomes. In addition, negative and cognitive symptoms have important roles in the ability of the patient to function after the onset of schizophrenia. Generally, those with more severe negative and cognitive symptoms have worse functional outcomes.

In terms of the causes of schizophrenia, dopamine dysregulation is the most widely accepted theory. The dopamine hypothesis proposes that schizophrenia results from increased levels of dopamine; an idea that is supported by how antipsychotics act on the D_2 receptor, schizophrenia patients having an increased number of D_2 receptors and heavy amphetamine usage produces schizophrenia-like positive symptoms. Further conceptualization of the dopamine hypothesis suggests that the NMDA receptor and glutamate neurotransmitters play a role in the regulation of dopamine levels. Overall, the result of the NMDA receptor and glutamate is that there is an increase in subcortical dopamine levels and a decrease in the cortical dopamine levels.

The role that genetic and developmental factors contribute to schizophrenia has also been investigated. In terms of genetics, twin and adoption studies showed that schizophrenia has a genetic component. Moreover, studies of patients' family members showed that they have a significant increase in the risk of developing the illness. Although a genetic component has been identified, specific genes and their roles in the pathway resulting in schizophrenia is unclear. The main reason for this is that multiple genes interact with each other and contribute in differing amounts to the pathway. Regarding developmental factors, endogenous and exogenous factors play roles in determining the risk for schizophrenia. Endogenous factors include elements such as birth and pregnancy issues and parents' ages during conception. Exogenous factors on the other hand feature birth season, being born in a city, the mother's health during pregnancy, etc.

Treatments of schizophrenia are split into pharmacological treatment and psychological treatments. Pharmacological treatments mainly utilize different antipsychotics which are sometimes paired with other medications such as antidepressants. Antipsychotics are effective at reducing positive symptoms and consequently secondary negative symptoms but have reduced efficacy with primary negative symptoms. Treatment in terms of the glutamate pathways have also been explored with mixed results. With psychological treatments, primarily there is cognitive behavioral therapy (CBT), social skills training (SST), family interventions and cognitive remediation therapy

(CRT). CBT is able to reduce positive symptoms to some degree and the chances of relapse. SST on the other hand are able to help patients be more assertive and cope better with stressors. Family intervention seeks to minimize the disruption to patients' family members and help them better manage the stress of taking care of the patient. Lastly, CRT aims to improve patients' cognitive abilities. Although results of CRT's effectiveness are mixed, generally utilizing CRT along with other forms of treatments, both medical and psychological, appear to be effective.

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