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Recent concepts in clinical psychiatry: drug treatment in schizophrenia

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RECENT CONCEPTS IN CLINICAL PSYCHIATRY: DRUG TREATMENT IN SCHIZOPHRENIA

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Schizophrenia had been a myth for many years in the world of Psychiatry. One can perhaps over simplify by saying that it seems torun in families, neuroleptics make it better and there may be something structurally abnormal in the brains of Schizophrenics[1] though one should not ignore the knowledge of epidemiology of this disorder nor the effect of psychological factors.

In order to understand the mechanism of action of antipsychotics, the complex patbogenesis of schizophrenia needs to be elaborated. Schizophrenia is broadly classified into two categories[2]. Type I with acute onset and mainly positive symptoms such as hallucinalions, delusions, formal thought disorder, affective incongruity and good social functioning during remission. Type II is said to have insidious onset, mainly negative symptoms, i.e. ,poverty of speech, blunting of affect, lack of initiative and goal orientated behaviour, social withdrawal, impaired attention and a poor outcome. Crow[3] (1980) suggested that the "positive" features of schizophrenia are due to functional abnormalities in the brain and are, therefore, reversible (type I). He also postulated that "negative" features are consequent upon structural brain damage and largely irreversible (type II) and though he delineated separate groups of patients, he was quite clear that while the two syndrome concept described separate dimensions of pathology, they could exist in the same patient. There is also considerable support that type II syndrome in which structural changes (such as enlarged ventricles) are related to negative symptoms, cognitive impairment and neurological 'soft' signs[3], responds less well to antipsychotic medication and that there is greater involvement of dopaminergic abnormalities in the type I than type II syndrome[3].

The finding of a seasonal distribution in the birth rates of schizophrenics, a disproportionate number being born in the late winter and early spring[4], suggests that the similar seasonality of some viral infection may have an effect on perinatal brain development. This may predispose individuals towards schizophrenic illness in adult life[4,5]".

It has also been concluded that while genetic factors are of overwhelming aetiological importance in familial cases, non- familial cases are more likely to have environmentally induced structural brain abnormalities[6]. A plausible mechanism exists which produce structural changes. Hypoxic-ischaemic damage during pregnancy and the neonatal period can lead to intraventricular and periventricular haemorrhagee and though the majority of such bleeds do resolve but in some cases, regions of periventricular necrosis ensue which cause a non-progressive enlargement of lateral and 3rd ventricles[8]. Widening of sulci can occur due to similar changes.

It has been suggested that the type II syndrome arises in childhood as a consequence of early neurodevelopmental damage[9]. It is also concluded by some authors[10] that symptomatic psychoses were more frequently associated with left than right temporal lesions. This had been supported by postmortem studies[11].

Though several biochemical hypotheses have been suggested but most attention has been paid to those concerned with dopaminergic, serotonergic, and recently gamma arninobutyric acid (GABA containing neurones) called GABAergic transmission. The neurotransmitters which appear to be relevant to the pathogenesis of schizophrenia are as follows:

1. Dopamine (DA)
2. Serotonin (5)
3. Nor-adrenaline (NA)

4. Gamma aminobutyric acid (GABA)
5. Glutamate
6. Peptides
7. Sigma

1. Dopamine (DA):

Overactivity of DA pathways in the brain may contribute to pathogenesis of schizophrenia. The discovery of DA hypothesis was a big landmark when metabolites of DA including homovanillic acid (HVA) were found to be greatly raised in the brains of animals given chlorpromazine which had been a known antipsychotic since 1952. This effect was interpreted as a feedback response of the presynaptic neurone to blockade of postsynaptic DA receptors and compensatory increase in the activity of the DA neurones, causing them to release more DA[12,13]. Amphetamine which releases DA at central synapses, also induces a disorder indistinguishable from schizophrenia in some normal people and worsens schizophrenic symptoms.

The brain contains three separate groups of DA neurones:

(i) The mesolimbic pathway
(ii) The nigrostrial pathway
(iii) The tubero-infundibular pathways.

Mesolimbic pathway is held responsible for the pathogenesis of schizophrenia. It is believed that antipsychotic effect ofneuroleptics arises from blockade of DA receptors in the terminal areas of the mesolimbic (and mesocortical) pathway. Mesolimbic DA neurones are in an area of brain stem, near to substantia nigra and run to the 'limbic areas' of brain which are concerned with emotions, goal-orientated behaviour and perception. The blockade of nigrostrial pathway which runs from the substantia nigra in the brain stem to the caudate nucleus in the basal ganglia produces parkinsonism. The blockade of tubero-infundibular pathway which is located in hypothalamus, in the area of cells that contain pituitary hormone-releasing and inhibiting factors causes hyperprolactinaemia[14].

The original belief that antipsychotic properties of neuroleptics are related to parkinsonian side effects and rise in prolactin is not held any more. Drugs which are effective only in the mesolimbic models but ineffective in the nigrostrial models are expected to have antipsychotic properties without inducing parkinsonism.

Drugs that modify psychosis may only have effect on different symptoms and are not disease specific. Dopamine agonists seem to worsen positive symptoms while they may improve negative symptoms; DA antagonists are reported to do the opposite. Though all these speculations need to be rigorously established, the suggestion of multiple subtypes of schizophrenia, with multiple pharmacologies of the syndrome is an interesting one[15].

The DA receptors are now also recognised as being of two main types[16]- Dl receptors which are coupled to adenylate cyclase and use cyclic AMP as their 'second messenger" and D2 receptors which are independent of adenylate cyclase.

Antipsychotics influence Dl and D2 receptors to different degrees. Most of them have little effect on Dl receptors including the substituted benzamides (e.g., sulpride) butyrophenones (e.g., haloperidol) while the diphenylbutylpiperidines (e.g., pimozide) have a more pronounced effect and phenothiazines (e.g., chlorpromazine) have weak Dl - blocking action. SCH 23390 is a pure Dl antagonist and is available for animal experimentation only[17].

2. Serotonin (S)

Elevated blood concentrations of S2 have been found in chronic schizophrenics[18] and it is also noticed that the subjective feelings induced by lysergic acid diethylamide (LSD) a purported serotonin agonist are found to be selectively antagonized by S2 antagonist.

3. Noradrenaline (NA)

The evidence of a primary noradrenergic over activity hypothesis had been reviewed[19]. Moreover it

seems that NA uptake inhibitors worsen schizophrenic symptomatology while the antipsychotic drug Pimozide lowers CSF NA[20]. There are also a number of studies quoting that B- adrenergics may have some antipsychotic properties[21].

4. Gama Amino Butyric Acid (GABA)

A role for GABA in the pathophysiology of schizophrenia was first suggested by Eugene Roberts in 197222 and it has traditionally been speculated that GABA exerts inhibitory influences on mesolimbic, dopantinergic and noradrenergic pathways and that GABAergic drugs given in combination with neuroleptics should consequently improve the symptoms of schizophrenia and tardive dyskinesia (TD), but the recent data had shown that in certain models GABA has opposite effect on dopaminergic function[23]. Although the GABA theory of schizophrenia is derived from the known interaction of GABA with dopaminergic system rather than by its direct experimentation but it is also observed that the administration of GABA - related drugs, e.g., sodium valproate and baclofen can provoke psychotic reactions and even worsen schizophrenic symptomatology when used to treat TD[24].

5. Glutamate/aspartate

This is an acidic amino-acid transmitterwhich exists in amygdala, nucleus accumbens and in most subcortical neclei. There is a possibility that the excitotoxic action of glutamate could lead to neuronal destruction[25]. Also regions such as hippocampus which appear degenerated in schizophrenics are the ones which should have the densest glutamatergic input[26]. Another finding[27] not only supports an excitotoxic hypothesis but also correlates very well with the ideas of lateralised pathology, is the specific loss of binding sites for kainic acid which is a glutamate analogue in the left hippocampus of schizophrenics.

6. Peptides

Although at present there are no consistent data available on the 20 or so other neuropeptides known to exist in human brain there is some evidence that cholecystokinin (CCK) plays some role in the pathogenesis of schizophrenia as a loss of CCK binding sites in schizophrenic frontal cortex and hippocampus compared to controls have been reported[28].

Research in opiate peptides has produced some conflicting results as there are reports of both worsening or improvement when antagonists such as naloxone or agonist, e.g., endorphin were given to chronic schizophrenics[29].

7. Sigma

Sigma sites can be distinguished from opium sites and D2 receptors. Sigma receptors are distributed in the cerebellum, cortex and mesolimbic system. Drugs which block C psychotic symptoms work at sigma sites. Haloperidol is most potent blocker of D2 and sigma site while remoxipride, a sigma antagonist selectively blocks sigma only and has more antipsychotic and less cxtrapyramidal action. Rimcazolc (BW-2344) is thought to act by blocking sigma opiate receptors and has proved to be effective in acute schizophrenics in open studies[30].

Receptors affinity proffle of Neuroleptics

Neuroleptics block multiple amine receptors in the brains. Some of them are highly D2 receptor selective, e.g., sulpiride, others could be nonselective or rather broad spectrum, e.g., clozapine, while pimozide and haloperidol are D2 selective but haloperidol affects serotonin and -1 receptors more than sulpiride and pimozide. Phenothiazines have a weak Dl blocking action whereas thioxanthines have a more pronounced effect. SCH-23390 is a pure D1 antagonist.

It is rather difficult to associate receptor affinity profiles with effects of neuroleptics, but is far easier to relate these receptor affinities to the side effects of the drugs e.g., the DA - selective antipsychotic drugs have few autonomic and sedating actions, but they induce extrapyramidal motor symptoms; the DA - nonselective drugs produce the opposite side effect profile.

Antipsychotic drugs can be classified as follows:

1. Non-specific DA blockers
2. DA specific drugs
3. Site specific DA antagonists
4. Broad spectrum DA receptors neuroleptics
5. Serotonin - S2 receptor blockers
6. Other DA nonselective neuroleptics
7. Other transmitter system drugs
8. Other empirical drug treatment

Drugs that block behaviour mediated by mesolimbic DA pathways but do not interact with behaviour associated with the nigrostrial DA pathways, have antipsychotic properties and a relatively low level of extrapyramidal symptoms (EPS). These drugs are also called “atypical neuroleptics". Substituted benzamides and clozapine are mcluded in this category.

1. Non specific DA blockers

Include phenothiazines, (chiorpromazine, promazine, thioridazine, fiuspiriline, trifluoperazine, and slow -release preparations such as fiuphenazine enanthate and fluphenazine decanoate), thioxanthines (flupenthixol, thiothixine and slow -release depot preparation fiupenthixol and clopenthixol decanoate) and butyrophenones (haloperidol, trifluperidol). These drugs also block other receptors in therapeutic doses. Due to nigrostrial receptor blockade, they cause cxtrapyramidal motor symptoms (parkinsonism, acute dystonia, akathesia). By bloking tubroinfundibular receptors they produce hyperprolactinaemia which causes galactorrhoca, reduced libido and amenorrhoea or irregular non-ovulatory cycles. Blockade of -1 receptors causes postural hypotension, sedation and possibly ejaculatory problems as well while blockade of ACFI (muscarine) receptors is somewhat beneficial and protects against EPS. Cholinergic blockade impairs concentration and attention in schizophrenia. There is also peripheral autonomic symptoms such as delayed gastric emptying, dry mouth, constipation, other gastrointestinal problems, urinary retention, blurred vision and tachycardia. Blocking of histamine receptors causes sedation and that of 5HT-l receptors and of — 1 receptors is thought to increase appetite and contribute to substantial weight gain. Some of these drugs have other actions such as inhibiting catecholamine re-uptake and blockade of presynaptic —12 receptors, both of which tend to endow the drug with antidepressant activity. It is worth mentioning that the beneficial effect on positive symptoms develop over the course of several weeks.

2. DA specific drugs

Diphenylbutylpiperidines. It includes pimozide which specifically blocks DA receptors both Dl and D2 but has little activity at other known receptors in clinical doses. It is non-sedating and effective in acute schizophrenia. It is also effective as a maintenance therapy[30] as it has a long plasma half-life (average 72 hours). It also has less propensity for causing weight gain. Since it lacks anticholinergic properties, it is associated with a high incidence of EPS. It is also known to be an activating drug and improves the schizophrenic defect state[31].

3. Site specific DA antagonists

a. Substituted benzamides. Sulpride is the oldest and clinically most established member of substituted benzamides. In clinical double blind studies sulpride had been shown to have an antipsychotic effect in chronic schizophrenic patients in doses which range from 800 to 2300 mg per day. Though this effect is not significantly different from that of chlorpromazine, haloperidol and trifluoperazine but the potential advantages of this drug are the relatively few EPS and in small to moderate doses, an antiautisitic and antidepressant effect. It is also effective in the treatment of acute schizophrenia at high doses of more than 1200 mg per day. It is known to be effective for negative symptoms as well. It causes pronounced rise in prolactin levels when given in high doses[32]. The concentrations of
HVA in cerebrospinal fluid are found to be increased to the same degree during sulpride treatment as that of chlorpromazine which indicates that the central DA receptor blockade effect of suipride is

comparable to that of choipromazine.
It has been claimed that sulpride should be less liable to induce TD than traditional neuroleptics. Sulpride induces no or weak DA supersensitivity with chronic administration and suppresses TD in monkeys, without subsequent TD rebound aggravation in contrast to traditional neuroleptics. It is also known that with long term treatment sulpride induces no increase in D2 receptors in the experimental animal but causes a significant increase in Di receptors in contrast to traditional neuroleptics like haloperidol which elevates the D2 but not D1 receptors. In the light of the new hypothesis that TD is caused by a blockade of sub-group of DA receptor related to the striatofugal GABA- mediated projections, the Dl receptor increase during prolong sulpride treatment may protect against TD development. Still the potential of sulpride to induce reversible or irreversible TD deserves to be more carefully evaluated in long term comparative clinical trials.
b. Other substituted benzamides. A series of novel substituted benzamides has been developed e.g., remoxipride and raclopride. Besides sharing the behavioral effects of sulpride they have the advantage of being more potent and causing less prolactin increase. Remoxipride [S-3-bromo-N-(1-ethyl-2 pyrrolidinyl) methy[1-2,6] dimethoxyben-zamide hydrochloride monohydrate] is a selective D2 receptor blocker with preferential action in mesolimbic areas and substantia nigra as well. Both remoxipride and raclopride I(-)- (5) -3,5-dichloro-N- (i-ethyl-2- pyrrolidinyl) methyl-6-methoxysali-cylamide tartrate] are effective at low doses and produce less rise in prolactin levels. Remoxipride has been tested in quite a few studies which all showed that the drug in dosage of 90-1200 mg/day is comparable to traditional neuroleptics. Only very few autonomic side effects have been observed and it causes only slight parkinsonism, akathisia, sedation, fatigue and headache. Raclopride is reported to be the first low dose benzamide comparable in motor side effects to haloperidol. It causes less parkinsonism and less àutonomic or cardiovascular reactions though it can cause akathisia. It seems that benzamide drugs do seem to cause relatively less parkinsonian side effect, but may not be so different concerning dystonia and akathisia.
4. Broad spectrum DA receptors neuroleptics
Clozapine. Clozapine [8-chloro-11(4 -methyl-ipiperazinyl)-5H-dibenzo (b,e) (1,4) diazepine] belongs to the chemical class of dibenzodiazepines which also include powerful traditional neuroleptics such as loxapine and clothapine. It is useful in treatment-resistant schizophrenic patients[33] . Around 30% of schizophrenic patients usually do not respond to antipsychotics and about 40% of these refractory cases do improve with clozapine. Clozapine binds to several types of receptors specially 52, -1 adrenergic, Hi receptors. Dl and D2 receptors are effected to a lessor degree. When given in small doses, clozapine decreases DA release in the brain of animals and in moderate doses of 225 mg per day it causes a decrease in HVA in CSF of schizophrenic patients. High doses of clozapine increase DA turnover in experimental animals and also in human patients. With chronic treatment in the experimental animal, clozapine produces no increase in D2 receptor number or affinity but like sulpride it may increase Di receptor. It is also noted that clozapine causes ahighly significant reduction not only in the productive schizophrenic symptoms but in anxiety and tension as well. Also a significant effect was noted on the negative symptoms of emotional withdrawal and blunted affect. A comparison between clozapine and haloperidol showed clearly that clozapine was superior in its effect on somatic concern, anxiety, conceptual disorganization, tension and mannerism as compared to haloperidol. Therefore in severely disturbed schizophrenics clozapine brings about an often very desirable relaxation and sedation, whereas haloperidol may instead cause restlessness often associated with anxiety and tension which can only partly be reversed by anti- parkinsonian drugs. This could be because of different effects on dopaminergic neurotransmission of these two drugs.
Clinical trials have demonstrated clearly that the antipsychotic effect of clozapine is equal to and often greater than the comparable effects with other high dose neuroleptics such as chlorpromazine and thioridazine.

The other advantage is that in the recommended dose of 600 mg per day clozapine does not induce EPS though some slowing down of movements and reduced facial expression related to the sedative effect have been reported. It is worth mentioning that clozapine has an antitremor effect not only in parkinsonian tremor, but also in essential tremor and that of neuroleptics induced parkinsonism in a dosage of 12.5 to 75 mg per day. In some cases the combination of clozapine and another traditional neuroleptic such as haloperidol seems particularly beneficial in view of sedative effect and antitremor effect of clozapine. Rise in prolactin level is very short lived. In high doses of 400-900 mg per day, clozapine can reduce the TD symptoms moderately but because of the other side effects of clozapine such high dose treatment cannot be recommended for elderly patients with TD though such a high dose may lead to improvement in a sub group of severely psychotic patients suffering from severe atypical TD associated with productive psychotic symptoms, bizarre behaviour and
some form of brain damage, In low doses of 50-250 mg per day clozapine has no significant suppressing effect on dyskinesia but a spontaneous recovery of the syndrome may be predicted to occur during the treatment because dozapine in such doses may not induce or aggravate the primary pathophysiological mechanism underlying TD. Some uncontrolled clinical observation and follow- up studies suggest that clozapine does not induce TD.

Unfortunately clozapine has some side effects on cardiovascular and autonomic nervous system; it may cause a fall in orthostatic blood pressure especially in the initial treatment phase and even sinus tachycardia. Tt can also induce some changes in EGG such as shortening of PQ interval and a flattening of the T wave though these changes do subside after sometime. Some studies have even reported agranulocytosis[34] in 1-2% of cases treated with clozapine. Other studies quote lower incidence. The clinician must monitor white blood counts particularly from week 4 to 14 when most of the cases of agranulocytosis occur and should be alert to the need of discontinuing the drug when the white count drops below 3000/mm^3 or neutrophil count drops below 1500/mm^3.

5. Serotonin - S2 receptor blockers

These include pipamperone, setoperone, ritanserin and risperidon (R 64766). Serotonin - S2 receptor blockers have a wide range of peripheral and central activities. Most of these drugs are still in experimental stages[35] . The major improvement in mood and drive reported by these drugs may be strongly associated with their properties of increasing human slow-wave sleep[36]. Also the reduction of EPS observed with all these serotonin antagonists needs special attention, since none of these drugs has any anticholinergic activity.

a. Pipamperone. It is reported tonormalise emotional tone and behaviour and has an anti-autistic and resocialising effect, It is helpful in treatment of schizophrenia and has low liability to cause EPS and is a good sleep inductor.

b. Setoperone. (Potent serotonin and moderate DA agonist) reported to be helpful in treating negative symptoms in chronic schizophrenia.

c. Ritanserin is shown to have a potent and selective binding to S2 receptors in rat frontal cortex and reported to help in negative and affective symptoms e.g., anergia, anxiety and depression. There is reduction in EPS especially when the patient was on existing neuroleptic therapy. It is reported to significantly increase slow wave sleep which is often impaired in schizophrenic patients[37]. Some authors from uncontrolled trials also reported improvement in parkinsonian and negative symptoms in chronic schizophrenics receiving neuroleptics[38].

d. Risperidone (R 64766) is a S2 receptors blocker and also DA receptors blocker. At slightly higher doses, an interaction with the noradrenergic and histaminergic system was also shown in animals. It is helpful in treating both positive and negative symptoms of schizophrenia. There is reported reduction in EPS as compared to previous therapy.

The arrival of S-2 receptor blockers or so called thymosthenic agents has also brought the notion of certain new strategies required for the future management of chronic schizophrenics. Perhaps it is

worth thinking of the single pharmacological treatment with either a selective D2 antagonist or selective S2 antagonist which will depend on the main complaints or presence of positive or negative symptoms. One should also think of a combined dopamine and serotonin antagonist treatment according to the needs of the individual patient or should think of a drug with combined serotonin/dopamine antagonistic properties e.g., risperidone. A drug with a double profile perhaps will be the best in modern pharmacotherapy and according to the above mentioned properties resperidone appears to be a promising drug.

6. Other DA non-selective neuroleptics

Fluperlapine and BW-234U belong to this category. Fluperlapine is an outcome of the search for new clozapine like neuroleptics. It is a dibenzazepine derivative chemically and pharmacologically related to clozapine and has the same weak affinity for Dl and D2 receptors and a strong affinity for S receptors but as compared to clozapine it does not cause -1-blockade but facilitates noradrenergic neurotransmission through presynaptic mechanism. BW-234U has minimal affinity for DA noradrenergic, sertonergic, histaminergic and muscarine receptors. They have weak EPS inducing effects but have a potential of causing agranalucytopenia, because of that further clinical research with these drugs have been stopped.

Amperozide is another DAnonselective drug which have a weak D2 blocking effect in limbic areas but enhances the release of presynaptic DA without causing a general increase in DA turnover. Like fluperlapine it facilitates noradrenergic neurotransmission and has also strong serotonin antagonistic action and in higher doses, agonistic effect. Amperozide has also been found to have an antiagressive effect in animals without causing sedation and has an anxiolytic and antistress effect similar to that of diazepam. In doses of 30-40 mgm/day, it has been reported to cause dizziness, tinnitus and some T-wave flattening in EGG. This drug is under clinical evaluation at present.

7. Other transmitter system drugs

Fenfiuramine releases and depletes serotonin and improves symptoms of autism. There is some evidence that either alone or combined with Phenothiazines, massive doses of propranolol (a B-adrenergic), or other receptor blockers may have a beneficial effect on patients resistant to neuroleptics39. It is also claimed that augmenting GABA mediated neural inhibition should therapeutically improve schizophrenia. Adjunct therapy with aiprazolam and antipsychotics is reported to improve both positivc and negative symptoms. Also high doses of diazepam have shown to improve a proportion of acute schizophrenics[40].

8. Other empirical drug treatment

This category includes lithium and carbamazepine. There have been claims that some schizophrenics benefit from lithium therapy either alone or combined with phenothiazines[41]. Carbamazepine had been found suitable as an adjunct therapy in some excited patients.

It is encouraging to see that the rapid rate of developments in the field of molecular genetics suggest that perhaps shortly, pharmacology in psychiatry may lead on to the level of genes and the genes product. The sophisticated technology for studying human brain pathophysiology will also contribute tremendously to the new approaches in the treatment of schizophrenia.

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