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Review Article

NEW PERSPECTIVES IN THE TREATMENT OF SCHIZOPHRENIA

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ABSTRACT: Following the introduction of chlorpromazine in 1950s, for many years little progress was made in the discovery of new drugs for schizophrenia. Dopamine D2 receptors blockade was recognized as the only therapeutic target for antipsychotic drugs and formed the basis for further developments in this area. Later on enhanced efficacy of clozapine in both positive and negative symptoms in schizophrenia opened a new channel for discovery of new pharmacological treatments for this illness. Further developments looked at designing compounds, which were chemically similar to clozapine and have efficacy in both negative and positive symptomatology with diminished risk of extrapyramidal side effects. This new family of drugs, the so-called atypical antipsychotics, mainly act as serotonin- dopamine antagonists (SDA) and have shown wider spectrum of antipsychotic activity than conventional antipsychotic drugs. Their use in clinical practice is now well established & despite some limitations, clinicians prefer their use as first line treatment in schizophrenia and other related illnesses.

This paper summarises current findings in the pharmacological treatment of schizophrenia and attempts to provide a review of these new drugs with future directions in this area.

KEY WORDS: Schizophrenia, antipsychotic drugs, 5-HT receptors, D2 receptors, extrapyramidal symptoms.

INTRODUCTION

Schizophrenia is one of the most disabling conditions of all mental disorders. This illness usually starts in late-adolescent or early adulthood and in most cases, has a chronic course. The lifetime prevalence of schizophrenia is about 1%[1], 10% patients commit suicide[2] and 30%-40% patients show poor response to conventional antipsychotic medication[3], leading to repeated hospital admissions and poor social and occupational functioning. Patients with schizophrenia occupy about 25% of all hospital beds[4] and pose a major burden in terms of expenditure in mental health services.

- Schizophrenia occurs in all cultures
- Incidence is about 2-4 cases per 10,000 population per year
- Life time risk is about 1%
- In industrialized countries there are more schizophrenic patients in the lower socio-economic classes
- Admission rates are higher in urban than in rural areas
- It affects patient for a life time whether in relapse or in remission

Drug treatment stays as one of the most important aspects of treatment in schizophrenia

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and clinical studies have consistently proved that delays in initiating treatment affect the outcome to a large extent. The history of drug treatment for schizophrenia dates back to the mid 1930's, when Promethazine, a compound from a group, called Phenothiazines, was shown to have a calming action in agitated and aggressive people. This triggered a search for other related drugs and led to the discovery of Chlorpromazine in the 1950's by a French Pharmaceutical company. It turned out to be a break through, as this compound was found to be very effective in controlling most symptoms in schizophrenic patients. This also proved perhaps a great contribution in the field of mental health, which demonstrated for the first time that medicines could alter the symptoms of a mental disorder.

Following the introduction of chlorpromazine in the mid-1950s, a number of other antipsychotic drugs were synthesized for the treatment of schizophrenia. All of them more or less relied on the principle of dopamine D2 receptor blockade. While these antipsychotics helped in the treatment of schizophrenia, their efficacy was limited to positive symptoms with little effect on negative symptoms. They also produced distressing side effects, including extrapyramidal side effects (EPS), tardive dyskinesia (TD), endocrine changes and sexual dysfunction.

Repeated attempts were later on made to develop new antipsychotics with a more favourable adverse effect profile especially on extrapyramidal motor symptoms (EPS). A subsidiary objective of these developments was to achieve greater efficacy than conventional drugs, particularly for negative symptoms and treatment resistance states.

In early 1960s developments in the chemical series of dibenzodiazepines produced a new drug named as clozapine that showed a comparable efficacy to the available antipsychotic drugs. Clozapine was later on withdrawn from clinical use in Europe following several deaths from agranulocytosis. This drug, however, reentered the scene in late 1980s when its advantages were demonstrated in resistant forms of schizophrenia[5]. Clozapine is now widely viewed as one of the most important advances in the treatment of schizophrenia and is regarded as the first antipsychotic compound, which has shown increased therapeutic efficacy and reduced levels of extrapyramidal side effects[5] as compared to conventional antipsychotics. It has also opened new avenues for the development of newer (atypical) drugs and has promoted the notion of atypicality, which rested on the idea that typical antipsychotics produce extra pyramidal syndromes (EPS), whereas atypical antipsychotics produce therapeutic effects without or with few EPS.

In terms of pharmacological profiles, development of new anti-psychotic drugs mainly centred on the approaches to find out compounds, which were specific and selective for different receptors. In addition to drugs effecting dopamine receptors, new compounds were developed having effects on other neurotransmitters as it was found that anti-5HT, anti-sigma, anti-cholinergic and anti-histaminic properties were also important for the therapeutic effects of these drugs. Following re-discovery of Clozapine, several drugs have become available in the market. These drugs generally fall into two groups: one having strong affinities for 5-HT2a receptors as well as D2-receptors, the other group having a mixed and complex pattern of affinities for numerous receptors, but relatively poor affinity for D2-receptors. In addition, a third group has recently become available that blocks both D2 and D/3 receptors without having any effects on 5HT2 receptors.

MECHANISM OF ACTION OF ANTIPSYCHOTIC MEDICATIONS

As mentioned earlier, development of chlorpromazine paved the way to modern neuro-psychopharmacology and set the scene for developments of new compound in this area. The mechanism of action of these drugs is viewed in terms of their effects on neurotransmitters and has generated different hypotheses in this area.

DOPAMINE HYPOTHESIS

The observation that all known antipsychotic drugs block the D2 subtype of the dopamine receptor in proportion to their clinical potency[6,7] provides the best support for dopaminergic involvement in schizophrenia[8,9]. It is generally thought that D2 blockade in the nigrostriatal dopamine system results in extrapyramidal side effects (EPS) of neuroleptics, whereas D2 blockade in the mesolimbic dopamine system is related more closely to antipsychotic effects. The mesocortical dopamine system, which includes projections from midbrain cell bodies to the frontal cortex, has few if any D2 receptors and is not clearly implicated in the action of common antipsychotic drugs, although its involvement in some symptoms is widely speculated upon [8,10].

SEROTONIN-DOPAMINE ANTAGONISM

It is evident that atypical antipsychotics have high affinity for 5HT2a receptors in vitro[11] as compared to D2 receptors and their mechanism of action is generally explained on the basis of dual action on both DA & 5HT systems. The understanding of interaction between dopamine and serotonin neurotransmitters thus became the focus of research and led to speculation that the balance between D2 and 5HT2-receptor blockade may be responsible for therapeutic actions of these novel drugs particularly against negative symptoms and protection against extrapyramidal side-effects[12]. The serotonin system has also been shown to act to inhibit dopaminergic function in the midbrain and forebrain, and serotonin antagonists to release dopamine from this inhibition. This mechanism, at the level of the striatum, may thus alleviate neuroleptic-induced EPS, and in the frontal cortex may be responsible for the improvement of negative symptoms and impaired cognition[13].

The notion that (relatively weak) D2 antagonism, coupled with potent serotonergic effects, including antagonism of the 5HT2 receptor subtype is critical to atypicality (in terms of low EPS and high therapeutic efficacy[14]) has thus emerged as the single most important influence in development of this class of anti-psychotic drugs. Recently 5HT2c, 5HT6, 5HT3 and 5HT7 receptor subtype have also been targeted for further research as most of the atypical antipsychotics have shown strong affinity for these receptor sites[15].

GLUTAMATE SYSTEM

Glutamate, an excitatory amino acid, has also become increasingly important in schizophrenia research because of its role in neurotransmission of cortical-cortical and cortical-subcortical systems. It has assumed significance because phencyclidine (PCT), an antagonist of the glutamatergic N-methyl-D aspartate receptor, produces a clinical syndrome in normal subjects bearing similarity to the psychosis of schizophrenia. Although application of the glutamate system in new drug development has been difficult, the pharmacology of glutamate system including delineation of multiple receptor types by molecular biological techniques, is emerging as a new area of research in psychopharmacology.

TYPICAL ANTIPSYCHOTIC DRUGS

The typical anti-psychotic drugs include older drugs, which are potent dopamine antagonists, and most importantly act at D2 receptors located in the nigrostriatal and mesolimbic pathways. These drugs do not necessarily differ in their actions but they do vary in their side effect profiles. The lack of selectivity of the old anti-psychotic compounds for D2 receptors in the mesolimbic areas compared with the nigrostriatal areas of the brain result in an association with extra-pyramidal side effects (EPS) and an increased risk for tardive dyskinesia (TD). As a rule, the higher the potency, the greater the risk of extra pyramidal side effects (EPS) is for these compounds. Together with other significant side effects like increased prolactin level, occurrence of EPS and TD have limited the acceptability of typical antipsychotic

EXTRAPYRAMIDAL SYMPTOMS WITH TYPICAL APD

Symptoms	*Prevalence*	*Time of appearance*	*Mechanism*
Akathisia	Upto 60%	Any time during therapy	DA receptor blockade in mesolimbic and Mesocortical pathways
Dystonia	Upto 20%	First few hours to few days	DA hyperactivity in basal ganglia
Rigidity	Upto 25%	5-90 days	Blockade of DA receptor in nigrostriatal tract
Tremor	Upto 35%		

drugs in the treatment of schizophrenia, resulting in poor compliance and increased risk of relapse in this illness.

ATYPICAL ANTIPSYCHOTICS

The introduction of clozapine challenged the view that all anti-psychotic drugs are similar in efficacy and mode of action. Development of new drugs therefore, emphasized the importance of findings compounds having beneficial effects on positive & negative symptoms and cognitive functioning and showing few or no side effects in patients with schizophrenia. The success of clozapine, thus, promoted large-scale efforts at new drug development for treating schizophrenia. These newly developed novel drugs show high affinities for a broad range of serotonin (5HT) receptors along with effects on other receptors. The notion of relatively week D2 antagonist activity coupled with potent serotonergic effects, including antagonism of the 5-HT receptor subtype, stays as critical to atypicality for all these new drugs.

Generally known as atypical anti-psychotics, these drugs can be classified into various groups: one having a mixed and complex pattern of affinities for numerous receptors, but, relatively poor affinity for D2 receptors, the other group having strong affinities for 5HT2 receptors, as well as, D2-receptors and a third group that selectively blocks D2 and D3 receptors. Drugs currently available from these groups include olanzapine, quetiapine, ziprasidone, zotepine, risperidone, sertindole and amisulpride.

Comparative receptor profile of atypical antipsychotics is given in table-I.

Clozapine

Clozapine, the prototype atypical antipsychotic is from dibenzodiazepine class and was first used in the late 1960's for the treatment of psychotic patients. It was withdrawn from regular clinical use after few years owing to reports of fatal agranulocytosis. It was resurrected in the mid-1980s as it was found working in patients who had failed to respond to other antipsychotic drugs. Strict haematological monitoring has, however, been mandatory for its use.

Clozapine has high affinity for serotonergic, D4, M1 muscarinic and α1-adrenergic receptors, but has weak affinity for D2 receptor[17]. There are two possible features that increase the importance of clozapine in clinical practice. First, it exerts almost no effect on EPS and secondly both positive and negative symptoms appear to improve with clozapine treatment[18]. Treatment with Clozapine has also shown improvement in the quality of life of patients by enhancing compliance due to lack of EPS[19] and thus reducing some direct and indirect costs of the illness.

Clozapine induces symptom reduction to

Table - I: Receptor binding profiles of antipsychotics[16]

	Affinity for receptor (Ki (nmol))							
Drug	*Dopamine D1*	*Dopamine D2*	*Dopamine D4*	*α1*	*α2*	*H1*	*5HT2a*	*5HT2c*
Clozapine	85	126	9	7	8	6	12	8
Haloperidol	25	1	5	46	360	>1000	78	>1000
Risperidone	75	3	7	3	155	0.6	26	
Olanzapine	31	112	27	19	228	7	4	11
Quetiapine	455	160	NA	7	87	11	220	615
Sertindole*+	28	41	NA	3.4	350	600	0.39	NA
Ziprasidone	68	8	7.4	7.9	NA	7.3	9	8

Adapted from Kerwin & Owen[16]+ value expressed as IC50. *Drug withdrawn from the market.

POTENTIAL ADVANTAGES OF ATYPICAL ANTIPSYCHOTICS

* Few neurological side effects
* Improved action against negative symptoms (?)
* Improved action against positive symptoms
* Improved acceptability, tolerability and compliance

effect of 15 to 25% beyond the improvement achieved by typical antipsychotic drugs. Another aspect is reduction in suicide symptoms[20] possibly by alleviating depression and hopelessness. It has also shown low propensity for drug-induced tardive dyskinesia, and can actually reverse such movements in 43% of patients.[21]

Olanzapine

It is a thienobenzodiazepine derivative and shows high affinities for 5HT receptors and structurally related to clozapine. Effectiveness in schizophrenic symptoms is well documented in a number of trials with this drug. The possible mechanisms of olanzapine's superior clinical effects to other anti-psychotic drugs are explained on the basis of its unique dopamine receptor profile (D1 to D4), greater regional specificity (mesolimbic) and modulating effects on other neurotransmitters like 5HT, ACH and glutamate.

Olanzapine has shown better efficacy than haloperidol in controlling both positive and negative symptoms of schizophrenia[22]. It possesses broader mood stabilizing property and has shown more effectiveness for depressive symptoms in schizophrenia[23]. The incidence of reported EPS is comparable with placebo. Sedation a commonly encountered side effect may be helpful in acutely excited patients. However, weight gain is a very undesirable side effect, which may become very troublesome in some patients. Laboratory findings also indicate some increase in liver enzymes that may require regular monitoring.

Quetiapine

This is a dibenzothiazepine piperazine derivative and has shown marked D1, D2, 5HT2 and

alpha-1 receptor blocking activities. The pharmacological profiles resemble other atypical anti-psychotics as quetiapine possesses higher affinity for 5HT2 receptors than D2 receptors. This drug demonstrates significant selectivity for limbic dopaminergic pathways. No appreciable affinity for muscarinic receptors has been observed.

Both positive and negative symptoms are improved and this drug has shown generally a better tolerability. It has been subject to extensive clinical testing using dosages ranging between 25 and 750 mg per day given in either 2 or 3 divided doses. Common side effects include postural hypotension, agitation and restlessness. However, somnolence and headache are the most undesirable side effects. Some disturbances in liver fuhction may be noted but there is no requirement for the routine monitoring of liver function tests. Reduction of free T4 and transient neutropenia has also been noted. Quetiapine does not lead to sustained elevation of prolactin in humans[24].

Ziprasidone

Ziprasidone from benzisothiazolyl class, is one of the newer atypical with a high serotonin/dopamine receptor affinity. Due to low affinity to alpha 2 adrenergic, histaminergic and muscarinic receptors, it produces less sedation. In clinical trials, this drug has shown overall efficacy in both positive and negative symptoms. The pharmacological profile also suggests potential advantages for treating anxiety and depression associated with schizophrenia psychopathology. It has an elimination half-life of upto 10 hours and is given twice daily immediately after food[25]. It has very easy dose range, 40mg twice daily or 80 mg twice daily.

Ziprasidone has not been associated with postural hypotension or elevation of hepatic enzymes. Somnolence and dizziness are most frequent side effects. Significance of QT prolongation is currently under investigation. It appears to have a low liability for EPS but this needs to be confirmed in further trials.

Zotepine

Zotepine is a dibenzothiepine that blocks serotonergic, dopaminergic, histaminergic and noradrenergic receptors[26]. The effect at 5HT2a receptors and the balanced D1/D2 effects of zotepine raise its atypical profile. Interestingly it is also a strong noradrenaline (norepinephrine) reuptake inhibitor. This may confer antidepressant properties to this drug. The recommended dosage range is 75 to 450 mg/day and steady-state plasma concentrations are reached after 3 to 4 days[27]. Several double blind clinical trials have documented its antipsychotic efficacy. Comparison with haloperidol has consistently indicated a lower EPS risk for zotopine[28]. Open studies have suggested efficacy against negative and depressive symptoms[29] and one meta-analysis has supported its efficacy in treating acute negative symptoms of schizophrenia[30].

In healthy volunteers, low dosages are well tolerated. Sedation has been reported as the main effect with dry mouth, dizziness, somnolence and tachycardia as other side effects.

Risperidone

This is a derivative of benzisoxasoles and has got potent antagonist for 5HT2 receptors in addition to D2 antagonism. Risperidone has a regional preference for blocking D2 receptors in the mesolimbic cortical bundle of the nigrostriatal pathways. It has no or very mild anti-cholinergic activity and studies have shown that this is equally effective as typical neuroleptics like chlorpromazine and haloperidol with less extra-pyramidal side-effects (EPS). However, the incidence of EPS appears to be dose related - being negligible in doses below 6 mg per day. Risperidone has also been shown to be efficacious against negative symptoms in acutely ill patients[31]. This effect is at least partly independent of potentially interfering EPS[32]. Risperidone is not associated with agranulocytosis but marked akathisia and significant elevation of prolactin level have been found in many patients. Other dose related adverse

effects include sedation, fatigue and accommodation disturbance in some patients.

Sertindole

Sertindole is an arylpiperidylindole derivative and shows affinity for a number of receptors like D1, D2, D3, 5HT2 and alpha1. Actions on 5HT2 are more potent and long lasting. Evidence from clinical trials supports the claim that sertindole is a potent antipsychotic drug at a dose of 12-24 mg/day. It is thought to give a lower incidence of extrapyramidal side effects than typical antipsychotic drugs. Other common side effects are rhinitis and orthostatic hypotension; both mediated by α1 adrenoceptor blockade. It is also a potent 5HT2c antagonist, which predisposes it for weight gain. Nasal congestion and sexual dysfunctions like delayed or decreased ejaculation are also reported by few patients but are mild and reversible on discontinuation.

The most undesirable side effect of sertindole is prolongation of QT interval requiring ECG monitoring prior to commencing treatment and also during the treatment period. This effect has led to concerns that patients receiving this drug maybe vulnerable to potentially fatal cardiac dysrhythmias. Hence, in December 1998 the manufacturers voluntarily withdrew the drug from the market for further research and investigations.

Amisulpiride

Amisulpiride is a substituted benzamide drug with selective affinity for dopamine (D2/D3) receptors and acts preferentially on the limbic system rather than the striatum. It has no or less affinity for other receptors like 5HT2, alpha adrenergic or muscarinic.

Recently marketed in Europe, this drug is showing promising results in the treatment of schizophrenic patients. Considered more effective in negative symptoms, amisulpiride does not offer any specific superior efficiency in the management of positive symptoms as compared to other atypical drugs. It's lower potential for causing EPS warrants it some frequent use. Common side effects include insomnia, agitation and postural hypotension.

CURRENT VIEW AND CLINICAL IMPLICATIONS

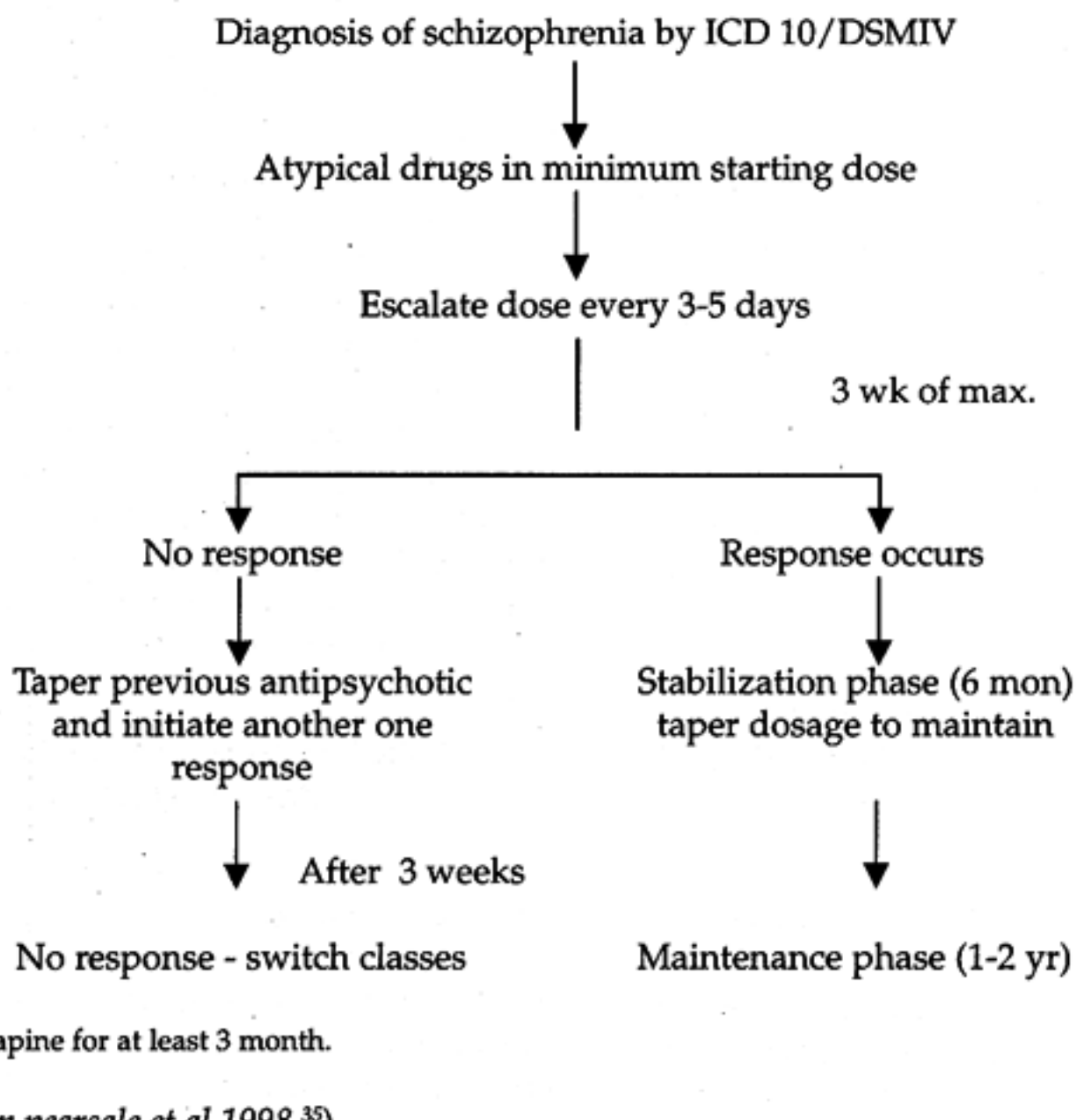
The last decade of 20th century did see landmark changes in pharmacotherapy of schizophrenia. The success of clozapine prompted large-scale efforts at new drug development for treating this illness and introduction of other atypical agents did provide higher expectations of treatment for schizophrenia than in the past. There is now no doubt that the efficacy and effectiveness of atypical antipsychotics have been well established and these new drugs are being used more commonly in clinical

Table - II: Percentage incidence of extrapyramidal symptoms (EPS)[33]

Haloperidol	*EPS (%)*	*Risperidone*	*EPS (%)*	*Olanzapine*	*EPS (%)*	*Sertindole*	*EPS (%)*	*Quetiapine*	*EPS (%)*	*Amisulpride*	*EPS (%)*	*Zotiepine*	*EPS (%)*
Placebo	27	Placebo	13	Placebo	16	Placebo	27	Placebo	16			Placebo	16
4mg	44	2mg	13	5mg	15	12mg	21	75mg	6	100mg	31	100mg	26
8mg	55	6mg	16	10mg	25	20mg	13	150mg	6	400mg	42		
16mg	56	10mg	20	15mg	32	24mg	24	300mg	4	800mg	45		
		16mg	31					600mg	8	1200mg	55		
								750mg	6				

Adapted from Goldstein MJ[33]

Diagram - 1: Outline for treatment of schizophrenia[36]



(Adapted from pearsale et al 1998 [35])

practice. Regional variations, however, still exit in their use, as for example, prescribing of atypical drugs in USA is far more than that of typical, but in United Kingdom only a minority of patients are receiving atypical medication[34]. Ever increasing clamour and counter-clamour about their advantages are also appearing in peer-reviewed journals. While the improvement in positive symptoms is greater or equal in degree with both typical and atypical drugs, there are definitely fewer incidences of EPS with the later. But at the same time, side effects like weight gain, sexual dysfunction and agranulocytopenia are giving serious consideration for a routine use of these new drugs. To make the choice more difficult, a recent study[35] inferred that the degree of improvement in symptomatology and incidence of side effects is the same with typical and atypical drugs provided that the typical drugs are used in not higher than recommended dosages (300-400 mg equivalent of chlorpromazine). And last but not the least, there is an issue of cost that makes the widespread use of new drugs a bit limited in many settings.

RECOMMENDED DAILY DOSAGE OF ATYPICAL ANTIPSYCHOTICS

Amisulpride (Solian)	400mg-800mg
Clozapine (Clozaril)	200mg-450mg
Olanzapine (Zyprexa)	5-20mg
Quetiapine (Seroquel)	300-450mg
Risperidone (Risperdal)	4-12mg
Sertindole (Serdolect)	12-20mg

Despite these limitations, atypical anti-psychotics are becoming more acceptable and there is a world-wide growing trend with a number of guidelines for their use as first line treatment, or at least a first alternative for many schizophrenic patients[36] and other schizophrenic related illnesses.

FUTURE TRENDS

Chemical neurotransmission and its role in brain functioning have assumed an important place in the field of neuro-science. The focus of research is gradually shifting from efficacy to the understanding as to how the new drugs might work. The main sites of interest still remain the novel dopamine receptors, especially the D2 isomers, D3 and D4 and some 5HT receptors, especially 5HT2a, 5HT2c and 5HT7. As most of these sites are not amenable to conventional assessment methods such as functional receptor imaging and post-mortem studies, recent work is therefore putting more emphasis on developing innovative techniques in this field.

Changes in the scientific knowledge are also concentrating in areas other than monoamine systems. Work on substance P antagonists, sigma-2 antagonists and a range of other drugs with no direct effect on the monoamine system is in progress. Similarly the developments within pharmacogenetics and neuro-imaging technology are fascinating and molecular genetic approaches are focusing on brain receptors more specifically. The future research is also directed towards the candidate gene and pharmaco-genetic studies. A lot of emphasis is also being placed on the precise mechanism of side effects like lack of EPS and prolactin elevation and limbic selectivity for these drugs.[37]

It is hoped that current research will be useful to find out where further work is needed and what future studies should be performed. As it will not be long before that we find more drugs in the field, it is hoped that further advances in drug treatment of schizophrenia will help us in understanding the pharmacological basis of this disorder with more precision and accuracy.

CONCLUSION

The development of new anti-psychotic drugs has provided an opportunity to the clinicians for a better treatment strategy in schizophrenia. These compounds have given the psychiatrists an advantage while choosing between old and newer drugs, in terms of patient's tolerability, better compliance, increased safety and efficacy. Most of the new drugs share the same profile of higher tolerability but they do differ in terms of their neurobiological actions, receptor occupancy, pharmacological properties and side effects. A closer look is, therefore, essential and warranted while choosing any particular drug from this new list.

Over the next few decades a number of other drugs are likely to be introduced into clinical practice and the prospect is that some of these newer drugs may not only replace conventional neuroleptics from the scene but also replace them as the standard against which future new compounds will be compared[38]. It is expected and also hoped that widespread use of newer types of antipsychotic drugs will lead to further developments in our knowledge and understanding of schizophrenia and provide new insights into the neurochemical pathology of this illness.

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