Herbal And Advanced Treatment In Schizophrenia

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1. Introduction

Schizophrenia is a complex, chronic mental health disorder characterized by an array of symptoms, including delusions, hallucinations, disorganized speech or behavior, and impaired cognitive ability. The early onset of the disease, along with its chronic course, make it a disabling disorder for many patients and their families.[1] Schizophrenia can be a debilitating psychiatric disorder, with the majority of patients experiencing significant comorbidity throughout the course of their illness. Studies have reported cognitive and psychosocial deficits already at the onset of disease.[2] Schizophrenia is a debilitating mental illness that affects 1 percent of the population in all cultures.[3]

It is now widely acknowledged that schizophrenia contributes substantially to the global burden of disease.[4] It is also well known that schizophrenia is associated with elevated suicide rates.[5]

World Health Organization defines schizophrenia as a severe mental disorder, characterized by disrupted thinking, affecting perception, and language. It often includes psychotic experiences, such as hearing voices or delusions.[6]

2. Symptoms-

1) Positive Symptoms-
   Positive symptoms can be easily identified and can be classified as psychotic behaviours not seen in healthy people. Such symptoms include hallucinations, delusions, and abnormal motor behaviour in varying degrees of severity.[7]

2) Negative symptoms-
   Negative symptoms are rather difficult to diagnose and are associated with high morbidity because they disturb the patient’s emotions and behaviour.[6]

   The most common negative symptoms are avolition (inability to initiate and persist in activities), alogia (relative absence of Speech), anhedonia (lack of pleasure) and diminished emotional expression.[9]

   Negative symptoms may be either primary to a diagnosis of schizophrenia or secondary to medication, or environmental factor a concomitant psychotic diagnosis.[10]

3. Common sub-types of schizophrenia-
   1. Paranoic-Delusions or hallucinations are prominent.
   2. Hebephrenic:-
      a. Sustained flattened or incongruous affect.
   b. Lack of goal directed behaviour
   c. Prominent thought disorder
   3) Catatonic-
      a. Sustained evidence over at least two weeks of catatonic behaviour including stupor, excitement, posturing, and rigidity
   b. Simple Considerable loss of personal drive
   c. Progressive deepening of negative symptoms
   d. Pronounced decline in social, academic, or employment performance.[11]

4. Causes of schizophrenia-

We will first discuss the possible causes of schizophrenia symptoms and how knowing them can lead to a successful holistic management of the disorder. There is no single cause of schizophrenia though several factors have been identified.[12] As mentioned above, the probability of developing schizophrenia was found to be larger in males than females.[13][14] Several studies have shown that schizophrenia may be hereditary.[15] It has been found that if one of the parents suffers from schizophrenia, the children have a 10% chance of having that condition. Individuals with schizophrenia may become sensitive to any family tension, which may cause relapse.[16] Alcohol and drug use, particularly cannabis and amphetamine, might initiate psychosis in people susceptible to schizophrenia.[17][18] Individuals with schizophrenia use alcohol and other drugs more than the general population.[19]

5. Pathophysiology of Schizophrenia-

Several brain imaging and neuro-pathological studies have tried to relate the signs of schizophrenia to different structure or function of specific brain regions and circuits. There has been advancement in connecting some aspects of the disorder to particular underlying neurobiology and numerous lines of evidence associate the participation of the prefrontal cortex, in specific the cognitive deficits (for example working memory and executive control).[20]

Nonetheless, delicate reductions in grey matter and irregularities of white matter have been found across many brain areas and circuits. The decrease of grey matter progresses with the period of illness, particularly in the temporal lobe, and seems to be related with antipsychotic treatment. Conversely, even drug-naive patients display volume decreases (although not as pronounced as treated patients), exclusively in the caudate nucleus and thalamus. Furthermore, in spite of many hundreds of studies, no restricted anatomical or functional abnormalities have been
identified that are specific to the disorder. This is expected to reflect the difficulty and heterogeneity of the psychopathology and related cognitive deficiencies, and the lack of clear margins separating schizophrenia from the other disorders.[20]

6. Diagnosis of Schizophrenia-

Before 1980 the literature on earlyonset schizophrenia often described diagnostically heterogeneous groups of patients, because "childhood schizophrenia" included patients who today would be diagnosed as having a psychotic disorder other than schizophrenia, or autistic or pervasive developmental disorders. However, some researchers, such as Kanner (1949) and Rutter (1972), regarded autism and schizophrenia as two distinct entities.[21]

If symptoms are present, your doctor will perform a complete medical history and physical examination. Although there are no laboratory tests to specifically diagnose schizophrenia, the doctor might use various diagnostic tests — such as MRI or CT scans or blood tests — to rule out physical illness as the cause of your symptoms.[22]

Diagnosis of schizophrenia involves ruling out other mental health disorders and determining that symptoms are not due to substance abuse, medication or a medical condition. Determining a diagnosis of schizophrenia may include:

- **Physical exam.** This may be done to help rule out other problems that could be causing symptoms and to check for any related complications.
- **Tests and screenings.** These may include tests that help rule out conditions with similar symptoms, and screening for alcohol and drugs. The doctor may also request imaging studies, such as an MRI or CT scan.
- **Psychiatric evaluation.** A doctor or mental health professional checks mental status by observing appearance and demeanor and asking about thoughts, moods, delusions, hallucinations, substance use, and potential for violence or suicide. This also includes a discussion of family and personal history.
- **Diagnostic criteria for schizophrenia.** A doctor or mental health professional may use the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published by the American Psychiatric Association. [23]
- **Blood tests** - in cases where drug use may be a factor a blood test may be ordered. Blood tests are also done to exclude physical causes of illness.
- **Imaging studies** - to rule out tumors and problems in the structure of the brain.
- **Psychological evaluation** - a specialist will assess the patient's mental state by asking about thoughts, moods, hallucinations, suicidal traits, violent tendencies, or potential for violence, as well as observing their demeanor and appearance. [24]

7. Treatment on schizophrenia-

Schizophrenia requires lifelong treatment, even when symptoms have subsided. Treatment with medications and psychosocial therapy can help manage the condition. In some cases, hospitalization may be needed. [23]

Antipsychotic drugs have been the mainstay of schizophrenia treatment since the introduction of chlorpromazine, focusing on decreasing the frequency and severity of psychotic episodes as well as improving the functional capacity of individuals with schizophrenia.[25] The goals in treating schizophrenia include targeting symptoms, preventing relapse, and increasing adaptive functioning so that the patient can be integrated back into the community.[26] Pharmacotherapy is the mainstay of schizophrenia management, but residual symptoms may persist. For that reason, nonpharmacological treatments, such as psychotherapy, are also important. [27]

8. Advanced treatment on schizophrenia-

1) **D2/D3 Partial Agonist-** Cariprazine is a dopamine D3-prefering, D3/D2 receptor partial agonist. Its mechanism of action resembles the one displayed by aripiprazole, but cariprazine has more robust D3 antagonist-partial agonist affinity. [28] The D3 receptor is an autoreceptor that appears to control the phasic, but not tonic, activity of dopamine, and it is mainly distributed in limbic areas, the ventral striatum, and the thalamus. [29]

2) Stepholidine-Stepholidine acts as a D2 antagonist, a D1 agonist, and a 5HT1A agonist and is being hypothesized as a drug effective in positive symptoms (through the D2 receptor), as well as in cognitive symptoms (through the D1 and 5HT1A receptors). [30] There is currently an ongoing clinical trial being performed at the University of Toronto.[31]

3) **L-DOPA-** Based on the different affinities of dopamine receptors and on the aLegedly, cognitive enhancer properties of the DA1 receptor, a clinical trial is being developed to investigate the potential effects of certain doses of l-dopa as an augmentation therapy for negative/cognitive deficits of schizophrenia.[31] A meta-analysis published in 2004 has suggested that adding l-dopa might be beneficial for those patients already taking antipsychotic medication. [30]

4) **YKP1358-YKP1358** is a D2/D3/SHT2A antagonist that is currently undergoing phase 2 of clinical study (SK Bio-Pharmaceuticals). Published studies thus far have investigated the binding properties of this drug on D2 receptors in the striatum. [33]

5) **Paliperidone-** Paliperidone is the active metabolite of risperidone and is available in oral and LAI formulations, both demonstrating efficacy and tolerability and a delay in time to relapse in schizophrenia. It is not hepatically metabolised, making it safe to use in hepatic impairment and with limited risk of pharmacokinetic drug interactions. [34] It can cause akathisia (increased occurrence at 10mg twice daily) and sedation (with 5mg twice daily), sedation and taste disturbance. [35]

6) **Lurasidone-** Lurasidone is licensed for the treatment of schizophrenia[36] Lurasidone is generally well tolerated, with low incidences of weight gain and metabolic dysfunction. It is associated with akathisia (increased incidence at doses of 120mg or greater), sedation and nausea, but similarly to asenapine, despite being a full D2 antagonist, it is not associated with higher incidences of EPSs (excluding akathisia)
and hyperprolactinaemia.\[35\]

7) Asenapine-Asenapine has demonstrated efficacy in the acute and maintenance phases of schizophrenia treatment and in the treatment of acute mania in BPAD, but it is only currently licensed for the treatment of mania in the UK.

8) First- and second-generation antipsychotics-More than 70 antipsychotics have been introduced. They are mainly categorized into first- and second-generation agents and share a similar pharmacological mechanism in blocking the dopamine D-2 receptors.\[37\] Their blocking mechanisms or actions are linked to their efficacy against positive and disorganization symptoms of schizophrenia.\[38-40\]

The first-generation antipsychotics (FGAs), or typical antipsychotics (eg, chlorpromazine, fluphenazine, and haloperidol, included in the World Health Organization’s list of Essential Medications in 2009)\[41\] were first introduced for the treatment of schizophrenia in the 1950s. The second-generation (atypical) antipsychotics (eg, clozapine, olanzapine, and risperidone) introduced in the last three decades.

9. Herbal remedy of Schizophrenia-

In spite of being the mainstream treatment, antipsychotic drugs are associated with many serious adverse effects. According to WHO, almost 80 % of the total population of Africa and Asia relies on the conventional herbal remedies. Conventional herbal medicines based upon age old practice, efficacy and belief has been widely accepted because of its lesser adverse effects, proven therapeutic value against a lot of medical conditions, easy availability and comfortable price tag.\[42-43\]. Herbs have always afforded major leads against a number of ailments and several such herbal drugs are marketed regularly.\[44\] The plantbased bioactive compounds are primarily secondary metabolites used as herbal therapeutics.\[45\]

1) Aegle marmelos L. / Wood-apple or Bel (Rutaceae) Aegle marmelos, commonly known as bel, stone apple or wood apple, is a tree indigenous to India and southeast Asia. The methanolic leaf extract of A. marmelos was reportedly exerted anti-anxiety and antidepressant properties on albino mice and was also suggested as a probable supply for natural psychotherapeutic reagent.\[46\]

2) Brassica juncea L. / Sorisha (Brassicaceae)-Brassica juncea, commonly known as green mustard or Indian mustard, is a specie of mustard plant. The plant is reported for its relaxant activity. It is also accounted for reducing the increased thyroid activity in the schizophrenic patients.\[47\]

3) Cannabis sativa L. / Siddhi (Cannabaceae)-Cannabis sativa, usually known as Ganja, Siddhi or Marijuana, is an annual herbaceous plant belonging to the Cannabaceae family. The plant is known to have anxiolytic activities and antipsychotic properties. Cannabidiol, a plant extract was cited effective in increasing patience and reducing the olanzapine-generated adverse effects in SZ patient.\[48\]

4) Matricaria recutita L. / Chamomile (Asteraceae) Chamomilla recuta, also known as chamomile or camomile, is an annual plant of the family Asteraceae. Chamomile is a herb showing both relaxing and stimulating activities. Its volatile oil extract, contains bisabolol and chamaequlene, reported for spasmodic and relaxing effect on CNS. It has been reported against nervous irritability and anxiety.\[49\]

5) Hypericum perforatum L. / St.John’s Wort (Hypericaceae)-Hypericum perforatum, commonly known as Saint John’s wort (St John’s wort), is a medicinal herb with antidepressant activity belongs to the family Hypericaceae. Extract of H. perforatum has been reported for ketamine-antagonising effect. S-ketamine remarkably reduced the N100P200 peak to peak (ptp) amplitude after the placebo treatment.\[50\]

6) Wuling Powder (WLP)-Wuling powder (WLP), a well known TCM is used in treating clozapine induced hypersalivation, mostly in children. This traditional herbal medication was first reported from Han Dynasty. It is formulated by the mixture of five Chinese herbal extractions, those are Zhuling (Polypropous), Fuling (Poria), Zexie (Rhizoma alismatis), Rougui (Cortex cinnamoni cassiae) and Baizhu (Rhizoma atracyloidis macrocephalae). WLP decreased the hypersalivation significantly induced by clozapine.\[51\]

7) Baicalin-Baicalin is a flavonoid (IUPAC name: 2S,3S,4S,5R,6S)-6-(5,6-dihydroxy-4-oxo-2-phenylchromen-7-yl)oxy-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid; molecular formula: C21H18O11) found in many species in the genus Scutellaria, including Scutellaria baicalensis, Scutellaria lateriflora and Scutellaria galericulata; family Lamiaceae. Baicalin was reportedly possessed prophylol oligopeptidase inhibitory function and has been reported to inhibit prolyl oligopeptidase. It was reported for being a potential candidate to develop new antipsychotic drugs for SZ like neuropsychiatric disorders.\[52\]

8) Ginkgo-Ginkgo trees (Ginkgo biloba) are native to East Asia and are grown ornamentally in Europe and North America. Used in China for more than 2,000 years as a tea for treatment of asthma, ginkgo is now the most commonly sold herbal product in Germany and one of the top three herbs in the United States, where it is taken primarily to prevent or treat memory problems.\[53\][54]

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